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Mitochondria and cell death signalling

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Mitochondria are essential organelles in the life and death of a cell. During apoptosis, mitochondrial outer membrane permeabilisation (MOMP) engages caspase activation and cell death. Under nonlethal apoptotic stress, some mitochondria undergo permeabilisation, termed minority MOMP. Nonlethal apoptotic signalling impacts processes including genome stability, senescence and innate immunity. Recent studies have shown that upon MOMP, mitochondria and consequent signalling can trigger inflammation. We discuss how this occurs, and how mitochondrial inflammation might be targeted to increase tumour immunogenicity. Finally, we highlight how mitochondria contribute to other types of cell death including pyroptosis and ferroptosis. Collectively, these studies reveal critical new insights into how mitochondria regulate cell death, highlighting that mitochondrial signals engaged under nonlethal apoptotic stress have wide-ranging biological functions.

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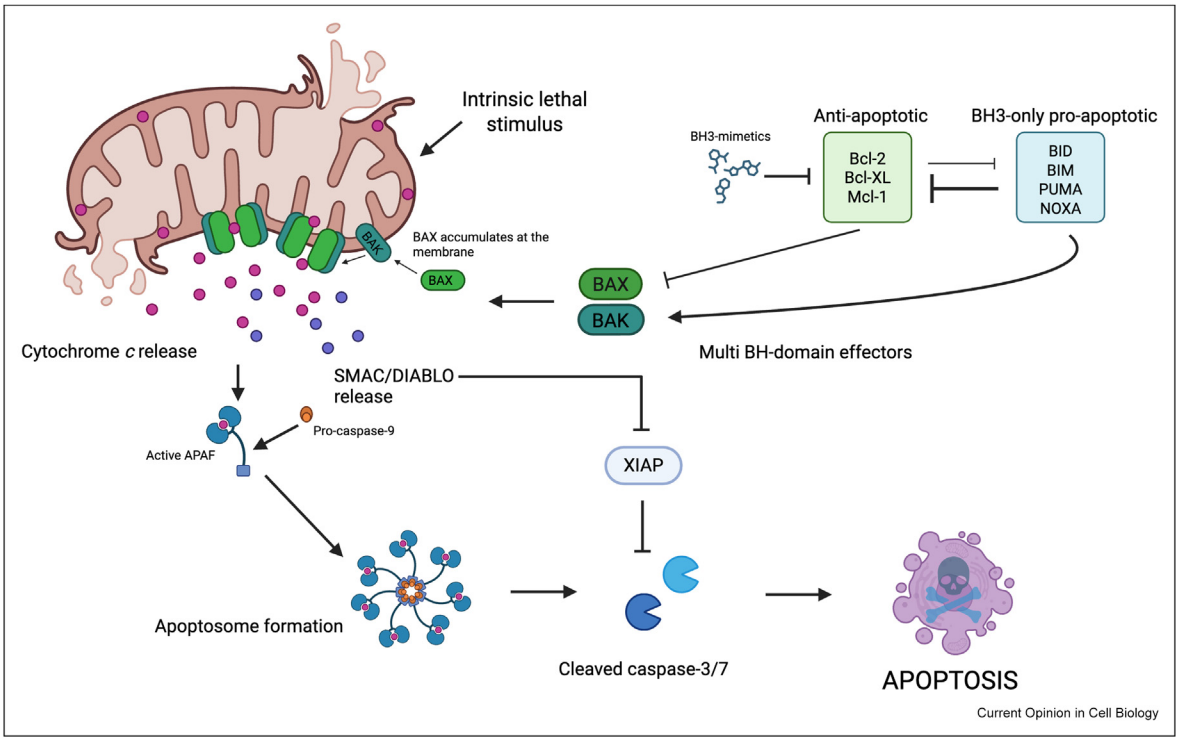
Introduction

Mitochondria have a central role in apoptosis-the best understood form of regulated cell death (RCD). It has recently become evident that mitochondria also contribute, often in a context-dependent manner, to other forms of RCD including pyroptosis and ferroptosis [1,2]. During apoptosis, mitochondria undergo mitochondrial outer membrane permeabilisation (MOMP), leading—via the mitochondrial release of cytochrome *c* through mitochondrial pores—to caspase activation and cell death (Figure 1) [3]. Due to its pervasive nature (often occurring in all mitochondria), MOMP was until recently considered a cellular death knell. However, accumulating evidence demonstrates that cells in response to sublethal stress cells can undergo a process called minority MOMP —whereby some mitochondria in a cell selectively permeabilise in the absence of cell death [4,5]. As we will discuss, sublethal stress via minority MOMP can have wide-ranging biological functions. Focusing on apoptosis, we centre our review on recent, novel insights into mitochondrial regulation of cell death, its biological functions, and how this may provide new approaches for therapeutic exploitation.

