Am J Physiol Cell Physiol 317: C111–C130, 2019.
First published April 24, 2019; doi:10.1152/ajpcell.00261.2018.

REVIEW | *Mitophagy, Autophagy and Cell Death*

Autophagy, apoptosis, and mitochondria: molecular integration and physiological relevance in skeletal muscle

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Submitted 28 June 2018; accepted in final form 23 April 2019

Bloemberg D, Quadrilatero J. Autophagy, apoptosis, and mitochondria: molecular integration and physiological relevance in skeletal muscle. *Am J Physiol Cell Physiol* 317: C111–C130, 2019. First published April 24, 2019; doi:10.1152/ajpcell.00261.2018.—Apoptosis and autophagy are processes resulting from the integration of cellular stress and death signals. Their individual importance is highlighted by the lethality of various mouse models missing apoptosis or autophagy-related genes. In addition to their independent roles, significant overlap exists with respect to the signals that stimulate these processes as well as their effector consequences. While these cellular systems exemplify the programming redundancies that underlie many fundamental biological mechanisms, their intertwined relationship means that dysfunction can promote pathology. Although both autophagic and apoptotic signaling are active in skeletal muscle during various diseases and atrophy, their specific roles here are somewhat unique. Given our growing understanding of how specific changes at the cellular level impact whole-organism physiology, there is an equally growing interest in pharmacological manipulation of apoptosis and/or autophagy for altering human physiology and health.

apoptosis; autophagy; mitochondria; mitophagy; skeletal muscle

INTRODUCTION

Depending on their status, stress signal integration will direct cellular response mechanisms, ultimately leading to survival or death. Many forms of regulated cell death (RCD) exist, allowing cells to appropriately mediate their own destruction. Apoptosis is a RCD process characterized by highly structured and well-conserved molecular signaling events that typically serves as the default cell death pathway. Currently attributed with both prosurvival and prodeath functions, autophagy is an intracellular degradation mechanism that activates in response to various stimuli. Interestingly, on a cellular level, several stressors induce autophagy before or during apoptotic processes. While initial assessments of these observations concluded that autophagy contributed to cellular demolition and elimination, subsequent analyses indicate that autophagy typically functions to mitigate the encountered stress. Although autophagy generally appears to enhance cell survival, it is likely that an optimal level exists and that specific conditions of overactive and underactive autophagy can lead to cell death or be pathological.

Although numerous forms and condition-specific cell death mechanisms exist, including necrosis, necroptosis, ferroptosis, pyroptosis, parthanatos, entotic cell death, NETotic cell death, and immunogenic cell death (68), this review outlines the molecular signals that mediate apoptosis and autophagy, highlighting those involved with regulating both. Moreover, we focus on mitochondrial apoptotic signaling and mitophagy, due to mitochondria's critical role in cell life and death. We also describe a general framework for the apoptosis/autophagy relationship and use several cellular mechanisms to explain how this unfolds. Finally, the roles that apoptotic and autophagic interactions play during pathophysiological conditions in skeletal muscle and other tissues are highlighted.

MITOCHONDRIAL APOPTOTIC PROCESSES

Apoptosis

Apoptosis is a physiological RCD mechanism responsible for eliminating abnormal, damaged, and/or unnecessary cells (68, 85, 138, 224). During development, specific cells undergo apoptotic cell death, thus regulating tissue/organ shape and function (224). In adult organisms, apoptosis is responsible for removing damaged and/or genetically disrupted cells as well as those affected by pathogens (138, 224). Apoptosis represents a relatively clean method of cell death that is considered almost immunologically silent (280).

The primary executioners of apoptosis are a family of enzymes known as caspases (CASPs), which cleave proteins between cysteine and aspartic acid residues (42, 68, 138, 224)

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(Fig. 1*A*). Effector CASPs (CASP3, -6, and -7) are activated by initiator CASPs (CASP8 and -9) and are responsible for cleaving >400 cellular proteins, thereby disassembling the cell (64, 169). The extracellular/extrinsic apoptotic pathways involve activation of formal death receptors embedded in the plasma membrane from the TNF receptor super family (TNFRSF) by their respective ligand (68, 82, 131) and activate CASPs using well-coordinated membrane-bound protein scaffolds.

Intracellularly, stressors sensed by various compartments induce apoptosis. Mitochondria are vital mediators of many apoptotic programs whereby toxic stimulants, growth factor exhaustion, DNA damage, and reactive oxygen species (ROS) disrupt electron transport, ATP production, and mitochondrial permeability, ultimately causing release of cell death signaling proteins into the cytosol (Fig. 1*A*) (68, 85, 138, 224). The BCL2 apoptosis regulator (BCL2) family plays a critical role in regulating these signals through their antiapoptotic and proapoptotic functions. Upon their activation or increased expression, members such as BCL2-associated X, apoptosis regulator (BAX) and BCL2 antagonist/killer 1 (BAK1) bind antiapoptotic members such as BCL2 and BCL2 like 1 (BCL2L1/BCLXL) (37, 125, 126, 143, 151, 200), thereby permeabilizing mitochondrial membranes (4, 22, 80), reducing membrane potential, and preventing ATP generation (62, 138). This causes release of cytochrome c, somatic (CYCS) and diablo IAP-binding mitochondrial protein (DIABLO/SMAC), which contribute to CASP activation, as well as release and translocation of apoptosis inducing factor mitochondrial-associated 1 (AIFM1/AIF) and endonuclease G (ENDOG), which directly

