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Review Article

The Nuptials of Autophagy and Apoptosis –A Review

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Abstract

Autophagy is a widely conserved catabolic process that is essential for maintaining cellular homeostasis under normal physiological conditions and driving the cell to switch back to this condition under times of starvation, hypoxia, and oxidative stress. The potential similarities and differences between basal autophagy and stimulus-induced autophagy are still largely unknown. Both act by clearing unusual or unnecessary cytoplasmic material, such as misfolded proteins, supernumerary and defective organelles. The relationship between reactive oxygen species (ROS) and autophagy is complex. Cellular ROS is predominantly derived from mitochondria. Autophagy is triggered by this event, and by clearing the defective organelles effectively, it lowers cellular ROS thereby restoring cellular homeostasis. However, if cellular homeostasis cannot be reached, the cells can switch back and choose a regulated cell death response. Intriguingly, the autophagic and cell death machines both respond to the same stresses and share key regulatory proteins, suggesting that the pathways are intricately connected. Here, the intersection between autophagy and apoptosis is discussed with a particular focus on the role ROS plays.

Keywords: Autophagy, apoptosis, cellular mechanism & programmed cell death.

INTRODUCTION

Autophagy and apoptosis play major roles in determining cellular fate. Accordingly, they participate in development, cellular homeostasis, and both physiological as well as pathological processes. Apoptosis and autophagy are dis- crete cellular processes that are mediated by distinct groups of regulatory and executioner molecules [1, 2]. Apoptosis is type I form of programmed cell death that is executed by activated caspases, which are specific enzymes that partici- pate in signalling cascades that culminate in the rapid removal of organelles and other cellular structures [3, 4]. Autophagy is a highly conserved cytoprotective process whereby cytoplasmic contents are sequestered, transported via double-membrane autophagosomes to lysosomes, and degraded. This process allows cells to mitigate various types of cellular stress. There is a basal level of autophagy, which allows for the physiological turnover of damaged organelles, long-lived proteins, and cytoplasmic contents. Autophagy has been characterized as both a unique cell-death pathway and an adaptation to stress that promotes cell survival. Autophagy ensures the delivery of metabolic substrates to cells in order to fulfill their energy demand during stress, thus supporting cell growth and survival [5-7]. The crosstalk between autophagy and apoptosis is complex, and studies have yielded conflicting results. Nevertheless, this crosstalk is critical to cellular fate. Under certain cellular conditions, autophagy can promote cell survival and avert apoptosis [7]. Under other conditions, autophagy may culminate in cell death either in concert with apoptosis or independently in the event of apoptotic failure. It remains uncertain whether autophagy represents a mechanism for preventing apoptosis or for enacting non- apoptotic programmed cell death.

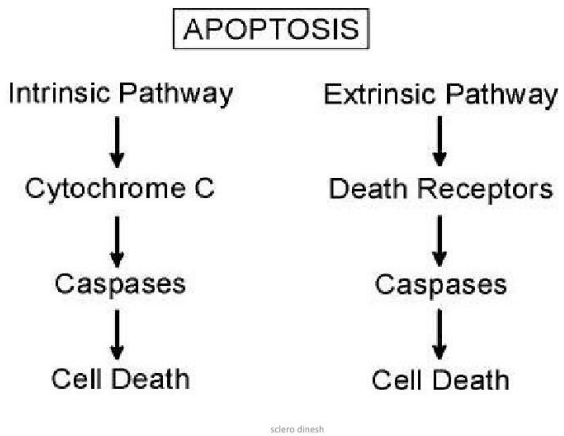

Figure-1

Apoptosis: The cell-death machinery

Autophagy/macroautophagy is a lysosome-dependent catabolic process characterized by increased formation of double-membrane autophagosomes for the sequestration of cytoplasmic components and subsequent degradation after autophagosome fusion with lysosomes [1, 2]. Autophagy occurs during normal development at the basal level, as well as under stress conditions. Autophagy is generally considered as a cell survival/protection mechanism because it removes toxic or obsolete proteins and organelles and recycles the degradation products for use as sources for energy and metabolites in anabolic pathways [3]. However, autophagy has also been recognized as a cell death pathway, first in Drosophila and recently in mammalian systems [4, 5]. Nevertheless, the definition of autophagic cell death (ACD) has been neither universally understood nor unanimously accepted in the field [4]. Therefore, the relationship between autophagy and cell death remains unclear and warrants further study to harness autophagy for the treatment of various human diseases.