Mitochondrial regulation of apoptosis

The mitochondrial pathway of apoptosis is regulated by members of the B-cell lymphoma 2 (BCL-2) protein family. BCL-2 proteins are broadly grouped into proapoptotic BH3-only proteins, proapoptotic pore-forming proteins (BAX, BAK and BOK) and antiapoptotic BCL-2 proteins [6]. Protein—protein interactions underpin how BCL-2 proteins regulate apoptosis (Figure 1). Antiapoptotic BCL-2 proteins bind to proapoptotic BH3-only proteins or activated BAX or BAK, blocking pore formation and thereby blocking MOMP. By sensitising cancer cells to apoptosis, drugs that target antiapoptotic BCL-2 proteins (called BH3 mimetics) hold great promise in oncology. The BH3-mimetic venetoclax that specifically targets BCL-2 is clinically approved to treat acute myeloid leukaemia and chronic lymphocytic leukaemia [7,8]. However, venetoclax fails to inhibit antiapoptotic MCL-1—one of the most highly expressed BCL-2 proteins in cancer [9]. Secondly, targeting MCL-1 has been associated with on-target cardiotoxicity, consistent with an essential role for MCL-1 in maintaining heart function [10,11]. Recently, a novel, potent and selective MCL-1 inhibitor has been reported, that has a short half-life, this is potentially beneficial to prevent potential cardiotoxicity [12]. MCL-1 also has roles in mitochondrial metabolism and signalling independent of cell death. Wright et al. recently found that MCL-1 promotes fatty acid oxidation and the disruption of this by MCL-1-inhibiting BH3 mimetics could help explain toxicity in cardiomyocytes, which are notably resistant to apoptosis [13]. Furthermore, MCL-1 inhibition can also cause DNA damage independent of BAX/BAK-mediated apoptosis [14]. Understanding noncanonical roles of MCL-1, and undoubtably other BCL-2 proteins, may offer new therapeutic strategies to both improve efficacy and limit toxicity.

Figure 1



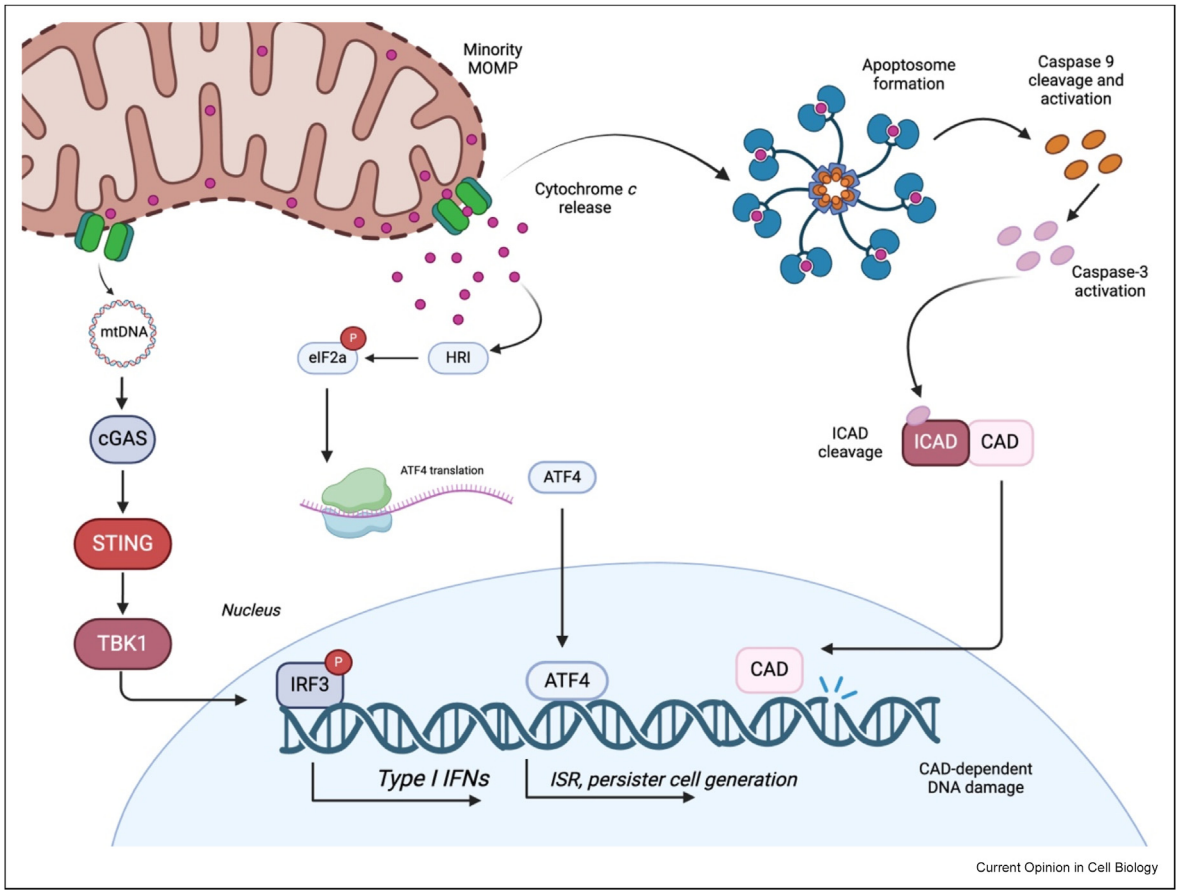
Mitochondrial regulation of apoptosis. The intrinsic apoptotic pathway is tightly regulated by BCL-2 family proteins. Upon an intrinsic lethal stimulus, BH3-only proapoptotic proteins are activated, upon which BAX is activated and accumulates at the mitochondrial membrane and associates with BAK to enable pore formation and ultimately MOMP. BOK, which shares structural homology with BAX and BAK, and truncated BID (tBID), a BH3-only protein, have also been implicated in pore formation in MOMP. During MOMP, intermembrane space proteins are released, including cytochrome *cc* and SMAC, into the cytosol. Cytochrome c interacts with APAF1 and pro-caspase-9 to form the apoptosome, leading to caspase-9 activation and consequently caspase-3 and caspase-7 activation, which go on to ultimately drive cell death. SMAC/DIABLO release inhibits the X-linked inhibitor of apoptosis protein (XIAP) releasing its inhibition on caspase-3 and caspase-7. BCL-2, B-cell lymphoma 2; MOMP, mitochondrial outer membrane permeabilisation.