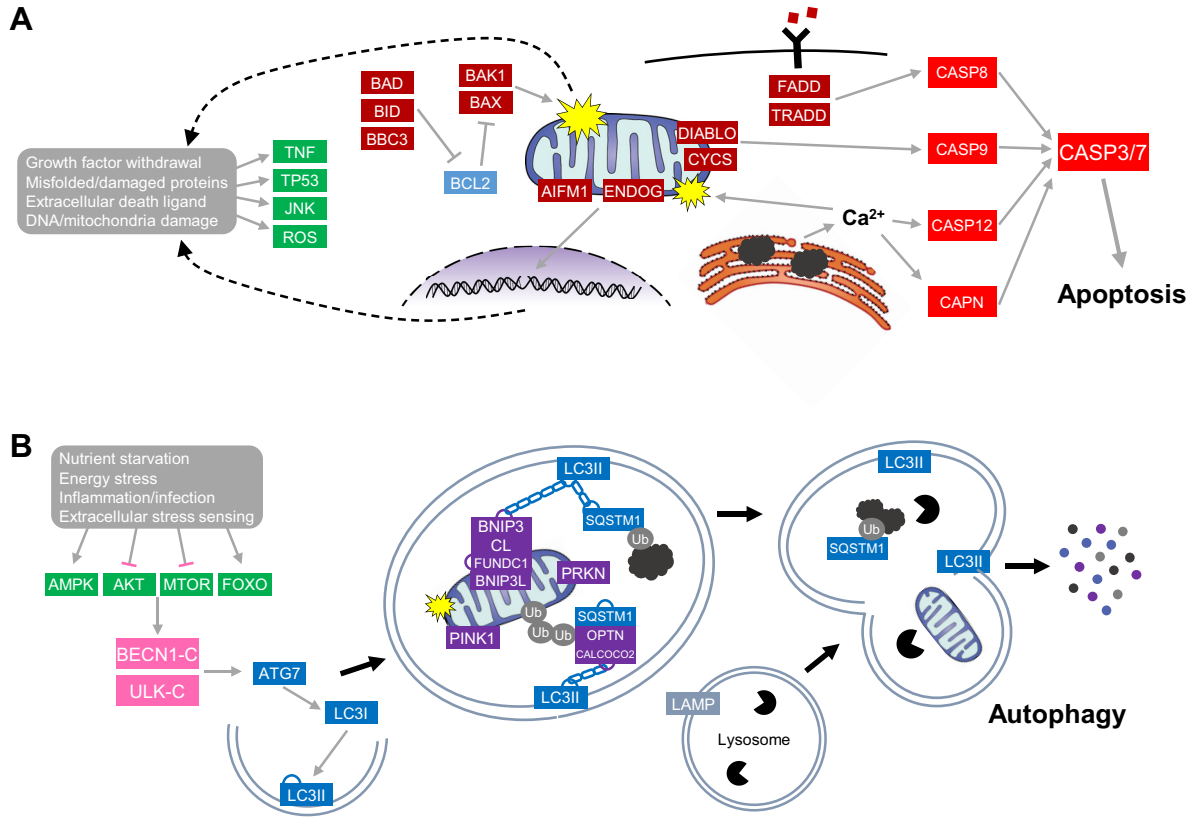

Fig. 1. Overview of apoptosis (*A*) and autophagy (*B*) signaling pathways. *A*: in response to various stimuli (gray box), several signaling families [tumor necrosis factor (TNF), Jun N-terminal kinases (JNK)] activate death-associated transcription factors [tumor protein P53 (TP53)] and effector signaling mechanisms [reactive oxygen species (ROS)] (green boxes). At the mitochondria, prodeath proteins (burgundy boxes) such as BCL2-associated agonist of cell death (BAD), BH3-interacting domain death agonist (BID), BCL2-binding component 3 (BBC3/PUMA), BCL2-associated X, apoptosis regulator (BAX), and BCL2 antagonist/killer 1 (BAK1) promote mitochondria permeability, thus causing the release of cytochrome *c*, somatic (CYCS), diablo IAP-binding mitochondrial protein (DIABLO/SMAC), apoptosis-inducing factor mitochondrial-associated 1 (AIFM1/AIF), and endonuclease G (ENDOG). Once released, these proteins directly fragment DNA or activate caspase (CASP)9 (red boxes), ultimately promoting apoptosis. The binding of extracellular ligands at death receptors causes CASP8 (red boxes) activation through protein scaffolds [Fas-associated with death domain (FADD), TNFRSF1A associated via death domain (TRADD)]. At the endoplasmic reticulum (ER), misfolded proteins (brown clouds) and calcium mishandling cause CASP12 and calpain (CAPN) (red boxes) activation. These mechanisms are significantly redundant (dashed lines). *B*: numerous stimuli (gray box) affect autophagy induction by activating [AMP-activated protein kinase (AMPK), forkhead box O3 (FOXO)] and/or inhibiting [AKT serine/threonine kinase (AKT), mechanistic target of rapamycin kinase (MTOR)] stress and energy/growth factor signaling (green boxes). Beclin 1 (BECN1) and unc-51 like autophagy activating kinase (ULK) complexes (BECN1-C and ULK-C; pink boxes) mediate autophagosome formation by modulating downstream autophagy related (ATG) proteins [ATG7, microtubule-associated protein 1 light chain 3 (MAP1LC3/LC3); blue boxes], including membrane incorporation of LC3II. Autophagic substrates are identified by sequestosome 1 (SQSTM1) binding to misfolded proteins (brown clouds) with ubiquitin tags (Ub), while mitochondria are identified by unique ubiquitin binding and complex kinase-dependent activation of parkin RBR E3 ubiquitin protein ligase (PRKN) and PTEN-induced kinase 1 (PINK1) (purple boxes). BCL2-interacting protein 3 (BNIP3), BCL2-interacting protein like (BNIP3L/NIX), FUN14 domain-containing 1 (FUNDC1), optineurin (OPTN), calcium-binding and coiled-coil domain 2 (CALCOCO2/NDP52), and cardiolipin (CL) (purple boxes) also identify mitochondria to be degraded. After lysosomal fusion, autophagosome contents are degraded by proteolytic enzymes. These peptides/amino acids are released into the cytosol for recycling or used for immunomodulatory functions.

causes DNA fragmentation (51, 138, 154, 155, 224, 251). These mechanisms are highly redundant and feedforward, ensuring apoptotic execution upon reaching a certain threshold of mitochondrial damage.

Mitochondrial Permeability Transition

Few aspects of cell death have generated more controversy than mitochondrial permeability transition pore (mPTP) formation (14, 18, 59, 75, 100, 113, 138). The existence of mPTP, or a transition to increased mitochondrial permeability, is widely accepted. mPTPs occur in response to severe oxidative stress or cytosolic ion overload through assembly of large protein channels that span both mitochondrial membranes (16, 18, 138). Physiological relevance for mPTP has been recognized for several years (15). In fact, clinical trials involving its pharmacological manipulation have been conducted using cyclosporine A (CsA) to inhibit peptidylprolyl isomerase D (PPID/CYPD) immediately following or during myocardial infarction (45, 181, 210, 281). Despite demonstration in rodent models that CsA administration or PPID inhibition prevents tissue damage and increases survival during ischemia/reperfusion (IR) in cardiac and neural tissues (77, 110, 160, 223), the final clinical data suggest that this is not as significant in humans (45, 161, 281). This is potentially due to the incomplete picture regarding mPTP formation and function. While PPID is considered a component and regulator of mPTP, several other proteins previously suggested to function similarly have been subsequently identified as irrelevant or unnecessary, including components of ATP synthase (1, 59, 75, 99, 100), voltage dependent anion channels (VDACs) (11, 289), and solute carrier family 25, member 4/5/6 (SLC25A4/5/6; ANTs) (19, 89, 134), among others (68, 138).

MOLECULAR REGULATION OF AUTOPHAGY

Overview

Autophagy is a degradative process responsible for breaking down subcellular content (2, 98, 152, 215). Autophagy is uniquely flexible given that it can degrade specific targets, entire organelles, and large portions of cytoplasm. Autophagy operates by generating double-membrane organelles, filling them with cargo, and fusing them with lysosomes, where their contents are degraded and recycled (Fig. 1*B*) (98, 152, 215). Autophagy's primary function is to sacrifice cellular material to provide energetic substrates during periods of starvation. As such, systemic deletion of many autophagy-related genes is lethal in mice, largely due to metabolic stress during the transition from in utero feeding (63, 135, 141, 225, 226, 246). However, autophagy is additionally involved in defense, remodeling, and removal of damaged and long-lived proteins and organelles. Given this, autophagy is generally considered cytoprotective, serving to prolong optimal cellular function (2, 98, 152, 215). Several classifications of autophagy exist; however, herein the mechanism of macroautophagy involving autophagosome-lysosome fusion will be referred to as autophagy (98, 152).

Initiation

Autophagy begins with the production of a double membrane structure known as the isolation membrane by two kinase complexes (98, 215). One complex contains unc-51 like autophagy activating kinase 1/2 (ULK1/2), autophagy related (ATG)13, and RB1-inducible coiled-coil 1 (RB1CC1/FIP200) (2, 98, 215). Under nutrient-rich conditions, the mechanistic target of rapamycin complex 1 (MTORC1) is active and exists in close association with ULK1/2 (2, 107). In this state, MTORC1 maintains ULK1/2 and ATG13 hyperphosphorylation, thereby inhibiting them (107, 119). Mechanistic target of rapamycin kinase (MTOR) inhibition causes its dissociation from ULK1/2, leading to ULK complex translocation to the site of isolation membrane production, where it activates other autophagy-related machinery (70, 107, 120). The second kinase platform is composed of beclin 1 (BECN1), phosphatidylinositol 3-kinase catalytic subunit type 3 (PIK3C3/VPS34), and phosphoinositide-3-kinase regulatory subunit 4 (PIK3R4/VPS15) as well as other components such as ATG14 and autophagy and beclin 1 regulator 1 (AMBRA1) (98, 215). This complex is a class III phosphatidylinositol 3-kinase (PI3K), and produces phosphatidylinositol 3-phosphate (PI3P) for the autophagosome membrane (257). The phosphatidylinositol (PI) for this reaction is sourced from other membranes, such as the plasma membrane (214), ER (95, 96), or mitochondria (88). ER-mitochondria contact sites, known as mitochondrial-associated membranes (MAMs), are the likely source of isolation membranes formation, as upstream autophagy-related proteins converge here during autophagy induction (71, 92). Ultimately, PI3P induces autophagosome development by recruiting adaptor proteins responsible for double-membrane production (9, 212).

