Autophagy is a key catabolic process for cell survival against different types of stress. During macroautophagy the cell carries out the sequestration of different substrates such as invading pathogens, proteins, lipids, or even damaged or superfluous organelles inside double-membrane vesicles termed autophagosomes. To degrade their cargo, autophagosomes fuse with the lysosome/vacuole, which contains various hydrolases able to break down the sequestered substrates. After this event, the basic components obtained from cargo degradation are released into the cytoplasm for recycling.

Autophagy is triggered by different stimuli such as hypoxia, oxidative stress, pathogen infection, endoplasmic reticulum (ER) stress, and most notably nutrient starvation. Autophagy can be divided into 3 main types: macroautophagy, microautophagy, and chaperone-mediated autophagy. Whereas microautophagy and macroautophagy can be selective or nonselective processes found in yeast and higher eukaryotes, chaperone-mediated autophagy is a selective process that has only been described in mammalian cells. During chaperone-mediated autophagy, specific protein substrates containing the amino acid sequence KFERQ are recognized by chaperones, unfolded and translocated into the lysosome through the lysosomal membrane protein LAMP2A (Figure 1A). In microautophagy uptake also occurs directly at the limiting membrane of the lysosome/vacuole. In this case, however, the process operates by directly sequestering...
the substrates through invagination of the vacuole/lysosome membrane.6 Of the 3 types mentioned, macroautophagy is clearly the most well-studied process (Figure 1B). Multiple autophagy-related (ATG) genes and proteins have been described as being involved in the different stages of autophagy, comprising what is now known as the core autophagy machinery that is required for autophagosome formation, and additional proteins that act in making the process selective, or in stages other than autophagosome biogenesis. Accordingly, macroautophagy (hereafter referred to as autophagy) can be dissected into different steps based on the proteins involved, including induction, nucleation of the autophagosome precursor (termed the phagophore), membrane expansion and maturation of the autophagosome, fusion with the lysosome/vacuole, and recycling of the degraded cargo.

### Autophagy Induction in Yeast

During growth in nutrient-rich conditions autophagy activity is kept to a minimum by different nutrient sensing pathways including those regulated by the target of rapamycin (TOR) kinase and cAMP-dependent protein kinase A. The ability of TOR to sense nutrient levels, in particular amino acids, makes it a critical negative regulator of autophagy. The rapamycin-sensitive TOR complex 1 (TORC1) inhibits autophagy in part by preventing the activation of the Atg1 kinase complex.7 In yeast, the Atg1 kinase complex is formed by the Ser/Thr kinase Atg1, the regulatory subunit protein Atg13, and the Atg17–Atg31–Atg29 complex, which is thought to function as a scaffold.7,8 Although specific substrates of Atg1 may remain to be discovered, the Atg1 kinase complex plays an essential role in autophagy induction by recruiting other Atg proteins to what is known as the phagophore assembly site (PAS), a perivacuolar location found in yeast that is proposed to be the organizing center for phagophore formation.9–12 Upon nutrient starvation or rapamycin treatment TORC1 activity is inhibited and Atg13 is rapidly but partially dephosphorylated leading to the activation of Atg1.13 Autophosphorylation of Atg1 within its activation loop is also important for activating its kinase activity and inducing autophagy (Figure 2A).14 Atg13 dephosphorylation was linked to an increased interaction with Atg1 leading to a model in which starvation increased affinity between the 2 proteins; however, recent data as well as interaction studies in other model organisms support the idea that Atg1 and Atg13 interact independently of nutrient conditions.15 In addition to Atg13, TORC1 may also inhibit autophagy by directly phosphorylating Atg1.16

Protein kinase A is also a negative regulator of autophagy. Protein kinase A suppresses autophagy by phosphorylating both Atg1 and Atg13.17–19 Although the 2 pathways target similar proteins, TOR and protein kinase A seem to work largely independent of one another by targeting different phosphorylation sites.19 Other nutrient-sensing kinases involved in autophagy induction are Snf1 and Gcn2. Although the former corresponds to the yeast homolog of 5′-AMP–activated protein kinase (AMPK), which will be discussed below, Gcn2 promotes autophagy during amino acid starvation by phosphorylating Sui2/eIF2α (suppressor of initiator codon 2). Phosphorylation of Sui2 blocks general protein synthesis and specifically activates