Autophagy is induced by adverse environmental conditions, such as starvation, growth factor deprivation, and pathogen infection. Extracellular cues, including those of hormones and cytokines, can also regulate autophagy. For example, Th1 cytokines, including interferon-γ, tumor necrosis factor-α, interleukin (IL)-2, IL-6, and transforming growth factor-β, stimulate autophagy, whereas Th2 cytokines, including IL-4, IL-10, and IL-13, inhibit autophagy and thus regulate inflammatory mediators [7]. Insulin and insulin-like growth factor 1 are known to inhibit autophagy. In a fasting state, increased glucagon and epinephrine and norepinephrine secretion induce autophagy, and glucocorticoids have also been shown to induce autophagy by stimulating the transcription of autophagy genes such as ATG5, LC3, and Beclin-1 in various tissues [8]. Including those of autophagy-inducing signals, the molecular details of autophagy and the techniques to assess autophagy flux have been well documented in other reviews [9]. The beneficial roles of autophagy in diverse aspects of human physiology and diseases, including development, metabolism, neurodegeneration, and aging, are also well covered elsewhere [10-13].

Autophagy: the self-degradative mechanism

As summarized in Figure-1, autophagy begins with an isolation membrane, also known as a phagophore that is likely derived from lipid bilayer contributed by the endoplasmic reticulum (ER) and/or the trans-Golgi and endosomes [9, 10], although the exact origin of the phagophore in mammalian cells is controversial. This phagophore expands to engulf intra-cellular cargo, such as protein aggregates, organelles and ribosomes, thereby sequestering the cargo in a double-membraned autophagosome [5]. The loaded autophagosome matures through fusion with the lysosome, promoting the degradation of autophagosomal contents by lysosomal acid proteases. Lysosomal permeases and transporters export amino acids and other by-products of degradation back out to the cytoplasm, where they can be re-used for building macromolecules and for metabolism [5]. Thus, autophagy may be thought of as a cellular 'recycling factory' that also promotes energy efficiency through ATP generation and mediates damage control by removing non-functional proteins and organelles.

How is this complex process orchestrated at the molecular level? There are five key stages (a) phagophore formation or nucleation; (b) Atg5–Atg12 conjugation, interaction with Atg16L and multi-merization at the phagophore; (c) LC3 processing and insertion into the extending phagophore membrane; (d) capture of random or selective targets for degradation; and (e) fusion of the autophagosome with the lysosome, followed by proteolytic degradation by lysosomal proteases of engulfed molecules.

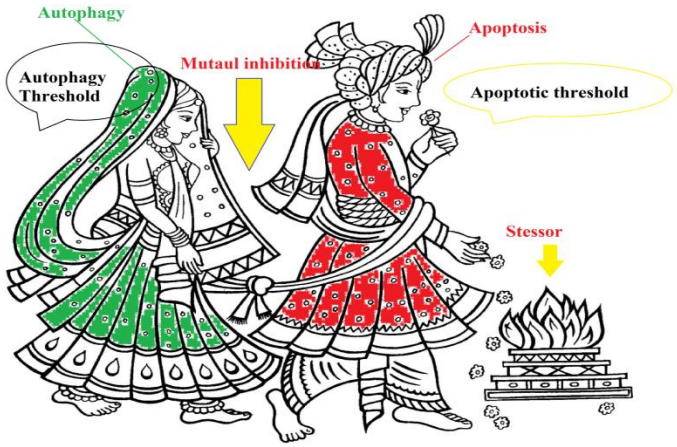

Figure-2

Connection between autophagy and apoptosis

Normally, autophagy and apoptosis are both tumor suppressor pathways. Autophagy fulfils this role as it facilitates the degradation of oncogenic molecules, preventing development of cancers, while apoptosis prevents the survival of cancer cells.

Since autophagy can block apoptosis and both autophagy and apoptosis can kill cells, one might expect that their regulation would be coordinated. It is perhaps a little less expected that the same proteins would regulate both processes. However, recent data show that this is often the case. Some connections occur upstream of the autophagic and apoptotic machinery itself where signaling pathways regulate both processes. For example, p53, which is a potent inducer of apoptosis, can also induce autophagy through increased expression of a direct p53 target gene called DRAM. Similarly activation of the PI3 kinase/ Akt pathway, which is a well known way to inhibit apoptosis, also inhibits autophagy. Thus important signaling pathways apparently simultaneously increase or decrease both autophagy and apoptosis. In addition, proteins that are themselves central components of the apoptosis or autophagy machinery (Bcl family proteins, FADD, and at least one of the Atg proteins) regulate both process directly.