Elongation and Execution

Autophagosomes are produced by ULK and BECN1 complexes with the help of two ubiquitin-like conjugation systems. The first involves a complex composed of ATG12, ATG5, and ATG16 (93, 183) that is activated by ATG7 in an E1-like manner. The second system is responsible for activating an important member of autophagosomes, microtubule-associated protein 1 light chain 3 (MAP1LC3/LC3). LC3 is a cytosolic protein whose autophagic role is initiated by ATG4-dependent cleavage, leaving a product known as LC3I (101, 255). LC3I is similarly activated by ATG7 and conjugated to phosphatidylethanolamine (PE) by the E2-like carrier ATG3 (121). The LC3I-PE conjugate, termed LC3II, is recruited by the ATG5-ATG12-ATG16 complex to the developing isolation membrane. Once the proper molecular machinery has been recruited, the ULK and BECN1 complexes guide autophagosome elongation in association with ATG5-ATG12-ATG16, making LC3II a major membrane component (121, 255). Upon their completion, autophagosomes fuse to lysosomes with the help of lysosomal associated membrane proteins (LAMPs), forming a structure known as the autolysosome (254). Finally, lysosomal hydrolases and cathepsins break down the autophagic cargo as well as the inner autophagosome membrane, including LC3II (98, 215). Degraded material is released into the cytosol, where it is used for energy metabolism, protein synthesis, and various other tasks (98, 152, 215).

Targeting

Autophagic substrates can be identified through the interaction of LC3II with the multifunctional adaptor protein

sequestosome 1 (SQSTM1/P62), which is commonly found in protein aggregates (98, 215). While damaged and misfolded proteins tagged by ubiquitin can be targeted by the proteasome, SQSTM1 can also identify mono- and polyubiquitinated proteins and directly bind to them via its ubiquitin-associated domain (UBA) (109, 205). SQSTM1 subsequently binds to LC3II, thus directing specific substrates for autophagic degradation (109, 205). This function is vital not only for the clearance of accumulated proteins but for basal autophagy, and therefore, SQSTM1 is commonly analyzed as an indicator of autophagic flux (133). NBR1 autophagy cargo receptor (NBR1) functions similarly and additionally binds directly to SQSTM1, where they act together as autophagy receptors (130). Another method of aggresome degradation involves the recruitment of heat shock proteins and the E3-ligase STIP1 homology and U-box containing protein 1 (STUB1/CHIP) along with the cochaperone BCL2 associated athanogene 3 (BAG3) (32, 69). Here, misfolded and ubiquitinated targets are sequestered by heat shock complexes and shuttled to developing autophagosomes through the interaction between BAG3, SQSTM1, and LC3 (32, 69).

Control

Because overactive autophagy would be unnecessarily catabolic, its execution is precisely regulated. MTORC1 is perhaps the most important autophagy control point (2, 98, 215). Active MTOR phosphorylates specific targets, resulting in promotion of protein synthesis and prevention of autophagy; therefore, its inhibition reduces mRNA translation and induces autophagy (215). Insulin, glucagon, and other growth factor signaling affect autophagy through an AKT serine/threonine kinase (AKT)-MTOR axis. Further, autophagy is highly sensitive to alterations in energy/substrate availability. For example, when amino acids are available, MTORC1 activity is promoted via the interaction between regulatory associate protein of MTOR complex 1 (RPTOR/RAPTOR) and the RAG family of small GTPases (124, 230). Therefore, reduced cellular amino acid concentrations caused by starvation remove the Ras homolog, MTORC1 binding (RHEB)-mediated sensitization of MTOR to nutrient availability, releasing the brake on autophagy induction (229). Similarly, nutrient unavailability increases the AMP/ATP ratio, resulting in AMP-activated protein kinase (AMPK) activation. AMPK inhibits MTORC1 by phosphorylating TSC complex subunit 2 (TSC2) and RPTOR (86, 111). Furthermore, AMPK can activate autophagy by directly phosphorylating ULK1/2 (128, 149).

MITOPHAGY AS TARGETED AUTOPHAGY

Overview

Mitophagy is a process often regulated independently of the nutrient/energy/stress signals that govern basal autophagy (7). It operates primarily as a quality control mechanism, targeting dysfunctional mitochondria that may otherwise contribute to the activation of death signaling (7). Additionally, mitophagy is responsible for eliminating healthy mitochondria during the differentiation of several cell types (10, 43, 144, 231, 242). While the stimuli for mitophagy and "nonspecific" autophagy may differ, mitochondria are degraded by autophagosome sequestration and subsequent lysosomal fusion (Fig. 1*B*). In this sense, mitochondria are simply treated as very large autophagic substrates, thereby requiring activation of similar autophagosome molecular machinery (i.e., BECN1, ULK, LC3, etc.) (7). However, because of the size and complexity of mitochondrial networks, specific mitophagy events related to mitochondrial identification and sequestration exist.

PINK1 and PRKN

Mitophagy involves unique and additional substrate identification mechanisms, notably PTEN-induced kinase 1 (PINK1) and parkin RBR E3 ubiquitin protein ligase (PRKN), two genes whose mutations were initially associated with recessive forms of parkinsonism (132, 263). Normally, PINK1 is constitutively transported into mitochondria, cleaved by the protease presenilin associated rhomboid like (PARL), and degraded by mitochondrial proteases (49, 117). When mitochondria become dysfunctional, PINK1 degradation is impaired, and it stabilizes on the outer mitochondrial membrane (117, 192, 193). In response, PRKN translocates to sites of mitochondrial damage denoted by PINK1 presence (73, 117, 192, 193). It is thought that mitochondrial proteins phosphorylated by PINK1 serve as PRKN docking sites or that direct phosphorylation of PRKN stimulates its translocation (7, 129). The phosphorylation of ubiquitin by PINK1 and formation of specific polyubiquitin chains has also been shown to regulate PRKN recruitment (240).

PRKN ubiquitinates outer mitochondrial membrane proteins following its translocation, causing mitochondrial sections to be isolated (36, 72). These fragments are identified by ubiquitin-SQSTM1-LC3 autophagosome targeting and degraded following lysosomal fusion (53, 73, 191). However, reports have indicated that SQSTM1 is required for mitochondrial clustering/fragmentation, but not in their degradation specifically (147, 191, 197). Several proteins identified as PRKN substrates appear to be important for mitochondrial fragmentation, including mitofusins (MFNs), translocases of outer mitochondrial membrane (TOMs), and VDACs (36, 250, 270, 282). PRKN-mediated MFN ubiquitination is thought to prevent defective mitochondria from fusing back into the mitochondrial network, although cells lacking MFNs can undergo mitophagy (36, 253). Importantly, excessive fusion caused by overexpression of OPA1 mitochondrial dynamin like GTPase (OPA1) or dominant-negative dynamin 1 like (DNM1L/DRP1) inhibits mitophagy (261). Thus, functioning mitochondrial fission/fusion machinery should be considered a prerequisite for mitophagy. VDACs are also required for efficient PRKN recruitment, and their ubiquitination is necessary for mitophagy (73, 250). PRKN also ubiquitinates TOMs during membrane depolarization, stimulating their degradation and permitting PINK1 accumulation (146, 282).

BNIP3 and BNIP3L

These BCL2 family members possess autophagy-promoting capabilities independent of their proapoptotic functions associated with being BH3-only proteins (91, 173, 218, 259, 285). BCL2-interacting protein 3 (BNIP3) and BCL2 interacting protein like (BNIP3L/NIX) induce autophagy by competitively

binding to and displacing BCL2 and BCL2L1 from BECN1 and perhaps by depolarizing mitochondria (13). Furthermore, both interact directly with LC3 via LC3-interacting region (LIR) domains and are important for autophagosome-mitochondria targeting, potentially inducing mitophagy independent of PINK1 and PRKN (94, 195, 218, 238). In fact, BNIP3 overexpression can compensate for PINK1 deficiency and reverses skeletal muscle degeneration in this context (286). Alternatively, although PINK1- or PRKN-mediated exposure of BNIP3 and BNIP3L LIR domains is enticing, such interactions have not been characterized. However, BNIP3 affects PINK1 function by suppressing its proteolytic cleavage, thus enabling PINK1-dependent mitophagy during hypoxia (286). In separate studies performed in cardiomyocytes, BNIP3 and BNIP3L triggered DNM1L translocation to mitochondria, resulting in mitochondrial fission followed by PRKN-dependent mitophagy (53, 150).

