

BREAKTHROUGHS AND VIEWS

The Shape of Cell Death

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Cell death, a scheduled event during development and tissue turnover, or the ultimate consequence of toxic or pathologic insults seems to involve a relatively limited number of execution pathways. This reflects the evolution of an organized sequence of events perhaps converging onto final common pathways that are used to dispose of unwanted or injured cells. In many cases, the ordered execution of this internal death program leads to typical morphological and biochemical changes that have been termed apoptosis. Apoptosis, often equated with developmental or programmed cell death, has been opposed to unscheduled or accidental cell lysis/necrosis. However, increasing evidence suggests that the two forms of cell demise share similar characteristics, at least in the signaling and early progression phase. Recent studies have shown that, when the intensity of the insult is very high and/or when ATP generation is deficient, cells fail to execute the ordered changes ensuing in apoptosis. Then cell lysis/necrosis supervenes before the processes leading to nuclear condensation and exposure of surface molecules can be completed. Thus, apoptosis and necrosis seem to represent only different shapes of cell demise, resulting from a more or less complete execution of the internal death program.

PROGRAMMED CELL DEATH, APOPTOSIS, AND NECROSIS

The notion that cell differentiation and proliferation follow seemingly programmed patterns is widely accepted. Conversely, the understanding that a similar program may control cell death is a more recent development in biology [1 - 5]. The term "programmed cell death" adopted from developmental biology has then

been used to describe the coordinated series of events leading to cell demise. In this field the term has been commonly used to allude to the existence of a genetic program for cell death. In fact, there may exist various transcriptionally controlled programs involved in signaling or in the initiation of cell death. However, the elements of a core program controlling the proper execution phase of cell death seem to be constitutively expressed in virtually every cell. A definition of this core program would include the series of self-regulatory elements/subroutines, beyond the signaling phase, that can lead to cell demise.

Cell death is more often defined by the use of morphological criteria [6, 7]. The term apoptosis introduced by Kerr and his colleagues [3] has been used to indicate cells that shrink, display surface alterations such as the exposure of molecules normally confined to the interior of the cell (e.g. exposure of phosphatidylserine (PS) on the outer surface) [8 - 11], and undergo a series of typical nuclear changes including chromatin margination and condensation, and DNA cleavage into large (i.e., 50 kb) and eventually small (oligonucleosomal-sized) fragments [12 - 14]. The whole nucleus may sometimes fragment into more or less small rounded bodies containing parts of the chromatin. In the cytoplasm, organelles appear to be intact. This set of changes is markedly different from the cellular breakdown seen in rapidly lytic cell death/necrosis. Notably, the concept of a death program is not linked to a specific morphology. For example, in non-vertebrate systems, programmed cell death does not always display an apoptotic-like morphology [15].

A major biological discriminant between apoptosis and necrosis is the implication that death of an individual cell or a group of cells has for its neighbours [16]. Apoptotic cells are rapidly sequestered by professional phagocytes or by neighbouring cells before they can lyse, spill their contents and cause an inflammatory reaction. This process is so efficient and rapid that the contribution of apoptosis to cell death in tissues has

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often been grossly underestimated. Notably, the discovery and characterization of pro-apoptotic genes such as *ced-3* and *ced-4* in *C. elegans* has greatly benefited from the availability of genotypically altered worms, lacking functional genes responsible for the uptake of dying cells [1, 17].

EVOLUTION OF CELL DEATH

Although the shape of death varies among unicellular organisms, invertebrates and various vertebrate cells, the machinery for cell death seems to have been well conserved. Thus, the study of cell death in *Drosophila* and *C. elegans* has contributed significantly to the understanding of death in mammalian cells [18]. Even in plants, bacteria, fungi and in unicellular organisms (*Leishmania*, *Trypanosoma*), elements of programmed cell death have been described which seem to be extremely well conserved [19 - 24]. E.g. overexpression of Bax can cause cell death in yeast and overexpression of Bcl-2 can prevent cell death induced by Bax or by SOD-deficiency [25, 26].