As discussed above, Beclin 1/Atg 6 is part of a Type III PI3 kinase complex that is required for the formation of the autophagic vesicle and interference with Beclin 1 can prevent autophagy induction. Beclin 1 was identified as a Bcl-2 interacting protein. Thus a key apoptosis regulator also interacts physically with an autophagy regulator. Beclin1 also interacts with the other major anti-apoptotic Bcl family protein (Bcl-xL) and this interaction has been shown to regulate autophagy so that not only does Bcl-2/ Bcl-xL inhibit apoptosis by binding to and interfering with the action of the pro-apoptotic proteins Bax and Bak, it also inhibits autophagy by binding with Beclin 1 and this interaction is important in the regulation of starvation-induced autophagy. There may however be differences in the regulation of these pathways depending on subcellular localization – Bcl-2 is found at the mitochondria and the ER however the autophagy inhibition function of Bcl-2 occurs only at the ER and mitochondrial targeted Bcl-2, which is a potent inhibitor of many apoptotic stimuli, cannot inhibit autophagy. Recent work from several groups has focused on further analysis of the Beclin 1-Bcl-2/Bcl-xL interaction. Structural and biochemical studies demonstrate that the interaction is via a BH3 domain in Beclin 1– i.e. Beclin 1 is a BH3-only protein. Furthermore, elegant experiments from Kroemer and colleagues show that disruption of the interaction between the Beclin 1 BH3 domain and Bcl-2 leads to increased autophagy. Thus, in this case a BH3 domain interaction with Bcl-2 serves not to regulate apoptosis but instead to control autophagy. It is also possible that the Beclin 1 BH3 domain may function like other BH3 domains and regulate apoptosis; however clear evidence for this has not been shown. Another mechanism by which Bcl-2 at the ER can control autophagy has been described. In this case Bcl-2 inhibits autophagy not because it interacts with Beclin 1 but instead because it can block calcium release from the ER. The calcium activates Ca^{2+}/ calmodulin-dependent kinase kinase-ß and AMP-activated protein kinase, which leads to inhibition of mTOR to activate autophagy. Therefore two quite separate mechanisms may allow Bcl-2 (and Bcl-xL) to inhibit autophagy instead of apoptosis; it is not known if both these mechanisms apply at the same time or if one is more important than the other in different contexts. Added complexity comes from the fact that under other circumstances – in cells that have lost both Bax and Bak and are therefore essentially completely resistant to the intrinsic apoptosis pathway– Bcl-2 (and Bcl-xL) appears to have the opposite effect because increasing their expression stimulates autophagic cell death while Bcl-xL knockdown reduces autophagy. Thus while the connections between Bcl family of apoptosis regulators and autophagy appear to be complicated it is clear that this family of proteins are intimately involved in regulating the two processes and that it may be where the proteins are– i.e. at the ER or elsewhere– that determines whether they regulate apoptosis or autophagy. Key components of the other well-characterized apoptosis pathway, the extrinsic death receptor pathway, can also control autophagy. Binding of the adaptor protein FADD to the ligand-bound death receptor (or other adaptors) is a required step in the formation of the DISCs that mediate death receptor signaling with FADD functioning as a platform upon which caspase-8 dimerization and activation occurs. FADD consists of two protein interaction domains, a death domain and a death effector domain. Unexpectedly, in normal epithelial cells the death domain of FADD is able to induce a novel cell death mechanism that involves high levels of autophagy. Since the FADD death domain has no catalytic activity it presumably induces autophagy by physically interacting with another protein. We don't know what that protein is as yet (although, as discussed below, it can interact with Atg5). Interestingly, and in keeping with a theme that will be discussed further below, the autophagy response is more easily observed when apoptosis is blocked, suggesting that autophagy and apoptosis are induced simultaneously by FADD death domain in the normal epithelial cells. This mechanism of FADD-regulated autophagy also applies when FADD-dependent signaling is induced by TRAIL, a cytokine that activates the DR4 and DR5 death receptors. A FADD-independent mechanism of inducing autophagy and autophagic cell death from the

DR5 receptor was also recently proposed in response to an activating antibody. Thus, there may be more than one way to activate autophagy from death receptors.

