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Non-apoptotic functions of caspases in cellular proliferation and differentiation

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Abstract

The cysteinyl aspartate-specific proteases (caspases) have been identified as key players in the cellular process termed programmed cell death or apoptosis. During apoptosis, activated apoptotic caspases cleave selected target proteins to execute cell death. Additionally to their established function in cell death, a variety of recent publications have provided increasing evidence that apoptotic caspases also participate in several non-apoptotic cellular processes. Activated caspases exhibit functions during T-cell proliferation and cell cycle regulation, but are also involved in the differentiation of a diverse array of cell types. In some cell types, their differentiation can be morphologically viewed as a kind of incomplete apoptosis. Analysis of well-known apoptotic targets of caspases implicates that the cleavage of a limited number of selected substrates plays a major role during non-apoptotic functions of caspases. Selective substrate cleavage might be regulated by activation of anti-apoptotic factors, via a compartmentalized activation of caspases, or through limited activity of caspases during apoptosis-independent functions. The increasing evidence for caspase function in non-apoptotic cellular events suggests that caspases play a much more diverse role than previously assumed.

Keywords: Apoptosis; Caspase; Cytokine; Cell cycle; Differentiation; Proliferation

1. Introduction

The cellular phenomenon of programmed cell death or apoptosis describes the regulated destruction and disposal of unwanted cells, staged by a finely organized genetic program. Two major pathways of apoptosis signaling have been described which trigger cell death either by activation of death receptors at the cell surface or via the disruption of the outer mitochondrial membrane barrier function with the simultaneous release of proapoptotic molecules from the mitochondria to the cytosol. Key players in both pathways are members of a family of cysteinyl aspartate-specific proteases (caspases), which are activated during apoptosis by proteolysis and cleave selected target proteins (reviewed in [1,2]).

The first member of the caspases identified was the interleukin 1β (IL-1β)-converting enzyme (ICE; caspase-1), which is involved in the generation of active IL-1β [3,4]. Subsequent research has led to the identification of a whole caspase family, which now consists of 10 murine and 11 human members (reviewed in [5]), several of which are also involved in cytokine maturation and belong to the group of inflammatory caspases (caspase-1, -4, -5, -11, -12, -14). Evidence that members of the caspase family also take part in the process of apoptosis was first fueled by the discovery that the *Caenorabditis elegans* death gene *ced-3* encodes a protein with homology to ICE [6]. Since then caspases have emerged as the main players in the execution of the cell death program, with apoptotic caspases being divided into executioner caspases (caspase-3, -6, -7) and initiator caspases (caspase-2, -8, -9, -10) (reviewed in [7]). While initial studies have firmly established the role of apoptotic caspases in cell death, more recent analyses have provided substantial evidence that apoptotic caspases have also important functions in several non-apoptotic cellular events. As summarized in Fig. 1 and outlined in this review, apoptotic caspases can participate in cellular proliferation and cell cycle regulation, as well as the differentiation of a widespread number of cell types.

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Abbreviations: FADD, Fas-associating protein with death domain; PARP, poly(ADP-ribose)polymerase.

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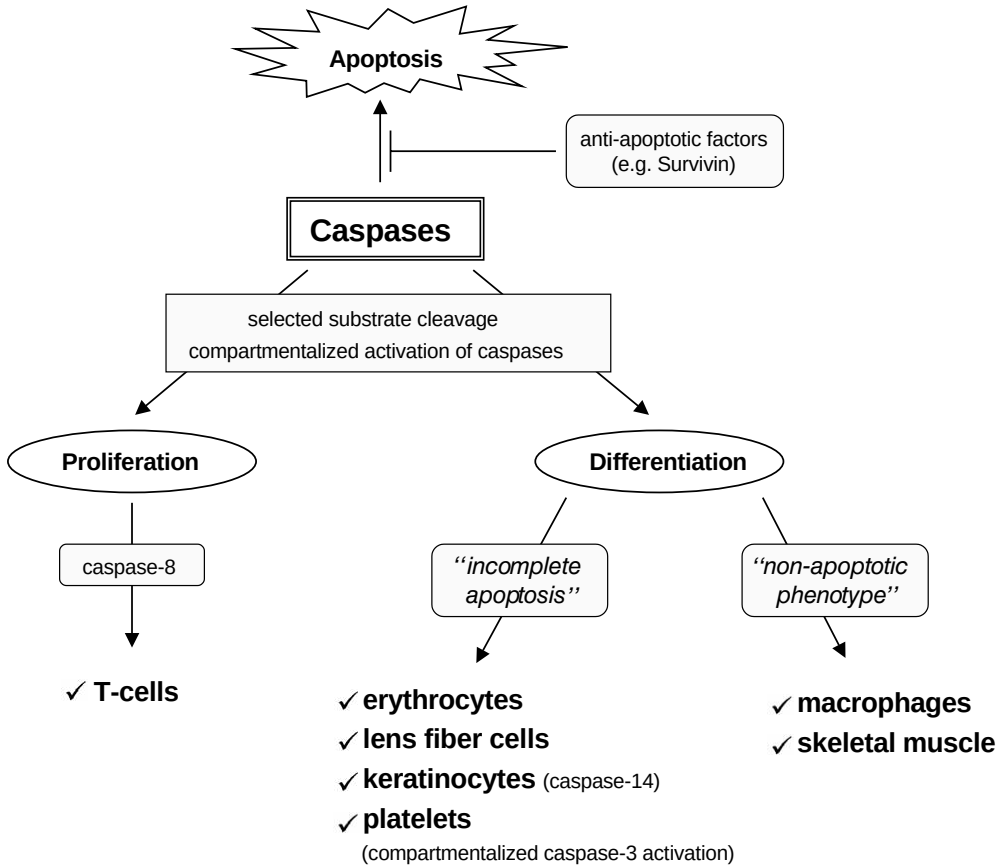

