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Research review paper

From nature to bedside: Pro-survival and cell death mechanisms as therapeutic targets in cancer treatment

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ABSTRACT

Cell death is an important physiological regulator during development, tissue homeostasis and stress response but it is also a protective tumor suppressive mechanism. Tumor cells almost universally acquire the ability to evade cell death pathways that in normal cells act as a protective mechanism to remove damaged cells. As a result, a population of death-resistant cells with accumulating genetic and epigenetic abnormalities contributes to malignant transformation.

Any alteration of the homeostatic balance between survival and death is therefore a critical factor in carcinogenesis. Several forms of cell death exist and cross talk among them is emerging; however, we still miss many molecular details. It becomes essential to revisit the role of each type of cell death to understand interconnections existing between different cell death pathways as well as the network of their mediators to eventually develop new effective strategies to kill cancer cells. More specifically, new therapies based on compounds selectively triggering apoptosis, necrosis or autophagy recently became both appealing and challenging.

Despite the rather clear classification of the different cell death modalities according to morphological criteria and the attempt to describe them with distinct signaling pathways, the reality reveals a complex interplay between apoptosis, regulated necrosis and autophagy involving a heterogeneous mix of molecular mediators.

Nature, presenting an almost endless plenitude of bioactive scaffolds, can efficiently contribute compounds that allow deciphering the intricate pathways of cell death pathways and thus eventually contribute to selectively target cancer-type specific pathways in an attempt to personalize cancer patient treatment depending on cancer death pathway specificities. The aim of this review is to provide first an overview of molecular cell death specificities and to highlight how compounds of natural origins, with or without hemisynthetic modifications, target unique thanatotic molecular constellations.

Contents

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Introduction

Apoptosis

Apoptosis is intensively studied as the major mechanism of programmed cell death and is characterized by cell shrinkage, nuclear fragmentation, plasma membrane blebbing and finally by the separation of the cellular components into apoptotic bodies that are removed by phagocytes attracted by the exposure of phosphatidylserine on the plasma membrane as "eat me" signal (Kerr et al., 1972). The apoptotic program may be initiated by intrinsic stimuli through the mitochondrial release of cytochrome c upon cellular stress or triggered by extrinsic stimuli that involve the activation of cell surface death receptors, e.g., Fas and Tumor Necrosis Factor receptor (TNFR). The earliest step preceding the activation of the caspase cascade either in the extrinsic or the intrinsic apoptotic pathways is the formation of multiprotein complexes, respectively the death-inducing signaling complex (DISC) and the apoptosome (Cecconi et al., 1998; Los et al., 1995; Zou et al., 1997). The function of both complexes is to recruit and properly activate effector caspases, i.e., -8 for the extrinsic and -9 for the intrinsic apoptotic pathways, which in turn converge into the activation of the executor caspase-3, -6 and -7 (Cecconi et al., 1998; Los et al., 1995).

Caspase activation induces morphological and physiological cellular changes during apoptosis by cleavage of cellular targets such as the poly(ADP-ribose)polymerase (PARP), endonucleases and proteases, that in turn initiate the cellular dismantling (Degterev et al., 2003).

Caspases may also play a role as modulators of autophagy and programmed necrosis by their ability to proteolytically regulate the activity of signaling molecules involved in both pathways (Walczak and Krammer, 2000; Wirawan et al., 2010).

Caspase-8 participates in the formation of the death receptor complex DISC recruited by the adapter proteins Fas-associated protein with death domain (FADD) and/or the Tumor Necrosis Factor Alpha Receptor 1-associated death domain protein (TRADD) (Fulda and Debatin, 2006). Besides, caspase-8 is essential also for the activation of a regulated form of necrosis, necroptosis, which may be induced whenever the apoptotic machinery is inhibited. Caspase-8 is involved in this instance in the formation of a death receptor-independent cytosolic complex called ripoptosome containing kinases of the receptor interacting protein (RIP) family, RIP1 and RIP3, FADD and FLICE-like inhibitory protein cFLIP (Bertrand and Vandenabeele, 2011). The composition of the ripoptosome complex is crucial for the cellular outcome. Caspase-8-mediated cleavage of Rip1 and Rip3 triggers the caspase activation cascade and induces apoptosis (Lin et al., 1999); vice versa the inhibition of caspase (i.e., by the pan-caspase-inhibitor z-VAD) or FADD knockout inhibits the apoptotic pathway and promotes necroptosis that acts as a backup death-inducing mechanism to ensure cell demise (Holler et al., 2000; Zhang et al., 2011).