Other Mitophagy Receptors

Several molecules aid autophagic identification of mitochondria. For example, BCL2 like 13 (BCL2L13/BCL-RAMBO) was demonstrated to be required for mitochondrial fragmentation and mitophagic degradation in HEK293 cells (189). This protein was capable of causing mitochondrial fragmentation independent of DNM1L through its BH domains, binding to LC3 using its LIR domains, and incorporating mitochondrial fragments into lysosomes and depleting mitochondrial proteins in the absence of PRKN. However, because of their relative complexity, previous research in mammalian cells has characterized a growing list of additional molecules that regulate mitochondrial targeting and mitophagy during various conditions, including SQSTM1, NBR1, FUN14 domain containing 1 (FUNDC1), AMBRA1, cardiolipin, Tax1 binding protein 1 (TAX1BP1), calcium-binding and coiled-coil domain 2 (CALCOCO2/NDP52), optineurin (OPTN), TANK-binding kinase 1 (TBK1), and FKBP prolyl isomerase 8 (FKBP8) (20, 21, 41, 63, 102, 130, 147, 164, 189, 195, 217, 218, 248).

Despite the array of mitophagy-related adaptors, OPTN and CALCOCO2 have been identified as the de facto receptor proteins required for mitophagy (102, 147, 217). These two receptors function partly redundantly to link phosphorylated polyubiquitin to LC3 and subsequent PRKN-dependent enhancement of mitochondrial membrane protein ubiquitination (147). Here, PINK1-dependent phosphorylation of ubiquitin is vital to activating ubiquitin, OPTN, and CALCOCO2, irrespective of PRKN presence. TBK1-dependent phosphorylation of OPTN, CALCOCO2, TAXBP1, and SQSTM1 in turn creates an amplification loop linking ubiquitinated receptors to autophagosomes (217). Importantly, PRKN-independent execution of mitophagy has also been described (249). For example, AMBRA1 promotes mitochondrial sequestration and mitophagy in PRKN-expressing cells; however, in the absence of PRKN and SQSTM1, AMBRA1 relocated to depolarized mitochondria and recruited LC3; a function dependent on its LIR (249). Similar observations of PRKN- (20, 156, 189, 245) and PINK1-independent (139) mitophagy have also been made by others. The existence of multiple and redundant mitochondrial targeting mechanisms underscores the importance of accurate substrate identification in mitophagy.

Mitophagy Control

As mitophagy requires autophagosome sequestration, several feedback mechanisms link to autophagy initiation. BECN1 is involved with mitochondrial translocation of PRKN, where it colocalizes with PINK1 and PRKN at MAMs (39, 74). Here, PINK1 aids in recruiting BECN1 to MAMs independently of PRKN, and this is required for proper MAM-associated autophagosome biogenesis (74). AMBRA1 traffics to depolarized mitochondria and promotes isolation membrane production and mitochondrial clearance (249, 264). Full-length PINK1, which would accumulate only during mitochondrial depolarization, also interacts with BECN1 to promote autophagy (182). BNIP3 and BNIP3L expression is similarly stress-induced by hypoxia through hypoxia inducible factor 1 subunit-α (HIF1A) (13) and by starvation through forkhead box O3 (FOXO3) (173). Finally, CALCOCO2 and OPTN phosphorylation activates upstream autophagy-regulating proteins (147). Therefore, it appears that mitochondria prepped for mitophagy are degraded alongside other autophagy substrates, and this occurs largely when markers of dysfunction (PRKN, ubiquitin, SQSTM1, PINK1, etc.) are present.

DEFINING THE RELATIONSHIP BETWEEN APOPTOSIS AND AUTOPHAGY

Delineating the mechanisms and functions of stress response processes is complex, as they depend on interacting stress- (type and duration) and cell-specific (type and status) variables. Although the mechanisms underlying the relationship between apoptotic signaling and autophagy are complex, their consequences can be summarized as follows. *1*) In the absence of stress, autophagy operates at a basal level, thereby providing important cellular functions, while apoptotic signaling is kept to a minimum; *2*) relatively low-level stress induces autophagy as well as activates some antiapoptotic mechanisms to resist or remove stress sources; *3*) if deemed unsurvivable, unabated stress activates proapoptotic mechanisms, thereby disabling autophagy to ensure cell elimination in a physiologically friendly manner (68, 79, 174, 265) (Fig. 2*A*). This is typically due to the attenuation of cellular stress by autophagy (Fig. 2*B*) and the subversion of autophagy by apoptotic mechanisms (Fig. 2*C*). As indicated by the numerous studies cited in this review, this dose-response relationship holds true for most cellular stressors in addition to nutrient starvation, including foreign chemicals, nonbiological stresses (heat, pressure), extracellular physiological stress signals (cytokines, DAMPs), changes to biologically relevant conditions (pH, redox), metabolic alterations (substrates, metabolic intermediates), external growth status factors/hormones, viral and bacterial infection, internal organelle dysfunction, and DNA damage; although, the degree of apoptosis to autophagy varies widely across these stimuli.

We approach describing how the stimuli, mechanisms, and consequences between apoptotic signaling and autophagy interact assuming such a model. Because separating the mechanisms that allow communication between apoptosis and autophagy from their stimuli is difficult, for simplicity we have separated these explanations by stimuli/mechanisms as appropriate.