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**Nonstandard Abbreviations and Acronyms**

- **AMPK**: 5′-AMP–activated protein kinase
- **Atg**: autophagy related
- **ER**: endoplasmic reticulum
- **HF**: heart failure
- **HFD**: high-fat diet
- **I/R**: ischemia/reperfusion
- **PAS**: phagophore assembly site
- **PtdIns3K**: phosphatidylinositol 3-kinase
- **PtdIns3P**: phosphatidylinositol 3-phosphate
- **T2DM**: type 2 diabetes mellitus
- **TOR**: target of rapamycin
- **TORC1**: TOR complex 1
- **ULK**: unc-51 like autophagy activating kinase

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**Figure 1. The 3 main types of autophagy.** A. Yeast cells carry out both macroautophagy and microautophagy. Although macroautophagy consists of the bulk degradation of cytoplasmic material that is sequestered inside double-membrane autophagosomes that then fuse with the vacuole, microautophagy works by directly taking up the substrates through invagination of the vacuole. B. In mammals along with microautophagy and macroautophagy, chaperone-mediated autophagy enables the degradation of specific protein substrates that contain a KFERQ motif that is recognized by chaperones that mediate the translocation of the unfolded protein into the lysosome through LAMP2A.
the translation of the transcription factor Gcn4, which in turn induces the transcription of various ATG genes.

**Autophagy Induction in Mammals**

In contrast to yeast, mammalian cells have multiple Atg1 homologs, and the ones most relevant to autophagy are unc-51 like autophagy activating kinase 1 (ULK1) and ULK2.22,23 Thus, in mammals the Atg1 kinase complex is now referred to as the ULK kinase complex and consists of ULK1/2, the mammalian homolog of Atg13 (ATG13), the functional homolog of Atg17 (RB1CC1), and the ATG13-stabilizing protein ATG101, which has no yeast counterpart. All members of the ULK kinase complex are required for autophagy induction in mammalian cells.24–26 As mentioned above, in mammalian cells the interaction between the members of the ULK kinase complex does not depend on nutrient conditions.27 Similar to the yeast Atg1 complex, regulation of the ULK kinase complex depends on the mechanistic target of rapamycin complex 1 (mTORC1). During nutrient-rich conditions, mTORC1 interacts directly with ULK1 through the scaffold protein regulatory associated protein of mTOR, complex 1 (RPTOR) and inhibits its kinase activity by phosphorylating both ATG13 and ULK1/2.25,26 Upon nutrient starvation or rapamycin treatment, mTORC1 is released from the ULK kinase complex leading to the dephosphorylation of both proteins and the activation of ULK kinase activity.25,27,28 Once activated, ULK1 phosphorylates ATG13, RB1CC1, and itself, stabilizing its enzymatic activity and inducing the autophagic process (Figure 2B).25,28,29

Another protein capable of sensing energy levels that is involved in autophagy regulation is AMPK. Through the upstream kinase serine/threonine kinase 11 (STK11/LKB1), AMPK is able to sense decreases in the cellular ATP/AMP ratio leading to its activation and autophagy induction.30 During glucose deprivation AMPK phosphorylates and activates the tuberous sclerosis complex, tuberous sclerosis (TSC) 1-TSC2, which in turn inactivates the GTPase-activating protein Ras homolog enriched in brain (RHEB), leading to mTORC1 inhibition and the release of the ULK kinase complex (Figure 3).31,32 Once mTORC1 leaves the ULK complex, AMPK directly phosphorylates ULK1, stimulating its catalytic activity and inducing autophagy.30 Interestingly, the ULK kinase complex also phosphorylates and inactivates AMPK, members of the complex can interact independently.27

**Figure 2. Autophagy induction.** A, In yeast in nutrient-rich conditions target of rapamycin complex 1 (TORC1) and protein kinase A (PKA) inhibit autophagy by phosphorylating autophagy related (Atg) 1 and Atg13. During starvation the Atg1 kinase complex is no longer repressed, Atg13 is partially dephosphorylated, and Atg1 is activated. Atg1 then phosphorylates itself and other targets to induce autophagy. B, In mammals in nutrient-rich conditions mechanistic TORC1 (mTORC1) directly binds unc-51 like autophagy activating kinase (ULK) 1 through regulatory associated protein of mTOR, complex 1 (RPTOR) and inhibits ULK1/2 and ATG13 by phosphorylation. Upon starvation mTORC1 dissociates from the ULK kinase complex, allowing ATG13 dephosphorylation and activating ULK1/2 that then phosphorylates members of the complex and other targets to induce autophagy.

