Review

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Kill one or kill the many: interplay between mitophagy and apoptosis

https://doi.org/10.1515/hsz-2020-0231
Received June 29, 2020; accepted September 22, 2020;
published online October 12, 2020

Abstract: Mitochondria are key players of cellular metabolism, Ca^{2+} homeostasis, and apoptosis. The functionality of mitochondria is tightly regulated, and dysfunctional mitochondria are removed via mitophagy, a specialized form of autophagy that is compromised in hereditary forms of Parkinson's disease. Through mitophagy, cells are able to cope with mitochondrial stress until the damage becomes too great, which leads to the activation of pro-apoptotic BCL-2 family proteins located on the outer mitochondrial membrane. Active pro-apoptotic BCL-2 proteins facilitate the release of cytochrome *c* from the mitochondrial intermembrane space (IMS) into the cytosol, committing the cell to apoptosis by activating a cascade of cysteinyl-aspartate specific proteases (caspases). We are only beginning to understand how the choice between mitophagy and the activation of caspases is determined on the mitochondrial surface. Intriguingly in neurons, caspase activation also plays a non-apoptotic role in synaptic plasticity. Here we review the current knowledge on the interplay between mitophagy and caspase activation with a special focus on the central nervous system.

Keywords: BCL-2 family; caspase-3; Parkin; Parkinson's disease; PINK1; synaptic plasticity.

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Introduction

In neurons, a functioning mitochondrial quality control system is of particular importance as they depend more than other cell types on a healthy pool of mitochondria due to high energy demand and importance of Ca^{2+} buffering. However, neurons are also particularly challenged in mitochondrial maintenance because of their highly extended, complex structures and long axons (Misgeld and Schwarz 2017). This is supported by the fact that mitochondrial dysfunction plays a central role in the pathogenesis of neurodegenerative diseases including Parkinson's disease (PD; Grünewald et al. 2019). Mutations in PINK1 and Parkin, two proteins involved in the removal of damaged mitochondria, cause familiar autosomal recessive PD, underlining the importance of a functioning mitochondrial quality control system in neurons (Kitada et al. 1998; Valente et al. 2004).

Excessive mitochondrial damage is deleterious to the cell. Many insults, which at lower levels are cleared through mitophagic processes, have the potential to induce programmed cell death (apoptosis). Apoptosis is usually a non-inflammatory process resulting in cell shrinkage, chromatin condensation, nuclear fragmentation, and ultimately in the formation of small intact vesicles called apoptotic bodies (Kerr et al. 1972). These apoptotic bodies are engulfed by phagocytes resulting in the recycling of the cellular components (deCathelineau and Henson 2003). In the last decades, many proteins and complexes were discovered to play a role in the induction of the mitochondrial apoptosis pathway (reviewed in Kalkavan and Green 2018). A family of proteins, named after the founding member B-cell lymphoma 2 (BCL-2), is responsible for the molecular arbitration to permeabilize the outer mitochondrial membrane (OMM) in response to cell stress. Whereas dysregulation of apoptosis underlies tumorigenesis, neuronal apoptosis accompanies neurodevelopment (Jacobson et al. 1997). Aberrant apoptosis has been implicated in PD, Huntington's disease and Alzheimer's disease as well as acute injuries of the spinal cord

and stroke (Mochizuki et al. 1996; Portera-Cailliau et al. 1995; Smale et al. 1995).

Here we discuss the cross-talk between the two outcomes of mitochondrial damage: the programmed "demise" of a single mitochondrion tied to the survival of the cell, or suicide of the entire cell by apoptosis. We focus specifically on neurons and how the mitophagy-apoptosis cross-talk may affect neuronal biology.

The PINK1/Parkin pathway of mitophagy

Mitophagy, mitochondria-specific autophagy, is the selective elimination of damaged mitochondria and thus essential for mitochondrial quality control (Ashrafi and Schwarz 2013). The removal of defective mitochondria is critical for cellular survival since dysfunctional mitochondria produce an excessive amount of reactive oxygen species (ROS) causing oxidative stress. Oxidative stress has been shown to damage cells by affecting Ca^{2+} homeostasis, disrupting the mitochondrial respiratory chain, and inducing mutations in mitochondrial DNA, thereby triggering neurodegeneration (Guo et al. 2013). Consequently, mitophagy promotes cell survival by selective degradation of damaged mitochondria (Narendra et al. 2008).

Mitophagy is mediated by the PINK1/Parkin pathway, which consists of the mitochondrial Ser/Thr kinase PINK1 and the cytosolic E3 ubiquitin ligase Parkin (Park et al. 2006). PINK1 mainly acts as a molecular sensor for damaged mitochondria, which Parkin labels for degradation by ubiquitination (Geisler et al. 2010; Matsuda et al. 2010; Narendra et al. 2010; Vives-Bauza et al. 2010). Since PINK1 determines whether mitochondria will be kept or removed by surveilling mitochondrial health, its activity has to be tightly regulated (reviewed in Sekine 2020). This is achieved by control of mitochondrial PINK1 import. Under healthy conditions, PINK1 is transported into mitochondria due to its N-terminal mitochondrial targeting sequence via the translocase of the outer membrane (TOM) and the translocase of the inner membrane (TIM) complexes (Silvestri et al. 2005). This import is favored by the interaction of the phosphorylated TOM receptor TOM22 and the PINK1 precursor (Kravic et al. 2018). Once it reaches the inner mitochondrial membrane (IMM), PINK1 is immediately cleaved by the matrix processing peptidase (MPP) and the IMM protease presenilin-associated rhomboid-like protein (PARL). Thereafter, PINK1 is translocated back into the cytosol (Yamano and Youle 2013). Subsequently, cytosolic E3 ligases recognize cleaved PINK1 as a target for ubiquitination, which eventually leads to PINK1 degradation by the proteasome via the N-end rule pathway (Yamano and Youle 2013). In damaged mitochondria, where the membrane potential across the IMM is often lost, PINK1 import and cleavage are inhibited. As a result, full-length PINK1 accumulates on the OMM in close proximity to the TOM complex (Lazarou et al. 2012). In addition to autophosphorylation (Okatsu et al. 2012), PINK1 phosphorylates several proteins on the mitochondrial surface, including ubiquitin molecules bound to mitochondrial protein substrates (Kane et al. 2014; Kazlauskaite et al. 2014; Koyano et al. 2014). Phosphorylated ubiquitin serves as a Parkin receptor recruiting Parkin to the OMM and leading to its partial activation. Interestingly, PINK1 phosphorylates then the ubiquitin-like domain of Parkin, thereby increasing its E3 ubiquitin ligase activity (Kondapalli et al. 2012; Shiba-Fukushima et al. 2012). Subsequently, activated Parkin ubiquitinates various mitochondrial proteins leading to the formation of ubiquitin chains, which are further phosphorylated by PINK1. The accumulation of phosphorylated ubiquitin chains on damaged mitochondria in turn results in further recruitment and activation of Parkin creating a positive feedback loop that drives mitophagy (Okatsu et al. 2015; Ordureau et al. 2014). Phosphorylated ubiquitin serves not only as a receptor for Parkin but also for autophagy receptor proteins, which then recruit and activate autophagosomes. Autophagosomes in turn deliver the damaged mitochondria to lysosomes for degradation (Figure 1; Lazarou et al. 2015). It should be noted that mitophagy does not entirely follow the linear model with PINK1 as a damage sensor and Parkin as the effector. The phospho-ubiquitin-mediated recruitment of autophagy receptor proteins requires PINK1 activity but is not fully dependent on Parkin. Consequently, PINK1 should be seen as both a sensor and an effector, whereas Parkin acts as an amplifier of the mitophagy signal (Lazarou et al. 2015).

