Cell Death and Differentiation (2008) 15, 1533–1541

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Review

The extrinsic cell death pathway and the *élan mortel*

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Early in the exploration of the chemical nature of life, it was widely believed that the molecules of living organisms, by their very nature, differ from those of inorganic material molecules and possess a vital force ('*élan vital*'). Similarly, early scientific thinking on the subject of cell death and its induction by cytotoxic cells of the immune system was pervaded by a sense that the molecules mediating these functions possess intrinsic deadly activity and are dedicated exclusively to death-related tasks. This impression was also reflected in the initial notions of the mode of action of intracellular proteins that signal for death. It is now gradually becoming clear, however, that proteins participating in death induction also have functions unrelated to death. Nevertheless, as exemplified by studies of the function of caspase-8 (an enzyme that signals both for activation of the extrinsic cell-death pathway and for non-death-related effects), analysis of the mechanistic basis for such heterogeneity might allow identification of distinct structural determinants in the proteins participating in death induction that do bear death specificity.
Cell Death and Differentiation (2008) **15,** 1533–1541; doi:10.1038/cdd.2008.41

Similar to other aspects of human progress, the evolution of scientific thinking displays repetitive patterns dictated by the basic features of our ways of thinking. Not surprisingly, therefore, the way in which the conception of cell death has developed in recent years bears a striking resemblance to the way the concepts of life evolved in earlier centuries.

Arguably, the most hotly debated issue in the history of the exploration of life mechanisms is the question of what distinguishes life from death. The notion at the core of this debate was 'vitalism' or, as it was termed at the beginning of the 20th century, *élan vital* (vital impetus[1]). This concept, which appeared to be supported by the evidence that non-living matter cannot spontaneously generate living matter,[2] implied that the molecules of living organisms possess certain unique feature(s) not found in inanimate materials, and that those features underlie life. That notion was refuted long ago (starting with the first successful synthesis of an organic molecule (urea) from inorganic reagents[3]). Nevertheless, its basic underlying cause – our inclination to conceive of complex systems in terms of elements with single, distinct functions – continues to influence our initial ideas of the mechanisms for other aspects of biological systems. Scientists keep on searching for biological molecules, or at least structures within them, that have a single, distinctive function.

The impact of this inclination on the initial conceptions of the molecular basis of cell death was very similar to its effect on conceptions of the mechanisms of life. Scientists were initially inclined to view the molecules participating in cell death as having '*élan mortel*,' with death induction as their intrinsic, distinctive and only function. As with the study of life and the notion of a 'vital impetus,' this naive point of view is being gradually disproved. There is probably no single cellular constituent of the cell-death process that does not also have some life-related functions.

The evolution of concepts relating to the molecular basis of programmed death will be traced in this essay by an account of its occurrence in the study of the extrinsic cell-death pathway, with examples from research carried out in our laboratory.

Death-specific Ligands?

As we know now, the proteins triggering the extrinsic cell-death pathway are ligands of the tumor necrosis factor (TNF) family, acting mainly in the form of type II membrane proteins anchored to cells of the immune system. Originally, however, these proteins were identified in the sera of animals and in the crude 'soups' of soluble proteins generated by activated leukocytes.[4–7] Those soups and sera were found to affect cells in a variety of ways, and during the time span of several decades between the initial detection of the various regulatory activities in these preparations and the eventual isolation of their mediators, there was no way to assess the heterogeneity of the compounds mediating these activities. Neither was there any way of knowing the molecular features allowing those compounds to mediate their cellular effects. However, as evidenced by the names that were given to the cell-killing and tissue-destructive activities in the protein soups (Figure 1), the inclination was to believe that the active compounds possessed some intrinsic damaging activity. The discovery that the damage to tissues by pathogens such as bacteria is indeed inflicted partly by 'toxins,'[8] proteins with

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Keywords: apoptosis; caspase-8; lymphotoxin; signaling; TNF
Abbreviations: BAC, bacterial artificial chromosome; CHI, cycloheximide; CTX, cytotoxin; LPS, lipopolysaccharide; LT, lymphotoxin; TNF, tumor necrosis factor
Received 31.1.08; revised 10.3.08; accepted 10.3.08; Edited by G Melino