**Figure 3. Autophagy regulation.** Through serine/threonine kinase 11 (STK11/LKB1), AMPK-activated protein kinase (AMPK) senses decreases in the ATP/AMP ratio and phosphorylates tuberous sclerosis (TSC) 1-TSC2, which then targets Ras homolog enriched in brain (RHEB), leading to mTORC1 inhibition and autophagy activation. insulin receptor/insulin-like growth factor 1 receptor (INSR/IGF1R) triggers the activation of the class I phosphoinositide 3-kinase (PI3K), inducing the formation of phosphatidylinositol(3,4,5)trisphosphate (PIP3) and AKT/PKB activation; AKT can inhibit TSC1-TSC2, blocking autophagy. Phosphatase and tensin homolog (PTEN) works as a PIP3 phosphatase generating phosphatidylinositol(4,5)bisphosphate (PIP2) and inducing autophagy.
through a mechanism that has been described as an inhibitory feedback loop.\textsuperscript{33}

Although functioning in part in a hormone-sensing pathway, AKT/PKB can also regulate autophagy by controlling MTORC1 activation. On ligand binding, dimerization, autophosphorylation, and activation of insulin receptor or insulin-like growth factor 1 receptor, the class I phosphoinositide 3-kinase is recruited to the plasma membrane and activated.\textsuperscript{34} Phosphoinositide 3-kinase catalyzes the phosphorylation of phosphatidylinositol(4,5)bisphosphate generating the lipid second messenger phosphatidylinositol(3,4,5)trisphosphate (PIP\textsubscript{3}), which in turn recruits AKT to the plasma membrane where it is activated via phosphorylation by PDPK1 and MTORC2.\textsuperscript{34,35} AKT-dependent phosphorylation of TSC2 prevents RHEB inhibition, leading to MTORC1 activation and autophagy inhibition.\textsuperscript{36,37} As a consequence, the tumor suppressor and lipid phosphatase and tensin homolog (PTEN) can induce autophagy by dephosphorylating PIP\textsubscript{3} and downregulating the AKT-phosphoinositide 3-kinase pathway (Figure 3).\textsuperscript{38}

**Membrane Nucleation and Source**

Once autophagy is induced, assembly of the phagophore is initiated by membrane nucleation. As mentioned above, in yeast the PAS corresponds to the location at which several Atg proteins are recruited to assemble the phagophore. In contrast, mammalian cells lack a single defined PAS, and autophagosome formation seems to be initiated at different locations inside the cell. In both yeast and mammals the class III phosphatidylinositol 3-kinase (PtdIns3K) catalyzes the nucleation of the phagophore by generating phosphatidylinositol 3-kinase 3-phosphate (PtdIns3P) and inducing the recruitment of PtdIns3P-binding proteins.\textsuperscript{37} In yeast the PtdIns3K is formed by the regulatory subunit vacular protein sorting 15 (Vps15), the catalytic subunit Vps34, Vps30/Atg6, Atg14 and Atg38, all of which are essential for autophagy.\textsuperscript{39–41} Similarly, the core mammalian PtdIns3K is composed of the Vps15 homolog phosphoinositide-3-kinase, regulatory subunit 4 (PIK3R4), the Vps34 homolog phosphatidylinositol 3-kinase, catalytic subunit type 3 (PIK3C3), and the Vps30/Atg6 homolog beclin 1, autophagy related (BECN1).\textsuperscript{37,42} Although these 3 proteins constitute the core machinery of the mammalian PtdIns3K, distinct interactions with specific proteins lead to the formation of ≥3 different PtdIns3K complexes that play different roles in autophagy.\textsuperscript{34–45} One of these complexes is formed by the interaction of the PtdIns3K core complex with the mammalian Atg14 homolog (ATG14) and autophagy/beclin-1 regulator 1 (AMBRA1).\textsuperscript{46,47} The ATG14-containing PtdIns3K complex is thought to positively regulate autophagy by promoting translocation of the complex to the phagophore and inducing the generation of PtdIns3P.\textsuperscript{44,47,48} The other 2 PtdIns3K complexes contain the BECN1-interacting protein UV radiation resistance associated (UVRAG) as a common component. Whereas the PtdIns3K complex formed by UVRAG and SH3-domain GRB2-like endophilin B1 (SH3GLB1/Bif-1) promotes autophagosome formation,\textsuperscript{46,49} the complex formed by UVRAG and KIAA0226/RUBICON downregulates autophagy by impairing autophagosome maturation (Figure 4).\textsuperscript{44,45} Other BECN1-interacting proteins include the antiapoptotic protein B-cell CLL/lymphoma 2 (BCL2), which inhibits the PtdIns3K complex by sequestering BECN1 under