Both PD-linked PINK1 and Parkin mutations prevent or impair the activation of mitophagy due to impaired PINK1 stabilization on the OMM, reduced PINK1 kinase activity, and/or compromised binding of PINK1 to Parkin. Studies in both mammalian cells and *Drosophila* confirm that mutations in the kinase domain of PINK1 fail to induce Parkin translocation to mitochondria (reviewed in Hou et al. 2020). While the extent of PINK1/Parkin-mediated mitophagy *in vivo* seems to be quite low at basal levels (McWilliams et al. 2018), its importance increases with age (Cornelissen et al. 2018). Defects in the mitophagic process likely contribute to the pathogenesis of PD due to accumulation of damaged mitochondria eventually leading to cell death.

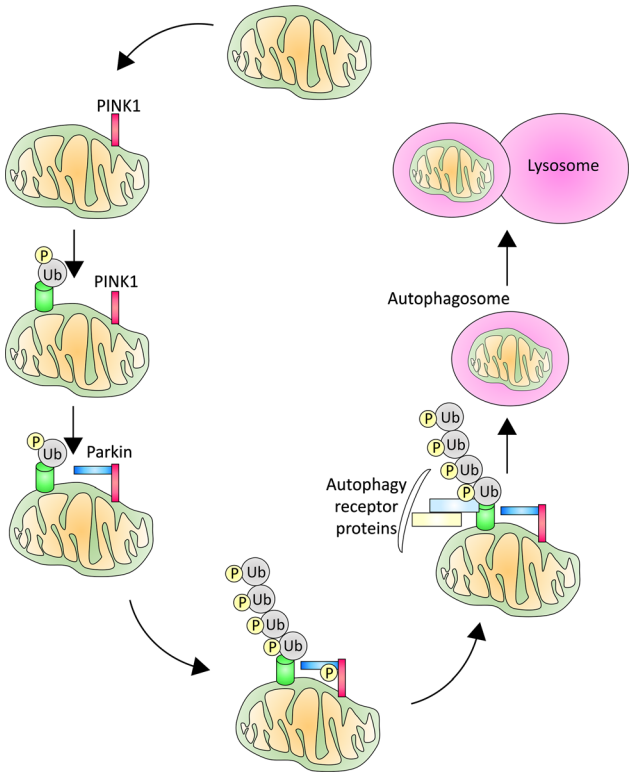

Figure 1: Schematic overview of the PINK1/Parkin pathway. Upon mitochondrial damage, PINK1 accumulates on the mitochondrial surface, where it phosphorylates ubiquitinated outer membrane proteins. This in turn triggers the translocation of Parkin, which binds to and continues to ubiquitinate surface proteins, which, in combination with PINK1 phosphorylation, leads to the formation of phospho-ubiquitin chains. The phospho-ubiquitin chain formation results in further recruitment of autophagy receptor proteins, ultimately triggering the formation of autophagosomes that deliver the damaged mitochondria to lysosomes for degradation.

Mitochondria are a central player in apoptosis

Mammalian cells can commit to apoptosis via the extrinsic and the intrinsic pathways. While the intrinsic pathway activates caspases dependent on the BCL-2 family in response to cell stress, the extrinsic pathway is initiated by ligands of the tumor necrosis factor (TNF) receptor family on the cell surface (Youle and Strasser 2008). However, both pathways are connected through the cleavage of the BCL-2 protein BID, and the involvement of the mitochondrial pathway is essential for efficient ligand-induced apoptosis in the majority of mammalian cell types (Li et al. 1998).

The BCL-2 protein family consists of the two pro-apoptotic proteins, BCL-2 associated X protein (BAX) and BCL-2 antagonist killer 1 (BAK), their pro-survival counterparts and the divers group of stress-signaling proteins with a single BCL-2 homology (BH) motif in their structures, termed BH3-only proteins accordingly. BAX and BAK can commit cells to apoptosis by permeabilizing the OMM (Eskes et al. 1998). Further, BAX/BAK double knockout results in severe developmental defects that manifest in perinatal lethality in most cases, whereas the respective single gene knockout mice are viable with only mild phenotypes (Lindsten et al. 2000). Several studies have established a dominant role of BAX in neuronal apoptosis (Deckwerth et al. 1996; Steckley et al. 2007). Mice lacking only BAX show, among other defects, hyperplasia in the neuronal and lymphoid system (Knudson et al. 1995). The importance of BAX activity in neuronal cells is supported by the discovery of neural-specific splicing of a BAK1 microexon that leads to nonsense-mediated mRNA decay and unproductive translation of BAK transcripts (Lin et al. 2020). Therefore, the programmed genetic depletion of BAK in developing neurons reduces the apoptosis competence of neuronal cells balancing the limited regeneration capability of mammalian brains and ensuring long-term survival of neurons.

