Heart Fail Rev (2016) 21:117–121
DOI 10.1007/s10741-016-9538-7

Cell death in the pathogenesis and progression of heart failure

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Published online: 17 February 2016

During evolution, all multicellular organisms develop the highly complex and interconnected processes of cell death. Initially thought to be an accidental uncontrolled development, during the past two decades a clear and comprehensive view has emerged on the many aspects of cell death, which are genetically programmed and therefore tightly regulated. Three major cell death modalities, apoptosis, necrosis and autophagy (Fig. 1), occur in cardiomyocytes, and both gradual and acute cell death are features of the cardiac pathophysiology, including ischemia/reperfusion (I/R), myocardial infarction (MI) and progressive heart failure (HF).

The term **'apoptosis'** (from ancient Greek word describing 'falling leaves') introduced in 1972 define a programmed cell death process distinct from 'necrosis,' which was initially considered as a purely accidental and passive type of cell death [1]. In apoptosis, the plasma membrane maintains its integrity until the late stages of the process, while in necrosis the plasma membrane rapture, swelling of organelles and loss of intracellular contents are early events [2, 3].

Other morphological characteristics of apoptotic cell death include cell rounding-up, reduction in cellular volume (pyknosis), chromatin condensation, nuclear fragmentation (karyorrhexis) and plasma membrane blebbing. A biochemical hallmark of apoptosis is activation of two groups of proteins, caspases (cysteinyl aspartyl proteases), and members of the Bcl2 extended family.

The intrinsic or mitochondrial pathway and the extrinsic or death receptor pathway are two distinct but interlinked pathways which mediate apoptosis. The intrinsic or mitochondrial apoptotic pathway is induced by various stress stimuli, including growth factors deprivation, oxidative stress (OS), genotoxic stress, hypoxia and various toxins. In response to these signals, the members of the Bcl-2 family are recruited to mitochondria and sarcoplasmic reticulum (SR), triggering release of apoptotic proteins from the former and release of Ca^{2+} from the latter. The extrinsic apoptotic pathway also known as the death receptor pathway is initiated by the binding of death ligands, such as FasL, tumor necrosis factor (TNF) or TRAIL, to their cognate cell surface death domain-containing receptors, known as death receptors [4, 5], which are members of the large TNF receptor family characterized by the presence of conserved intracellular death domains (DD), which are essential for the initiation of the apoptotic response [6].

Chronic cardiac remodeling and transition to overt HF have been associated with modestly increased apoptosis [7, 8], although the actual burden of chronic cell loss attributable to apoptosis is not clear. Indeed, measures of actual rates are highly variable and depend on the species, type of injury, timing, location and method of assessment. When viewed in absolute terms, the rate of apoptosis is quite low [9]; however, when the relatively low rates are viewed in the context of months or years, it is entirely plausible that the apoptotic burden could be substantial. Unfortunately, the timing of the apoptotic process is not well defined and the assessment of the true rates and their consequences is still quite limited.

Necrosis (from the Greek word 'necros' for corpse) is characterized morphologically by cell and organelle

This editorial refers to a group of 8 review articles invited for this thematic issue on Cell Death in the Pathogenesis and Progression of Heart Failure, guest edited by José Marín-García.

