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Review

Crosstalk between apoptosis, necrosis and autophagy ☆

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ABSTRACT

Apoptosis and necrosis are the two major modes of cell death, the molecular mechanisms of which have been extensively studied. Although initially thought to constitute mutually exclusive cellular states, recent findings reveal cellular contexts that require a balanced interplay between these two modes of cellular demise. Several death initiator and effector molecules, signaling pathways and subcellular sites have been identified as key mediators in both processes, either by constituting common modules or alternatively by functioning as a switch allowing cells to decide which route to take, depending on the specific situation. Importantly, autophagy, which is a predominantly cytoprotective process, has been linked to both types of cell death, serving either a pro-survival or pro-death function. Here we review the recent literature that highlights the intricate interplay between apoptosis, necrosis and autophagy, focusing on the relevance and impact of this crosstalk in normal development and in pathology. This article is part of a Special Section entitled: Cell Death Pathways. Guest Editors: Frank Madeo and Slaven Stekovic.

1. Introduction

Distinct modes of cell death were for a long time studied in isolation, as the prevailing model suggested that they represented mutually exclusive cellular states. However, the past decade has witnessed a steady accumulation of findings suggesting that apoptosis, necrosis and autophagy are often regulated by similar pathways, engage common sub-cellular sites and organelles, and even share initiator and effector molecules. Depending on the cellular context and death trigger, the two main modes of cell death often co-operate in a balanced interplay that involves autophagy, or they are employed by cells in a complementary fashion to facilitate cellular destruction.

Apoptosis has been intensively studied in the past two decades and is widely appreciated as a major mechanism of regulated death, employed not only upon cell damage or stress, but also during normal development and morphogenesis. For example, the peripheral nervous system of vertebrates is shaped by the apoptotic death of almost half of the new born peripheral neurons during development in order to regulate their number such that it matches to the need of their target tissues in the periphery [1]. Apoptosis may be triggered either by extrinsic stimuli through cell surface death receptors, such as TNFα (tumor necrosis factor-α), Fas (CD95/APO1) and TRAIL (TNF related apoptosis inducing ligand) receptors or by intrinsic stimuli via the mitochondrial signaling pathway [2,3]. In either case, activation of cysteine aspartyl proteases, called caspases, results in mitochondrial membrane permeabilization, chromatin condensation and DNA fragmentation, thereby leading to the destruction of the cell [4]. These events bestow the apoptotic cell a distinct and characteristic morphology (Fig. 1c) that includes the rounding up of the cell so that it appears pyknotic, the condensation of chromatin, the fragmentation of the nucleus and the shedding of apoptotic bodies, vacuoles containing cytoplasm and intact organelles.

Apoptosis has been classically contrasted to pathological necrosis, which for a long time was thought to represent a diametrically "opposite" mode of unordered and passive cellular explosion in response to acute and overwhelming trauma. Morphologically, necrotic cells are characterized by the swelling of organelles, such as the endoplasmic

Abbreviations: AIF, Apoptosis Inducing Factor; AMPK, Adenosine Monophosphate activated Kinase; APAF1, Apoptotic Protease Activating Factor 1; BCL-2, B-cell lymphoma 2; BCL-X_L, B-cell lymphoma extra large; BEC1, Beclin-1; BH, Bcl-2 homology; cIAP1, cellular inhibitor of apoptosis 1; cIAP2, cellular inhibitor of apoptosis 2; DAPK, death associated protein kinase; DRAM, Damage-Regulated Autophagy Modulator; FADD, FAS Associated Death Domain; FLICE, caspase 8; FLIP, FLICE-Like Inhibitory Protein; FOXO1, Forkhead Box Protein O1; HDGF, Hepatoma Derived Growth Factor; HMGB1, High Mobility Group protein B1; IGF1, Insulin Growth Factor 1; IL1β, interleukin 1β; LKB1, Liver Kinase B1; MEFs, mouse embryonic fibroblasts; MNNG, N-methyl-N0-nitrosoguanidine; MOMP, mitochondrial outer membrane permeabilization; mTOR, mammalian target of rapamycin; NEMO, NF-kB essential modulator; NF-kB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family pyrin domain containing 3; PAMP, Pathogen Associated Molecular Patterns; PARP1, Poly(ADP ribose) Polymerase 1; PCD, programmed cell death; PI3K, Phosphatidyl Inositol 3 Kinase; PRR, pathogen recognition receptor; PTP, permeability transition pore; PUMA, p53-Upregulated Modulator of Apoptosis; RIP1, Receptor Interacting Protein 1; RIP3, Receptor Interacting Protein 3; SIRT2, Sirtuin 2; tAIF, truncated Apoptosis Inducing Factor; TNFα, Tumor Necrosis Factor alpha; TNFR1, TNFα Receptor 1; TNFR2, TNFα receptor 2; TRADD, TNFR Associated Death Domain; TRAF2, TNFR Associated Factor 2; TRAF5, TNFR Associated Factor 5; TRAIL, TNF related apoptosis inducing ligand; TRAILR1, TRAIL Receptor 1; TRAILR2, TRAIL Receptor 2

