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Review

Regulation of cardiomyocyte autophagy by calcium

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Shaikh S, Troncoso R, Criollo A, Bravo-Sagua R, García L, Morselli E, Cifuentes M, Quest AF, Hill JA, Lavandero S. Regulation of cardiomyocyte autophagy by calcium. *Am J Physiol Endocrinol Metab* 310: E587–E596, 2016. First published February 16, 2016; doi:10.1152/ajpendo.00374.2015.—Calcium signaling plays a crucial role in a multitude of events within the cardiomyocyte, including cell cycle control, growth, apoptosis, and autophagy. With respect to calcium-dependent regulation of autophagy, ion channels and exchangers, receptors, and intracellular mediators play fundamental roles. In this review, we discuss calcium-dependent regulation of cardiomyocyte autophagy, a lysosomal mechanism that is often cytoprotective, serving to defend against disease-related stress and nutrient insufficiency. We also highlight the importance of the subcellular distribution of calcium and related proteins, interorganelle communication, and other key signaling events that govern cardiomyocyte autophagy.

autophagy; heart; calcium; cardiomyocyte; interorganelle communication

AUTOPHAGY (from the Greek words auto, which means "self," and phagein, which means "to eat") is a lysosome-mediated catabolic process of protein degradation, organelle turnover, and recycling of cytoplasmic constituents. To date, we know of three broad categories of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy (38). During macroautophagy, proteins or cytosolic components are sequestered in vesicles called autophagosomes that emerge in the cytoplasm, engulf cytoplasmic material, and ultimately fuse with lysosomes, leading to degradation of their cargo. In microautophagy, proteins are enclosed within vesicles that are generated directly from invagination of the lysosomal membrane. In chaperone-mediated autophagy (CMA), no vesicles are formed; rather, cytosolic proteins are translocated by the heat shock cognate protein 70/heat shock protein-α8 to the lysosomal lumen to be degraded (23, 24, 39). Of these processes, macroautophagy, hereafter termed "autophagy," is the most carefully characterized, and this process specifically in the cardiomyocyte constitutes the main focus of this review.

All cells within our organism, and particularly cardiomyocytes, maintain a "basal level" of autophagy that is required for cellular homeostasis and quality control of essential cellular components (23, 62). In the heart, "induced" autophagy is triggered by changes in environmental cues and cellular stress such as nutrient deprivation, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, or hypoxia. Because autophagy is required as a housekeeping mechanism under basal conditions, it must be strictly regulated; when autophagic flux is excessive or insufficient, depending on the cell type and the duration of the stimulus, it promotes maladaptive events (65). Indeed, excessive induction of autophagy has been associated with pathological cardiac remodeling following chronic ischemia, ischemia-reperfusion injury, and elevated mechanical afterload (40). Its induction, however, is protective when cells are deprived of nutrients (46). Of note, many of these same cellular stress responses involve modulation of cytosolic calcium (Ca^{2+}) levels, raising the prospect of mechanistic links.

The Autophagic Machinery and Its Regulation

Several autophagy-related genes (ATG) participate in the formation of the autophagosome (Fig. 1*A*). The first steps of this process take place at the phagophore assembly site (PAS), which in eukaryotic cells may form at different cellular locations, such as the ER-mitochondria contact points or in specific regions of the plasma membrane (30, 50). At the PAS, a large macromolecular complex is formed to generate the phagophore, the precursor of the autophagosome. This complex comprises the class III phosphoinositide 3-kinase, vacuolar protein sorting (VPS)34, ATG6 [also known as beclin 1