Fig. 1. Schematic representation of apoptosis-independent functions of caspases. Caspases are involved in non-apoptotic processes leading to either cellular proliferation or differentiation. A key role might play the proteolysis of selected substrates regulated by anti-apoptotic factors or a compartmentalized caspase activation. The outlined processes are discussed in detail in the text of this review.

2. A role of apoptotic caspases in T-cell proliferation

Removal of lymphocytes after an immune response by death receptor mediated apoptosis is critical for the maintenance of lymphocyte homeostasis. Accordingly, functional deficiency of the Fas (CD95/APO-1) receptor or its ligand (FasL) has been identified as the cause of disease in mice (reviewed in [8]) and humans [9,10] with lymphadenopathy and autoimmunity, which are characterized by an uncontrolled accumulation of lymphocytes. These observations confirmed the important role of apoptosis in lymphocyte homeostasis and it was assumed that mutations in other components of the Fas/FasL pathway, e.g. in the FADD, would lead to a similar phenotype. Therefore, it was surprising when it was discovered that impairment of FADD function did not only cause resistance to Fas-mediated apoptosis, but also led to a defect in activation-induced proliferation of T-lymphocytes rather than overproduction of lymphocytes [11–15], pointing to an additional role of FADD and possibly apoptotic caspases in T-cell proliferation. Interestingly, earlier data had shown activation of caspases (caspase-3) in PHA-stimulated T-lymphocytes in the absence of apoptosis [16]. Employing cell-permeable caspase inhibitors, it was subsequently discovered by Alam *et al.* [17] and Kennedy *et al.* [18] that caspases are required for proliferation of primary human T-cells *in vitro*. Both reports indicated that T-cell receptor activation after CD3 ligation leads to activation of an upstream caspase (most likely caspase-8) but not to apoptosis. More direct evidence for a role of caspases in T-cell proliferation was provided in a recent study by Chun *et al.* [19], who demonstrated that in patients with a defect in caspase-8 function T-cell proliferation is impaired. Caspase-8 function in lymphocyte activation is probably independent of Fas, since patients with defects in Fas do not display immunodeficiency [20].

Still, important questions remain to be answered. Some of these concern the observation that mice, which overexpress the caspase-1 and -8 inhibitor CrmA, do not display defects in T-cell proliferation [11] and the fact that FADD-deficient mice produce interleukin (IL)-2 [14], while the patients described by Chun *et al.* [19] are deficient in IL-2 production, indicating that the defect in T-cell proliferation in the two systems occurs at different levels. Further experimentation is required to decipher the observed differences in the described systems.

How do apoptotic caspases mediate a function in cell proliferation? Analyses of proteins cleaved by caspases have identified a large number of targets, which are involved in cell cycle regulation (reviewed in [21,22]).

