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Review

Non-apoptotic Caspase regulation of stem cell properties

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ABSTRACT

The evolutionarily conserved family of proteins called caspases are the main factors mediating the orchestrated programme of cell suicide known as apoptosis. Since this protein family was associated with this essential biological function, the majority of scientific efforts were focused towards understanding their molecular activation and function during cell death. However, an emerging body of evidence has highlighted a repertoire of non-lethal roles within a large variety of cell types, including stem cells. Here we intend to provide a comprehensive overview of the key role of caspases as regulators of stem cell properties. Finally, we briefly discuss the possible pathological consequences of caspase malfunction in stem cells, and the therapeutic potential of caspase regulation applied to this context.

Contents

1. General overview of the caspase protein family

In nature, being in the wrong place often has fatal consequences. At the cellular level, this situation normally ends with the elimination of misplaced elements via genetically encoded systems of programmed cell death. Caspases are Cysteine-ASPartic proteASES present in all metazoans that have been intensively studied for being the major regulators of programmed cell death through apoptosis [1–8] (Fig. 1). They execute this biological function by utilizing their protease activity over a plethora of target substrates located in different subcellular organelles [7], which ultimately provokes a generalized collapse of all metabolic functions. Structurally, all caspases contain one large and one small subunit that form the catalytic pocket responsible for enzymatic function. Additionally, some members incorporate a large pro-domain of variable composition appended to the N-terminal end. Depending on the structural composition of the pro-domain – some of which include CAspase Recruiting or Death Effector Domains (CARDs and DEDs) – different adaptor complexes can interact with the several members of the

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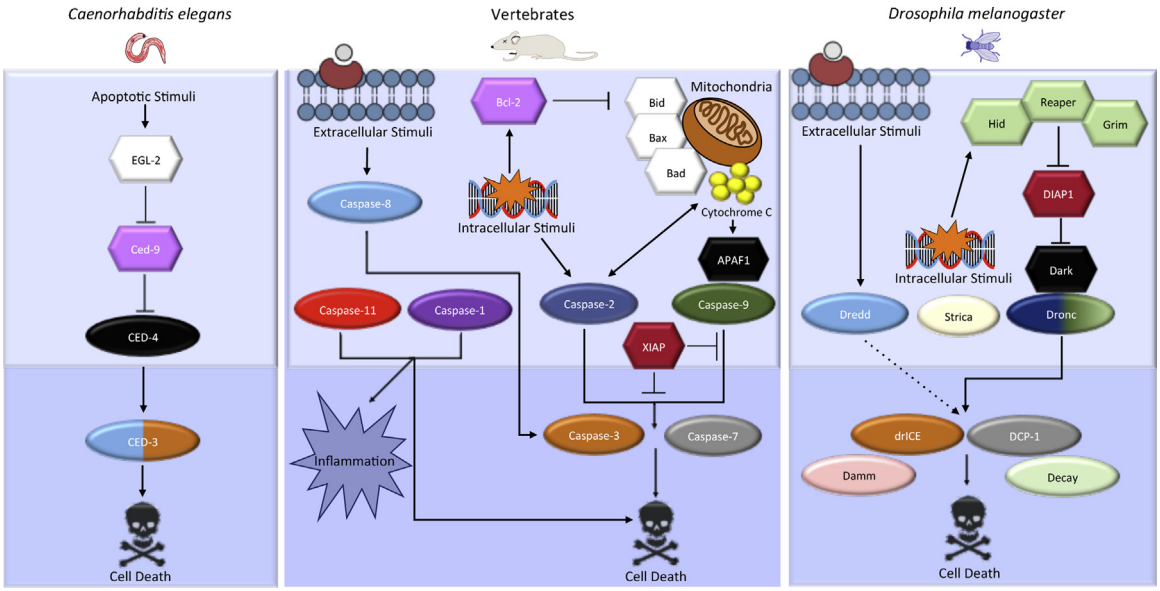

Fig. 1. Diagram showing the evolutionary conservation of the main caspase regulators of apoptosis. The ellipsoid shape designates all caspase members included in the apoptotic pathway, whereas the hexagons are accessory apoptotic proteins. Similar proteins across species follow the same colour scheme. The light blue region encompasses what are considered the apical/initiator caspase members, whereas the dark blue area sorrounds the effector/executioner caspases.

caspase family [7,8]. Historically, the caspase members have been grossly classified as apoptotic or inflammatory, taking into account their primary roles, but this classification does not accurately reflect their diverse functional nature, since several caspases can participate in both of these processes, as well as others [8]. At least in the context of apoptosis, it is more precise to classify the caspases as initiator/apical and executioners/effector caspases, based on their early or late activation during this process [8] (Fig. 1).