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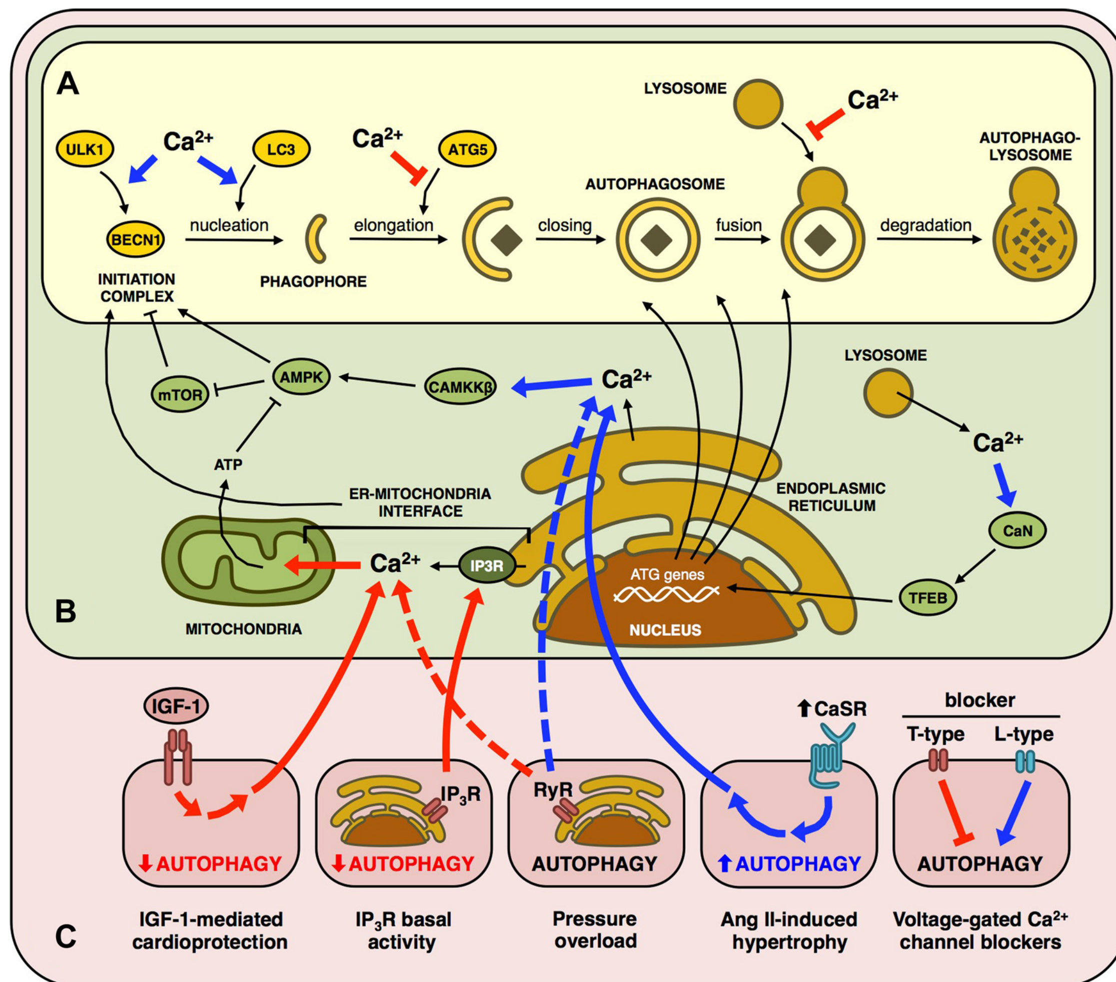