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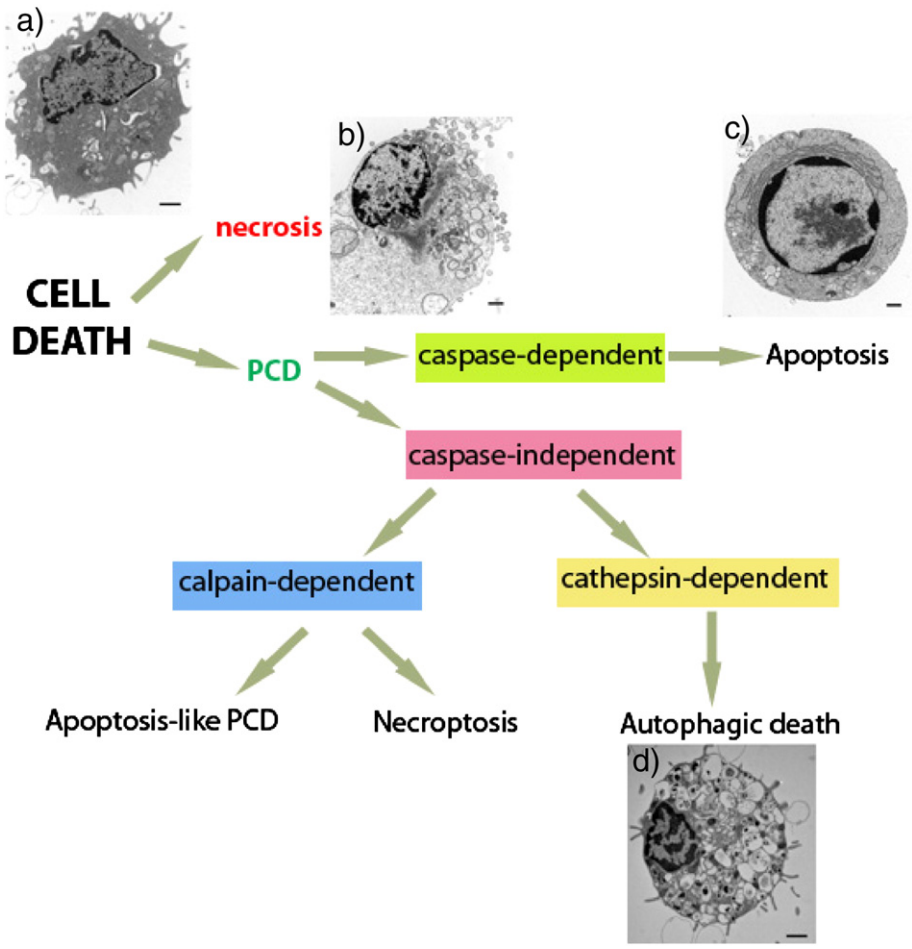

Fig. 1. Types of cell death and their morphological hallmarks. Diagrammatic classification of different types of cell death. PCD: programmed cell death. Morphological features of a) a healthy cell, b) a necrotic cell, c) an apoptotic cell and d) an autophagic cell. (Electron micrograph pictures adapted from ref. [150]. Scale bar: 1 mm.)

reticulum and mitochondria, the rupture of the plasma membrane and the lysis of the cell [5,6], while, unlike in apoptosis, the nucleus becomes distended and remains largely intact (Fig. 1b). Necrotic death is typically followed by inflammatory reactions [7]. Necrotic cells selectively release factors like HMGB1 and HDGF to evoke an inflammatory response [8] and are sensed by NLRP3, a core protein of the inflammasome, resulting in inflammasome activation and the subsequent release of the pro-inflammatory cytokine IL1β. NLRP3 inflammasome activation is triggered mainly through ATP produced by mitochondria released from damaged cells [9]. Mechanistically, necrosis is typically not associated with activation of caspases, and it is thought that it mediates cell demise in response to damage, or in pathology [10,11], but not during normal development. Despite this, it turns out that a programmed form of necrotic death (termed necroptosis) is very common in vivo, not only in physical traumas, but mainly in diverse forms of neurodegeneration, and death inflicted by ischemia or infection. In addition, progress in the field has revealed that unlike unordered necrosis, this more physiological and programmed type of necroptotic death shares several key processes with apoptosis, as discussed later.

A cellular process that has been involved in both main types of cell death mentioned above is macroautophagy (hereafter referred to as autophagy), a self-cannibalization mechanism that involves the engulfment of cytoplasmic material and intracellular organelles within double-membrane vesicles, called autophagosomes. Completion of the autophagosome is followed by fusion with a lysosome to form an autolysosome, where the captured material is degraded by specific acidic hydrolases [12]. Although it is primarily considered to have a cytoprotective function, autophagy can also promote cell death during normal development (reviewed in [13]), as well as, in disease (reviewed in [14]). A low level of constitutive autophagy has an important housekeeping role in the normal turnover of long-lived proteins and whole organelles, thereby being crucial for maintaining healthy cells. The homeostatic role of autophagy is particularly critical in post-mitotic differentiated cells, such as neurons and cardiomyocytes. Starvation and other environmental and hormonal cues such as nutrient deprivation, growth factor depletion and hypoxia are known to activate autophagy [15,16]. As a consequence, degradation of cytoplasmic components is enhanced in response to stress conditions, thereby promoting survival. However, excessive autophagy or activation of autophagy in the context of specific diseases may be harmful. Indeed, accumulating evidence, discussed below, reveals that autophagy is linked to cell death under certain circumstances. Here, we overview the recent literature on the interplay between cell death mechanisms and autophagy. Our aim is to highlight the cellular states, sub-cellular sites and signaling mechanisms that participate in, and are crucial for this interplay, the significance of which during normal development and disease is currently being explored.

2. Crosstalk between apoptosis and necrosis

2.1. Programmed necrosis: necroptosis

In the late 1980s it became clear that necrosis can also function as an alternative programmed mode of cell death, triggered by the same death signals that induce apoptosis. More specifically, it was shown that while in F17 cells TNFα treatment induced a classical form of