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Apoptotic cell death in disease—Current understanding of the NCCD 2023

Apoptosis is a form of regulated cell death (RCD) that involves proteases of the caspase family. Pharmacological and genetic strategies that experimentally inhibit or delay apoptosis in mammalian systems have elucidated the key contribution of this process not only to (post-)embryonic development and adult tissue homeostasis, but also to the etiology of multiple human disorders. Consistent with this notion, while defects in the molecular machinery for apoptotic cell death impair organismal development and promote oncogenesis, the unwarranted activation of apoptosis promotes cell loss and tissue damage in the context of various neurological, cardiovascular, renal, hepatic, infectious, neoplastic and inflammatory conditions. Here, the Nomenclature Committee on Cell Death (NCCD) gathered to critically summarize an abundant pre-clinical literature mechanistically linking the core apoptotic apparatus to organismal homeostasis in the context of disease.

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FACTS

- Intrinsic and extrinsic apoptosis are forms of regulated cell death (RCD) promoting the cellular demise along with the activation of proteases of the caspase family.
- In mammalian organisms, executioner caspases are activated after cells are already committed to die.
- Apoptosis can be manipulated by genetic or pharmacological means, and multiple genetically engineered animal models and pharmacological tools to modulate apoptosis have been developed.
- Apoptosis is intimately involved in both (post-)embryonic development and adult tissue homeostasis.
- Apoptosis deregulation promotes oncogenesis and contributes to the etiology of multiple human disorders, including cardiovascular, hepatic, renal, inflammatory and neurological conditions.
- To date, venetoclax is the only apoptosis inducer that has received regulatory approval for use in humans.

OPEN QUESTIONS

- Will inhibitors of apoptotic caspases with elevated target specificity become available?
- Will agents specifically conceived to modulate apoptosis enter the clinical practice to treat solid tumors or other human disorders beyond hematological malignancies?
- Is it conceivable to design combinatorial strategies aimed at inhibiting apoptosis while interrupting compensatory activation of other RCD signaling cascades?
- Will it be possible to specifically inhibit apoptotic signaling without impacting on other processes dependent on apoptosis regulators such as differentiation, proliferation, and inflammatory reactions?

INTRODUCTION

The health and homeostasis of multicellular organisms depend on the tight balance between cell proliferation and cell death. In this context, a large body of experimental evidence has demonstrated the existence of a form of regulated cell death (RCD) that is executed by a genetically programmed process, and hence amenable to manipulation by genetic or pharmacological means [1]. Over the past decades, multiple variants of RCD have been characterized at the genetic, biochemical, functional, and immunological level [2–8]. For instance, programmed cell death (PCD) has been functionally defined as a modality of RCD activated under purely physiological conditions (i.e., in the absence of perturbations of extracellular or intracellular homeostasis) in the context of embryonic/post-embryonic development or adult tissue homeostasis [1, 9]. Conversely, pathological RCD is invariably initiated in the context of failure to adapt to shifts in extra-cellular or intra-cellular homeostasis, constituting a *de facto* organismal program for the elimination of excessively damaged and/or potentially harmful cells, such as cells infected with pathogens [1, 10]. From a biochemical perspective, an increasing number of RCD modalities have been defined by the Nomenclature Committee on Cell Death (NCCD) based on the mechanistic involvement of specific molecular components [1, 11]. For instance, apoptotic cell death has been defined as a form of RCD that is promoted by proteases of the caspase family, namely caspase 3 (CASP3), CASP6 and CASP7, and initiated by CASP8 and CASP9 [1, 12, 13]. However, in mammalian organisms, with the exception of CASP8, apoptotic caspases simply accelerate RCD

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because their activation occurs when cells are already committed to die [1, 14–16]. This means that contrarily to simpler organisms (e.g., *Caenorhabditis elegans*), in which apoptotic caspase elimination fully rescues cells from death, in mammals, apoptotic cell death can at most be retarded but not prevented by pharmacological or genetic strategies inhibiting the activity of these caspases. Mitochondrial permeability transition (MPT)-driven necrosis, necroptosis, ferroptosis, pyroptosis, parthanatos, entotic cell death, NETotic cell death, lysosome-dependent cell death, and autophagy-dependent cell death represent forms of RCD that involve precise molecular events and hence can also be manipulated with pharmacological or genetic interventions [1–6, 17–19]. Other RCD modalities have been recently identified, such as alkaliptosis [20], cuproptosis [21] and PANoptosis (involving the simultaneous activation of pyroptosis, apoptosis, and necroptosis) [22], and their signal transduction modules are under investigation. The importance of these latter forms of RCD in health and disease is not yet known.

Along with the identification of key RCD regulators and the advent of modern tools for genetic manipulation, a great experimental effort has been devoted to elucidating the role of RCD in the physiopathology of multi-cellular organisms [23]. Thus, various studies in animals (mostly rodents) genetically altered to lack or over-express components of the apoptotic apparatus (either at the whole-body level or in selected cell/tissue types) have provided formal proof of the relevance, but not always the exquisite requirement, of apoptosis for embryonic and fetal development or adult tissue homeostasis [24–26].

Along similar lines, pharmacological and genetic tools aimed at altering apoptotic signaling in pre-clinical disease models revealed the mechanistic contribution of apoptosis to the etiology of various conditions associated with the loss of post-mitotic or (in certain settings) non-post-mitotic cells, including a panel of neurological, cardiovascular, renal, hepatic, and inflammatory disorders [24]. Extensive studies over the last five decades highlighted the apoptotic machinery as a major target for the development of new therapeutic interventions [27], not only for the induction of cell death in the context of disrupted tissue homeostasis (e.g., for neoplastic diseases) [28], but also for the inhibition of cell death in the context of ischemic, degenerative and inflammatory conditions [29, 30]. However, while at least one drug designed to induce apoptosis is currently approved for use in humans, namely the BCL2 apoptosis regulator (BCL2) inhibitor venetoclax [31–34], which is used alone or in combinatorial regimens for the treatment of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma and acute myeloid leukemia (AML) [31, 35–38], no other agents specifically conceived to inhibit the apoptotic apparatus have been licensed for clinical practice so far. The broad-spectrum caspase inhibitor emricasan received fast-track designation by the US Food and Drug Administration (FDA) for the treatment of non-alcoholic steatohepatitis in 2016 but demonstrated inconsistent clinical efficacy [39–41], and – as of now – is not approved for therapy in humans.

The lack of clinically approved, selective apoptosis inhibitors and the inconclusive performance of emricasan in recent trials reflect several aspects of (apoptotic and non-apoptotic) RCD that began to emerge only recently (Fig. 1). First, while detecting cell death as well as biomarkers of specific RCD variants in vitro is relatively straightforward [42], precise quantification of cell death in vivo in adult tissue remains challenging, at least in part because of rapid disposal of cell corpses by efferocytosis [43–46]. Thus, the actual contribution of cell death to the etiology of various human disorders is difficult to quantify by observational approaches [47, 48]. Second, while for a long-time, specific forms of RCD were considered virtually independent entities, it recently became clear that the molecular machinery for RCD is composed of highly interconnected modules characterized by substantial redundancy, backup pathways and feedback loops [10, 49, 50]. Thus, molecules that inhibit one specific form of RCD may ultimately be unable to confer actual cyto- and tissue protection instead only altering the kinetic and biochemical manifestations of death by allowing the engagement of a different RCD sub-routine. For instance, while CASP8 is a major signal transducer in death receptor (DR)-driven apoptosis (see below), it intrinsically inhibits necroptosis induced by DRs and other signaling pathways, such as Toll-like receptor (TLR) signaling [51–53], suggesting that caspase inhibition in the context of DR signaling may promote necroptotic cell death [54–57]. Together with a low target specificity and selectivity within the caspase family [57], this can explain the inadequate efficacy of emricasan observed in pre-clinical and clinical studies. Third, even in the hypothetical scenario of agents capable of simultaneous inhibition of all (known and unknown) RCD pathways, loss of cellular homeostasis due to failing adaptation to stress generally involve degenerative processes that at some stage cannot be reversed, such as widespread mitochondrial permeabilization and loss of RNA and protein synthesis [4, 58–60], i.e., even if all RCD modalities could be blocked effectively, cells might undergo uncontrolled necrotic death. In this setting, cell death may occur as a consequence of an irremediable degeneration of cellular functions that can no longer be rescued pharmacologically or even genetically [61]. Supporting these latter notions, accumulating literature indicates that, at least in mammalian systems, perhaps with the exception of CASP8, so-called apoptotic caspases mainly control the kinetics of apoptotic cell death and its immunological manifestations, but not whether cell death ultimately occurs or not [15, 16]. This points to the caspase family as a major regulator of organismal

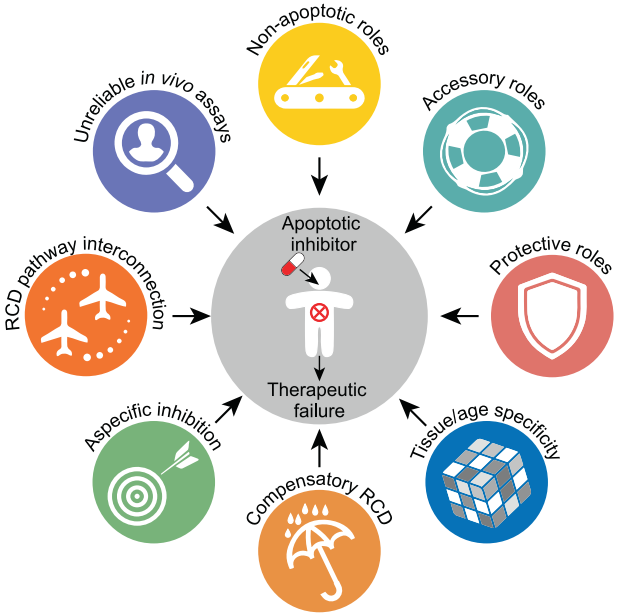

Fig. 1 Principal causes of the therapeutic failure of intrinsic or extrinsic apoptosis inhibitors. The clinical development and success of agents inhibiting apoptosis is limited by multiple contributory causes, including potential non-apoptotic, accessory or even protective roles of the targeted proteins (exemplified by the involvement of certain BCL2 family members, caspases and death receptors in processes as diverse as inflammation, cell differentiation, cell proliferation and cell survival), the high interconnectivity between RCD pathway (potentially leading to the activation of compensatory RCD variants in response to the inhibition of a specific RCD type), the low specificity and selectivity of the inhibitors developed so far (exemplified by the broad-spectrum caspase inhibitors) and the difficulty to precisely determine and quantify cell death in vivo. RCD regulated cell death.

Box 1. Principle of intrinsic apoptosis

Intrinsic apoptosis is a type of regulated cell death (RCD) initiated by perturbations of the extracellular or intracellular microenvironment including (but not limited to) DNA damage, endoplasmic reticulum or oxidative stress, growth factor withdrawal, and microtubular alterations. The critical step is mitochondrial outer membrane permeabilization (MOMP) [4, 59, 1054, 1055]. MOMP is modulated by the activity of multiple pro-apoptotic and anti-apoptotic members of the BCL2, apoptosis regulator (BCL2) protein family [1056–1060]. In response to apoptotic stimuli, MOMP leads to the sequential activation of the initiator caspase 9 (CASP9) and then executioner caspases CASP3 and CASP7 [12, 13, 1061–1063]. Two functionally distinct classes of pro-apoptotic BCL2 proteins have been identified. The first class encompasses the apoptotic activators BCL2 associated X, apoptosis regulator (BAX), BCL2 antagonist/killer 1 (BAK1), and BCL2 family apoptosis regulator (BOK) [1064]. Once activated by apoptotic stimuli, BAX, BAK1 and BOK induce MOMP by generating pores across the outer mitochondrial membrane (OMM) [1065–1069]. These pro-apoptotic factors promote the release into the cytosol of several apoptogenic factors, including cytochrome c, somatic (CYCS) and diablo IAP-binding mitochondrial protein (DIABLO; also known as second mitochondrial activator of caspases, SMAC) [1070]. CYCS exerts apoptogenic activity by associating with apoptotic peptidase activating factor 1 (APAF1) and pro-CASP9 to generate a complex known as the apoptosome, leading to sequential activation of CASP9 and executioner caspases CASP3 and CASP7 [1071]. DIABLO/SMAC contributes to CASP3 and CASP7 activation by associating with and inhibiting X-linked inhibitor of apoptosis (XIAP) and other members of the inhibitor of apoptosis (IAP) protein family that restrain caspase activation [1072].

The second class of pro-apoptotic BCL2 proteins (known as BH3-only proteins [1073]) include BCL2 associated agonist of cell death (BAD), BCL2 binding component 3 (BBC3; best known as p53-upregulated modulator of apoptosis, PUMA), BCL2 interacting killer (BIK), BCL2 like 11 (BCL2L11; best known as BIM), Bcl2 modifying factor (BMF), BH3 interacting domain death agonist (BID), BCL2 interacting protein harakiri (HRK, also known as DP5), and phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1; best known as NOXA [1074, 1075]). Of these, caspase-cleaved BID (tBID), BIM, PUMA, and NOXA have been reported to also be able to promote BAX and BAK1 activation through a direct interaction with these proteins at mitochondria [1076–1082]. All BH3-only proteins, including BAD, BIK, BMF and HRK activate BAX and BAK1 indirectly by associating with anti-apoptotic BCL2 family members, thereby blocking the inhibitory binding of the latter to BAX and BAK1 [1056, 1060, 1080–1084]. Some BH3-only proteins, particularly BIM, PUMA and tBID, can potently bind and inhibit all anti-apoptotic BCL-2 proteins whereas others bind only some (e.g., NOXA only binds MCL1 and A1) [1080, 1082, 1085, 1086]. It is noteworthy that BAX and BAK1 can induce apoptosis in the absence of all BH3-only proteins when the anti-apoptotic BCL2 proteins are genetically removed or inhibited by BH3 mimetic drugs [1082, 1083]. However, BAX and BAK1 activation in the absence of BH3-only proteins occurs at slower kinetics compared to that in the presence of BH3-only proteins [1082]. These findings support the existence of both BH3-dependent and BH3-independent BAX and BAK1 activation mechanisms (in the latter scenario, BH3-only proteins function as catalysts for BAX and BAK activation) [1082, 1087]. In this context, BAX and BAK are also reported to be activated by tumor protein p53 (TP53; best known as p53) in a fashion independent of BH3-only proteins [1088, 1089]. The anti-apoptotic members of the BCL2 family encompass BCL2, apoptosis regulator (BCL2), BCL2 like 1 (BCL2L1; best known as BCL-X_L), MCL1, BCL2 family apoptosis regulator (MCL1), BCL2 like 2 (BCL2L2; best known as BCL-W), and BCL2 related protein A1 (BCL2A1; best known as A1) [1056–1059]. The anti-apoptotic activity of these BCL2 proteins mainly involves MOMP inhibition, although, a non-canonical, cellular redox-dependent mechanism of cytoprotection has also been reported in cancer cells, at least for BCL2 [1090–1093]

homeostasis via control of inflammatory responses [62, 63]. The simultaneous inhibition of multiple caspases, as for instance by emricasan, may thus also impact inflammation, as was demonstrated for tumor necrosis factor (TNF)-induced systemic inflammatory respiratory syndrome (SIRS) in vivo for the pan caspase-inhibitor zVAD-fmk [54, 64]. To complicate matters, multiple components of the core apoptotic machinery, including caspases and multiple members of the BCL2 family have been reported to regulate a variety of non-apoptotic functions beyond inflammation, such as mitochondrial energy production, Ca^{2+} signaling and terminal differentiation [65–72]. Structurally, distinguishing between apoptotic and non-apoptotic functions of caspases and the BCL2 family remains challenging. Finally, there is a hitherto unclarified heterogeneity in the regulation of RCD at distinct anatomical sites (possibly linked to micro-environmental features) at distinct stages of cellular differentiation, and in the context of diverse patho-physiological states (e.g., in young *vs*. adult and aged individuals).

All these issues should also be kept under consideration in the context of the present review, in which the NCCD aims at critically discussing a large amount of pre-clinical data in support of a key role for the apoptotic machinery in mammalian diseases. Specifically, the interpretation of results of genetic and pharmacological experiments presented herein should place particular attention on the aforementioned connectivity amongst different RCD variants as well as on discriminating between essential *vs*. accessory aspects of cell death [14]. Another issue to be considered is the fact that most conclusions are based on use of knockout/congenic mice which often present other passenger mutations potentially influencing the observed phenotype [73]. Our objective is not only to provide a critical summary of the existing literature, but also to offer an updated framework for interpretation of these findings in view of currently accepted models of RCD signaling.

INTRINSIC APOPTOSIS IN DISEASE

There are substantive supporting data from genetic studies to demonstrate that the molecular machinery for intrinsic apoptosis (described in Box 1 and Fig. 2) is involved in embryonic and fetal development as well as in adult tissue homeostasis. Numerous preclinical studies in animal models of disease demonstrate that intrinsic apoptosis contributes to etiology in various disorders involving the loss of not only post-mitotic, but also non-post-mitotic tissues, including neurological, cardiac, renal, hepatic, autoimmune/inflammatory, oncological, and infectious conditions. However, as discussed above, the interpretation of these results should be taken with caution given the high interconnectivity of RCD pathways and the crosstalk between RCD and inflammatory response. Moreover, the activation of executioner caspases occurs after cells are already committed to intrinsic apoptosis [15, 16]. Accordingly, caspase inhibition only delays the execution of cell death. In this context, the phenotypes observed under apoptotic caspase-deleted or inhibited conditions may reflect cell-extrinsic effects of caspase activity such as the release of immunomodulatory and cytotoxic signals from dying/dead cells, including damage-associated molecular patterns (DAMPs) or cytokines (this concept is extensively discussed in [14]). These phenotypes may also stem from the lack of processes independent of intrinsic (or extrinsic) apoptosis, as, for instance, the lack of CASP3-mediated cleavage of gasdermin E (GSDME) leading to impaired pyroptosis and associated inflammatory response [74, 75].

Below, we will provide details of the pro-apoptotic BCL2 proteins, the anti-apoptotic BCL2 proteins, the components of the apoptosome—a platform for the activation of initiator caspases composed of cytochrome c, somatic (CYCS), apoptotic peptidase activating factor 1 (APAF1) and pro-CASP9—and effector caspases in disease. The instances of involvement encompass participation in the pathogenic mechanisms as well as experimental deletion or inhibition as a means of exploring potential utility as treatment targets. The effects of these regulators and effectors of the intrinsic apoptosis pathway on health are described in Box 2, Box 3 and Box 4.

Neurological disorders

Intrinsic apoptotic factors are implicated in the pathophysiology of numerous neurological diseases (Fig. 3). In a mouse model of amyotrophic lateral sclerosis (ALS), deletion of BCL2-associated X protein (*Bax*) reduces neuronal cell death coupled to attenuated motor dysfunction and neuromuscular degeneration [76]. Additional ablation of BCL2-antagonist/killer 1 (*Bak1*) further enhances neuroprotection, resulting in improved overall animal survival [77]. Similar protective effects were observed in mice lacking the BH3-only proteins BCL2 like 11 (BCL2L11, best known as BIM) and BCL2

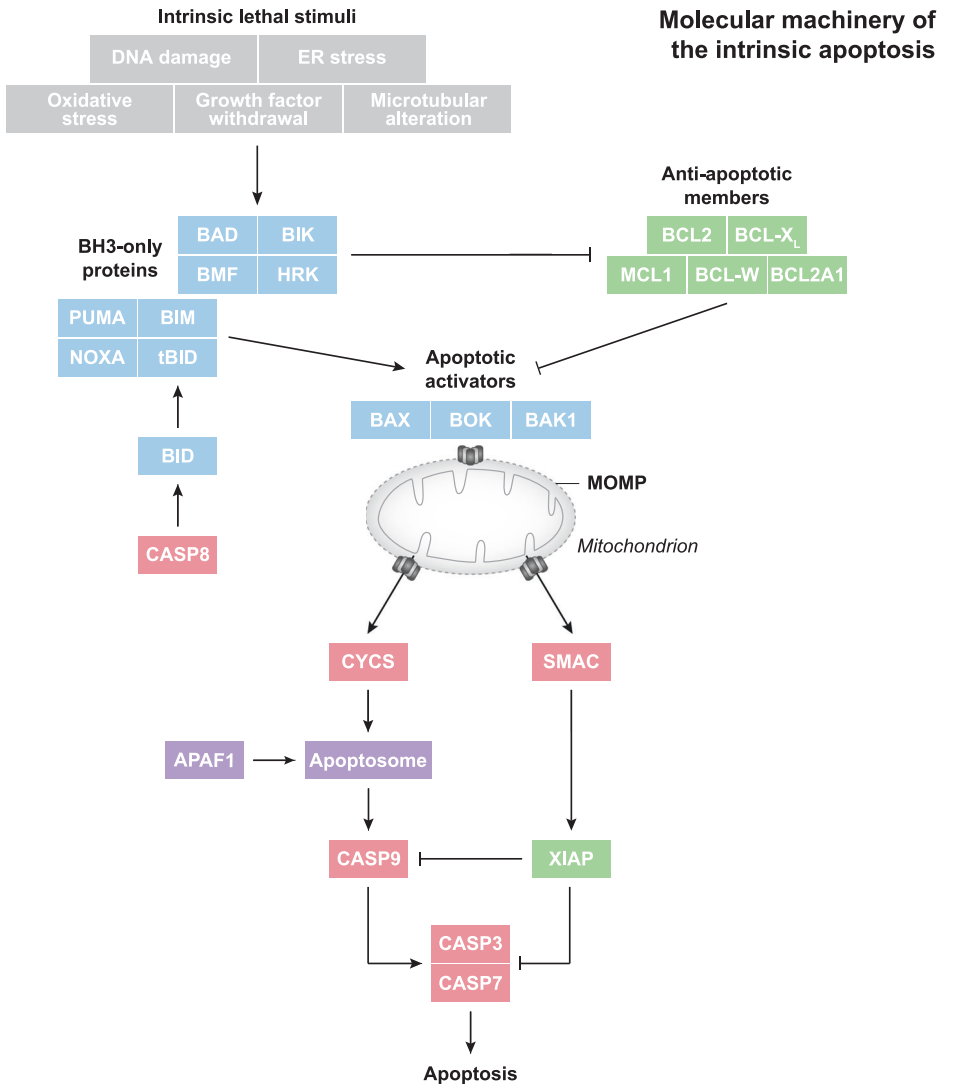

Fig. 2 Molecular machinery of the intrinsic apoptosis. Intrinsic apoptosis can be activated by a range of extracellular or intracellular stimuli, including, but not limited to, DNA damage, endoplasmic reticulum (ER) or oxidative stress, growth factor withdrawal or microtubular alterations. The critical step of the intrinsic apoptosis is the activation of the pro-apoptotic effectors of the BCL2 family, BAX, BAK and possibly BOK, which drives the outer membrane permeabilization (MOMP) and commits cells to death. MOMP results in the release from the mitochondrial intermembrane space into the cytosol of proapoptotic proteins, including CYCS and SMAC. CYCS assembles with APAF1, dATP and pro-CASP9 into the apoptosome, leading to the activation of CASP9, which in turn promotes the activation of the executioner caspases CASP3 and CASP7. The activation of the executioner caspases is facilitated by SMAC, which sequesters and/or degrades members of IAP family that inhibit apoptosis.

binding component 3 (BBC3, best known as PUMA), as well as in transgenic mice overexpressing BCL2, X-linked inhibitor of apoptosis (XIAP) [78–82]. Moreover, intra-cerebroventricular administration of the broad-spectrum inhibitor Z-VAD-FMK protects mice from ALS [83], although whether such protection arises from the inhibition of intrinsic apoptosis remains to be formally established. *Bax* deletion also attenuates neuromuscular dysfunctions in a mouse model of congenital muscular dystrophy (another neurodegenerative disease affecting motoneurons) [84], while BCL2 overexpression limits neuromuscular disease progression in some (but not all) mouse models of progressive motor neuronopathy and muscular dystrophy [85–87]. Finally, genetic or pharmacological inhibition of poly (ADP-ribose) polymerase family, member 1 (PARP1) and PARP2 halts axonal degeneration and improves related motor phenotypes in *C. elegans* models of ALS [88].