Fig. 1. Ca^{2+}-mediated regulation of autophagy in the heart. *A*: the autophagic process. Autophagy begins with the formation of the initiation complex and nucleation of the phagophore, with both processes being stimulated by Ca^{2+}. Conversely, elongation of the phagophore to form the autophagosome and its fusion with lysosomes is antagonized by Ca^{2+}. Ultimately, autophagy leads to the lysosomal degradation of the autophagosome content. *B*: Ca^{2+}-mediated autophagy regulation. Ca^{2+} from the endoplasmic reticulum (ER) stimulates the Ca^{2+}/calmodulin-dependent protein kinase kinase-β (CaMKK)β/5′-AMP-activated protein kinase (AMPK) pathway, which inhibits mechanistic target of rapamycin (mTOR), thus prompting autophagy initiation. In contrast, Ca^{2+} transfer from ER to mitochondria stimulates ATP production, thereby inhibiting AMPK and preventing autophagy. Interestingly, the ER-mitochondria contact sites have been proposed as the hotspots for phagophore nucleation. Lysosomal-derived Ca^{2+}, on the other hand, stimulates the calcineurin (CaN)/transcription factor EB (TFEB) pathway, leading to the transcription of ATG genes crucial for autophagy. *C*: Ca^{2+}-mediated regulation of autophagy in the heart. Both insulin-like growth factor I (IGF-I) and inositol trisphosphate receptor (IP_3R) signaling in the heart decrease the autophagic flux via increased Ca^{2+} transfer to mitochondria. Increased Ca^{2+}-sensing receptor expression during angiotensin II (Ang II)-induced hypertrophy stimulates autophagy through the CaMKKβ/AMPK pathway. Decreased levels of ryanodine receptor (RyR) expression have been shown to increase or decrease autophagic flux, depending on whether RyR downregulation is global or heart specific. In the case of cardiovascular medication, T-type Ca^{2+} channel blockers have been reported to inhibit autophagy, whereas blockers of L-type Ca^{2+} channels display the opposite effect. ULK1, UNC-51-like autophagy-activating kinase 1; BECN1, beclin 1; LC3, light chain 3.

(BECN1)], ATG14, and VPS15 (p150) (58). BECN1 is crucial to the activation of the lipid kinase VPS34, leading to autophagy induction. Importantly, the BH3 domain of BECN1 can interact with ER-targeted BCL-2 or BCL-XL, which blocks the autophagic pathway. Given that BCL-2 and BCL-XL are antiapoptotic proteins, this step represents a point of cross-talk between autophagy and apoptosis (43, 44). During these first steps of autophagosome formation, the focal adhesion kinase family-interacting protein of 200 kDa (FIP200) interacts with ATG1 [also referred to as UNC-51-like autophagy-activating kinase 1, (ULK1)] and the mammalian ortholog of ATG13 to control induction of autophagy (3, 68).

Early hints of a role for Ca^{2+} emerged from studies where calcium phosphate precipitates were found to induce autophagy (17). The mechanism that regulates calcium phosphate precipitate-induced autophagy relies on the aforementioned autophagic core machinery. Indeed, lack of FIP200, ULK1, and BECN1 inhibits this process (17), suggesting that Ca^{2+} affects the activity of different ATG essential genes involved in autophagosome formation. In addition, when autophagosomes are formed, the concentrations of phosphatidylinositol 3-phosphate (PI3P) and phosphatidylinositol 5-phosphate increase at the PAS, eliciting a signal that promotes recruitment of the autophagic core machinery. Proteins that bind to PI3P include WD repeat protein interacting with phosphoinositides-1 (WIPI-1) (ATG18), which forms punctate structures that can be used to identify the PAS. WIPI-1 responds to the increase in cytosolic Ca^{2+} by localizing to autophagosome membranes, and Ca^{2+} chelation inhibits puncta formation, thus suggesting that Ca^{2+} levels increase at the site where autophagosomes form (26).

Following phagophore formation, the autophagosome membrane elongates in a process that is mediated by two ubiquitination-like reactions. The process is initiated by ATG12 conjugation to ATG5 to generate ATG12-ATG5 conjugates that then interact noncovalently with ATG16L, which in turn oligomerizes to form a large multimeric complex. In the second ubiquitination-like reaction, the microtubule-associated protein 1 light chain 3 (MAP-LC3/ATG8/LC3) is cleaved by proteases of the ATG4 family and is then conjugated to the lipid phosphatidylethanolamine by ATG7 (E1-like) and ATG3 (E2-like), generating the autophagic vesicle-associated form LC3II (76). Interestingly, reducing intracellular Ca^{2+} in glioma H4 cells has been shown to inhibit the cleavage of ATG5 mediated by calpains. This increases the levels of full-length ATG5 and the ATG12-ATG5 conjugate, promotes the accumulation of LC3II, and induces autophagy (74). Additional membrane regions required for autophagosome formation are provided by ATG9, which is transported in vesicles from the plasma membrane to the recycling endosome, where it joins ATG16L to promote autophagosome formation (54).

