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Chronic heart failure: Ca^{2+}, catabolism, and catastrophic cell death

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Abstract

Robust successes have been achieved in recent years in conquering the acutely lethal manifestations of heart disease. Many patients who previously would have died now survive to enjoy happy and productive lives. Nevertheless, the devastating impact of heart disease continues unabated, as the spectrum of disease has evolved with new manifestations. In light of this ever-evolving challenge, insights that culminate in novel therapeutic targets are urgently needed. Here, we review fundamental mechanisms of heart failure, both with reduced (HFrEF) and preserved (HFpEF) ejection fraction. We discuss pathways that regulate cardiomyocyte remodeling and turnover, focusing on Ca^{2+} signaling, autophagy, and apoptosis. In particular, we highlight recent insights pointing to novel connections among these events. We also explore mechanisms whereby potential therapeutic approaches targeting these processes may improve morbidity and mortality in the devastating syndrome of heart failure.

Keywords

Heart failure; Remodeling; Calcium homeostasis; Autophagy; Apoptosis

1. Introduction

Age-adjusted mortality from cardiovascular disease has declined a remarkable 75% over the past 50 years [1]. As a result, many individuals, who previously would have succumbed to heart disease now survive to enjoy happy and productive lives. However, many live with a heart that has been injured. This fact, coupled with deterioration in lifestyle-related issues and the pandemic of obesity, has culminated in dramatic increases in the prevalence of heart failure (HF). By 2030, more than 40% of the US population is projected to suffer from HF

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or other cardiovascular disease, with estimated costs, direct plus indirect, exceeding $1 trillion [2].

HF is a syndrome that arises from multiple diseases. Myocardial infarction, hypertension, valvular disease, genetic disorders, and many more funnel ultimately into a state in which the heart is no longer able to pump blood adequately to meet the metabolic demands of the body. HF is categorized based on the mechanism of pump dysfunction: diminished ability to contract forcefully during systole to pump blood forward is typically marked by a reduced ejection fraction (HFrEF). In up to half of cases of HF, ejection fraction is preserved (HFpEF) and the major limitation in performance lies in restricted filling during diastole.

Acute HF by definition is the sudden occurrence of signs or symptoms of congestion and diminished forward flow (e.g. extremity swelling, paroxysmal nocturnal dyspnea, breathlessness) requiring medical attention [3,4]. However, if the heart is persistently unable to deliver adequate circulation to the body, then the condition is categorized as chronic HF [4,5]. Aside from differences in presentation, acute and chronic HF have distinct and very significant impact on our healthcare system [6,7]. Central to each of these syndromes is pathological remodeling of the myocardium [8].

Another major mechanism central to both HFrEF and HFpEF is altered excitation–contraction (EC) coupling. This altered EC coupling derives, in part, from changes in the architecture of the cell membrane, altered expression and function of Ca^{2+}-handling proteins, and mal-adaptive redistribution of intracellular Ca^{2+}. Importantly, remodeling entails numerous other changes, including a wide range of transcriptional, signaling, metabolic, and electrophysiological events. Finally, myocyte death is a critical part of many forms of HF.

Mechanisms of HF pathogenesis have been extensively reviewed [9–11] and are summarized (Table 1). Here, we focus on Ca^{2+} dysfunction and its relation with autophagy and apoptosis within failing cardiomyocytes.

2. EC coupling and HF

In order to accomplish fast and powerful muscle contraction, both cardiac and skeletal muscle have evolved a complex membrane architecture to facilitate EC coupling. Electrical depolarization of the myocyte membrane travels rapidly toward the center of the cell via membrane invaginations termed the transverse tubular (t-tubule) network. T-tubules dive into the cell, terminating close to the sarcoplasmic reticulum (SR) to form structures, termed dyads, which are situated at the Z-line regions of the sarcomere. Within the dyad, the t-tubule pit is separated from the SR by a 12 nm gap, a short distance which facilitates rapid diffusion of Ca^{2+} from the extracellular space to the SR [12]. Membrane depolarization within the t-tubule triggers Ca^{2+} entry mainly through L-type Ca^{2+} channels (LTCC), eliciting Ca^{2+}-induced calcium release (CICR) from the SR through the type 2 ryanodine receptor (RyR2). Ca^{2+} pouring onto the sarcomere relieves actin from troponin C-dependent inhibition, activating cross-bridge cycling and myocyte contraction. Subsequently, Ca^{2+} is pumped back into the SR by the SR Ca^{2+} ATPase 2a (SERCA2a) [13]. It is generally accepted that alterations in Ca^{2+}-handling proteins, coupled with remodeling of the t-tubule

architecture, contribute to HF pathogenesis, promoting impaired contraction and reductions in cardiac output (Fig. 1).

2.1. Ca^{2+} homeostasis

A hallmark of failing cardiomyocytes is altered EC-coupling, including reduced Ca^{2+} transients (Ca^{2+} released from SR stores during excitation), as well as delayed onset and decay of those transients. Together, these changes culminate in reduced force of contraction, delayed onset of contraction, and slowed relaxation [14]. In addition, spontaneous Ca^{2+} release events, normally rare, occur more frequently [13]. Alterations in Ca^{2+} handling have been ascribed to impaired function of the RyR2, SERCA2a, Na^{+}–Ca^{2+} exchanger (NCX), and transient receptor potential cation (TRPC) channels (Fig. 2).