Multiple components of the molecular machinery for intrinsic apoptosis, including BAX, PUMA, BH3 interacting domain death agonist (BID), Harakiri, BCL2 interacting protein (contains only BH3 domain) (HRK), were shown to drive neuronal death in Alzheimer's disease (AD) and Parkinson's disease (PD) models [89–101]. Thus, overexpression of BCL2 decreases the appearance of early pathological markers of AD, such as amyloid precursor protein (APP) and microtubule-associated protein tau (MAPT, best known as tau) cleavage, which depend on caspases [102–104], resulting in attenuated neurological defects [105, 106]. Some findings indicate a role of apoptotic caspases in the pathogenesis of AD. However, as discussed above, during intrinsic apoptosis, caspases simply accelerate the course of cell death, and, so, such effects may be linked to the release of cytotoxic and pro-inflammatory factors from dying cells. In more detail, pharmacological inhibition

Box 2. Impact of pro-apoptotic BCL2 proteins on health

Deletion of BCL2-associated X protein (*Bax*), BCL2-antagonist/killer 1 (*Bak1*) or BCL2-related ovarian killer (*Bok*) does not significantly affect mouse development [1094–1096], with the exception of a mild lymphocyte and neuron accumulation in *Bax*$^{-/-}$ mice which also exhibit male infertility due to seminiferous tubule malformation [166, 1094]. Of note, a recent study has demonstrated that such defects in germ cells occur in the fetal period [1097], supporting the requirement for intrinsic apoptosis in testicular development [1098, 1099]. Subsequent studies confirmed the role of BAX in neurogenesis, in particular the development of hippocampal and cerebellar neurons, cortical interneurons and astrocytes [1100–1105]. Accordingly, *Bax*$^{-/-}$ mice exhibit impaired neurological functions manifesting with increased anxiety, depression-like traits, compromised social and sexual behavior, and impaired spatial representation and olfactory system function [1106–1108]. These mice also show accelerated medulloblastoma formation [389], which is in line with the oncosuppressive activity of apoptotic (and non-apoptotic) regulated cell death (RCD) [1109].

Ablation of *Bok* does not compromise the relatively normal development of BAK1- or BAX-deficient mice, although *Bax*$^{-/-}$*Bok*$^{-/-}$ mice exhibit an increased number of mature oocytes [1110]. In contrast, co-deletion of *Bax* and *Bak1* causes perinatal death in the vast majority (more than 90%) of mice, mainly due to multiple developmental abnormalities and feeding difficulties [26, 1095]. Importantly, the developmental defects of *Bax*$^{-/-}$*Bak1*$^{-/-}$ mice are exacerbated by additional deletion of *Bok*, underscoring not only some functional redundancy between BAX, BAK1 and BOK, but also a crucial role of pro-apoptotic BCL2 family members in the development of the central nervous system (CNS) and hematopoietic compartment [26]. However, since some *Bax*$^{-/-}$*Bak1*$^{-/-}$ and *Bax*$^{-/-}$*Bak1*$^{-/-}$*Bok*$^{-/-}$ mice can reach adulthood [26, 1095], additional systems must be at play to compensate for defects in apoptosis in other organs. In is worth noting that the developmental defects of *Bax*$^{-/-}$*Bak1*$^{-/-}$ mice can be further aggravated by deletion of autophagy related 5 (*Atg5*) [1111], which is involved in autophagy as well as in non-canonical vesicular pathways like LC3-associated phagocytosis [1112, 1113]. However, whether autophagy-dependent cell death compensates for the apoptotic defects of *Bax*$^{-/-}$*Bak1*$^{-/-}$ mice remains to be formally determined [1114, 1115].

Further corroborating the relevance of intrinsic apoptosis for proper development, the few surviving *Bax*$^{-/-}$*Bak1*$^{-/-}$ mice and *Bax*$^{-/-}$*Bak1*$^{-/-}$*Bok*$^{-/-}$mice display phenotypes related to defective programmed cell death (PCD), including webbed feet (due to the incomplete removal of interdigital webs), imperforate vagina and midline fusion defects including facial cleft [26, 1095]. CNS issues exhibited by these animals include a striking expansion of the tissue regions that harbor the neural stem cell pool [26, 1095] as well as impaired function of the motor [1116] and visual [1117, 1118] systems. Although the number of apoptotic cells were reduced to the limit of detection in embryos lacking BAX, BAK1 and BOK [26], anomalies in the urinary tract were conspicuously absent in these animals [26]. This sparked a study examining if BID, in addition to linking the death receptor (DR) pathway and the intrinsic apoptotic pathway (Box 5), could act in a way similar to BAX and BAK1. Indeed, while loss of BID alone did not lead to anomalies during embryonic and fetal development, additional deletion of *Bid* in *Bax*$^{-/-}$*Bak1*$^{-/-}$*Bok*$^{-/-}$mice mice revealed a redundant requirement for BID in urogenital tract development [1119]. In its previously recognized role, BID in the form of tBID activates BAX and BAK1, which would not have caused additional anomalies in the absence of BAX and BAK1. Therefore, these results indicate that BID can act in parallel with BAX, BAK1 and BOK. Congruently, full-length BID [1119] or tBID [1120] can mediate mitochondrial permeabilization and cause cytochrome c, somatic (CYCS) release. In this context it is worth considering that BID has been reported to be structurally similar to the multi-BH domain BCL2 family proteins, such as BAX and BCL-X_L [1060, 1121–1123].

Tissue-specific ablation of *Bax* and *Bak1*, confirmed the crucial role of these proteins in the hematopoietic system, and specifically in the homeostasis and functionality of B cells [1124], T cells [1125], megakaryocytes [1126] and platelets [1127]. Mice reconstituted with fetal liver cells from *Bax*$^{-/-}$*Bak1*$^{-/-}$ mice display massive lymphadenopathy and defective T cell proliferation, and the severity of these defects is even more pronounced when *Bak1*$^{-/-}$*Bax*$^{-/-}$*Bok*$^{-/-}$ fetal liver cells are used for reconstitution, an experimental setting that also reveals signs of autoimmunity [1128–1130]. Similarly, mice reconstituted with a *Bak1*$^{-/-}$*Bax*$^{-/-}$ hematopoietic compartment develop a fatal systemic lupus erythematosus (SLE)-like autoimmune disease [411]. Moreover, the inducible co-deletion of *Bax* and *Bak1* in lymphocytes of adult mice results in the development of severe autoimmune glomerulonephritis [1124]. Finally, conditional knockout mouse models reveal a crucial contribution of BAX and BAK1 to endothelial cell homeostasis [164, 1131], but little impact on cardiac and intestinal functions, as shown by the absence of hyperplasia [223, 453]. These results demonstrate that the multi-BH domain pro-apoptotic BCL2 proteins play critical roles for the normal development of multiple tissues, but that, surprisingly, a few mice can reach weaning or even adulthood when all of these effectors of apoptosis are removed [26].

Amongst BH3-only proteins, BCL2 like 11 (BCL2L11, best known as BIM) appears the most critical for embryonic development and tissue homeostasis, as shown by the fact that approximately 30% of BIM-deficient mice die during embryogenesis [410]. Surviving BIM-deficient mice display severe defects in the hematopoietic system including lymphoid hyperplasia and marked splenomegaly, and on a mixed C57BL/6 x 129SV background many of these mice spontaneously develop systemic autoimmunity often resulting in fatal kidney disease [410], a condition that can be accelerated by depletion of immunosuppressive $CD4^+CD25^+FOXP3^+$ regulatory T (T_{REG}) cells [1132]. Cells from BIM-deficient mice are profoundly resistant to growth factor deprivation, glucocorticoids, deregulated calcium flux and ER stress [410, 1133]. Accordingly, BIM-deficient mice also display dysregulated T cell development and homeostasis [1134–1138] and hence exhibit defective cellular [480, 1139, 1140] and humoral [1141–1143] immune responses. *Bcl2l11* deletion (loss of BIM) has also been shown to extend the survival of granulocytes [1144] and to perturb the development of mammary glands [1145, 1146], gastric epithelium [1147] and the retina [1148]. Moreover, aged BIM-deficient mice show reduced adiposity [1149]. Of note, systemic deletion of *Bax* or *Bak1* exacerbates the hematopoietic dysregulation of BIM-deficient mice [1150]. Conditional knockout systems confirmed a key role for BIM in the hematopoietic system homeostasis [1151–1154], and revealed a role for BIM in the survival and differentiation of hippocampal neurons [1155]. Finally, myeloid cell-specific deletion of *Bcl2l11* induces a SLE-like disease that resembles the pathology developing in mice that lack BIM in all cells [1156].

Mice lacking BH3 interacting domain death agonist (BID), phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1, best known as NOXA) or BCL2 binding component 3 (BBC3, best known as PUMA) display normal embryonic development [278, 479, 1157, 1158]. In these studies on BID-deficient mice, substantial reduction in FAS ligand (FASL)-induced apoptosis was seen in hepatocytes [278, 761], pancreatic cells [278, 1159, 1160] and possibly neurons [181, 1161]. Moreover, *Bid*$^{-/-}$ mice display a dysregulated myeloid compartment resulting in an increased likelihood of leukemogenesis [1161], as well as cardiac dysfunction [1162]. Conditional gene deletion studies confirmed the relevance of BID in the homeostasis and functionality of hepatocytes and T cells [301, 760, 1163].

PUMA contributes to normal ovarian development, as shown by the evidence that two-thirds of the germ cells produced during embryonic development undergo PUMA-mediated cell death shortly after formation [1164]. Moreover, cells from PUMA-deficient mice are profoundly resistant to p53-induced apoptosis triggered by genotoxic drugs, and lymphoid cells are also resistant to glucocorticoids, phorbol ester and growth factor deprivation [479, 1158, 1165–1167]. Cells from NOXA-deficient mice also showed resistance to DNA damage-inducing drugs, although to a lesser extent compared to cells lacking PUMA [479, 1168]. Moreover, *Pmaip1*$^{-/-}$ mice (lacking NOXA) show limited stress-induced erythropoiesis [1169]. Germline deletion of the gene encoding PUMA or NOXA also affects humoral immune responses [1170, 1171] and increases the abundance of multiple cell types in the retina [146].

Co-deletion of two or more genes coding for BH3-only proteins confirmed the pronounced relevance of BIM for development and underscored some degree of functional redundancy in the system. On the one hand, mice lacking both PUMA and NOXA develop normally but their cells are profoundly resistant to genotoxic agents, as much as cells lacking p53 [1172]. Concomitant loss of PUMA but not the additional loss of NOXA, BAD, BID or BIK increases the severity of hematopoietic defects imposed by the lack of BIM [282, 1173–1175]. On the other hand, *Bcl2l11*$^{-/-}$*Bbc3*$^{-/-}$*Bid*$^{-/-}$ and *Bcl2l11*$^{-/-}$*Bbc3*$^{-/-}$*Bid*$^{-/-}$*Pmaip1*$^{-/-}$ mice displayed perinatal embryonic lethality and increased incidence of developmental defects, including webbed feet, imperforate vagina, and supernumerary neurons similar in extent to those seen in *Bax*$^{-/-}$*Bak1*$^{-/-}$ mice [1082, 1176]. Of note, triple deficiency of BID, BIM, and PUMA completely abrogates BAX/BAK1-dependent apoptosis in cerebellar granule neurons and T lymphocytes [1176], providing in vivo evidence supporting direct activation of BAX and BAK1 by the BH3-only proteins.

Mice lacking BCL2-associated agonist of cell death (*Bad*), BCL2 interacting killer (*Bik*), BCL2 modifying factor (*Bmf*) and harakiri, BCL2 interacting protein (contains only BH3 domain) (*Hrk*) are viable and develop normally [168, 1177–1179]. That said, BAD-deficient mice display a prolonged platelet lifespan [1180], while *Bmf*$^{-/-}$ mice are characterized by mild lymphadenopathy, vaginal atresia [1178, 1181] as well as minor defects in mammary gland development and oogenesis [1146, 1182]. Interestingly, female *Bmf*$^{-/-}$ mice had significantly more primordial follicles than wild-type control animals associated with an extended fertile life span [1183], while *Bmf*$^{-/-}$ mice developed an accelerated gamma irradiation-induced thymic lymphoma [1178]. Combined deletion of some of the above listed BH3-only protein-coding genes does not cause significant embryonic lethality or developmental abnormalities. Moreover, increased spontaneous tumorigenesis has been documented in *Bad*$^{-/-}$*Bmf*$^{-/-}$ mice [1184]. Conversely, the absence of some of these BH3-only proteins aggravates the defects caused by the loss of *Bcl2l11* (the gene encoding BIM). This applies to: (1) *Bad* co-deletion with *Bcl2l11*, which enhances lymphocyte accumulation [1180], (2) *Bik* co-deletion with *Bcl2l11*, which causes male infertility due to defective spermatogenesis [1185], a phenotype resembling that of BAX-deficient mice, and (3) *Bmf* co-deletion with *Bcl2l11*, which considerably increases the incidence of developmental defects, vaginal atresia, lymphadenopathy, autoimmune glomerulonephritis, and spontaneous development of hematological malignancies [1181, 1186, 1187].

Box 3. Impact of anti-apoptotic BCL2 proteins on health

While myeloid cell leukemia sequence 1 (*Mcl1*) deletion in mice induces embryonic lethality at the blastocyst (embryonic E3) stage prior to implantation [1188, 1189], embryos lacking BCL2-like 1 (BCL2L1, best known as BCL-X_L) die around embryonic day 13.5) with substantial cell depletion in the developing central nervous system (CNS) and erythroid progenitors [1190]. Concomitant deletion of BCL2-associated X protein (*Bax*) or caspase 9 (*Casp9*) considerably limited neuronal cell death genotype caused by the absence of BCL-X_L [1191, 1192]. Concomitant deletion of BCL2 like 11 (*Bcl2l11*, encoding BIM) rescues erythroid progenitor (but not the neuronal) cells from death in BCL-X_L-deficient mice [1193]. *Bcl2*$^{-/-}$ mice are born but exhibit severe defects in their kidneys, alterations of the CNS, lymphoid cell depletion as well as premature graying of their hair and they succumb to polycystic kidney disease at a young age [1194–1200]. These defects can all be rescued by concomitant deletion of the gene encoding BIM, and, remarkably, in the case of some defects, the loss of even a single allele of *Bim* is sufficient [1194]. Mice with deletion of B cell leukemia/lymphoma 2 related protein A1a (*Bcl2a1a*, one of three isoforms of BCL2A1 in mice) or loss of all isoforms of BCL2A1 (best known as A1) show no developmental defects but display minor defects in the hematopoietic compartment [1201–1204]. The absence of BCL2 like 2 (BCL2L2; best known as BCL-W) results in male infertility due to defective spermatogenesis [1205–1207].

As opposed to homozygous deletion, haploinsufficiency for genes encoding MCL1 or BCL-X_L did not result in defects in normal development [1188, 1190]. However, *Mcl1*$^{+/-}$ mice display significant, albeit minor decreases in certain hematopoietic cell types [1208, 1209], and poor hematopoietic recovery from stress, such as gamma-radiation or treatment with 5-FU, which can be rescued by deletion of BCL2 binding component 3 (*Bbc3;* encoding PUMA) [1209]. Moreover, the loss of one *Bcl2l1* (encoding BCL-X_L) allele limits male fertility due to defects in germ cell development [1210] and shortens platelet lifespan [1211]. Of note, while combined haploinsufficiency for *Mcl1* and *Bcl2*, for *Mcl1* and *Bcl2a1a* or for *Bcl2l1* (encoding BIM) and *Bcl2* does not markedly affect embryonic development in mice [1212–1214], *Mcl1*$^{+/-}$*Bcl2l1*$^{+/-}$ double heterozygote mice display severe developmental defects and die during embryogenesis or early postnatally [1213]. Remarkably, this defect can be rescued by concomitant deletion of a single allele of the gene encoding BIM. These observations suggest that embryonic development is safeguarded by a delicate balance between pro- and anti-apoptotic BCL2 proteins.

Conditional knockout studies confirmed the importance of the different pro-survival BCL2 family members in specific tissues at precise developmental stages. These studies showed that MCL1 is critical for the development and/or maintenance of most (but not all) hematopoietic cell populations including stem and progenitor cells [1215], immature as well as mature B and T lymphocytes [1216–1220], natural killer (NK) cells [1221], neutrophils [1222, 1223], mast cells and basophils [1224], as well as Ig-secreting plasma cells [1225, 1226]. Accumulating evidence suggests that the survival of some hematopoietic cell subsets is safeguarded by the combined activity of two or even more anti-apoptotic BCL2 family members [1227]. Conditional deletion of *Bcl2l1* alone (leading to lack of BCL-X_L) or in combination with loss of *Mcl1* demonstrated functional redundancy between BCL-X_L and MCL1 in developing lymphocytes [1228, 1229] and megakaryocytes [1211, 1230–1232]. Conversely, BCL2 and A1 appear to have overlapping actions in the survival of B cells and neutrophils [1212, 1233, 1234] but not megakaryocytes and platelets [1235]. Data from chimeric mice confirm the role of these proteins in hematopoiesis [1144, 1190, 1236, 1237]. BCL2 is reported to contribute to the development and homeostasis of the mouse epidermis [1238]. Along similar lines, MCL1 and BCL- X_L play roles in the development and homeostasis of several tissues including the myocardium [1239, 1240], the CNS [148, 1241–1248], the hepatic parenchyma [298, 845, 1249–1251], vascular endothelium [1252], thymic epithelium [1253], as well as the intestinal [1254], mammary [1255, 1256], lung [1257] and renal [277] epithelium.

There are substantial differences in the severity of the defects caused by the conditional deletion of different pro-survival BCL2 family genes and between distinct tissues. For instance, conditional deletion of *Mcl1* in mouse hematopoietic stem/progenitor cells [1214], erythroid cells [1258] or T_{REG} cells [1259] is lethal. In the latter case, lethality is ascribed to multiorgan autoimmunity caused by the depletion of the pool of T_{REG} cells [1259]. Similarly, the megakaryocyte-specific combined deletion of the genes encoding MCL1 and BCL-X_L provokes embryonic or perinatal lethality [1230], which can be rescued by the absence of BCL2-antagonist/killer 1 (BAK1) [1126]. Similar findings have been obtained upon the ablation of *Mcl1* from the CNS or the myocardium, or the specific removal of the gene encoding BCL-X_L from the respiratory epithelium, although these experiments did not include rescue approaches [1240–1242, 1257]. The functional overlap between MCL1 and BCL-X_L appears to be particularly relevant in the CNS and liver [1247, 1249]. Of note, the requirement of MCL1 and BCL-X_L for neurogenesis appears to fluctuate between different stages of differentiation. The neurodevelopmental defects imposed by the deletion of *Mcl1* or *Bcl2l1* can be rescued in the absence of BAX [1192, 1247]. The detrimental effects of the hepatocyte-specific ablation of *Bcl2l1* or *Mcl1* can be rescued by deletion of *Bax* and *Bak1* as well as by that of *Bcl2l11* and/or BH3 interacting domain death agonist (*Bid*) [1260, 1261]. These observations demonstrate that organogenesis and adult tissue homeostasis depend on the balance between both anti-apoptotic and pro-apoptotic members of the BCL2 family. Further substantiating this notion, the hepatocyte-specific deletion of *Mcl1* promotes spontaneous hepatic carcinogenesis [1262], as does the deletion of *Mcl1* in intestinal epithelial cells [1254]. These latter findings may appear counterintuitive, as pre-malignant cells are expected to be more susceptible to succumb to environmental stress in the absence of MCL1 or BCL-X_L. However, both hepatic and intestinal carcinogenesis involve a robust inflammatory component that is exacerbated by tissue damage and cell death [1263]. Moreover, MCL1-deficient tissues show an increased cell turnover, which results in elevated level of replicative stress and genetic instability, potentially promoting carcinogenesis [845, 1254]. Also, when many cells die, progenitors get mobilized and must divide extensively. This increases the risk of such cells acquiring mutations that may drive neoplastic transformation, as firstly shown in a murine model of radiation induced thymic T cell lymphoma development [359, 360].

of CASP3 reduces early synaptic failure in mouse models of AD, ultimately improving cognitive defects [107]. Moreover, expression of a mutated form of amyloid β (an APP cleavage product) or administration of broad-spectrum caspase inhibitors attenuates synaptic defects in models of AD, an effect only partially recapitulated by CASP3-specific inhibitors [108]. Along similar lines, deletion of *Casp2* was reported to provide protection from synaptic loss and cognitive decline in a mouse model of AD [109]. Such protection may be linked to the generation of a specific tau cleavage product (Δtau314) by CASP2, which is reported to impair cognitive and synaptic function by promoting the missorting of tau to dendritic spines [110, 111]. Accordingly, CASP2 inhibitors blocked tau truncation and restored excitatory neurotransmission in mouse models of tauopathies, including AD [112, 113]. A role for CASP4 in AD pathogenesis has also been reported [114, 115]. Moreover, studies using the senescence-accelerated OXY5 rat model of AD demonstrated that the treatment with mitochondria-targeted antioxidant SkQ1 improved mitochondrial fitness and slowed down the signs of Alzheimer's disease-like pathology in older rats [116]. Lack of BIM (due to deletion of *Bcl2l11*) also confers protection to dopaminergic neurons in experimental PD imposed by inhibition of mitochondrial complex I, an effect that depends on BAX activation [117]. In addition, genetic deletion or down-regulation of *Casp3*, as well CASP3 inhibition by transgenic, neuron-restricted expression of XIAP, protects mice against pharmacologically induced PD, attenuating both dopaminergic neuron alterations and behavioral deficits [118–121]. Whether protection arises from the lack of cell-intrinsic or cell-extrinsic processes dependent on apoptotic caspases has not been investigated. Finally, pharmacological inhibition of CASP3 confers neuroprotection in a rat model of Huntington's disease (HD) [122–124]. That said, the precise mechanisms whereby components of the molecular apparatus for intrinsic apoptosis influence neurodegeneration need to be further explored. Two studies in clear contradiction to each other reported that, at sublethal doses, pharmacological inhibition of myeloid cell leukemia sequence 1 (MCL1) improved disease outcome in a mouse model of AD with a mechanism independent of apoptosis induction and involving the stimulation of mitophagy [125], but that *Mcl1* haploinsufficiency accelerated the degeneration and dysfunctionality of motor neurons in mice [126]. Also, there is evidence that necroptosis or ferroptosis rather than apoptosis can be the major contributor in neuronal cell destruction during AD [127, 128]. Finally, although *Bax* deletion prevents the demise of cerebellar granule neurons in a transgenic model of inherited prion disease [129], the direct contribution of BAX to neurotoxicity during prion disorders remains a matter of controversy [130].

BCL2 family proteins have also been reported to contribute to axonal degeneration and neuronal cell death in animal models of brain trauma, degeneration, or neurotoxicity [131–133]. Thus, BAX- or BID-deficient mice, as well as transgenic mice overexpressing BCL2, display increased survival of cortical or hippocampal neurons after experimental traumatic brain injury, as compared to wild-type mice [134–137]. Moreover, transgenic BCL2 overexpression protects mouse neurons against the detrimental

Box 4. Impact of the apoptosome and apoptotic caspases on health

The whole-body deletion of apoptotic peptidase activating factor 1 (*Apaf1*) or caspase 9 (*Casp9*) is associated with fetal lethality around E14.5–E16.5 [1264–1266]. Severe abnormalities in APAF1-deficient fetuses include webbed feet, craniofacial malformations, incomplete neural tube closure and/or excessive brain growth and exencephaly resulting in alteration of the central nervous system (CNS) including in the visual, olfactory, and auditory systems [47, 1264, 1266–1269]. Similar defects in the developing brain result from *Casp9* deletion [1189, 1266, 1270], a phenotype that was not exacerbated by *Casp2* co-deletion [1271]. The absence of CASP9 did not rescue neuronal defects due p53 hyperactivation in neural crest cells [323].