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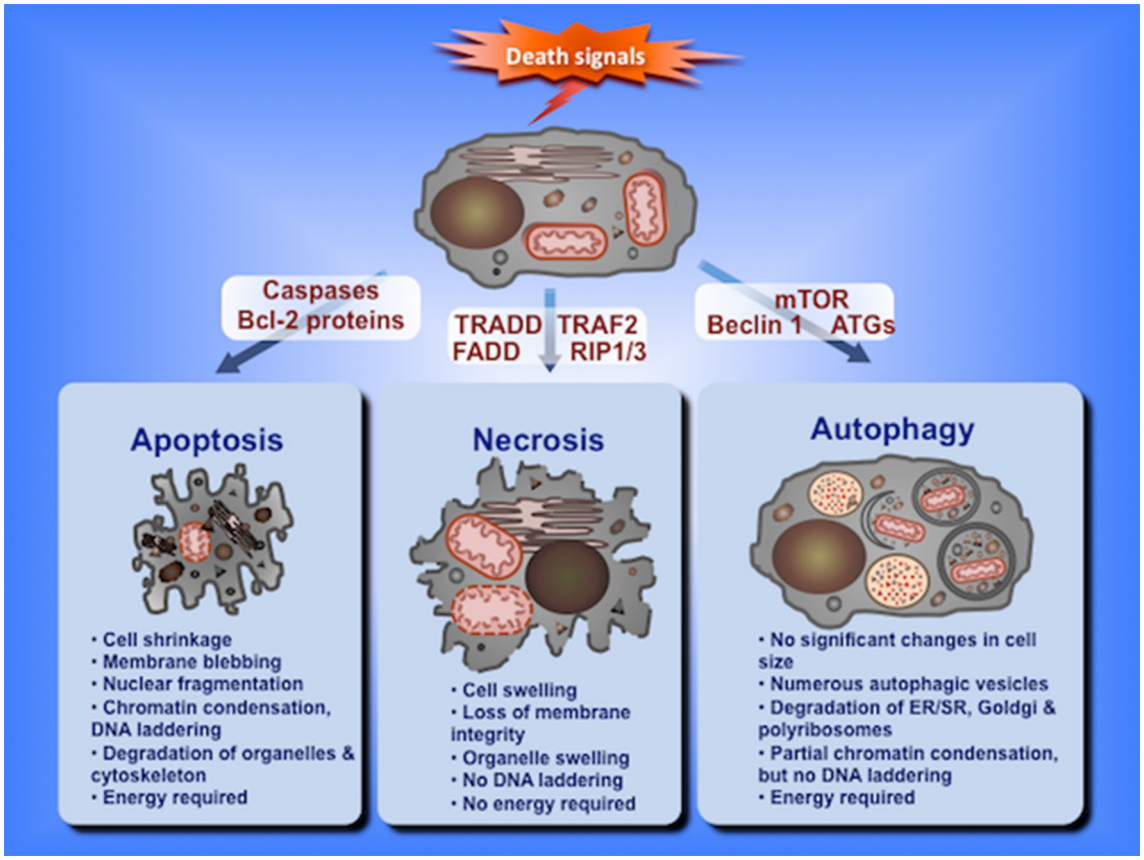

Fig. 1 Schematic representation of the three modes of cell death. Major mediators and morphological characteristics associated with apoptosis, necrosis and autophagy are shown

swelling (oncosis), early plasma membrane rapture and resultant loss of intracellular contents (Fig. 1) [10, 11]. In contrast to apoptosis, this cell death modality has been considered a merely accidental uncontrolled process, but growing evidence suggests that many aspects of necrosis are programmed and tightly regulated. Investigators have proposed that 'necroptosis' describes regulated necrotic cell death [4, 12, 13] with numerous interlinked pathways implicated in necrosis; however, the precise molecular mechanisms of this process is not yet known.

Autophagic cell death or 'macroautophagy,' herein referred to as 'autophagy' (from the Greek 'phagy'—to eat, and 'auto'—oneself), is a tightly orchestrated stress-induced pathway, which involves lysosome-mediated degradation of cytosolic components and organelles [4, 14–18]. Morphologically, autophagy is characterized by massive formation of single- or double-membrane lysosomal-derived vesicles, which sequester degenerating cytoplasmic particles, organelles and protein aggregates (Fig. 1). This evolutionary conserved catabolic pathway plays an essential role during mammalian development and differentiation [19, 20]. Autophagy is usually induced under various stress conditions, including starvation, OS, I/R and pathogen infections, and helps organisms to fight against degenerative, infectious, inflammatory and neoplastic disorders. This type of cell death is primarily a survival response to nutrient deprivation, to recycle intracellular components, and maintain nutrient and energy homeostasis [21, 22]. It is also a cytoprotective mechanism to eliminate damaged and harmful cellular organelles and toxic misfolded proteins [23–25]. Autophagy is initiated by the formation of double-membrane cup-shaped structures, called isolation membranes, also known as phagophores [17]. The phagophores can be generated from various membrane sources, including plasma membrane, mitochondria outer membrane (MOM) and endoplasmic reticulum (ER); different sources might be used in response to distinct stress stimuli [18]. Sealing the edges of the phagophores completes the formation of autophagosomes resulting in sequestering cytosolic components and organelles.