2.1.1. RyR2—Multiple lines of evidence point to relative redistribution of intracellular Ca^{2+} from SR stores to the cytosol in HF caused by impaired RyR2/SERCA2a function. This redistribution reduces the electrochemical gradient for Ca^{2+}, reduces the amplitude of systolic Ca^{2+} levels, slows contraction kinetics (promoting systolic dysfunction), and elevates resting Ca^{2+} (promoting diastolic dysfunction).

It is generally accepted that HF is characterized by an increase in Ca^{2+} leak from the SR via RyR2, but there exists controversy regarding molecular mechanisms underlying this leak. Numerous factors modulate RyR2 function (reviewed in [15]), such as cytosolic and SR Ca^{2+}, ATP, and Mg^{2+} concentrations. In addition, a number of signaling pathways govern RyR2 function. Some evidence points to PKA-dependent hyperphosphorylation of RyR2 (at S2808) in the context of the chronic hyperadrenergic activation typical of HF, provoking FKBP12.6 (aka calstabin 2) dissociation from the channel [16]. Dissociation of FKBP12.6 from RyR2, in turn, increases SR Ca^{2+} leak, which consequently depletes SR Ca^{2+} stores partially and diminishes Ca^{2+} transients after membrane depolarization. These events likely contribute to reduced contractibility in failing hearts. More recently, this Ca^{2+} leak has been associated with mitochondrial Ca^{2+} overload and dysfunction [17]. Some evidence suggests that stabilization of RyR2-FKBP12.6 with small molecules (“rycals”, S107) protects against post-myocardial infarction HF and reduces arrhythmias in mouse models of Duchenne muscular dystrophy and catecholaminergic polymorphic ventricular tachycardia [18]. A small molecule “rycal” (ARM136) is presently in phase 2 trials for HF and for catecholaminergic polymorphic ventricular tachycardia. Also, adenovirus-mediated over-expression of S100A1, a regulator of both RyR2 and SERCA2, improves heart function in rodent and swine models of HF [19,20].

On the other hand, some data suggest that PKA phosphorylation of RyR2 (S2808) is not a major mechanism in cardiac failure [13,21–23]. Some work has suggested that FKBP12.6 does not modify RyR2 gating properties and that PKA phosphorylation of RyR2 does not displace FKBP12.6 (reviewed in [13,22]). RyR2 can be phosphorylated by CaMKII, rather than by PKA, at a different site. Additional mechanisms including direct RyR2 oxidation, reduced calmodulin binding to RyR2, and reduced S100A1 have been described [13]. In any case, controversy persists, as counter-arguments have been marshaled supporting PKA-induced phosphorylation of RyR2 in HF [18].

Regardless of the specific molecular events leading to SR Ca^{2+} leak, it is generally accepted that RyR2-mediated Ca^{2+} leak induces: 1) Ca^{2+} redistribution from SR to cytosol, reducing the electrochemical gradient and diminishing systolic contractile performance; 2) an increase in basal, cytosolic Ca^{2+} concentration impairing diastolic function; 3) spontaneous Ca^{2+} release events ("sparks"); 4) membrane depolarization through the forward mode of NCX (Ca^{2+} out/Na^{+} in), triggering delayed afterdepolarizations; and 5) excessive energy consumption to restore Ca^{2+} gradients.

2.1.2. SERCA—SERCA2a drives ATP-dependent re-uptake of Ca^{2+} into the SR following mechanical contraction. In some species, e.g. mouse and rat, SERCA2a activity accounts for ≈93% of Ca^{2+} removal from the cytosol [13]. In other species, e.g. human and rabbit, it represents closer to 74% of Ca^{2+} removal, with a relatively greater proportion of Ca^{2+} extrusion occurring to the extracellular space via NCX [13].

SERCA is negatively regulated by several small proteins, including phospholamban (PLB) [24] and sarcolipin [25]. In response to adrenergic drive, PLB is phosphorylated by PKA, releasing SERCA from PLB-mediated inhibition. Similarly, CaMKII can phosphorylate PLB and suppress its inhibitory actions on SERCA [26]. PLB dephosphorylation is mediated by protein phosphatase 1 [27].

Multiple lines of evidence demonstrate that SERCA function is reduced in HF due to reduced expression [28] and/or hypophosphorylation of PLB [29]. Reduced SERCA activity plus increased SR Ca^{2+} leak synergize to promote systolic and diastolic dysfunction. Supporting this model, cardiomyocyte-restricted silencing of SERCA2a triggers HF [30]. Conversely, SERCA2a over-expression improves myocardial contractility in both human and animal models of HF [31,32]. Recently, a small phase 2 clinical trial (CUPID1) demonstrated beneficial effects of SERCA2a over-expression in patients with NYHA class III/IV HF [33]. Improvements in several parameters were noted, including NYHA functional class, 6-min walk test, peak maximum oxygen consumption, and left ventricular end-systolic volume [33], improvements which persisted at 3 years [34]. However, recently released findings from a phase 2b trial, CUPID2 (ClinicalTrials.gov. Identifier: NCT01643330) [35] showed no improvement in clinical endpoints in patients with HF (http://ir.celladon.net/releasedetail.cfm?ReleaseID=908592). Additional trials are underway testing the effects of SERCA over-expression delivered via intracoronary infusion (ClinicalTrials.gov. Identifier: Phase 2 NCT01966887, NCT00534703, NCT02346422). A possible explanation for failure in the most recent SERCA trial is the complexity of fine-tuning Ca^{2+} cycling in HF; derangement in cardiomyocyte t-tubule ultrastructure coupled with alterations in Ca^{2+}-handling proteins make it challenging to normalize EC coupling in failing hearts.