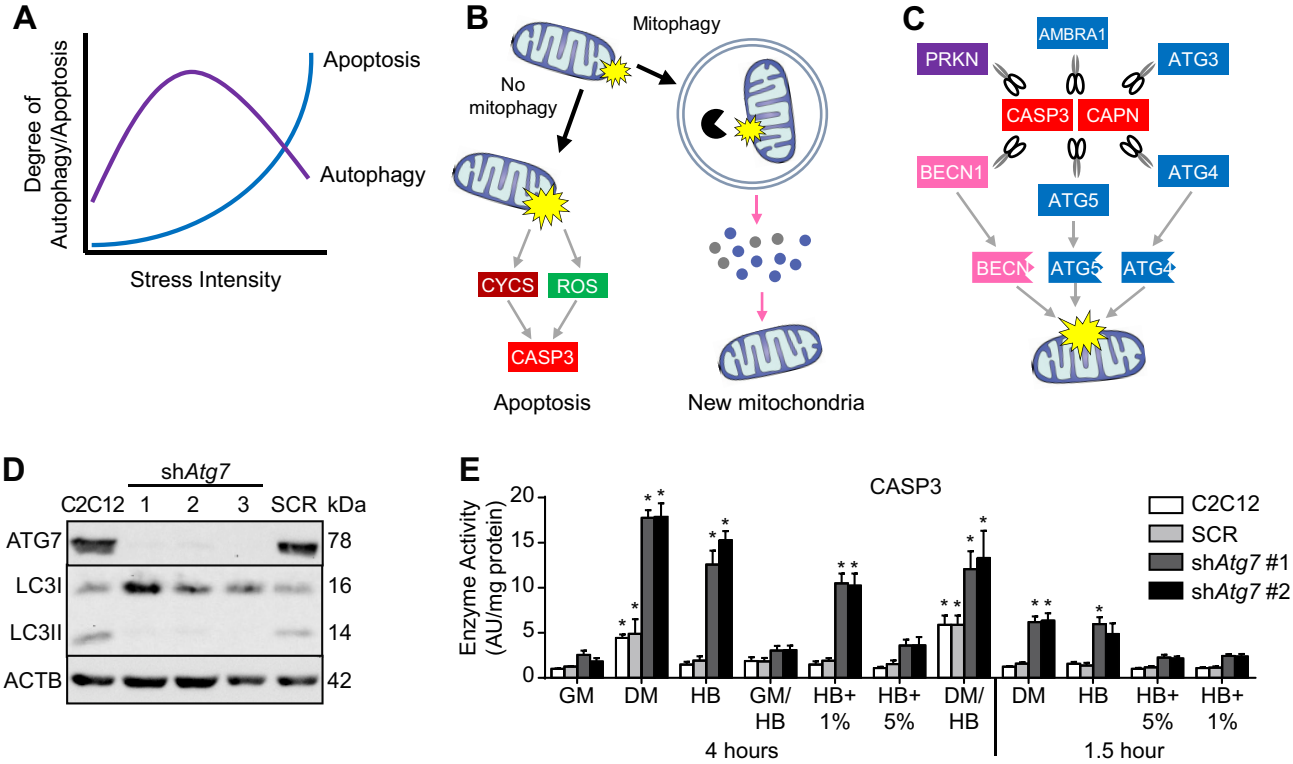

Fig. 2. General relationship between autophagy and apoptosis. *A*: most stresses progressively induce autophagy and apoptosis. Furthermore, cells with larger autophagy responses display relative resistance to apoptosis, suggesting that higher sensitivity to autophagy induction causes resistance to that stress. Typically, autophagy induction occurs at relatively low stress levels, followed by activation of apoptosis as intensity and/or duration increases. *B*: autophagy is generally cytoprotective by removing stress sources. In this example, mitochondrial dysfunction eventually leads to permeabilization, reactive oxygen species (ROS) generation, release of prodeath stimuli [i.e., cytochrome *c*, somatic (CYCS)], caspase (CASP) activation, and apoptosis. However, degradation of impaired mitochondria removes this potential stress source and allows for the generation of new mitochondria. *C*: prolonged activation of apoptotic effectors eventually subverts stress-induced autophagy by cleaving numerous autophagy-related proteins [beclin 1 (BECN1), parkin RBR E3 ubiquitin protein ligase (PRKN), autophagy and beclin 1 regulator 1 (AMBRA1), autophagy related (ATG)3, ATG4, and ATG5]. The BECN1, ATG5, and ATG4 cleavage products additionally acquire prodeath functions, reinforcing cell death. *D* and *E*: experiment demonstrating cytoprotective and dose-response nature of autophagy and apoptosis during various starvation conditions. *D*: we generated 3 ATG7-deficient clonal mouse myoblast (C2C12) cell lines using shRNA (sh*Atg7*) as well as a scramble control line (SCR). *E*: these cells were subjected to various starvation modes. sh*Atg7* cells displayed significantly elevated CASP3 activity that was highly time and growth factor dependent. *Significant difference between the denoted group and C2C12 normal culture growth media [GM; DMEM (DM) with 10% FBS] calculated using a *t*-test; $P < 0.05$. GM/HB or DM/HB, 1:1 mixture; HB, Hanks' Balanced Saline Solution; 1%/5%, percentage of FBS. HB contains similar glucose as DM but contains no amino acids.

MECHANISMS UNDERLYING THE APOPTOSIS/AUTOPHAGY RELATIONSHIP

Overview

The sequential induction of autophagy and apoptosis likely allows cells to mediate damage using autophagy before reaching a level obliging death (7). In fact, cells that mount the most robust autophagic response display the greatest apoptotic resistance (278). This cytoprotection is routinely demonstrated, where induction of autophagy prevents apoptosis or inhibition of autophagy promotes apoptosis (174). Given that this response is well established and beyond the scope of this review, we will focus on describing a number of key cellular processes shared by autophagy and apoptosis, as well as how these diverse factors influence the autophagy/apoptosis response.

Starvation and Growth Factor Signaling

Relative starvation robustly induces autophagy in cultured cells and whole organisms (184, 186, 228). However, prolonged starvation leads to both death of cells [through programmed signaling pathways (241)] and organisms. Studies showing that autophagy inhibition induces apoptosis during starvation were performed early during its examination in mammalian cells (25). Moreover, starvation-sensitive decisions regarding autophagy and apoptosis are influenced by growth factor receptor signaling in a dose-dependent manner. For example, in a small experiment presented here, we clearly observed elevated CASP3 activity in autophagy-deficient cells during starvation that was growth factor and time dependent (Fig. 2, *D* and *E*). In apoptosis-resistant $Bax^{-/-}/Bak1^{-/-}$ cells, autophagy helps prolong viability during extended starvation, and this is sensitive to extracellular growth factors (167). Mechanistically, Jun N-terminal kinases (JNK)-dependent phosphorylation of BCL2 decreases its inhibition of BECN1, thereby permitting autophagy induction during starvation (272). JNK signaling also contributes to mitophagy by inducing FOXO3-dependent transcription of *Bnip3* (35). Similarly, extracellular signal-regulated kinases (ERK) and MAPK kinases (MEK) inhibition partially and completely, respectively, prevents autophagy during starvation and in response to rapamycin (269). However, it is also well established that ERK and JNK signaling events activate apoptosis (29, 52). ERK-depen-

dent apoptosis occurs in response to numerous stimuli, particularly DNA-damaging chemicals and extracellular ligands, and involves CASPs, BCL2, and tumor protein P53 (TP53) (29). Notably, these responses are typically observed during prolonged (≥24 h) or constitutive stimulation (29, 52).

Mitochondria

Mitochondria are central regulators of apoptosis and autophagy. Briefly, mitochondria contribute to the stress-response relationship because dysfunctional mitochondria (i.e., with decreased membrane potential) are preferentially targeted for mitophagy, thereby removing them as potential sources of cellular damage (Fig. 3*A*) (65, 127, 192, 193, 261, 271). Left unabated, mitochondria become increasingly permeabilized, pores form across their membranes, and feed-forward apoptotic processes reinforce the release of death-inducing proteins and collapse of ATP production (138). Mitophagy has repeatedly been shown to limit mitochondrial ROS production (142, 235), but additional mechanisms have been observed, including attenuation of CYCS release and CASP3 activity (279). Reducing PRKN protein levels sensitized neural cells to apoptotic cell death (170), while overexpression protected cardiomyocytes from apoptotic death during hypoxia (140). BNIP3-mediated mitophagy also limits mitochondrial amplification of apoptosis by reducing CYCS release (290). In addition to sequestering dysfunctional mitochondria, other actions associated with mitophagy prevent apoptosis. Upon mitochondrial depolarization, PINK1 stabilizes the antiapoptotic abilities of BCL2L1 by phosphorylating and preventing its cleavage (6). Although cytosolic TP53 can bind to and inhibit mitochondrial PRKN translocation, PRKN prevents TP53-induced CASP3 activation by acting as a transcriptional repressor of TP53 (46). Cardiolipin externalization also contributes to mitochondrial targeting by binding LC3 (41) in addition to promoting CYCS release when oxidized (202).

BCL2 Proteins

BCL2 family proteins constitute a straightforward explanation for the apoptosis-autophagy relationship. As BECN1 contains a BH3 domain, activity of the BECN1 complex is reduced by physical interactions between antiapoptotic BCL2 and BCL2L1 with BECN1; accordingly, BH3-only proteins bind to BCL2 and BCL2L1, freeing BECN1 and thus promoting autophagy (Fig. 3*B*) (172, 207). BNIP3 and BNIP3L similarly interrupt BECN1-BCL2 binding in addition to functioning as mitophagy receptors (13, 94, 195). Notably, BH3-only proteins exist under strong transcriptional and posttranslational control by death-inducing and stress-sensing mechanisms (68). Similarly, BNIP3 and BNIP3L expression is hypoxia inducible (13). When considered as a model, *1*) in the absence of stress, BCL2 and BCL2L1 bind to BECN1 and restrain autophagy, *2*) stress activates BH3-only proteins which replace BECN1, thereby allowing BECN1 complex activation, and *3*) prolonged stress increases BH3-only protein levels above the absorbing threshold of BCL2 and BCL2L1, causing BAX and BAK1 activation, widespread mitochondrial permeabilization, CASP activation, and apoptosis. The mitochondrial location of BCL2 proteins suggests that BH3-only proteins and BAX and BAK1 may contribute to mitochondrial depolarization and mitophagy at low activation levels but promote apoptosis during prolonged stress.

Reactive Oxygen Species

ROS also illustrate this dose-response relationship (Fig. 3*C*). Despite their connection to apoptosis, cancer development, and cellular aging, ROS are vital second messengers that execute various functions (237). This includes augmenting growth factor signaling, activating metabolic enzymes, enhancing the inflammatory response, increasing transcription of protective and antioxidant genes, and mediating long-term metabolic adaptations (237). Although ROS induce autophagy by causing cellular damage that autophagy attempts to mitigate, ROS also directly regulate autophagy (152, 174, 215). In fact, antioxidant administration depresses starvation- (236) and ROS-induced (30, 163) autophagy. Specifically, oxidation of ATG4 by H_2O_2 is required for autophagosome production (236), ROS initiate PRKN-dependent mitophagy (271), and ROS-induced inhibition of MTOR is AMPK dependent (3). In this latter paper, ROS-induced autophagy required the DNA damage sensor ATM serine/threonine kinase (ATM), and rescuing autophagy in ATM-deficient mice by administering rapamycin reversed ROS-induced lymphomagenesis (3). Typically, autophagy protects from ROS-induced apoptosis (174, 215, 235). Despite this, in specific cell types suppression of autophagy-related genes actually ameliorates ROS-induced apoptosis (38), demonstrating the complexity of this relationship. However, eventually, cellular ROS-mitigating mechanisms become saturated, preventing their conversion to H_2O_2 and H_2O and causing highly reactive superoxide and hydroxyl radicals to accumulate (237). In addition to actively promoting programmed death mechanisms (i.e., TP53 and JNK), these species nonspecifically damage DNA, proteins, and lipids, thereby promoting apoptosis (243).