Autophagy, initially viewed as a non-selective process for bulk degradation of damaged organelles and protein aggregates, it is now well appreciated that molecular mechanisms exist for the selective recruitment of the cargo to autophagosomes. Selective forms of autophagy mediate degradation of specific damaged organelles: mitochondria

(mitophagy), ER (ER-phagy), peroxysomes (pexophagy), ribosomes (ribophagy) and intracellular pathogens (xenophagy) [26–30]. Given the paramount multifacetal roles of mitochondria, selective autophagic removal of dysfunctional mitochondria, mitophagy, is attracting increasing interest. Multiple proteins, including ATG32, Parkin, PTEN-induced putative kinase 1 (PINK1), BNIP3, NIX (also called BNIP3L) and the autophagy adaptor protein p62/SQSTM1, appear to contribute to selectivity during mitophagy [31, 32]. Moreover, mitophagy is intimately linked to mitochondrial fusion and fission as discussed in Marin-Garcia and Akhmedov's review [33]. However, the precise molecular mechanisms underlying these complex interconnected processes in HF remain yet to be determined. The dual role that autophagy plays as a cardioprotective and as a harmful process is at present the subject of intensive investigation, although the mechanisms responsible for switching autophagic cardioprotection to damaging outcomes are still largely unknown.

Initial attempts to classify the different types of cell death were mainly based on morphological criteria [34]; however, recent technological advances in biochemistry, molecular biology and genetics have led to important breakthroughs that made possible a functional classification built on the molecular distinctions between the different types of cell death. The Nomenclature Committee on Cell Death (NCCD) has proposed new recommendations on the definition of distinct cell death modalities and guidelines on the use of cell death-related terminology [4, 35, 36]. According to the most recent classification by NCCD, cell death subroutines can be subdivided into four types: apoptosis (including extrinsic and intrinsic apoptosis), regulated necrosis, autophagy and mitotic catastrophe. The term 'mitotic catastrophe' defines cell death which occurs in mitosis as a mechanism avoiding genetic instability [4, 37, 38]. Since the extent to which adult cardiac myocytes are capable of cell cycle reentry is controversial and species-specific differences may exist [39] presently, a discussion on 'mitotic catastrophe' is beyond the scope of this spotlight issue.

It is well established that mitochondria represent key integrators which sustain cell survival, control stress responses and mediate cell death pathways. As discussed by Goldenthal's review [40] in this thematic spotlight, there is evidence that mitochondrial dysfunction contributes to impaired myocardial energetics and increased OS in cardiac I/R and HF. Excessive ROS/RNS generation, which overwhelms cardiac antioxidant defense system, induces cardiomyocytes death and ultimately leads to HF. In this context, the mitochondrial permeability transition pore (MPTP) opening appears as a critical trigger of cardiomyocyte death and of myocardial remodeling. Mitochondria coordinate both apoptotic and necrotic cell death, while a selective autophagic removal of damaged mitochondria, mitophagy, can attenuate mitochondria-mediated apoptosis and necrosis playing a cardioprotective role. Moe and Marin-Garcia [41] present a review on the mechanisms of different types of cell death with clear evidence that mitochondria play pivotal roles in intracellular signaling in both cell death and cardioprotective pathways. Potential strategies for targeting mitochondria in cases of HF are also examined.