It is not surprising that initially simple death programs, developed early during phylogeny have been largely modified and refined to yield the complex picture now evident from the study of mammalian cells. The increasing complexity of higher organisms as compared to plants or worms has led to the evolution of large gene families, whose interacting and overlapping members provide a more intricate control of cell death, perhaps depending on the degree of differentiation. For example, studies in *C. elegans* have revealed at least three groups of genes whose activity is linked to cell death: the genes involved in the direct control of cell death, those involved in phagocytosis and degradation of cell corpses, and the genes involved in the upstream signals initiating or blocking apoptosis [1, 27]. In mammalian cells, more than a dozen homologues of *C. elegans* thanatogene *ced-3* are now known [28 - 31], and a large family of mammalian homologues, which contains both pro- and antiapoptotic members [32] are the counterpart of the nematode thanatoprotective gene, *ced-9*. Furthermore, functions of cell death proteins may have been taken over by functionally similar proteins, that may not have structural similarities. This may explain why many different proteases besides caspases have been involved in mammalian programmed cell death [33 - 41]. Probably, expression of multiple functional analogues in mammalian cells has so far eluded the attempt to identify a homologue to the nematode *ced-4*, which may function as general modulator of the core machinery of death execution (*ced-3* - dependent) [2, 42, 43]. This function may have been taken over by different proteases or proapoptotic members of the *Bcl-2* family (e.g. *Bax* or *caspase 8*).

Also, effective signals have multiplied in high organisms. While most of cell death in *C. elegans* or in

Drosophila is cell-autonomous or signaled by reaper or hid, there is a large variety of identified and not yet identified signals that trigger death of mammalian cells. This complicates the understanding of the sensors that link death signals to execution. Perhaps the most-extensively studied case is that of CD95 signaling via proteins containing cell death domains, which leads to activation of caspase-8/10 [31, 44 - 47]. Even in this paradigm it is not yet clear, where and how the effector phase of the death program joins the execution part. Important findings on mitochondrial function, Bcl-2 control, ceramide generation and ras-activation in this process do not yet yield a consistent picture [43, 48 - 57].

Some characteristics of the original cell death machinery that would affect predominantly the shape of death may have become more significant or predominant in mammalian cells. For instance, ribosomal RNA-degradation [58] or DNA fragmentation are prominent features of mammalian cell apoptosis. Oligonucleosomal DNA-fragmentation is a relatively late event during cell death [59]. Nevertheless, although apoptosis can occur in the absence of oligonucleosomal fragmentation [57, 60 - 62], the latter may be relevant in some instances, and at specific locations. DNA-fragmentation ensures irreversibility and prevents the spread of possibly infectious or mutated DNA. Accordingly, DNA-fragmentation is generally extensive and rapid in immune cells, in tumor cells and in cells killed by immune mediators such as TNF or CD95L, but not after the size regression that follows liver hypertrophy [63].

Other downstream mechanisms, which have possibly evolved in higher organisms to modify not the execution, but the shape of death may include the cleavage of Poly-(ADP-ribose)-Polymerase (PARP) [64 - 67] or of small nuclear ribonucleoprotein-U1 (snRNP-U1) [68, 69], the translocation of phosphatidylserine [70] and the export of reduced glutathione [71]. Cleavage of the two nuclear proteins may serve to maintain cellular energy. E.g. PARP-cleavage prevents NAD/ATP-depletion, whereas dysfunction of snRNP-U1 inhibits new protein synthesis by preventing any mRNA processing and subsequent translocation of RNA into the cytoplasm. PS-translocation favours the early phagocytosis of apoptotic cells.

Assuming that the whole program of sequential steps leading to cell death is highly conserved, it would not be surprising to find out that short cuts have been developed in specific cases. One example may be the death pathway triggered by cytolytic bacteria. E.g. shigella invasion causes the direct activation of caspase-1 and subsequent apoptosis by binding to the inactive proform of the enzyme [72, 73]. Possibly, the proteolytic cascade triggered by trimerisation of the CD95 receptor also bypasses many control-elements and sensors of the entire program and leads directly to activation of

the execution by caspases, although the links are not yet entirely clear [44, 74 - 78].