2.1.3. NCX—NCX is a bidirectional, electrogenic cation cotransporter that exchanges a single Ca^{2+} ion for three Na^{+} ions. As such, each cycle of NCX action generates a current (net transfer of one positive charge). NCX function is governed by the transmembrane gradients of both $Na^{+}$and Ca^{2+} and by transmembrane potential. NCX can operate in forward mode (Ca^{2+} efflux) or reverse mode (Ca^{2+} influx) [36]. During depolarization, increases in intracellular Na^{+} mediated by voltage-dependent Na^{+} channels lessen NCX-dependent Ca^{2+} extrusion; in extreme circumstances, it can lead to reverse-mode NCX

activity, where NCX pumps Ca^{2+} into the cell. As a result of this mechanism, the junctional cleft is primed with Ca^{2+}, facilitating EC-coupling. During diastole, cytosolic Ca^{2+} increases from RyR2 activation promote Ca^{2+} extrusion through NCX activity [37].

It has been proposed that NCX activity is up-regulated in failing heart [38], but divergent evidence also exists [37]. SR Ca^{2+} leak increases cytosolic Ca^{2+} and forward mode-dependent Ca^{2+} extrusion, exacerbating declines in SR Ca^{2+} and promoting Na^{+} entry [13]. In addition, due to reduced Na^{+}/K^{+} ATPase, and possibly increased TRPC channel function in failing hearts [37,39], cytosolic Na^{+} concentrations are elevated. Na^{+} accumulation diminishes the transmembrane Na^{+} gradient, suppressing NCX-dependent Ca^{2+} extrusion. This can culminate in arrhythmia or even cell death due to Ca^{2+} overload.

The dual function of NCX (forward and reverse) makes it difficult to target this mechanism pharmacologically for HF treatment. Moreover, lack of selectivity of several NCX blockers, such as KB-R7943 (targeting also RyR1/2 and TRP channels) [40,41], renders clinical translation challenging.

Targeting Na^{+} overload might be an effective treatment to prevent NCX-mediated Ca^{2+} overload and alterations in cellular excitability. Na^{+}/K^{+} ATPase over-expression has been reported to reduce cardiac remodeling after pressure overload [42]. Similarly, inhibition of the late Na^{+} current using ranolazine improves some hemodynamic parameters, although improvement in relaxation was not observed in patients with HFpEF [43]. Recently, increased late Na^{+} current has been reported to induce diastolic arrhythmogenesis mediated by CaMKII-dependent SR Ca^{2+} leak, and inhibition of late Na^{+} current blunted arrhythmias in failing human cardiomyocytes [44].

2.1.4. TRPC channels—TRPC channels participate in store-operated Ca^{2+} entry (SOCE), serving to refill depleted SR Ca^{2+} stores. TRPC channel expression increases during pathological hypertrophy and HF [39], possibly as an adaptive mechanism to compensate for SR Ca^{2+} leak and consequent store depletion. TRPC channels conduct Ca^{2+} and Na^{+} [45], and their activation can contribute to Ca^{2+} and Na^{+} overload in failing cardiomyocytes. Inhibition of TRPC subfamilies represses both pressure overload- and angiotensin II-induced cardiac hypertrophy [46]. Furthermore, TRPC channels are implicated in ventricular pathological remodeling and increases in RyR2 leak [47]. Moreover, increased TRPC3 expression increases ischemia/reperfusion (I/R)-induced apoptosis [48], and reduction in TRPV1 levels following cold exposure is associated with cardiac hypertrophy and reduced cardiac function [49]. Together, these lines of evidence suggest that TRPC channels play a deleterious role in HF.

2.2. T-tubule network

Intricately organized dyads along the myocyte promote coordinated Ca^{2+} release responses and synchronous activation of the sarcomeres. In addition, numerous signaling proteins reside within the t-tubules, facilitating localized signaling. Thus, these structures play a vital role in orchestrating cardiomyocyte function. Ca^{2+} entry through LTCC increases the local Ca^{2+} concentration at the dyad, promoting RyR2-dependent Ca^{2+}-induced Ca^{2+} release. HF-associated disruption in dyad organization can have a negative impact on cardiac

performance due to heterogeneous Ca^{2+} gradients and delayed responses. Indeed, HF is marked by distorted organization of the t-tubule network, a decrease in both transverse and longitudinal elements, and increased t-tubule diameter (reviewed in [12,14]). Whereas most work in this area has centered on ventricular myocytes, alterations in t-tubule organization in atrial cardiomyocytes have been described [50].

Recently, it has been proposed that t-tubule network remodeling is a progressive process that commences early and contributes to HF pathogenesis [51]. Distortions of the t-tubule network are associated with alterations in both electrical activity and Ca^{2+} release. Recently, simultaneous recording of action potentials and Ca^{2+} transients by random access multiphoton microscopy demonstrated impaired action potential propagation, along with delayed and reduced Ca^{2+} rises, in adult cardiomyocytes isolated from failing hearts [52]. Moreover, an increase in sparks and spontaneous action potentials was observed [52].