A new concept of cardiomyocyte regeneration has been proposed, based on the premises that cardiomyocyte death and regeneration are homeostatic mechanisms intrinsic to both the normal and diseased heart [42].The mechanisms of cardiac remodeling, particularly those underlying the transition from stable hypertrophy to cardiac dilatation and ultimately to overt HF, remain unclear. Many factors including neurohormonal and cytokine activation and impaired Ca^{2+} handling are thought to play a contributory role, particularly following MI [42]. In this regard, the review by Briasoulis et al. [43] focus on the role of inflammation in the pathogenesis of HF where proinflammatory markers levels have been associated with mortality and increased admission rates. Indeed, sustained expression and exposure to cytokines may lead to cardiac dysfunction, alterations in cardiac metabolism, myocardial remodeling and HF progression. The review also highlights the value of proinflammatory cytokines as biomarkers and the application of immunomodulation in HF patients.

Further discussion on the role that apoptosis plays in the pathogenesis of HF, which may be induced by different stimuli and perpetuated by OS and inflammation, is presented by Virzi et al. [44]. In their review, these investigators discuss how HF may trigger various cell-mediated and humoral pathways affecting distant organs such as kidneys, which contribute to increase morbidity and mortality. Thus, the term cardiorenal syndromes referring to this condition may be an important model to investigate the pathophysiology of cardiac and renal malfunction. The role of apoptosis in heart–kidney crosstalk, and mainly its role in cardiorenal syndromes pathogenesis, is also discussed.

With increased work load, the adult heart develops pathological growth and activation of the fetal program of gene expression followed by LV dilatation, thinning of the wall and pump failure. Although alterations in cardiomyocyte contractility contribute to cardiac dysfunction, it cannot adequately account for the profound structural changes that occur in both the cells and the surrounding extracellular matrix (ECM) that characterize cardiac remodeling. Progressive cytoskeletal stiffness, contractile dysfunction and fibrosis typical of the failing heart may be partly explained by the up-regulation of many genes encoding cytoskeletal proteins, sarcomeric proteins and ECM proteins and up-regulation of profibrotic genes. The review by Heckle et al. [45] addresses the important issue

of rescue and recovery of atrophic myocardial cardiomyocytes usually present within the contractile mass of the failing heart. In his investigative studies on hypertensive heart disease, they have found numerous foci of microscopic fibrosis with an endogenous population of atrophic cardiomyocytes. The rescue and recovery of these cells were complemented with the regeneration of the myocardium with circulating stem cells or heart progenitor cells.

Also Piek et al. review [46] provides further evidence that increasing workload of single cardiomyocytes occurs in the fibrotic heart, which will cause augmentation in cell death and replacement of the lost cardiomyocytes by more fibrosis and worsening of cardiac function. Cracking this fibrosis–cell death axis could halt the progression of HF by reversing the remodeling process. Finally, the review by Adameova et al. [47] describes new paradigms for cardiomyocytes death by necroptosis, i.e., combination of necrosis and apoptosis, and the mechanisms of induction and progression of necroptic cell death. Pharmacotherapeutic interventions capable of limiting cell death to improve cardiomyocytes viability are also discussed.

In summary, this thematic issue brings to the forefront the important role that cell death plays in the pathophysiology and pathogenesis of HF and its progression. Although attention has been mainly focused on apoptosis as an essential mechanism contributing to CVD, the significance of necrosis and autophagy in the pathogenesis of I/R, MI and HF is increasingly evident [48]. The dual role of autophagy as a cardioprotective and detrimental process has been the subject of intensive investigations; however, the mechanisms which are responsible for switching autophagic cardioprotective to adverse outcome are still largely unknown.

Thus far, therapeutic approaches that employ reduction in ROS levels have been unsuccessful; therefore, specific targeted treatments based on better knowledge of the precise molecular mechanisms that underlie OS response and ROS/RNS-induced cell death pathways are desirable. Hopefully, the application of modern 'omics' technologies will likely improve our understanding of these mechanisms and will facilitate the development of successful therapeutic strategies for the prevention and treatment of HF.

Compliance with ethical standards

Conflict of interest None.

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