The newly formed autophagosomes then fuse with lysosomes to degrade the material within the vesicle. The fusion process between the two organelles is mediated by several SNARE-like proteins, including vesicle-associated membrane protein 8, and vesicle transport is facilitated by interaction with the t-SNARE homolog 1B (31). Chronic increases in the cytosolic concentration of Ca^{2+} in hepatocytes inhibit autophagosome-lysosome fusion; however, the molecular mechanism and in particular the ATG proteins involved in this process have not been defined (51). Furthermore, a role for lysosomal Ca^{2+} in autophagy regulation was identified recently (48). In conditions of nutrient deprivation, a classical approach employed to stimulate autophagy, increased lysosomal Ca^{2+} activates the phosphatase calcineurin, which dephosphorylates and activates the transcription factor EB (TFEB), thereby promoting the transcription of ATG and lysosomal genes (48).

Regulation of Autophagy by Calcium

As indicated in the previous section, intracellular Ca^{2+} governs proteins involved in different stages of autophagosome formation (Fig. 1*B*). Furthermore, in the last decade, a number of Ca^{2+}-dependent pathways have been found to be involved in the initiation of the autophagic pathways. Høyer-Hansen et al. (34) showed that free cytosolic Ca^{2+} is a potent inducer of autophagy in mammalian cells. Using MCF-7 breast cancer cells, they reported that the exposure to compounds that mobilize intracellular Ca^{2+} from the ER, such as vitamin D3, ionomycin, and ATP, stimulate autophagy by inhibiting the activity of the mechanistic target of rapamycin (mTOR). They also show that the Ca^{2+}/calmodulin-dependent kinase kinase-β (CaMKKβ) regulates this process, activating the protein AMP-activated protein kinase (AMPK), thereby inhibiting mTOR and promoting autophagosome formation. Interestingly, this signaling pathway is inhibited by BCL-2 localized at the ER in a BECN1-independent manner (34).

Another cellular pathway that involves Ca^{2+} and regulates autophagy is the constitutive inositol 1,4,5-triphosphate receptor ($InsP_3R$)-Ca^{2+} signaling pathway, which has been shown to be active in a range of mammalian cell types (14). $InsP_3R$ localized at the ER is essential to maintain constitutive release of low levels of Ca^{2+}, which is then taken up by mitochondria to support oxidative phosphorylation. Suppression of mitochondrial Ca^{2+} uptake decreases the production of ATP, which represents a bioenergetic deficit signal that activates AMPK, thereby inducing autophagy as a prosurvival response. Interestingly, this pathway is independent of the activity of mTOR because it is induced when the concentration of amino acids in cells is sufficient to maintain mTOR in the activated state (14).

More recently, lysosomal Ca^{2+} has been identified as an additional signaling element that controls starvation-induced autophagy in different cell types via a mTOR-independent mechanism (48). Lysosomal Ca^{2+} release, through the activity of mucolipin 1, a cation channel localized at the lysosomal membrane, regulates the phosphatase calcineurin, which, when active, dephosphorylates TFEB at Ser^{211} and Ser^{142}, thereby promoting its nuclear translocation. Once in the nucleus, TFEB activates a transcriptional program that promotes the autophagic pathway (48).

In conclusion, these studies demonstrate that intracellular Ca^{2+} regulates autophagy. However, whether Ca^{2+} induces or inhibits autophagy is not entirely clear. Indeed, it is likely that Ca^{2+}-dependent induction or inhibition of autophagic flux is dependent on the subcellular distribution of Ca^{2+} and may well be cell type dependent.

Calcium Homeostasis in the Heart

Calcium-handling machinery. Ca^{2+} entry into the cell from the extracellular space occurs via ion channels located within the plasma membrane (Fig. 2), which are gated by agonists, changes in transmembrane potential, or binding of regulatory