Among those are factors that inhibit cell cycle progression like the cyclin inhibitors $p21^{Cip1/Waf1}$ and $p27^{Kip1}$ [23] as well as the protein kinase Wee1 [24]. Wee1 mediates cell cycle arrest by phosphorylation and thereby inhibition of the cell-cycle regulating kinase cdc2 (reviewed in [25]). Cleavage of Wee1 by activated caspases prevents phosphorylation of cdc2 and therefore promotes kinase activity of cdc2 and progression through the cell cycle. In apoptotic Jurkat cells processing of Wee1 caused a strong decrease in Wee1 activity that correlated with an increase in cdc2 activity [24]. Importantly, Alam *et al.* [17] observed cleavage of Wee1, PARP and lamin B by activated caspases during T-cell proliferation. While the reason for cleavage of PARP and lamin B is less clear, processing of Wee1 would be in agreement with a function of caspases in cell cycle progression. In contrast, cleavage of DNA fragmentation factor (DFF45) or replication factor C, events that would be detrimental for cellular proliferation, could not be observed, indicating that selective substrate specificity might play a key role in non-apoptotic functions of caspases [17]. Interestingly, a target of active cdc2 is the protein survivin [26]. Survivin is involved in the regulation of proliferation as well as inhibition of apoptosis and could therefore participate in cell cycle progression mediated by caspase-induced cleavage of Wee1 and at the same time provide a tool to control substrate specificity of activated caspases [27]. It should be interesting to determine, whether other apoptosis-inhibiting proteins can be employed to restrict caspase-activity during non-apoptotic functions.

3. Functions of apoptotic caspases in cell differentiation and other cellular events

3.1. Cell differentiation viewed as incomplete apoptosis

Additionally to the putative role of apoptotic caspases in cell proliferation, several reports have provided substantial evidence that apoptotic caspases are also involved in the differentiation of diverse cell types. A potential participation of caspases in differentiation had first been described by Ishizaki *et al.* [28], who had reported the activation of a caspase-3 like protease during the terminal differentiation of rodent lens epithelial cells into lens fibers *in vivo*. During differentiation lens cells displayed typical features of apoptosis like cleavage of PARP and the presence of TUNEL-positive nuclei. Interestingly, the cell nucleus and other organelles are lost during this process, a phenomenon that also resembles the appearance of apoptotic cells. These observations lead the authors to propose a possible involvement of activated caspases during the development of erythrocytes and skin keratinocytes, cell types which also loose their nuclei during differentiation [28]. In fact, subsequent studies have identified a role of caspases both during erythropoiesis as well as keratinocyte differentiation [29–32]. Therefore, apoptosis in these cell types might be considered as a kind of incomplete apoptosis.

Terminal differentiation of keratinocytes into corneocytes is required for the formation of a barrier that protects an organism against external damaging influences and water loss (reviewed in [33]). Implicated in keratinocyte differentiation is caspase-14, which is the only caspase with a restricted tissue expression. Caspase-14 is mainly confined to epidermal keratinocytes [34], and expression of caspase-14 in this cell type is regulated by retinoids in a differentiation-associated manner [35]. Activation of caspase-14 occurs during the terminal differentiation of keratinocytes *in vitro*, suggesting a role of this caspase in skin barrier formation [36].

While in the case of lens cells and keratinocytes activated caspases seem to promote cell differentiation, the role of caspases during erythrocyte differentiation might be more variable. Strictly required for the maturation of erythroblasts is the transcription factor GATA-1, which is involved in the expression of erythroid-specific genes [37]. Studies by De Maria *et al.* [29] proposed that erythropoiesis is regulated by a negative feedback loop in which mature erythroblasts inhibit the differentiation of immature erythroblasts by expression of FasL. Exposure of immature erythroblasts to anti-Fas antibodies at a concentration that does not induce apoptosis led to a selective cleavage of GATA-1 by activated caspases and inhibition of erythrocyte maturation [30]. Although these results pointed to a negative function of caspases in erythropoiesis following death receptor engagement, more recent reports identified a distinct process in which apoptotic caspases played a positive role in differentiation of human and murine erythroblasts [32,38]. Both groups reported that caspase inhibitors arrested or delayed the maturation of erythroid progenitors. Intriguingly, as observed during T-cell proliferation, activated apoptotic caspases cleaved selected substrates during the differentiation process [32]. While, consistent with a role in enucleation, processing of PARP, lamin B and the putative chromatin condensation factor Acinus could be detected, DFF45 and GATA-1 were not cleaved. Regulation of the function of caspases in eryhtropoiesis might be controlled by the kinase Raf-1, since differentiation-associated caspase activation is accelerated in erythroid progenitors lacking Raf-1 [38].