Synthesized as inactive zymogens, caspases only become fully active after several steps of self-processing upon multimerization [8–10]. Initiator caspases are responsible for the exponential activation of effector caspases during apoptosis [11]. Complex signalling events arising from intracellular organelles (mainly mitochondria) and/or extracellular receptors facilitate the engagement of multimeric adaptor platforms (apoptosome, inflammasome, piddosome) that promote caspase activation [8]. Conversely, caspases are inactivated through either post-translational modifications – mainly phosphorylation and ubiquitylation – or interactions with modulatory proteins [6,9,10,12,13]. Stringent regulation of caspase activation is crucial to avoid the inadvertent activation of cell death as well as an onset of diseases [1,2,8,14]. Beyond this well-characterized apoptotic role, recent investigations have shown that moderate levels of caspase activation can transiently process localized substrates in specific subcellular compartments without causing cell death [2–6,15]. For example, it has been reported that moderate caspase activity in neuronal dendrites is crucial to remodel such cellular projections without causing apoptosis, thus reconfiguring the network of neural connectivity [16]. These non-lethal activities are able to modify the function of binding partners and substrates, often stimulating their degradation, but also triggering their subcellular delocalization, activation or differential binding to other proteins. Indeed, the non-lethal caspase activities can be exclusively mediated by protein–protein interactions without the need for enzymatic function (e.g. [17]). Importantly, non-lethal caspase activation has been shown to be instrumental in controlling a broad range of essential cellular processes (e.g proliferation, cell fate determination, differentiation, migration, secretion, cytoskeleton remodelling [1–6,8]) in a tissue-specific manner. Furthermore, if deregulated, they can contribute decisively to the pathophysiology of multiple diseases [1,3,5,8,18–24]. Although our current knowledge concerning the biochemistry of caspase activation is quite detailed during apoptosis, much remains unknown in non-lethal contexts. Furthermore, the identity of tissue specific target substrates participating in these non-apoptotic functions, remains elusive. The elucidation of these questions is essential to fully understand caspase biology, and potentially develop efficient therapeutic interventions against caspase-associated diseases.

2. Stem cells: fundamental concepts

One of the most remarkable achievements in the biology of multicellular organisms is the sophisticated variety of differentiated cells and tissues generated from a single primordial cell throughout development. Equally astonishing is the enduring potential for regeneration present in most organs, which protects against the cellular wear and tear triggered by various intrinsic or environmental insults. Both scenarios demand the presence of undifferentiated cellular precursors with the capacity for self-renewal and differentiation, known as stem cells [25,26] (Fig. 2A). In this review, we intend to provide a comprehensive compilation of the most recent findings that associate the non-lethal activity of caspases with the regulation of stem cell physiology.

The self-renewing capability and the competency to acquire multiple cell fates are the basic properties defining a stem cell. Several types of stem cells, distinguishable by their cellular ontogeny and differentiation potential, have been described. Embryonic stem cells (ESCs) are present in early embryos (usually before pre-implantation) and possess unlimited differentiation potential (totipotent or pluripotent). They can therefore give rise to virtually any cell type of the organism [25]. Adult or somatic stem cells retain the ability to self-renew, but are restricted in their differentiation potential to those cell derivatives existing within its host tissue. Adult stem cells can show either unipotent or multipotent differentiation capabilities, if they can give rise to one or several cell types of the resident tissue, respectively [26]. Importantly, somatic stem cells are responsible for maintaining and repairing their host tissues upon demand, remaining most of the time in quiescence [26] (Fig. 2A). The exit from quiescence (reactivation of proliferation and differentiation) relies heavily on complex cellular interactions

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