Amino Acids (2015) 47:2089–2099
DOI 10.1007/s00726-015-2084-0

REVIEW ARTICLE

Intimacy and a deadly feud: the interplay of autophagy and apoptosis mediated by amino acids

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Received: 10 August 2015 / Accepted: 24 August 2015 / Published online: 9 September 2015

Abstract Autophagy (i.e., "self-eating") and apoptosis (i.e., type I programmed cell death) are essential and intimately involved in molecular, cellular, and whole-body homeostasis in humans and animals. Autophagy has been categorized as a mechanism of intracellular degradation, recycling, defense, and survival. To date, three types of autophagy have been identified: macroautophagy, microautophagy, and chaperone-mediated autophagy. Recent discoveries strongly suggest that macroautophagy also modulates type II programmed cell death under specific circumstances. Autophagy and apoptosis are fundamentally distinct processes, but are interconnected by common stress initiators and intermediate regulators. During the past two decades, the role of amino acid metabolism and signaling in the regulation of apoptosis and autophagy has been intensively studied. In this review, we summarize recent advances in our understanding of the molecular mechanisms that regulate both autophagy and apoptosis in the context of amino acid signaling.

Keywords Amino acid · Autophagy · Apoptosis · Crosstalk · Metabolism · Nutrition

Abbreviations

AIF	Apoptosis-inducing factor
AMBRA1	Activating molecule in BECN1-regulated autophagy protein 1
AMPK	AMP-activated protein kinase
Apaf-1	Apoptotic protease-activating factor-1
ApoL6	Apolipoprotein L6
Atg	Autophagy-related gene
BAD	Bcl-2-associated death protein
Bcl-2	B cell lymphoma 2
Beclin 1	Bcl-2 interacting protein 1
Bfl-1	Bcl-2-related gene expressed in fetal liver
BH3	Bcl-2-homology-3 domain
BH	Bcl-2 homology
BID	BH3 interacting-domain death agonist
Bif-1	Bax-interacting factor-1
DAPK	Death-associated protein kinase
DISC	Death-inducing signaling complex
DRAM	Damage-regulated autophagy modulator
ER	Endoplasmic reticulum
ERK	Extracellular signal-regulated kinase
FADD	FAS-associated death domain protein
FLICE	FADD-like interleukin-1 β-converting enzyme

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FIP200	Focal adhesion kinase family-interacting protein of 200 kDa
hVps34	Human vacuolar protein sorting-34
IAPs	Inhibitors of apoptosis proteins
IGF-1	Insulin-like growth factor-1
IRS	Insulin receptor substrate
JNK	c-Jun N-terminal kinase
LC3	Microtubule-associated protein 1 light chain 3
MAPK	Mitogen-activated protein kinase
MOMP	Mitochondrial outer membrane permeabilization
mTOR	Mammalian target of rapamycin
PCD	Programmed cell death
PI3K	Phosphoinositide 3-kinase
ROS	Reactive oxygen species
PRAS40	Proline-rich AKT substrate of 40 kDa
SMAC	Second mitochondrial-derived activator of caspase
TIGAR	TP53-inducible glycolysis and apoptosis regulator
TNF-α	Tumor necrosis factor-α
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
TSC1/2	Tuberous sclerosis complex1/2
ULK1	unc-51-like autophagy activating kinase 1
UVRAG	Ultraviolet irradiation resistance-associated gene
SLC38A9	Member 9 of the solute carrier family 38

Introduction

Autophagy and apoptosis are intimately involved in molecular, cellular, and organismal homeostasis in humans and animals, and their relationship can be harmonic or deadly. Autophagy (i.e., "self-eating") is a conserved intracellular pathway used to degrade and recycle cytoplasmic components, such as long-lived proteins or organelles, via a lysosome-dependent pathway (Choi et al. 2013). To date, three types of autophagy have been identified: macroautophagy, microautophagy, and chaperone-mediated autophagy. Among these, the major type is macroautophagy, a synonym of autophagy, which has been extensively studied and characterized (Boya et al. 2013; Delgado et al. 2014; Kim and Lee 2014; Noda and Inagaki 2015; Yang and Klionsky 2010). Apoptosis (type I programmed cell death) is characterized by the activation of a family of cysteine proteases known as caspases. Caspases cleave and inactivate specific target proteins, resulting in biochemical and morphologic features of apoptosis (Hengartner 2000; Li and Yuan 2008; Pop and Salvesen 2009; Taylor et al. 2008). Functionally, both apoptosis and autophagy are required for the maintenance of cellular homeostasis. Although autophagy and apoptosis utilize fundamentally distinct interactomes and pathways, numerous lines of evidence show that autophagy and apoptosis are highly interconnected and share many key regulators (e.g., p53, B-cell lymphoma 2 [Bcl-2], and other Janus proteins). In addition, they both utilize a key organelle, the lysosome, which can convert autophagy to apoptosis or vice versa (Delgado et al. 2014; Giansanti et al. 2011; Kang et al. 2011; Marino et al. 2014; Walsh and Edinger 2010). The main objective of this review is to highlight recent advances in our understanding of the molecular mechanisms that regulate both autophagy and apoptosis in the context of amino acid signaling and nutrition.