**Figure 4.** Class III phosphatidylinositol 3-kinase (PtdIns3K) complexes. Three class III PtdIns3K complexes can be observed in mammals. All of them require phosphatidylinositol 3-kinase, catalytic subunit type 3 (PIK3C3/VPS34), phosphoinositide-3-kinase, regulatory subunit 4 (PIK3R4/VPS15) and beclin 1, autophagy related (BECN1). Specific subunits regulate the function of the different complexes. Binding of ATG14 and autophagy/beclin-1 regulator 1 (AMBRA1) leads to autophagy induction. UV radiation resistance associated (UVRAG) and SH3-domain GRB2-like endophilin B1 (SH3GLB1) binding also activates autophagy, whereas binding to KIAA0226/RUBICON inhibits autophagosome maturation.

**Figure 5.** Autophagosomes have a diverse range of potential membrane sources. The trans-Golgi network, mitochondria, mitochondrial-associated membrane, and endoplasmic reticulum (ER) have been postulated as membrane donors. Omegasomes have been described as the ER structures that work as a platform for autophagosome formation. The phagophore (shown in red) elongates and engulfs part of a cisternae before it buds off the ER and becomes an autophagosome. MAM indicates mitochondria-associated ER membrane.
nutrient-rich conditions. Besides alterations in protein interactions, BECN1 post-translational modifications also regulate PtdIns3K activity. For example, BECN1 phosphorylation by DAPK promotes dissociation of BCL2 and autophagy induction. ULK1-dependent phosphorylation of BECN1 activates the ATG14- and UVRAG-containing PtdIns3K complexes inducing autophagy during amino acid starvation. Activation of both these PtdIns3K complexes by ULK1-mediated BECN1 phosphorylation would argue for the importance of this post-translational modification for autophagosome induction and later maturation and provides a link between the ULK kinase initiation complex and the membrane nucleation complex. Most recently, AMPK was described as regulating the activity of different PtdIns3K complexes by phosphorylating BECN1 and PIK3C3.

Although membrane nucleation has been established as a key step in the autophagic process, the origin of the membrane that gives rise to the phagophore, and subsequently the autophagosome, remains an open question. Different studies have described the ER, mitochondria, plasma membrane, and trans-Golgi network as possible membrane donors (Figure 5). Evidence supporting the ER as a possible membrane source include 3-dimensional tomography studies showing a connection between the phagophore and ER, as well as ATG14-containing PtdIns3K complex localization to the ER to initiate autophagosome formation. Generation of PtdIns3P at the ER triggers the recruitment of the PtdIns3P-binding protein ZFYVE1/DFCP1 (zinc finger, FYVE domain containing 1) and one of the mammalian homologs of Atg18, WD repeat domain, phosphoinositide interacting 2 (WIP2). Both of these proteins have been linked to autophagosome formation from a PtdIns3P-enriched ER-associated structure termed the omegasome for its Ω-like shape. Omegasomes have been described as platforms for autophagosome formation, which seem to depend on PtdIns3P, because ATG14 depletion leads to omegasome disappearance. Although the role of ZFYVE1 in autophagy is not well defined, WIP2 silencing results in accumulation of omegasome structures and failure to mature into autophagosomes, suggesting that WIP2 is involved in the transition between omegasomes and autophagosomes. Other ATG proteins that have been associated with omegasomes include the ULK kinase complex, which localizes transiently to omegasomes in a PtdIns3P-dependent manner. The precise mechanism by which the ER gives rise to autophagosomes via an omegasome intermediate is unknown, and several questions remain to be answered about the conditions, specific proteins involved, and the selectivity of the process (Figure 5).