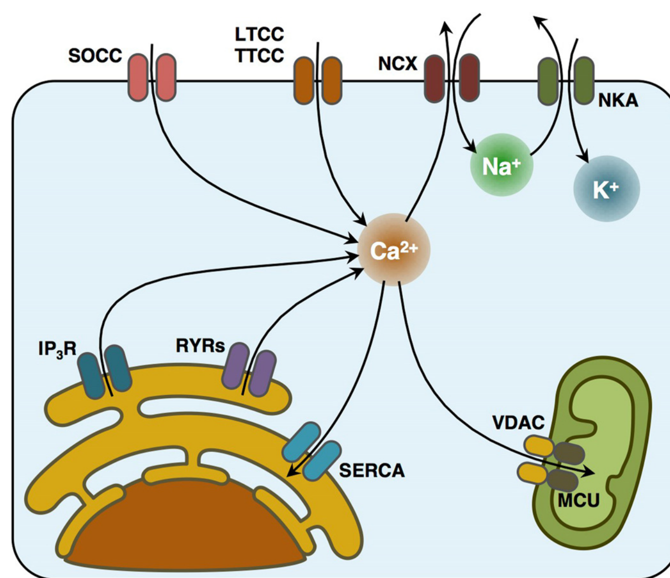

Fig. 2. Ca^{2+}-handling machinery in the heart. From the extracellular milieu, Ca^{2+} enters into the cytoplasm through voltage-gated (LTCC, TTCC) or store-operated Ca^{2+} channels (SOCC). Ca^{2+} is eliminated from cells via Na^+/Ca^{2+} exchange (NCX), which is possible thanks to the potent Na^+ gradient maintained by the Na^+/K^+ ATPase (NKA). Once in the cytoplasm, Ca^{2+} enters mitochondria through voltage-dependent anion channels (VDAC) and mitochondrial Ca^{2+} uniporter (MCU) in the outer mitochondrial membrane and inner mitochondrial membrane, respectively. Sarcoplasmic/ER calcium ATPase (SERCA) at the ER surface pumps Ca^{2+} into the ER lumen, which can be released later back into the cytoplasm via IP_3R and RyR Ca^{2+} channels.

proteins. Given the electrical excitability of cardiomyocytes, the most prominent mechanism governing transmembrane ion flux involves voltage-sensitive L- and T-type Ca^{2+} channels (32). A parallel pathway for Ca^{2+} transport into cells is store-operated Ca^{2+} entry (SOCE), a mechanism activated upon depletion of sarcoplasmic reticulum (SR) Ca^{2+} stores. This event leads to activation of the SR-membrane protein stromal interaction molecule-1, which interacts with and activates Ca^{2+} release-activated Ca^{2+} modulator 1 and transient receptor potential channels in the plasma membrane (15, 37, 57). Activation of these channels leads to Ca^{2+} elevations in the proximity of the SR stores, thus allowing for their direct replenishment (15, 57). Ca^{2+} extrusion occurs via the Na^+/Ca^{2+} exchanger (NCX), which couples Ca^{2+} removal from the cytoplasm with Na^+ entry. In this case, ion exchange is tightly linked with Na^+ export and K^+ import via the Na^+/K^+ ATPase (75).

Ca^{2+} elevations in the cytoplasm trigger activation of ryanodine receptors (RyR), which release more Ca^{2+} into the cytoplasm from SR stores. This Ca^{2+}-induced Ca^{2+} release links Ca^{2+} entry due to electrical excitation with changes in intracellular Ca^{2+} that culminates in sarcomere activation and cellular contraction (8, 25). In the heart, the major Ca^{2+}-gated Ca^{2+} release channel participating in excitation-contraction coupling is RyR2 (25). The second most important SR resident channel is the $InsP_3R$. These ligand-gated channels release Ca^{2+} upon the binding of $InsP_3$, which is produced in response to extracellular signals. RyR2 abundance is greater than that of the $InsP_3R$ such that $InsP_3$-induced Ca^{2+} release in cardiomyocytes is dwarfed by RyR2-mediated Ca^{2+} waves. Therefore, the $InsP_3R$ signal is relatively localized, involved mostly in the control of local Ca^{2+} signals (45). Nevertheless, the $InsP_3R$ is a key element governing $[Ca^{2+}]_i$ maintenance (53), as well baseline autophagy (14), in both neonatal and adult cardiomyocytes.