Autophagy

During autophagy, acidophilic lysosomal enzymes digest and recycle cytosolic macromolecules and aged and damages organelles, under both normal and stress conditions (Boya et al. 2013; Kim and Lee 2014; Murrow and Debnath 2013; Noda and Inagaki 2015; Steele et al. 2015) (Figs. 1, 2). Unlike apoptosis, autophagy is reversible (Noda and Inagaki 2015). Autophagy is important during normal growth and development, as well as in response to environmental stimuli, and it, and unlike apoptosis, is reversible. Autophagy is also used to eliminate damaged organelles, for example (e.g., mitochondria), and to help in the elimination of intracellular pathogens (Noda and Inagaki 2015; Deretic and Levine). In addition, recent discoveries have shown a role for autophagy in fine-tuning inflammation and innate immunity (Abdel Fattah et al. 2015; Cuervo and Macian 2012; Deretic et al. 2013; Kuballa et al. 2012; Mathew et al. 2014). Although autophagy is typically referred to as macroautophagy, there are two other types of autophagy: microautophagy and chaperone-mediated autophagy, which share the same lysosomal mechanism but differ in the way that a target substrate is delivered to the lysosome (Kaushik and Cuervo 2012; Mizushima 2007; Sahu et al. 2011; Yang and Klionsky 2010).

Autophagy possesses has several characteristic features, including the formation of distinct intracellular interactomes (e.g., unc-51-like kinase 1 [ULK1], phosphatidylinositol 3-kinase [PI3K]CIII/Bcl-2 interacting protein 1 [Beclin 1], Atg12-Atg5-Atg16L interactomes) and de novo synthesized organelles (e.g., isolation membrane/phagophore, autophagic vesicles) (Boya et al. 2013; Noda and Inagaki 2015; Yu et al. 2008). The four major phases of autophagy are: initiation, elongation, maturation, and completion. Initiation involves the formation of a double-membrane structure, from an isolation membrane to an autophagosome. During this process, a portion of the cytoplasm is engulfed in the autophagosome and subsequently the autophagosome fuses with endosomes and lysosomes, becoming an amphisome and an autolysosome, respectively. In the completion phase, lysosomal enzymes degrade the contents and the inner membrane of the autolysosome

