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When dying is not the end: Apoptotic caspases as drivers of proliferation

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ABSTRACT

Caspases are well known for their role as executioners of apoptosis. However, recent studies have revealed that these lethal enzymes also have important mitogenic functions. Caspases can promote proliferation through autonomous regulation of the cell cycle, as well as by induction of secreted signals, which have a profound impact in neighboring tissues. Here, I review the proliferative role of caspases during development and homeostasis, in addition to their key regenerative function during tissue repair upon injury. Furthermore, the emerging properties of apoptotic caspases as drivers of carcinogenesis are discussed, as well as their involvement in other diseases. Finally, I examine further effects of caspases regulating death and survival in a non-autonomous manner.

Contents

1. Introduction

Apoptosis is the most relevant form of programmed cell death during development and homeostasis. It plays a crucial role in the removal of unwanted tissues, shaping organs and adjusting cell numbers. Mechanistically, apoptosis is triggered by the activity of caspases, a family of cysteine proteases that are present in most cells as inactive zymogens. Their activation is dependent upon the formation of a multimeric protein complex called the apoptosome, which cleaves and activates "initiator" caspases. This in turn results in activation cleavage of "effector" caspases, the actual execution-

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ers of apoptosis, which can proteolyse multiple substrates leading to the demise of the cell [1].

Given the lethal role of caspases, it might seem surprising that these dangerous killers are used for a plethora of non-apoptotic functions, oftentimes essential for vital processes. Some of these roles involve extensive protein degradation and can be regarded as controlled forms of apoptosis, where caspases are utilized for a localized proteolitic purpose without facilitating cell death. This restricted function plays a key role in neuronal pruning, spermatid maturation or erytrocyte enucleation [2]. But caspases are also involved in non-degradative processes such as differentiation, motility, cell fusion and cell proliferation [3]. The role of caspases in triggering proliferation is specially striking: it seems counterintuitive that enzymes that have the ability to destroy the cell can also induce cell division. However, it is becoming increasingly clear that caspases are much more versatile than previously thought. In some cases, caspases can carry out their apoptotic and mitogenic roles simultaneously, and while prompting the destruction of one cell, they can induce proliferation of neighboring cells, a mechanism that can be very valuable to compensate for cell loss [4–6]. Yet, in other situations, cells can tolerate certain levels or localized activation of caspases without compromising their viability [7]. In this scenario, the same cell that activates these lethal enzymes can be the one that is instructed to divide.

2. Mechanisms of caspase-induced proliferation

As mentioned before, caspases can induce proliferation both in the same cell where they get activated and in the surrounding cells. This autonomous versus non-autonomous effect usually involves different mechanisms: autonomous proliferation can be triggered for instance by the specific cleavage of a particular substrate that inhibits cell cycle progression, while non-autonomous proliferation often relies on the secretion of mitogenic signals from the caspase-containing cell [3]. There are mainly 3 different scenarios where caspase-induced proliferation can be studied:

2.1. Autonomous proliferation

In this scenario, the same cell that exhibits caspase activation displays enhanced proliferation (Fig. 1A). This implies that the cell is able to survive the self-terminating function of caspases, which can be achieved in several ways. On one hand, if the intensity of caspase activation is kept below a certain threshold, the cell might be able to sustain these low levels of caspase activity without dying [8]. Moreover, appropriate expression of certain caspase inhibitors can keep caspases in check and limit the extent of their activation [9,10]. Additionally, caspases can be activated in a localized fashion, concentrating these dangerous enzymes in the specific subcellular compartment where they have to exert their non-apoptotic role and keeping them away from other potential substrates [10–12]. Finally, it has been recently shown that cells can reverse apoptosis, even when they already reached late stages in the apoptotic process. This remarkable phenomenon has been called “anastasis” – “rising to life” in greek – [13]. Different tracking methods have been generated to label cells that have at some point activated caspases and survived [14,15]. However, the physiological role of anastasis, or whether it even occurs during development is still debated, since these methods not only label cells that have initiated apoptosis and reversed the process but also cells where caspases is activated independently of cell death. Nevertheless, these studies have revealed that there are numerous cells in different tissues that might activate caspases for non-lethal purposes during and after development.