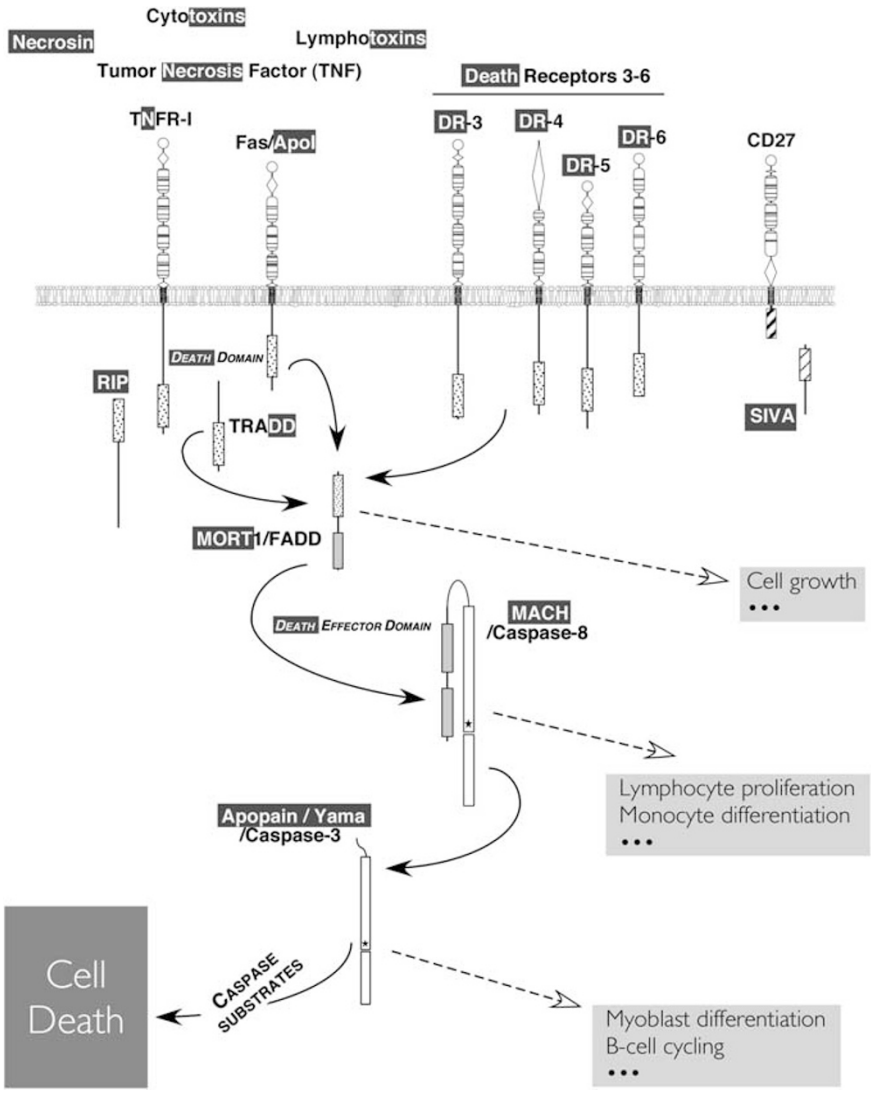

Figure 1 Diagrammatic presentation of the extrinsic pathway. 'Death-dedicated' names of proteins are highlighted

enzymatic or structural features that interfere with vital cellular functions had a profound influence on both the conceptual and the experimental advancement in modern pathology and immunology. The antibodies, for example, which were initially developed by immunization with such toxins,[9] were described as agents that serve to protect the body against the toxin-induced damage and were accordingly called 'antitoxins.' The influence is also evident from the term 'lymphotoxins' (LTs)[5,6] given to the hypothetical factors mediating the cell-killing activity found to be generated by leukocytes. It was reflected also in other names given to those factors, such as 'necrosin,'[4,10] TNF[7] or 'cytotoxins' (CTX)[11] (Figure 1). Likewise, the hypothetical compounds mediating various other functions in the crude cytokine soups were given names such as 'pyrexine,' 'leuotaxine'[4] or 'macrophage migration inhibitory factor,'[12,13] reflecting the feeling that, as with the pathogenic toxins, these various other activities correspond to the dedicated roles of their mediators.

Similar to the terms coined for the death-inducing mediators, speculations about their mechanisms of action were also dominated by the *élan mortel* notion. A study published in 1976 raised the possibility that 'LT, as measured biologically by lysis of mouse L cells, and ribonuclease activity are the same molecule'[14] and a comprehensive review of the state of knowledge of these factors in 1981 posited that 'the protein component of TNF serves as a specific carrier for a phospholipid toxin' or, alternatively, that 'TNF exists as a zymogen in the more traditional sense…perhaps pro-enzyme'.[15]

Notably, at a very early stage in the development of this field, before any of the death-mediating proteins were isolated, several studies were already pointing to correlations between generation patterns as well as between fractionation patterns of cell-death-inducing and various non-deadly activities of the crude cytokine soups or sera (e.g., Hoffmann *et al*.[16] and Wallach;[17] Figure 2). Those observations raised suggestions that the proteins mediating cell death might not be dedicated exclusively to death and that they might even have the ability to restrict their own cytotoxicity by inducing cellular resistance to death.[17] Accordingly, along with the