The above studies indicate that components of the core apoptosis machinery regulating the intrinsic and extrinsic pathways can also control autophagy. Other recent studies show the converse – i.e. that autophagy regulators can control apoptosis. In experiments examining interferon- and Atg5-induced autophagic cell death, it was shown that FADD can interact with Atg5. This study suggested that the interaction resulted in cell death (but not the autophagic vesicle formation) that required FADD and involved caspases. The implication of these studies is that Atg5 can regulate components of the extrinsic apoptosis pathway. Another mechanism by which Atg5 can regulate apoptosis has also been described. The key step in this mechanism is the cleavage of Atg5 by calpain to create a truncated form of the protein that translocates to the mitochondria to cause cytochrome c release and activation of the intrinsic apoptosis pathway that can be blocked by Bcl-2. The general significance of this mechanism is suggested by data showing that Atg5 knockdown protects tumor cells towards a variety of apoptosis stimuli while Atg5 expression sensitized to these apoptotic stimuli. Again the situation may be rather complex and calpain activity may both increase and decrease autophagy because while calpain cleavage of Atg5 produces a protein that cannot activate autophagy, other studies show that calpain activity is required for autophagy induction by rapamycin and amino acid starvation [14].

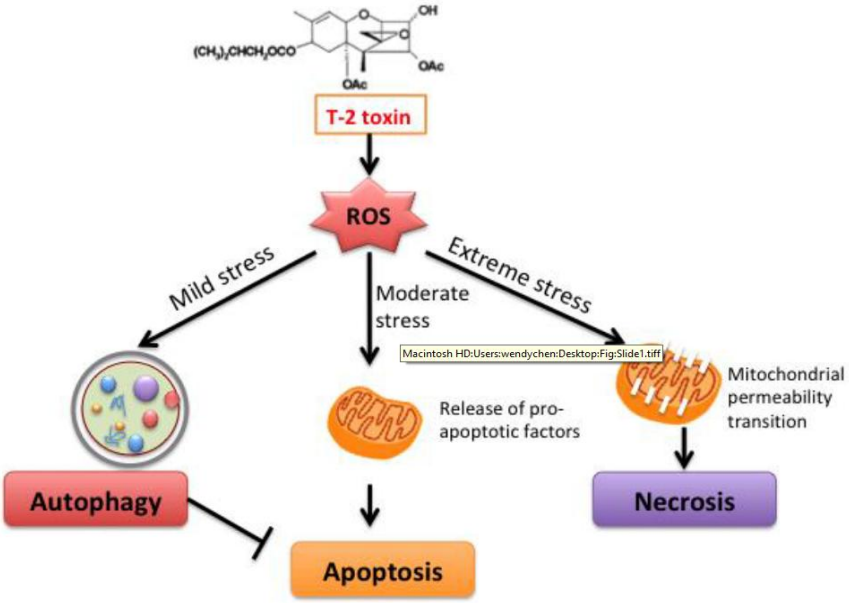

Figure-3

Apoptosis-regulating proteins in the modulationof autophagy

Recently, several proteins known to regulate apoptosis have also been identified as inducers of autophagy T able-1). The first pro-apoptotic protein identified as an inducer of autophagy was the BH3-only protein Bad, which disrupts the interaction between Bcl-2 and Beclin-1 to induce autophagy. Several other pro-apoptotic proteins, including Bak, BNIP3, and Nix, have been iden- tified as regulators of autophagy by disrupting the interaction between Bcl-2 and Beclin-1. In addition, during apoptosis, Bax promotes caspase-mediated cleavage of Be- clin-1 at the D149 position, which prevents autophagy.

Table 1 Proteins with dual role in autophagy and apoptosis

Protein	Role in autophagy	Role in apoptosis
Autophagic proteins		
mTOR	Inactive form involves in initiation	mTOR regulates apoptosis
Beclin-1	Autophagosome nucleation	Cleaved C-fragment induces mitochondrial apoptosis
UVRAG	Upregulates Vps34–Beclin1 interaction	Antiapoptotic, inhibits Bax translocation from cytosol to mitochondria
AMBRA	Upregulates Vps34–Beclin1 interaction	Regulate mitochondrial apoptosis; cleaved by caspases and calpains
Atg3	Conjugates with Atg12	Regulates mitochondrial cell death
Atg5	Conjugates with Atg12, autophagosome elongation	Interacts with FADD to inhibit apoptosis, cleaved N-fragment induces mitochondrial apoptosis
Atg12	Autophagosome elongation	Stimulates mitochondrial apoptosis by inactivating Bcl-2 and Mcl-1
Atg4D	LC3 processing	Cleaved Atg4D localize to mitochondria and induces apoptosis
p62	Binds with LC3, promotes degradation of polyubiquitinated protein aggregates	Caspase-8 processing and activation
Apoptotic proteins		
Bcl-2, Bcl-xL	Interacts with Beclin-1 and inhibit autophagy	Antiapoptotic
Bad, Bak, BNIP3, Nix	Proautophagic, disrupting Beclin-1/Bcl-2 interaction	Proapoptotic
Bax, PUMA	Proautphagic, noncanonical type	Proapoptotic
p53	Inhibits by cytoplasmic p53	Proapoptotic
	Induces by nuclear p53 through DRAM	Proapoptotic
Noxa	Induces autophagy by disrupting Mcl-1/Beclin-1 interaction	Proapoptotic
Bim	Sequesters Beclin-1, inhibits autophagy	Proapoptotic
XIAP	Inhibits by Mdm2-p53 signalling	Inhibits caspase 3,7
cFLIP	Prevent interaction between Atg3 and LC3	Inhibits caspase 8