Of note, evidence linking mutations in *APAF1*, *CASP9* and *CASP3* to neural tube defects in humans has been reported [1272, 1273]. Mice lacking cytochrome c, somatic (CYCS) die in midgestation [1274], while the deletion of cytochrome c, testis (*Cyct*), which is specifically expressed in male gonads is associated with normal development but male infertility [1275]. The neuron-specific ablation of *Cycs* results in postnatal cell death [1276]. Confirming that the detrimental effects of *Cycs* deletion result from impaired apoptosis, mice expressing a mutant CYCS that retains the ability to shuttle electrons as a component of the mitochondrial respiratory chain but is unable to assemble the apoptosome exhibit perinatal lethality and developmental brain defects similar to APAF1- and CASP9-deficient mice [1277].

Importantly, the genetic background of mouse strains appears to significantly influence the impact of the absence of core components of the apoptotic machinery on embryonic development. Thus, while genetic deletion of *Casp3* in 129S1/SvImJ mice results in embryonic or early postnatal lethality due to the severe defects in brain development that are only partially rescued by concomitant deletion of the gene encoding BCL-X_L, on a C57BL/6 background *Casp3*$^{-/-}$ mice develop normally and survive into adulthood [1278–1281]. A similar impact of genetic background on phenotype has also been observed for *Apaf1*$^{-/-}$ and *Casp9*$^{-/-}$ mice [1282, 1283]. Although *Casp3*$^{-/-}$ mice reach adulthood on a C57BL/6 background, they exhibit defects in complex brain functions including attention and (in males) social behavior [1284, 1285], as well as ear and vestibular dysfunction including hearing loss [1286–1290], Abnormalities were also seen in the kidney and spleen of aged *Casp3*$^{-/-}$ mice [1291]. Survival of *Casp3*$^{-/-}$ mice to adulthood in C57BL/6 mice was ascribed to the compensatory activation of CASP7 [1292]. The combined ablation of *Casp3* and *Casp7* causes embryonic lethality on the C57BL/6 background, although death is caused by severe cardiac rather than brain defects [1293]. Such phenotypic differences may originate from some degree of substrate selectivity exhibited by CASP3 *vs*. CASP7 [444, 1294–1297]. Moreover, a recent study performed in *Casp7*$^{-/-}$ mice indicates that CASP7 acts as a facilitator of the variants of RCD occurring in the context of pore-driven lysis rather than an apoptotic executioner [1298].

Approximately 5% of APAF1-deficient mice develop normally and survive into adulthood, although males are often sterile due to defective spermatogenesis [1265] a phenotype that is reminiscent of mice deficient for BAX, BAK1 and BOK (*i.e.*, *Bak1*$^{-/-}$*Bax*$^{-/-}$*Bok*$^{-/-}$ mice) [26]. Of note, rare adult *Apaf1*$^{-/-}$ male mice that retain fertility display expansion of the lateral brain ventricles coupled with behavioral abnormalities and growth retardation [1283]. Conversely, the rare mice expressing a CYCS variant specifically deficient in apoptotic functions that survive into adulthood exhibit impaired lymphocyte homeostasis [1277]. Whole-body deletion of diablo, IAP-binding mitochondrial protein (*Diablo*, coding for a pro-apoptotic factor also known as SMAC) alone or along with HtrA serine peptidase 2 (*Htra2*) does not result in developmental defects in mice [1299, 1300], while the *Diablo*$^{-/-}$*Casp3*$^{-/-}$ genotype accrues the perinatal lethality observed in *Casp3*$^{-/-}$ mice [1301]. Mice lacking the X-linked inhibitor of apoptosis (XIAP, the main target of the pro-apoptotic activity of SMAC and HTRA2) are also viable and develop normally, possibly due to functional compensation by other members of the inhibitor of apoptosis protein (IAP) family [1302, 1303], but they exhibit mild defects in late pregnancy that do not compromise lactation [1302]. Consistent with this SMAC-mimetic drugs that were designed to induce apoptosis by antagonizing IAPs are quite well tolerated [1304]. *Xiap*$^{-/-}$ mice also show dysregulated innate immune responses [1305], most likely linked to the modulatory role of XIAP in inflammation and necroptosis [459, 462, 1306], or to the inability of these animals to resolve infections [1307]. Accordingly, loss-of-function mutations in *XIAP* are associated with X-linked lymphoproliferative syndrome type 2 in humans [458–461].

The myocardium-specific deletion of *Casp3* and *Casp7* impairs heart development in mice resulting in myocyte hypertrophy [1308]. The role of APAF1, CASP9 and CASP3 in hematopoiesis remains debated. Specific ablation of *Apaf1* or *Casp9* from the hematopoietic system using lethally irradiated wild-type mice reconstituted with hematopoietic stem/progenitor cells deficient for these factors does not result in alterations in the lymphoid or myeloid cell compartments [15]. Likewise, no hematopoietic defects emerge from the whole-body deletion of *Casp3* [1293]. Moreover, mice lacking *Casp9* in the hematopoietic system display a proper generation and functionality of megakaryocytes and platelets [1309]. Moreover, the clearance of *Casp9*$^{-/-}$ thymocytes seems to occur in a caspase-independent fashion [1310]. In the same line, although apoptosis is widely believed to be crucial for epithelial cell death and shedding in the intestine, during steady state, executioner CASP3 and CASP7 are dispensable for intestinal epithelial cell turnover at the top of intestinal villi, intestinal tissue dynamics, microbiome, and immune cell composition, suggesting high redundancy in non-challenged conditions [464]. Apparently at odds with these observations, *Casp3*$^{-/-}$ mice were reported to have abnormally increased numbers of splenic B cells manifesting increased proliferative capacity [1311], as well as a dysregulated activity in bone marrow stromal stem cells that attenuated osteogenic differentiation [1312]. A similar debate revolves around the requirement for APAF1 and caspase activity in thymocyte selection and/or T cell responses [15, 1313–1317]. Mouse bone marrow chimeras deficient for APAF1 or CASP9 in their hematopoietic cells displayed a defect in hematopoietic stem/progenitor cells that is caused by the aberrant type 1 interferon production caused by the fact that hematopoietic cells undergoing normal programmed cell death do not die in a "neat" non-inflammatory manner [243, 1318]. Taken together, these findings suggest that BAX/BAK1-dependent death of hematopoietic cells does not require caspases, but that caspases are needed to prevent inflammation caused by cell demolition [1319–1322]. However, neither the degree of functional redundancy exhibited by CASP3, CASP6 and CASP7, nor the potential for APAF1-independent CASP3 activation has been formally excluded in these studies, most of which involved single genetic alterations.

effects of transection of the sciatic nerve [138]. Likewise, BAX deficiency enhances the survival of oligodendrocytes in mice subjected to spinal cord injury [139]. Both neuroprotection and functional improvements were observed in rat or mouse models of traumatic spinal cord injury upon local administration of Z-VAD-FMK) and other caspase inhibitors [140–142]. However, these findings need to be validated given the low selectivity of these inhibitors among caspases. Of note, in rats, post-traumatic neuroprotection can further be improved by combined inactivation of PARP1 and CASP3 [143], suggesting a potential involvement for PARP1-dependent parthanatos in the process.

Deletion of *Bax* (but not the genes encoding BIM, PUMA or BID), as well as *Bax* haploinsufficiency, prevents the death or degeneration of retinal ganglion cells in mice subjected to optic nerve injury [144–147]. Moreover, the demise of injured retinal ganglion cells is exacerbated in mice with a conditional loss of *Bcl2l1* (leading to lack of BCL-X_L) [148] and decreased in transgenic mice over-expressing XIAP [149] or BCL-X_L [150] in the eye, as well as in rodents treated with an XIAP-derived cell-permeant peptide targeting CASP9 [151], or a CASP3-targeting small-interfering RNA (siRNA) [152, 153]. Moreover, transgenic or adenovirus-driven XIAP expression protects the retina in various animal models of retinal disease, degeneration, or ischemia [154–159], while a BCL-X_L inhibitor alleviates pathogenic neo-vascularization during diabetic retinopathy [160]. Genetic deletion of *Casp9* from endothelial cells protected retinal ganglion cells from ischemic death, supporting non-cell autonomous functions of CASP9 [151]. Of note, CASP7 seems to play a crucial role in retinal ganglion cell death, as demonstrated in a model of optic injury in *Casp7*$^{-/-}$ mice [161]. However, both pro-survival (BCL2) and pro-apoptotic (BAK1, BAX and BIM) BCL2 family members contribute to retinal neo-vascularization in response to experimental ischemic retinopathy [162–164]. In one of these models, such an effect was linked to an increased survival of endothelial cells in the absence of BAX and BAK1 [164]. Persistent endothelial cells promote indeed rapid tissue re-vascularization, thus preventing the occurrence of a pathogenic excessive neovascularization. Moreover, the inhibition of the intrinsic apoptotic pathway by c-Jun N-terminal kinase 1 (*Jnk1*) deletion or the administration of a broad-spectrum caspase inhibitor led to reduced choroidal neo-vascularization in the murine model of wet age-related macular degeneration (AMD) [165]. These observations may indicate that factors released by dying cells regulate neo-vascularization in the retina or other eye tissues.

Deletion of *Bax*, *Hrk* or *Casp3* as well as transgenic over-expression of XIAP prevents neuronal loss and/or axon degeneration in mouse models of trophic factor deprivation including nerve growth factor (NGF) withdrawal [166–168]. Conversely, lack of BIM or PUMA does not limit hippocampal neuronal injury upon experimental excitotoxicity [169, 170]. Moreover, while in vivo delivery of an XIAP fusion protein protects neurons against death induced by glutamate or kainic acid [171], kainic acid-mediated

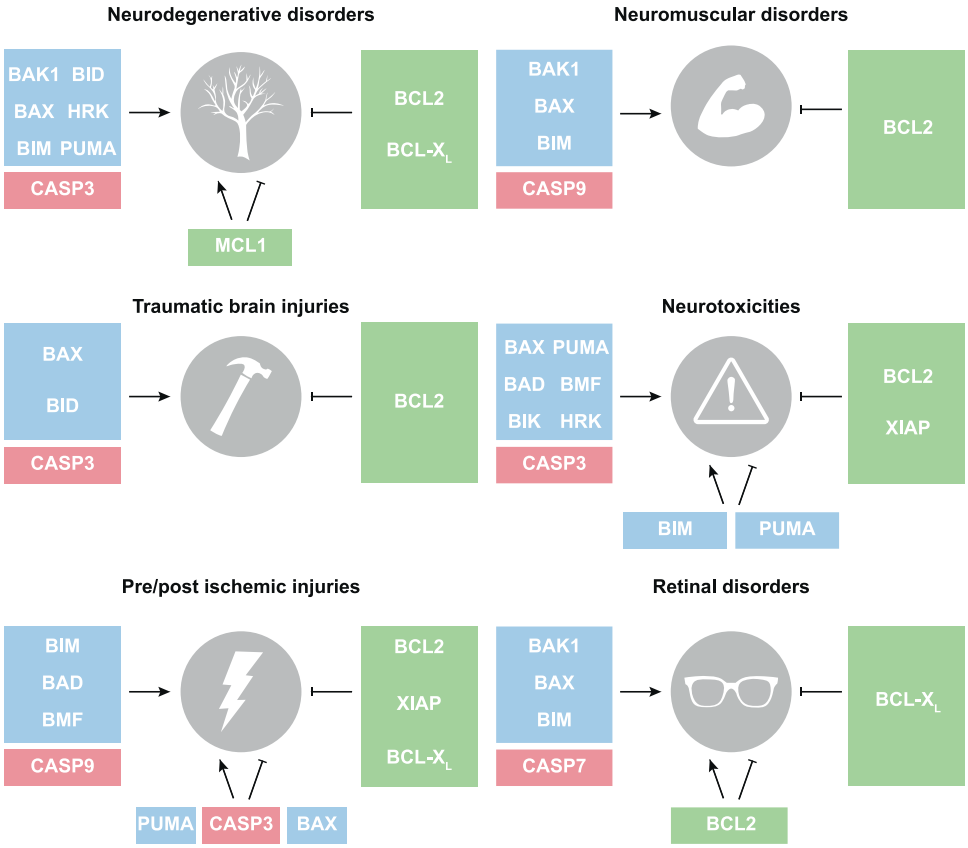

Fig. 3 Impact of intrinsic apoptosis players on neurological disorders. Intrinsic apoptosis is directly or indirectly involved in the pathogenesis of multiple neurological disorders, including neurodegenerative diseases, brain damage caused by traumatic injury or neurotoxicity as well as neuromuscular and retinal disorders.

neurodegeneration cannot be rescued by the CASP3 inhibitor DEVD-CHO [172]. Conversely, BIM appears to be activated during excitotoxicity [173], and *Bcl2l11*$^{-/-}$ mice (which lack BIM) display attenuated neuro-degeneration after experimental seizures induced by administration of kainic acid into the amygdala, at least in part because of decreased neuronal cell death in the hippocampus (but not in the neocortex) [174]. Moreover, data from knockout mice suggest that experimental seizure-induced neuronal death involves BCL2-associated agonist of cell death (BAD), BCL2 interacting killer (BIK), BCL2 modifying factor (BMF), or PUMA [175–178] and that BCL2-like 2 (BCL2L2; best known as BCL-W) may provide neuroprotective, seizure-suppressive functions [179]. Confirming a certain degree of functional redundancy, phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1, best known as NOXA) and BID seem dispensable for RCD driven by excitotoxicity, as shown in kainic acid-treated animals [180, 181].

Intrinsic apoptosis is also involved in neuronal apoptosis post-ischemic injury in both developing and adult brains. In a mouse model of neonatal hypoxia-ischemia, neuroprotection was documented upon deletion of *Bax* [182], simultaneous absence of BIM and BAD [183], or transgenic overexpression of XIAP [184]. Conversely, *Xiap*$^{-/-}$ mice are sensitized to neonatal hypoxia-ischemia injury [185]. Apparently at odds with these findings, *Casp3*$^{-/-}$ mice display increased vulnerability to such experimental perturbation, possibly due to complementary over-activation of CASP3-independent pathways [186]. Of note, the absence of CASP3, BAX, or PUMA (but not the absence of NOXA, BIM or HRK) also confers neuro-protection to newborn mice acutely exposed to ethanol [187–189], while loss of BAX is neuroprotective in newborn mice exposed to isoflurane [190] as well as ionizing radiation [133, 191]. At the same time, it is interesting to note that BAX-dependent neuronal RCD also contributes to reactive microgliosis during the recovery of the developing brain from acute alcohol exposure [192], pointing to an etiological role for activation of microglial cells by dead neurons.

Bax$^{-/-}$ mice displayed pronounced neuroprotection when subjected to distinct experimental brain injuries, including middle cerebral artery occlusion [193]. A similar protection against experimental ischemic insults has been observed in mice deficient for BMF [194], or BID [195–197]. Conversely, NOXA seems to be dispensable for neuronal damage induced by experimental ischemic stroke [194]. Moreover, the absence of BID fails to protect mice from ischemia-reperfusion, although it limits the associated inflammatory response [198]. Transgenic over-expression of BCL2, BCL-X$_L$ or XIAP as well as inhibition of apoptotic caspases or genetic deletion of *CASP6* ameliorates neuronal survival upon global ischemia, focal ischemia or stroke [199–215]. It should be noted, however, that in these settings neuroprotection by inhibition or deletion of caspases may be related to the lack of cell-extrinsic or apoptotic-unrelated roles of caspases. Morevoer, various examples of caspase-independent neuronal death after cerebral ischemia have been reported [216–219]. In this context, it is important to note that apoptosis is dynamically regulated during lifespan in the brain [24]. Indeed, while immature brain cells express high levels of many BCL2 proteins [133, 220, 221], most of these proteins are downregulated in the adult brain, when most post-mitotic neural cells become resistant to apoptosis [131, 222]. This may help explain the divergent findings on the mechanisms of neural cell death reported above.

Cardiovascular conditions

While a role for RCD in non-reperfused myocardial infarction remains questionable, apoptosis and other cell death programs including necroptosis, MPT-driven necrosis, ferroptosis, pyroptosis and autosis appear to contribute to cardiomyocyte death and tissue damage during myocardial infarction with reperfusion (also referred to as myocardial ischemia-reperfusion injury). However, the relative importance of the specific RCD mode and how it interconnects mechanistically and functionally with other RCD pathways to produce an integrated response remains poorly understood. For example, *Bak1*$^{-/-}$mice with a cardiomyocyte-specific deletion of *Bax* displayed considerably reduced infarct size as compared to their wild-type littermates when subjected to experimental myocardial ischemia-reperfusion, although it remains unclear whether these effects are attributable to reductions in apoptosis or MPT-driven necrosis [223–225], a RCD variant shown to participate in the pathogenesis of ischemic stroke [226]. Protection against myocardial ischemia-reperfusion has also been reported in transgenic mice overexpressing BCL2 [227–229] or a BCL-X_L-derived peptide [230]. Likewise, deletion of *Bbc3* (leading to lack of PUMA) ameliorates myocardial ischemia-reperfusion injury [231], ultimately translating into increased survival [232]. Moreover, neurotrophin-3 was reported to confer cardioprotection fromischemic and reperfusion injuries by reducing BIM levels [233]. Broad spectrum caspase inhibition [234–236] and XIAP mimicking peptides [237] were shown to modestly reduce myocardial infarct size. Finally, simultaneous deletion of *Casp3* and *Casp7* had no cardioprotective effect during reperfused myocardial infarction [238], in line with the notion that the absence of caspases only delays cell death.

In contrast to the large burst of cell death over several hours characterizing myocardial infarction, cardiomyocytes are lost gradually over months to years during heart failure with reduced ejection fraction [3]. The role of intrinsic apoptosis in these heart conditions is, however, debated. In a mouse model of cardiomyopathy based on the deletion of desmin (*Des*), the cardiomyocyte-specific overexpression of BCL2 reduces cardiac lesions and hypertrophy coupled to ameliorated cardiac functionality [239]. However, despite improved survival, these mice show increased levels of necrosis due to the activation of alternative cell death pathways [240]. Moreover, *Casp3*$^{-/-}$ mice display enhanced vulnerability to experimental cardiomyopathy, at least in part reflecting the inefficient activation of pro-survival AKT serine/threonine kinase 1 (AKT1) signaling [241]. As an alternative explanation, the absence of CASP3 may foster RCD-driven inflammation associated with increased type I interferon (IFN) release [242–244]. Indeed, experimental data linking dysregulated type I IFN release and cardiac conditions have recently emerged [245].

As for therapeutic interventions, cardioprotective effects have been achieved by inhibition of CASP3 in rodent models of myocardial dysfunction induced by endotoxin [246], burn injury [247] or hypoxia [248], although perhaps such effects can be attributed to the lack of cell-extrinsic or apoptosis-unrelated effects of caspase activity. Moreover, inhibition of BAX prevents cardiotoxicity induced by doxorubicin in zebrafish and mice without affecting the anti-neoplastic activity of doxorubicin [249]. Similarly, the endothelial cell-specific expression of B cell leukemia/lymphoma 2 related protein A1a (BCL2A1A) promotes survival in a model of allogeneic heart transplantation [250].

Finally, the mechanistic links between intrinsic apoptosis and atherosclerosis remain a matter of debate. Indeed, while *Casp3* deletion favors plaque development in mouse models of atherosclerosis [251], the absence of DNA fragmentation factor subunit beta (DFFB, best known as CAD)) [252] protects mice against the disease. Likewise, while conditional deletion of *Mcl1* in myeloid cells is pro-atherogenic [253], genetic or pharmacological inhibition of BCL-X_L reduces atherosclerosis via a mechanism involving the depletion of platelets [254]. Moreover, the macrophage or leukocyte-specific deletion of the gene encoding BIM in mice has modest effects on plaque development, especially in the early phase of atherosclerosis [255, 256]. As the etiology of atherosclerosis involves a major inflammatory component, these apparently discrepant results may reflect (at least in part) the key role of some components of the apoptotic machinery in the control of inflammatory responses.

Renal disorders

Germline or kidney-specific deletion of *Bax* attenuates acute kidney damage in mice subjected to experimental renal ischemia/reperfusion [257]. A similar nephron-protection has been observed in *Bid*$^{-/-}$ mice [258], as well as in transgenic mice specifically expressing BCL-X_L in the kidney [259]. Moreover, the simultaneous deletion of *Bax* and *Bak1* in kidney proximal tubules limits tubular apoptosis and ameliorates kidney inflammation and fibrosis in a mouse model of renal fibrosis based on unilateral ureteral obstruction [260, 261]. Apoptotic caspases also appear to contribute to the etiology of renal conditions, although this may reflect cell-extrinsic effects of caspase activity. *Casp3* deletion reduces microvascular rarefaction and renal fibrosis in mice subjected to experimental ischemia-reperfusion injury [262], resulting in better long-term outcomes [263]. Moreover, the lack of CASP3 increases the survival of mice with chronic kidney disease caused by a congenital mutation in cystin 1 (*Cys1*) [264]. In this setting, CASP3-deficient mice display increased CASP7 and decreased BCL2 expression, which is in line with recent clinical evidence of constitutive BCL2 down-regulation in patients with polycystic kidney disease [265]. Administration of broad-spectrum caspase inhibitors limits kidney damage and improves renal functionality after a variety of experimental insults to kidneys, as observed in animal models of renal ischemia [266, 267], polycystic kidney disease [268], glomerulonephritis [269], lupus nephritis [270] and diabetic renal disease [271]. Nonetheless, the specific targeting of apoptotic caspases will reveal whether this effect reflects the inhibition of intrinsic apoptosis. Indeed, these studies do not rule out the involvement of non-apoptotic RCD pathways in the etiology of acute and chronic kidney injury [272, 273]. Moreover, some of the nephron-protective effects of broad-spectrum caspase inhibitors have been linked to decreased post-RCD inflammation rather than the sole inhibition of apoptosis [266, 274]. In this context, Z-VAD-FMK aggravates (rather than ameliorates) renal dysfunction in a mouse model of cisplatin nephrotoxicity, by a mechanism involving the abrogation of cyto-protective autophagy [275]. Similarly, Z-VAD-FMK is ineffective in mouse models of osmotic nephrosis and contrast-induced acute kidney injury [276], and this may be linked to the ability of Z-VAD-FMK to inhibit CASP8 (and hence promote necroptosis). Finally, acute loss of BCL-X_L in all tissues of adult mice, except for hematopoietic cells, caused severe renal tubular degeneration leading to fatal anemia due to the loss of erythropoietin production [277].

Hepatic diseases

Abundant evidence highlights pathogenic roles of apoptosis in acute liver injuries, as well as in alcohol-related and alcohol-unrelated chronic liver disorders. Hepatocytes express high levels of BID, which connects DR signaling to mitochondrial outer membrane permeabilization (MOMP) upon CASP8-dependent cleavage [278], and this complicates distinguishing between the intrinsic and extrinsic pathways. Here, we will focus on studies performed in animal models of liver injury unrelated to overt signaling engaged by the Fas cell surface death receptor (FAS; also known as CD95 or APO-1) or TNF receptor superfamily member 1A (TNFRSF1A, best known as TNF-R1), which instead will be discussed in the next section.

