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Review

Caspase signaling, a conserved inductive cue for metazoan cell differentiation

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ABSTRACT

Caspase signaling pathways were originally discovered as conveyors of programmed cell death, yet a compendium of research over the past two decades have demonstrated that these same conduits have a plethora of physiologic functions. Arguably the most extensive non-death activity that has been attributed to this protease clade is the capacity to induce cell differentiation. Caspase control of differentiation is conserved across diverse metazoan organisms from flies to humans, suggesting an ancient origin for this form of cell fate control. Here we discuss the mechanisms by which caspase enzymes manage differentiation, the targeted substrates that may be common across cell lineages, and the countervailing signals that may be essential for these proteases to 'execute' this non-death cell fate.

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Contents

1. General introduction

Caspases are a family of 12-fate determining cysteine-dependent aspartate-directed proteases [1,2] that were originally discovered for their role in the initiating and executing of the process of programmed cell death, or apoptosis [3–5]. Caspases have been sub-divided into three main groups based on sequence homology and biological function. Group I consist of the inflammatory caspases-1, -4, and -5 (caspase-11 in mouse); Group II are classically described as the 'executioners' and comprises the caspases-3, -6, and -7; and Group III are the 'initiator' caspases-8, -9, and -10. The most studied forms of apoptosis are largely focused on two signaling pathways that utilize Group II and Group III caspases together. In one case, this cascade is driven by mitochondrial signaling events where release of cytochrome C stimulates the assembly of a multi-protein complex comprising the initiator caspase, caspase 9, Apaf-1 and cytochrome C. Once assembled, this complex leads to proximity induced activation of caspase 9 which then cleavage activates

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effector caspases (3/7) to propagate an apoptosis signal. The second cascade is referred to as the extrinsic cell death pathway, which is triggered by ligand stimulation of membrane receptors of the larger TNF family. Once stimulated, these receptors scaffold then activate initiator caspases (8/10), which in turn target and cleavage activate effector caspase enzymes. The convergence of these pathways on effector caspase proteins is the critical step in the death process, where unrestrained activation of these proteases can result in global cleavage of the proteome.

In addition to apoptosis, caspases are also involved in many non-apoptotic processes including cell cycle progression, proteostasis and cellular remodeling. Arguably, the most prominent role for these proteases is in the mediation of cellular differentiation, with compelling evidence demonstrating that the core intrinsic and extrinsic pathways (along with individual caspase proteins) induce and manage the differentiation program [6,7]. In the following review, we will discuss this conserved non-apoptotic role of caspase proteases. We will examine the cell lineage and species diversity that utilize caspase signaling to control differentiation; the structural and genomic alterations that are managed by caspase activity to drive the differentiation process; and finally, the regulatory mechanisms that initiate and specify caspase signaling outcomes.

2. Caspase mediated cell differentiation – a conserved metazoan phenomenon

Caspase regulation of differentiation was first reported in a number of lineages, including lens fiber epithelial cells, keratinocytes and red blood cells [8–10]. The rationale to investigate caspase signaling derived from the observation that the differentiation process in these short-lived cell types was remarkably similar to apoptosis, where the final maturation step involved nuclear extrusion or destruction. As such, the role of caspase activity in the maturation of these cells aligned with the prevailing death centric view for these proteases. However, three seminal studies quickly followed, demonstrating that transient effector caspase activity was required for the differentiation of cells that did not display an attenuated apoptosis phenotype. Specifically, effector caspase activity was shown to be essential for 1) murine muscle cell differentiation and the fusion into mature myofibers [11]; 2) the differentiation of human monocytes into macrophages [12]; and 3) the differentiation and maturation of Drosophila spermatids [13]. Unlike the enucleation phenotypes, differentiated skeletal muscle fibers are a long-lived cell type, and spermatids as the male germ cell require obvious vigilance in protecting a heritable genome. Together, these latter studies spurred an intensification in the field, which has culminated in the knowledge that caspase signaling is essential for differentiation across a plethora of cell types and in divergent metazoan organisms (including round worms, fruit flies, amphibians, mice and humans) [7]. What is particularly noteworthy is that many of these studies confirmed that transient activation of the intrinsic/mitochondrial death pathway was essential for completion of the differentiation program (reviewed in Bell and Megeney 2017 [7]).