As mentioned above, mitochondria are another organelle that have been proposed as a membrane source for the phagophore. During starvation conditions an outer mitochondria membrane fluorescent marker colocalizes with autophagosomes; mitochondrial lipids also seem to transit to autophagosomes. The same study showed that autophagosome formation during nutrient starvation is impaired in cells lacking the ER-mitochondria tethering protein mitofusin 2. Mitochondria-associated ER membrane, which are sites where the mitochondria and ER are in close proximity to each other, have been implicated in autophagosome formation. ATG14 and other autophagy markers localize to the mitochondria-associated ER membrane during starvation conditions. In mitofusin 2-depleted cells, which are unable to tether the ER to the mitochondria, ATG14 localization to the mitochondria-associated ER membrane is impaired. In addition, the omegasome protein marker ZFYVE1 localizes to the mitochondria-associated ER membrane upon starvation. This remarkable finding opens the possibility that the functions of omegasomes and mitochondria in autophagosome formation are essentially one and the same, unified by the association between the 2.

Other studies on the transmembrane protein Atg9 have advanced our understanding of the membrane source from which phagophores are assembled. Atg9 has been characterized as a self-interacting protein containing 6 putative transmembrane domains, with both its carboxyl and amino termini facing the cytosol. In yeast, Atg9 cycles from the PAS to peripheral membranes; Atg9-containing vesicles are thought to be part of the initial membranes that will generate the phagophore. The Atg9-containing membrane reservoir seems to be composed of tubules and vesicle clusters formed through the ER-Golgi trafficking pathway; however, Atg9 also cycles between perimembranous sites and the PAS. Although the precise mechanisms by which Atg9 cycling is controlled remains unknown, several Atg proteins are involved in the regulation of Atg9 movement. Atg9 anterograde transport, which is defined as movement from the peripheral sites to the PAS, depends on Atg11, Atg23, and Atg27, whereas retrograde transport, that is from the PAS to the peripheral sites, is directed by the Atg1–Atg13 complex, Atg2, Atg18, and the PtdIns3K complex. In mammalian cells, nutrient starvation induces ATG9 redistribution from the trans-Golgi network to phagophores. Both ULK1 silencing and PtdIns3K inhibition block ATG9 trafficking to phagophores, suggesting both complexes are involved in mammalian ATG9 cycling. The MAPK pathway is also implicated in mammalian ATG9 traffic, SUPT20H/FAM48A/p38IP (suppressor of Ty 20 homolog [Saccharomyces cerevisiae]) interacts with ATG9 and induces its redistribution leading to autophagy activation. Conversely, binding between SUPT20H and MAPK14/p38α inhibits ATG9 interaction with SUPT20H and autophagy.

**Phagophore Expansion**

Elongation and expansion of the phagophore membrane are key steps in the autophagic process. The Atg12–Atg5–Atg16 and Atg8 conjugation systems, 2 inter-related ubiquitin-like conjugation pathways, regulate this stage in both yeast and mammals. Before being covalently linked to their final substrates, both Atg12 and Atg8 go through an activation and conjugation reaction, triggered by an E1-like and an E2-like enzyme, respectively. In the Atg12–Atg5–Atg16 system, Atg12 is first activated in an ATP-dependent manner by the E1-like activating enzyme Atg7, forming a thioester bond between the 2 proteins. After this event, Atg12 is transferred to the E2-like conjugating enzyme Atg10, generating the Atg12–Atg10 intermediate through the formation of another thioester bond. Finally, Atg12 is covalently attached to a specific lysine residue on Atg5 in a process that, unlike ubiquitination, seems to be constitutive, irreversible and does not require an E3-like
Further interaction between Atg12–Atg5 and Atg16 leads to the formation of the Atg12–Atg5-Atg16 complex. Unlike Atg12, Atg16 is not covalently bound to Atg5 and is able to self-interact when bound to Atg12–Atg5 forming a large multimeric protein complex. The Atg12–Atg5-Atg16 complex is essential for autophagy and localizes to the phagophore. In yeast the second ubiquitin-like conjugation system catalyzes the lipidation of Atg8 by covalently linking it to phosphatidylethanolamine. The first event in this process corresponds to the cleavage of the carboxyl terminus of Atg8 by the cysteine protease Atg4, exposing a glycine residue. In the next step, Atg7, again working as an E1-like enzyme, activates Atg8. The activated protein is then conjugated to the E2-like enzyme Atg3, before finally being linked to phosphatidylethanolamine through an amide bond. Different studies have proposed that the E3-like enzyme that facilitates the Atg8–phosphatidylethanolamine linkage is the Atg12–Atg5-Atg16 complex. In its conjugated form Atg8 is bound to both sides of the autophagosome membrane and thus its N terminus GFP-tagged form is widely used as an autophagosome marker. However, Atg8 lipidation is a reversible process because Atg8–phosphatidylethanolamine bound to the external autophagosome membrane can be cleaved by Atg4, releasing it from the autophagosome (Figure 6).