Apoptotic Enzymes

As previously alluded to, apoptotic signaling mechanisms are graded and do not automatically cause cell death. Particularly, CASPs participate in the differentiation of various epithelial tissues, erythrocytes, and skeletal muscle (62). Although evidence of CASP-dependent autophagy at relatively low activation levels is uncommon, one study showed that CASP9 was required for cytoprotective autophagy induced by an anti-inflammatory chemical in MCF7 cells (115). However, effector CASPs eventually advance apoptotic execution, partly by subverting autophagy (Fig. 2*C*). CASP3 cleaves BECN1 during apoptosis induced by BAX, thereby inhibiting autophagy (168). In fact, the COOH-terminal fragment of BECN1 translocates to mitochondria, where it causes membrane permeabilization (168, 275). AMBRA1 is also cleaved by CASPs and calpains (CAPNs) during staurosporine induced apoptosis, subsequently contributing to inhibition of autophagy (203). Similarly, the BECN1 complex member ATG3 undergoes CASP cleavage during apoptotic stress (201). Substrates for apoptosis-induced inactivation of autophagy apart from the BECN1 complex have also been identified. Of note is that CAPN-mediated ATG5 cleavage sensitizes tumor cells to apoptotic stress and produces a cleavage product that undergoes mitochondrial translocation, thereby contributing to CASP activation (284). Similarly, the product of CASP cleavage of ATG4 has apoptosis-promoting effects (17). Finally, CASPs cleave and inactivate PRKN, preventing mitophagy and promoting cellular damage (122). The large number of ATGs

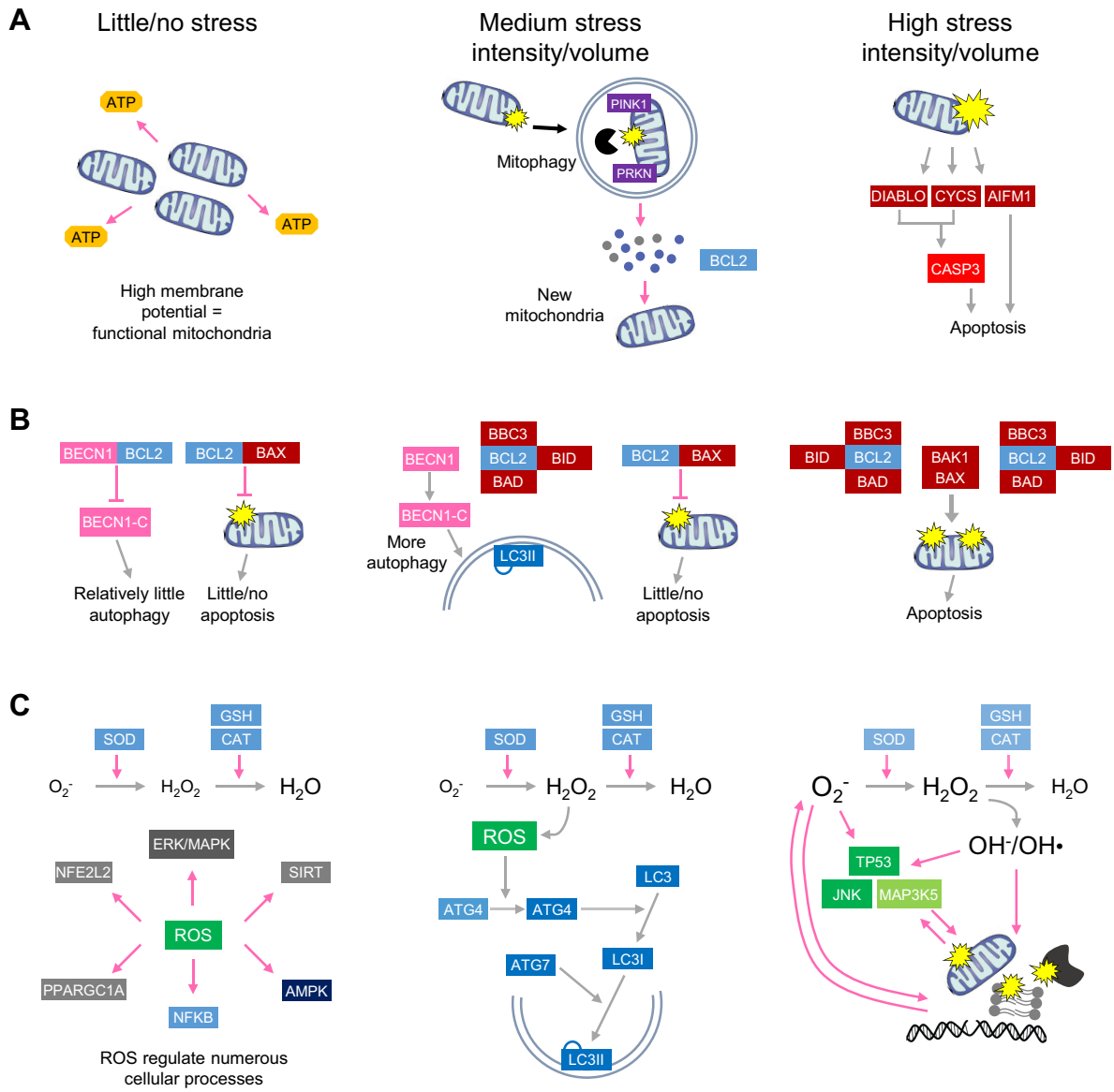

Fig. 3. Examples of shared stress response signaling mechanisms that allow interaction and tuning of apoptosis and autophagy. *A*: mitochondrial damage [i.e., via reactive oxygen species (ROS), mtDNA mutations, or mitochondrial permeability transition pore (mPTP)] causes membrane depolarization and recruits mitophagy machinery [PTEN-induced kinase 1 (PINK1) and parkin RBR E3 ubiquitin protein ligase (PRKN)]. Unchecked or widespread mitochondrial damage leads to permeabilization, release of death signaling factors [cytochrome *c*, somatic (CYCS), diablo IAP-binding mitochondrial protein (DIABLO/SMAC), apoptosis inducing factor mitochondrial-associated 1 (AIFM1/AIF)], caspase (CASP) activation, and apoptosis. *B*: anti-death BCL2 apoptosis regulator (BCL2) family members [BCL2, BCL2 like 1 (BCL2L1/BCLXL)] inhibit autophagy by physically binding to beclin 1 (BECN1). BH3-only members [BCL2 binding component 3 (BBC3/PUMA), BH3-interacting domain death agonist (BID), BCL2-associated agonist of cell death (BAD)], which increase or are activated in response to stress, sequester BCL2, thereby relieving its inhibition of BECN1. Eventually, BCL2 becomes saturated with BH3-only proteins, leading to BCL2 antagonist/killer 1 (BAK1) and BCL2-associated X, apoptosis regulator (BAX) activation and apoptosis. *C*: ROS (O_2^-, H_2O_2) can be scavenged by various antioxidants [superoxide dismutase (SOD), glutathioine (GSH), catalase (CAT)] and are important second messengers and regulate numerous cellular processes [extracellular signal-regulated kinases (ERK), mitogen-activated protein kinases (MAPK), sirtuins (SIRT), AMP-activated protein kinase (AMPK), nuclear factor-κB (NFKB), PPARG coactivator-1α (PPRAGC1A/PGC1α), nuclear factor, erythroid 2 like 2 (NFE2L2/NRF2)]. With respect to autophagy, elevated H_2O_2 is required to activate autophagy related 4 (ATG4), which in turn participates in LC3 maturation. Unrestrained ROS production activates death-inducing signaling mechanisms [tumor protein P53 (TP53), Jun N-terminal kinases (JNK), mitogen-activated protein kinase kinase kinase 5 (MAP3K5/ASK1)] and damages lipids, DNA, and proteins, ultimately reinforcing apoptosis.

targeted by apoptotic enzymes strongly supports the view that autophagy is an evolutionarily conserved cell survival process.