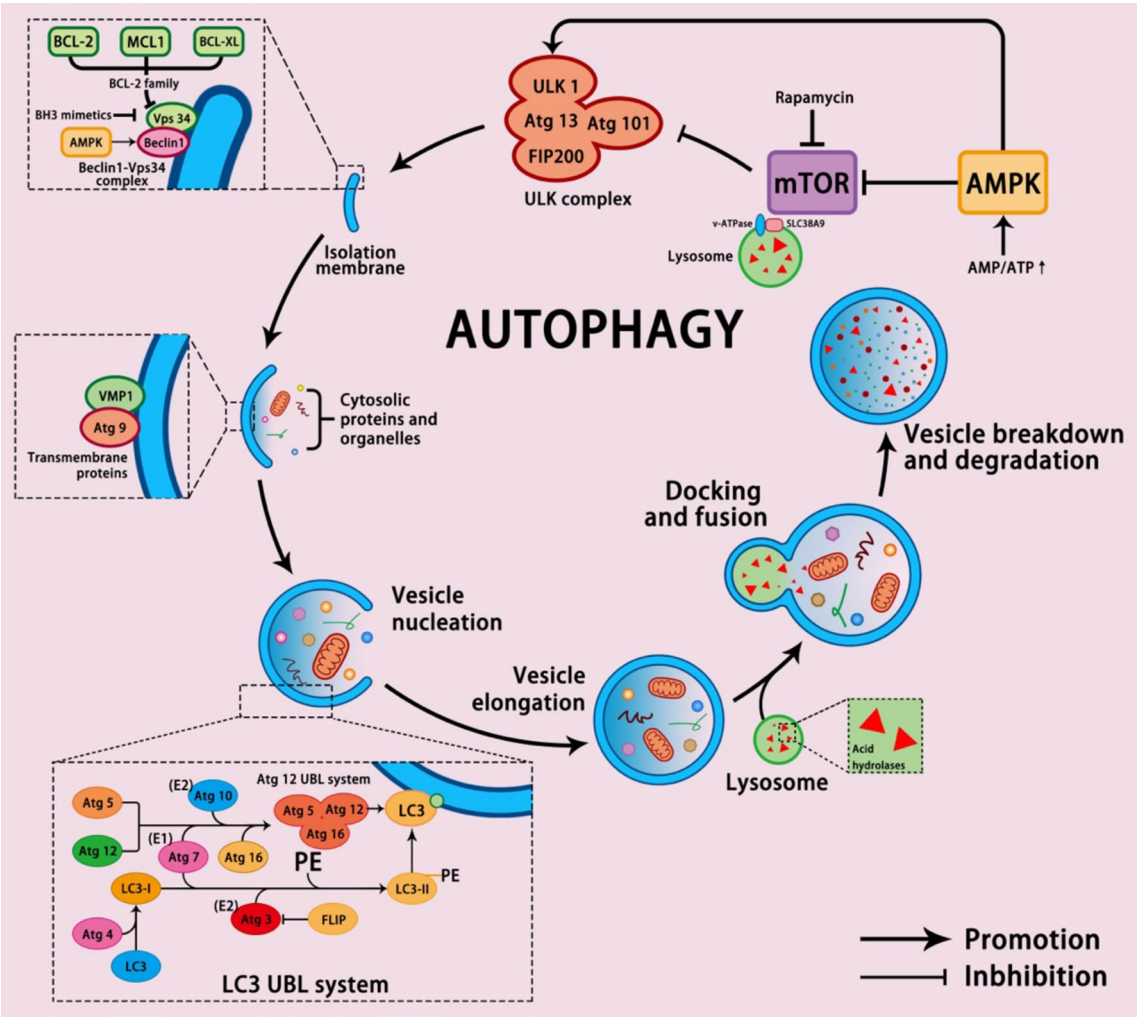

Fig. 1 Schematic diagram showing the progression of autophagy. In the presence of an autophagy inducer, cytoplasmic materials, such as protein aggregates and organelles, are sequestered by the isolation membrane, also known as a phagophore. The phagophore then expands and encloses to form a double-membrane vesicle, called an autophagosome. The outer membrane of the autophagosome fuses with a lysosome to form an autolysosome, in which the internal materials, together with the inner membrane of the autophagosome, are degraded by acid hydrolases. The resultant amino acids either are used to synthesize protein or are oxidized by mitochondria to generate ATP for cell survival. However, when autophagy occurs at excessive levels, it can lead to autophagy-associated cell death. Additional details are provided in the text

(Mizushima 2007; Yu et al. 2004b, 2010; Fig. 1). The formation of a double-membrane structure is a complex process involving specific kinases and numerous autophagy-related proteins (Atgs) (Itakura and Mizushima 2010; Mizushima 2007; Schmid and Munz 2007). Currently, more than 35 *ATG* genes have been identified, including the microtubule-associated protein complex light chain 3 (*LC3*). *LC3* is a homologue of yeast *Atg8*, which is required for the formation of autophagic membranes. Processed and lipidated LC3-II is recruited to the isolation membrane, which ultimately develops into the autophagosome where cellular targets are sequestered in preparation for degradation (Itakura and Mizushima 2010; Mizushima 2007; Schmid and Munz 2007; Mizushima and Yoshimori 2007; Tanida et al. 2008). The conversion of LC3-I to LC3-II has been used as an indicator of the autophagic state in in vitro model systems. In addition, autophagy uses two essential conjugation systems/complexes, Atg7 (E1-like), Atg3 and Atg10 (E2-like), and Atg5-Atg12-Atg16L (E3-like), for the successful progression of autophagosome elongation and completion, similar to the ubiquitin-targeting system (Fullgrabe et al. 2014; Mizushima 2010; Shpilka et al. 2012; Yousefi et al. 2006; Yu et al. 2004a; Fig. 2).

It is well documented that amino acids play an important role in regulating autophagy primarily through the mechanistic target of rapamycin complex 1 (mTORC1) and its downstream signaling pathway and the lysosome (Chen et al. 2014; Efeyan et al. 2012; Jewell et al. 2013;