To counterbalance Ca^{2+} release, Ca^{2+} is continuously pumped back into the SR by the sarcoendoplasmic reticulum Ca^{2+} ATPase (SERCA) (28). SERCA is regulated by phospholamban, a member of the FXYD family of integral membrane proteins (18). Monomeric phospholamban binds and inhibits SERCA. By contrast, in its pentameric form, phospholamban is released from SERCA into an inactive pool in the SR membrane (18). Both cAMP-dependent protein kinase A and Ca^{2+}/calmodulin-dependent protein kinase mediate phospholamban phosphorylation, which leads to increased Ca^{2+} leak from the SR (5, 7). Phospholamban also regulates NCX and Na^+/K^+ ATPase at the plasma membrane (19).

Because of their negatively charged interior, mitochondria are also important regulators of Ca^{2+} homeostasis that import the cation into their matrices (11). Thus, mitochondria are important local Ca^{2+} buffers that, together with the other mechanisms mentioned in this section, define the nature of Ca^{2+} signals within the cell. Moreover, in cardiac muscle, mitochondria are strategically positioned within the intracellular space to provide ATP and regulate Ca^{2+} signals in the vicinity of SR cisternae (22). The interface between SR and mitochondria, termed mitochondria-associated membranes, provides appropriate compartmentalization for the fine-tuning of mitochondrial function. This communication must be tightly regulated, as disruption of organelle proximity has been associated with insulin resistance during cardiac hypertrophy (29), whereas exacerbated SR-to-mitochondria Ca^{2+} transfer has been reported to mediate cell death during hypoxia-reoxygenation injury (42).

In addition to the SR and mitochondria, the plasma membrane also provides sites for localized Ca^{2+} signaling in conjunction with other compartments. As mentioned previously, SOCE relies on contact sites between the plasma membrane and SR to channel Ca^{2+} into the SR lumen. On the other hand, we have shown that invaginations of the cardiomyocyte plasma membrane in close proximity with the nuclear envelope allow for rapid increases in nuclear Ca^{2+} from extracellular stores independent of cytosolic signaling (35).

Calcium-regulated processes in the heart. Calcium homeostasis in cardiomyocytes is characterized by continuous waves of intracellular Ca^{2+} traversing the cytoplasm every second, thereby enabling muscle contraction regulated by synchronous RyR opening (4). Given this unrelenting activity, cardiomyocytes rely on mitochondria for continuous ATP production. Accordingly, elevations of cytoplasmic Ca^{2+} lead to Ca^{2+} uptake into the mitochondrial matrix, where it stimulates ATP production (21, 47). Persistently elevated afterload promotes a Ca^{2+}-dependent signaling response termed cardiac hypertrophy, which remodels a wide range of cardiomyocyte features, including cellular architecture, metabolic profiles, electrophysiological characteristics, and more (33). This condition may render cardiomyocytes more susceptible to damage elicited by pathological situations such as ischemia-reperfusion injury or diabetes. In both of these latter conditions, excessive amounts of Ca^{2+} enter mitochondria, leading to Ca^{2+} overload and oxidative stress. Both factors contribute to mitochondrial dysfunction and loss of mitochondrial integrity, ultimately leading to the collapse of energy supply, apoptotic cell death, and necrosis (1, 33).

Calcium-Mediated Autophagy Regulation in Heart

Calcium-sensing receptor. In an attempt to unravel the cell signaling mechanisms and mediators involved in the development of cardiac hypertrophy, a recent study proposed a role for the calcium-sensing receptor (CaSR) (71). This seven-transmembrane G protein-coupled receptor localizes to the plasma membrane in a number of cell types, where it has been ascribed many roles since its discovery in 1993 (13). The $InsP_3$-induced release of ER Ca^{2+} and subsequent increases in the levels of the cation in the cytosol are among the signaling events triggered by the activation of this receptor. The CaSR protein is functionally expressed in cardiomyocytes (67, 72), and its expression is upregulated in an angiotensin II-induced cardiac hypertrophy model (71). Moreover, CaSR activation induces cardiac hypertrophy via an increase in intracellular Ca^{2+} concentration and calcineurin protein content, whereas a calcineurin inhibitor blunts the effects of CaSR activation (71). More recently, it was shown that the abundance of CaSR increases in rat hearts in the setting of severe transverse aortic constriction-induced ventricular hypertrophy (41). In addition, this state was marked by an increase in autophagic flux, as evidenced by ultrastructural analysis, increased BECN1 expression, and LC3II processing, as well as decreased p62 protein levels (41). Exposure to a CaSR inhibitor ameliorated these changes (41). And these in vivo data were complemented by results obtained in an in vitro hypertrophy model using neonatal rat cardiomy-