Both ubiquitin-like conjugation pathways are conserved and work similarly between mammals and yeast with the specific difference being that mammalian cells have several Atg8 homologs further divided into the microtubule-associated protein 1 light chain 3 (MAP1LC3/LC3) and GABA(A) receptor-associated protein (GABARAP) subfamilies. Although all of the homologs go through a similar conjugation process, each subfamily works at different stages of autophagy; the LC3 subfamily is involved in expansion of the phagophore and the GABARAP subfamily participates at a later stage in autophagosome maturation.

Lysosome/Vacuole Fusion and Recycling of the Degraded Cargo

The fusion of autophagosomes with lysosomes/vacuoles results in the generation of autolysosomes in higher eukaryotes and autophagic bodies in yeast. In either case, the fusion process seems to involve similar machinery that plays a role in other transport processes that terminate at these degradative organelles. In yeast, this machinery includes the class C Vps/HOPS complex, the SNARE family proteins Ypt6, Vii1, Van3, and Van7, the small GTPase Ypt7, and the proteins Mon1 and Ccz1. Fewer details are known in mammalian cells; however, the Ypt7 homolog RAB7 is required. One difference between yeast and mammals is that there is a clear convergence between autophagy and the endocytic pathway in the latter; autophagosomes can fuse with endosomes to form amphisomes that subsequently fuse with the lysosome. Once fusion occurs, the inner autophagosomal membrane and its cargo are degraded inside the lysosome/vacuole by various hydrolases. The resulting macromolecules such as amino acids that are obtained after cargo degradation are transported back into the cytoplasm for recycling. In yeast this process is regulated by protein permeases such as Atg22.

Autophagy in the Cardiovascular System

According to the World Health Organization, cardiovascular disease is the leading cause of mortality in the globalized world, accounting for 30% of all deaths. As expected, considerable resources have gone toward understanding the nature of cardiovascular disease and to search for possible therapeutic targets.
Autophagy has been described widely in the cardiovascular system, and our understanding of the molecular machinery as described above provides the possibility for specific therapeutic intervention in treating cardiovascular disease. Autophagic activity is linked to cardiovascular development, preserving heart and vascular homeostasis, as well as in the onset and progression of several cardiovascular diseases. Interestingly, whether autophagy plays a survival role or has a deleterious effect during heart disease it is still a matter of discussion.

**Autophagy and Cardiovascular Development**

Autophagy plays a role in the regulation of mammalian cardiac development starting at an early stage. Morpholino knockdown of atg5, atg7, and becln1 result in abnormal heart structure, including defects in cardiac looping, abnormal chamber morphology, and aberrant valve development in zebrash.

Similarly, Atg5 knockout mice display defects in heart valve development and chamber septation indicating that autophagy regulates cardiac progenitor cell differentiation and is involved in heart development.

**Autophagy in the Genesis of Cardiovascular Diseases**

Several risk factors underlie the genesis and progression of cardiovascular diseases. These factors include age, tobacco, unhealthy diet, insufficient physical activity, excessive weight/obesity, hypertension, diabetes mellitus, and hyperlipidemia/hypercholesterolemia. Hypertension is one of the largest contributors to the worldwide burden of cardiovascular diseases, and its prevalence is close to 30% in the world population. The main mechanisms involved in the regulation of blood pressure are the sympathetic, parasympathetic, renin–angiotensin–aldosterone and antidiuretic hormone systems. Dysregulation of these systems, as well as obesity and diabetes mellitus, is associated with the genesis and development of hypertension. Because most of the peptides and hormones belonging to these systems are capable of regulating autophagy, it is possible to speculate that dysregulation of autophagy could be associated with hypertension, obesity, diabetes mellitus, and end organ damage (Figure 7).