DNA Damage

Apoptosis resulting from DNA damage typically manifests in the mechanisms just described (i.e., BH3-only protein transcription, ROS generation, and CASP activation). However, the apoptosis regulator TP53 has independent autophagy-regulating roles, where it is primarily inhibitory (256). Cytosolic localization of TP53 protein allows its direct interaction with and inhibition of RB1CC1 (187) and PRKN (106), thereby reducing BECN1 complex activity and preventing mitochondrial autophagic clearance. However, during situations of induced autophagy, TP53 is responsible for activating transcrip-

tion of tuberous sclerosis complex (TSC) and AMPK components, two platforms that promote autophagy (61). The TP53 transcriptional target DNA damage regulated autophagy modulator 1 (DRAM1) is also responsible for executing TP53-dependent autophagy during DNA damage and inhibition of mitochondrial respiration (44, 287). While the autophagy versus apoptotic interactions that determine these responses are relatively unknown, it is likely that the type and intensity of stress stimuli create an environment favoring one or the other following DNA damage.

Autophagy-Dependent Cell Death

Unrestrained autophagy and mitophagy would be unnecessarily catabolic and theoretically lead to mitochondrial depletion. While this is not commonly observed in mammalian cells, *1*) some autophagy machinery is involved in cell death execution, and *2*) some cancer cells undergo autophagy-dependent cell death (174). Although CASP8 is typically activated by the death-induced signaling complex (DISC), a similar platform forms on autophagosomes and is required for complete enzyme activation (283). ATG12 can also promote apoptosis by binding to and inhibiting BCL2, a function required for full CYCS release during staurosporine-induced apoptosis (221). Furthermore, autophagy inhibition prevents cell death induced by falcarindiol in breast cancer cells (166), by MG-2477 in neuroblastoma cells (87), and by sunitinib in prostate cancer cells (268). Similarly, adiponectin attenuated mitophagy and apoptosis induced by H_2O_2 in C2C12 cells (216). Interestingly, mitophagy inhibition decreased cell loss during starvation by causing mitochondrial fusion, thereby maintaining ATP production (76). However, when fission and, therefore, mitophagy were enhanced, starvation increased death (76).

PHYSIOLOGICAL IMPLICATIONS ACROSS THE APOPTOSIS/AUTOPHAGY AXIS

Overview

Importantly, the consequences of autophagy's impact on cellular stress resistance and function are relevant to numerous pathological conditions. Due to overlapping regulatory mechanisms, defective autophagy and mitophagy contribute to unnecessary apoptosis and tissue loss, and the development of cellular proapoptotic environments that can decrease the limit of survivable stress (98, 152, 215).

Autophagy/Mitophagy and Apoptosis in Various Tissues

Numerous tissues show examples of altered mitophagy impacting their pathophysiology. For example, insufficient mitophagy is directly related to neuronal cell loss and/or dysfunction during Parkinson's (132, 263), Alzheimer's (12, 220), and aging (12). Pancreatic β-cells display reduced mitophagy during type 1 and type 2 diabetic conditions (104). Similarly, mitophagy in kidney proximal tubule cells is responsible for maintaining mitochondrial function during metabolic acidosis (190), whereas impaired mitophagy contributes to cell damage, such as that which occurs during diabetic nephropathy (103). In the heart, mitophagy and PRKN levels increase in the infarct border following a myocardial infarction (140), while *Prkn*$^{-/-}$ mice display larger infarct areas, ultimately demonstrating that mitophagy prevents cell loss (140). Further, mitophagy is impaired in hearts of aged *Prkn*$^{-/-}$ mice (106). In contrast, elevating mitophagy by decreasing TP53 expression is associated with increased cardiac resistance to ischemic stress (105, 106), while mice overexpressing PRKN are resistant to the age-related decline in cardiac function, and this is associated with elevated mitochondrial activity, decreased ROS production, and reduced inflammation (106). Therefore, mediation of mitochondrial-related stresses by mitophagy is necessary for preserving cell number and function.

Decreased autophagy can also contribute to tumor development (152, 273). Several common genetic alterations, such as TP53 mutations, BCL2 upregulation, and BECN1 inactivation, cause cell death avoidance and alter cell cycle while also impairing autophagy (152, 158, 177). With respect to tumor initiation, *1*) autophagy impairment increases cellular stress, leading to genomic instability and oncogene activation, mediated through SQSTM1-induced nuclear factor, erythroid 2 like 2 (NFE2L2/NRF2) (58, 83, 176), and *2*) without autophagy, tumor-associated stress causes immunologically noisy cell death and alters oncogenic antigen processing, leading to cancer progression (50, 152, 177, 273). Conversely, it is well established that enhanced autophagy promotes the growth of established cancers and contributes to therapy resistance (273).

Autophagy and Apoptosis in Skeletal Muscle Development

Skeletal muscle development involves dramatic morphological transformation as single-nucleated myoblasts fuse into complex and multinucleated contractile muscle fibers. Unsurprisingly, skeletal muscle differentiation is characterized by significant stress-related processes, including increased ROS production (136), MAPK signaling (277), DNA damage response (DDR) (145), CASP activation (24), mitochondrial fission (23), and autophagic (180) and mitophagic (10, 242) flux. However, despite their links to apoptosis, skeletal muscle differentiation is actually impaired by individual inhibition of many of these processes. In this context, we repeatedly observe that various modes of autophagy inhibition, including 3-MA administration (180), ATG7 knockdown (10, 180), and *Bnip3* knockout (10), potentiate apoptotic signaling resulting in skeletal muscle differentiation impairment. Importantly, we found augmented mitochondrial apoptotic signaling (i.e., CYCS and AIFM1 release, increased mPTP formation, CASP9 activation) in ATG7-deficient cells (10). This suggests that autophagy induction facilitates differentiation by attenuating cellular and mitochondrial stress sources that may otherwise lead to apoptosis. In fact, we additionally demonstrated that inhibiting the augmented CASP3 or CASP9 in ATG7-deficient myoblasts recovered the differentiation ability of these autophagy-impaired cells (10). Importantly, the mechanisms of skeletal muscle formation (i.e., myoblast fusion) are similar to those regulating mature skeletal muscle adaptation, growth, and regeneration; therefore, these interactions have implications regarding the treatment of various muscle myopathies, dystrophies, and atrophies.

Autophagy in Mature Skeletal Muscle

In mature tissue, autophagy has been suggested to both contribute to and protect from specific pathological conditions (232). Primarily, autophagy degrades energetic substrates in skeletal muscle during nutrient deprivation (184, 186, 232,

288). This function is likely vital for converting and mobilizing skeletal muscle's large protein and glycogen stores into fuel for use by other tissues. In fact, mice lacking skeletal muscle AMPK display hypoglycemia during fasting, a finding attributed to their inability to supply the liver with alanine for gluconeogenesis resulting from depressed skeletal muscle autophagy (28). However, this catabolic response must be properly regulated, and therefore, autophagy may unnecessarily contribute to atrophy during specific circumstances (232). Elevated skeletal muscle autophagic activity has been observed in response to denervation (66, 67, 84, 198, 288), fasting (184, 196, 288), exercise (97, 162), oxidative stress (54, 208), chemotherapy (26), endotoxin (114), inflammation (234), glucocorticoid administration (234, 260), and disuse (108, 252), while decreased autophagy activity has been observed in skeletal muscle during aging (116), type 2 diabetes (185), and critically ill patients (266). Although fewer examinations of specific mitophagy have been performed, indirect measurements have suggested altered mitophagy during fasting, denervation, and disuse (67, 123, 198). Additionally, PRKN-deficient mice display delayed atrophy and decreased ubiquitin proteasome system (UPS) activation during denervation (67).