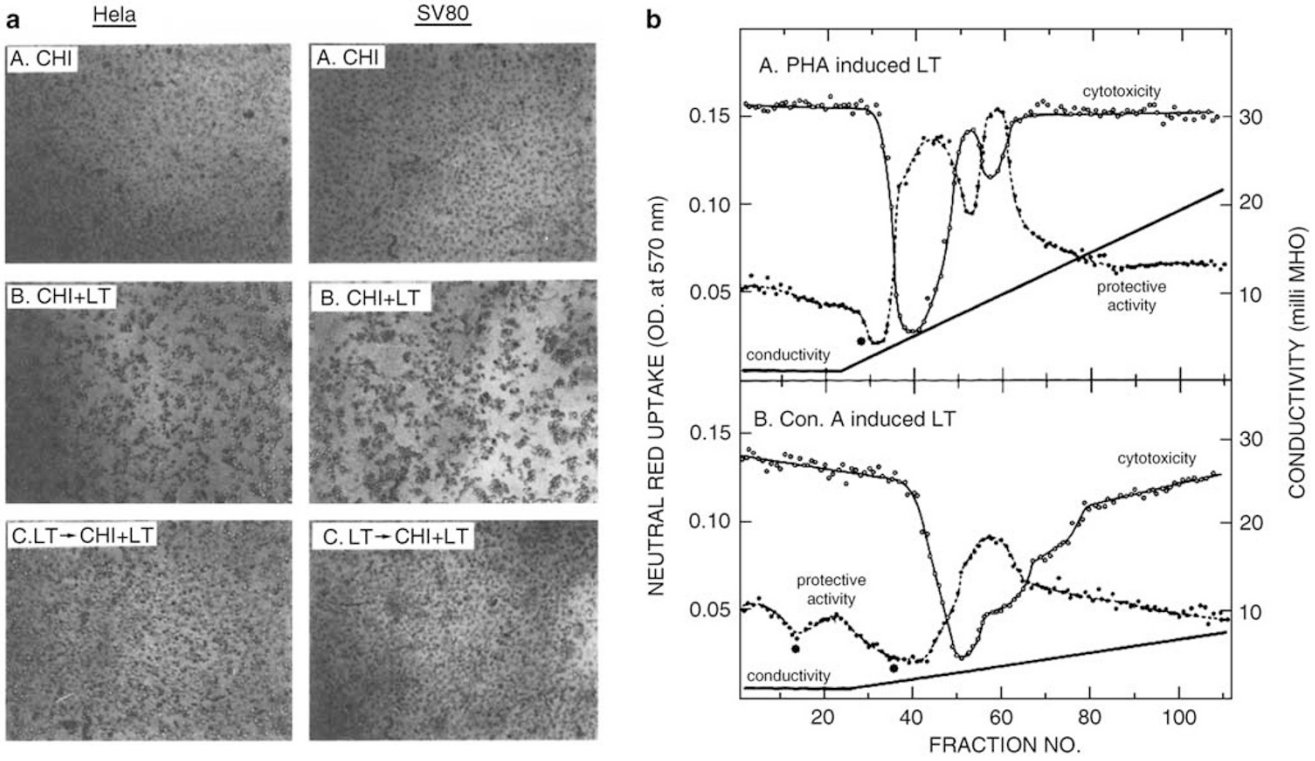

Figure 2 The 'death ligands' can have other activities as well: ability to induce in cells resistance to their own cytotoxicity. Besides cytotoxic activity, crude cytokine preparations also possess the ability to induce in cells resistance to their own cytotoxicity, and these two opposing activities co-fractionate. (**a**) Cytotoxic and protective activities. Crude preparations of cytokines (called LT in this study), produced in human peripheral blood mononuclear cells in response to stimulation with phytohemagglutinin, are shown to induce death in human HeLa and SV80 cells when protein synthesis is blocked by concomitant treatment with the protein-synthesis inhibitor cycloheximide (CHI, top and middle panels). However, when the same cytokine preparations are applied to these cells under conditions in which protein synthesis is allowed (i.e., in the absence of CHI), they induce resistance to death, as indicated by the decreased ability of these preparations to induce death when applied again in the presence of CHI (bottom panels). (**b**) The cytotoxic and protective activities co-fractionate, suggesting that they might be mediated by the same cytokine. Preparations of lymphokines, induced as in (**a**) (top) or produced by the stimulation of leukocytes with concanavalin A (bottom), were fractionated on columns of DEAE-cellulose, and the ability of the proteins in each fraction to cause death of HeLa cells in the presence of CHI, or to induce resistance to death in the absence of CHI, was assessed as described in (**a**) (from Wallach[17])

suggestion that those proteins had intrinsic cell-killing activity, a few scientists did suggest that they might act as hormones or cytokines by binding to specific cellular receptors.[15,18] Naturally, among the first things to be examined once these proteins were isolated was whether the cell-killing components of the crude soup/sera, besides causing cell death and tissue damage, also had other activities (Hahn *et al*.,[11] Beutler *et al*.[19] and Sugarman *et al*.[20] Figure 3). However, even after it was widely acknowledged that these proteins do also possess non-cytotoxic activities and that when they kill cells they do so not by any intrinsic toxic function but rather by triggering aggregation of specific cell-surface receptors to which they bind (Engelmann *et al*.[21] and Dhein *et al*.[22] Figure 4), the inclination to believe that these molecules possess *élan mortel* was not fully abandoned. A potentially deadly intrinsic activity of TNF and LT – an ability to form pores in biomembranes under certain conditions – was still found of interest as late as 11 years after these proteins were first isolated.[23,24]

Death-Specific Signaling Proteins?

Not only the extracellular ligands themselves but also their receptors, as well as certain intracellular signaling proteins and distinct regions within the receptors and the signaling proteins, were initially viewed as having some intrinsic cell-killing activity or as triggering such activity in other components of the cells. That conception was mainly inspired by the marked cytotoxic effect observed when those proteins were overexpressed. This, too, was reflected in the 'death-specific' names given to some of these receptors and signaling proteins and to those motifs within them that demonstrated cytotoxic effects (Figure 1). Receptors with pronounced cytotoxic activity are to this day often called 'death receptors (DRs)'. One of them was initially called Apo1,[25] hinting at its ability to trigger apoptosis. (It is now more widely called Fas[26]). Four others were called 'DR' 3, 4, 5 and 6 (see http://www.genenames.org/genefamily/tnftop.html). Two adapter proteins that bind to the receptors were called MORT1[27] (later called FADD[28]), and RIP (for 'receptor-interacting protein', yet with obvious ominous overtones[29]). Another protein that reportedly binds to receptors of the TNF family and, when overexpressed, causes death of cells was dubbed 'SIVA', recalling the Hindu deity of destruction.[30] One of the names given to the proximal signaling enzyme (now called caspase-8) in the extrinsic pathway was 'MACH' (MORT1-associated CED homologue, also meaning 'impoverished' in Hebrew[31,32]), whereas caspase-3, the main caspase acting