ocytes. There, the authors confirmed that hypertrophy was associated with elevated CaSR levels. Furthermore, CaSR activation enhanced cardiac hypertrophy and autophagy (41). Regarding the signaling pathways involved, CaSR activation led to increases in p-CaMKKβ and p-AMPK, whereas p-mTOR was decreased, changes that were reverted by the CaSR inhibitor (41).

IGF-I. IGF-I plays a central role in the regulation of cell survival, proliferation, differentiation, and metabolism (69). IGF-I activates the Akt/mTOR signaling pathway, a key regulator of autophagy (9, 36, 69). IGF-I inhibits autophagy in osteocarcinoma cells (27), vascular cells from patients with atherosclerotic lesions (36), mammary epithelial cells (64), fibroblasts (9), and cardiomyocytes (69). Moreover, in mice with reduced levels of IGF-I, increased levels of autophagy are observed in several tissues (9). By contrast, IGF-I induces autophagy in H9c2 cell lines (2) and Purkinje neurons (6).

In cardiomyocytes, autophagy is enhanced under conditions of nutrient deprivation. Glucose starvation decreases intracellular ATP and oxygen consumption, leading to AMPK activation. Short-term treatment with IGF-I is cardioprotective against nutrient deprivation-induced stress and cell death (69). In this regard, IGF-I diminished glucose deprivation-induced autophagy by increasing ATP levels and promoting mitochondrial metabolism via mechanisms involving enhanced mitochondrial Ca^{2+} uptake and oxygen consumption, activation of the Akt/mTOR signaling pathway, and reduced AMPK signaling (69).

$InsP_3$. $InsP_3$ is a second messenger produced by hydrolysis of phosphatidylinositol 4,5-bisphosphate by phospholipase C (66). The concentration of $InsP_3$ can increase ≥10-fold in cells upon $InsP_3R$ activation (10). $InsP_3R$ activation leads to Ca^{2+} release through the opening of a tetrameric $InsP_3R$ ion channel (20, 61). Three different $InsP_3R$ isoforms, $InsP_3R$-I, IP_3R-II, and IP_3R-III, have been described, where IP_3R-II represents the major isoform expressed in cardiomyocytes (56). Although many signaling pathways are activated after ER-Ca^{2+} release induced by $InsP_3$, basal $InsP_3$ has been shown to be necessary to regulate cellular homeostasis (59). Basal $InsP_3$ concentrations are regulated indirectly by the inositol monophosphatase cycle, where the IMPase catalyzes the hydrolysis of inositol monophosphate to generate free inositol, which is then utilized for resynthesis of an array of phosphoinositides (60). IMPase inhibitors such as L,690,330 and lithium decrease basal intracellular levels of free inositol and reduce IP_3 levels. Studies have shown that L,690,330 and lithium stimulate autophagy in different cell types, and these data correlate with decreased levels of IP_3 and IP_3R-dependent Ca^{2+} leak (14, 16). Furthermore, additional studies in primary neonatal cardiomyocytes have shown that treatment with the IP_3R antagonist 2-aminoethoxydiphenyl borate upregulates autophagic flux (73). These data are consistent with those showing that reduced basal concentrations of $InsP_3$ induced by overexpression of Ins 1,4,5P_3-5-phosphatase trigger autophagy in cardiomyocytes (73). In addition, as described previously in HeLa cells, $InsP_3R$ acts as a scaffolding protein that sequesters BECN1 through its ligand-binding domain (LBD) (16, 70). In fact, overexpression of GFP-IP_3R-LBD inhibits autophagy by interaction with BECN1 (73). Together these studies reveal that $InsP_3$ and the $InsP_3R$ act as inhibitors of autophagy in cardiomyocytes, an observation that is suggestive of a potential role in cardiovascular disease.