As mentioned previously, cardiomyocytes from failing hearts are marked by reduced contractile force and prolonged relaxation times [53]. Exposure to formamide, an experimental means of detubulating adult cardiomyocytes, elicits reduced force generation with slower kinetics of contraction/relaxation, a process which can be reversed by RyR2-sensitizing agonists [54]. Together, these findings suggest that cardiomyocytes from failing hearts manifest asynchronous Ca^{2+} release, leading to slowed contraction and relaxation kinetics, as well as arrhythmogenesis, and that distortion of the t-tubule network is a contributing factor (Fig. 1).

In addition, it has been proposed that t-tubule remodeling generates “orphan RyR2s”, i.e. SR Ca^{2+}-release channels localized relatively distant from the dyad. Activation of these isolated RyR2s can generate a second wave of Ca^{2+} release triggered by delayed arrival of Ca^{2+} diffusing from normal RyR2 channels localized appropriately at the dyad. This, in turn, elicits asynchronicity in EC coupling, perturbing both systolic and diastolic function and promoting arrhythmia [55].

Disruption of the t-tubule architecture, as observed in failing hearts, is involved not only in Ca^{2+} mishandling but may also disrupt cell signaling. In HF, β_2-adrenergic receptors are redistributed from deep within the t-tubules to the cell surface, disrupting localized β_2-adrenergic signaling [56]. In addition, precise organization of the t-tubule network is required for IGF-1 (insulin-like growth factor-1) signaling in cardiomyocytes [57]. In some cases, a t-tubule may extend to reach the nuclear envelope, allowing IGF-1 or other ligands to signal directly into the nucleus to induce nuclear Ca^{2+} signals that modulate gene expression [57,58]. IGF-1 is notable for its anti-apoptotic and pro-survival effects in cardiomyocytes and has been proposed as a therapeutic approach for HF [59,60].

2.2.1. Therapeutic manipulation?—In light of the fundamental role of t-tubule architecture in cardiomyocyte function, it is intriguing to speculate that slowing or arresting the progressive deterioration of t-tubule architecture is a target worthy of consideration. Would it even be possible to restore that architecture? Several approaches have been proposed. For one, there is a correlation between the rigidity of the microtubule network and cardiac pathology. Microtubule-stabilizing drugs (e.g. taxol) can cause cardiotoxicity [61,

62], whereas microtubule-destabilizing drugs (e.g. colchicine) are associated with reduced myocardial infarction size [63]. In the setting of cardiomyocyte stretch, activation of NOX2 leads to ROS production and RyR2 sensitization ("X-ROS signaling") [64]. However, enhanced signaling due to excessive microtubule stabilization can provoke excessive Ca^{2+} sparks and arrhythmogenesis.

Microtubule depolymerization with colchicine attenuates pressure overload-induced t-tubule remodeling and improves survival and cardiac function, whereas taxol (microtubule-stabilizing drugs) amplify cardiac damage [65]. Microtubule depolymerization is associated with increases in Ca^{2+} transient amplitude, accelerated transient upstroke, and reduced Ca^{2+} spark frequency [65]. These findings suggest that t-tubule architecture can be remodeled in injured hearts and raise the intriguing prospect that these events could be targeted therapeutically in established HF. Colchicine has demonstrable benefits in several cardiovascular disorders, including pericarditis, atrial fibrillation, ischemia, and chronic HF [66].

Many proteins contribute to the maintenance of the t-tubule network in both skeletal and cardiac muscle, including junctophilin-2 (JP-2), amphyphisin-2 (BIN-1), telethonin, and caveolin [14]. JP-2 spans the gap between the t-tubule and SR membranes, maintaining dyad structure [12]; it is also required for proper pre- and post-natal development of the t-tubule network [67,68]. Reduced JP-2 levels correlate with HF, and silencing of JP-2 impairs EC-coupling and induces cardiomyocyte hypertrophy [69]. Conversely, JP-2 over-expression reduces the incidence of HF and preserves t-tubule network integrity in mice after pressure overload [70]. It has been proposed that either de-stabilization of microtubules or suppression of Gαq-dependent signaling are related to JP-2 and t-tubule network remodeling [65,71]. Furthermore, reduced abundance of amphiphysin-2 (protein associated with vesicle trafficking) is associated with HF and t-tubule remodeling, likely contributing to Ca^{2+} mishandling [72].

2.3. Mitochondrial Ca^{2+}

In addition to their vital role as fuel burning sources of energy, mitochondria function as sinks for intracellular Ca^{2+}. Indeed, mitochondrial Ca^{2+} is required for normal functioning of metabolic enzymes, serving as a cofactor for several of them. In HF, however, elevated cytosolic Ca^{2+} facilitates accumulation of Ca^{2+} within mitochondria, which promotes ROS generation, impairs mitochondrial function, and can activate cell death pathways. ROS generation induced by mitochondrial Ca^{2+} overload may increase RyR2 oxidation, thereby exacerbating cytosolic Ca^{2+} accumulation and mitochondrial Ca^{2+} overload [17].

Anatomical and functional coupling between mitochondria and ER has been proposed in several cell types, including cardiomyocytes [73,74]. Whereas definitive studies are lacking, so-called mitochondria-associated ER membranes (MAMs) may play a role in HF pathogenesis. Cardiomyocyte hypertrophy induced by norepinephrine is associated with reduced SR-mitochondria coupling and mitochondrial dysfunction, suggesting disrupted communication between these organelles [75]. More recently, it has been reported that glycogen synthase kinase-3β (GSK-3β) is an essential regulator of MAMs in cardiomyocytes, acting by regulating inositol triphosphate receptor (IP_3R) function.

