

Cell death and cancer: an introduction

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The omission or repression of cell death has a dual impact on medical oncology. First, disabling the signal transduction mechanisms leading to cell death and/or suppression of the biochemical program involved in cell death execution is likely to play a primordial role in the process of oncogenesis. Death resistance thus enables the Darwinian selection of clones whose vital needs for external growth factors, nutrients and contact-dependent survival signals progressively diminish, thereby increasing the autonomy of tumor cells and enabling them to spread and to metastasize to sites at which, in normal conditions, they could not subsist. Second, conventional therapy with chemotherapeutic agents or ionizing irradiation aims at killing tumor cells, usually by triggering a latent biochemical death program. In the standard scenario, however, after an initial response, resistant tumor cells are selected and ‘escape’ from death induction, thus determining subsequent therapeutic failure. It is plausible that increased death resistance of tumor cells thus participates in sealing the patient’s inexorable fate.

Death pathways can follow different subroutines, which, unfortunately enough, are classified according to mere morphological criteria. Apoptosis, the most preponderant type of cell death (‘type 1 cell death’) can be opposed to other types of cell death such as autophagic (‘type 2’) cell death, mitotic catastrophe, as well as necrosis (oncosis), according to morphological criteria such as chromatin condensation (present in apoptosis), accumulation of autophagic vacuoles (exclusive for type 2 cell death), mitotic features (as observable in mitotic catastrophe), or massive swelling of cytoplasmic organelles (oncosis) (Jaattela, 2004). Nonetheless, this clear distinction is probably not relevant in functional terms because the same lethal stimuli can trigger different subroutines of cell death, depending on the cellular context, for instance, the ATP content (Melino and Nicotera, 2004). Moreover, regulators of the apoptotic pathway can also act on other cell death subroutines, and mitotic catastrophe is probably executed through the activation of caspases and mitochondrial membrane permeabilization, two processes that are generally considered to be pathogenic for apoptosis (Castedo *et al.*, 2004).

Scientific reductionism has led many investigators to consider apoptosis as a type of cell death resulting from the explosive activation of caspases. This implies that many research projects have been focusing on the

elucidation of caspase-activating pathways and the identification of endogenous caspase inhibitors, some of which (e.g. the IAP proteins) may be cancer relevant (Salvesen and Abrams, 2004). Although caspases are important for the regulation/execution of apoptosis, it is now widely acknowledged that caspases are frequently involved in cellular activation and differentiation process that are not linked to cell death. Moreover, there is no doubt that many if not most morphological features of apoptosis can be mediated by other proteases than caspases and other DNases than the caspase-activated DNase (CAD) (Lockshin and Zakeri, 2004). This has relaunched the interest in caspase-independent death effectors, including in cancer research (Cregan *et al.*, 2004).

In addition, during recent years it has become increasingly clear that different organelles can participate in cell death, at two levels. Either the organelle suffers a primary damage by a physical or chemical agent (e.g. nuclear DNA in response to γ -irradiation; primary mitochondrial permeabilization induced by reactive oxygen species), or the organelle participates in the signaling events linking proapoptotic damage or signal transduction pathways to the final steps of self-execution. Thus, nuclear DNA damage causes mitochondrial membrane permeabilization, through a variety of different mechanisms (whose local protagonists are p53, histone H1.1, Nur77, caspase-2, Ku70, DAXX, FADD, and PML) (Norbury and Zhitovovskiy, 2004; Takahashi *et al.*, 2004). Then, the mitochondrion sets off the apoptotic cascade, by the release of multiple caspase-dependent or caspase-independent death effectors (Saelens *et al.*, 2004). In this complex interplay, p53 is one molecule that constitutes a particularly important link between nuclear damage and mitochondria, a link that can be inactivated in cancer at multiple levels (Slee *et al.*, 2004). Stress kinases emerge as an additional link between different types of cell damage and the apoptotic default pathway (Wada and Penninger, 2004). Lysosomes and the endoplasmic reticulum now are also increasingly recognized as instigators or propagators of lethal pathways (Distelhorst and Shore, 2004; Guicciardi *et al.*, 2004). As a result, noncaspase proteases such as the lysosomal cathepsins emerge as important cell death regulators (Guicciardi *et al.*, 2004).

These considerations are not purely academic, since they allow for an operative (re)interpretation of some cancer-relevant data. For instance, Beclin-1 and DAP kinase are two proteins which are frequently under-expressed in epithelial tumors, and both proteins are important for autophagic cell death. Autophagy, which

can be induced by chemotherapeutic agents, may constitute a mechanism of cellular defense against organelle damage or starvation, as well as a mechanism of cellular demise (Gozuacik and Kimchi, 2004). Importantly, a whole series of anticancer agents including monoclonal antibodies targeted to cell surface receptors can induce atypical nonapoptotic cell death (Jaattela, 2004). In addition, it is conceivable to create novel therapeutic strategies by targeting other organelles than the nucleus and mitochondria or by neutralizing the inhibitors of noncaspase death effectors (Blagosklonny, 2004; Jaattela, 2004).

Evidence is accumulating that tumor cells acquire defects in the core apoptosis machinery (that is in genes that function primarily to control or execute apoptosis) and later on manifest gene expression changes that enhance proliferation and that, in normal cells (when the core apoptotic program is functional), would trigger apoptosis (Pommier *et al.*, 2004). Among these changes, constitutive activation of heat-shock proteins (Mosser and Morimoto, 2004), the NF- κ B antiapoptosis

pathway and the Akt survival pathway are frequent (Pommier *et al.*, 2004). In conditions in which the core apoptotic program is disabled, chemotherapy may induce premature cellular senescence, a condition that may be reversible and thus explain dormancy and/or chemotherapy resistance (Shay and Roninson, 2004).

Future will tell whether targeting antiapoptosis (for instance that mediated by NF- κ B, Akt, heat-shock proteins, or multidomain proteins from the Bcl-2 family) (Henry-Mowatt *et al.*, 2004; Mosser and Morimoto, 2004; Pommier *et al.*, 2004), mitochondrion-permeabilizing agents (Debatin *et al.*, 2002), death receptor agonists (Debatin and Krammer, 2004), combination therapies coupling apoptosis inducers to additional molecules (such a cell-cycle specific, antiangiogenic or differentiating agents etc.) (Blagosklonny, 2004), or novel strategies of preventing senescence (Shay and Roninson, 2004) may overcome chemotherapy resistance in cancer cells. The present special issue of *Oncogene* provides state-of-the-art reviews on this important topic.

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