BAX activity is counteracted by pro-survival BCL-2 proteins, including BCL-2 itself, B cell lymphoma extra large (BCL-x_L), myeloid cell leukemia 1 (MCL-1), BCL-2-like protein 2 (BCL-w), BCL-2-like protein 10 (BCL-B) and BCL-2-related gene A1 (A1, also known as BFL 1). Pro-survival BCL-2 proteins protect mammalian cells from BAX/BAK activities by retrotranslocation of mitochondrial BAX and BAK to the cytosol (Edlich et al. 2011; Todt et al. 2015). Retrotranslocation and OMM association thus form a localization equilibrium for mitochondrial BAX/BAK pools defined by various interactions between BAX/BAK BH3 motifs and pro-survival BCL-2 proteins. The corresponding cellular location of these BCL-2 proteins is regulated by interactions both between BCL-2 proteins as well as with the voltage-dependent anion channel 2 (VDAC2) within the BAX/BAK retrotranslocation complex (Cheng et al. 2003; Lazarou et al. 2010). VDAC2 not only ensures OMM-specific membrane targeting of BAX, but is the molecular platform for BAX shuttling (Lauterwasser et al. 2016). In cultured cells, BAX is predominantly found in the cytosol, where it exhibits an inactive monomeric conformation (Hsu et al. 1997; Vogel et al. 2012), while BAK primarily resides at the OMM (Griffiths et al. 1999).

In addition to direct transient interactions with BAX and BAK (Antonsson et al. 1997; Willis et al. 2007), pro-survival BCL-2 proteins can inhibit apoptosis by the sequestration of members of the apoptosis promoting

BH3-only proteins (Letai et al. 2002). BH3-only proteins are transducers of stress signaling, as they are either transcriptionally induced or post-translationally activated upon perturbations of homeostasis in specific cellular compartments, and subsequently regulate core BCL-2 protein activity. Some BH3-only proteins like caspase-8 cleaved and truncated BID (tBID), BCL-2 interacting mediator of cell death (BIM), and p53 upregulated modulator of apoptosis (PUMA) have been proposed as direct activators of BAX and BAK (Dai et al. 2011; Kim et al. 2009). In addition, these and other BH3-only proteins, such as the BCL-2-associated agonist of cell death (BAD), BCL-2-interacting killer (BIK), BCL-2-modifying factor (BMF) bind pro-survival BCL-2 proteins and, therefore, inhibit their capacity to counteract BAX and BAK. Importantly, BAX and BAK can self-activate and commit the cell to apoptosis even in the absence of BH3-only proteins (O'Neill et al. 2016). BAX activation depends on its mitochondrial dwell-time or its direct interaction with BH3-only proteins, with the balance of its localization equilibrium between OMM and cytosol determining cellular apoptosis predisposition (Reichenbach et al. 2017; Todt et al. 2015).

Similar to the dominant role of BAX in neuronal apoptosis, the BH3-only protein PUMA seems to have a paramount function in mediating apoptotic stress to the OMM in neuronal cells. Despite the stress-induced regulation of several BH3-only proteins, PUMA knockout alone provides substantial apoptosis resistance and PUMA was demonstrated to activate BAX in neuronal cells (Steckley et al. 2007). PUMA has further been discovered to mediate DNA damage and p53--dependent apoptosis, but it also plays an essential role in p53-independent apoptosis via cytokine deprivation, kinase inhibition, and ER stress signaling (Villunger et al. 2003). PUMA was also shown to respond to ER stress in cortical neurons through a p53-independent mechanism mediated by the ER-stress-inducible transcription factor ATF4 (activating transcription factor 4) via the transcription factor CHOP (C/EBP homologous protein) (Galehdar et al. 2010). In neurons, PUMA induction is also dependent on the activation of JNK and the inactivation of AKT (Ambacher et al. 2012). Both kinases have been implicated in neuronal apoptosis associated with neuronal development as well as several neurodegenerative diseases. In addition, AKT has been shown to phosphorylate the BH3-only protein BAD and, therefore, marking BAD for sequestration by protein 14-3-3 and inhibition of its pro-apoptotic activity (Datta et al. 1997; del Peso et al. 1997). The regulation of PUMA through this pathway in neuronal cells emphasizes the importance of this BH3-only protein for the apoptosis competence of neurons.

Upon activation, BAX and BAK adopt a characteristic conformation and oligomerize, which coincides with OMM permeabilization and the initiation of the caspase cascade (Antonsson et al. 2000; Griffiths et al. 1999; Hsu and Youle 1998). Although this process has been extensively studied, the nature of the active BAX complex remains enigmatic. BAX activation is associated with the transient exposure of the BH3 motif as well as the disengagement of the proteins into a 'latch' (α6–8) and a 'core' (α2–5) domain (Czabotar et al. 2013; Suzuki et al. 2000). Activation-associated oligomerization of BAX requires the BH3 motif in helix α2 as well as the helices α4 and α5 (George et al. 2007). However, conformational changes separating α5 and α6 are also involved in BAX translocation to the OMM and pro-survival BCL-2 protein-mediated BAX retrotranslocation (Cakir et al. 2017). Active BAX is not uniformly distributed over the OMM, but instead it concentrates in foci at the tips and constriction sites of mitochondria (Nechushtan et al. 2001). These clusters could contain BAX (and BAK) oligomers that perforate the OMM to form proteinaceous or proteo-lipidic pores to release IMS proteins (Annis et al. 2005; Kuwana et al. 2002). Different mutually exclusive models on potential BAX pores have been put forward based on different experimental approaches (Bleicken et al. 2014; Czabotar et al. 2014). Noteworthy, BAX fails to respond to apoptotic signals in the absence of VDAC2, whereas BAK seems to be significantly less affected (Chin et al. 2018). Super resolution microscopy has demonstrated either large ring-like structures or small lines and arcs (Große et al. 2016; Salvador-Gallego et al. 2016). Interestingly, large complexes of activated BAX can protrude into the cytosol and exceed the expected size of a pore, perhaps suggesting functions of active BAX complexes beyond OMM permeabilization.