**Sympathetic and Renin–Angiotensin–Aldosterone Systems**

Although there is not a lot of information on the parasympathetic system and autophagy, studies involving the sympathetic system have shown that autophagy protects cells against excessive β-adrenergic stimulation. Regarding the renin–angiotensin–aldosterone system, autophagy is stimulated by angiotensin II via the angiotensin II receptor, type 1 (AGTR1) but diminished via AGTR2 in neonatal rat cardiomyocytes overexpressing AGTR1, AGTR2, or both receptors after adenoviral transduction. Cardiomyocytes derived from a genetic rat model of heart hypertrophy are more susceptible to the development of type 2 diabetes mellitus (T2DM). In this model autophagy plays a protective role by limiting death of β cells. On exposure to a HFD, β-cell–specific Atg7-deficient mice display a decrease in the β cell number and an impairment of glucose tolerance because of a reduction in insulin secretion. In these mice, the lack of autophagy results in a range of defects including impairment in INS secretion and a reduction in glucose tolerance. The connection between autophagy and diabetes is observed not only in situations where the genetic defect is specifically induced as with the atg7 model, because cardiomyocytes from db/db mice that exhibit T2DM have a reduction in autophagy. There is some controversy, however, as to whether autophagy in the diabetic model is beneficial. For example, an increase in autophagy in T2DM mice resulting from a high-fructose diet may cause systemic INS resistance and decreased survival due to pathological myocardial remodeling. Along these lines, cells from human patients with T2DM may display elevated levels of autophagy and increased cell death; however, it is not possible to verify in these cells that autophagy is the cause of cell death.

**Obesity**

Autophagy is upregulated in adipose tissue of obese patients, correlating with the degree of obesity, visceral fat distribution, and adipocyte hypertrophy. Xu et al showed that the autophagosome maturation process is involved in high-fat diet (HFD)–induced and AKT2 knockout–induced cardiac hypertrophy and contractile dysfunction. In the heart, HFD promotes the initiation and accumulation of autophagy, although it disrupts autophagosome maturation probably at the step of autophagosome–lysosome fusion. However, although AKT2 knockout does not affect the initiation of autophagy by HFD, it rescues HFD-induced disruption of the autophagosome maturation process and facilitates the transition from autophagosomes to autolysosomes, indicating a cardioprotective effect of cardiac autophagy in the presence of a HFD.

**Diabetes Mellitus**

On insulin resistance, pancreatic β cells enhance their insulin secretion to compensate for hyperglycemia. However, the progressive diminution of the number of pancreatic β cells, mainly because of apoptosis, and the decrease of their function lead to the development of type 2 diabetes mellitus (T2DM). In this model autophagy plays a protective role by limiting death of β cells. On exposure to a HFD, β-cell–specific Atg7-deficient mice display a decrease in the β cell number and an impairment of glucose tolerance because of a reduction in insulin secretion. In these mice, the lack of autophagy results in a range of defects including impairment in INS secretion and a reduction in glucose tolerance. The connection between autophagy and diabetes is observed not only in situations where the genetic defect is specifically induced as with the atg7 model, because cardiomyocytes from db/db mice that exhibit T2DM have a reduction in autophagy. There is some controversy, however, as to whether autophagy in the diabetic model is beneficial. For example, an increase in autophagy in T2DM mice resulting from a high-fructose diet may cause systemic INS resistance and decreased survival due to pathological myocardial remodeling. Along these lines, cells from human patients with T2DM may display elevated levels of autophagy and increased cell death; however, it is not possible to verify in these cells that autophagy is the cause of cell death.

**Autophagy in Cardiovascular Diseases**

In the heart, isolated cardiomyocytes, vascular epithelial cells, and vascular smooth muscle cells, autophagy is strongly induced by physiological conditions, such as nutrient starvation. In those conditions, autophagy is important for the turnover of organelles and protein aggregate degradation at low basal levels under normal conditions. During conditions of cardiovascular stress, including ischemia/reperfusion (I/R) and HF, among others, autophagy is also activated. However, whether autophagy in these contexts is beneficial or detrimental is not well defined.