The multi-BH domain effectors of apoptosis, BAX and BAK are activated through BCL-2 protein interactions; either by direct activation by the binding of BH3 "activator" proteins BID (in its active, truncated form), BIM and PUMA, which lead to conformational change and pore formation, or the binding of the prosurvival proteins, which keep BAX and BAK in an inactive state, by BH3 proteins [6]. Recently, the GTPase that regulates mitochondrial fission, Dynamin-related protein 1 (Drp1), has been described as a noncanonical activator of BAX that promotes apoptosis, demonstrating that BAX activity can occur independent of canonical BH3-only proteins [15]. Expanding on this theme, a new mechanism was identified by which the E3 ubiquitin ligase MARCHF5 regulates apoptotic cell death through control of BAK conformation. The authors found that the deletion of MARCHF5 resulted in constitutive BAK activation independent of canonical BH3-only activators [16]. Moreover, mitochondrial outer membrane (MOM) pore-forming capability isn't just restricted to the multidomain apoptosis effectors since the cleaved, activated form of BID (tBID) can permeabilise the MOM and independent of BAX, BAK and BOK. tBID-mediated MOMP releases SMAC from the mitochondria and can dampen X-linked inhibitor of apoptosis protein—mediated immune response [17]. The additional loss of BID layered on top of loss of BAX, BAK and BOK in an embryonic *in vivo* setting also exacerbates birth defects, suggesting a parallel physiological role of BID-mediated MOMP [18]. Collectively, these data suggest significant additional complexity in the regulation of MOMP, expanding the repertoire of proteins that can both signal to and execute MOMP.

Mitochondria, MOMP and signalling

Accumulating evidence demonstrates that MOMP can occur without a cell committing to die, in a process termed minority MOMP [4]. Minority MOMP can have a variety of cellular effects, not least through its ability to trigger limited caspase activity (Figure 2) [19]. Cells can tolerate direct low-level activation of executioner caspases, with, as yet, undefined cellular determinants regulating whether a cell lives in response to given caspase activity [20]. MOMP of selected mitochondria