Increased GSK-3β activity during hypoxia/reoxygenation increases IP_3R phosphorylation and Ca^{2+} transfer to mitochondria, promoting cell death [76].

3. Cardiomyocyte death in HF

3.1.Apoptosis

Apoptosis is a mechanism of programmed cell death driven primarily by caspases, particularly the final common “executioner” caspases 3, 6, and 7 [77]. Inactive cytosolic caspase isoforms are cleaved in response to cell death signals, triggering their activation and consequent degradation of essential cardiac proteins, including multiple sarcomeric proteins [77–79].

It is well recognized that failing heart is often marked by apoptotic loss of cardiomyocytes. Patients with severe HF exhibit a low, but definitively increased, rate of cardiomyocyte apoptosis of 0.1 −0.25% [80]. This low level activation nevertheless represents 100-fold greater activation relative to basal rates in normal heart and if persistent for a year could result in greater than 30% loss of cardiac mass [81,82].

3.1.1. Mechanisms—There are two primary pathways of apoptosis, and both the “extrinsic” and “intrinsic” cascades play important roles in cardiomyocyte demise (Fig. 3). These pathways lead to activation of caspase-8 or caspase-9 respectively, which in turn signal downstream to caspase-3 and caspase-7 to trigger cell death. As cardiomyocytes harbor numerous mitochondria, accounting for up to 70% of their volume, it is not surprising that regulation of apoptosis by this organelle plays a significant role in cardiomyocyte homeostasis [83,84]. HF, particularly secondary to ischemic disease, is marked by activation of the intrinsic pathway, a cascade characterized by loss of mitochondrial membrane integrity [85,86]. This, in turn, stimulates mitochondrial outer membrane permeabilization secondary to activation and oligomerization of specific Bcl-2 proteins, such as Bax and Bak. This allows release of multiple proapoptotic factors, including apoptosis-inducing factor (AIF), DIABLO, and cytochrome c from the intermembrane space into the cytoplasm [87,88]. Cytochrome c leads to oligomerization of Apaf-1 (apoptotic protease-activating factor-1) and formation of the apoptosome, leading to subsequent cleavage of caspase-9 and consequent apoptotic cell death [89]. The flavoprotein AIF promotes chromatin condensation and DNA fragmentation, and DIABLO blocks the apoptosis-suppressing actions of IAP, leading to increased inherent caspase activity.

Ca^{2+} concentrations also play an essential role in apoptosis during HF, as increases in Ca^{2+} within mitochondria can result in increased ROS and cytochrome c release, as well as activation of ERK and JNK stress pathways [89]. Furthermore, Ca^{2+} can stimulate calpain, a cysteine protease which can cleave Bax, creating pro-apoptotic fragments [90].

In contrast, the extrinsic apoptotic pathway is launched by activation of so-called death receptors, for example when Fas ligand (FasL) binds its receptor (FasR) [91]. This FasL–FasR interaction triggers Fas-associated death domain protein (FADD) to accumulate caspase-8 molecules, ultimately resulting in their activation [92].

3.1.2. Apoptosis and HF—FasL and FasR are abundant in cardiomyocytes, and their expression increases during pathological cardiac stress or obesity [93–96]. In addition, up-regulation of circulating FasR in murine models of I/R and HF has been long associated with increased cardiomyocyte death [97,98]. In a rat model of autoimmune myocarditis-induced HF, increases in apoptosis and FasL/FasR signaling were reported [99]. Similarly, a study of ischemic HF in sheep reported that increases in LV wall stress were linearly correlated with levels of FasL, and both FasL and caspase-8 were localized by immunohistochemistry to the cardiomyocyte intercalated disk [100]. Some evidence suggests that serum levels of FasL are elevated in patients experiencing an ST segment elevation myocardial infarction, a finding predictive of worse outcomes [101].

Some studies report no correlation between HF and levels of Fas in patients, whereas others have shown that worse NYHA HF class correlates with higher levels of FasR and FasL [102,103]. In a meta-analysis of HF clinical trials testing levosimendan, it was suggested that in patients with decompensated HF, efficacy in reducing hospitalization relates to the drug's ability to reduce soluble apoptosis mediators such as FasL/FasR [104,105]. In a similar fashion, it has been suggested that some of the beneficial effects on reducing pathologic remodeling with olmesartan derive from inhibition of Fas-directed apoptosis [106]. There is also significant evidence that the benefits of beta-blockers and ACE inhibitors in HF derive, at least in part, from decreases in apoptosis and improvements in G-protein signaling [107,108–111].

Also important is the Bcl-2 family of oncogenic proteins, molecules which have either anti-apoptotic (Bcl-2, Bcl-xL) or pro-apoptotic (Bax, Bak) roles. Dysregulation of cardiomyocyte Ca^{2+} levels during HF can subsequently lead to mitochondrial Ca^{2+} overload and dissipation of the mitochondrial transmembrane gradient [92]. However, as this loss of transmembrane potential does not appear to require increasing permeability of the outer mitochondrial membrane (or release of cyto-chrome c or caspase), this inner membrane MPTP opening likely has a significant role in necrotic cell death [112]. For instance, in Bax/Bak-deficient cardiomyocytes, thapsigargin, which inhibits SERCA, causes Ca^{2+} overload and MPTP opening, eventually leading to cellular necrosis [113]. In addition, mice deficient in cyclophilin D- and Bax/Bak, both of which are known regulators of the MPTP, are resistant to necrotic cell death [114].