OMM permeabilization releases apoptotic factors, including cytochrome *c*, apoptosis-inducing factor (AIF), SMAC/Diablo and the protease HtrA2/Omi, from mitochondria into the cytosol (Cory and Adams 2002). In healthy cells, cytochrome *c* is found in the mitochondrial intermembrane space, as a component of the electron transport chain. Loss of cytochrome *c* from mitochondria increases the generation of ROS, which potentiates mitochondrial dysfunction and promotes cell death. Cytosolic cytochrome *c* interacts with apoptotic protease activating factor 1 (APAF1) and triggers major conformational changes and oligomerization of APAF1 in the presence of ATP or dATP (Li et al. 1997). Subsequent recruitment of the caspase-9 zymogen to this multimeric

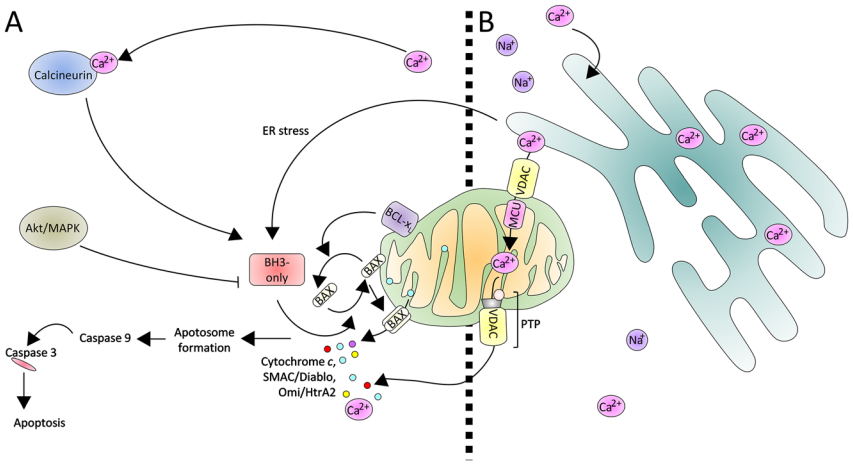

Figure 2: Mitochondrial activation of apoptosis in neurons.
(A) A schematic overview of the intrinsic apoptotic pathway. Under normal circumstances, BH3-only proteins are either downregulated or latent (i.e. BAD or PUMA activated by Akt/MAPK). However, after an apoptotic stimulus (ER stress, excess Ca^{2+} levels, etc.) BH3-only proteins translocate to the mitochondria, where they inhibit the retrotranslocation of pro-apoptotic BAX by suppressing pro-survival BCL-2 proteins, such as BCL-x_L. BAX then integrates into the outer mitochondrial membrane (OMM) and forms oligomers. The OMM is permeabilized and inter mitochondrial membrane space proteins, including SMAC/Diablo, Omi/HtrA2, and cytochrome *c* (cyt *c*), are released. Cytosolic cyt *c* initiates apoptosome assembly activating caspase-9, which activates in turn effector caspases, such as caspase-3, and commits the cell to apoptosis. (B) Mitochondria are capable of storing large quantities of Ca^{2+}, which they take up from the cytosol via VDAC and MCU. Most often, this takes place at mitochondria ER contact sites. Mitochondrial Ca^{2+} overload triggers the opening of the PTP, causing the release of inter membrane space proteins and Ca^{2+} into the cytosol, potentially amplifying the apoptotic signal.

protein complex called apoptosome results in caspase-9 activation (Srinivasula et al. 1998). Active caspase-9, in turn, proteolytically activates effector caspase-3 and -7 (Figure 2A).

Gain or loss of function of substrates cleaved by caspases play an important role in demise of cellular structures, whilst many substrate proteins have been identified as "innocent bystanders". Regarding the major effect of caspase activity regarding cellular fate, coincidental activity must be excluded. Therefore, X-linked inhibitor of apoptosis (XIAP) binds and inhibits mature caspase-9, -3 and -7 in non-apoptotic cells (Deveraux et al. 1997). Like cytochrome *c*, SMAC/DIABLO and Omi/HtrA2 are situated in the IMS and are released during apoptosis. They compete with caspases for XIAP binding, therefore neutralizing the inhibitory action on caspases (Du et al. 2000; Suzuki et al. 2001).

There are several proteins involved in apoptosis regulation including the BCL-2 associated athanogene (BAG) family. However, the importance of BAG proteins is not entirely understood. Members of this group have been reported to enhance cell proliferation and survival through interaction with BCL-2, TNF-receptors or by regulating cytochrome *c* release (Miki and Eddy 2002; Takayama et al. 1995; Thress et al. 1998). Interestingly, BAG5 has been shown to bind Parkin but seems to lack a specific binding partner among regulators of apoptosis (Kalia et al. 2004). As we will discuss below, the two pathways are intricately linked. Interestingly, BAG3 but not BAG5 has been identified as a PD associated gene (Chang et al. 2017), underlining the importance of understanding the connections between the two pathways.

Finally, mitochondria also harbor a channel in the inner mitochondrial membrane termed the mitochondrial permeability transition pore (PTP). Mitochondrial Ca^{2+} overload is known to be a key regulator of the PTP (Figure 2B; Hurst et al. 2017). Ca^{2+} enters mitochondria through the combined action of VDAC in the OMM and the mitochondrial Ca^{2+} uniporter MCU in the inner mitochondrial membrane (Perocchi et al. 2010). This happens usually in close contact with the ER (Figure 2B; Giorgi et al. 2009). Sustained PTP opening causes depolarization of the inner membrane and matrix swelling (Rasola and Bernardi 2007). This in turn results in unfolding of cristae and breaks in the OMM, through which stored Ca^{2+} and pro-apoptotic factors are released and trigger the initiation of apoptosis (Kroemer et al. 2007). The exact composition of the PTP is still unresolved (Rasola and Bernardi, 2007), yet it is thought to cooperate with VDAC on the OMM. It has been suggested that VDAC may play a central role in switching between mitophagy and cell death pathways as discussed below.