Ryanodine receptor. Increases in cytosolic Ca^{2+} activate RyRs, which then release more Ca^{2+} to the cytoplasm from the SR. RyR type 2 contributes to myocardial contractile function, and impairment of its activity promotes cardiac failure (77). When subjected to a 3-wk period of pressure overload, hearts from mice with reduced expression of RyR2 in all tissues ($RyR2^{+/-}$) show signs of hypertrophy, fibrosis, and decreased autophagy compared with wild-type mice (77). Interestingly, cytosolic release of Ca^{2+} from the SR was impaired in primary cardiomyocytes from these mice, suggesting that the altered Ca^{2+} release might be associated with the dysregulation of autophagy. This hypothesis was corroborated in a study by Bround et al. (12), who showed that in vivo depletion of cardiac RyR2 alters Ca^{2+} mitochondrial fluxes and autophagy. In contrast to the study by Zou et al. (77), they observed increased autophagy evidenced by increased levels of LC3II (12). The discrepancy between these results might be explained by the different models used (total body vs. cardiomyocyte-restricted protein downregulation). Nevertheless, additional in-depth studies of autophagic flux are required to fully define the effect(s) of RyR2 dysregulation on autophagy. Interestingly, RyR2 is degraded by chaperone-mediated autophagy under conditions of oxidative stress (52), suggesting that different forms of autophagy are associated with the RyR2 function and turnover.

Voltage-gated calcium channel blockers. Recently, Pushparaj et al. (55) showed that voltage-gated calcium channel blockers lead to dysregulated autophagy in cardiomyocytes. These channels are targeted regularly for therapeutic benefit in a range of cardiovascular disorders. The L-type channel blocker nifedipine and its congeners act as an arterial vasodilator and are widely used as antihypertensive and antianginal agents (63). Nifedipine induces activation of autophagy by increasing the lipidation of LC3, decreasing the levels of polyubiquitin-binding protein p62/SQSTM1 and ubiquitinated protein aggregates followed by increased cell death (55). However, interestingly, mibefradil, a T-type channel blocker, displays antiarrhythmic properties (49) in cardiomyocytes associated with reduced autophagy and cell death, raising the prospect of using this agent for cardioprotective activity in hypertrophy or postmyocardial infarction remodeling (55).

Summary and Perspective

Recent work has uncovered a variety of mechanisms whereby intracellular $[Ca^{2+}]_i$ regulates cardiomyocyte autophagy (Fig. 1*C*). Ca^{2+} homeostasis is involved in stress-induced autophagy in various cell types, and there are several reports of Ca^{2+}-dependent regulation of autophagy in cardiomyocytes. Autophagy is known to be an essential process for modulating ischemia-reperfusion injury, pathological ventricular remodeling, and heart failure. Nevertheless, different models exist regarding the underlying mechanisms and roles of cardiomyocyte autophagy. Autophagy is a predominantly protective mechanism against disease-related stress, but dysfunctional or impaired autophagy may contribute to the morbidity and mortality associated with cardiovascular diseases. Precisely fine-tuned Ca^{2+} signaling is likely to be essential for controlling the intricate autophagic machinery. Therapies that

target autophagy are emerging as promising new avenues for the treatment of diseases (39). Thus, precise elucidation of Ca^{2+}-dependent control mechanisms is important and may emerge with clinical implications.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of our institutions.

AUTHOR CONTRIBUTIONS

S.S., R.T., R.B.-S., and S.L. prepared figures; S.S., R.T., A.C., R.B.-S., E.M., L.G., A.F.G.Q., M.C., J.A.H., and S.L. drafted manuscript; S.S., R.T., A.C., E.M., L.G., A.F.G.Q., M.C., J.A.H., and S.L. edited and revised manuscript; S.S., R.T., A.C., R.B.-S., E.M., L.G., A.F.G.Q., M.C., J.A.H., and S.L. approved final version of manuscript; E.M., L.G., M.C., J.A.H., and S.L. conception and design of research.

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