Apoptosis is driven by Bax/Bak-triggered permeabilization of the mitochondrial outer membrane, which subsequently releases cytochrome c and other apoptotic factors into the cytoplasm [115]. In contrast, Bax and Bak stimulation of sustained MPTP opening on the inner mitochondrial membrane leads to mitochondrial rupture and necrotic cellular demise [112]. Indeed, Bax/Bak-driven opening of the mitochondrial outer membrane and Ca^{2+} dysregulation may actually enhance MPTP opening at the inner membrane, blurring the lines between necrotic and apoptotic cell death.

Cardiomyocyte-restricted over-expression of Bcl-2 preserves mitochondrial function and structural integrity [116], promotes stabilization of the mPTP, and decreases infarct size after I/R injury [87]. Another study with Bcl-2 transgenic mice also reported partial rescue of HF in a model of inherited cardiomyopathy [117]. Patients with higher levels of

myocardial Bcl-2 and BcL-xL also appear to have decreased levels of apoptosis, which can be associated with diminished pathological remodeling in HF [118].

Members of the IAP (inhibitor of apoptosis protein) family, as the name implies, inhibit caspase-driven apoptosis and include XIAP, ts-IAP, survivin, and apollon [119]. In patients with end-stage HF, myocardial levels of IAP are decreased, which may increase the susceptibility of the heart to the pathological effects of excessive apoptosis [120]. Chen and colleagues have also suggested that ARC (apoptosis regulator with caspase recruitment domain), an apoptotic repressor prevalent in cardiac muscle, is degraded by deficiency of SNX13 (sorting nexin-13) with consequent increases in cardiac apoptosis, increases in cardiomyocyte death and worsened cardiac function [121]. Similarly, inhibition of XIAP by XAF1 (XIAP-interacting protein-1) promotes caspase-induced apoptosis in cardiac myocytes. In particular, XAF1 is abundant in the heart and is up-regulated in HF [122,123] suggesting that suppression of XIAP-dependent inhibition may render the heart less susceptible to apoptotic cell death. In a porcine model of cardiac arrest, therapeutic hypothermia appeared to increase levels of survivin and decrease levels of XAF1 and cleaved caspase-3 [123].

IGF-1 is recognized to have many roles in the heart, particularly in physiological cardiac growth, and possibly in protection from I/R and metabolic (e.g. diabetic/high-fat diet) injury [124]. There are also studies suggesting that IGF-1 can promote reverse remodeling in several models of preclinical cardiomyopathy [125]. Clinically, higher levels of circulating IGF-1 predict survival in HF patients [126]. While there appear to be several pathways involved, the ability of IGF-1 to provide salutary effects in HF derives, at least in part, from down-regulation of apoptosis via suppression of Bax and caspase-3 activation [127,128].

Some data link increased guanine nucleotide-binding protein activity and pathological hypertrophy/failure with apoptosis [107]. Several established stimulators of hypertrophy, such as norepinephrine, angiotensin, and endothelin-1, provoke hypertrophy via this G protein pathway. Mice over-expressing Gαq exhibit cardiac hypertrophy and increases in HF markers [129,130]. Furthermore, these Gαq mice manifest worsened cardiac decompensation, pulmonary congestion, and mortality, with increased susceptibility to dilated cardiomyopathy elicited by transverse aortic constriction (TAC) or volume overload. This Gαq-mediated transition to hypertrophy and failure is in part linked to increased rates of cardiomyocyte apoptosis. Further, activation of upstream pathways (e.g. using norepinephrine or angiotensin) or constitutive activation of Gαq increases apoptosis levels in cultured cardiac myocytes, and exacerbated HF has been observed in several preclinical models [107,131].

The primary driver whereby these G proteins activate apoptosis is under debate [132,133]. For instance, in dilated cardiomyopathy, Gαq over-expression is associated with opening of the MPTP and cytochrome c release [130], suggesting a role of the intrinsic apoptotic pathway. Furthermore, utilization of MPTP inhibitors or polycaspase inhibitors partially rescues this phenotype.

One of the proapoptotic Bcl-2 proteins, Nix, is increased in both human and animal models of pressure-overload hypertrophy [134,135]. Transgenic mice expressing cardiomyocyte-restricted Nix die of HF within 2 weeks, whereas mutant mice that over-express Gαq but lack Nix harbor reduced levels of apoptosis and are relatively resistant to pressure overload-induced HF [135].

Scherer and colleagues have engineered transgenic mice expressing a cardiomyocyte-specific cassette encoding a fusion protein consisting of procaspase-8 and amutated FK506-binding protein (FKBP) dimerization domain. In this model, dimerization of the mutant protein can be triggered by injection of AP20187, activating caspase-8-mediated apoptosis [136]. Expression and activation of this transgene causes widespread cardiomyocyte apoptosis with 50% mortality from cardiac catastrophe within 20 h of administration. Similarly, Kitsis and colleagues reported low, but definitively increased, levels of cardiomyocyte apoptosis in a model of transgenic caspase-8-driven apoptosis triggering dilated cardiomyopathy and early mortality [137]. Whereas there is some debate as to whether the presence or absence of GP130, a subunit that is part of the IL-6 family, promotes HF, dysregulation of this protein increases mortality by promoting apoptosis and pathological changes in preclinical models [138]. In addition, the Controlled Rosuvastatin Multinational Trial in HF (CORONA) demonstrated that in elderly patients with ischemic HF, elevations in soluble gp130 correlate with worsening HF as well as increased total and cardiovascular mortality [139].