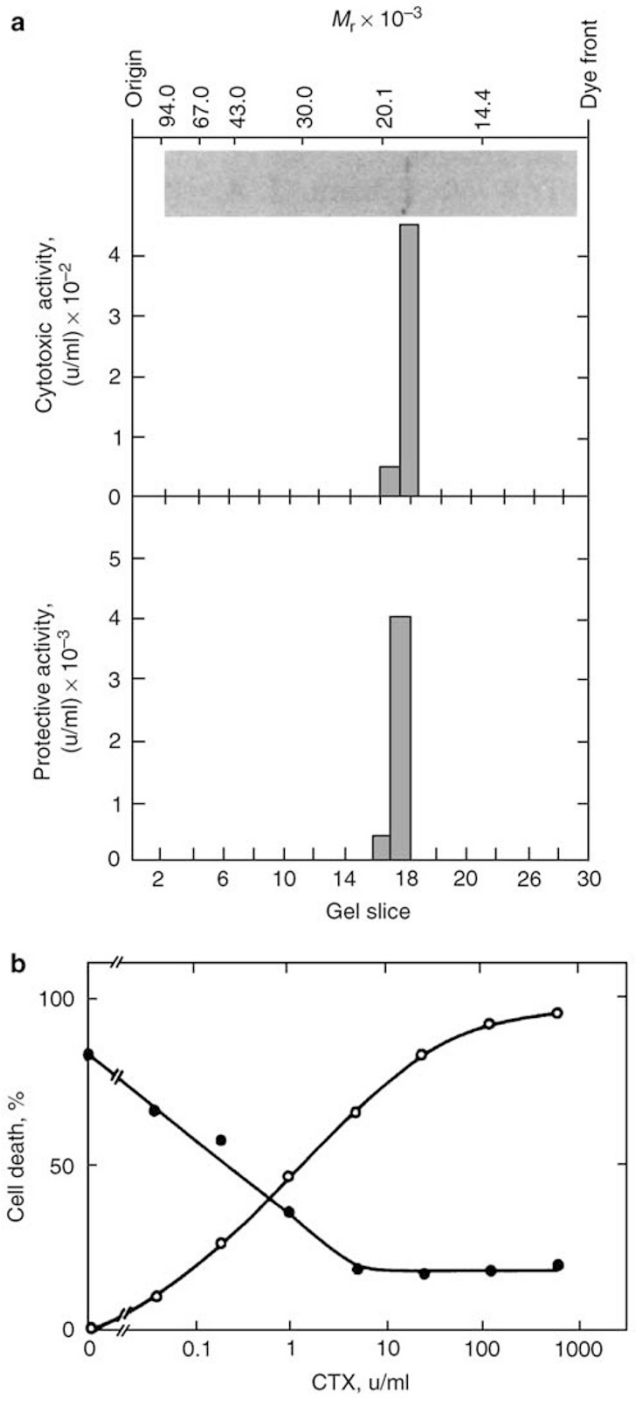

Figure 3 The 'death ligands' can have other activities as well: the same protein can induce both cell death and cellular resistance to death. TNF (still called CTX in this study) was isolated from crude leukocyte-produced cytokine preparations by the use of a monoclonal antibody raised against these preparations and then electrophoresed in SDS-PAGE gel. The gel was sliced (**a**) and the cytotoxic and protective activities in each slice were titrated, as shown in (**b**), by the tests illustrated in Figure 2a (○, cytotoxic; ● protective effects; from Hahn *et al*.[11])

downstream of caspase-8, was called 'Apopain'[33] and 'Yama'[34] (the latter being one of the names of the Hindu lord of death). The motifs corresponding to regions within the receptors and the proximal signaling proteins whose overexpression resulted in cell death were called the 'death domain' and the 'death effector domain.'

We now know that the marked cytotoxic effect of overexpression of at least some of these proteins is indeed due to a genuine role in activation of signaling for death. We also know that this pronounced effect reflects both their action as part of a cascade, in which individual elements become activated upon their imposed juxtaposition, and the fact that their activation tends to be triggered merely upon their overexpression (that imposes such juxtaposition artificially). However, the deadly consequence of such overexpression hindered some other signaling activities possessed by each of these proteins. Thus, for example, all of the 'DRs' also have other non-deadly activities (see, e.g., Engelmann *et al*.[21] Peter *et al*.[35]). FADD/MORT1, while indeed playing a crucial role in death induction by receptors of the TNF/NGF family, also contributes to cell-cycle regulation independently of those receptors.[36] The most solidly established functional role of RIP is not induction of death but rather signaling for NF-κB activation, which in various cells enhances cell resistance to death.[37]

Although several other effector mechanisms for death induction by ligands of the TNF family have been suggested, the only one for which there is solid evidence and fairly detailed molecular understanding is the activation of caspase cysteine proteases by the FADD/MORT1–caspase-8 axis. Of the various enzymatic activities known to mediate signaling, protease activity is the one that we can most readily conceive of as being associated with death. More than any other known kind of signaling activity, proteases appear to have the capacity to harm vital functions by destroying the molecules required for them. Besides, proteolysis is the only enzymatic signaling activity whose immediate impact, similar to death, is irreversible. Whereas, for example, the effects of protein kinases can be reversed by phosphatases, and the generation of cyclic nucleotides can be reversed by phosphodiesterases, there is no protein ligase assigned to reverse the cleavage of linear polypeptide chains by proteases. The natural inclination to see deadly potential in the chemical nature of biological molecules that mediate death might have therefore appeared to be met in the identification of caspases as the crucial enzymes in signaling for death.