Mitochondrial dynamics in mitophagy and apoptosis

Mitochondria are highly dynamic organelles that constantly undergo fusion and fission events. Fission of a mitochondrion into two independent organelles is mediated by the cytosolic GTPase Dynamin-related protein 1 (Drp1) following its targeting by Mitochondrial fission factor (Mff) and the Mitochondrial Dynamics proteins of 49 and 51 kDa (MiD49/51) to the OMM, while the Mitofusins 1 and 2 (Mfn1/2) and Optic atrophy 1 (Opa1) are involved in mitochondrial fusion (reviewed in Giacomello et al. 2020). Fusion is thought to equilibrate metabolites across the mitochondrial network, whereas mitochondrial fission serves two purposes: On one hand, mitochondrial fission is essential to spread the mitochondrial network across the cell and specifically allows transport of mitochondria into axons (Lewis et al. 2018). This transport depends on the motor adaptor complex formed by the OMM protein Miro (also RHOT1/2) and Milton (also TRAK1/2), which connects mitochondria to the molecular motors dynein and kinesin (reviewed in Saxton and Hollenbeck 2012). On the other hand, mitochondrial fission allows to dissipate dysfunctional parts from the mitochondrial network, which facilitates the removal of these individual organelles by mitophagy (Burman et al. 2017; Twig et al. 2008).

The link between mitophagy and mitochondrial dynamics is supported by the fact that Miro and Mfn2 are among the proteins that are phosphorylated and ubiquitinated by PINK1 and Parkin, respectively (Figure 3; Chen and Dorn 2013; Wang et al. 2011). Miro and Mfn2 are both targeted for proteasomal degradation before the actual mitophagic clearance occurs. Consequently, the PINK1/Parkin pathway promotes mitochondrial fission and inhibits mitochondrial motility as a requirement for the selective degradation of damaged mitochondria via mitophagy. In this way, damaged mitochondria are quarantined prior to their elimination since both motility and fusion are blocked. This has two advantages: (1) Immobile unhealthy mitochondria that are unable to fuse are prevented from damaging other healthy mitochondria. (2) Damaged mitochondria release ROS. By stopping these mitochondria from moving and fusing, a smaller region of the cell is affected by ROS (Wang et al. 2011). Similarly, during apoptosis Drp1 as well as Mfn2 co-localize with BAX at mitochondrial scission sites, and calcineurin-mediated dephosphorylation of Drp1 has been shown to facilitate apoptotic cell death (Cribbs and Strack 2007; Karbowski et al. 2002; Maes et al. 2019). In response to cellular stress, JNK phosphorylates Mfn2, which leads to its ubiquitination by the E3-ligase Huwe1 and its proteasomal degradation and thereby mitochondrial fragmentation (Leboucher et al. 2012). Interestingly, BAX- or BAX/ BCL-x_L- expressing cells also display reduced motility of their fragmented mitochondrial networks (Sheridan et al. 2008). We currently do not understand how pro-apoptotic proteins modulate mitochondrial arrest mechanistically. It has been shown, however, that OMM permeabilization by BAK also activates the PINK1/Parkin pathway (Bernardini et al. 2019). Thus, the quarantining of apoptotic mitochondria could employ the PINK1/Parkin-dependent mechanisms of mitochondrial quarantine to also restrict the apoptotic signal within a cell. Further experiments will be needed to identify the responsible mechanisms of mitochondrial arrest during apoptosis, which may be particularly important in large and morphologically distinct cells such as neurons.

Interestingly, caspase-3 activation has been observed to be restricted to individual neurites or synapses, leading to elimination of only parts of the neuron (Campbell and Holt 2003; Ertürk et al. 2014; Gilman and Mattson 2002). This process is thought to be important for memory formation, in particular a process termed long term depression (LTD) that leads to the weakening and finally elimination of individual synapses (reviewed in Li and Sheng 2012). Intriguingly, PINK1 knock out mice display reduced caspase-3 activity after induction of LTD compared with wild type mice (Imbriani et al. 2019), which may explain some of the observed cognitive defects in PINK1 knock out mice (Kitada et al. 2007). It is interesting to speculate that loss of PINK1 function or other mutations in PD proteins lead to a failure to arrest apoptotic mitochondria at the targeted synapse. This may result in spread of the apoptotic signal to neighboring synapses, leading to increased neuronal vulnerability to apoptotic stimuli and dementia. Thus, exploring the mechanisms of mitophagy-apoptosis cross-talk may lead to insights into the pathogenesis of the disease.

Interplay between mitophagy and apoptosis signaling

Both activation of mitophagy and activation of pro-apoptotic BCL-2 family members happen on the OMM, yet the outcome for the cell could not be more different. Either mitophagy is activated and the cell eliminates just one mitochondrion in order to survive, or cytochrome *c* is released, which induces further mitochondrial damage through excessive ROS production. This requires the cell to commit itself to apoptosis. The decision between one fate

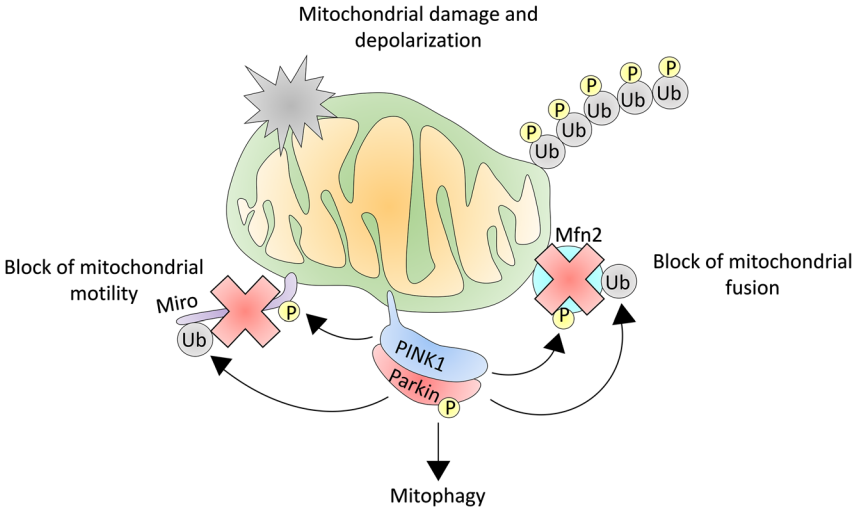

Figure 3: PINK1/Parkin pathway blocks mitochondrial motility and fusion. The activation of PINK1 leads to the recruitment of Parkin and results in blockage of mitochondrial motility and fusion by phospho-ubiquitination of Miro and Mfn2, respectively.