Finally, in mammalian cells, proteins involved in cell death serve also other functions. For example, independent of its apoptosis-inhibitory function, Bcl-2 seems to have a role in cell signaling or neurite outgrowth after lesion [79, 80]. In addition, several caspases are involved in processing of proteins required for cell signaling and development [81 - 83].

ARE THERE UBIQUITOUS COMMON EVENTS IN CELL DEATH?

From the above considerations, it seems that a possibly ubiquitous cell death program may have been optimized and further developed to adapt to the properties of specialized, differentiated cells. If common denominators still exist, it is likely that they have been preserved because they regulate processes and/or structures whose function is essential for survival. There are several candidates for a fairly ubiquitous role in cell death:

(i) The mitochondrial permeability transition: Under stressful conditions, the mitochondrial inner membrane can lose its impermeability to ions and other small molecules up to a molecular weight of ca. 2 kDa [84, 85]. Accumulating evidence supports the idea that PT is a controlled process, involving the formation of pores at contact sites between the inner and outer mitochondrial membranes. Opening of these pores can be regulated by agonists or antagonists (such as atractyloside, bongkrekic acid, as well as ligands of the mitochondrial benzodiazepine receptor or mitochondrial cyclophilin). In addition, pore opening can occur following a selective proteolytic step (activation of caspase-1 or calpain) [86 - 90]. Candidate pore-forming proteins have been isolated and reconstituted to functioning pores in liposomes [91]. Key proteins may include the adenylate translocator, multimeric hexokinase and outer membrane porin. Recent evidence suggests that PT is closely related to cell death (apoptotic and necrotic) induced by a large variety of different stimuli [90 - 94]. Extensive work performed in G. Kroemer's laboratory has shown that PT can lead to typically apoptotic nuclear alterations [94], by stimulating the release of an apoptosis-inducing factor (AIF), a protease of about 50 kDa. PT and the release of AIF seem to be inhibited by Bcl-2, a ubiquitous negative controller of apoptosis [41, 87].

(ii) The release of holocytochrome c (cyt-c) from mitochondria: Another process that seems to be conserved from amphibians to mammalian cells is the release of cyt-c from mitochondria [95 - 97]. Cyt-c is a small, 13 kDa protein that is loosely attached to the outer surface of the inner mitochondrial membrane. In contrast to the mechanisms operating after PT, cyt-c may also be

released from energized mitochondria. However, it has recently been observed that cyt-c release may also follow the early phase of PT [98] providing a link between the two events. Notably, cyt-c release from energized mitochondria can also be prevented by Bcl-2 [95, 96]. Neither the mechanism of release, nor the mechanism whereby PT and/or AIF/cyt-c release are negatively regulated have yet been elucidated. It is instead apparent that cyt-c in conjunction with other unknown factors in the cytoplasm can activate caspases. Cells lacking cytochrome c are probably not viable. This would ensure that the key step of the program for cell death cannot be lost by simple mutation.

(iii) Caspase activation: work on programmed cell death in *C. elegans* has led to the identification of a new class of proteases with a central role in the execution of the death program [1, 99 - 101]. About a dozen different caspases have been identified in mammals [28]. Evidence for the role of caspases in cell death is based on findings that their inhibition can prevent apoptosis, whereas their overexpression and activation causes apoptosis.

