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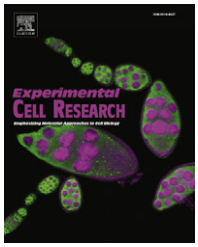

Review Article

Non-apoptotic roles for death-related molecules: When mitochondria chose cell fate

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ABSTRACT

The decision between death and survival is a difficult phase of a cell life. It may depend on the intensity of a stress stimulus, on the presence of invasive pathogens, or on specific signals from neighbouring cells. Death-related molecules are being shown to possess different, and sometimes opposite roles, which they play also according to a number of environmental clues. In this review, we will analyse some of these molecules and their roles, with particular regard to mitochondria-related factors, such as BCL2 family members, the apoptosome components, the autophagy/death cross-talkers and molecules regulating mitochondrial structure and functions. Turning the double-edged swords of death molecules into plougshares may turn out to be strategically crucial in molecular oncology.

Contents

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Introduction

Besides their important role in regulating or executing apoptosis, several key molecules in this process are being identified as key modulators of a number of alternative functions. After the seminal discovery of the mitochondrial pathway of cell death [1], it became clear that the definition 'death molecule' would have been quite limitative, if not inappropriate in most cases. The best example of this mysnomer is cytochrome-*c* (Cyt-*c*), the small and charged activator that, once released from mitochondria, enables Apaf1 conformational changes and apoptosome activation [1,2]. Cyt-*c* is an essential component of the electron transport chain in the oxidative phosphorylation process. Thus, it acts also as a key pro-survival factor in a cell life (and, in fact, its downregulation *in vivo* leads to early lethality, due to lack of energy production). But the list of dual-function or pleiotropic proteins in the context of apoptosis is growing fast. As we will review here, several proteins, which contribute to the maintenance or the change of mitochondrial structure, and rearrange their network in response to a number of stimuli, may also have a pro-death role [3]. *Vice versa*, the apoptosome key component Apaf1 [4] or the best known death-executors, the members of the caspase family of proteases [5], can sustain cell survival, by orchestrating several processes during cell differentiation and development [6]. Finally, on the verge between cell death and survival, other molecules can regulate both apoptosis and autophagy, a degradation pathway essential for recycling cell components both in basal conditions and upon a number of stressors [7,8].

All these new evidence are of the highest importance in cancer biology. Inducing apoptosis in cancer cells is, at present, the major goal of chemo- or radio-therapy [9] and the finding that molecules can play alternative roles within the cell, in some cases paradoxically opposite, can induce the research field to switch towards a more comprehensive analysis of the single molecular functions that can or cannot be modulated when treating tumors.

Cytochrome c, 'good' and 'bad' at the same time

Cyt-*c* is widely known as an efficient biological electron-transporter that, through the transition between the ferrous and ferric states of its heme group, plays its major role in cellular respiration by transporting electrons from Cyt-*c* reductase (Complex III) to cytochrome oxidase (Complex IV). This shuttling takes place at the level of the mitochondrial intermembrane space. Cyt-*c* null mice die very early in embryogenesis, due to a severe energy imbalance [10]. Besides this role as an essential pro-survival protein, a key role for Cyt-*c* has been established in mitochondria-mediated apoptosis: its release from the mitochondrial *cristae*, and from its cardiolipin-mediated anchoring to the mitochondrial membranes, is regulated by a number of BH3-containg pro- and anti-apoptotic protein and is permitted by *cristae* opening (see below) [11]. Once in the cytosol, Cyt-*c* binds the apoptosome core molecule Apaf1 and permits caspase-9 recruitment and its lethal activation [1,4]: A clear pro-death role, for such a generally *good* molecule. Of note, this function in apoptosis is absent in some lower eukaryotes (*Caenorhabditis elegans*) and controversial or very limited in others (*Drosophila melanogaster*) [4]. By elegant *in vivo* experiments, the double-side capacities of Cyt-*c* in vertebrates were finely dissected at the molecular level [12]. How can we explain these contradictory roles? A startling hypothesis is that Cyt-*c* pro-apoptotic activity is a secondary function, acquired from vertebrate cells during evolution to quickly respond with a death program to any mitochondrial damages above a certain threshold. A sensitivity that may have a crucial importance during embryogenesis, far more complicated in higher eukaryotes.

Caspase-3 and friends: problem solvers, not only killers

Cyt-*c* regulation of caspase-9 (Casp-9), through Apaf1 and the apoptosome assembly, allows the mitochondria to signal caspase-3 (Casp-3) towards a lethal program of destruction. Tens of targets for destruction, by this efficient cysteine aspartate protease, have been identified and, with a snap, a cell can be reduced in the goofy mass of an apoptotic body, ready to be orderly phagocytosed by professional or uncoventional phagocytes.

But this is not the only role for deadly Casp-3. Terminal differentiation of vertebrate lens fiber cells [13] and erythrocytes [14], as well as the transition from spermatid to spermatozoa in *Drosophila* [15], all involve proteolytic degradation of major cellular compartments by Casp-3. In these cases, Casp-3 helps removing huge portions of cytosol or controls an ordered DNA fragmentation mediated by caspase-activated DNases, in cells undergoing a terminal differentiation process. Of note, in the case of sperm maturation [15], a specific form of Cyt-*c* contributes to mitochondria-induced activation of Casp-3, indicating a possible secondary acquisition of this role for Cyt-*c* during evolution; and, more important, the fact that an ubiquitin-conjugating enzyme (dBruce), protects *Drosophila* sperm nucleus from degeneration, indicates the possibility that other regulators of Casp-3 (e.g., the inhibitor of apoptosis proteins, IAPs) may protect cells from a more 'general' destruction [16].

Obviously, all these processes are reminiscent of apoptosis by a number of viewpoints: from conceptual to molecular and morphological. The only difference with a death program is that cell destruction is partial, not complete, and functional to a specific morphological sculpture of the cytosol or nucleus.

But other roles, completely unrelated to apoptosis, can be played by caspases. A particular caspase, caspase-1, plays a key role in the inflammation process [17]; another of these cysteine protease, caspase-14, is a major regulator of keratinocyte terminal differentiation, which is important for the formation of the skin barrier [18].

Casp-3 does not make ecception. Disruption is its standard job, but at least another non-apoptotic function can be achieved by this enzyme. Indeed, caspase-3 may act in synaptic plasticity by specifically destroying dendritic spines upon physiological or pathological (such as excessive mitochondria depolarization in Alzheimer's Disease) signaling [19,20]. In the latter case, the accumulation of toxic Aβ (in its monomeric or oligomeric forms) drives the release of Cyt-*c* from post-synaptic mitochondria, thus activating Casp-3 (Fig. 1, bottom-right corner). This leads to Casp-3 targeting of the phosphatase calcineurin, whose cleavage product is constitutively active, being the main cause of dephosphorylation of the AMPA receptor subunit GluR1; internalization of de-phosphorylated GluR1 within the spine is the main trigger for the consequent spine degeneration [19].