Caspase-3-specific and polycaspase inhibitors are capable of antagonizing pathological cardiac remodeling, as well as mortality, in several preclinical models of HF [140]. Furthermore, rescue of both I/R injury and HF by these or similar inhibitors suggests that ongoing apoptotic cell death is a significant mechanism contributing to I/R-induced heart disease. In fact, there are multiple lines of evidence that increases in myocardial apoptosis correlate with pathological remodeling and worsened outcomes in ischemic HF. Some evidence suggests that reverse remodeling in the setting of mechanical unloading correlates with decreases in apoptotic index and apoptotic signaling [79,141].

3.1.3. Necrosis and HF—Although necrosis can exist as an unregulated process of cell death involving ATP depletion, cell swelling and ultimately lysis, several forms of regulated necrosis have been described in recent years. Necroptosis is programed cell death by necrosis, triggered by activation of the necrosome, which is formed by receptor interacting protein kinase-1 (RIP1), −3 (RIP3) and substrate mixed lineage kinase like (MLKL) [142]. Diverse stimuli can trigger necroptosis, including TNF-α, Fas-L, and ROS [reviewed in [143]. In cardiomyocytes, necroptosis contributes in part to cell death after I/R injury. In fact, necrostatin-1, an inhibitor of RIP-1, can reduce cardiomyocyte death after I/R injury and mitigate adverse cardiac remodeling [144–146].

More recently, TGFβ-activated kinase 1 (TAK1) has emerged as a factor which plays a pivotal role in regulating cardiomyocyte death by necroptosis in myocardial remodeling and HF [147]. It has been proposed that TAK1 acts as a molecular switch that regulates the formation of two cell death complexes, RIP1-FADD-caspase 8 and RIP1-RIP3 [147]. In

addition, TAK1 ablation increases cell death by both apoptosis and necroptosis, a cascade which is blunted by silencing of TNFR1, RIP1, or RIP3 [147].

As outlined above, multiple points in the apoptotic cascade could be envisioned as therapeutic targets. Although the current arsenal of small molecules targeting this death pathway is limited, further elucidation of apoptosis regulation in a cardiomyocyte-specific fashion is warranted. Pan-anti-apoptotic agents may have detrimental effects in conditions such as cancer, in which there is a deficiency in apoptotic cell death. Indeed, it is conceivable that non-selective long-term suppression of apoptosis may not be beneficial. Further, despite an abundance of research effort, it remains unclear whether apoptosis is a primary or secondary event in HF progression. Regardless, there exists clear evidence that manipulation of programmed cardiomyocyte death can have beneficial effects in preclinical models, suggesting promise in the clinical context.

3.2. Autophagy

Autophagy is a phylogenetically conserved process of protein and organelle recycling, essential to cell survival and stress responsiveness. There are 3 main types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy [148]. Our discussion will focus on macroautophagy, as this is the predominant and best characterized form.

The autophagic process involves several steps that lead to formation of double-membrane organelles called autophagosomes within the cytoplasm that sequester intracellular elements (e.g. damaged proteins or organelles). Subsequently, autophagosomes fuse with lysosomes to form autolysosomes with consequent transfer of acidic pH and acid hydrolases. The autolysosome cargo is degraded and ultimately released into the cytoplasm to preserve cellular homeostasis. This pathway involves class III phosphoinositide-3-kinase (PI3K) and Beclin-1 for the initiation and nucleation steps of autophagy, along with a number of so-called ATG (autophagy-related genes) proteins for completion of the autophagosome [149].

In states of cardiac stress, cardiomyocyte autophagy is an indispensable cell survival mechanism [150]. Although there is some variation in the literature, autophagy occurs in failing cardiomyocytes at a prevalence of 0.03–0.08% [151]. In a rodent model of pulmonary hypertension-induced impairment of ventricular relaxation, failing cardiomyocytes were marked by activated autophagy as denoted by increases in LC3-II (a marker of autophagosomes) as well as in the number of autophagic vacuoles [152]. A study of NYHA class II-III HF patients reported autophagic dysregulation, increased LAMP2 levels, and impaired mTOR activity [153]. In explanted cardiac muscle from stage IV HF patients undergoing partial ventriculectomy, electron microscopy demonstrated significantly increased numbers of autophagic vacuoles harboring partially digested intracellular contents [154].

In states of ATP depletion, the heterotrimeric protein AMPK is activated, leading to TSC complex-mediated inhibition of Rheb and subsequently mTOR1 (mechanistic target of rapamycin 1), a negative regulator of autophagy [148,155]. Ca^{2+}/calmodulin-dependent protein kinase 2B (CaMK2B) can also elicit AMPK phosphorylation and activation,

increasing the level of autophagic flux within the heart [156]. Alternatively, protein kinase A (PKA), a primary downstream effector of the second messenger cAMP, suppresses cardiomyocyte autophagy by inactivating several ATG proteins (e.g. ATG 8, 13) [157–159].

3.2.1. Selective autophagy—When initially described in the 1960s, autophagy was believed to be a non-specific process utilized by cells for bulk degradation [160]. However, it is clear now that autophagy can be selective in nature, and that there exist important differences between baseline autophagy and targeted autophagy elicited by different stimuli [148]. Although detailed mechanisms are still being elucidated, a number of organelle-specific autophagic pathways have been described. For instance, autophagy of ER, lipids, mitochondria, or protein aggregates are termed reticulophagy, mitophagy, lipophagy, and aggrephagy, respectively. In addition, a variety of cellular stresses, such as energy deficiency, starvation, infection, and protein aggregation likely stimulate autophagic flux in unique ways [155]. It can be surmised then that these distinct forms of autophagy, which recognize different substrates, must have divergent signals and mechanisms driving these differences. However, elucidation of molecular elements governing specific target recognition and autophagic regulation is still in its infancy.