Caspases seem to be constitutively expressed in mammals, similar to Ced 3 in *C. elegans* and in analogy with cyt-c or components of the PT pore [2, 17, 102, 103]. Complications in the understanding of their role arise from the multiplicity of isoenzymes [99]. In mammalian cells, different sets of caspases may be recruited in different paradigms of cell death [39, 104 - 106]. Most studies on the involvement of specific isoenzymes are based on the use of peptide inhibitors such as DEVD-CHO, that were thought to be relatively selective for individual members of this family, e.g. for caspase-3 related isoenzymes. In fact, they probably inhibit various members of the family [107]. The vital function of death executing caspases for the cell remains to be shown. In fact, deletion of *ced-3* in *C. elegans* has no further effect than the survival of the cells that would normally die during development [1]. Like the mitochondrial processes described above, activation of caspases seems to be controlled by Bcl-2 in mammalian cells or its homologue, Ced-9 in the nematode [108 - 110]. When evaluating the role of caspases as ubiquitous step in programmed cell death, some caveats should be mentioned. Not all cell death in *C. elegans* requires functional Ced-3 (e.g. the male linker cell) [1]. In mammalian cells, several forms of cell death seem to be independent of caspases [39, 105, 106, 111, 112] and other protease families have also been implicated in cell death [99, 112, 113]. It is tempting to speculate that if caspases are absent or inhibited, death may still occur through activation of other proteases, if the stimulus for cell death is intense enough. Evidence for the role of caspases in the fine tuning of the shape of cell death comes from studies showing, that general inhibition of caspases does not alter the extent of pro-

grammed cell death but rather the form of demise [39, 106, 39].

(iv) Overriding Bcl-2's antiapoptotic effect: Bcl-2 the mammalian homologue of the *C. elegans* protein Ced-9 [114] seems to function upstream of both mitochondrial alterations and caspase activation, even in CD95-signalled cell death, where a linear protease cascade has been suggested [108]. Recent data show that Bcl-2 may be physically linked to caspases via the *C. elegans* gene product of *ced-4* [43]. As mentioned above, although *ced-4* is actively inducing apoptosis in mammalian cells if overexpressed, its real mammalian counterpart has not yet been identified [115]. One or more of the proapoptotic Bcl-2 family members may be suitable candidates. Indeed, *ced-4* shares an important feature with the Bcl-2 family. It may be proapoptotic (in its full-length form) or antiapoptotic (as a shortened splice-variant) [17, 42, 116]. While pro- and antiapoptotic functions may be combined in the single *ced-9* gene in *C. elegans*, in mammalian cells, a whole family of Bcl-2-like proteins may be required. Some of these proteins would prevent cell death (e.g. Bcl-2, Bcl-x_L) and others would interfere with this function or induce cell death themselves (e.g. Bax, Bad, Bcl-x_S) [32, 117]. Since all the members of this protein family seem to be able to form homo- and heterodimers (or possibly multimers) the balance between death and survival could be decided by the amount of the individual proteins. Other factors may control the function of these proteins and their interaction. The activity of Bcl-2-like proteins can be modulated by phosphorylation [118]. One example is the recruitment of the kinase Raf to the mitochondrial membrane by Bcl-2 [119] followed by Raf phosphorylation of Bad, which results in its inactivation. In line with this observation, the protection by Bcl-2 from apoptosis is greatly attenuated in cells lacking functional Raf [119]. The mitochondrial localization of Bcl-2 seems to be critical for its protective effect [41, 43, 120, 121], although Bcl-2 also exerts anti-apoptotic effects by transcriptional regulation [122] and by controlling Ca²⁺ pools [123, 124]. The observations that Bcl-2 knockout animals are viable [125, 126], and that apoptosis may eventually proceed also in Bcl-2 overexpressing cells [117, 127] is a further indication that a high degree of redundancy preserves cell ability to control death. Accordingly, Bcl-2 overexpressing animals are marked by neuronal hypertrophy due to defective apoptosis during development [128], but they do not display a generalized inability to undergo cell death.

(v) Transcriptional control: transcriptional control may be important in signaling some forms of cell death. Genes that have been involved include *c-fos*, *p53* or the product of *ces-2* in *C. elegans* [27, 129, 130]. It is unlikely that such factors have a universal role, since there is an overwhelming number of examples of cell death that take place in the absence of transcription [102]. However, transcriptional activation may be im-

portant to generate the link from extracellular signals to the execution phase of cell death.

Intracellular protein localization or transport may also be relevant to determine the shape of cell death. Some death signals (e.g. those activated after irradiation or treatment with topoisomerase inhibitors) are predominantly generated within the nucleus. Since controllers and execution systems are believed to be located in the cytoplasm/mitochondria [43, 57], then yet unknown death signals have to be transmitted from the nucleus to these compartments. Conversely, most caspases seem to be localized in the cytoplasm, whereas important substrates may be located in mitochondria and the nucleus. Thus, the permeability of the nuclear pore and/or the accessibility of mitochondrial sites may be a relevant factor in apoptosis [131].