Ever since the caspases were first identified, it was recognized that some of the members of this protease family serve other death-unrelated functions. Caspase 1, the first known human member of this family, contributes very little to lethality and serves mainly to process precursor proteins of inflammatory cytokines. The initial feeling, however, was that those members of the caspase family that do participate in death induction are activated only for that purpose. It is no wonder, then, that the term coined for the subgroup of caspases that are most intimately associated with the apoptotic process was 'executioner caspases.' It is becoming increasingly evident, however, that the initial feeling is not borne out by the facts. Whereas cleavage of certain caspase targets, for example the I-CAD/CAD complex,[38] might well operate exclusively to cause death, none of the caspases themselves are dedicated only to death. Rather, depending on the identity of their activating signal and on the cellular set-up in which this activation occurs, those same caspases that signal for death can instead serve non-deadly functions.[39]

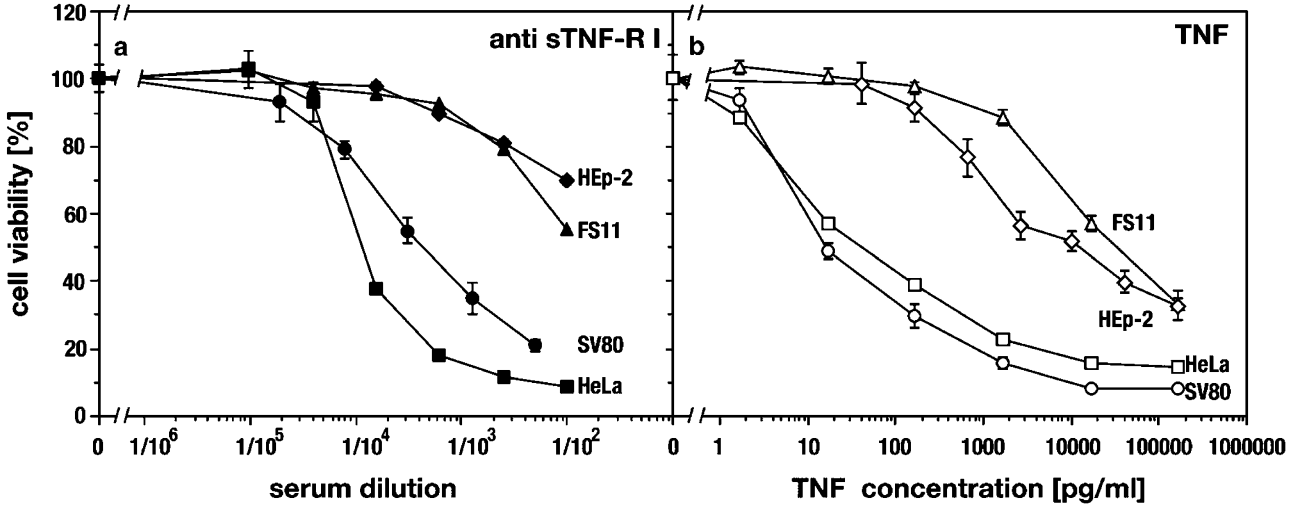

Figure 4 The cytotoxic effect mediated by TNF can be exerted in the absence of TNF. Cytotoxic effects of antibodies raised against the extracellular domain of the p55 TNF receptor (**a**), and of TNF (**b**), on SV80 (circles), HeLa (rectangles), FS11 (triangles) and HEp-2 (diamonds) cells (from Engelmann *et al.*[21])

From the emerging picture, it is becoming clear that in the signaling pathway for induction of death by ligands of the TNF family, not a single component serves that purpose only.

Such is also the case with proteins that contribute to other cell-death processes. Best known is the duality of function of cytochrome *c* as well as of several other mitochondrial proteins, such as HtrA2/Omi and AIF. All of these serve vital functions within the mitochondria; yet, once released to the cytoplasm, they act as major initiators of death events.[40–42] Exploration of the mechanisms underlying this duality disclosed distinct 'death-specific' and 'life-specific' structural determinants in these mitochondrial proteins. Cytochrome *c*, for example, known since 1884 for heme binding,[43] which endows this protein with redox capacity, crucially depends on this capacity for its function as a mediator of electron transfer between respiratory complexes within the mitochondria.[44] Once released from the mitochondria, however, it activates caspase-9 (by allosterically modulating the interactive properties of the caspase-9-binding protein Apaf1) and thus initiates the intrinsic cell-death pathway[40] in a way that does not depend on its redox capacity.[45] Conversely, certain features of the amino-acid sequence of cytochrome *c* that are crucial for Apaf1 binding have little bearing on the contribution of cytochrome *c* to oxidative phosphorylation (see, e.g., Kluck *et al.*[46]).