The assembly of the ripoptosome is regulated by inhibitors of apoptosis (IAPs) and by different isoforms of cFLIP as well (Feoktistova et al., 2011). Under basal condition IAPs constitutively target RIP1 for proteasome degradation. The inhibition of IAPs by genotoxic stress or Smac-mimetic treatments prevents RIP1 degradation and stimulates formation of the ripoptosome complex. The apoptotic and necroptotic cell death pathways depend on the differential regulation of caspase-8 activities by cFLIP (Tenev et al., 2011). Indeed, the expression of cFLIP binds to caspase-8 suppressing the ability of caspase-8 to trigger the apoptotic machinery and stimulates necroptosis (Feoktistova et al., 2011). It has been demonstrated that the anti-apoptotic cFLIP is also a negative regulator of autophagy through its inhibitory interaction with the autophagy-related gene 3 (ATG3); ATG3, in turn, is involved in the formation of autophagosomes, the multi-membrane vesicles formed during autophagy (Lee et al., 2009). Because of the critical role played by the ripoptosome, its regulation is an important potential target whenever developing new therapeutic strategies based on the modulation of cell death pathways in cancer cells. IAP inhibitors or the second mitochondria-derived activator of caspase (Smac) mimetics by inhibiting IAPs can activate necroptosis or apoptosis thereby sensitizing various chemotherapy-resistant cancer cells to death (Du et al., 2000; Tenev et al., 2011). Thus, Smac mimetics may be used as cancer cell death-promoting drugs. Of interest, several IAP inhibitors and Smac mimetics are being tested in clinical trials for treatment of solid tumors and lymphomas.

Autophagy

Autophagy is another important housekeeping process to degrade and/or recycle cell components, i.e., damaged organelles and misfolded proteins. Autophagy therefore may represent a protective and pro-survival response at the initial stages of cancer development thanks to its catabolic roles (Levine and Kroemer, 2008). If defective, autophagy can increase oxidative stress thereby promoting genome instability and malignant transformation (Mathew et al., 2009). Formation of autophagosomes involves different steps characterized by the involvement of specific subsets of autophagy-related genes (ATG). The initial step is the formation of an isolation membrane or phagophore that elongates to form a double-membrane vesicle with the accumulation of LC-3 II protein with the final goal to entrap those cellular components to be degraded (Mehrpour et al., 2010). Accumulating evidence shows autophagy as an alternative cell death mechanism. The detection of autophagosomes in dying cells exhibiting atypical nuclear apoptotic features suggests the occurrence of autophagy in these cells and a death-promoting role of autophagy by subsequently triggering apoptosis (Long and Ryan, 2012; Yu et al., 2008). Moreover, the knockdown of autophagy-related genes ATG5, ATG7 and Beclin-1 prevents cell death in several instances (Castino et al., 2011; Shimizu et al., 2004; Yu et al., 2004).

Despite several studies that suggested a tumor suppressive role for autophagy, other reports support the hypothesis that this process is instead exploited by cancer cells to prime their proliferation and promote their survival (Yu et al., 2008). Autophagy is indeed often activated to maintain high ATP levels and satisfy the higher energetic demand of pre-cancerous and cancer cells. The same availability of ATP levels and energetic sources, however, might also support the bioenergetics requirements of a dying cell and specifically promote apoptosis, which requires a high level of ATP to drive the apoptosome formation and the caspase activation (Eguchi et al., 1997; Salvesen and Duckett, 2002). Besides, the inhibition of autophagy may lead to a bioenergetic crisis thereby rather triggering necroptosis (Degenhardt et al., 2006). Thus, the bioenergetic consumption within a dying cell can influence the final cellular outcome.

Recent findings underline the molecular interplay between autophagy and apoptosis. Induction of apoptosis is associated with a caspase-mediated or calpain-mediated cleavage of different mediators of autophagy such as Beclin-1 and ATG5, which localize to mitochondria subsequently promoting the switch from autophagy to apoptosis (Wirawan et al., 2010; Yousefi et al., 2006). Moreover, the crosstalk between autophagy and apoptosis was demonstrated by a physical interaction between the B-cell lymphoma 2 (Bcl-2) homology (BH)-3 domains of Beclin-1 and the anti-apoptotic Bcl-2/Bcl-XL proteins. This modulation inhibits anti-apoptotic Bcl-2 proteins and activates pro-apoptotic Bax and Bak (Galonek and Hardwick, 2006). Due to the crosstalk between the apoptotic and autophagic pathways at the level of Bcl-2, the use of BH3 mimetics as cancer treatment is recommended against tumors where autophagy is rather tumor promoting and aggravates the outcome of the disease. BH3 mimetics indeed are well known to promote apoptosis; however they were also shown to induce autophagy by disrupting the physical interaction between Beclin-1 and Bcl-2/Bcl-XL (He and Levine, 2010; Maiuri et al., 2007a). Mammalian ATG12 also contains a BH3 domain-like sequence motif important to bind myeloid cell leukemia-1 (Mcl-1) that prevents Bcl-2 homologs from binding pro-apoptotic proteins, thus triggering apoptosis. Mutation of ATG12 within the BH3-like

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