APOPTOSIS AND NECROSIS: TWO DIFFERENT MODES OF CELL DEATH?

Apoptosis and necrosis have been regarded as morphologically and conceptually distinct modes of cell death. Nevertheless, there is increasing evidence that typical apoptosis and necrosis represent only the extreme ends of a wide range of possible morphological and biochemical deaths. The two classical types of demise can occur simultaneously in tissues or cell cultures exposed to the same stimulus, and often the intensity of the same initial insult decides the prevalence of either apoptosis or necrosis. This suggests that then some early events may be common to both types of cell death. Downstream controllers may be required to direct cells towards the organized execution of apoptosis or cell lysis/necrosis.

Early definitions of apoptosis emphasized the difference between cell death caused by physiological stimuli (i.e., apoptotic) from that caused by accidental, toxic or "catastrophic" insults (necrosis). There is now convincing evidence that apoptosis can be elicited by toxins or during disease processes. In fact, many signals as diverse as heat shock [132], viruses [133], protein synthesis inhibition [134], oxidative stress [135], hypoxia [136] or toxic challenge with Ca²⁺ ionophore, radiation [137], glutamate [138] or nitric oxide [139] can induce both apoptosis and necrosis. Not only the trigger, but also activators/second messengers and also steps further downstream may be common to either form of cell death. For example, second messengers like Ca²⁺ or stress-dependent transcription factors such as c-Fos have been implicated in both modes of cell death. The same applies to cellular structures that might act as sensors for irreversible damage such as mitochondria or the cytoskeleton. Recent findings show that even signaling molecules thought to be highly specific for apoptosis, such as caspase-8/10 participate in necrosis [140]. This is exemplified by the finding that stimula-

tion of ATP-depleted T-cells by CD95 leads to necrosis, which is inhibitable by inhibitors of caspases, including caspase 8. Thus, at least some of the effector molecules, those active upstream in the death program may have a role in both types of demise [140 - 142]. In fact, the role of proteases as effectors of necrosis has been shown long before the discovery of caspases and their role in mammalian cell death [143, 144].

Another criterion used to distinguish apoptotic from necrotic cell death has been the sensitivity of apoptosis to Bcl-2 control [61]. On the other hand, several studies now show that overexpression of Bcl-2 can inhibit also necrotic cell death elicited by stimuli as diverse as viruses [133], hypoxia [141], oxidative stress [145, 146] or exposure to toxicants [147, 148].

The removal of the corpses/remnants of apoptotic cells by phagocytosis remains perhaps the most relevant biological discriminant between apoptosis and necrosis. Cells dying by apoptosis display on the outer surface molecular components, which are normally masked or restricted to the cell interior [16]. This facilitates phagocytosis of the dying cell by professional macrophages or neighbouring cells before the plasma membrane lyses. Necrotic cells seem to be removed only after lysis of the cell membrane. The difference in the time course of phagocytosis has major implications for the surrounding tissue and it is assumed that apoptosis occurs generally without ensuing inflammation. However, under certain conditions, apoptotically dying cells may be able to elicit inflammatory responses and perhaps extended immune responses, which would be of importance for the elimination of invading pathogens. This is suggested by the observation that apoptosis-executing caspases are important for the processing of pro-IL-1 and IFN- γ -inducing factor, two proinflammatory cytokines [82, 149]. By this mechanism, on the other hand, pathogens like *Shigella flexneri* induce an "apoptotic inflammation" to break the tissue barrier and invade the intestine [72, 150, 151].

INCREASING THE INTENSITY OF THE INSULT CHANGES THE SHAPE OF DEATH

If indeed common events are shared by apoptosis and necrosis, what is the significance of these different modes of cell death? In their most typical appearance apoptosis and necrosis have little similarity and are clearly distinguishable mechanistically and morphologically [6]. However, it can be argued that the death program may not be uniformly progressing in all conditions. If left undisturbed, the death program would predominantly yield an apoptotic-like morphology, whereas when elements of the program are disturbed or inhibited, or when the insult is so high that some of the subroutines cannot be terminated, then the shape of death can change. According to this view apoptosis and necrosis may be seen as extremes of a continuum

of possible shapes of cell death, and necrosis may be the result of an aborted apoptosis [140].