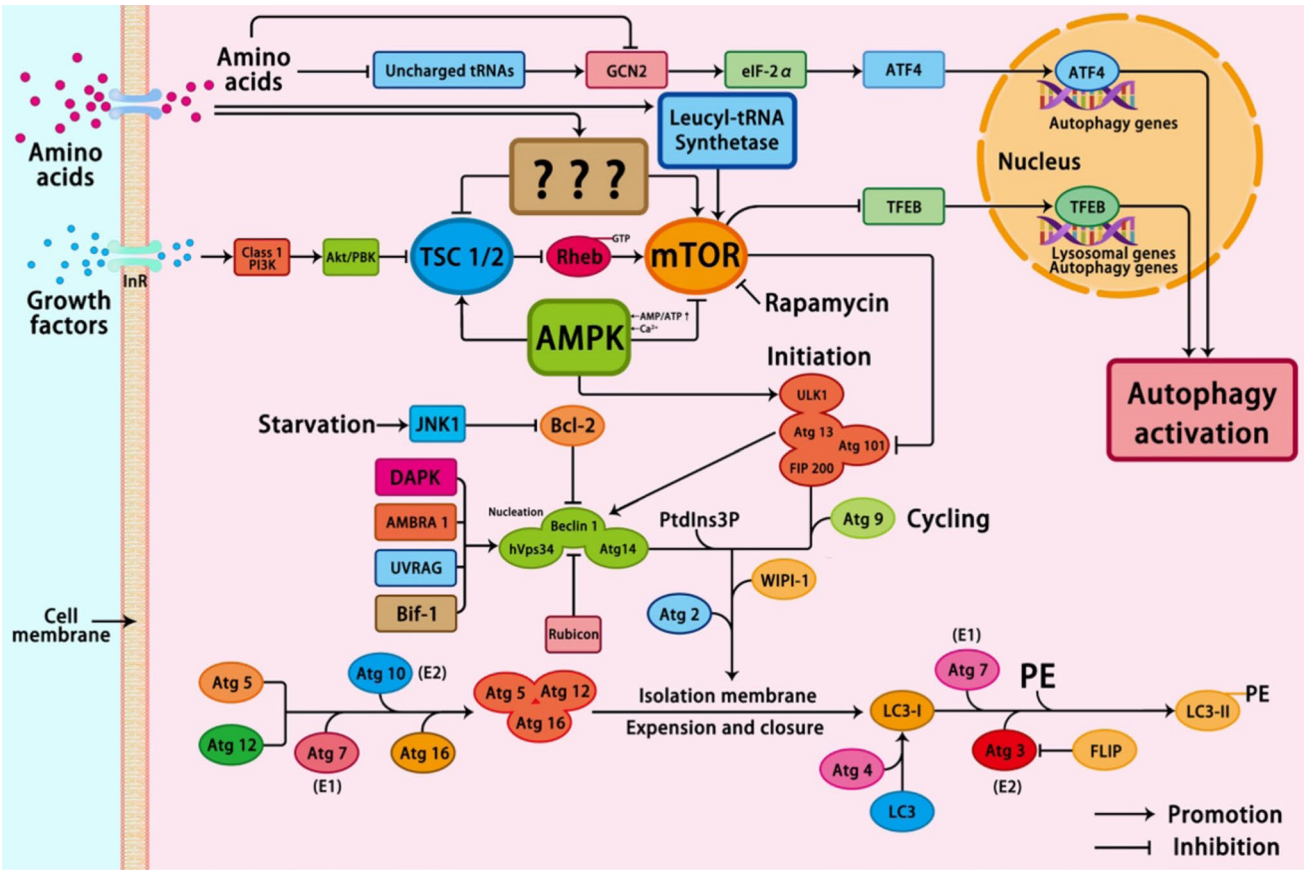

Fig. 2 Regulation of the autophagy pathway. The autophagy signaling pathway is regulated by nutrients, growth factors, and energy levels. In the presence of amino acids (e.g., leucine, glutamine, and arginine), mTORC1 is activated through an amino acid sensor (e.g., a leucine sensor), amino acyl-tRNA synthetase (e.g., leucyl-tRNA synthetase), or other unknown mechanisms. Activation of mTORC1 by amino acids represses autophagy by inhibiting the kinase activity of ULK1. In contrast, in the absence of amino acids or growth factors, or in response to an increase in the AMP/ATP ratio [via activation of AMP-activated protein kinase (AMPK)], mTORC1 is inhibited and autophagy is initiated by the ULK1 complex. In addition, mTORC1 can indirectly regulate autophagy by controlling lysosome biogenesis through the phosphorylation of transcription factor EB (TFEB) or by activating GCN2, which drives the transcription of several lysosome- and autophagy-specific genes. The activity of the Beclin 1/human vacuolar protein sorting-34 (Vps34)/Atg14 complex is important for the nucleation of the autophagosomal membrane. Starvation can activate JNK1, which in turn phosphorylates Bcl-2 and abolishes its inhibitory effect on the Beclin 1/Vps34/Atg14 complex, resulting in autophagy. In addition, several Beclin 1-interacting proteins have been identified. For example, death-associated protein kinase (DAPK), Ambral, ultraviolet irradiation resistance-associated gene (UVRAG), Bax-interacting factor-1 (Bif-1) positively regulates the Beclin 1/hVps34/Atg14 complex, whereas Rubicon negatively regulates the Beclin 1/hVps34/Atg14 complex. The functional relationship between the ULK1/Atg13/focal adhesion kinase-interacting protein FIP 200 fragment (FIP200) and Beclin 1/hVps34/Atg14 complexes remains to be determined. Production of PtdIns3P by Vps34 in the nucleation complex allows the recruitment of WIPI-1 and Atg2 to the phagophore. The expansion and closure of the isolation membrane are dependent on the Atg12 and LC3 conjugation systems. The Atg12-Atg5-Atg16L complex contributes to the stimulation of LC3-II lipidation with phosphatidylethanolamine (PE). The anti-apoptotic protein FLIP inhibits autophagy by interacting with Atg3. V-ATPase and SLC38A9 regulate the binding of mTORC1 to the lysosome and thus the activity of mTORC1

Kim and Guan 2011; Mizushima and Klionsky 2007; Nicklin et al. 2009; Steele et al. 2015). In the context of nutrition the 20 amino acids that are the building units of proteins should be obtained through the diet to optimize the growth, development, and health of animals (Marazzi et al. 2008; Wu 2014; Wu et al. 2014). In humans and animals, autophagy in multiple tissues (e.g., liver, small intestine, and skeletal muscle) is activated under conditions of fasting or nutrient deprivation, thereby providing amino acids for glucose synthesis in the liver and kidneys, the regulation of acid–base balance, immune responses, and endocrine function, as well as the production of gaseous signaling molecules (e.g., NO, H_2S, and CO) and neurotransmitters (Hou et al. 2015; Wu 2013; Wu et al. 2014). These physiologic processes result in the loss of tissue proteins, but are essential for the survival of organisms. Inactivation of the mTORC1 cell signaling pathway due to reduced concentrations of insulin and certain amino acids (e.g., glutamine

and arginine) in plasma contributes to the increased activity of autophagy under those catabolic conditions (Kim and Guan 2011; Sarbassov et al. 2005). Upon re-feeding to the adequate level, autophagy in cells is inhibited to restore proteins because mTORC1 is phosphorylated by the signals of anabolic hormones and nutrients. These adaptive mechanisms can be used to develop nutritional strategies for feeding humans and animals (Wu 2009, 2010, 2013; Wu et al. 2013). For example, supplementing glutamine and arginine to pregnant swine consuming less amounts of proteins enhances the survival and growth of fetuses (Chen et al. 2014; Wu 2013). Therefore, we surmise that supplementing glutamine and arginine to obese individuals consuming low-energy diets may enhance the loss of white adipose tissue while sparing protein in tissues (e.g., skeletal muscle, small intestine, and liver) (Jobgen et al. 2009; McKnight et al. 2010, 2011; Tan et al. 2011).