or the other is made at the mitochondrial surface and it is therefore not surprising that there is cross-talk between the two programs. In the following chapters we describe how (i) PINK1 signaling prevents cell death, (ii) Parkin activation can both prevent and promote cell death, (iii) BCL-2 family proteins influence Parkin translocation and (iv) how the interplay extends beyond mitophagy and apoptosis induction to inflammatory signaling.

Activation of PINK1 signaling prevents cell death

PINK1 has been described as an anti-apoptotic protein (Li and Hu 2015; Valente et al. 2004), as its activation leads to the removal of damaged organelles from the cell, thus preventing further cellular damage and cell death. Beyond this general protective effect, PINK1 also phosphorylates several substrates either directly or affects their phosphorylation indirectly that may affect the cellular response to an apoptotic stimulus (Table 1). Most prominently, PINK1 phosphorylates BCL-x_L and thereby prevents its pro-apoptotic cleavage (Arena et al. 2013). In addition to the association of PINK1 with pro-survival proteins, PINK1 has also been shown to regulate BAD by phosphorylating the BH3-only protein at Ser112/136. Consequently, phosphorylation of BAD raises the threshold of apoptosis as BAD fails to localize to mitochondria and initiate the mitochondrial apoptosis pathway (Figure 4; Wan et al. 2018).

Dysregulation of mitochondrial Ca^{2+} and opening of the PTP has been suggested as the underlying mechanism of cell death in PINK1-deficient neurons (Gandhi et al. 2009). How PINK1 affects mitochondrial Ca^{2+} levels mechanistically remains to be determined. Among the PINK1-regulated proteins (compare Table 1) are proteins that affect mitochondrial Ca^{2+} load (Huang et al. 2017) as well as OXPHOS (Morais et al. 2014), making them likely mediators of PINK1-mediated control of mitochondrial Ca^{2+} levels.

Finally, PINK1 kinase activity has been shown to affect the activity of the Akt pathway (Akundi et al. 2012) and vice versa (Soutar et al. 2018). Akt activation in response to insulin-like growth factor 1 (IGF-1) requires recruitment of Akt to the plasma membrane due to the accumulation of phosphatidylinositol (3,4,5)-trisphosphate (PIP_3) (Manning and Toker 2017), which has recently been shown to be defective in PINK1 knock out cells (Furlong et al. 2019). Mechanistically, PINK1 kinase activity is necessary to activate the PI3-kinase p85 and to redistribute PIP_3 towards the plasma membrane in response to IGF-1 (Furlong et al. 2019), yet the actual PINK1 target and its subcellular localization are unknown. Nevertheless, activation of PINK1 favors the activation of the pro-survival PI3K/Akt signaling pathway, thereby inhibiting the FOXO-dependent expression of BH3-only proteins like PUMA and BIM (Manning and Toker 2017) and promotes phosphorylation and thereby inhibition of BAD (She et al. 2005). Activation of PINK1 signaling therefore serves on many levels as a pro-survival signal for the cell.

Parkin activation can both prevent and promote cell death

Much like PINK1, Parkin has been described as a neuroprotective agent (Feany and Pallanck 2003). Several interactions with apoptotic proteins have been described,

Table 1: PINK1-dependent phosphorylation events and their impact on apoptosis.

Phospho-protein	Subcellular localization	Impact on mitochondrial function	Impact on apoptosis	Reference
BCL-x_L	Cytosol/OMM	Phosphorylation of BCL-x_L by PINK1 does not regulate mitophagy	Phosphorylation of BCL-x_L by PINK1 protects the cell against apoptosis, by preventing the pro-apoptotic cleavage of BCL-x_L	(Arena et al. 2013)
BAD	Cytosol/OMM	The localization of BAD to the mitochondria is decreased	As BAD normally exerts its pro-apoptotic function by localizing to the mitochondria, PINK1 phosphorylation results in an increased mitochondrial threshold for apoptosis	(Wan et al. 2018)
Ubiquitin	Cytosol/OMM	Phosphorylated ubiquitin is an activator of Parkin and is essential for its translocation from the cytosol to the OMM	NA	(Kane et al. 2014; Koyano et al. 2014; Okatsu et al. 2015)
Parkin	Cytosol/OMM	PINK1 phosphorylates and activates Parkin at Ser65, whereafter Parkin labels defective mitochondria for degradation by ubiquitination	Parkin is known to interact with both BCL-x_L and BAG5 to promote their anti-apoptotic functions, as well as with BAK to inhibit its pro-apoptotic activation by ubiquitination	(Kondapalli et al. 2012)
HTRA2/ Omi	IMS	Phosphorylation of HtrA2 likely modulates the proteolytic activity of the protein and promotes cellular resistance against mitochondrial stress	HtrA2 is released from the IMS during apoptosis and contributes to pro-apoptotic signaling	(Plun-Favreau et al. 2007)
TRAP1	IMS	Protects against oxidative stress and suppresses the release of cytochrome *c* from the mitochondria	Protects against oxidative stress-induced apoptosis	(Pridgeon et al. 2007)
Mic60	IMM	PINK1 maintains cristae junctions by phosphorylating Mic60	NA	(Tsai et al. 2018)
NdufA10	IMM	NdufA10 phosphorylation stimulates the ubiquinone reductase ability of complex I	Phosphomimetic NdufA10 protects against H_2O_2-induced apoptosis	(Morais et al. 2014)
LETM1	IMM	Mitochondrial Ca^{2+} export is increased upon LETM1 phosphorylation	LETM1 regulation protects against mitochondrial stress and sensitization to cell death	(Huang et al. 2017)
Miro	OMM	PINK1 phosphorylation marks Miro for degradation resulting in dissociation from kinesin and ultimately preventing mitochondrial movement	NA	(Wang et al. 2011)
Mfn2	OMM	PINK1 as well as Parkin catalyze phosphoubiquitination of Mfn2 to trigger disassembly of Mfn2 complexes from the outer mitochondrial membrane, dissociating mitochondria from the ER and thereby facilitating mitophagy	NA	(McLelland et al. 2018; Chen and Dorn 2013)