In agreement with this assumption, it has been shown that increasing the intensity (exposure time or concentration) of the insult, cell death changes its shape from apoptotic to necrotic. In the case of glutamate, nitric oxide, reactive oxygen species (ROS) and many other toxins this overstimulation leads to recruitment of additional lethal reactions, which cause cell lysis prior to the completion of the "default" apoptotic program [135, 139, 138]. Notably, it has been observed that intracellular energy levels are rapidly dissipated in necrosis, but not in apoptosis [135, 138]. These results suggest that while initial events may be common to both types of cell death, certain metabolic conditions would be required to activate downstream controllers, which direct cells towards the organized execution of apoptosis.

INTRACELLULAR ENERGY LEVEL AND THE SHAPE OF CELL DEATH

To investigate whether the same insult (i.e. same intensity) could still produce either form of cell death an alternative strategy has been used: individual parts of the death program have been blocked by manipulating the intracellular ATP level. In this study, when ATP levels were reduced, typically apoptotic stimuli resulted in cell necrosis [140]. ATP could be depleted and repleted to defined levels and for defined periods of time. Therefore, it has been possible to identify a period of 90 min after the exposure of cells to apoptogenic stimuli such as staurosporin or an agonist anti-CD95 monoclonal antibody as the energy-dependent period for the completion of the apoptotic program. If ATP concentrations were markedly reduced during this period, activation of caspases and the induction of typically apoptotic changes were prevented. Stimulated cells died nonetheless. However, death had necrotic features. These findings provide direct evidence that the complete apoptotic program involves energy-requiring steps. An interesting corollary of these observations is that proteolytic degradation of lamin B typical of apoptosis did not occur in necrosis. Lamin cleavage is effected by the activation of caspases or other proteases during apoptosis [37, 152 - 154]. This suggests that at least one component of cell death execution may be specific for apoptosis. In agreement with the concept that caspases may be in certain cases responsible for the fine-tuning of the shape of cell death without modification of the death rate, cells treated with a caspase-inhibitor and subsequently exposed to an apoptogenic stimulus died by necrosis [39, 106].

Several forms and subroutines of the death program in mammals might have evolved because of their significance for tissues and organs and may not be intelligible from in vitro studies. Since most of the cited work

has been performed in cell culture, the question arises, whether the viewpoint of apoptosis and necrosis as extremes of a continuum of multiple forms of death is supported by in vivo observations. In fact, it seems that in many pathological situations apoptosis and necrosis coexist. An example for this is ischemic brain damage. In the core of ischemic regions, necrotic cell death is prevalent. Towards the border regions, where energy-depletion and excitotoxic stimulation are less severe and prolonged, apoptotic neuronal death is commonly observed [155 - 158]. An other example of the concomitant occurrence of apoptosis and necrosis is liver damage, induced by toxins, TNF or CD95 [159 - 161]. In these models, pure apoptosis was observed at early time points. However, hepatocytes exposed to stressful stimuli for extended times, may lose cell membrane permeability rapidly, before the apoptosis program can be terminated. In fact, the rate of non-apoptotic death increased over time and in the end widespread necrosis is the dominant form of death in these models of liver damage [161, 162]. The question remains open whether the sequential activation of apoptosis and necrosis is based on similar or different mechanisms of cell death. Recent studies using the *in vivo* models of TNF- or CD95-mediated liver failure have demonstrated that both types of cell death share similar signaling/execution events, since apoptosis as well as necrosis are completely blocked by treating of mice with inhibitors of caspases [142, 163, 164] or by overexpressing Bcl-2 [54]. Thus, also in vivo evidence suggests that cell death, either by necrosis or by apoptosis may be the manifestation of a differently complete execution of an initially similar program.

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