Distinct preclinical models of hepatic ischemia-reperfusion injury demonstrated that deletion of *Bcl2l11* (leading to lack of

BIM) and/or *Bid* as well as over-expression of BCL2 or administration of pharmacological broad-spectrum caspase inhibition mediate robust hepatoprotective effects [279–282]. A similar improvement of hepatocyte survival and liver functionality was observed in rodents specifically expressing a mutated variant of BID in the liver and subjected to warm ischemia/reperfusion injury [283]. As for other models of liver injury, BIM-deficient mice are protected against viral hepatitis [284]. Moreover, deletion of the genes encoding BIM or PUMA, but not BCL2-related ovarian killer (*Bok*) limits liver injury in mice exposed to the hepatotoxic agent acetaminophen [285–287]. Moreover, pre-treatment with Z-VAD-FMK improves the survival of mice subjected to extensive hepatectomy [288].

There is contrasting evidence on the role of BID in the etiology of liver conditions unrelated to overt FAS and TNF-R1 signaling. In a model of alcohol-related liver disease, the lack of BID confers some protection against ethanol-induced fibrosis, although mice display persisting signs of inflammation and steatosis [289]. Moreover, mice with a hepatocyte-specific deletion of *Bid* present reduced liver inflammation and fibrosis when subjected to a choline-deficient diet to cause non-alcoholic steatohepatitis (NASH) [290]. Also, administration of BID-targeting antisense oligonucleotides exerted significant hepatoprotective effects [291]. However, BID deficiency fails to ameliorate liver injury and fibrosis upon bile duct ligation (as a model of obstructive cholestasis and chronic liver disease) [292]. Of note, in the same experimental model, the liver-specific overexpression of MCL1 but not BCL2 protects animals from hepatic damage [293, 294], suggesting some specificity for MCL1. To add a layer of complexity, conditional deletion of *Xiap* in hepatocytes does not result in liver injury, steatosis, or fibrosis, possibly due to compensatory effects of other inhibitor of apoptosis protein (IAP) isoforms [295]. That said, *Xiap*$^{-/-}$ and *Casp3*$^{-/-}$ mice subjected to diet-induced hepatic steatosis and/or fibrosis, display exacerbated and attenuated liver damage, respectively [296, 297]. These effects have been linked to the modulation of the inflammatory response rather than apoptosis. Finally, genetic co-deletion of *Mcl1* and transformation-related protein 53 (*Trp53*, best known as p53) [298], as well as conditional deletion of the genes encoding BCL-X_L or MCL1, promote fibrosis and/or carcinogenesis, two common final stages of liver disease [299]. In this latter study, the additional deletion of *Bak1* limited hepatotoxicity, which is in line with evidence indicating that deletion of *Bid* and/or *Bok* protects mice against experimentally induced hepatocarcinogenesis [300–302].

CASP2 was found to be upregulated in a mouse model of NASH and in NASH patients, and was implicated in driving lipogenesis and steatohepatitis with a mechanism involving the cleavage of the site-1-protease (S1) followed by the activation of sterol regulatory element binding proteins (SREBP) [303]. In this study, the ablation or pharmacological inhibition of CASP2 prevented diet-induced steatosis and NASH progression. Of note, CASP2 deficiency was also reported to protect mice from diet-induced obesity and metabolic syndrome [304]. Supporting the etiological contribution of caspase activation to liver disease, the administration of broad-spectrum caspase inhibitors (e.g., emricasan, VX-166) reduced liver injury, inflammation and fibrosis in mice fed a diet rich in fat or deficient in methionine and choline [305, 306]. Along similar lines, emricasan reportedly decreased portal pressure, fibrogenesis and hepatic inflammation, and preserved liver function in rodent models of chronic carbon tetrachloride (CCl_4)-mediated cirrhosis or cholestasis driven by bile duct ligation [307–309]. Preliminary anti-inflammatory effects coupled with improved liver function have also been observed in patients with NASH-related cirrhosis treated with emricasan [39, 310]. However, follow-up, randomized clinical studies failed to observe beneficial effects of this agent on portal pressure and clinical outcome [40, 41, 311]. At least in part, these findings may reflect the complex interconnection between multiple RCD variants involved in the pathogenesis of NASH. Supporting this possibility, the administration of CASP3-specific inhibitors that abrogate both pro-apoptotic and pro-pyroptotic activities of CASP3 protected mice against acute liver injury caused by bile duct ligation [312]. Additional pharmacological and genetic studies specifically targeting intrinsic apoptosis (over other RCD pathways controlled by caspases) are needed to formally ascertain the involvement of this pathway in the etiology of hepatic disorders.

Hematological malignancies and solid cancers

The role of intrinsic apoptosis in preventing oncogenesis has been demonstrated in multiple animal models of induced hematological and solid tumors. In particular, a wide range of evidence demonstrates that over-expression of BCL2, BCL-X_L or MCL-1 accelerates the onset of leukemia and lymphoma induced by over-expression of the MYC proto-oncogene, bHLH transcription factor (MYC) [313–317]. Accordingly, the pharmacological inhibition of anti-apoptotic BCL2 proteins is effective against MYC-driven tumors, even when they lack p53 functions [318–321]. In this context, p53 has been shown to exert multiple roles in RCD (e.g., [322–324]). In particular, it acts as a direct or indirect regulator of the expression of several apoptotic genes [325–328] and connects apoptosis induction and cell cycle arrest [329]. One main target of p53 is cyclin dependent kinase inhibitor 1A (*CDKN1A*, best known as p21). p53-induced expression of p21 leads to the activation of DREAM and RB/E2F transcriptional repressor complexes, in turn promoting cell cycle arrest by downregulating crucial cell cycle regulators such as cyclins and cyclin-dependent kinases [326, 327, 330]. However, recent finding indicates that the p53-p21-DREAM or p53-p21-RB/E2F axis can also downregulate CASP2 and CASP8-associated protein 2/FLASH (CASP8AP2), generating a feedback loop centered on p53 that limits rather than promoting the induction of apoptosis [326, 327]. Of note, when analyzing the impact of endogenous proteins, it was shown that the absence of BCL-X_L but not BCL2 limits the development of lymphoma in transgenic mice expressing MYC under the IgH enhancer (Eμ-myc mice) [331, 332], thus supporting the therapeutic use of BCL-X_L inhibitors against these hematological cancers. Along similar lines, MCL1 overexpression [317] or *Mcl1* ablation [318, 333, 334] accelerates and suppresses MYC-driven lymphomagenesis, respectively. Lending further support to the relevance of MCL1, prevalence and onset of MYC-driven lymphoma development were reduced by *Mcl1* haploinsufficiency [318, 334], or B cell-specific deletion of *Mcl1* [335]. Of note, loss of one allele of *Mcl1* (but not deletion of the gene encoding BCL-X_L) also impairs the development of thymic lymphoma in p53-deficient mice [336], which possibly explains the limited effect of the BCL-X_L, BCL2 and BCL-W inhibitor ABT-737 in these models of tumorigenesis [337]. The contribution of pro-survival BCL2 proteins in the development of AML has been demonstrated by using mice reconstituted with genetically modified bone marrow cells overexpressing MYC [338] and in human Burkitt lymphomas and diffuse large B-cell lymphomas [339]. Notably, the acute genetic removal of *Mcl1* prevents the sustained survival and proliferation of AML driven by diverse oncogenic fusion proteins [340]. Accordingly, MCL-1 specific BH3 mimetic drugs, such as S63845, are able to potently kill a diverse range of lymphoid and myeloid malignant cells in culture and even in tumor transplanted mice [341]. Finally, ablation of *Bcl2l2* (leading to lack of BCL-W) limits the development of MYC-mediated B cell lymphoma [342].

Numerous studies demonstrated that the development of MYC-driven lymphoma and leukemia is accelerated in mice lacking the genes encoding BAX [343], BIM [344, 345], BAD [346], BMF [346] or PUMA [347–349]. In particular, these studies report that loss of only a single allele of *Bcl2l11* (encoding BIM) accelerates the development of lymphoma and this effect can be reversed following full ablation of *Bcl2l1* (leading to lack of BCL-X_L) [345]. In this context, the presence of all prosurvival BCL2 proteins is shown

to limit the impact of BIM in *Eμ-Myc* transgenic mice [350]. Instead, the combined ablation of the genes encoding BIM and p53 or PUMA and p53 accelerates MYC-driven lymphomagenesis [351]. This is in line with the evidence that loss of the genes encoding BAX or BIM augmented lymphomagenesis in p53-deficient mice [352, 353]. Of note, PUMA seems to exert a strong tumor-suppressive role in hematological cancers, as shown by the evidence that *Bbc3* deletion accelerates the development of MYC-driven B-cell lymphomas and that *Eμ-Myc* lymphomas developing in PUMA-proficient mice display downregulated expression of PUMA [348, 349, 354]. On the contrary, the loss of the gene encoding NOXA does not accelerate MYC-driven lymphomagenesis, and the role of BIK in this murine lymphoma model is debated [348, 355]. Along similar lines, while CASP2 suppresses MYC-induced lymphomagenesis in mice [356], the tumor suppressive role of apoptosome components (Box 1) is questioned, as shown in lethally irradiated mice reconstituted with *Eμ-Myc* transgenic APAF1-deficient or CASP9-deficient fetal liver cells which showed no difference in the incidence of lymphoma compared to their wild-type counterparts [357]. This is consistent with the notion that APAF1 and caspase-9 function downstream of the commitment to cell death (MOMP) and therefore do not act as tumor suppressors [15].

Concerning other experimental animal models of hematological malignancies, the absence of PUMA (due to ablation of *Bbc3*) abrogated the development of both myelodysplasia, as shown in transgenic mice expressing a nucleoporin 98 (NUP98)-homeobox D13 (HOXD13) fusion protein [358], and thymic T cell lymphoma induced by gamma radiation [359, 360]. The explanation for these surprising findings is based on the fact that the absence of PUMA prevents the extensive death of hematopoietic cells caused by gamma radiation, which causes mobilization and extensive proliferation of hematopoietic stem and progenitor cells, resulting in elevated replication stress and genetic instability and lymphomagenesis. These observations show that inhibition of apoptosis does not only promote the development of hematological malignancies, but in certain conditions can do the exact opposite and prevent lymphoma development. The absence of NOXA, augments the development of chronic lymphocytic leukemia in T cell lymphoma breakpoint 1 (TCL1) transgenic mice [361] and accelerates the development of thymic T lymphoma induced by gamma radiation [359]. Moreover, conditional deletion of *Bcl2l11* in B cells (leading to the absence of BIM) accelerates the development of mantle cell lymphoma in mice driven by cyclin D1 (CCND1) overexpression [362]. Overexpression of MCL1 and/or BCL2 promotes the development of acute myeloid leukemia driven by lysine (K)-specific methyltransferase 2A (KMT2A, best known as MLL) fusion proteins [340, 363] and plasmacytoma driven by ABL proto-oncogene 1, non-receptor tyrosine kinase (ABL1) [364]. Conversely, the loss of one *Mcl1* allele suppresses the development of T cell lymphoma, as shown in models based on sequential low-dose irradiation or the expression of a transgene encoding an IL2 inducible T cell kinase (ITK)-spleen tyrosine kinase (SYK) fusion protein [365]. Finally, the absence of CASP2 accelerates lymphomagenesis in ataxia telangiectasia mutated (ATM)-deficient mice [366], but this may be due to the loss of the function of CASP2 in mitotic cell division [367]. Lending support to the role of intrinsic apoptosis in hematologic malignancies, the BCL2 inhibitor venetoclax has entered clinical practice for the treatment of CLL as single agent or more effectively in combination with other therapeutic agents [31, 35–37]. Combinatorial regimens of BCL2 inhibition with epigenetic modulation have entered center stage in certain settings of AML [38, 368]. However, mechanisms of resistance of CLL and AML to venetoclax related to defects in p53 and the apoptotic network or deregulated energy metabolism have been described [369–372]. Venetoclax-based regimens also display effectiveness in patients with high-risk myelodysplastic syndromes [373], suggesting a potential application of venetoclax to other hematological cancers [374, 375].

Significant work demonstrated a tumor suppressor role of the intrinsic apoptotic pathway in many cancers. For example, BCL2 overexpression accelerates the development of MYC-induced mammary tumorigenesis [376]. A similar acceleration of tumor development has been described for the loss of genes encoding BAX, BIM, CASP2 or PUMA in distinct models of breast cancer induced by expression or overexpression of C3(1)/SV40 T-antigen, MYC, or erb-b2 receptor tyrosine kinase 2 (ERBB2, best known as HER2) [377–380]. At odds with these results, BCL2 overexpression in the mammary gland suppresses the development of breast tumors driven by the administration of dimethylbenz(a)anthracene [381]. This latter finding may be explained in a similar way as was mentioned for the suppression of radiation-induced thymic T cell lymphoma development by over-expression of BCL-2 or loss of PUMA (see above). Conditional deletion of the genes encoding BCL2 or BCL-X_L in intestinal epithelial cells delays the development of colorectal cancer driven by inflammation [382, 383], which is in line with the evidence that the absence of PUMA (due to *Bbc3* deletion) exacerbates colorectal tumorigenesis as shown in a mouse model of intestinal oncogenesis driven by colitis or APC, WNT signaling pathway regulator (APC) [384]. Interestingly, doxorubicin-induced intestinal cytotoxicity requires PUMA but not BIM, whereas the reverse is true for MYC-driven apoptosis in the gut, indicative of differential roles for different BH3-only proteins in this tissue [385]. Intriguingly, treatment with BCL-X_L, but not BCL2-targeting BH3 mimetics is sufficient to prevent intestinal tumorigenesis, suggesting that BCL-X_L is the crucial mediator of protection of early neoplastic cells in this model [386]. In agreement, earlier work showed a pronounced BCL-X_L dependency of cell lines derived from both colorectal and non-small cell lung cancers [387, 388]. Moreover, a tumor suppressive effect has been ascribed to BAX and CASP2 in murine models of brain [389, 390] and lung [391] oncogenesis, respectively. In line with this evidence, pharmacologic/genetic inhibition of MCL1 delayed tumor development in a mouse model of mutant KRAS-driven adenoma/adenocarcinoma [392]. In the same model, tumor progression was promoted by the ablation of pro-apoptotic *Bok* [393]. Of note, there is evidence of a certain tissue-specificity in the epigenetic regulation of *Bcl2* and *Mcl1*, such as the epigenetic mechanism centered on the deubiquitinase BRCA1 associated protein 1 (BAP1) [394], a tumor suppressor that is frequently mutated in some cancers [395] and has been associated with tumor aggressiveness and therapy resistance [396, 397]. Finally, age-related differences in the expression of pro-apoptotic members of the BCL2 family have been linked to the increased sensitivity of neonatal/childhood tissues, relative to adult counterparts, to chemotherapy and radiotherapy. This was causally linked to the MYC-dependent expression of genes encoding BAX, BID and BIM, both in mice and humans [133].

Cancer-specific roles have been attributed to particular BCL2 protein family members. For example, deletion of *Bax* accelerates the development of MYC-induced pancreatic tumors [398], which was not seen with ablation of *Bak1* or *Casp3* [398, 399], but was achieved by BCL-X_L overexpression [314, 400]. Likewise, BOK seems to be crucial in hepatocarcinogenesis, as demonstrated in a mouse model of diethylnitrosamine-induced liver cancer which was accelerated on a $Bok^{-/-}$ genetic background [300]. Using the same mouse model, accelerated hepatic carcinogenesis has also been demonstrated for the deletion of the genes encoding PUMA or CASP2 [401, 402]. Conversely, overexpression of BCL2 was shown to limit transforming growth factor alpha (TGFA)-driven hepatic tumorigenesis [403, 404], perhaps because the death of some cells in the liver causes massive mobilization and proliferation of progenitor cells, leading to acquisition of oncogenic lesions that drive tumorigenesis in a manner similar to radiation-induced thymic lymphoma development (see above). Finally, the

transgenic overexpression of BCL-X_L (but not BCL2) and the keratinocyte-specific deletion of *Bcl2l1* (leading to lack of BCL-X_L) accelerates or limits, respectively, carcinogen- and/or ultraviolet B (UVB)-induced skin tumorigenesis [405–408]. It will be important to investigate and better understand why in specific settings inhibition of apoptotic cell death promotes tumorigenesis whereas it inhibits tumorigenesis in others.

Autoimmune and inflammatory diseases

There is substantial evidence linking intrinsic apoptosis to the development and progression of autoimmune diseases. However, the interpretation of these findings should take into consideration the crosstalk between the apoptotic and inflammatory pathways and the fact that apoptotic caspases accelerate cell death as they regulate its immunological manifestations.

The first evidence that defects in the intrinsic apoptosis pathway can cause the development of autoimmune disease was reported when over-expression of BCL-2 in B lymphocytes [409] or loss of BIM in all tissues [410] was shown to cause a fatal systemic lupus erythematosus (SLE)-like disease. Consistent with a critical role for the intrinsic apoptotic pathway in preventing autoimmune disease, the combined loss of the genes encoding BAX and BAK1 in hematopoietic cells, achieved by transplantation of lethally irradiated wild-type mice with hematopoietic stem/progenitor cells from the livers of E14.5 $Bax^{-/-}Bak1^{-/-}$ embryos also causes a fatal SLE-like disease [411]. In mouse models of rheumatoid arthritis, ablation of the genes encoding BIM, BID or BAD, but not the loss of *Bax* and *Bak1*, accelerated the emergence and increased the duration and severity of this disorder [412–414]. Consistent with these findings, administration of a BIM mimetic suppressed inflammatory arthritis in mice [415]. Mice deficient for BAX as well as transgenic mice expressing XIAP display increased severity of autoimmune encephalomyelitis induced by immunization with myelin oligodendrocyte glycoprotein (MOG) [416, 417]. Similar results have been obtained in mouse models of autoimmune encephalomyelitis genetically engineered for the hematopoietic cell-specific deletion of *Bcl2l11* (leading to BIM deficiency), or the neuron-specific overexpression of BCL2 [418, 419]. Consistent with the notion that inhibition of apoptosis can promote the development of auto-immune disease, inhibition of BCL2, BCL-X_L and BCL-W using the BH3 mimetic ABT-263 substantially reduced pathology in several mouse models of autoimmune disease, including scleroderma [420]. In apparent contrast with these results, studies using models of type 1 (autoimmune) or type 2 (non-autoimmune) diabetes revealed that deletion of *Bax* alone or combined loss of *Bax* and *Bak1* [421, 422], deletion of the gene encoding BIM, alone or together with the gene encoding PUMA [418, 423–425] as well as the loss of BMF [426], protect pancreatic β cells from autoimmune destruction. Moreover, the absence of BIM prevents the emergence of type 1 diabetes in non-obese diabetic (NOD) mice [418, 423], while ablation of *Trp53* in pancreatic β cells failed to halt cell death in multiple experimental models of diabetes [427].

Based on the studies described above, inhibiting or deleting pro-apoptotic proteins or genes can have conflicting effects on autoimmune disease progression. This may depend on the cell type in which the major effect on apoptosis occurs, e.g., the immune cells or their targets. Inhibiting cell death in the target cells would indeed provide protection and may improve disease outcome, whereas inhibiting cell death in the immune cell may lead to an accumulation of immune cells and aggravation of the autoimmune disease. The distinction could be explored by studying tissue-specific deletion of apoptosis regulator genes.

In this context, there is evidence that inflammatory and autoimmune disorders may derive from increased survival of specific immune cell population. For instance, elevated levels of cytokines such as colony stimulating factor 2 (CSF2, best known as GM-CSF), interleukin 3 (IL3) and IL5 in immune disorders have been associated with prolonged survival of neutrophils, eosinophils or basophils with a mechanism involving the upregulation of anti-apoptotic proteins MCL1, BCL-X_L and baculoviral IAP repeat containing 2 (BIRC2, best known as cIAP2) [428–435]. Apoptosis also plays a relevant role in some hemopathies with inflammatory features, including beta thalassemia [436], Diamond-Blackfand anemia [437], and in the Cohen syndrome neutropenia [438]. BIM, BID and BAD have all been shown to influence survival in mouse models of septic shock, as their targeting confer protective effects from tissue damage of multiple organs [439–441], as well as in patients with severe sepsis [442]. On the contrary, the role of apoptotic caspases in septic shock is contentious [54, 73, 443, 444]. The precise impact of apoptosis in widespread inflammation during sepsis requires further investigation.

Concerning other inflammatory diseases, while broad-spectrum caspase inhibition reportedly protected rats against severe acute pancreatitis [445], activation of intrinsic apoptosis appears to attenuate the severity of this disease by limiting inflammation, as shown in vivo in a pancreatitis mouse model lacking XIAP [446]. These data reinforce the notion that inhibiting (apoptotic) cell death may exacerbate unwarranted inflammatory reactions that contribute to the pathology of various autoimmune and inflammatory disorders. In line with this notion, chronic colitis driven by dextran sulfate sodium in mice manifests with increased (rather than decreased) severity in BID- or BIM-deficient hosts as compared to their wild-type littermates, at least in part owing to immune dysregulation [447, 448]. Similarly, inhibition of BCL2 and/or BCL-X_L reduces inflammation and ameliorates experimental colitis [449, 450], an effect that was abrogated by concomitant deletion of the gene encoding BIM [450]. PUMA-deficient mice display reduced levels of apoptosis amongst intestinal epithelial cells but not reduced inflammation in an experimental model of colitis [451]. Corroborating the specific relevance of PUMA for intestinal homeostasis, mice deficient for PUMA but not $Bax^{-/-}Bak1^{-/-}$ mice were protected against the gastrointestinal side effects of radiotherapy, at least in part due to increased survival of intestinal stem/progenitor cells [452, 453]. Moreover, the absence of PUMA conferred protection to intestinal epithelial cells in mouse models of hypertensive gastropathy [454], ulcerative colitis (UC) [455] and intestinal ischemia/reperfusion [456]. In the latter model, transgenic BCL2 expression limited intestinal epithelial cell death [457]. On the other hand, defects in XIAP cause X-linked lymphoproliferative syndrome type 2, with one-third of these patients suffering from severe and therapy-refractory inflammatory bowel disease [458–461]. Absence of XIAP also results in enhanced TNF production and TNF-R1/TNF-R2 targeting of TLR5-expressing Paneth cells and dendritic cells (DCs), leading to ileitis and dysbiosis [462]. In this context, it is interesting to note that CASP3- or CASP7-deficient mice display an altered gut microbiome [463], which may play a hitherto unexplored role in multiple autoimmune and inflammatory disorders beyond intestinal conditions. However, it has recently been found that under steady state conditions the absence of CASP3 and CASP7 in the intestinal epithelial cells apparently neither affects the microbiome nor causes spontaneous inflammation, suggesting that apoptosis may be dispensable for intestinal epithelium turnover and homeostasis at baseline [464].

Infectious diseases

Activation of RCD constitutes a protective mechanism against many microbial infections by eliminating infected cells and potentiating pathogen-targeting immune responses. Accordingly, both viruses and bacteria have developed multiple strategies to overcome or disable host intrinsic apoptosis, thus improving survival of both host cells and the infectious organisms [465, 466]. Mice with loss of one BCL-X_L-coding allele displayed reduced pathology and had improved survival rates when challenged with Japanese encephalitis virus (JEV), as compared with wild-type mice. This was attributed to compromised viral propagation within

JEV-infected cells succumbing to intrinsic apoptosis [467]. There is also evidence of a contribution of BAX and BAK1 to the response to murine cytomegalovirus (MCMV) infection. In particular, the MCMV genome encodes inhibitors of BAK1 (m41.1 protein) and BAX (m38.5 protein) that promote viral replication by inhibiting the induction of intrinsic apoptosis in infected cells [468, 469]. Supporting the requirement of the inhibition of intrinsic apoptosis for optimal in vivo MCMV dissemination, the titers of m41.1-deficient viruses were higher in salivary glands and other organs in *Bak1*$^{-/-}$ mice as compared to wild-type animals [468]. Intrinsic apoptosis also protects against bacterial infections, as demonstrated by the lethal course of disease in *Bbc3*$^{-/-}$ mice (which lack PUMA) after *Streptococcus pneumoniae* infection [470]. Such an effect has been attributed to insufficient immune-mediated bacterial clearance because of an increased neutrophil lifespan in the absence of PUMA-mediated apoptosis.