Apoptosis

Apoptosis, or type I programmed cell death, is characterized by the activation of a group of cysteine-activated aspartate-specific proteases known as caspases (Shalini et al. 2015). During apoptosis, cells display a series of biochemical and morphologic characteristics (e.g., protein cleavage, cell shrinkage, externalization of phosphatidylserine, chromatin and DNA condensation, membrane blebbing, and formation of apoptotic bodies) (Hengartner 2000; Hotchkiss et al. 2009; Li and Yuan 2008; Pop and Salvesen 2009). Caspases can be grouped as effector/downstream caspases, which cleave diverse protein species critical for cell survival and DNA synthesis, and initiator/upstream caspases, which cleave and activate the effector caspases (Feinstein-Rotkopf and Arama 2009; Hengartner 2000). Apoptosis takes place in four sequential stages: stimulus/initiation, signaling, regulation, and execution. Initiation can be stimulated by extracellular ligand (extrinsic) or intracellular stress (intrinsic) such as genomic toxicity (Elmore 2007). Subsequently, regulatory proteins, such as p53 (Chand et al. 2014), Bcl-2 (Chand et al. 2012), inhibitors of apoptosis (IAPs), and signaling interactomes, such as the apoptosome, fine-tune this dynamic process. Then, caspases are activated and used for cleaving proteins critical for cell structure, survival, and proliferation (Berthelet and Dubrez 2013; Hengartner 2000; Li and Yuan 2008; Portt et al. 2011). The intrinsic apoptotic signaling pathway is dependent on the formation of the apoptosome, an interactome composed of apoptotic protease-activating factor-1 (Apaf-1), procaspase-9, cytochrome C, and (d)ATP (Czabotar et al. 2014; Kroemer and Reed 2000; Riedl and Salvesen 2007; Verhagen et al. 2001; Zou et al. 1997).

The death receptor pathway is activated by death ligands, such as Fas ligand, tumor necrosis factor (TNF)-α, or TNF-related apoptosis-inducing ligand (TRAIL), that bind to a specific receptor (e.g., Fas, TNF receptor 1 [TNFR1], or death receptor 5 [DR5]) on the plasma membrane (Czabotar et al. 2014; Lavrik and Krammer 2012; Schmitz et al. 2000; Yang et al. 2010). The binding of the death receptors to their cognate ligands results in receptor trimerization and the recruitment of procaspase-8 and adaptor proteins, such as the Fas-associated death domain protein (FADD), to form a death-inducing signaling complex (DISC) (Guicciardi and Gores 2009; Lavrik and Krammer 2012). The procaspase is activated inside the DISC and then promotes cell death by activating downstream effector caspases such as caspase-3, with no involvement of the Bcl-2 family proteins (Kroemer et al. 2007) (Fig. 3). Alternatively, active caspase-8 can cleave the Bcl-2 homology 3 domain (BH3)-only protein, BH3 interacting-domain death agonist (BID), into truncated BID (tBID). Then tBID translocates into the mitochondria to facilitate the release of second mitochondria-derived activator of caspase (SMAC) and cytochrome c into the cytosol, thereby triggering mitochondria-dependent apoptosis (Kantari and Walczak 2011; Li et al. 1998; Ott et al. 2009).

In contrast, initiation of the intrinsic apoptotic pathway occurs in response to stress signals, such as growth factor deprivation, hypoxia, oxidative stress, DNA damage, or cytotoxic cues. The Bcl-2 family proteins are critical regulators of mitochondrial apoptosis signaling (Czabotar et al. 2014; Youle and Strasser 2008; Adams and Cory 2007; Choi et al. 2013). According to function, this family of proteins is further classified into two groups, the anti-apoptotic and the pro-apoptotic members. The anti-apoptotic members include proteins with four BH domains (i.e., BH1–BH4), such as Bcl-2, Bcl-xL, Bcl-w, myeloid cell leukemia 1 (Mcl-1), and A1. The pro-apoptotic proteins are divided into two distinct subgroups, the multi-domain proteins containing BH1–BH3 domains (e.g., Bax, Bak, and Bok) and the BH3-only proteins [e.g., Bcl-2 associated death promoter (Bad), Bid, Bik/Nbk, Bim, Bmf, Nix/BNIP3, Hrk, Noxa, p53 upregulated modulator of apoptosis (PUMA), and apolipoprotein L6 (ApoL6)] (Martinou and Youle 2011; Willis et al. 2003; Zhaorigetu et al. 2011). The precise mechanisms by which the BH3-only proteins contribute to apoptosis are not clear. Generally, these proteins have been proposed to either bind and inhibit the anti-apoptotic Bcl-2 family member proteins or directly interact with and enhance the activity of the pro-apoptotic Bcl-2 family member proteins to elicit a pro-apoptotic effect (Czabotar et al. 2014; Gordy and He 2012; Gross et al. 1999).