3. Caspase induced morphology during cell differentiation

The relative conservation of effector caspase proteins as mediators of apoptosis and differentiation suggest that these enzymes may induce a cohort of universal morphologic changes, irrespective of cell fate. The corollary to this hypothesis is that differentiation associated caspase signaling is transient and therefore unlikely to spur morphologic change that is contrary to maintaining cell viability. For example, apoptosis is typically associated with membrane alterations, organelle changes, chromatin condensation and DNA damage, yet these same alterations present as consistent, yet transient features of differentiating cells, across a variety of metazoans. Apoptotic membrane inversion was one of the first cell death related morphology changes to be linked with cell differentiation. Apoptotic cells invert the plasma membrane, exposing the inner phosphatidylserine layer, which relays a signal for phagocyte engulfment and clearance of the dying cell [14], and an early study noted that fusion of individual skeletal muscle myoblasts to form mature myofibers required phosphatidylserine inversion at the points of contact between fusing cells [15]. As noted above, caspase 3 activity is essential for differentiation and fusion of myoblasts [11,16] and the latter process has been linked to caspase activation of phosphatidylserine binding proteins such as BAI1 [17]. Differentiation and fusion of cytotrophoblasts to form the syncytial structure of the placenta also requires elevated caspase 3 activity, which cleave and reorient cytoskeletal proteins [18].

In addition to regulation of cell fusion, caspase activation has also been linked to managing profound structural changes that occur in other differentiating cell lineages. In a series of elegant studies, Arama et al. demonstrated that the individualization and maturation of Drosophila spermatids was dependent on cytochrome C activation of the effector caspase drICE. In turn, drICE controlled spermatid differentiation through bulk removal of cytoplasm [19]. More recent studies from the Arama group indicate that the caspase/drICE activity in spermatid differentiation is controlled through a restricted subcellular localization pattern, where the active caspase is tethered to a larger protein regulatory complex at the outer mitochondrial membrane [20]. At this juncture, it is not clear whether this caspase control of sperm differentiation and maturation is specific to Drosophila or whether this activity is conserved across metazoan organisms.

One trait of caspase induced cell morphology that appears more broadly conserved is the cytoskeletal reorganization that occurs during neuronal differentiation and adaptation. Caspase control of neural differentiation was initially reported in both Drosophila and murine models. In the Drosophila model, dark-dependent caspase activity was shown to be critical for macrochaete formation, key sensory organs of the peripheral nervous system [21]. In the murine study, caspase 3 activity was shown to be required for the differentiation of a broad range of neural cell lineages including oligodendrocytes, astrocytes and neurons. Here, caspase activity was reported to control the expression of maturation specific markers and to promote dendrite formation in differentiating striatal neurons [22]. Following these pioneering studies, caspase control of neural differentiation has been intently studied and more recent investigations have focused on how these proteases manage neural adaptation and plasticity [23]. The emerging data suggests that effector caspase activity manages intra and extra neuron communication by targeting a cohort of cytoskeletal proteins to prune dendrites, synapses and axons [24–26].

4. Caspase/CAD directed DNA strand breaks and the control of cell differentiation

Caspase proteolytic activity has a direct impact on the structural features of differentiating cells, yet this function alone does not explain how these proteases so profoundly alter cell fate. Indeed, it was patently clear from the earliest studies in this area that caspase activation was concurrent to if not responsible for the dramatic alterations in gene expression that occur during differentiation. As such, understanding how caspase signaling communicates with the nucleus is essential to unraveling its differentiation specific function.

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