Death Determinants of Non-Death-Specific Proteins of the Extrinsic Pathway

In view of the likelihood that none of the components of the extrinsic cell-death pathway are fully dedicated to death, it becomes important to identify, also in these proteins, the molecular determinants that dictate whether in a given situation their activation will result in death. We already know quite a lot about the identity of those determinants with respect to the function of the proximal components of the extrinsic cell-death pathway. One example of a factor that is likely to determine, at this mechanistic level, the extent to which TNF induces cell death or a non-deadly function is the effectiveness of its shedding, which is mediated mainly by the metalloproteinase TACE.[47] In the soluble form that its shedding generates, TNF mainly activates the p55 TNF receptor, whereas cell-bound TNF molecules effectively stimulate the p75 TNF receptor as well.[48] Triggering of the p55 receptor can, in addition to signaling for the extrinsic cell-death pathway, effectively activate anti-death mechanisms, mainly through NF-κB activation. When the p75 receptor is triggered in addition to the p55 receptor, however, the latter's signaling for anti-death mechanisms is suppressed (apparently owing to recruitment and downregulated expression of the adapter protein TRAF2,[49] as well as of cIAP1 and cIAP2[50,51]). Therefore, in cells that express both p55 and p75 TNF receptors, the arrest of TNF shedding in immune cells that interact with them is likely to shift the functional response to TNF from a non-deadly effect to cell-death induction.

We also have fairly detailed knowledge of molecular determinants that make life-or-death decisions at the levels of the proximal complexes of adapter and signaling proteins. cFLIP, a non-enzymatic caspase-8 analogue, on being recruited to FADD/MORT1 interferes with caspase-8 activation and promotes recruitment to the signaling complex of proteins that signal for non-apoptotic functions. The cellular level of cFLIP is therefore an important factor in determining the effectiveness of death induction through the extrinsic pathway.[52] Association of cIAP1 and cIAP2 with signaling complexes of receptors of the TNF/NGF family also suppresses the induction of death by these complexes, via mechanisms that are not yet well understood.[53,54]

Whatever the mechanisms by which these and other molecular determinants affecting cell vulnerability at this level of activation mediate their regulatory effects, it is widely assumed that the pivotal outcome is the extent of activation of caspase-8 (or, alternatively, caspase-10) and, as a consequence, of executioner caspases such as caspase-3. However, from the accumulating evidence that caspase-8, as well as the caspases acting downstream of it, also serves

non-deadly functions, it is becoming clear that the occurrence of cell death depends not only on whether these caspases are activated but also on the manner in which this activation occurs.

Little knowledge is available on the nature of the determinants that dictate the functional consequence of activation of these caspases. Some recent findings from our study of their nature are presented in Figures 5–7. These findings were obtained by generation of a bacterial artificial chromosome (BAC) transgenic mouse strain in which the site of initiation of the self-processing of caspase-8 following its activation is mutated (BAC-D387A). Previous studies had shown that whereas the executioner caspases possess enzymatic activity only when proteolytically processed, the inducer caspases require only juxtaposition of pro-caspase molecules to become enzymatically active.[55] The functional significance of the self-processing of these caspases that occurs after the molecules are juxtaposed, however, was not clear.

The new findings exemplified in Figures 5–7 revealed that mutational interference with the self-processing of caspase-8 virtually abolishes activation of the extrinsic cell-death pathway while not significantly affecting the ability of this enzyme to mediate its non-apoptotic functions. In thymocytes, for example, as shown in Figure 5, this mutation did not affect the recruitment of caspase-8 to Fas upon receptor stimulation, yet it prevented processing of the enzyme within the receptor complex (Figure 5a) and almost completely blocked death induction (Figure 5b). We found that the mutation blocked induction of death by Fas in various other cells as well.[56] Moreover, it blocked the *in vivo* death of hepatocytes induced in mice by injected anti-Fas antibodies, thus protecting the mice from the antibodies' fatal effect (Figure 6). However, unlike caspase-8-deficient mice, which die *in utero* at mid-gestation, BAC transgenic mice expressing the 'non-cleavable' enzyme developed normally, suggesting that caspase-8 also mediates activities that do not depend on its processing.

Indeed, as shown in Figure 7, whereas B lymphocytes deficient in caspase-8 failed to respond to the growth-stimulatory effect of bacterial lipopolysaccharide (LPS), lymphocytes of the BAC-D387A mice did respond effectively to such stimulation. The mutation was also found to not affect various other known non-apoptotic functions of caspase-8, including its contributions to the proliferation of T lymphocytes upon stimulation of the T-cell-antigen receptor, the differentiation of bone-marrow macrophage precursors in response to M-CSF, and the generation of myeloid colonies by the bone marrow hematopoietic progenitors.[56]