In mitochondria, activation of the pro-apoptotic Bcl-2 family proteins Bax and Bak by the BH3-only proteins (including Bid, Bim, or PUMA) is required to trigger mitochondrial outer membrane permeabilization (MOMP) (Delbridge and Strasser 2015; Lomonosova

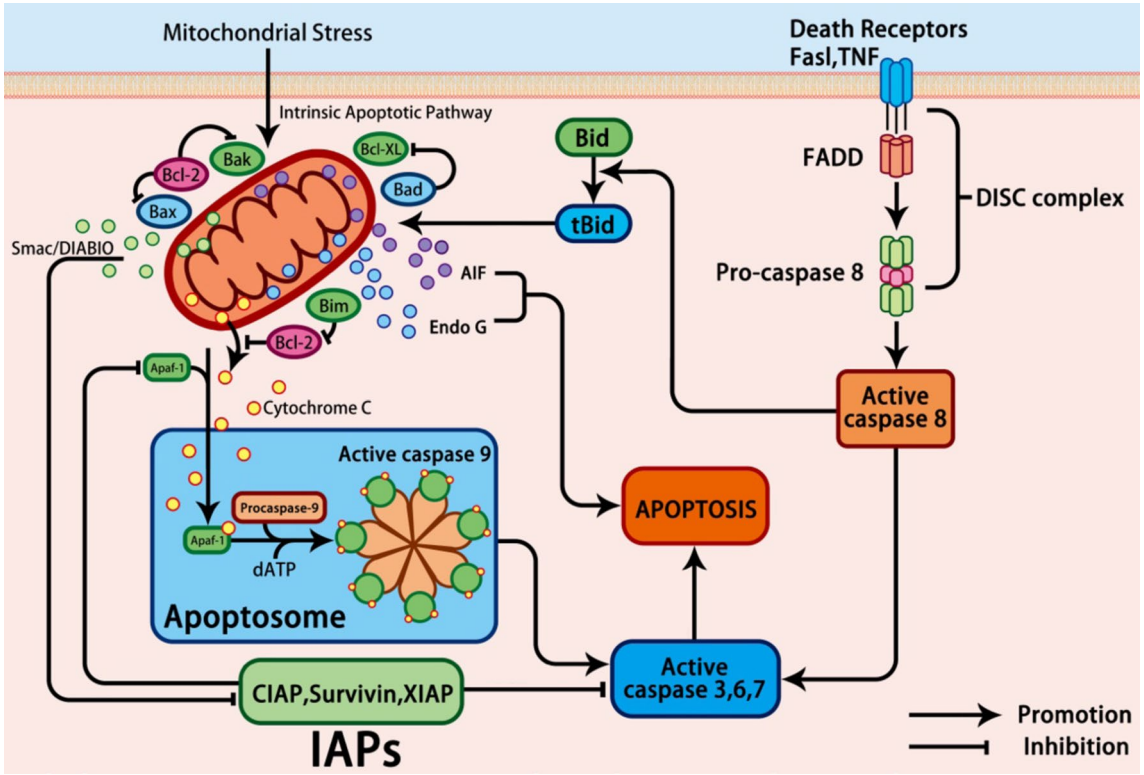

Fig. 3 The extrinsic (death receptor-mediated) and the intrinsic (mitochondria-mediated) pathway of apoptosis. In the extrinsic pathway of apoptosis, ligation of death receptors such as Fas by Fas ligand (FasL) results in receptor trimerization, recruitment of the Fas-associated death domain protein (FADD), and activation of caspase-8, which can be inhibited by FLIP. Activated caspase-8 promotes cell death by activating caspase-3 or by cleaving BID into tBID, which triggers the mitochondria-mediated apoptosis pathway. In the intrinsic pathway, activation of Bax and Bak in response to diverse stimuli results in an increased mitochondrial outer membrane permeabilization (MOMP) and release of cytochrome c, AIF, SMAC/DIABLO, HtrA2/Omi, and endo G. Cytochrome c, procaspase-9, and dATP bind to Apaf-1 to form the apoptosome that subsequently activates caspase-9 and downstream effector caspases, such as caspase-3

and Chinnadurai 2008; Ren et al. 2010; Wei et al. 2001; Zong et al. 2001). An increase in MOMP results in the release of proteins from the mitochondrial inter-membrane space into the cytosol, including apoptogenic molecules such as cytochrome c, apoptosis-inducing factor (AIF), SMAC/direct inhibitor of apoptosis-binding protein with low pI (DIABLO), the serine protease HtrA2/Omi, endonuclease G (endoG), and caspase-activated deoxyribonuclease (Lomonosova and Chinnadurai 2008; Otera and Mihara 2012; Tait and Green 2010; Vaux 2011). Upon release, cytochrome c and dATP bind to apoptotic Apaf-1 to form the apoptosome. The apoptosome then activates the initiator caspase-9, which in turn activates downstream effector caspases (Yuan et al. 2013).

Apoptosis through mitochondria can be inhibited on different levels by anti-apoptotic proteins, including IAPs and the anti-apoptotic Bcl-2 family members Bcl-2 and Bcl-xL. IAPs inhibit the activation of caspase-9 and caspase-3, although this inhibition can be blocked by SMAC/DIABLO and lead to apoptosis (Fulda and Vucic 2012). Bcl-2 and Bcl-xL prevent apoptosis either by inhibiting the activation of caspases or by preventing the release of mitochondrial apoptotic factors such as cytochrome c and AIF into the cytoplasm (Fulda and Vucic 2012; Adams and Cory 2007; Czabotar et al. 2014; Youle and Strasser 2008; Willimott and Wagner 2010) (Fig. 1). It should be noted that the levels or the activities of the Bcl-2 family proteins are subjected to transcriptional or posttranslational regulation in association with their function. Moreover, Bcl-2 family proteins can also be regulated by survival signals. For example, the activation of the PI3K/AKT or PI3K/mitogen-activated protein kinase (MAPK) signaling pathway can phosphorylate and inactivate the pro-apoptotic Bcl-2 family member Bad, therefore inactivating its pro-apoptotic effect (She et al. 2005; Fang et al. 1999). Taken together, the multiple levels of control on Bcl-2 family proteins and the antagonistic regulation between these proteins constitute a complex network that regulates apoptosis through mechanisms that are poorly understood (Czabotar et al. 2014) (Fig. 3).