Autophagic proteins in intrinsic apoptosis

The intrinsic apoptosis pathway is initiated by, for example, chemotherapy and/or radiotherapy. It is activated by a range of exogenous and endogenous stimuli, such as DNA damage, ischemia, and oxidative stress. Moreover, it plays an important function in development and in the elimination of damaged cells.

In the intrinsic pathway, the functional consequence of pro-apoptotic signaling is mitochondrial membrane perturbation and release of cytochrome c in

the cytoplasm, where it forms a complex or apoptosome with apoptotic protease activating factor 1 (APAF1) and the inactive form of caspase-9. This complex hydrolyzes adenosine triphosphate to cleave and activate caspase-9. The initiator caspase-9 then cleaves and activates the executioner caspases-3/6/7, resulting in cell apoptosis. It's totally different from the extracellular signals, which are usually generated by cytotoxic cells of the immune system and trigger apoptosis mainly through the extrinsic pathway [15]

The intrinsic apoptosis pathway induces apoptosis by directly activating caspase-3 or by cleaving bid (BH3 interacting domain death agonist), resulting in mitochondrial dysfunction and subsequent release of cytochrome c and activation of caspases-9 and caspases-3. Caspase-3 promotes the typical apoptosis features, including DNA fragmentation and cell death in several tissues.

The B-cell lymphoma 2 (Bcl-2) protein family tightly controls activation of the intrinsic pathway. It is found in follicular lymphoma and first identified as one of the genes involved in the cell death by either activating pro-apoptotic or inhibiting anti-apoptotic apoptosis. Proteins in one subgroup, including Bid, Bad, Bim, Bmf, Puma, and Noxa, contain a single Bcl-2 homology 3 domain (BH3-only proteins) and have pro-apoptotic activity. Two other protein subsets have multiple BH domains. The first subset, including Bcl-2 associated X protein (Bax), Bcl-2 homologous antagonist/killer (Bak) and Bcl-2 family apoptosis regulator (Bok), is pro-apoptotic; the other subset, including Bcl-2, Bcl-XL, and Mcl-1, is anti-apoptotic. The mitochondrial pathway is partly influenced by Bcl family members bound to the mitochondrial membrane, including both pro-apoptotic regulatory proteins Bax and anti-apoptotic regulatory proteins Bcl-2.

The pro-apoptotic molecules cause permeabilization of the outer mitochondrial membrane, leading to efflux of cytochrome c, which binds the adaptor Apaf-1 and the initiator caspase-9 in the cytosol to form the apoptosome complex. This stimulates caspase-9, which in turn activates the effector caspases. The mitochondrion also releases a protein called Smac/DIABLO into the cytosol. Smac/DIABLO indirectly promotes apoptosis by blocking the effects of a group of anti-apoptotic proteins called inhibitor of apoptosis proteins (IAPs).

The anti-apoptotic proteins Bcl-2 and Bcl-XL inhibit cytochrome c release, whereas Bax, Bak, and Bid, all pro-apoptotic proteins, promote its release from mitochondria. Cytochrome c and deoxyadenosine triphosphate (dATP) bind to APAF-1 to form a multimeric complex that recruits and activates pro-caspase-9, an apoptosis-mediating executioner protease that in turn activates the caspase cascade, resulting in cell apoptosis. During this process, caspase-2, caspase-8, caspase-9 and caspase-10 are involved in the initiation of apoptosis. Caspase-3, caspase-6 and caspase-7 are involved in apoptosis. Caspase-3 and caspase-7 regulate the inhibition of DNA repair and start DNA degradation. In addition, caspase-6 regulates the disintegration of the lamina and cytoskeleton [17].