However, in other contexts, excessive activation of the intrinsic apoptosis pathway has been reported to drive, rather than prevent, microbial disease pathogenesis and lethality. For example, loss of *Xiap* increased the susceptibility of mice to *Shigella* infection, manifesting with coalescing necrotic areas and a high bacterial burden in the liver, an effect that was associated with an inefficient immune-mediated resolution of the bacterial infection [471]. Of note, at least part of this effect may be due to the requirement for XIAP to activate NOD signaling, rather than its ability to inhibit caspases [459, 471, 472]. Moreover, mice lacking the genes encoding BIM and NOXA (i.e., *Bcl2l11*$^{-/-}$*Pmaip1*$^{-/-}$ mice) display pronounced resistance to challenge with high doses of *Listeria monocytogenes*, as shown by a decreased bacterial burden and reduced apoptosis induction in the spleen [473]. The overexpression of BCL2 in the hematopoietic compartment increase the survival of mice infected with Ebola virus [474], while deletion of *Bok* promote resistance of lung epithelial cells to apoptosis induced by SARS-CoV-2 virus membrane (M) protein [475]. Intriguingly, this latter study showed that the SARS-CoV-2 M protein activate BOK to trigger apoptosis in the absence of BAX and BAK1 [475]. In another example, conditional deletion of *Casp3* in the murine intestinal epithelium conferred protection from pathogenic *Salmonella enterica*, and this was attributed to a reduction in cell death-induced nutrients that are critical for sustaining bacterial growth [476]. Finally, *Casp3*$^{-/-}$ mice subjected to intracranial inoculation of reovirus type 3 (strain Dearing) displayed limited injuries in the central nervous system (CNS) and extended survival compared to wild-type mice [477]. As discussed above, the interpretation of the infection phenotypes observed in CASP3-, CASP7- and/or CASP9-deficient mice requires particular caution because of the crucial roles of these caspases in modulating immune and inflammatory responses [242–244]. That said, there is evidence for a role of specific regulators of apoptosis in the host response to infection with human herpes simplex virus 1 (HSV-1). On the one hand, a significant accumulation in total leukocyte and CD8$^+$ T cells was observed in mice deficient for BIM and PUMA upon infection with HSV-1 [478], which is in line with a role of these BH3-only proteins in controlling the survival of lymphoid and myeloid cells [410, 479, 480]. On the other hand, mice deficient for NOXA, BAD or BID were reported to mount a normal CD8$^+$ T cell immune response to HSV-1 infection [478]. Some of these contradictory results may arise from the divergent effects of inhibition or promotion of apoptosis on immune cells versus other cell types affected by the infectious disease, a distinction that cannot be addressed using mice in which apoptotic regulators have been deleted in the germline. In this context, it is noteworthy to note that the myeloid cell-specific deletion of the gene encoding BCL-X_L or its inhibition using BH3 mimetic drugs massively reduced bacterial burden in the lung and extended the survival of mice infected with *Legionella* [481]. This indicates that BH3 mimetic drugs might be effective for the treatment of intracellular bacterial infections.

Other diseases

Pro-apoptotic BCL2 proteins and caspases have also been implicated in disorders affecting other tissues/organs, such as skeletal muscle and lungs. For instance, the conditional ablation of *Bax* and *Bak1* protected mouse skeletal muscles against pressure-induced injury [482]. Similar results have been obtained in rats receiving Z-VAD-FMK after being subjected to muscular compression or blunt injury [483, 484]. Moreover, deletion of *Casp3* or CASP3 inhibition with Ac-DEVD-CHO limited muscular damage and atrophy in experimental models of plaster-mediated immobilization [485, 486]. In mouse models of catabolic disorders, muscle wasting due to protein degradation was decreased by lentiviral expression of XIAP [487, 488], although whether this effect reflects the inhibition of intrinsic apoptosis needs further confirmation. Finally, *Casp3*$^{-/-}$ mice were protected against denervation-induced muscular atrophy [489], while expression of a dominant-negative variant of CASP9 improved the neuromuscular activity in a transgenic mouse model of slow-channel syndrome [490].

In a mouse model of oxidant-induced lung injury, the tissue-specific ablation of *Bax* and *Bak1* but not that of the genes encoding BID, BIM, NOXA or PUMA protected lung epithelial cells from degeneration [491]. Among the anti-apoptotic BCL2 proteins, BCL2 related protein A1 (BCL2A1, best known as A1) seems to exert a crucial role in this setting, as *Bcl2a1* deletion aggravated lung injury in mice subjected to hyperoxia [492], while lung-specific overexpression of BCL2 did not confer protection to mice exposed to excessive oxygen supply [493]. That said, no critical cytoprotective effect of A1 was seen in acute lung inflammation and peritonitis [494]. Intrinsic apoptosis has also been reported to be involved in pulmonary fibrosis [495]. *Bid*$^{-/-}$ mice display decreased levels of pulmonary fibrosis after intra-tracheal bleomycin administration than their wild-type counterparts [496]. In apparent contradiction, in the same model of fibrotic pulmonary damage, a similar degree of protection was reported in mice lacking *Bcl2* [497] or in animals treated with inhibitors of BCL2 [497] or caspases [498, 499]. Along similar lines, ablation of *Bid* limited acute lung injury in mice induced by exposure to lipopolysaccharide (LPS) [500]. Moreover, CASP3 depletion using short-hairpin RNAs (shRNAs) protected the lungs of mice subjected to pulmonary ischemia/reperfusion [501], a protection further strengthened when necroptosis was concomitantly also suppressed [502]. BCL2 overexpression or caspase inhibition protected rodents subjected to lung transplantation [503, 504]. This is in line with the notion that delivery of the caspase inhibitor Z-VAD-FMK to rodents ameliorated lung injury developing as a consequence of severe acute pancreatitis or LPS administration [505, 506] but not as a result of pneumovirus infection [507]. In the latter case, lung damage was exacerbated by Z-VAD-FMK, perhaps due to increased inflammation downstream of necroptotic RCD [507].

The studies summarized above illustrate that components of the intrinsic apoptosis pathway can be part of the pathogenic mechanism of disease, and, in certain cases, this may offer the opportunity for therapeutic intervention. It is important to note that in many pathogenic processes intrinsic apoptotic cell death is the endpoint, and simply inhibiting it will not be curative. If the cells continue being exposed to the initiating insult, they will likely undergo less regulated forms of cell death. However, inhibiting the intrinsic apoptotic cell death may buy time to control the factors that are damaging the cells in first place. Ischemia and hypoxia, in cases where the ensuing cell death has a substantial intrinsic apoptotic component, are examples. If cells in the ischemic region were kept alive until adequate circulation was restored, therapeutic benefits might be achieved. Other examples include metabolic disorders, which may be amenable to correction, and traumatic injury, where healing might be supported by inhibiting apoptosis. It would be worth concentrating on

Box 5. Principles of extrinsic apoptosis

Extrinsic apoptosis is a regulated cell death (RCD) variant frequently triggered by death receptor (DRs) upon binding of a cognate ligand [1323–1325]. The principal DRs that will be discussed in the review are the Fas cell surface death receptor (FAS; also known as CD95 or APO-1), the TNF receptor superfamily member 1A (TNFRSF1A; best known as TNF-R1), the TNF receptor superfamily member 10a (TNFRSF10A; best known as TRAIL-R1 or DR4) and the TNF receptor superfamily member 10b (TNFRSF10B; best known as TRAIL-R2 or DR5). FAS is activated by the binding of FAS ligand (FASLG; also known as CD95L or APO-1L; FASL in mice), which is primarily expressed by effector immune cells [1325]. TNF-R1 is activated by tumor necrosis factor (TNF), a functionally pleiotropic cytokine expressed in cells in the spleen, thymus and certain other adult tissues [1323]. Of note, while the soluble form of TNF preferentially binds to TNF-R1, the membrane-anchored form mainly interacts with the TNF receptor superfamily member 1B (TNFRSF1B, best known as TNF-R2), which does not have death domain and therefore is not a DR [1326]. Finally, TRAIL-R1 and TRAIL-R2 are specifically activated by the binding of TNF superfamily member 10 (TNFSF10; best known as TRAIL), which is expressed by a variety of cell subtypes of the innate as well as adaptive system, including monocytes, macrophages and effector T cells, as either a soluble or membrane-bound version [1327]. Of note, mice express only one TRAIL receptor (TRAIL-R2, referred in this article as mTRAIL-R) which is equally homologous to human TRAIL-R1 and TRAIL-R2.

Upon ligand binding and trimerization and in certain instances formation of higher order complexes, the engagement of DRs promotes the assembly of multi-protein complexes, such as the death-inducing signaling complex (DISC) and complex II, resulting in the activation of caspase 8 (CASP8) and apoptosis [1328–1331]. The DISC, which is assembled on the cytoplasmic tail of ligated FAS, TNF-R1, TRAIL-R1 or TRAIL-R2, is comprised of the molecular adaptor Fas-associated death domain protein (FADD), Fas (TNFRSF6)-associated via death domain (FADD), CASP8, and distinct isoforms of CASP8 and FADD like apoptosis regulator (CFLAR; best known as c-FLIP), including alternative splicing variants, the long form c-FLIP$_L$ and the short form c-FLIP$_S$, and (in human) c-FLIP$_R$ [1332–1337]. Of note, c-FLIPs are catalytically inactive CASP8-like molecules acting as a modulator of CASP8 activation. Unlike FAS- and TRAIL-R-associated DISCs, complex II is a cytosolic complex assembled secondarily upon TNF-R1 ligation, in conditions of reduced pro-survival signaling and protein synthesis as for instance upon administration of inhibitor of apoptosis proteins (IAP) blockers and cycloheximide [1338]. Complex II consists of FADD and CASP8 in association with either TNF-R1-associated death domain protein (TRADD) (complex IIa) or receptor interacting serine/threonine kinase 1 (RIPK1) (complex IIb), which is involved in the modulation of apoptosis and necroptosis [1339]. Upon the recruitment to the DISC (complex I), CASP8 is activated by a process involving CASP8 oligomerization and autoproteolysis. CASP8 then acts as the executor of extrinsic apoptosis by favoring the proteolytic activation of the effector caspases CASP3 and CASP7 [1340]. This direct pathway is sufficient for the FASLG-driven killing of thymocytes and mature lymphocytes (so-called type I cells), but the efficient killing of hepatocytes, pancreatic β cells, and most cancer cells (so-called type II cells) requires pathway amplification through the CASP8-dependent proteolytic activation of the BH3-only protein BH3 interacting domain death agonist (BID), leading to engagement of the intrinsic apoptotic pathway [278, 1341–1346]. Of note, the absence of X-linked inhibitor of apoptosis (XIAP) converts type II cells into type I cells [1160], indicating that a limited amount of caspase activity is needed for cell killing.

Once activated, CASP8 also cleaves RIPK1 leading to the inhibition of necroptosis and the maintenance of inflammatory homeostasis [1347]. As a further layer of complication, the engagement of DRs by their respective ligands does not necessarily culminate in the activation of the extrinsic apoptosis signaling pathway. Indeed, the engagement of FAS, TRAIL-Rs and TNF-R1 can also result in the activation of pro-survival pathways, which is often - but not always - dependent on NF-κB signaling [1327, 1348], or, alternatively, in the initiation of inflammatory responses, cell differentiation/activation (as is the case of lymphocytes), and the regulation of other RCD variants, particularly necroptosis and pyroptosis [1349]. The induction of inflammatory chemokines and cytokines downstream of the activation of FAS and TRAIL-Rs is mediated by FADD and CASP8 by a mechanism that can be independent of apoptosis induction [872, 1350].

Extrinsic apoptosis can be activated by another class of cell surface receptors known as dependence receptor. In this case, cell death is ignited by a decrease in the availability of a specific ligand on which these receptors depend [1351, 1352]. Dependence receptors include (but are not limited to) the DCC netrin 1 receptor (DCC) and distinct types of unc-5 netrin receptors (UNC5A, UNC5B, UNC5C, and UNC5D), all of which are bound by netrin 1 (NTN1), and the neurotrophic receptor tyrosine kinase 3 (NTRK3) and patched 1 (PTCH1), which are ligated by neurotrophin and sonic hedgehog (SHH), respectively. The activation of dependence receptors stimulates hitherto poorly characterized signaling cascades often dependent on caspase activation, leading to the induction of cell death [838, 1353]. Of note, the relevance of dependence receptor-induced apoptosis for normal physiology and disease remains to be formally established.

inhibiting intrinsic apoptotic cell death in conditions where the initiating tissue insults can be (at least partially) reversed. In contrast, failure to undergo intrinsic apoptosis is the initial pathogenic step or a contributing factor in certain malignancies. Here, the induction of apoptosis, for example by using BH3 mimetic drugs [33, 34], directly targets pathogenesis.

EXTRINSIC APOPTOSIS IN DISEASE

The molecular apparatus for extrinsic apoptosis is described in Box 5 and illustrated in Fig. 4. Unlike the intrinsic apoptotic pathway, DR-induced apoptosis is not required for embryonic or fetal development but plays a critical role in adult tissue homeostasis, as detailed in Box 6 and Box 7. Of note, various components of the extrinsic pathway of apoptosis are involved in the etiology of multiple human disorders, although (1) with a considerable degree of context-dependency, and (2) with an effect not necessarily linked to the activation of apoptosis but often due to the role of DR signaling in necroptosis and inflammation, as outlined below.

Neurological diseases

Although numerous studies investigated FAS and TNF-R1 signaling in the pathogenesis of multiple neurological diseases, the precise role of extrinsic apoptosis remains unclear (Fig. 5). Loss-of-function mutations of Fas ligand (TNF superfamily, member 6) (*Fasl*) as well as *Fas* silencing prevented moto-neuron loss in mouse models of ALS driven by defect in superoxide dismutase 1, soluble (SOD1) [508, 509]. Conversely, the lack of TNF did not affect motor neuron loss and mouse survival in this model [510], while signaling via TNF receptor superfamily member 1B (TNFRSF1B, best known as TNF-R2) appeared to mediate neuroprotective effects [511]. As an additional layer of complexity, TNF mediates neuroprotective functions in wobbler mice - another mouse model of ALS that carries a point mutation in VPS54 GARP complex subunit (*Vps54*), at least in part by promoting the upregulation of ADAM metallopeptidase domain 8 (ADAM8) [512]. CASP8 has not yet been implicated in the pathogenesis of ALS, and non-apoptotic forms of FAS-driven RCD may play a predominant role in this context. For example, FAS stimulation reportedly triggered the demise of motoneurons in mouse models of ALS by aggravating endoplasmic reticulum stress [513]. Similarly, cleavage of BID by CASP1 (and not CASP8) appears to contribute to neurodegeneration in transgenic mice expressing a mutant form of human SOD1 [514]. However, the precise contributions of endoplasmic reticulum stress and CASP1 in ALS and other motoneuron disorders remain to be elucidated.

The ability of TNF-R1 signaling to influence neurodegenerative conditions involves not only the induction of extrinsic apoptosis but also the activation of an inflammatory response. In distinct murine models of AD, deletion of *Tnf*, modification of its untranslated region (UTR) as well as pharmacological TNF inhibition reduced plaque formation, resulting in attenuated neurological deficits [515–522]. Mechanistic studies in mice and monkeys revealed that TNF-R1 activation stimulates the protein activator of interferon-induced protein kinase EIF2AK2 (PRKRA) network [523], which is linked to PD in humans [524]. Moreover, TNF-R1 signaling has been shown to favor microglial reactivity during neurodegeneration, culminating in neuronal loss [525]. Amelioration of disease was seen in mouse models of AD upon genetic or pharmacological inhibition of TNF-R1 [526, 527]. AD-associated neuroinflammation seems to depend on TNF-induced necroptosis rather than extrinsic apoptosis [528, 529]. Unexpectedly, AD pathogenesis was shown to be enhanced in mice bearing a co-deletion of *Tnfrsf1a* and *Tnfrsf1b* [530], a phenotype that appears to impinge on a complex network of mutual interactions between TNF-R1 and TNF-R2 signaling [531]. Such a network may also contribute to PD pathogenesis. Genetic ablation of *Tnf* or

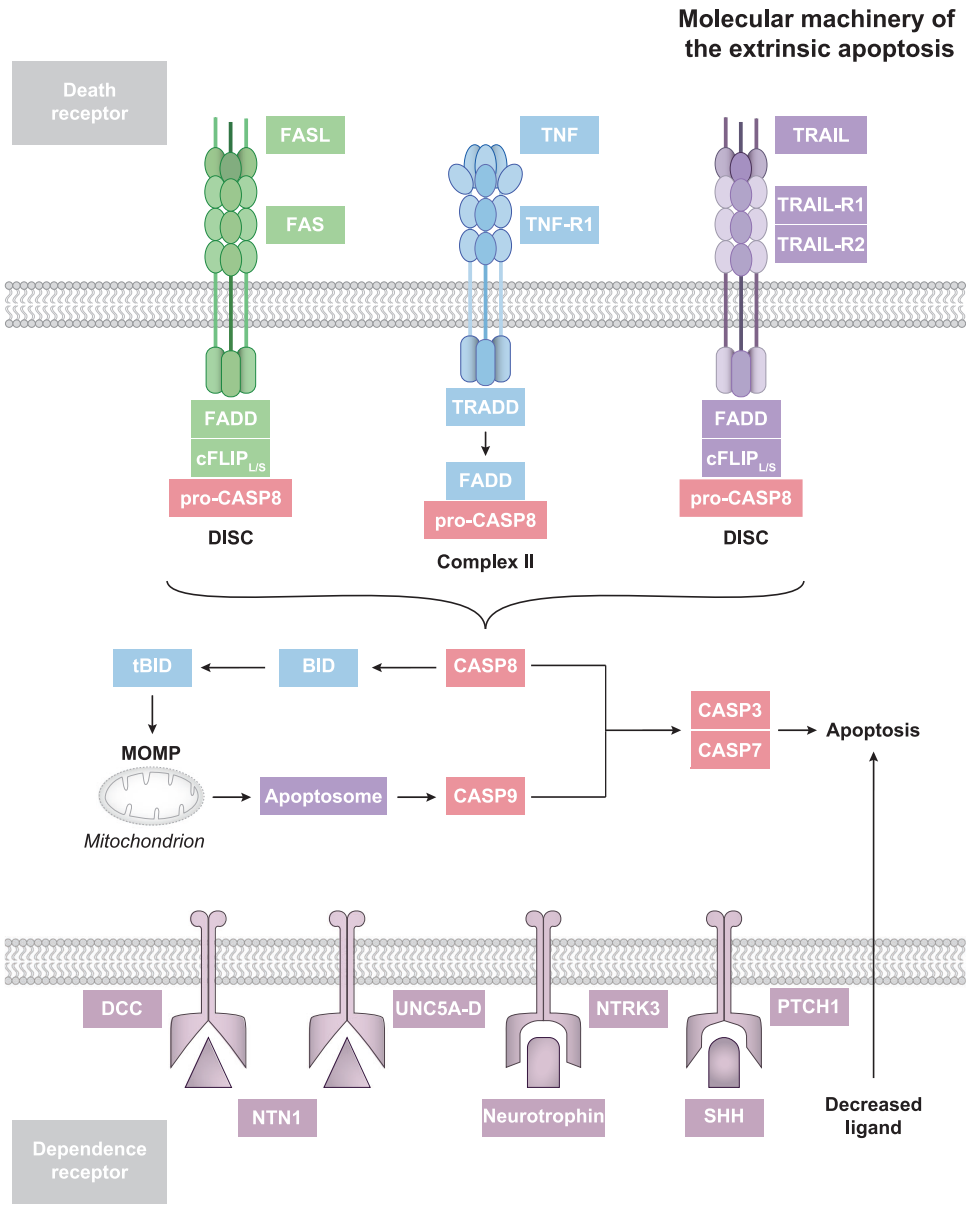

Fig. 4 Molecular machinery of the extrinsic apoptosis pathway. Extrinsic apoptosis is initiated by the binding of FASL to FAS or TRAIL to TRAIL-R1 or TRAIL-R2, which promotes the assembly, on the cytoplasmic tail of these death receptors, of a platform known as the DISC. Extrinsic apoptosis is also triggered by the binding of TNF to TNF-R1, which promotes the assembly of the Complex II. The DISC comprises FADD, c-FLIPs and pro-CASP8. Complex II is a platform consisting of FADD and pro-CASP8 in association with either TRADD (complex IIa) or RIPK1 (complex IIb). The assembly of these complexes promotes the activation of CASP8, which mediates CASP3 and CASP7 activation either directly, by catalyzing the proteolytic activation of CASP3 and CASP7 (in type I cells) or indirectly, via the proteolytic activation of the BH3-only protein BID and outer membrane permeabilization (MOMP) (in type II cells). At least in some cells, extrinsic apoptosis can also be induced by dependence receptors like DCC, NTRK3, PTCH1, or UNC5A-D, which are activated by decreased concentration of the related ligand, as illustrated in the figure. However, the role of this pathway in normal physiology and disease is not yet established.

Tnfrsf1a plus *Tnfrsf1b* (leading to the lack of both TNF receptors), as well as pharmacological inhibition of TNF, were reported to protect dopaminergic neurons in murine models of PD following the administration of 1-metil 4-phenyl 1,2,3,6-tetraidro-piridina (MPTP) or 6-hydroxydopamine [532–535]. Notably, in the aforementioned experimental settings, TNF is thought to induce neuronal death in vivo by promoting microglia reactivity [536] with a complex interaction between TNF-R1 and TNF-R2 signaling [537]. Clinical evidence from AD patients subjected to perispinal administration of the TNF blockers infliximab or etanercept suggests that the inhibition of TNF can ameliorate AD [538, 539]. In contrast, a dominant-negative variant of TNF failed to protect mice against neuronal degeneration in a model of HD [540], suggesting that this approach may not be viable in patients with HD.

TRAIL/TRAIL-R signaling has also been implicated in the onset and progression of AD [541, 542]. Specifically, in a mouse model of AD, neutralization of TNF superfamily member 10 (TNFSF10, best known as TRAIL) with a monoclonal antibody resulted in decreased neuroinflammation and a reduction in cognitive defects [541]. However, these findings were not extensively validated. Similarly, the impact of FASL-FAS signaling on neurodegenerative conditions is debated. Indeed, *lpr*/*lpr* mice, which lack FAS [543] and to a lesser extent *gld*/*gld* mice, which lack FASL [543], are particularly susceptible to neuronal degeneration driven by MPTP [544]. However, contrasting results have been

Box 6. Impact of death receptors on health

A large body of data demonstrates that death receptor (DR) signaling is crucial for the maintenance of adult tissue homeostasis but nor for embryonic development, as demonstrated by the normal appearance of mice lacking caspase 8 and mixed lineage kinase domain like (*Casp8*$^{-/-}$*Mlkl*$^{-/-}$ mice) or CASP8 and receptor-interacting serine-threonine kinase 3 (*Casp8*$^{-/-}$*Ripk3*$^{-/-}$ mice), before they develop lymphadenopathy and splenomegaly [52, 876, 1354–1357]. Mouse strains with spontaneous mutations in Fas (TNF receptor superfamily member 6) (*Fas*) - the so-called *lpr*/*lpr* mice – or Fas ligand (TNF superfamily, member 6) (*Fasl*) - the so-called *gld*/*gld* mice - are viable but develop progressive lymphoproliferative and systemic lupus erythematosus (SLE)-like disorders [543, 875, 1358–1360]. The severity of these pathologies is greatly influenced by genetic background: fairly mild on a C57BL/6 background but very severe on MRL and NOD backgrounds. That said, mice with heterozygous *Fas* or *Fasl* mutations are normal [1360]. These lymphoproliferative and autoimmune disorders are not accompanied by impaired thymocyte development [1361]. Transgenic overexpression of BCL2 apoptosis regulator (BCL2) [1342] or MCL1, BCL2 family apoptosis regulator (MCL1) [1362] in the lymphocyte compartment of *lpr*/*lpr* mice or the absence of BCL2 like 11 (BCL2L11; best known as BIM) [1363] massively exacerbate lymphadenopathy. This is consistent with the notion that intrinsic apoptosis and DR-induced apoptosis are distinct in lymphoid cells and act additively. FAS or FASL deficiency also perturbs the homeostasis or function of other mouse tissues, including (but not limited to) the liver [1361], kidney [1364], retina [1365], pancreas [1366] and intestinal epithelium [1367], but these effects may all be a consequence of the deregulation of the lymphoid system, for example causing excess production of certain cytokines and chemokines.