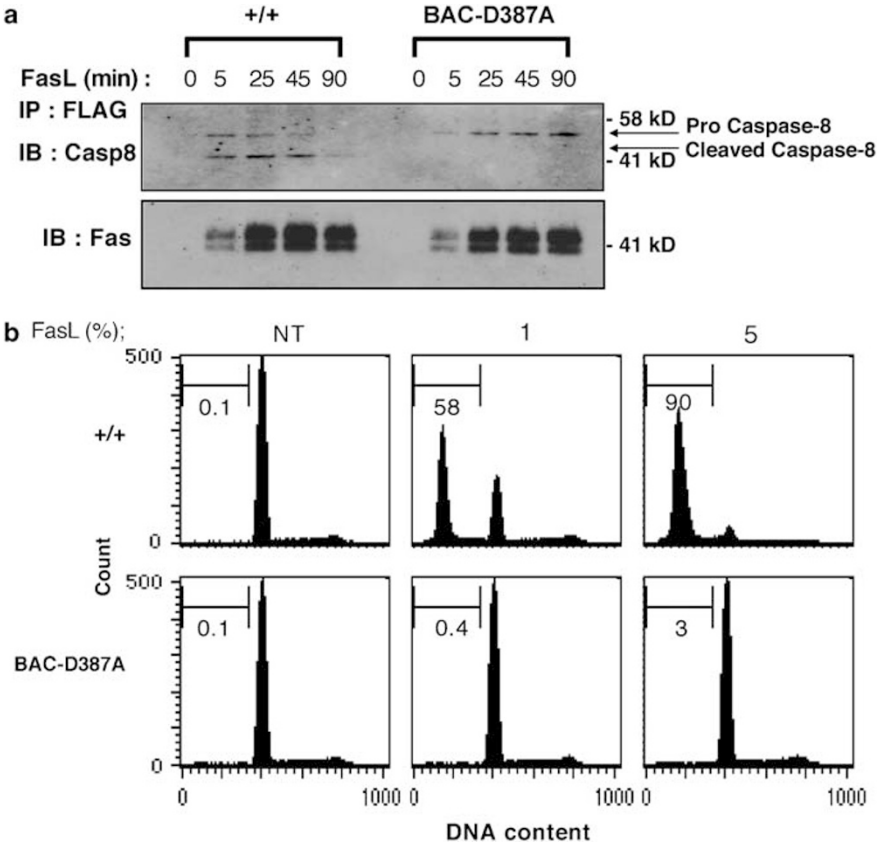

Figure 5 The caspase-cleavage site between the two subunits of the mature inducer caspase molecule seems to be a 'death-specific' structural determinant: mutation of the site ablates Fas-induced death *in vitro*. (**a**) In thymocytes from BAC transgenic mice with mutation of the D387 residue in caspase-8 (the site of initiation of self-processing of this enzyme), caspase-8 is recruited to Fas in response to stimulation by Fas ligand. Unlike the wild-type enzyme (left), the mutated enzyme is not processed (right). The figure shows western blot analysis of caspase-8 and Fas in the death-inducing signaling complex isolated from thymocytes following their incubation for the indicated times with Fas ligand. (**b**) The D387 mutation compromises death induction in thymocytes by Fas ligand *in vitro*. FACS quantitative analysis of death (cells with subdiploid DNA) of thymocytes of wild-type (+/+) and mutant (BAC-D387A) strains[56]

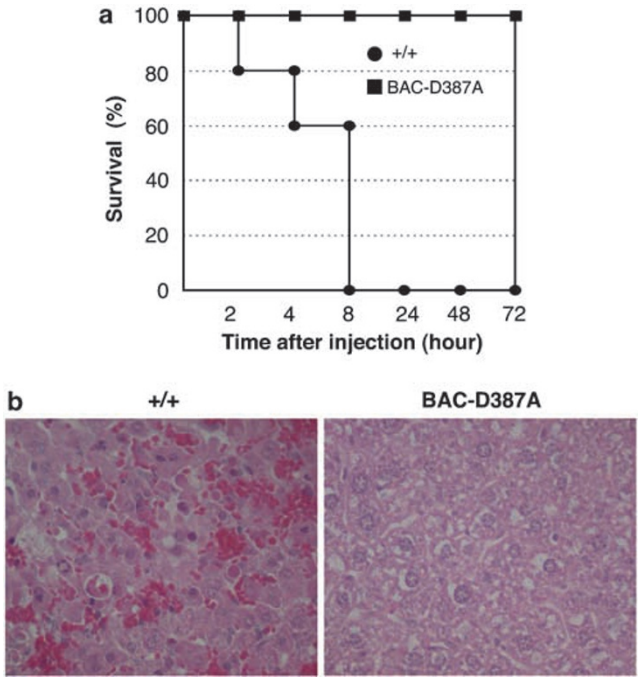

Figure 6 The caspase-cleavage site between the two subunits of the mature inducer caspase molecule seems to be a 'death-specific' structural determinant: mutation of the site ablates Fas-induced death *in vivo*. (**a**) Mouse survival graph after injection of anti-Fas antibody. (**b**) Hematoxylin and eosin staining of mouse livers, 3 h after anti-Fas injection[56]

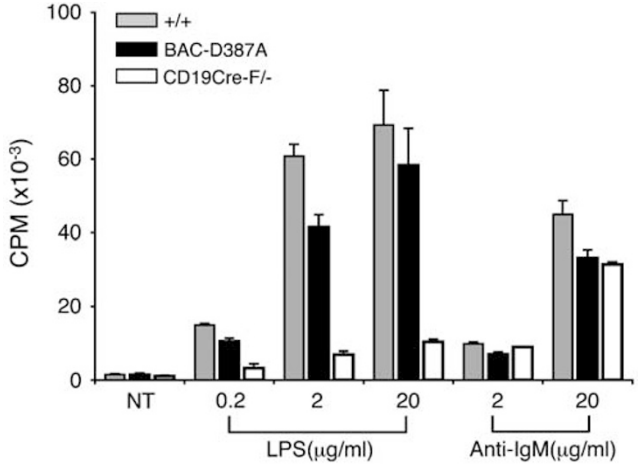

Figure 7 The caspase-cleavage site between the two subunits of the mature inducer caspase molecule seems to be a 'death-specific' structural determinant: mutation of the site does not interfere with the non-cytotoxic functions of caspase-8. B cells deficient in caspase-8 (generated by mating of mice possessing a floxed caspase-8 allele with mice expressing the enzyme Cre under control of the CD19 promoter, white bars) fail to respond to growth stimulation by LPS (although they do respond to stimulation with andti-IgM). In contrast, B cells expressing the D397A caspase-8 mutant (black bars) do respond to LPS. Various other non-apoptotic functions of caspase-8 are similarly unharmed by the D397A mutation (not shown)[56]

It seems, therefore, that the extent to which caspase-8 activation leads to its self-processing is a 'death-specific determinant' in the function of this enzyme.