Figure 2



Consequences of nonlethal mitochondrial signalling. Under nonlethal stresses, cytochrome c can be released from the mitochondrial that can lead to the formation of the apoptosome, caspase-9 cleavage and activation and caspase-3 activation. Caspase-3 activation has a multitude of substrates, many still to be determined, but one of note in minority MOMP is the inhibitor of caspase-activated DNAse (ICAD), which is then cleaved, permitting CAD to enter the nucleus and promote CAD-dependent DNA damage, which can induce genomic instability and oncogenic transformation. Alternatively, cytochrome c release in miMOMP has recently been shown to engage the integrated stress response (ISR) and promote drug-tolerant persister cell generation through the activation of haem-regulated inhibitor (HRI) kinase and ultimately eIF2α phosphorylation and ATF4 synthesis. Furthermore, under nonlethal stress, the release of mtDNA acts as a damage-associated molecular pattern (DAMP) to activate the cGAS-STING pathway to promote a proinflammatory response, which has been shown to have a role in senescence associated secretory phenotype (SASP). BCL-2, B-cell lymphoma 2; CAD, caspase-activated DNase; MOMP, mitochondrial outer membrane permeabilisation.

is driven, in part, through mitochondrial heterogeneity in apoptotic priming, as well as mitochondrial dynamics, where mitochondrial fission promotes miMOMP, whereas fusion suppresses it [5]. One consequence of engaging nonlethal caspase activity is the promotion of DNA damage through caspase-activated DNase (CAD). Cleavage of the inhibitor of CAD enables CAD to migrate to the nucleus causing genome instability that can promote oncogenic transformation [4]. Within established cancers, Haimovici et al. identified that CAD activity contributes to the accumulation of micronuclei and the deletion of CAD-reduced metastasis in xenograft models [21]. The same group also defined a novel role of CAD in the promotion of cellular senescence [22].

Importantly, MOMP-dependent DNA damage may also present a therapeutic vulnerability for cancer cells, by creating a dependence on the ataxia telangiectasia mutated (ATM) kinase, a central mediator of the DNA damage responses. Indeed, Ali et al. found that a variety of targeted therapies (such as EGFR inhibitors) synergise with ATM inhibitors, slowing tumorigenesis in mouse models of non−small cell lung cancer [23]. Nonlethal MOMP has also been shown to drive drug persistence through its ability to engage the integrated stress response (ISR) [24]. Cytosolic cytochrome *c*, displaying a novel function, activates haem-regulated inhibitor (HRI) kinase, phosphorylating eIF2α, which leads to ATF4 synthesis and drug persistence (Figure 2) [24]. Importantly, persister cells display increased

sensitivity to ferroptosis [24–26]. Thus, targeting the ISR and/or ferroptosis along with apoptosis inducing therapies may help eradicate cancer.

While caspases are dispensable for cell death during mitochondrial apoptosis, they act to silence inflammation. Perhaps stemming from their bacterial ancestry, permeabilised mitochondria are potent inducers of inflammation [27]. For instance, upon MOMP, formation of BAX/BAK pores enables the herniation of the mitochondrial inner membrane and release of mtDNA [19,28]. While largely considered redundant for cell death, BAK appears to be more effective than BAX in the formation of macropores and the release of mtDNA than BAX following apoptotic stress [29]. Importantly, triggering mitochondrial apoptosis under caspase-inhibited conditions engages immunogenic cell death due—at least in partto—inflammation in the dying cell. Killarney et al. [30] recently demonstrated that, ds mt dsRNA (generated as a by-product of bidirectional mtDNA transcription) is released during MOMP, under caspase-inhibited conditions, activating MDA5/MAVS/IRF3 pathway to drive a type I interferon response and immunogenic cell death. From a therapeutic perspective, this suggests that caspase inhibition could enhance the immunogenicity of chemotherapy-induced apoptosis in immune cold cancers that lack a functional cGAS-STING pathway. Permeabilised mitochondria also activate inflammation independent of nucleic acid release. For instance, upon MOMP, permeabilised mitochondria are extensively ubiquitinated, and mitochondrial ubiquitination serves to recruit the NF-κB adaptor molecule NEMO to drive inflammation [31,32].

It is not fully clear what the physiological roles of miMOMP are, and whether it is an accidental by-product or a form of regulated cell signalling. One example is that mitochondrial fission promotion of miMOMP mediates mtDNA release and coordinates the senescence-associated secretory phenotype, which as senescence is a natural part of the aging process, this suggests at least one physiological role of miMOMP [33]. Interestingly, functional p53 is also required for optimised BH3 mimetic efficiency, and defective p53 can render both leukaemia and lymphoma resistant to BH3 mimetics [34]. Minority MOMP in sublethally stressed cells has recently been found to activate p53, which feeds forward into the induction of proapoptotic BH3-only proteins engaging full-blown MOMP and cell death [35]. How MOMP engages p53 activation remains uncertain, yet it occurs independent of caspase-dependent DNA damage. Importantly, minority MOMP was also found to activate cGAS-STING signalling dependent on release of mtDNA. Exploiting this knowledge, the authors found that STING agonists enhanced the ability of venetoclax to kill leukaemia cells—highlighting a potential new combinatorial approach [35].