Conditional deletion of *Fas* and *Fasl* in specific immune cell subsets as well as transgenic expression of FAS in lymphocytes confirms the crucial role of FASL-FAS signaling in the homeostasis of lymphocytes and dendritic cells (DCs) [1020, 1368–1371]. In this context, experiments in *lpr*/*lpr* mice deleted of BH3-only protein BCL2 like 11 (*Bcl2l11*, encoding BIM) demonstrate some degree of cooperation between FAS and BIM in preserving the functionality of the immune system [1363]. However, abrogating FAS-FASL signaling ultimately has heterogeneous organismal consequences. The lymphoproliferative disorder caused by *Fas* or *Fasl* deletion confers protection from autoimmune diabetes [922]. This may be explained by the fact that the distortion of the T cell repertoire caused by the lymphadenopathy in the *lpr*/*lpr* and *gld*/*gld* mice prevents the development of diabetogenic T cells. Finally, FAS appears to exert tumor suppressive effects in lymphoid cells. Indeed, both *gld*/*gld* mice as well as *lpr*/*lpr* mice lacking the T cell compartment have increased incidence of B cell lymphoma [816, 1372, 1373]. Loss of FAS also predisposes humans to B cell lymphoma (see below).

As for other DRs, mice lacking TNF receptor superfamily member 10b (TNFRSF10B, best known as TRAIL-R2 or mTRAIL-R) or its ligand TNF superfamily member 10 (TNFSF10, beast known as TRAIL) are viable, fertile, and do not spontaneously develop autoimmune diseases [883, 1374–1376]. Moreover, these mice exhibit normal immune system development and function [1377–1380]. Along similar lines, the whole-body deletion of tumor necrosis factor (*Tnf*) does not affect mouse development and fertility [1381, 1382]. However, *Tnf*$^{-/-}$ mice often show early hearing loss and, despite presenting with an overtly functional immune system, exhibit abnormally increased susceptibility to spontaneous bacterial infection, which has been ascribed to multiple defects including defective lymphoid organ architecture as well as deficient granuloma and germinal center formation [1381–1385]. Impaired responses to pathogens have been documented in *Tnf*$^{+/-}$ mice [1381] as well as in mice lacking TNF receptor superfamily member 1A (TNFRSF1A, best known as TNF-R1) [1383–1387]. Conversely, mice overexpressing TNF in cardiomyocytes suffer from lethal dilated cardiomyopathy, demonstrating that balanced TNF signaling is essential for the homeostasis of the cardiac tissue [1388–1390]. Of note, while the lack of TRAIL enhances the severity of lymphoproliferative and autoimmune disorders in *gld*/*gld* mice [1391], the lack of TNF attenuates the lymphoproliferative phenotype, extending the survival of *gld*/*gld* mice [1392]. The latter is probably due to the reduction in TNF-mediated inflammation attenuating lymphadenopathy caused by the absence of FASL. These findings confirm the pleiotropy and redundancy of DR signaling, encompassing not only apoptotic and non-apoptotic regulated cell death (RCD)-related effects, but also various pro-survival and pro-inflammatory modules.

Multiple clinical observations support the role of FAS signaling in human hematopoiesis [1393, 1394]. Most patients with autoimmune lymphoproliferative syndrome (ALPS) —a primary immunodeficiency manifesting with lymphadenopathy, splenomegaly as well as abnormal numbers, development and function of lymphocytes —carry loss-of-function mutations in *FAS* or *FASLG* [874, 1395–1400]. ALPS patients also display an increased incidence of non-Hodgkin and Hodgkin lymphoma [1401]. While no mutations in the genes encoding TRAIL, TRAIL-R1 and TRAIL-R2 have so far been linked to human autoimmune diseases, autosomal dominant mutations in *TNFRSF1A* (leading to lack of TNF-R1) have been identified in patients affected by TNF receptor-associated periodic syndrome (TRAPS), characterized by severe abdominal pain, arthralgias, and myalgias [1402–1404].

obtained in another study involving FAS-deficient mice treated with MPTP [545, 546]. In this context, FAS-associated factor 1 (Faf1, a FAS binding protein that can initiate or enhance apoptosis) was found to be increased in midbrain in murine models of PD [547]. Moreover, a reduction in Faf1 expression limited MPTP-induced dopaminergic cell loss [548]. Such an apparent discrepancy in results may originate from the pleiotropic role of FAS in apoptosis and inflammation and other pro-survival/regenerative signals.

CASP8 activation has been detected in the brain of both AD [549] and HD [550] patients as well as in dopaminergic neurons of MPTP-treated mice and PD patients, a setting in which BID cleavage has also been documented [119]. This is in line with the ability of the broad-spectrum caspase inhibitor Q-VD-OPH to inhibit BID cleavage and mediate neuroprotection in MPTP-treated mice and rats [551]. Of note, CASP8 was also reported to promote microglia reactivity potentially leading to neuronal loss [552–554]. In this context, genetic loss or pharmacological inhibition of CASP8 attenuated neurotoxicity by reducing microglial reactivity, thus extending survival of neurons, at least in part by stimulating the necroptotic death of activated microglial cells [552–554]. Consistent with this notion, *Casp8* deletion in myeloid cells protected mice from MPTP-mediated neurotoxicity [555], suggesting that CASP8 inhibitors may be harnessed for the treatment of neurodegenerative conditions. Corroborating this idea, a pharmacological inhibitor of TNF-R1-associated death domain protein (TRADD) protected mice from disease in a model of AD-like proteinopathy driven by mutant tau [556]. However, pharmacological inhibition of CASP8 only partially prevented neuronal alterations in other models of AD [108], and even exacerbated dopaminergic neuronal necrosis in mice developing PD upon MPTP administration [557]. Moreover, rare *CASP8* loss-of-function variants have been associated with AD in a large cohort of patients [558]. Thus, the precise contribution of CASP8 signaling to neurodegenerative disorders and whether this relates to its function in driving extrinsic apoptosis, inhibiting necroptosis or promoting inflammatory cytokine production remains to be formally defined. Concerning dependence receptors, Netrin 1 (NTN1) upregulation was shown to confer neuroprotection in murine models of PD, suggesting a potential role of dependence receptors in neurodegenerative disease [559].

DR signaling has also been shown to contribute to neuronal death and inflammation in preclinical models of CNS trauma. In a compression model of spinal cord injury, mice with loss of FAS (i.e., *lpr*/*lpr* mice) as well as mice treated with FASL blockers displayed reduced post-traumatic neuronal degeneration and inflammation coupled to considerable functional improvement [560–562]. This beneficial effect also involved reduced engagement of the intrinsic apoptosis pathway [563]. Myeloid cell-specific deletion of *Fasl* promoted neuronal regeneration and functional recovery in mice subjected to spinal cord injury [564]. A similar functional improvement after spinal injury was observed in mice with conditional deletion of *Tnf* in macrophages and neutrophils, but not in microglia [565]. Moreover, neuroprotection and limited neuroinflammation have been documented in *lpr*/ *lpr* mice subjected to traumatic brain injury [566], as well as in mice subjected to experimental spondylotic myelopathy and exposed to FASL-neutralizing antibodies [567]. Studies on mice with loss of *Fas* and *Tnfrsf1a* revealed at least some redundancy between FAS and TNF-R1 signaling in the context of experimental brain trauma [568–572]. Furthermore, TNF inhibition reduced damage in mice or rats experiencing spinal cord injury [573–575], and also reduced the appearance of signs of autonomic dysreflexia, a cardiovascular disease associated with high-level spinal cord injury [573, 576]. Interestingly, some of these studies point to a neuroprotective function for TNF-R2 [568, 570, 572], which is in line with at least some results from models of ALS [511, 531]. Moreover, several studies question a purely detrimental effect of TNF signaling in these experimental settings [577–580]. In particular, TNF was

Box 7. Impact of extrinsic apoptosis complexes and caspases on health

Several signal transducers in the death receptor (DRs) pathway are essential for embryonic development in mice. Thus, deletion of Fas (TNFRSF6)-associated via death domain (*Fadd*), caspase 8 (*Casp8*) or CASP8 and FADD-like apoptosis regulator (*Cflar*, encoding c-FLIP) is embryonic lethal at mid-gestation as a consequence of severe vascular as well as cardiac defects associated with spontaneous intra-abdominal hemorrhage [1405–1410]. Of note, CASP8-deficient mice also exhibit neural tube defects [1409]. A similar embryonic lethality has also been documented in mice expressing a mutant form of FADD deficient in its death domain [1406]. The absence of other components of DR-associated signaling complexes, such as TNFRSF1A associated via death domain (TRADD) and receptor-interacting serine/threonine kinase 1 (RIPK1), causes different abnormalities. Thus, while *Tradd*$^{-/-}$ mice develop normally and do not display major hematopoietic defects [1411–1413], *Ripk1*$^{-/-}$ mice die early after birth due to severe multiorgan inflammation [1414, 1415]. These findings are attributed to the pleiotropic contribution of RIPK1 and TRADD to a variety of processes beyond apoptosis, most notably necroptotic regulated cell death (RCD) and inflammation. This is exemplified by the observation that the embryonic lethality caused by the absence of CASP8 or FADD can be rescued by the concomitant loss of mixed lineage kinase domain like (MLKL) or receptor-interacting serine-threonine kinase 3 (RIPK3) (see below). Mice lacking baculoviral IAP repeat-containing 3 (BIRC3; best known as cIAP1) and X-linked inhibitor of apoptosis (XIAP), or cIAP1 and BIRC2 (best known as cIAP2), but not mice lacking cIAP2 and XIAP, display embryonic lethality [1416]. These findings indicate specific functional redundancies among the inhibitor of apoptosis protein family. cIAP1/cIAP2-deficient mice display mid-gestation lethality, which can be rescued to birth by the deletion of TNF receptor superfamily member 1A (*Tnfrsf1a*, encoding TNF-R1) but not that of TNF receptor superfamily member 1B (*Tnfrsf1b*, best known as TNF-R2) [1416]. Loss of one allele of *Ripk1* or loss of *Ripk3* prolonged embryonic survival of these mice [1416]. It is noteworthy, that, as discussed above, genetic background effects might contribute to the phenotype, as mice with concomitant knockout of the genes encoding cIAP1 and cIAP2 using mutant alleles generated in C57BL/6 embryonic stem cells die in midgestation [1416], whereas *Birc3*$^{-/-}$ and *Xiap*$^{-/-}$ double mutants generated using 129Sv embryonic stem cells are viable [1417].

It was demonstrated that embryonic lethality in *Casp8*$^{-/-}$ and *Fadd*$^{-/-}$ mice is due to excessive necroptosis, reflecting the ability of CASP8 to limit necroptosis downstream of DR activation [51–53, 1354]. Accordingly, deletion of genes encoding key components of the necroptotic machinery such as RIPK3 or MLKL prevents all developmental defects and embryonic lethality in FADD- or CASP8-deficient embryos [51, 52, 876, 1354–1357, 1418]. Of note, *Casp8*$^{-/-}$*Ripk3*$^{-/-}$ and *Casp8*$^{-/-}$*Mlkl*$^{-/-}$ mice develop progressive lymphoproliferative disorders that resemble those caused by the absence of FAS or FASL [51, 52, 876]. Moreover, embryonic lethality around E10.5 in mice lacking c-FLIP and the perinatal lethality of *Ripk1*$^{-/-}$ mice depend on aberrant activation of both DR-induced apoptosis and DR-induced necroptosis. Indeed, the lethality of these animals can be rescued by concomitant deletion of *Fadd* and *Ripk3*, *Casp8* and *Ripk3*, or *Fadd* and *Mlkl* [52, 876, 1354–1357]. Of note, mice with a mutation in *RIPK1* that prevents its CASP8-mediated cleavage die around E10.5 of embryonic development, and this can be prevented by the combined absence of RIPK3 and CASP8 [1347, 1419, 1420]. In a heterozygous state, mutations in the gene encoding RIPK1 cause severe auto-inflammation. As an additional layer of complexity, although the deletion of *Tradd* rescues *Ripk1*$^{-/-}$*Ripk3*$^{-/-}$ embryos from perinatal lethality, triple knockout mice die postnatally [1421, 1422]. Moreover, TRADD deficiency does not prevent the embryonic lethality caused by the loss of FADD [1422]. Additional studies confirm the importance of the inter-connectivity between multiple RCD pathways. Mice with a mutation that prevents auto-proteolytic activation of CASP8 develop normally [1423], but akin to complete loss of *CASP8*, mutations in the CASP8 catalytic site result in embryonic lethality around E10.5 due to aberrant necroptosis, phenotype that can be delayed (but not prevented) by *Mlkl* deletion [1419, 1424]. While the genetic ablation of *Mlkl* or *Mlkl* plus *Fadd* prevent E10.5 embryonic lethality in these mice, the compound mutant mice die soon after birth, likely due to aberrant inflammation and pyroptosis [1425, 1426]. These observations point to the central role for CASP8 in the regulation of multiple RCD variants and inflammatory processes [10].

The tissue-specific deletion of *Fadd* or *Casp8* in mouse endothelial cells results in an embryonic lethal phenotype that resembles that of germline *Fadd* or *Casp8* deletion [596, 1427]. Conversely, the absence of FADD in cardiomyocytes or cardiac progenitor cells appears to have no impact on embryonic development [1427]. Again, abrogation of necroptosis rescued the lethal phenotype of endothelial cell specific *Fadd* or *Casp8* deletion [1427], lending additional support to inhibitory role of FADD and CASP8 in necroptotic RCD. FADD, CASP and c-FLIP have also been implicated in hematopoietic homeostasis. However, the abrogation of FADD in specific immune cell subsets in mice via distinct experimental approaches, such as conditional gene deletion, injection of *Fadd*$^{-/-}$ embryonic stem cells into *Rag1*$^{-/-}$ blastocysts or transgenic expression of a dominant-negative variant of FADD, does not drive lymphoproliferative disorders. Instead, FADD appears to be critical for the proliferation and/or development of T lymphocytes [955, 1428–1437] and B cells [1438], most likely by preventing necroptosis through activation of CASP8. Similar conclusions were derived from the analysis of mice with lymphocyte-specific ablation of *Casp8* or *Cflar* [1439–1444]. A role for CASP8 in T cell proliferation has also emerged from the realization of the anti-proliferative effects of caspase inhibitors [1445]. The T cell-specific deletion of *Casp8* attenuates autoimmunity and improves the survival of mice lacking the BH3-only protein BCL2 like 11 (BCL2L11, best known as BIM) by limiting T cell proliferation and survival [1446]. Apparently at odds with these findings, the conditional deletion of *Casp8* in T cells has also been associated with an age-dependent, lymphoproliferative immune disorder resembling the condition of patients with *CASP8* mutations [1447]. Whether mouse genetic background or other contextual variables (e.g., the mouse microbiota) underlie such apparent discrepancies remains to be elucidated.

The conditional loss of the functions of FADD or CASP8 also revealed a role for these proteins in early hematopoiesis, which may relate to their ability to promote the proliferation and differentiation of hematopoietic stem and progenitor cells by preventing necroptosis [596, 1448, 1449]. Conditional deletion of *Fadd* in myeloid cells resulted in increased myeloid and B cell populations coupled to activation of inflammatory responses [1450]. Along similar lines, the macrophage-restricted deletion of *Casp8* induced a mild systemic inflammatory disease potentially linked to altered macrophage polarization [1451, 1452], while the DC-specific deletion of the genes encoding c-FLIP or CASP8 elicited splenomegaly, inflammatory responses and autoimmune disorders [1453–1455]. These effects all seem to be unrelated to the pro-apoptotic functions of FADD and CASP8 but reflect their ability to prevent necroptosis [51, 52, 1434, 1450, 1451, 1456–1458]. Corroborating these findings, loss-of-function mutations in *FADD* [1459–1462], *CASP8* or *CASP10* [1463–1465] and *TRADD* [1466] have been associated with ALPS-like syndromes and hematological diseases in humans. Of note, patients with ALPS bearing mutations in *FADD* or *CASP8* but not ALPS patients with mutations in *FAS* or *FASLG* also exhibit immunodeficiency coupled with lymphocytic infiltrations in multiple organs, granulomas and/or inflammatory bowel disease [1459, 1463, 1467–1469].

Tissue-specific deletion of *Fadd*, *Casp8* and *Cflar* has also revealed a role for these proteins in the homeostasis of the liver, skin and intestine, although severity of the phenotype varies quite considerably, ranging from mild inflammatory responses to embryonic or early postnatal lethality, again likely due to unleashed necroptosis. Conditional deletion of *Cflar* (resulting in lack of c-FLIP) in intestinal epithelial cells, hepatocytes or keratinocytes resulted in embryonic or perinatal lethality due to aberrant activation of cell death [1470–1473]. The inducible deletion of *Cflar* from the intestinal epithelium of adult mice caused severe inflammation that was often fatal [1473]. These findings are in line with the crucial role of c-FLIP as an inhibitor of necroptosis [1354, 1474]. Along similar lines, *Fadd* deletion in epidermal keratinocytes or intestinal epithelial cells causes severe chronic inflammation due to the induction of aberrant necroptosis [1475–1481]. Accordingly, the removal of FADD (or CASP8) in intestinal epithelial cells resulted in chronic inflammatory colitis and ileitis, which was prevented by concomitant deletion of *Ripk3* or *Mklk* [1424, 1426, 1476, 1478, 1481, 1482]. In one of these studies, acute deletion of *Casp8* in the gut of adult mice resulted in enterocyte death, leading to disruption of tissue homeostasis, sepsis and death [1481]. In this context, CASP8-deficient enterocytes displayed decreased in vivo survival and migration potential [1483]. Specific deletion of *Casp8* in endothelial cells results in small intestinal hemorrhage and bowel inflammation, suggesting a key role of CASP8 in vascular homeostasis in the small intestine [1484]. Loss of CASP8 catalytic activity specifically in intestinal epithelial cells induced intestinal inflammation similar to absence of CASP8 in the intestinal epithelium [1424]. This intestinal phenotype was aggravated by *Mlkl* deletion, resulting in premature death dependent on the induction of inflammatory responses and pyroptosis [1424]. As an added layer of complexity, deletion of tumor necrosis factor (*Tnf*) or *Tnfrsf1a* (encoding TNF-R1) attenuated colitis, but not ileitis, in mice with an intestinal epithelial cell-specific deletion of *Fadd* or *Casp8* [1473, 1476]. A recent study indicated that this effect may also involve the aberrant activation of pyroptosis. Indeed, the CASP8-dependent activation of gasdermin D (GSDMD) appears to promote ileitis in mice with FADD-deficient intestinal epithelial cells [1485]. These results are in line with the crucial involvement of CASP8 and FADD in the activation of inflammation [63, 1486] and indicate that the FADD-CASP8 axis regulates tissue homeostasis by balancing apoptosis, necroptosis, pyroptosis and inflammation.

reported to support, at least in part, regeneration and long-term functional recovery in mice exposed to traumatic brain injury [578–580]. Conversely, TRAIL neutralization stands out as a promising strategy to promote neuronal regeneration and functional recovery based on mice with spinal cord injuries [581, 582]. In this context, injured neurons seem to undergo Fas-associated via death domain (FADD)- and CASP8-dependent RCD [583]. Accordingly, *Casp8* deletion or transgenic expression of a FADD inhibitor (the glycoprotein P45) protected mice after spinal cord injury [584, 585]. Similarly, transgenic expression of a dominant negative mutant of FADD (FADD-DN) limited moto-neuron loss in mice undergoing axotomy [586].

Components of the molecular apparatus for the extrinsic pathway are associated with disorders of the visual system, again in the context of both exacerbated cell death and inflammation. Thus, in mouse and rat models of optic nerve injury, deletion of

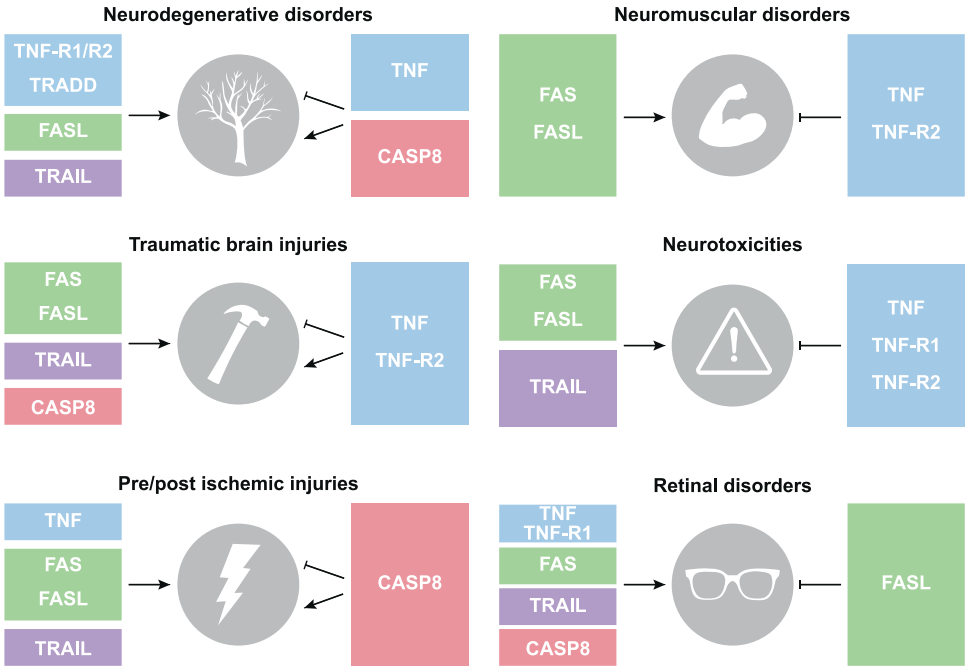

Fig. 5 Impact of extrinsic apoptosis players on neurological disorders. Death receptor-induced apoptosis is directly or indirectly involved in the pathogenesis of multiple neurological disorders, including neurodegenerative diseases, in brain damage due to traumatic injury or neurotoxicity as well as in neuromuscular and retinal disorders.

Tnfrsf1a (encoding TNF-R1) or inhibition of CASP8 with Z-IETD-FMK inhibited the degeneration of retinal ganglion cells [587, 588]. Moreover, the absence of TNF-R1 (but not the absence of TNF-R2) attenuated neurodegeneration in a mouse model of retinal ischemia, despite neuronal survival not being improved [589]. Along similar lines, deletion of *Tnf* [590] as well as inhibition of FAS [591] or TNF [592, 593] protected mice against retinal ganglion cell death in a model of glaucoma. Similar neuroprotective effects were documented for the conditional deletion of *Casp8* in astrocytes or intra-ocular Z-IETD-FMK administration [594]. In this context, the conditional inducible ablation of *Casp8* from endothelial cells reduced postnatal retinal angiogenesis and pathological neovascularization in a mouse model of oxygen-induced retinopathy [595] (note that ablation of *Casp8* in endothelial cells is embryonically lethal [596]; see Box 7). Moreover, CASP8 inhibition could prevent experimental neovascularization of the cornea [597]. Finally, TRAIL neutralization protected the retinal tissue from damage associated with AD in a mouse model [598].