Connection between autophagy and extrinsic apoptosis

Multiple direct and indirect interactions have been described suggesting mechanistic overlap and interaction between the apoptosis machinery and autophagy proteins. The majority of these interactions have been apoptosis altering autophagy; less is known at the mechanistic level about how autophagy controls apoptosis. We concentrate here on two proteins that have multiple connections between autophagy and cell death but there are other molecules with connections between the two processes that may also be critical links.

Two autophagy proteins at the crux of autophagy-apoptosis interactions are p62, a protein that is important for Ras-induced tumorigenesis, and the tumor suppressor Beclin-1. p62 is a key player in the selective autophagic degradation of many proteins (and mitochondria) and is known to interact directly with several apoptotic and survival pathway proteins including Caspase-8, TRAF6 (which modulates NF-kB survival pathways) and ERK. The interaction between caspase-8 and p62 is particularly intriguing because p62 is critical for efficient activation of caspase-8 but caspase-8 also cleaves p62 in response to death receptor activation. Furthermore, caspase-8 has recently been shown to be degraded by autophagy (presumably via p62). This creates a paradigm where autophagy and apoptosis might be involved in a complicated balancing act wherein autophagy alters the extent and kinetics of apoptosis and apoptosis alters the autophagic degradation of p62 and p62-dependent autophagic cargos, including caspase-8.

Beclin-1 is a critical regulator of autophagy that directly interacts with anti-apoptotic Bcl-2. When Bcl-2 and Beclin-1 are bound, Beclin-1 is incapable of activating autophagy. Autophagy is induced by release of Beclin-1 from Bcl-2 by pro-apoptotic BH3 proteins, Beclin-1 phosphorylation by DAP kinase (DAPK) or Bcl-2 phosphorylation by JNK. Conversely, overexpression of Bcl-2 or Bcl-XL can inhibit autophagy. Another Beclin-1-dependent mechanism by which apoptosis can inhibit autophagy is through caspase-3 cleavage of Beclin-1 to produce a truncated protein that is unable to promote autophagy thus leading to overall autophagy inhibition. Thus, Beclin-1 regulation by components of the apoptosis machinery

can either promote or inhibit autophagy perhaps depending on the relative activities of BH3 proteins and initiator and/or executioner caspases. These examples show that there can be mutual regulation of apoptosis and autophagy, so that when apoptosis is promoted autophagy is reduced to provide a mechanism to ensure that autophagy is switched off when a cell "decides" to go through with apoptosis.

Other potential avenues by which autophagy may regulate apoptosis are through the active degradation of apoptotic proteins. It should be noted however that although autophagy is capable of specifically degrading components of the apoptotic machinery (e.g. Caspase-8, mitochondria), the significance of these events in terms of actually changing the amount of cell death in a physiologic or disease setting is unclear. For example, although sequestration and degradation of mitochondria in autophagosomes occurs, this happens to only some of the mitochondria in a cell. Thus an unanswered question is: even if autophagy is increased, why would an apoptotic stimulus not still cause cytochrome c release from the other mitochondria in the cell to induce apoptosome formation and apoptosis? Perhaps by reducing the number of mitochondria, autophagy might alter the kinetics of cell death or reduce the threshold of pro-apoptotic activity necessary to induce apoptosis. Therefore, autophagy might control an apoptosis "threshold", i.e. some kind of regulator that ultimately decides whether apoptosis should proceed or not. This, in turn, may provide a way to ensure the rapid and complete demise of the cell to thus control the degree of apoptosis in the population of cells. One prediction (that has been untested so far) of this idea is that in a population of cells where some die and some don't die, the molecular mechanisms outlined above like Beclin-1 or p62 cleavage, will only take place in those cells that actually die and these will be the same cells that have lower levels of autophagy. Thus, although we have evidence of connections between the two processes and it makes intuitive sense that such connections might exist, a clear mechanistic explanation of how autophagy can inhibit apoptosis for any defined apoptotic pathway is still lacking [18].

The autophagosome in apoptosis

Autophagosomes are double-membrane sequestering vesicles that are the hallmark of the intracellular catabolic process called macroautophagy. They are formed by the orchestrated interplay of the AuTophaGy-related (ATG) proteins. The cargo molecules targeted by autophagosomes ranges from long-lived proteins and superfluous or excess organelles to invading pathogens. Autophagosomes finally fuse with lysosomes delivering the sequestered material in the interior of these organelles where it is degraded by resident hydrolases. Autophagy represents a key survival mechanism because it clears the cytoplasm from unwanted and potentially toxic structures, and the autophagosomes are the central stage of it.