Several plausible explanations for this differential requirement for processing come to mind. The processing of caspase-8 is likely to relieve the local restriction of its action imposed by association between the unprocessed protein (through the 'death-effector domain' motifs in its prodomain) and the signaling complex that triggered its action. The processing is also likely to result in increased generation of active caspase-8 via repeated cycles of recruitment of new caspase-8 molecules to the signaling complex, as well as in increased stability of the enzyme's active conformation.[57] It might conceivably also result in altered substrate specificity of caspase-8.[58] Further studies will be required to clarify which, if any, of these potential consequences of caspase-8 cleavage are crucial for its induction of cell death. It seems likely that various additional determinants, such as the identity of the cellular components with which the caspase molecules interact, and of the subcellular site in which the activation occurs, also contribute to the life-or-death decision at this mechanistic level.

Concluding Remarks

The inclination to ascribe a biological phenomenon to distinct physical matter dedicated to it is not unique to studies of cell life and death; it seems rather to be a basic feature of human thinking, which informs the initial mechanistic explanation for almost any complex phenomenon. Other examples that come to mind are the belief that fire is a reflection of a dedicated material found within burning materials (phlogiston) and, going further back in history, that a single material – the 'philosopher's stone' – can endow us with youth and/or longevity or, alternatively, transform inexpensive metals into gold.

A particularly relevant example of this feature of the way we think is the evolution of scripts. In many cultures, scripts in their early stages of development were pictographic. Words were presented not by combinations of letters but by a unique picture representing their meaning. No wonder that initial notions of the 'scripts' by which cells communicate, whether for induction of life or death or for conveying messages of other kinds, were also 'pictographic,' with the molecule that conveys a particular message being viewed as having a single functional implication. However, although simple to design and explain, the versatility of pictographic scripts is limited, and all over the world they have time and again been found to evolve into 'syllabic' scripts, where a notion is represented by a combination of symbols or letters.

Molecular 'scripts' for inter- and intracellular molecular communication might conceivably have evolved in a similar way.[59] In the early stages of primitive life forms, signaling molecules might well have served to convey one distinct functional message. With the growing complexity of biological systems, however, more sophisticated communication was needed. Simple instructions such as 'grow' or 'die' were no longer adequate for the cells; they began to need a molecular 'script' allowing for 'contextual' messages, such as: '*die, but only if your gene expression mechanisms have been damaged by pathogens to the extent that you can no longer produce cellular proteins that will neutralize this death instruction*' or: '*if you receive both mitogenic and co-mitogenic*

signals, grow; but if you keep receiving a mitogenic without a co-mitogenic signal kindly respond to that signal by dying.'

The contextual nature of the molecules that mediate cell death endows the term 'programmed cell death' with a particular operational implication as to how the program should be studied. It is becoming clear that if we wish to fully understand what underlies decisions relating to life and death in the natural world, it will not be enough to identify the molecules mediating these processes. We will also need to understand the rules of the 'program' that defines the particular activity being mediated in a given situation. The advent of systems biology is endowing us with the means to explore this programming aspect of programmed death.

There is still a large difference, though, between the design of scripts for written languages and the function of signaling molecules in biology. The former have evolved from pictorial forms to abstract 'syllabic' forms in which individual letters can express any meaning, depending on their context (the identity of the letters to which they are joined). In contrast, biological molecules, including those that signal for death, although also operating in a contextual manner, each have their own distinct realm of functions. Moreover, they operate in hierarchies, with some having a much more important role in mediating a particular effect than others. Thus, although it seems likely that molecules fully dedicated to death probably do not exist, the molecules that are most crucially involved in death induction can nevertheless be identified, and within those molecules distinct structural features dedicated to this function can probably be defined.

The natural inclination that drives us to keep searching for physical entities that correspond to distinct biological phenomena has acquired an additional important incentive in our time. With the advent of drug design and drug screening, the ability to associate a potentially harmful biological process with a distinct cellular protein and a distinct structure within it has become the key to development of drugs that can affect this process. Thus, identification of the molecules and the motifs within them that are crucial for the mediation and control of cell death will open doors to the development of drugs that will specifically arrest the harmful loss of needed cells.

Acknowledgements. Work cited from the authors' laboratory was supported in part by grants from Ares Trading SA, Switzerland, a Center of Excellence Grant from the Flight Attendant Medical Research Institute (FAMRI) and the Kekst Family Center for Medical Genetics at the Weizmann Institute of Science.

This article was originally commissioned to form part of the Special Issue to celebrate Richard Lockshin's 70th Birthday, published in July this year (http://www.nature.com/cdd/journal/v15/n7/index.html) and was written with this goal in mind. Unfortunately, its publication had to be delayed until a research paper by David Wallach and colleagues, referenced in this review, had been accepted.

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