including BCL-x_L and BAG5 (De Snoo et al. 2019; Hollville et al. 2014). Parkin has also been suggested to directly influence apoptosis by ubiquitinating the BH3-binding site of BAK (Bernardini et al. 2019). Ubiquitination of this hydrophobic groove could influence regulatory interactions with BH3-only proteins as well as prosurvival BCL-2 proteins. However, the impact on neuronal apoptosis is unclear, as BAX is the dominant pro-apoptotic BCL-2 protein in neurons. Parkin has also been suggested to ubiquitinate BAX (Figure 4; Cakir et al. 2017; Johnson et al. 2012). Initial research suggested Parkin-dependent BAX ubiquitination in the N-terminus of cytosolic BAX preventing BAX translocation to the OMM (Johnson et al. 2012). However, several studies have shown that mitochondrial localization is a prerequisite for BAX interactions (Hsu and Youle 1998; Roucou et al. 2002; Vogel et al. 2012). Consequently, Parkin has been shown to ubiquitinate BAX on lysine 128 on the OMM (Cakir et al. 2017). This mechanism allows cells to prevent activation of retrotranslocation-incompetent BAX and favors mitophagy over apoptosis, opening a window of

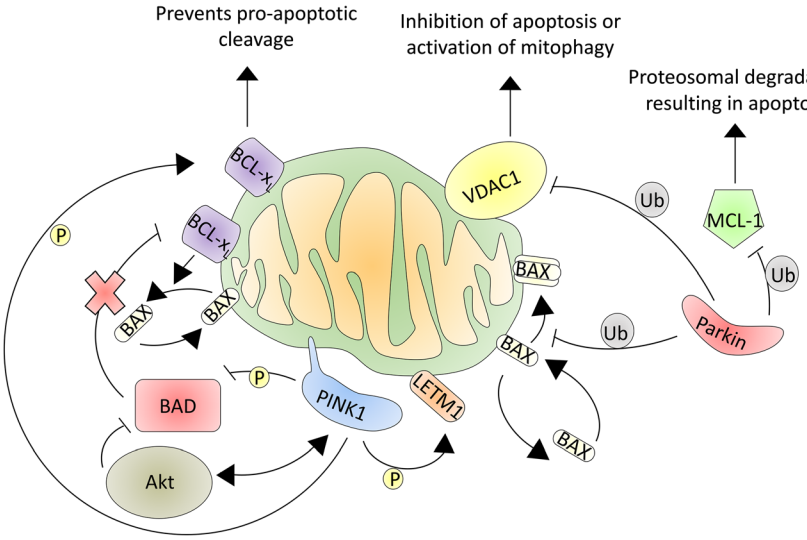

Figure 4: Schematic overview of mitophagy and apoptosis interplay.
Mitophagy-associated PINK1 serves as an anti-apoptotic protein by phosphorylating various proteins including LETM1 and BCL-x_L, in order to prevent dysregulation of Ca^{2+} storage and pro-apoptotic cleavage, respectively. PINK1 also phosphorylates and, therefore, prevents mitochondrial association of the BH3-only protein BAD. Parkin exerts an anti-apoptotic function by ubiquitinating BAX at the OMM, which leads to the degradation of retrotranslocation incompetent BAX. Parkin also can ubiquitinate VDAC1. Monoubiquitination of VDAC1 has been proposed to delay cell death by altering mitochondrial Ca^{2+} levels, while poly-ubiquitination plays a role in the induction of mitophagy. Parkin, however, can also ubiquitinate the anti-apoptotic protein MCL-1, thereby acting as a driver of cell death.

opportunity for the cell to cope with mitochondrial stressors rather than commit to death.

Under specific circumstances, such as extensive mitochondrial damage, Parkin may also act as a driver of apoptosis (Zhang et al. 2014). Parkin has been reported to specifically target the pro-survival BCL-2 protein MCL-1 for proteosomal degradation (Figure 4; Carroll et al. 2014; Zhang et al. 2014). In a recent study, Ham et al. (2020) propose that the decision between mitophagy or apoptosis induction by Parkin depends on the ubiquitination of VDAC (Figure 4; Ham et al. 2020). It has been proposed that Parkin either mono- or polyubiquitinates VDAC1. While polyubiquitination promotes Parkin-mediated mitophagy, VDAC1 monoubiquitination inhibits apoptosis by preventing Ca^{2+} influx into mitochondria. Interestingly, *Drosophila* mutants expressing a Parkin mutant defective in VDAC1 monoubiquitination display defective locomotive activity and loss of dopaminergic neurons, symptoms reminiscent of PD and observed upon loss of Parkin in flies (Yang et al. 2006). It has been shown previously that overexpression of BCL-2 in Parkin mutant flies rescues the Parkin and PINK1 null phenotypes (Park et al. 2006), arguing that loss of neurons due to apoptosis could be a main driver of the observed defects. While requirement of VDAC1 polyubiquitination in mitophagy is dabatable (Geisler et al. 2010; Narendra et al. 2010), the importance of VDACs as interactors for BCL-2 family proteins as well as a putative component of the PTP is well documented (reviewed in Shoshan-Barmatz et al. 2006). However, loss of the VDAC2 isoform has a stronger effect on BAX mitochondrial localization (Lauterwasser et al. 2016), but whether Parkin-mediated mono- or poly ubiquitination of VDAC2 is relevant in the decision between apoptosis and mitophagy has not been tested.