Autophagosome maturation and final fusion with the lysosome occurs in the vicinity of the centrosome and depends on several lysosomal membrane proteins, such as the small GTPase Rab7 (Ras-related protein 7) and the transmembrane lysosome-associated membrane protein 2 (LAMP2) [22]. These fusion events are also dependent on SNAREs. VAMP3 contributes to the fusion of multivesicular bodies with autophagosomes to form amphisomes [23]. Recently, syntaxin 17 has been shown to be targeted by autophagosomes to control fusion with endosomes/lysosomes [24]. Interestingly ATG14L binds syntaxin 17 and stabilizes the syntaxin 17-SNAP29 (synaptosomal-associated protein 29) complex [25]. This interaction primes the interaction with VAMP8 to control autophagosome–endosome fusion.

Connection between autophagy and apoptosis under pathological conditions

Autophagy Defends against Metabolic Stress

Thus, a critical physiological role of autophagy appears to be the mobilization of intracellular energy resources to meet cellular and organismal demands for metabolic substrates.

Autophagy Works as a Cellular Housekeeper

The repertoire of routine housekeeping functions performed by autophagy includes the elimination of defective proteins and organelles, the prevention of abnormal protein aggregate accumulation, and the removal of intracellular pathogens. Such functions are likely critical for autophagy-mediated protection against aging, cancer, neurodegenerative diseases, and infection.

Autophagy in Life and Death Decisions of the Cell

The intricate interplay between autophagy and life and death decisions of the cell mirrors some of the complexities in deciphering the roles of autophagy in human diseases and their treatments.

Autophagy and Neurodegenerative Diseases

Early reports demonstrating that autophagosomes accumulate in the brains of patients with diverse neurodegenerative diseases, including Alzheimer's disease, transmissible spongiform encephalopathies, Parkinson's disease, and Huntington's disease [26, 27], led to the initial hypothesis that autophagy contributed to the pathogenesis of these disorders. In mice with cerebellar degeneration due to mutations in glutamate receptor, autophagy was also postulated to be a mechanism of nonapoptotic cell Death [19].

Autophagy and Liver Disease

Tissue-specific knockout studies in mice (discussed above) indicate an important role for basal hepatocyte autophagy in intracellular protein and organelle quality control. The protein qualitycontrol function may be important in the pathogenesis of the most common genetic cause of human liver disease, α1-antitrypsin deficiency, which is associated with chronic inflammation and carcinogenesis [28]. Perhaps, similar to neurodegenerative disorders caused by aggregate-prone proteins, pharmacological activation of autophagy may be helpful in this setting.

Autophagy and Muscle Disease

Similar to neurodegenerative diseases, the pathogenesis of myodegenerative diseases may involve either the failure of autophagosomes to fuse with lysosomes or the aggregation of misfolded proteins that exceed the autophagic clearance capacity of the myocyte. Danon disease, a genetic disease characterized by cardiomyopathy, myopathy, and variable mental retardation, results from a mutation in the lysosomal protein LAMP-2 and is associated with extensive accumulation of autophagosomes in the muscles of LAMP-2-deficient mice and patients.

Autophagy and Cardiac Disease

As noted, defective autophagy (due to impaired autophagosome-lysosome fusion) may play a role in relatively rare forms of inherited diseases of the heart (e.g., Danon disease, Pompe disease). Of greater medical significance is the possibility that autophagy may constitute an important physiological or pathophysiological response to cardiac stresses such as ischemia or pressure overload, which are frequently encountered in patients with coronary artery disease, hypertension, aortic valvular disease, and congestive heart failure.

Autophagy and Cancer

In the past decade, several genetic links have emerged between autophagy defects and cancer, providing increasing support for the concept that autophagy is a bona fide tumor suppressor pathway.