Apoptosis in Mature Skeletal Muscle

Apoptotic signaling in skeletal muscle is typically associated with atrophy and dysfunction (213). Death-associated signaling mechanisms are unique in skeletal muscle, as they do not generally cause complete cell death due to its multinucleated morphology (213). Instead, CASPs cleave complex myofibrillar proteins into proteasome-compatible sizes, thereby prepping these targets for further degradation (56). The connection between apoptosis and muscle atrophy is most strikingly illustrated in *Bax*$^{-/-}$ (244), *Bax*$^{-/-}$*/Bak1*$^{-/-}$ (198), and *Casp3*$^{-/-}$ (211) mice, which display resistance to denervation-induced atrophy. Apoptotic signaling may also damage or eliminate individual skeletal muscle nuclei and theoretically influence the cytoplasmic volume/area that could be supported and thus contribute to fiber atrophy (5). However, the myonuclear domain concept has long been questioned (27, 238) given the additional roles of satellite cells and flexibility in this ratio (188, 239). Regardless, apoptotic markers are observed in skeletal muscles of dystrophic mice (112, 258) and humans (233) as well as in lysosomal (159) and mitochondrial (8) myopathies, suggesting that apoptotic mechanisms generally contribute to pathology or indicate the existence of underlying pathological alterations.

Autophagy and Apoptosis During Skeletal Muscle Atrophy, Aging, and Pathology

Although autophagy increases during atrophy, whether this is pathological is unclear. As a catabolic process, autophagy could independently or cooperatively contribute to protein degradation and muscle loss during disuse, fasting, or stress. In our hands, skeletal muscle-specific autophagy deficiency (*Atg7*$^{-/-}$) in the absence of additional stress increased centralized nuclei (a pathological sign of regeneration) and impaired contractility while elevating CAPN and proteasome activity in an age-dependent and muscle-specific manner (206). Interestingly, we also found elevated cytosolic CYCS and AIFM1 nuclear translocation in oxidative muscle of *Atg7*$^{-/-}$ mice, indicating generalized dysfunction and mitochondrial stress. Others have similarly shown that inactivating autophagy causes muscle dysfunction and elevates apoptotic DNA fragmentation, thereby implying that autophagy executes specific functions that protect skeletal muscle (81, 175). Furthermore, autophagy deficiency enhances atrophy and dysfunction during atrophy-inducing conditions (175), and autophagy induction during denervation does not affect atrophy (209), suggesting that autophagy's catabolic contribution is likely not pathological. Another mouse model (miR-378^{KO}) demonstrates impaired autophagy, mitochondrial abnormalities, muscle atrophy, and decreased running performance alongside mitochondrial CYCS release and CASP activation (157). Notably, miR-378 is dramatically induced during fasting and activates autophagy while inhibiting apoptosis by targeting CASP9 (157). The observation that chemical CASP inhibition induced autophagy and improved running performance of miR-378^{KO} mice (157) further supports the protective role of autophagy and mitophagy against mitochondrial-associated dysfunction and apoptotic signaling.

The importance of autophagy in skeletal muscle is further highlighted by its depression during age-related atrophy, known as sarcopenia (116). Here, skeletal muscles display SQSTM1 accumulation (227, 274), depressed denervation-induced autophagy (199), downregulated autophagy gene expression (55, 118, 276), and elevated CASP activity and apoptotic nuclei (57). In this context, *Prkn*$^{-/-}$ mice display significantly impaired ADP-stimulated mitochondrial respiration and increased mPTP formation (78), while PRKN overexpression prevented aging-associated functional declines and atrophy (148); changes that were associated with maintenance of mitochondrial enzyme activity and attenuated apoptotic nuclei (148). In fact, numerous interventions, including small molecules (60, 222), caloric restriction (276) and exercise (60, 90, 267, 274, 276) attenuate skeletal muscle dysfunction and atrophy, likely due to increased autophagy and decreased apoptotic signaling.

Autophagy and Apoptosis During Skeletal Muscle Dystrophies

Several studies have shown impaired autophagic flux and elevated apoptotic signaling during several models of muscular dystrophy (31, 48, 81). Remarkably, when autophagic flux was promoted by feeding *mdx* mice a low-protein diet, their functional and structural abnormalities improved and the number of apoptotic nuclei decreased (48). Likewise, inducing autophagy by administering a low-protein diet, rapamycin, or spermidine decreased apoptotic markers and improved functional parameters of *Col6*$^{-/-}$ dystrophic mice (40, 81). In fact, the increased mitochondrial permeability and apoptotic nuclei seen in these mice (112) are reversed by these three autophagy inducers (40, 81), indicating an association between apoptotic signaling and pathology. Furthermore, overexpressing BECN1 independently reduced apoptotic nuclei in dystrophic mice, suggesting that autophagy induction specifically can improve pathology (81). Translating these results to humans, a low-protein diet was shown to induce autophagy and stabilize functional measures of disease progression in muscular dystrophy patients with *Col6* mutations, as well as being associated with decreased apoptotic nuclei and improved mitochon-

drial function in skeletal muscle (33). However, emphasizing autophagy's dual nature, in the studies just mentioned, both a long-term, low-protein diet (48, 81) and spermidine administration (40) increased apoptotic nuclei in muscle of wild-type mice, while inhibition of autophagy improved clinical symptoms of muscular dystrophy in a mouse model of MDC1A (laminin a2 chain deficiency) (31).

PERSPECTIVE ON THE PHYSIOLOGICAL RELEVANCE OF AUTOPHAGY AND APOPTOSIS

We like to characterize autophagic degradation of cellular material in a "worst is first" manner that ultimately serves to protect cells from stress. Whether these stressors stem from hazardous protein aggregates, dysfunctional organelles, ROS-damaged molecules, or invading pathogens, autophagy typically functions as one of the cell's first lines of defense. However, in response to prolonged/high intensity stress, cells eventually capitulate to self-destruction; in this sense, apoptotic cell death would follow autophagy. Conceptually then, forced autophagy induction in the absence of additional stress preferentially degrades the most appropriate targets present at that time (i.e., relatively depolarized mitochondria, any SQSTM1-bound aggregates) despite these species not being harmful enough to autonomously induce autophagy.

This feature of autophagy likely partly explains the long-known health benefits of proper diet and regular exercise, two inducers of autophagy. In fact, genetic autophagy impairment abolishes the longevity effects of relative caloric restriction in model research organisms and animals (47, 171). Furthermore, the investigations of caloric restriction in nonhuman primates concluded that "caloric restriction without malnutrition…improves health and survival of rhesus monkeys" (178), supporting the translation of these observations to humans. Because of these findings, there is growing interest in pharmacological and lifestyle interventions that mimic caloric restriction and/or simply induce autophagy (34, 137, 153, 171, 204).

Importantly, as progress is made toward conducting a human trial investigating the effects of rapamycin on human aging (262), this means that rational design of autophagy-manipulating drugs requires deep understanding of the interplay between autophagy and apoptosis in specific cell types and in specific contexts (137). Notably, despite our expanding understanding of mitophagy, the myriad of relevant molecular mediators complicates its pharmacological targeting. For example, while ATG32 independently executes mitophagy in yeast, it is unsurprising that the complexity of mammalian cells and their relationship with mitochondria has evolutionarily optimized mitophagy by supplementing it with regulators in addition to PINK1 and PRKN. As research continues, we will likely find that defined mechanisms are relevant to individual stimuli, in the same sense that specific conditions induce ATG5/ATG7-independent autophagy (194) and mitophagy-independent lysosomal degradation of mitochondrial segments (179, 219, 247). Furthermore, as nonregulated health supplements purported to slow aging appear on the market and the trend of intermittent fasting becomes more common, determining these complexities is relevant and warranted.

CONCLUSION

Cells are continuously created and eliminated in a communal effort to optimize tissue function efficiency and overall health. Unsurprisingly then, unintentional malfunctions in these systems, whose consequences range from the undesired elimination of healthy cells to the undesired persistence of unwanted cells, manifest in various human pathologies. As research into the mechanisms that mediate autophagy and apoptosis generates an ever-expanding understanding of their complexity, it becomes increasingly relevant to consider these processes together. Importantly, as we identify new potential interventional targets through which to alter human biology, we must simultaneously be aware of the potential corresponding side effects such interventions may incur.

GRANTS

This work was supported in part by Natural Sciences and Engineering Research Council of Canada Grant RGPIN 258590 (J. Quadrilatero).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.B. prepared figures; D.B. and J.Q. drafted manuscript; D.B. and J.Q. edited and revised manuscript; D.B. and J.Q. approved final version of manuscript.

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