Experimental models of ischemic stroke and hemorrhage revealed a role of DR signaling in the pathophysiology of brain damage. In models of focal ischemia induced by middle cerebral artery occlusion, *lpr*/*lpr* as well as *gld*/*gld* mice (deficient for FAS or FASL, respectively) displayed decreased infarct size and neuroinflammation [599–601]. Robust neuroprotection was also observed in *lpr*/*lpr* mice subjected to neonatal hypoxia-ischemia [602], as well as in *lpr*/*lpr* and *gld*/*gld* mice subjected to hyperoxia [603]. Accordingly, inhibition of FAS or FASL exerted neuroprotective effects in an experimental murine model of stroke [604, 605]. Likewise, TRAIL neutralization limited brain injury in rats and mice subjected to middle cerebral artery occlusion [601, 606] or transient ischemia-reperfusion [607]. Moreover, despite some contention in this respect [608–611], abrogation of TNF/TNF-R1 signaling by genetic or pharmacological means prevented brain injury in rodent models of intracerebral hemorrhage [612] and focal cerebral ischemia [613–621]. Further corroborating a pathogenic role of DR signaling, transgene-driven expression of dominant-negative CASP8 mutant and of FADD-like apoptosis regulator (CFLAR; best known as c-FLIP) attenuated brain damage after middle cerebral artery occlusion [622, 623]. This is in line with the ability of CASP8 to drive BID activation upon focal cerebral ischemia [196], as well as with the neuroprotective effects afforded by pharmacological CASP8 inhibitors seen in mice experiencing subarachnoid hemorrhage [624] or mice and rats subjected to focal cerebral ischemia [625, 626]. Importantly, FADD and CASP8 expression and/or activation have also been associated with ischemic stroke in humans [627, 628].

Perhaps surprisingly, TNF appears to protect mice against experimental seizures, not only through the engagement of TNF-R2 but also through TNF-R1 signaling [611, 629–634] and consequent modulation of NF-κB [635, 636]. Conversely, *lpr*/*lpr* mice [637], mice with neuron-specific deletion of the gene encoding TNF-R1 [638] as well as mice and rats treated with Z-IETD-FMK [585, 639, 640] display reduced sensitivity to experimental seizures, pointing to a detrimental role for apoptotic DR signaling in this condition. The precise mechanisms through which TNF-R1 signaling promotes anti-apoptotic and anti-inflammatory effects in the context of excitotoxic insults remain unclear.

Cardiovascular disorders

Data from preclinical models of ischemic and non-ischemic conditions indicate the involvement of FASL, TRAIL and TNF in the onset and progression of myocardial infarction with reperfusion and other heart diseases. In particular, both *lpr*/*lpr* mice (lacking FAS), as well as hearts isolated from these animals, displayed reduced cardiomyocyte death and infarct area upon experimental ischemia-reperfusion [641, 642]. Nonetheless, no protection against ischemia-reperfusion was found in hearts from $Fas^{-/-}$ or $Fasl^{-/-}$ mice [643]. However, supporting the therapeutic potential of the inhibition of DR signaling for the management of myocardial infarction, FASL-neutralizing antibodies conferred cardioprotection, limited inflammation, and improved cardiac function in mice experiencing cardiac ischemia-reperfusion [644–646]. Likewise, TRAIL blockade protected monkeys, pigs, and rats against experimental infarction by increasing

cardiomyocyte survival and reducing inflammation [647]. This is in line with the predictive value of TRAIL levels as a biomarker for heart failure in patients [648, 649]. Of note, TRAIL has also been reported to exert apoptosis-independent roles in cardiomyocyte growth and heart hypertrophy [650], as well as in angiogenesis and neovascularization upon experimental hindlimb ischemia [651]. Similar to neurological conditions, while TNF-R2 signaling appears to exert cardioprotective effects, the engagement of TNF-R1 drives cardiac hypertrophy, inflammation and cardiomyocyte loss [652–659]. The opposite outcome of TNF-R1 *vs* TNF-R2 signaling has been invoked to explain the clinical failure of TNF blocking agents in patients with chronic heart failure [660], despite encouraging preliminary findings [661, 662], as well as the cardiotoxic effects associated with the use of TNF blockers in patients with rheumatoid arthritis [663]. Confirming the involvement of extrinsic apoptosis in cardiac diseases, cardiomyocyte-specific deletion of *Fadd* in mice improved cardiomyocyte survival and heart function after ischemia/reperfusion [664]. Accordingly, haploinsufficiency of the gene encoding c-FLIP increased infarct area and aggravated cardiac dysfunction in mice experiencing myocardial infarction, while the cardiomyocyte-specific overexpression of c-FLIP attenuated pathology [665, 666]. Cardioprotection has also been observed in a mouse model of ischemia/reperfusion upon shRNA-mediated CASP8 depletion [667] or treatment with the CASP8 inhibitor Q-LETD-OPh [668]. Moreover, transplantation of *Casp8*$^{-/-}$ cells did not increase neovascularization in wild-type mice subjected to hindlimb ischemia [669], in line with a crucial role of CASP8 in the maintenance of endothelia in healthy conditions [596] (see Box 7). That said, combined pharmacological inhibition of apoptosis and necroptosis exerted greater cardioprotection than monotherapy in myocardial ischemia-reperfusion injury [670], suggesting the involvement of multiple RCD pathways in cardiovascular disorders.

FASL neutralization has been reported to improve cardiomyocyte survival and cardiac function in a model of cirrhotic cardiomyopathy [671]. Conversely, a cardioprotective effect of TRAIL and TNF was observed in mice developing cardiomyopathy upon the deletion of apolipoprotein E (*ApoE*) [672] or *Des* [673], respectively. Both FASL deficiency and administration of CASP8 inhibitors decrease tissue inflammation and aneurysm formation in mice subjected to $CaCl_2$-induced abdominal aortic aneurysms [674]. A potential role of extrinsic apoptosis in gradual cardiomyocyte attrition during heart failure with reduced fraction has also been reported in a transgenic mouse model of inducible CASP8 overexpression [675]. Concerning TNF receptors, deletion of *Tnfrsf1b* resulted in increased cardiomyocyte death and hypertrophy induced by isoproterenol [676]. In contrast, deletion of *Tnfrsf1a* (but not *Tnfrsf1b*) was shown to be cardioprotective in murine models of vascular thrombosis [677], and heart failure based on angiotensin II administration [678]. Similar cardioprotection in this model has been reported after silencing of *Tnfrsf1a* [679]. In line with these findings, *Cflar*$^{+/-}$ mice (which lack one copy of the gene encoding c-FLIP) displayed increased sensitivity to cardiac injury upon angiotensin II administration [680].

FASL and TNF have also been reported to promote cardiac maladaptation and hypertrophy in models of pressure overload [681–685]. Consistent with this notion, TNF inhibition [686] or transgenic c-FLIP overexpression [687] limited experimental heart hypertrophy driven by hypertension. Moreover, treatment with etanercept reduced cardiac fibrosis in a diet-induced mouse model of obesity [688]. Conversely, both FAS and TNF receptor superfamily member 10b (TNFRSF10B, best known as TRAIL-R2 or mTRAIL-R) were reported to protect mice against atherosclerosis, at least in part by modulating TNF superfamily member 11 (TNFSF11, best known as RANKL) signaling [689–693], while the impact of TNF on experimental atherosclerosis remains a matter of debate [694–697]. Finally, pharmacological inhibition of TNF prevented cardiotoxicity induced by doxorubicin in mice [698–700]

Renal conditions

FASL, TNF and TRAIL have all been implicated in the development of acute kidney injury by driving the activation of both extrinsic apoptosis and inflammation. Loss-of-function mutations in *Fasl*, inhibition or depletion of FASL [701–703] as well as *Fas* [704] or *Tnf* [705] silencing, TNF neutralization [706, 707], or TRAIL blockade [708] exerted nephron-protective effects in mouse models of renal ischemia/reperfusion. Generation of chimeric mice reconstituted with spleen cells from *gld*/*gld* mice (lacking FASL) revealed a particular impact of FASL signaling in the hematopoietic compartment on ischemic acute kidney injury [702]. However, some functional overlap between DRs has also been reported. Indeed, while one study suggested that FASL neutralization was more effective than *Tnfrsf1a* deletion (leading to lack of TNF-R1) in preventing renal inflammation and cell death after acute kidney injury [701], another study reported that the neutralization of TNF but not FASL prevented tubular apoptosis and renal atrophy upon ischemia/reperfusion injury [706].

TRAIL blockade reportedly protects mice against renal damage after full-thickness scald burn, burn of all layers of the skin including epidermis and dermis [709], while TNF inhibition limited nephrotoxicity in mice treated with cisplatin [710], and acute tubulointerstitial nephritis in cancer patients administered with immune checkpoint inhibitors [711]. TNF neutralization also reduces tubulointerstitial fibrosis and renal injury in a mouse model of unilateral urethral obstruction [712, 713]. Contesting these findings, *Tnf*$^{-/-}$ mice showed increased fibrosis at later stages of ureteral obstruction [714]. This apparent discrepancy may reflect the distinct contribution of TNF-R1 and TNF-R2 signaling to different stages of renal fibrosis driven by urethral obstruction [715]. Conversely, experiments with *lpr*/*lpr* mice subjected to unilateral urethral ligation demonstrated a limited impact of FAS signaling to pathology [716]. The involvement of CASP8 in acute kidney injury is debated. While *Casp8* and *Casp3* deletion protected kidneys against damage induced by renal ischemia, increasing the survival of these mice [704, 717], such a nephroprotective effect was not observed after treatment with the broad-spectrum caspase inhibitor Z-VAD-FMK [718], potentially due to caspase inhibition promoting necroptosis after DR stimulation. In line with this notion, chemical inhibitors of receptor-interacting serine/threonine kinase 1 (RIPK1) as well as deletion of *Ripk3* exerted robust nephroprotection in mouse models of ischemia/reperfusion [718, 719]. However, combined deletion of *Casp8* and *Ripk3* did not extend the beneficial effects of the genetic loss of *Ripk3* and was associated with a more pronounced demise of tubular epithelial cells by intrinsic apoptosis [720].

DR activation has also been associated with chronic kidney disorders, but evidence involving CASP8-mediated apoptotic death is lacking. The conditional deletion of *Tnf* from macrophages [721], as well as the administration of TNF inhibitors [721–724], were reported to mediate beneficial effects in murine models of diabetic nephropathy. Conversely, the impact of TRAIL on this renal condition remains unclear [725–727], like that of TNF on polycystic kidney disease [728, 729]. As for glomerular inflammation, *gld*/*gld* mice (lacking FASL), as well as wild-type mice treated with TNF blockers, displayed reduced tissue damage during crescentic glomerulonephritis [730–733]. Indeed, balanced TNF-R1 and TNF-R2 signaling appeared to be critical for mice to resist experimentally induced glomerulonephritis [734–739]. This may explain apparently discrepant findings obtained with TNF-targeting measures.

Hepatic disorders

TNF-deficient mice, as well as rodents treated with TNF inhibitors, present with attenuated liver injury and apoptosis upon experimental ischemia/reperfusion, resulting in improved survival [740–742]. Of note, this beneficial effect cannot always be

recapitulated in *lpr*/*lpr* and *gld*/*gld* mice, lacking FAS or FASL, respectively [742]. Similarly, FAS inhibition, FASL neutralization, as well as administration of low-dose TNF (as a pre-conditioning maneuver) have been shown to protect the liver against ischemia/reperfusion injury by reducing hepatic cell apoptosis and/or inflammation [743–745]. Protection of the liver from ischemia/reperfusion has also been observed in mice deficient for TRAIL [746], as well as upon the conditional knockdown of CASP8 or CASP3, the combined deletion of *Casp8* and *Ripk3*, and the transgenic expression of a BID mutant that cannot be cleaved by CASP8 [283, 747, 748].

Lpr/*lpr* mice [749], *Tnfsf10*$^{-/-}$ mice (which lack TRAIL) [286], as well as animals exposed to TRAIL blockers [750], were protected against acetaminophen-induced liver damage, in line with the notion that FAS signaling and TRAIL receptor exacerbate acetaminophen hepatotoxicity [751]. Along similar lines, the hepatocyte-specific deletion of the gene encoding c-FLIP enhances liver injury and fibrosis induced by treatment with CCl_4 or thioacetamide [752]. Moreover, a large body of evidence demonstrates that the abrogation of extrinsic apoptosis protects mice against fulminant hepatitis and hemorrhage in the liver induced by FASL and TNF. This has been achieved with strategies including (but not limited to) FADD blockade [753, 754], *Casp8* [596, 755, 756] or *Fadd* [757] ablation, and *Casp8* silencing [758]. Accordingly, hepatocyte-specific deletion of *Cflar* augments liver damage in mouse model of acute hepatic injury [759]. Consistent with the notion that engagement of the intrinsic apoptotic pathway is critical for DR induced cell killing in the liver, *Bid*$^{-/-}$ mice resist fatal hepatitis induced by FAS or TNF [278, 282, 760, 761], a protection that is enhanced by the concomitant loss of BIM or CASP8 [282]. Conditional deletion of the genes encoding BAX, BAK1 or PUMA, as well as overexpression of BCL2, can also protect hepatocytes from FAS-induced killing [762–765]. The impact of loss of BAD on TNF-induced hepatitis is controversial [766, 767]. Mice deficient for CASP3 or treated with CASP3 or CASP8 inhibitors have also been shown to be less sensitive to FAS-induced hepatocyte apoptosis [768, 769]. Of note, some degree of functional compensation between caspases and alternative mechanisms of caspase activation have emerged from studies in hepatocytes responding to FAS agonists [770]. Finally, FAS and TNF-R1 signaling, as well as FADD activation, are involved in liver regeneration following partial hepatectomy [771–775]. In this context, the liver-specific deletion of *Casp8* resulted in dysregulated hepatocyte proliferation upon partial hepatectomy coupled to the initiation of an inflammatory response [776]. It has been suggested that CASP8 modulates liver regeneration by balancing NF-κB activation and necroptosis rather than by inducing apoptosis [777].

Gld/*gld* mice (lacking FASL) chronically fed with ethanol display reduced liver injury, steatosis and inflammation as compared to wild-type mice, but exhibit signs of incipient fibrosis [778]. Some degree of protection against alcohol-induced liver damage has also been documented in mice deficient for the apoptosis-inducing TRAIL receptor mTRAIL-R [779] or TNF-R1 (but not TNF-R2) [780], as well as in mice receiving a TRAIL-neutralizing antibody [781]. Accordingly, the hepatocyte-specific ablation of *Casp8* limited hepatic steatosis in murine models of ethanol administration, although it failed to prevent apoptotic RCD [782]. Conversely, apoptosis driven in hepatocytes by chronic ethanol exposure could be abolished by systemic inhibition of CASP3 with Ac-DEVD-FMK [783].

The liver-restricted overexpression of FAS induces hepatic steatosis and insulin resistance in mice subjected to a high-fat diet (HFD) [784]. In the same experimental setting, hepatoprotection was observed with the hepatocyte-specific ablation of *Fas* or germline deletion of *Bid* [784]. Moreover, *Tnf* deletion [785, 786], whole-body deletion of *Tnfrsf1a* (encoding TNF-R1) alone or in combination with the gene encoding TNF-R2 [787, 788] as well as inhibition of TNF [789–791] or TNF-R1 [792] significantly reduced hepatic steatosis, fibrosis, damage, and metabolic alterations in several diet-induced or genetic models of non-alcoholic fatty liver disease (NAFLD). In apparent contrast with these findings, the hepatocyte-specific deletion of *Tnfrsf1a* failed to protect mice from diet-driven NASH [793]. Moreover, *Tnfrsf1a* deletion accelerated the progression of steatosis to steatohepatitis in mice on a HFD [794]. Taken together, these findings underscore the pleiotropic and context-dependent effects of TNF/TNF-R signaling in NAFLD. The impact of TRAIL on NAFLD is also debated. Indeed, contrasting evidence from experiments with mice deficient for TRAIL or treated with recombinant TRAIL suggests either a detrimental or a beneficial role to TRAIL in NAFLD induced by HFD [795–797].

The absence of mTRAIL-R promoted hepatic inflammation and fibrosis in a genetic mouse model of cholestasis [798]. Similarly, *lpr*/*lpr* mice lacking FAS [799–801] as well as TNF-deficient [802, 803] and TRAIL-deficient [804, 805] mice displayed reduced hepatocyte apoptosis and fibrogenesis after experimental cholestasis induced by bile duct ligation. In line with these results, expression of a phosphorylated FADD mimicking mutant attenuated HFD-induced hepatomegaly and steatosis [806]. Experiments based on the hepatocyte-specific deletion of *Cflar* (encoding c-FLIP) or transgenic overexpression of c-FLIP revealed a role for this modulator of CASP8 activation as a suppressor of hepatic steatosis and inflammation induced by HFD [807]. Moreover, the hepatocyte-specific deletion of *Cflar* in mice resulted in enhanced cholestatic liver injury and inflammatory responses upon bile duct ligation [808]. Similarly, the hepatocyte-specific deletion of *Casp8* protected mice against liver injury in models of cholestatic hepatitis caused by the administration of 3,5-diethoxycarbonyl-1,4-dihydrocollidine [809], as well as in models of steatosis caused by the feeding of a methionine- and choline-deficient diet [810]. A comparable hepatoprotection against obstructive cholestasis has been documented in mice with hepatocyte-specific *Casp8* deletion [811]. Furthermore, liver parenchymal cell-specific ablation of the gene encoding FADD prevented RIPK1-dependent but not TNF-R1-, FAS-, and TRAIL-R-dependent hepatocyte apoptosis, chronic liver inflammation and hepato-carcinogenesis in mice with liver-specific deficiency in inhibitor of kappaB kinase gamma (IKBKG, best known as NEMO or IKKgamma) [812, 813]. Finally, decreased BID cleavage has been associated with attenuated liver injury in mouse models of chronic cholestasis [814].

Hematologic malignancies and solid cancers

Human patients with autoimmune lymphoproliferative syndrome (ALPS) caused by defects in FAS are known to show abnormally increased predisposition to lymphoma development [815]. Accordingly, FAS-deficient *lpr*/*lpr* mice develop a plasmacytoma-like disease in advanced age [816]. TRAIL also seems to exert a tumor suppressive function in lymphomagenesis. The ablation of the gene encoding mTRAIL-R accelerated the development of lymphoma in *Eμ-Myc* transgenic mice [817]. Moreover, deficiency in TRAIL (but not in mTRAIL-R) promoted the development of lymphoma and other tumors in mice with haploinsufficiency for *Trp53* [818, 819]. Interestingly, mice engineered to express exclusively either membrane-bound or secreted FASL showed an increased incidence of spontaneous tumor formation when expressing only soluble FASL, which is unable to induce FAS-mediated apoptosis but may exert pro-inflammatory effects [820].

The role of FAS and TRAIL-R in the development of colorectal cancer is controversial. For instance, the loss of FAS was reported to enhance *Apc* mutation-induced but not inflammation-induced intestinal tumorigenesis [821–823]. Along similar lines, while the ablation of *Tnfrsf10b* (leading to lack of mTRAIL-R) in mice did not impact tumorigenesis induced by *Apc* mutations [819], the administration of TRAIL suppressed tumorigenesis in a mouse model of colitis-associated colon cancer [824]. Despite some contention in this respect [825–828], TNF seems to contribute to

the development of colorectal cancer, although whether such effects depend on the apoptotic function of TNF needs to be formally established. The administration of TNF blockers [829–833] or ablation of *Tnf* [834] or *Tnfrsf1a* [834, 835] limits colorectal oncogenesis, as shown in animal models of colorectal cancer induced by colitis, chemicals, or mutations in *Apc*. Finally, loss of the dependence receptor DCC netrin 1 receptor (*Dcc*) accelerates cancer progression in a mouse model of *Apc* mutation-driven colorectal oncogenesis [836]. A tumor suppressor role in colorectal cancer has also been described for the dependence neurotrophic tyrosine kinase, receptor, type 3 (NTRK3, best known as TRKC) [837]. Of note, the association between gain of dependence receptors ligands (e.g., NTN1) with tumor progression [838], may make their targeting a promising anti-cancer approach [839].

With regard to other tumor types, both TNF-R1 and FAS display a pro-oncogenic role in hepatic and ovarian oncogenesis. Specifically, conditional deletion of *Fas* in hepatocytes delays carcinogen-driven hepatocarcinogenesis, while *Fas* ablation suppresses the development of ovarian tumors in phosphatase and tensin homolog (PTEN)-deficient mice bearing mutant Kirsten rat sarcoma viral oncogene (*Kras*) [840]. Likewise, TNF neutralization limits the onset of hepatic cancer driven by experimentally induced cholestatic hepatitis [841]. Consistent with these findings, *Casp8*$^{-/-}$ mice are protected against the development of inflammation-driven liver cancer [755]. Hyperactivation of CASP8 in the context of RIPK1 and TNF receptor-associated factor 2 (TRAF2) deficiency has indeed been implicated in the development of hepatocellular carcinoma [842], although such effects may be independent of apoptosis induction [843, 844]. In contrast, recent studies show a tumor-suppressive function of CASP8 in the liver and certain other tissues [845–848]. In particular, there is evidence of a role of CAPS8 in early tumorigenesis (but not tumor progression) exerted by modulating the DNA damage response [845] or the level of chromosomal instability (CIN) [846].

Consistent with a pro-tumorigenic effect of TNF, the ablation of *Tnf* or *Tnfrsf1a* or the blockade of TNF in mice conferred protection against carcinogen-induced skin oncogenesis [849–854]. In contrast, the impact of genetic and pharmacological inhibition of TNF in UVB-induced skin cancer is debated [855, 856]. Of note, the comparison between TNF-R1- *vs*. TNF-R2-deficient mice revealed a primary role of TNF-R1 in chemically induced skin oncogenesis [851]. Furthermore, TNF-R1 deficiency suppresses the development of skin cancer induced by NF-κB inhibition [857]. A similar role for TNF-R1 in supporting tumorigenesis was described in murine models of N-methyl-N-nitrosourea(NMU)/testosterone-induced prostate cancer [858] and methylcholanthrene (MCA)-induced fibrosarcoma [859]. As opposed to TNF-R1, TNF-R2 shows tumor-suppressive functions in mouse models of tumorigenesis, such as the development of fibrosarcoma triggered by MCA [859], and mammary oncogenesis induced by transgenic expression of wingless-type MMTV integration site family, member 1 (*Wnt1*) [860]. Moreover, the absence of TNF impairs tumor growth in HER2-driven mammary tumorigenesis in mice [861], and TNF neutralization suppresses chemically induced oral [862] and pulmonary [863] tumorigenesis. Conversely, TNF overexpression in the airway epithelium enhanced mutant *Kras*-driven lung oncogenesis [864].

Pre-clinical evidence points to some tumor type-specificity for the role of TRAIL and its receptor(s) in tumorigenesis. Transgenic expression of TRAIL in the skin delays chemically induced carcinogenesis [865]. This effect can be recapitulated in mice lacking TRADD [866] but, curiously, not in mTRAIL-R-deficient mice [867], with the latter actually showing enhanced lymph node involvement. In support of an anti-tumor function for the TRAIL/TRAIL-R system, TRAIL-deficient mice as well as mice treated with TRAIL blockers displayed increased susceptibility to MCA-induced fibrosarcoma [868, 869]. In a recent study, administration of recombinant TRAIL coupled to inhibition of cyclin-dependent kinase 9 (CDK9) was effective in a wide range of cancers [870]. Yet in contrast to this and in support of a tumor-supportive role of endogenous TRAIL, deficiency in mTRAIL-R limits tumor growth and improves survival in mouse models of mutant *Kras*-driven lung and pancreatic tumorigenesis [871]. Moreover, malignant cell-specific ablation of genes encoding mTRAIL-R or FADD reduced lung cancer growth and tumor-promoting inflammation [872], while systemic ablation of *Tnfsf10* (leading to lack of TRAIL) had no impact on HER2-driven mammary oncogenesis [818]. Interestingly, *KRAS* mutations have been shown to promote the switch of FAS and TRAIL receptors from a predominantly death-inducing into a metastasis promoting function [873]. Since TRAIL as well as FASL can trigger either apoptosis, necroptosis, inflammation or pro-invasive signaling, cancer-specific preferences for one or the other of these outputs are likely accounts for the apparently discrepant effects observed in various cancer models.