Influence of BCL-2 family proteins on Parkin translocation

Overexpression of pro-survival BCL-2 family proteins, and specifically BCL-x_L, in cultured cell lines has been shown to inhibit Parkin translocation to the OMM (Hollville et al. 2014; Yu et al. 2020; Zhang et al. 2020). This seems contradictory to the pro-survival role of BCL-x_L, as this would decrease the amount of mitophagy, thereby increasing the risk of dysfunctional mitochondria generating ROS. It also would prevent the monoubiquitination of VDAC1 described above, leading to increased mitochondrial Ca^{2+} influx, exacerbating the mitochondrial dysfunction and eventually leading to cell death. Nevertheless, it fits the observation that BCL-x_L is frequently overexpressed in cancer cells (Sasi et al. 2009), while Parkin is frequently deleted (Gong et al. 2014).

It has been proposed that BCL-x_L acts on VDAC and increases the release of ATP, which helps overcome the apoptotic stimulus and thereby decreases the probability of OMM permeabilization (Vander Heiden et al. 2001). As cancer cells are typically glycolytic cells, mitochondrial damage may be also more tolerable. Indeed, low levels of ROS have been shown to promote

cancer growth (Moloney and Cotter 2018). Therefore, high levels of BCL-x_L in tumor cells on the one hand prevent apoptosis, while they on the other hand prevent Parkin-mediated mitophagy and thereby increase ROS signaling. If overexpression of BCL-x_L is also capable of inhibiting Parkin translocation in neurons remains to be tested.

Mitophagy and apoptosis interplay in inflammation

Due to their bacterial ancestry, many mitochondrial components have a high immunogenic potential. Normally, mitochondrial immunogenic components are shielded from cytosolic and endosomal pattern recognition receptors by the dual mitochondrial membranes. OMM permeabilization allows mitochondrial components to be liberated for immune recognition, thereby providing a strong cellular distress signal.

Release of mitochondrial DNA (mtDNA) can act a driver of inflammation, by engaging the innate immune cytosolic cGAS/STING (cyclic guanosine monophosphate-adenosine monophosphate synthase/stimulator of interferon genes) pathway resulting in type I interferon production (Rongvaux et al. 2014; White et al. 2014). This pathway has recently been connected to the mitochondrial apoptosis machinery: BAX and/or BAK macropores in the OMM have been suggested to facilitate the release of mitochondrial DNA into the cytoplasm (McArthur et al. 2018; Riley et al. 2018). In the absence of caspases, mitochondrial DNA is thought to activate pro-inflammatory signaling, likely via the activation of cGAS–STING. However, further research may be required to understand the release of mitochondrial DNA through IMM ruptures (Ader et al. 2019). Interestingly, in the absence of PINK1 or Parkin, mitochondrial stress leads to a strong inflammatory response in mice, which is mediated by the cGAS/STING pathway and results in type I interferon production (Sliter et al. 2018). Loss of STING completely rescued the consequent neurodegeneration and motor defects in mice that combine mtDNA mutations with Parkin deficiency. Therefore, PINK1/Parkin-mediated mitophagy could play a role in mitigating the cGAS/STING-induced inflammatory response and neurodegeneration by removing damaged mitochondria and, therefore, preventing the release of DAMPs, such as mtDNA, into the cytoplasm.

Furthermore, PINK1/Parkin mediated mitophagy has been shown to be instrumental to suppress the presentation of mitochondria-derived peptides on MHC class I receptors (Matheoud et al. 2016). Loss of PINK1 allows the production of cytotoxic mitochondria-specific $CD8^+$ T cells upon infection with gram negative bacteria (Matheoud et al. 2019), which led to reversible loss of dopaminergic neuron axon terminals in this normally unaffected mouse line. It is unclear why the damage would be localized in such a restricted fashion, as it was shown that addition of these $CD8^+$ T cells was enough to induce the apoptosis (via the extrinsic pathway) in cultured neurons *in vitro* (Matheoud et al. 2019).

Finally, the release of mitochondrial components into the cytosol can act as a driver of inflammasome formation (reviewed in Holley and Schroder 2020). Upon activation, Nod-like receptor protein 3 (NLRP3) self assembles and forms a multiprotein complex called inflammasome that activates the pro-inflammatory caspase-1 (Agostini et al. 2004). BAX and BAK activity on the OMM have been shown to further activate NLRP3 in a caspase-3/-7-dependent manner (Vince et al. 2018). Activated caspase-1 cleaves and inactivates Parkin (Kahns et al. 2003), and hence initiates a feed forward loop that exacerbates mitochondrial damage. These findings exemplify the role of neuroinflammation in PD pathology, and it is therefore not surprising that inhibition of inflammasome formation is explored as potential treatment for PD (Gordon et al. 2018).

Closing remarks

As outlined above, the outcome of mitochondrial damage is ambivalent: mitophagy and cellular survival on the one side, apoptosis on the other. BCL-2 family proteins as well as the mitophagy proteins PINK1 and Parkin hold a delicate balance that decides the outcome. Likewise, activation of apoptotic proteins in neurons can either be subthreshold and important for synaptic plasticity, or lead to neuronal cell death and neuroinflammation. Mitophagy-apoptosis cross-talk is an important determinant of these cellular decisions and research into this direction will undoubtedly lead to novel insights into the etiology of neurodegenerative diseases like PD.

Acknowledgments: We are grateful for the support of all members of the Harbauer lab. ABH is a Max Planck Research Group Leader and associated with the DFG funded Munich Center for Systems Neurology (SyNergy). FE was supported by the DFG Heisenberg program, the Else Kröner-Fresenius-Stiftung, the Wilhelm-Sander Foundation and Germany's Excellence Strategy (CIBSS – EXC-2189 – Project ID 390939984).

Author contribution: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: Else Kröner-Fresenius-Stiftung; Max-Planck-Gesellschaft; and Deutsche Forschungsgemeinschaft (CIBSS – EXC-2189 – Project ID 390939984), Heisenberg Program, Munich Cluster for Systems Neurology.

Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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