Surprisingly, one of the reasons why a cell might decide to activate caspases is to enter cell division. Multiple observations point to a possible role of caspases in cell cycle regulation. For example, caspases have been shown to be upregulated right before or during mitosis, and treatment with caspase inhibitors can delay mitotic progression [16]. Likewise, non-apoptotic caspase activation has been reported in tissues that exhibit active proliferation [17,18]. However, very little is really known about the mechanism behind these observations. On one hand, caspases have the ability to cleave cell cycle regulators. For example, $p21^{Cip1/Waf1}$, a cyclin-dependent kinase (CDK) inhibitor, is specifically cleaved by caspases upon induction of apoptosis [19]. This would suggest a potential mechanism for inducing proliferation in cells that contain active caspases but resist cell death.

Additionally, an alternative mechanism has recently been proposed. Several studies have shown that sub-lethal activation of caspases promote genetic instability and oncogenic transformation [13,20,21]. Insights into the underlying mechanism are starting to emerge. In an elegant study, Liu et al. showed that caspase-3 activation following irradiation induces persistent DNA strand breaks and chromosome aberrations in cells that survive the initial insult [21]. Furthermore, high levels of caspase-3 activation promoted tumorogenesis in different in vitro and in vivo assays, which was blocked in a caspase-3 mutant background. Importantly, they showed that a key player in the promotion of DNA damage and oncogenic transformation is the apoptotic nuclease Endonuclease G (EndoG). Upon caspase-3 activation EndoG moves from the cytoplasm to the nucleus, and knockdown of EndoG reduced the number of DNA strand breaks and chromosomal aberrations after irradiation, as well as the ability of irradiated cells to form soft agar colonies, an indication of their attenuated oncogenic potential [21]. Remarkably, a recent study by Cartwright et al. has found that activation of EndoG downstream of caspase-3 is at the basis of the tumor promoting properties of the proto-oncogene Myc, one of the most commonly affected genes in human cancers (see Section 4.1) [22]. Further research will be needed to explain why caspase-induced DNA damage specifically promotes cell proliferation and carcinogenesis, and which are the tumor suppressor genes affected under these circumstances.

2.2. Apoptosis-induced proliferation

In certain paradigms the proliferative function of caspases is in line with their deadly nature. Although apoptosis has been traditionally regarded as a silent way of dying, it is now well established that dying cells can release mitogenic signals that promote proliferation in a non-autonomous manner [4]. In this scenario caspases play a crucial role both in the destruction of the cell in which they are activated as well as in the proliferation of the neighboring cells (Fig. 1B). By coupling intrinsic death and non-autonomous growth, caspases provide a very useful mechanism to compensate for cell elimination after stress or injury. And indeed apoptosis-induced proliferation has been proven to be crucial during homeostasis, wound healing, response after injury and regeneration in a wide range of organisms, from flatworms to mammals [4,5,23]. As the other side of the coin, apoptosis in tumors, both as a result of the interaction with surrounding cells or as a consequence of treatment, can induce tumor growth, cancer relapse and metastasis [7]. Consistently, the mechanism behind these phenomena is the production and secretion of signals by dying cells. Some of these signals seem to be conserved across species. For example Wnt, one of the first mitogenic signals that was found to be emitted by dying cells, is produced both in stress-induced apoptosis in the imaginal discs of fruit flies [24–26] and during the re-growth of the head after decapitation in Hydra (see below) [27]. Likewise, Hedgehog (Hh) has been shown to drive compensatory proliferation in *Drosophila* eye discs [28], as well as regeneration in mouse liver [28,29]. Moreover, one of the most recurrent players involved in wound healing,

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