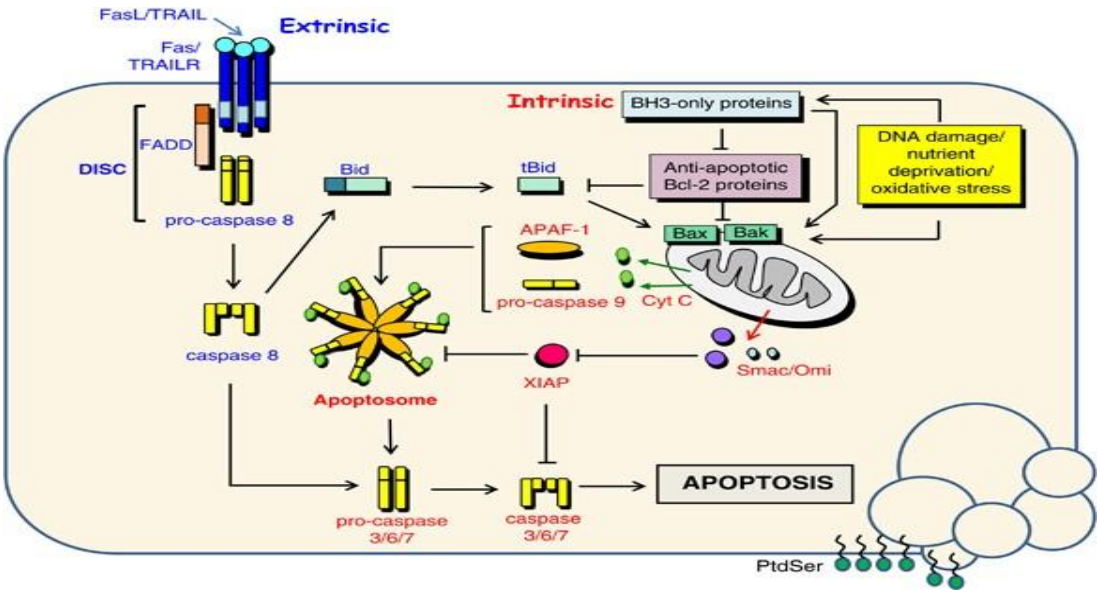

Figure-4

Autophagy and Aging

The notion that intermittent fasting promotes longevity is not merely a cultural belief shared by diverse civilizations throughout history; it is a scientific truth that extends across eukaryotic organisms, including yeast, flies, worms, and rodents [29]. Dietary restriction is a potent inducer of autophagy in virtually all species [30]. In the model organism, C. elegans, autophagy is required for the life-extending effects of dietary restriction; feeding-defective worms do not live longer if treated with siRNA against atg genes [20]. A similar requirement exists for atg genes in the longevity phenotype of worms with a loss-of-function mutation in the insulin/IGF-1 signaling pathway [21], a hormonal pathway that negatively regulates autophagy and life span in diverse species. Interestingly, dietary-restricted or long-lived insulin/IGF-1 mutants are resistant to many age-related diseases, including Huntington's disease and cancer in C. elegans disease models, sarcopenia in worms, heart failure in Drosophila, and cancer in rodents. In view of the protective role of autophagy in certain age-related diseases such as neurodegeneration, cardiomyopathy, and cancer, a critical question is whether autophagy activation in long-lived mutant animals is mechanistically responsible for resistance to age-related disease.

Autophagy in Infection, Immunity, and Inflammatory Diseases

The autophagic machinery is used in a multipronged defense against microbes, including the selective delivery of microorganisms to degradative lysosomes (a process referred to as xenophagy) and the delivery of microbial nucleic acids and antigens to endo/lysosomal compartments for activation of innate and adaptive immunity [31, 32] for detailed reviews) (Figure-4). Numerous medically important pathogens are degraded in vitro by xenophagy, including bacteria such as group A Streptococcus, Mycobacterium tubercuolosis, Shigella flexneri, Salmonella enterica, Listeria monocytogenes, Francisella tularensis; viruses such as herpes simplex virus type I (HSV-1); and parasites such as Toxoplasma gondii. It is predicted that xenophagy participates in pathogen protection in vivo, but data supporting this are limited to certain viral diseases such as tobacco mosaic virus in plants and HSV-1 and Sindbis virus in mice [31]. With the availability of tissue-specific ATG gene knockout mice, it should be possible to more broadly evaluate the role of xenophagy in microbial pathogenesis.

CONCLUSION

A connection between apoptosis and autophagy has long been suggested. Recently, the molecular link has been elucidated by the discovery that several genes are shared by both pathways. Despite progress in elucidating the mechanism of autophagy and its interaction with apop- tosis, its role in cancer and other diseases remains a topic of debate. In particular, it is difficult to define a single function for autophagy, as the process has different effects depending on cell type, stimuli, and escape from apoptosis (e.g., in response to drug treatment). Nonethe- less, it remains a promising challenge to understand how a cell responds to similar stimuli by undergoing apoptosis versus autophagy. In contrast to the initial descriptions of autophagic cell death, accumulating evidence points to antagonistic roles for apoptosis and autophagy. Future studies investigating the interplay between apoptosis and autophagy will have significant implications for our understanding of both processes under physiological and pathological conditions.

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