The fine-tuning of apoptosis and autophagy by Bcl-2 family proteins

The Bcl-2 family proteins play critical roles in regulating and fine-tuning apoptosis and autophagy. A change in the homeostatic balance of Bcl-2 family proteins can alter cell fate (Chipuk et al. 2010; Youle and Strasser 2008; Zalckvar et al. 2009). For example, in an animal model of atherosclerosis, increased levels of Bcl-xL were found in the intima of early proliferative lesions. Furthermore, the downregulation of Bcl-xL in the neointima resulted in the apoptosis of vascular cells and the regression of lesions (Pollman et al. 1998). In another study, Bcl-xL levels were higher in apoptosis-resistant cells of human advanced lesions than in control specimens, and Bcl-xL had a protective effect against apoptotic insults (Saxena et al. 2002). Moreover, in our previous study in which we performed transcript profiling in atherosclerotic lesion-derived cells (LDCs) that underwent Fas-mediated apoptosis, we found that upregulated expression of Bcl-xL is a major determinant of resistance to Fas-mediated apoptosis (Gagarin et al. 2005; Yang et al. 2007). Importantly, we have documented that human apolipoprotein L6 (ApoL6), a BH3-only pro-death protein, induces apoptosis in LDCs in a time- and concentration-dependent manner and that this apoptosis is mediated by reactive oxygen species (ROS) and mitochondria. This is achieved, in part, through the binding of ApoL6 with Bcl-xL. Interestingly, ApoL6 also blocks Beclin 1-initiated autophagy in LDCs (Zhaorigetu et al. 2011). We recently found that proline and tryptophan can block ApoL6-induced apoptosis by inducing the autophagic survival mechanism in various cell types, demonstrating that amino acids can directly influence the homeostatic balance of the Bcl-2 family member proteins that leads to the fine-tuning of cell survival and death (Hu et al., this issue).

Amino acids and apoptosis

Interestingly, when levels of some amino acids and their metabolites are high, they can actually initiate apoptosis and block autophagy. For example, Zhang et al. (2000) have shown that above normal physiologic concentrations glutamate, an excitatory neurotransmitter, induce excitotoxicity and apoptosis in mammalian neurons. Kulbe and colleagues (Kulbe et al. 2014) recently showed that glutamate insults induce apoptosis by blocking autophagic flux in hippocampal neurons. Proline also has dichotomous roles in the induction of apoptosis and autophagy. In some cell types, when proline oxidase (POX) is induced in the presence of physiologic concentrations of proline, cells undergo apoptosis (Hu et al. 2007; Liu et al. 2006; Maxwell and Rivera 2003). In addition, POX responds to nutrient stress in an mTORC1-dependent manner and increases the generation of ATP, which links POX to autophagy. Oxidized low-density lipoprotein (LDL) has been shown to have cytotoxic effects on cancer cells in vitro and to activate both apoptosis and autophagy. POX is inducible by oxLDL through peroxisome proliferator-activated receptor (PPAR)γ. Interestingly, POX overexpression is sufficient to activate autophagy and is directly dependent on POX catalytic activity, namely the generation of POX-dependent superoxide. Thus, POX is critical in the cellular response to the noxious effects of oxidized LDL through its activation of protective autophagy (Pandhare et al. 2009).

Lysosomes, mTORC1, and lysosomal membrane proteins in autophagy

The lysosome, one of the organelles required for autophagy, is an intracellular depot of acidophilic hydrolases with a single lipid-bilayer membrane. However, how the lysosome membrane fuses with the autophagic membrane is still largely unknown (Aits and Jaattela 2013; Johansson et al. 2010). The lysosome also functions as a platform to integrate signals in regulating mTORC1 kinase activity. Furthermore, the lysosome is not only the endpoint of autophagy, but also of endocytosis and phagocytosis (Efeyan et al. 2012, 2014). However, it is also well documented that alterations in lysosomal structure or damage to its membrane can lead to lysosomal destabilization. Interestingly, factors such as ROS, p53, the Bcl-2 family proteins, and certain proteases that contribute to lysosomal membrane permeabilization (LMP) can affect both apoptosis and autophagy (Boya and Kroemer 2008; Yuan et al. 2002; Crighton et al. 2006; Guicciardi et al. 2004). LMP can occur in response to cell death signals, resulting in the leakage of lysosomal cathepsins and hydrolases. Excess ROS have been shown to destabilize the lysosomal membrane, resulting in a rapid release of cathepsins to the cytosol (Werneburg et al. 2007, Appelqvist et al. 2013; Oberle et al. 2010). In addition, pro-apoptotic Bax can translocate and co-localize with Bim to lysosomes, resulting in Bax-mediated LMP and apoptosis. LMP may also occur in p53-induced apoptosis, whereby p53 translocates to the lysosome and triggers LMP (Li et al. 2007). P53 may upregulate LMP and Bax-mediated mitochondrial permeabilization through the upregulation of the genes *PUMA* and *Noxa* (Oda et al. 2000; Yu et al. 2001; Nakano and Vousden 2001). Both PUMA and Noxa are Bcl-2 BH3-only members of the Bcl-2 protein family. When PUMA is ectopically expressed, it localizes to the mitochondrial outer membrane where it interacts with and suppresses the anti-apoptotic Bcl-2 family member proteins, such as Bcl-2 and Bcl-xL, resulting in the release of cytochrome c and the activation of caspase-9.