**Ischemia/Reperfusion**

During ischemia, autophagy is triggered as an adaptive mechanism providing nutrients and eliminating damaged mitochondria. The selective autophagic removal of dysfunctional...
organelles can be a critical aspect of maintaining cellular homeostasis. For example, damaged mitochondria can result in the production of excess reactive oxygen species that can further harm organelles or cause DNA damage, leading to apoptosis. During mild ischemic stress, autophagy activation depends on AMPK-mediated inhibition of MTOR. Pharmacological inhibition of autophagy increases cardiomyocyte death, indicating that autophagy functions as a pro-survival mechanism. During chronic ischemia, autophagy can inhibit apoptosis and diminish tissue damage. During reperfusion, cardiomyocyte autophagy is upregulated dramatically in rat, rabbit, and swine hearts, and primary neonatal cardiomyocytes. Cardiac autophagy triggered by reperfusion can be either adaptive or detrimental and involves BECN1 activation. In cultured neonatal cardiomyocytes exposed to simulated I/R, inhibition of autophagy with 3-methyladenine enhances cell viability. In contrast, other studies describe protective actions of autophagy in simulated I/R. One possible explanation to these discrepancies is the dual role of BECN1 during I/R. While BECN1 is critical in the initial stage of autophagy induction, excessive amounts of this protein during reperfusion may result in an autophagic imbalance that leads to cell death, providing another example of the dual relationship between autophagy and cardiovascular physiology.

Heart Failure
The initial response of the heart to several stresses is hypertrophy. If the stresses persist, a pathological hypertrophy is developed followed by heart failure, and there is some indication that autophagy plays a role in the progression of structural remodeling that leads to HF in the pressure-overloaded human heart. Cardiomyocyte-specific overexpression of BECN1 amplifies the pathological remodeling response. Conversely, BECN1 haploinsufficiency partially rescues HF. Collectively, these data provide yet another example of autophagy having a maladaptive role in cardiovascular disease. Analysis of human samples has supported additional evidence that autophagic cell death contributes to HF pathogenesis, however, it is important to keep in mind that autophagy is fundamentally a cytoprotective response, and a complete block in this process generally has severe negative consequences. For example, in adult mice acute cardiac-specific ATG5 deficiency leads to cardiomyopathy, consistent with the notion that basal levels of cardiomyocyte autophagy are required for cellular proteostasis. Thus, whether elevated autophagy observed in human failing heart promotes cell death and contributes to the progression of HF, or if it represents an adaptive response of the heart to promote survival remains to be elucidated. Accordingly, with regard to therapeutic intervention, we propose that there is an optimal zone of cardiomyocyte autophagy that may be beneficial, and that treatments resulting in either decreased or elevated levels of autophagy are likely to be deleterious (Figure 8).

Conclusions and Perspectives
As one of the major catabolic pathways in the cell, autophagy has become an important focus of research in a diverse range of biological fields. Autophagy is essential in normal cardiovascular homeostasis. However, alterations in autophagic flux are seen in all forms of cardiovascular diseases. The relationship of autophagy to cardiovascular physiology is complex and can be either beneficial or harmful, depending on the timing and magnitude. Despite all knowledge accumulated to date, a substantial amount of work must be done to clarify the real contribution of autophagy in cardiovascular systems. This knowledge will not only help develop our basic understanding on how and to what end autophagy is activated but may also give rise to potential drug treatment for several diseases. To this end, we must advance our current comprehension of the autophagic pathway and its various modulators. We are optimistic that in the near future pharmacological targeting of autophagy will emerge as a therapeutic alternative to treat cardiovascular diseases.

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None.
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Correction

For the Circulation Research article by Gatica et al (Molecular Mechanisms of Autophagy in the Cardiovascular System. Circ Res. 2015;116:456-467. doi: 10.1161/CIRCRESAHA.114.303788.), it was brought to our attention that a few sections of the text of the article were very similar to passages in a review article simultaneously published elsewhere by some of the same authors. Those passages have now been significantly revised, and this revised version of the article is available at http://circres.ahajournals.org/content/116/3/456.full. The authors apologize for this oversight.