Autoimmune and inflammatory diseases

The interpretation of results on the impact of extrinsic apoptosis in the etiology of autoimmune and inflammatory disease should consider the fact that DR engagement can also result in the initiation of an inflammatory response not related to RCD (*see* Box 6 and Box 7), meaning that DR deregulation may lead to inflammatory diseases independently of the induction of extrinsic apoptosis. The notion that defects in DR signaling can cause autoimmune disease is supported by the observation that *lpr*/*lpr* as well as *gld*/*gld* mutant mice, deficient for FAS or FASL, respectively, as well as humans with defects in FAS develop an SLE-like autoimmune disease accompanied by lymphadenopathy, splenomegaly and hepatomegaly [874, 875]. A critical role for loss of CASP8-mediated apoptosis in this disease was demonstrated by the observation that a similar condition is seen in mice lacking *Casp8* and also *Ripk3* or *Mlkl* (to prevent necroptosis) [51, 52, 876]. However, the roles of DRs in autoimmune disease are complex. TRAIL/TRAIL-R signaling was reported to protect mice and rats against autoimmune encephalomyelitis [877–882], autoimmune arthritis [883–887] and type I diabetes [690, 883, 888–891]. Perhaps surprisingly, the presence of FAS and TNF-R1 is associated with the development of certain autoimmune conditions. Indeed, both *lpr*/*lpr* lacking FAS and *gld*/*gld* mice lacking FASL, as well as TNF-R1-deficient mice, appear to be protected against experimental encephalomyelitis [892–895]. Similar results were obtained in mice with *Tnf* deletion in monocytes and macrophages, but not in mice lacking TNF in microglial cells [896]. Protection against experimentally induced autoimmune conditions were also found in mice subjected to neutralization of TNF or TNF-R1 inhibition [897–904]. FAS-independent mechanisms also appear to support the pathogenesis of experimental autoimmune encephalomyelitis [892, 905], with some studies pointing to a protective role for FAS-induced RCD amongst lymphocytes in this disease model [906]. Moreover, FAS engagement was reported to differentially contribute to the initiation *vs*. the recovery from autoimmune encephalomyelitis [907, 908]. In particular, FASL expression in astrocytes appears to promote recovery from experimental autoimmune encephalomyelitis, as shown by persisting demyelination and paralysis of mice with an astrocyte restricted deletion of *Fasl* [907]. Finally, at least in some studies, *Tnf* deletion or TNF neutralization failed to attenuate the severity of autoimmune encephalomyelitis once the disease was established [909, 910].

Mice with defects in FASL or TNF signaling are protected against arthritis induced by immunization with xenogeneic type II collagen in complete Freund's adjuvant [911–914]. Similar protection was observed in mice transplanted with mesenchymal stem cells engineered to express TNF inhibitors [915]. In keeping with this evidence, the myeloid cell specific deletion of *Fas* or the administration of antibodies that target both TNF and chemokine (C-X-C motif) ligand 10 (CXCL10) resulted in accelerated disease

resolution in a model of rheumatoid arthritis induced by K/BxN serum transfer [916, 917]. Genetic loss of *Fas* or pharmacological inhibition of FAS conferred protection against autoimmune diabetes in specific animal models, including NOD mice [918–923]. However, whether the impact of FAS on the pathogenesis of autoimmune diabetes depends on its role in the death of pancreatic β-cell [918] or its role in inflammation (e.g., in the context of insulitis) remains a matter of debate [921]. Other studies found no role for FAS in diabetes [924–926]. TNF neutralization is effective only in a limited sub-group of patients with inflammatory bowel disease [927, 928]. This is in line with the finding that deletion of the gene encoding TNF-R1 exacerbated colitis in IL10-deficient mice [929]. A similar protection was ascribed to TRAIL/TRAIL-R signaling in a dextran sodium sulfate-induced model of colitis [930, 931]. Finally, it has been suggested that FASL and TNF signaling contribute to the pathogenesis of acute pancreatitis [932, 933]. A similar detrimental role has been proposed for TNF in autoimmune neuritis [934–936], although there is also some contention [937], as well as in spondylarthritis [938] and psoriasis [939]. Conversely, mTRAIL-R appears to mediate beneficial effects in autoimmune thyroiditis [940–944] At least in part, these findings reflect the pleiotropic effects of whole-body inhibition of DRs signaling, which concomitantly impacts both the target (i.e., parenchymal) and the perpetrator (i.e., immune cells) of damage.

Some experimental evidence links CASP8 activation to autoimmune and inflammatory disorders. In a recent study using a chemically-induced model of intestinal inflammation, the selective absence of CASP8 in intestinal epithelial cells decreased their survival, also resulting in gut barrier dysfunction and chronic inflammation [945]. Of note, in this setting, inflammation can occur via a mechanism independent of the induction of necroptosis (which is inhibited by CASP8) and involving the activation of RIPK1 and RNA sensor RIG-I (RIGI; best known as RIG-I) [946, 947]. Along similar lines, chronic proliferative dermatitis in mice deficient for components of the linear ubiquitin chain assembly complex (LUBAC) has been associated with an increased keratinocyte apoptosis mediated by the engagement of TNF-R1 and the activation of the RIPK1- and/or FADD-CASP8 cascade [948–952]. Importantly, in this mouse model of an inflammatory disease the relevant contributions of cell death versus inflammatory signalling from TNF-R1 were genetically dissected demonstrating that excess apoptosis/necroptosis drove different elements of the inflammatory response depending on the affected tissue. In a mouse model of autoimmune encephalomyelitis, the oligodendrocyte-specific deletion of *Fadd* reduced demyelination and this was accompanied by limited immune cell infiltration in the spinal cord [953]. Likewise, experimental autoimmune encephalomyelitis could be prevented by transgenic expression of FADD-DN (dominant negative form of FADD) in T cells [954], but it must be noted that this reflects the death of activated T cells [955]. Therefore, this protective effect is due to the removal of T cells that would cause tissue destruction. Activation of CASP8 was identified in the microglia of patients with multiple sclerosis [956]. Moreover, transgenic expression of FADD-DN or *Casp8* ablation in pancreatic β cells protects mice from autoimmune diabetes [957]. Finally, BID appears to be dispensable for the development of diabetes in NOD mice [958].

There are also contrasting observations on the impact of DR-induced apoptosis on the development and resolution of autoimmune rheumatoid arthritis. The absence of c-FLIP (due to *Cflar* deletion) increased disease severity but limited disease resolution in mice experiencing arthritis upon intraperitoneal injection of serum from K/BxN mice [959]. In the same model, deletion of *Casp8* in all myeloid cells enhanced disease resolution, while deletion of *Casp8* selectively in DCs accelerated disease onset [960]. Further experiments are required to unveil the reasons for such cell type specificity in the role of CASP8 in this and (perhaps) other autoimmune disorders.

Infectious diseases

Extrinsic apoptosis is reported to act as an anti-infective mechanism. FAS-deficient *lpr/lpr*, FASL-deficient *gld/gld* and *Bid*$^{-/-}$ mice exhibit delayed clearance of *Citrobacter rodentium* and increased intestinal pathology [961]. Confirming the importance of DR-induced apoptosis, this pathogen was shown to inhibit extrinsic apoptosis of infected enterocytes by expressing specific virulence proteins, such as the N-acetylglucosamine transferase NleB1, which prevents FADD-mediated recruitment and activation of CASP8 [962]. Along similar lines, *Fas*$^{-/-}$ mice have shorter lifespan than wild-type mice after challenge with *L. monocytogenes*, succumbing to neurolisteriosis. This was proposed to be promoted by an impaired loss of monocytes due to upregulated expression of c-FLIP by the bacterial protein InlB [963]. In support of this result, conditional deletion of *Cflar* in myeloid cells improved *L. monocytogenes* clearance and host survival [964]. FAS signaling also conferred protection from infection with (i) human herpes simplex virus 2 (HSV-2), as demonstrated by a decrease in the loss of monocyte and immune cell recruitment at the infection site in *Fas*$^{-/-}$ and *Fasl*$^{-/-}$ mice [965], and (ii) *C. rodentium* or lymphocytic choriomeningitis virus, as demonstrated by an increased neutrophil fraction in mice with conditional deletion of *Fas* in the myeloid compartment [966].

Supporting an anti-infection role of CASP8, mice lacking RIPK1 kinase activity fail to control systemic *Yersinia* infection, rapidly dying because of excess apoptosis driven by a kinase-independent function of RIPK1 [967, 968]. In line with this finding, *Ripk3*$^{-/-}$*Casp8*$^{-/-}$ (but not *Ripk3*$^{-/-}$) mice die from *Toxoplasma gondii* infection due to acute toxoplasmosis [969]. Moreover, the hepatocyte-specific deficiency for CASP8 facilitates mouse liver infection by *L. monocytogenes*, resulting in inflammation and development of necrotic lesions [776]. These results also suggest an interconnection of multiple RCD pathways in controlling infection. Indeed, the deletion of Z-DNA binding protein 1 (*Zbp1*), an essential cytoplasmic sensor of Influenza A virus (IAV) Z-RNA required for the activation of MLKL-dependent necroptosis, RIPK1/FADD-dependent apoptosis and NLR family, pyrin domain containing 3 (NLRP3) inflammasome-dependent pyroptosis, as well as co-deletion of the genes encoding MLKL and FADD, causes a defect in the control of IAV infection and lethal respiratory failure. These findings support an essential role of apoptosis, necroptosis and pyroptosis in IAV clearance [970–974]. Similarly, combined activation of apoptosis and other RCD pathways contribute to the response of mice to *Burkholderia thailandensis* infection [975]. Finally, pharmacological or tissue specific genetic deletion of baculoviral IAP repeat-containing 3 (*Birc3*, encoding cIAP1) and baculoviral IAP repeat-containing 2 (*Birc2*, encoding cIAP2) results in better control of hepatitis B virus and liver stage malaria parasites due to increased TNF induced death of infected cells [976–978].

Experimental evidence also suggests a detrimental role of extrinsic apoptosis during some infections. Mice deficient for both TNF-R1 and TNF-R2 display decreased sensitivity to LPS, suggesting a critical role for TNF in tissue injury during gram-negative bacterial infection [979]. Along similar lines, TNF-R1-deficient mice are more resistant than wild-type mice to the cytopathic effects of TNF during Sindbis virus infection, as evidenced by delayed paralysis and reduced mortality [980]. Moreover, ablation of *Ripk1* protected mice from acute liver injury after infection with *L. monocytogenes* [981], while knockout of *Fas* or *Fasl* reduced the effect of toxin A-induced enteritis in mice infected with *Clostridium difficile*, which has been attributed to a reduction in enterocyte loss [982]. Additionally, the infectious spleen and kidney necrosis virus (ISKNV) induced

tissue damage in zebrafish by activation of DR-induced apoptosis by a viral protein encoding a TRADD interactor [983]. Of note, in this study, the absence of CASP8 protected zebrafish from ISKNV infection. Finally, *Ripk3*$^{-/-}$*Casp8*$^{-/-}$ mice exhibit high levels of protection from LPS-induced septic shock [984] or a lethal cytokine shock and tissue damage driven by TNF and interferon gamma (IFNG), mirroring that of SARS-CoV-2 [985]. This suggests that the several types of RCD can mediate infection-associated pathogenesis, as demonstrated for infection with *Salmonella* [50].

Other diseases

TNF is reported to impair myogenesis in a mouse model of skeletal muscle regeneration after hindlimb immobilization (hindlimb suspension) [986]. Moreover, silencing of TRAIL improved muscle regeneration in mice with acute skeletal muscle injury due to local injection of $BaCl_2$ [987]. An inhibitory role in myogenesis has also been ascribed to FADD, at least in response to freezing-induced muscle injury [988]. In apparent contrast with this result, combined deletion of the genes encoding TNF-R1 and TNF-R2 limited skeletal muscle regeneration after cardiotoxin-induced injury [989, 990], suggesting the relevance of a balance between TNF-R1 and TNF-R2 signaling in this model. TRAIL neutralization increased muscular strength in a mouse model of Duchenne muscular dystrophy [991], while other studies associated TRAIL and FASL signaling to myositis [992, 993].

Activation of DRs has also been implicated in the pathogenesis of acute lung injury. *Fas* silencing as well as TNF neutralization protected mice from lung injury induced by ischemia-reperfusion [994, 995]. Similarly, deletion of *Tnfrsf1a* (encoding TNF-R1) or pharmacological inhibition of TNF-R1 or CASP8 attenuated pulmonary edema formation and improved alveolar epithelial function in a murine model of acute lung injury induced by acid inhalation [996, 997]. A similar protective effect was provided by pharmacological inhibition or genetic deletion of FASL or TNF in a LPS-induced mouse model of acute lung injury [998–1004]. However, in one study FAS signaling was shown to contribute to the resolution of acute lung injury by depleting macrophages [1005]. Using distinct mouse models of acute lung damage following sepsis, it has been shown that abrogation of FAS and TNF-R1 signaling decreases pulmonary apoptosis and ameliorates pathology, with a survival benefit in some settings [1006–1012]. Hyperoxia-induced lung injury and bleomycin-induced pulmonary fibrosis, a model for cancer therapy-induced lung injury, are also impacted by DR signaling. Thus, FAS and TNF deficiency exacerbated hyperoxia-induced lung injury and/or inflammation in newborn mice [1013, 1014]. In contrast, TNF inhibition conferred protection against hyperoxia-induced lung damage in a murine model [1015–1017]. Moreover, the absence of TNF-R1 (but not TNF-R2) improved survival in mice subjected to excessive oxygen supply, and this was not linked to decreasing inflammation [1018]. In support of these results, specific ablation of *Fas* in murine fibroblasts or T cells exacerbates pulmonary fibrosis induced by bleomycin [1019, 1020]. However, the level of bleomycin-induced pulmonary fibrosis is reduced in FAS-deficient *lpr*/*lpr* or FASL-deficient *gld*/*gld* mice [1021], but remains unchanged in mice treated with FAS-neutralizing agents [1022]. Likewise, contrasting findings support or refute a role for TNF [1023–1025] and TRAIL [1026, 1027] in the onset and resolution of pulmonary fibrosis after administration of bleomycin. TNF neutralization has been reported to attenuate and enhance interstitial pulmonary fibrosis induced by nitrogen mustard [1028] or rituximab [1029]. Finally, FASL, TNF and/or TRAIL have been implicated in infectious or non-infectious lung disorders, including (but not limited to) infection with respiratory syncytial virus (RSV) [1030–1036], adenovirus type 1 respiratory disease [1037, 1038], allergic reaction and asthma [1039–1050] and idiopathic pneumonia syndrome [1051], as well as to chronic lung diseases (e.g., chronic obstructive pulmonary disease) [864, 1052, 1053].

The studies discussed above illustrate that DR-induced apoptosis is at the heart of many disorders either promoting recovery or exacerbating disease. The active involvement in disease severity and progression makes this pathway a potentially tractable target for therapeutic interventions in a wide range of diseases, typically those with an inflammatory component. However, this effect may be linked to the role of DR signaling in other RCD pathways and in inflammation. Moreover, there is little consensus on the roles of FASL, TNF and/or TRAIL in these pathologies, highlighting a high complexity of the system that calls for further investigation.

CONCLUDING REMARKS

Abundant preclinical evidence demonstrates that the intrinsic and the extrinsic pathways of apoptosis not only contribute to adult tissue homeostasis and, in the case of the intrinsic pathway, to embryonic development – the implication of CASP8 in development is mainly linked to its role as necroptosis inhibitor (*see* Box 6 and Box 7) - but also contribute to the pathogenesis of multiple diseases, including various cardiovascular, hepatic, neurological and renal disorders as well as multiple infectious, autoimmune, inflammatory and oncological conditions. However, despite great potential as targets for therapeutic interventions and a considerable research effort dedicated to developing effective approaches, the success of intrinsic or extrinsic apoptosis-targeting agents in clinical settings is so far limited to BH3 mimetic drugs, SMAC mimetics, caspase inhibitors as well as activators or inhibitors of DR signaling, with only one compound, the BCL2 inhibitor venetoclax being approved for the treatment of patients with CLL or AML.

Rather than mitigating the enthusiasm about the clinical potential of modulators of apoptosis, this challenge suggests the need for a substantial change in the experimental design and re-interpretation of results, at different levels (Fig. 1). One major issue is that studies evaluating the impact of apoptotic cell death on disease have not always addressed the connections between the core components of the intrinsic and extrinsic apoptotic machinery or their potential interaction and functional overlap with other RCD pathways. Also, the potential activation of alternative RCD modalities as a mechanism to compensate for the inhibition of apoptotic RCD has not always been explored as an approach to achieve superior outcomes. The importance of independent replication of findings that suggest success from targeting a pathway in the treatment of a disease cannot be emphasized enough. Only then can the costly process of clinical translation be approached with confidence and with an increased chance of success. For example, the findings that overexpression of BCL2 or its pro-survival relatives can promote tumorigenesis and can render malignant cells resistant to diverse anti-cancer therapeutics had been reproduced hundreds of times before the initiation of BH3 mimetic development. This is not yet the case for many of the other studies discussed herein, as best demonstrated by the fact that certain experiments have provided diametrically opposing results in different laboratories. These questions must be resolved before considering novel drug development programs around apoptotic RCD.

Moreover, some regulators of apoptosis and signaling cascades have been reported to exert a variety of functions beyond cell death control, including (but not limited to) inflammation (e.g., multiple caspases and IAPs), cell differentiation (e.g., pro-and anti-apoptotic BCL2 proteins), cell proliferation and survival (e.g., DR engagement). The relevance of these functions is often dependent on cell/tissue type (as it is related to variable expression levels and activation status of other regulators of RCD) and the intensity and duration of the initiating stimulus (as they can direct to a distinct biological outcome, as exemplified by DR ligation). Of note, some

of these cell death unrelated functions of bona fide cell death regulators are highly controversial and much more work must be done to verify or discard them. On the one hand, this pleiotropy may result in a variable (even including an antagonistic protective vs. promoting) impact of apoptosis on distinct human diseases, which may also explain the considerable degree of context-dependency observed during its experimental modulation. On the other hand, the pathogenic effect of core components of the apoptotic machinery is often mediated by apoptosis-unrelated functions including inflammation, which may point to unexplored targets for the development of new therapeutic approaches.

In our opinion, investigating the molecular cascade of apoptotic cell death in the context of the functional interconnection between apoptotic and non-apoptotic RCD pathways, for instance by interrupting some of the molecular connections between different RCD signaling cascades, may instigate new advances, ultimately leading to the development of novel, clinically-viable apoptosis modulators for use in multiple disease settings.

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L. Galluzzi and I. Vitale conceived the review and wrote the first version of the manuscript with constructive input from all authors. E. Guilbaud, C. Galassi and G. Manic prepared display items under the supervision of L. Galluzzi and I. Vitale. I. Vitale, F. Pietrocola and L. Galluzzi addressed requests from the Reviewers and Editors of *Cell Death and Differentiation*. All authors approved the final version of the article and figures.

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COMPETING INTERESTS

All Editorial Board Members of Cell Death Differentiation, Cell Death Disease, or Cell Death Discovery are included among the authors. A. Degterev is shareholder in Denali Therapeutics. A. D. Garg has received renumeration, honorarium or consultancy fees from Boehringer Ingelheim, Miltenyi Biotec or IsoPlexis. A. Strasser and P. E. Czabotar (PEC) are employees of the Walter and Eliza Hall Institute, which has an agreement with Genentech and AbbVie and receives milestone and royalty payments related to venetoclax. Employees of the Walter and Eliza Hall Institute may be eligible for financial benefits related to these payments. PEC receives such a financial benefit as a result of previous research related to venetoclax. B. De Strooper (BDS) has no COI with the content of this paper. Possible perceived COI: BDS is or has been a consultant for Eli Lilly, Biogen, Janssen Pharmaceutica, Eisai, AbbVie and other companies. BDS is also a scientific founder of Augustine Therapeutics and a scientific founder and stockholder of Muna therapeutics. B. R. Stockwell is an inventor on patents and patent applications involving small molecule drug discovery, ferroptosis, and the antibody 3F3-FMA; co-founded and serves as a consultant to Exarta Therapeutics, and ProJenX Inc.; holds equity in Sonata Therapeutics, and serves as a consultant to Weatherwax Biotechnologies Corporation and Akin Gump Strauss Hauer & Feld LLP, and receives research funding from Sumitomo Dainippon Pharma Oncology. C. M. Troy has the following patent applications US20200164026, US20190142915, US20150165061, US20140024597. US2020058683, WO2018013519, WO/2020/223212. D. C. Rubinsztein serves as a consultant for Alladdin Healthcare Technologies Ltd., Mindrank AI, Nido Biosciences, Drishti Discoveries and PAQ Therapeutics. D. J. Murphy receives funding from the Merck Group (Darmstadt, Germany) & Puma Biotechnology (Los Angeles, CA, USA). D. Ofengeim is employed at SANOFI. JTO serves as a consultant for Anji Pharmaceuticals. J. T. Opferman receives research funding from AbbVie. D. W. Andrews receives funding for research in apoptosis from Amylyx. F Di Virgilio is Member of the Scientific Advisory Board (SAB) of Biosceptre Ltd (UK), and a consultant with Axxam SpA (Italy). F. Madeo has financial interest in TLL, The Longevity Labs and Samsara Therapeutics. P. Mehlen is founder and shareholder of NETRIS Pharma. G. A. Calin is the scientific founder of Ithax Pharmaceuticals. G. L. Kelly (GLK) is an employee of the Walter and Eliza Hall Institute which receives milestone and royalty payments related to venetoclax. GLK has received research funding from Servier. J. R. Cubillos-Ruiz is a scientific consultant for NextRNA Therapeutics, Inc. and Autoimmunity Biologic Solutions, Inc. K. Rajalingam is a founder and MD of KH Biotec GmbH. CVR is a scientific founder and member of the Scientific Advisory Board (SAB) of Surface Oncology, a member of Janssen Immunology SAB, and a consultant for the Roche Immunology Incubator. C. V. Rothlin has received grant support from Mirati Therapeutics. K. Schroder is a co-inventor on patent applications for NLRP3 inhibitors which have been licensed to Inflazome Ltd, a company headquartered in Dublin, Ireland. Inflazome is developing drugs that target the NLRP3 inflammasome to address unmet clinical needs in inflammatory disease. K. Schroder served on the Scientific Advisory Board of Inflazome in 2016–2017, and serves as a consultant to Quench Bio, USA and Novartis, Switzerland. L. Altucci receives funding for research from Merck and has shares in Epic SRL and CIRCE SRL. B. Joseph is cofounder of CERVO Therapeutics AB. M. Carbone received donations from the UH Foundation through donations from: the Riviera United-4-a Cure, the Melohn Family Endowment, the Honeywell International Inc., the Germaine Hope Brennan Foundation, and the Maurice and Joanna Sullivan Family Foundation. M. Carbone has a patent issued for BAP1. M. Carbone and two patents issued for HMGB1. M. Carbone is a board-certified pathologist who provides consultation for pleural pathology, including medical-legal. M. Conrad is a co-founder and shareholder of ROSCUE Therapeutics GmbH. M. Karin received support from Jansen Pharmaceuticals, Merck and Gossamer Bioscience. M. Karin is founder and member of

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ADDITIONAL INFORMATION

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