Another type of anucleate cells is platelets, which are produced by megakaryocytes. Interestingly, a recent report has provided evidence that apoptotic caspases are also involved in platelet formation [39]. During this process caspase-3 and -9 are activated causing proteolysis of the substrates gelsolin and PARP, in the absence of detectable DNA fragmentation. Formation of platelets could be prevented by a caspase inhibitor but not by an inhibitor of calpain. Most importantly, while maturing megakaryocytes exhibited a punctuate cytoplasmatic localization pattern of

caspase-3, in senescent megakaryocytes active caspase-3 was distributed diffusely over the cytosol. These observations lead the authors to propose that cleavage of selected substrates is achieved by a compartmentalized activation of caspase-3 [39]. It will be interesting to see, whether a localized distribution of caspases can also be observed during other non-apoptotic cellular processes that involve cleavage of specific substrates by activated caspases.

It is noteworthy that restriction of substrate cleavage might also depend on the level of caspase activation. It has been shown that mild activation of caspases, like it occurs during differentiation processes, leads to partial proteolysis of the GTPase RasGAP, a regulator of Ras- and Rho-dependent signaling pathways [40]. Partial cleavage of RasGAP produces an N-terminal fragment (fragment N), which mediates anti-apoptotic function via an unusual mode of Ras activation [40,41]. The anti-apoptotic function of fragment N could help to control caspase activity during cell differentiation. In contrast, high levels of caspase activation lead to generation of pro-apoptotic fragments [40], suggesting that RasGAP might be a sensor of caspase activity to either inhibit or facilitate cell death.

3.2. Functions of caspases in cells with "non-apoptotic" morphology

While the caspase-regulated differentiation processes mentioned in the previous section all involved cell types with morphological features resembling apoptotic cells (e.g. enucleation), a function of activated apoptotic caspases has also been suggested in the differentiation of cells with a "non-apoptotic" morphology. Activation of caspase-3 and -9 was demonstrated in human peripheral blood monocytes induced to differentiate into macrophages [42]. Caspase activation was specific, since it could not be observed in monocytes undergoing dendritic cell differentiation. Macrophage differentiation-associated caspase activation lead to specific cleavage of Acinus, while PARP was not proteolysed and involved the release of cytochrome C from the mitochondria. Although inhibition of differentiation by caspase inhibitors or overexpression of Bcl-2 supported the role of activated caspases, the exact mechanisms of regulation of caspase activity are not clear [42].

Another recent report showed that caspase-3 activity is involved in skeletal muscle differentiation, since primary myoblasts from caspase-3 knock-out mice displayed a severe lack of myotube and myofiber formation as well as reduction of muscle-specific gene expression [43]. A target of caspase-3 is the Mammalian Sterile Twenty-like kinase (MST1), which is activated upon caspase cleavage [44]. Active MST1 kinase rescued the differentiation defect in the caspase-3-deficient myoblasts, thus identifying MST1 as a crucial effector of caspase-3 [43]. It is of interest that apoptotic cells and differentiating myoblasts share certain features, e.g. disassembly and reorganization of the actin fiber. This conservation might explain the requirement of active caspases in muscle cell differentiation.

Besides the above-mentioned functions in differentiation apoptotic caspases play a role in other cellular events. A very recent publication has reported a requirement of activated caspase-3 for neuroprotection in ischemic preconditioning, in which a prior exposure to sublethal challenges renders neurons less vulnerable to subsequent insults [45]. The authors proposed that during preconditioning limiting amounts of activated caspases are held in check by the heat shock cognate protein (HSC) 70. Depletion of HSC 70 then leads to upregulation of the neuroprotective heat shock protein (HSP) 70 [45]. Other reports have suggested a role of caspases in cell spreading, cell migration and receptor internalization [46], adding to the broad variety of functions mediated by apoptotic caspases.

4. Conclusions

Apoptotic caspase are not only the major executioners of programmed cell death, but they also play important roles in diverse non-apoptotic cellular processes like proliferation, cell cycle regulation and differentiation. It will be important to find out, how the caspases mediate these functions without driving the cell into apoptosis and which factors regulate their activity. While the specific cleavage of selected target proteins emerges as one important factor for the save execution of non-apoptotic functions by apoptotic caspases, it remains to be clarified how cells can restrict the proteolytic activity of activated caspases to the selected substrates. Possible and not mutually exclusive solutions to this question include the regulation of caspase activity by anti-apoptotic factors, via a localized activation in distinct cellular compartments, or through a limited activity during cell differentiation.

It is likely that in the future a non-apoptotic role of activated caspases will be discovered in many more cell types and cellular events. A precise understanding of these processes would not only require a detailed knowledge of the specific targets and their function, but also to decipher the regulatory mechanisms, which control the activity of the apoptotic caspases before and after activation.

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