Mitochondrial and nonapoptotic cell death

Pyroptosis is an inflammatory form of RCD mediated through gasdermin D (GSDMD), which is cleaved and activated by the inflammatory caspases 1,4 and 5, forming pores in the plasma membrane leading to cytolysis and release of mature proinflammatory interleukin 1 (IL-1) [36]. However, gasdermins can also permeabilise intracellular membranes, including the MOM and mitochondrial inner membrane (MIM), promoting inflammatory signalling through release of intermembrane space content, promoting pyroptosis [37,38]. The N-terminal pore-forming fragment of GSDMD (GSDMD-NT) has recently been found to target the inner and outer mitochondrial membranes dependent on its interaction with the inner mitochondrial lipid [38]. Normally, present on the MIM, during pyroptosis, cardiolipin translocates to the outer membrane. Cleaved GSDMD induces mitochondrial permeabilisation independent of BAX and BAK enabling the release of intermembrane space proteins and mtDNA, an example of which, exo-RNase PNPT1, enhances pyroptosis through global mRNA decay [38]. Cleaved gasdermins E(GSDME) and A (GSDMA) have also been shown to permeabilise the MOM and MIM, with GSDMA even preferentially localising to the mitochondria [39]. Along with GSDMD, GSDME can elevate caspase-3 activity through mitochondrial disruption and cytochrome *c* release, partaking in a signalling feedback loop promoting mitochondrial damage and axon degeneration and neuron loss in amyotrophic lateral sclerosis mouse models [40,41].

Ferroptosis is an iron-dependent death driven by lipid peroxidation [42]. Although, mitochondria do not undergo MOMP during ferroptosis, metabolic changes and decreased ATP production, as well as being sensitive to lipid peroxidation, can regulate ferroptosis [42]. Depletion of mitochondria confirmed their role in cysteine depletion-mediated ferroptosis but not GPX4-mediated ferroptosis [43]. Glutathione peroxidase 4 (GPX4) is a master regulator of ferroptosis through inhibiting membrane lipid peroxidation, and although mitochondria may not be required for its role in ferroptosis, recent studies have linked mitochondrial regulation to the integrated stress response and GPX4 accumulation through the Oma-1-Dele-1-Atf4 signalling axis [44–47]. OMA-1 is an inner membrane protease that when activated upon mitochondrial stress can cleave Opa1 GTPase resulting in inhibition of mitochondrial fusion and fragmentation of the mitochondrial network [48]. Recently, DELE1 (DAP3-binding cell death enhancer 1) was found to associate with the IMS and was recognised as a substrate of OMA-1 upon stress; cleavage of which activated the HRI kinase to induce the ISR [49,50]. However, whether MOMP enables DELE1 release potentially promoting the ISR under sublethal apoptotic stress remains unexplored.

Conclusions and perspectives

Mitochondria sit at a hub of cellular signalling and are critical in how a cell responds to lethal or sublethal cues. We have discussed how BCL-2 family member proteins can moonlight in other signalling pathways beyond their canonical roles. For instance, MCL-1 can promote fatty acid oxidation, whilst its absence can cause DNA damage independent of apoptotic signalling. In addition to this, BID, a BH3 "activator" also has pore-forming ability, and BAX and BAK have been shown to be regulated by proteins other than BH3 proteins, including the mitochondrial GTPase, Drp1, and the E3 ubiquitin ligase, MARCHF5. This demonstrates increased complexity in the control of apoptotic signalling opening new options for therapeutic targeting such as demonstrated by Diepstaten et al. in combining BH3 mimetics with STING agonists. Whether MOMP can be inflammatory under physiological conditions such as in cells with reduced caspase activity or the extent of the occurrence of nonlethal MOMP *in vivo* remains an open question. Nonetheless, our understanding is increasing as miMOMP appears to have a role in cellular senescence, an integral part of aging, as well as in cancer and therapy resistance. Further understanding of RCD signalling networks, such as how apoptosis interacts with other cell death modalities, under physiological and disease states could have huge therapeutic benefit, as well as understanding of aging and longevity.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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