A regulator of protein translation, metabolism, autophagy, and cell growth, mTORC1 is composed of several core components: the serine/threonine kinase mTOR, regulatory-associated protein of mTOR (RPTOR), mammalian lethal with SEC13 protein 8 (MLST8), AKT1 substrate 1 (AKT1S1), and DEP domain containing mTOR-interacting protein (DEPTOR). mTORC1 functions as a platform for the integration of signals, such as the nutritional state, growth factors, and energy level. Some of these signals, such as insulin stimulation or low energy levels, are converged by phosphorylation of the tuberous sclerosis complex (TSC). The TSC is composed of the proteins TSC1, TSC2, and TBC1D7 and acts as a GTPase-activating protein (GAP) for the small GTPase RHEB (Ras homolog enriched in brain), stimulating the transition of RHEB from its active GTP-bound state to its inactive GDP-bound state. RHEB is anchored to lysosomes and promotes mTORC1 activity in its GTP-bound state (Sancak et al. 2008, 2010; Zoncu et al. 2011; Efeyan et al. 2012).

The regulation of mTORC1 by amino acids has been studied extensively, and a growing number of proteins have been shown to modulate the activity and/or localization of mTORC1. Depending on their nucleotide binding state, Rag GTPases recruit mTORC1 to the lysosome where mTORC1 activity is stimulated via RHEB, while Ragulator recruits and anchors the Rag GTPases to the lysosome (Martina and Puertollano 2013; Puertollano 2014). Several other interactions are also dependent on cellular amino acid status, such as those between Rag and LAMTOR/p18 proteins and between Rags and their GAPs and GEFs. In addition, depletion of GATOR1 leads to mTORC1 hyperactivation and renders cells resistant to amino acid removal. Furthermore, lysosomal translocation and activation of mTORC1 upon amino acid stimulation requires the vacuolar H^+-ATPase ATPase (V-ATPase), which hydrolyzes ATP to produce a proton gradient across the lysosomal membrane and binds Ragulator in an amino acid–sensitive manner (Zoncu et al. 2011). Aside from these recent advances in our understanding of this complex signaling cascade, the exact mechanism by which amino acids are sensed to control mTORC1 remains elusive. Recently, the amino acid transporter solute carrier family 39 member 9 [SLC38A9] has been identified as an additional component of the Rag-Ragulator complex. mTORC1 activation was reported to be abolished in SLC38A9 knockout cells, whereas SLC38A9 overexpression caused mTORC1 hyperactivation even during amino acid starvation (Rebsamen et al. 2015; Wang et al. 2015). Furthermore, during starvation, cells can activate amino acid uptake and biosynthesis through the general amino acid control (GAAC) pathway, whereas "excess/stored" cellular constituents are recycled by autophagy. Interestingly, it has been shown that the GAAC pathway couples exogenous amino acid availability with autophagy. Starvation caused the downregulation of mTORC1, which then upregulated autophagy. In parallel, serum/glutamine starvation activated the GAAC pathway, which upregulated amino acid transporters, leading to increased amino acid uptake (Jewell et al. 2013). When intracellular amino acid level is elevated, mTORC1 is reactivated and subsequently suppresses autophagy. Knockdown of activating transcription factor 4, the major transcription factor in the GAAC pathway, or silencing of the leucine transporter SLC7A5, caused impaired mTOR reactivation and much higher levels of autophagy. Thus, the GAAC pathway modulates autophagy by regulating amino acid uptake and mTOR reactivation during serum/glutamine starvation (Chen et al. 2014). Finally, another interesting group of proteins, Sestrin 1, 2, and 3, has been shown to interact with GATOR2 in an amino acid-sensing manner and to negatively regulate mTORC1's localization to the lysosome and, therefore, mTORC1's kinase activity (Chantranupong et al. 2014). These findings have indicated a role for Sestrins in amino acid sensing, mTOR regulation, autophagy, and apoptosis.

In summary, autophagy and apoptosis are interconnected by common stressors, intermediate regulators and a number of organelles, such as mitochondria, endothelial reticulum, and lysosomes. Numerous lines of evidence have demonstrated a direct involvement of lysosomes and late endosomes in amino acid sensing and mTORC1 interactome in autophagy. Thus, understanding the function and interplay between amino acid-sensing-transport-signaling and mTORC1-V-ATPase-SLC38A9 is of great interest and importance not just in fundamental biology but also in treating associated diseases.

Acknowledgments This work was supported by the National Institute of Health (5RO1CA106644 to CAAH), the National Key Basic Research Program of China (2013CB127302 to Z.W. and G.W.), and the Natural Science Foundation of China (31172217, 31272450, and 31272451 to Z.W. and G.W.), the Chinese Universities Scientific Fund (2013RC002), the Program for New Century Excellent Talents in University (NCET-12-0522), and the Program for Beijing Municipal Excellent Talents, the Agriculture and Food Research Initiative Competitive Grant from the USDA National Institute of Food and Agriculture (No. 2014-67015-21770), and Texas A&M AgriLife Research (H-8200).

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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