Some evidence suggests that unique forms of autophagy rely on specific autophagy receptors and adaptors that recognize specific substrates, triggering a link between the conserved ATG cascade proteins and unique targets [161]. Thus, although these organelle- and stress-specific forms of autophagy eventually recruit the core ATG-driven autophagy proteins, unique autophagy receptors and adapters may accomplish specific functions to allow for substrate-specific degradation. As one example, receptors defined by a conserved amino-acid sequence termed the LC3-interacting region (LIR) motif bridge autophagic cargo to the LC3 machinery [162]. There exist multiple LIR domains highlighting differences between targeted and baseline autophagy [162].

The established autophagy scaffolding protein p62/SQSTM1 has been implicated in bulk autophagy and in the ubiquitination of peroxisomes and mitochondria during cardiac injury [163,164]. Another scaffolding protein termed autophagy-linked FYVE (ALFY) may help degrade protein aggregates via p62 and ATG5 [165–167]. Histone deacetylase 6 has been suggested to be involved in maturation of ubiquitin-positive autophagosomes and in directing protein aggregates to the aggresome [168–170]. Genetic silencing of ATG5 (a vital autophagy protein involved in the elongation of the autophagosome) elicits dysregulated autophagy with impaired vesicle formation, cardiac dysfunction, ventricular dilatation, and pathological hypertrophy [171,172]. These mutant animals manifest impaired cardiomyocyte autophagy and cardiac dysfunction at 10 months, with elevated mortality by 1 year of age. Alternatively, expression of ATG5 to promote autophagic flux is necessary for proper cardiac remodeling and function following mechanical unloading [173,174].

3.2.2. Basal autophagy—Maintenance of basal levels of autophagy is critical to cardiomyocyte homeostasis, as impairment of any of the essential autophagy factors leads to cellular dysregulation and if prolonged, cardiomyocyte death [150,175–178]. For instance, Danon cardiomyopathy derives from mutations in the gene coding for LAMP2, a protein essential for lysosome-autophagosome fusion. Blunting of autophagic flux by blocking this

fusion event leads to pathologic accumulation of undigested material within autophagosomes, triggering cardiomyocyte dysfunction and eventual lethal cardiomyopathy [179–181]. Vps34 is an important mediator of the autophagy initiation complex and is necessary for autophagosome formation. In mice selectively depleted of cardiomyocyte Vps34, impaired autophagy with subsequent contractile dysfunction and pathologic hypertrophy arise at an early age [182,183].

mTOR is a serine/threonine kinase that functions as a master regulator of cardiomyocyte homeostasis, including autophagy. Comprising 2 distinct complexes with differing functions (mTORC1 and mTORC2), mTOR1 is stimulated during states of energy and nutrient plenty, where it serves to inhibit autophagy in part via stimulation of AKT and phosphorylation/deactivation of ULK-1. Dysregulation of mTOR's control of cardiomyocyte autophagy leads to a variety of pathological outcomes [184]. Members of the Rag family of GTPases sense amino acids, promoting mTOR activation and consequent autophagy inhibition. A transgenic model over-expressing constitutively active RagA in cardiomyocytes is marked by mTORC1 over-activation even during periods of nutrient starvation [185]. This culminates in mice lacking the ability to activate autophagy during the perinatal period, resulting in early mortality. Rheb, a member of the RAS superfamily, is a GTPase that is an established activator of mTORC1. Mice silenced of Rheb selectively in cardiomyocytes manifest overactive autophagy even during feeding and lack normal physiological cardiomyocyte hypertrophy following birth, leading to death by 10 days [186].

Alternatively, selective silencing of mTORC1 in cardiomyocytes triggers cell death and embryonic lethality [187]. Dynamin-related protein 1 (Drp1), a GTPase involved in mitochondrial fission, is also important in the regulation of mitochondrial autophagic flux [188,189]. In particular, conditional cardiomyocyte-deficient Drp1 mice manifest impaired mitochondrial autophagy, resulting in accumulation of dysfunctional mitochondria. These Drp1 knockouts exhibit cardiac dysfunction with demise by 3 months. In cardiomyocyte Drp1 heterozygotes, contractile function was normal at 3 months but deteriorated in the setting of starvation or I/R injury. Together, these findings reinforce the notion that maintenance of basal levels of autophagy is essential for cardiomyocyte survival.

3.2.3. Autophagy in cardiac stress—Recent studies have revealed that autophagy participates in a multitude of physiological and pathophysiological processes. Further, down-or up-regulation of autophagic flux can be beneficial or detrimental, depending on the context and extent of flux change [190–192]. In particular, autophagic flux has been shown to have a particularly important role in the heart [193]. Under resting conditions, cardiomyocytes manifest autophagic turnover of organelles at low basal levels, but this process is altered in stress states such as infarction, metabolic derangements (e.g. diabetes, lipotoxicity), I/R injury, cardiac hypertrophy, and HF [194,195]. Notably, dysregulated autophagy appears to be key in pathological cardiac remodeling [196].

Under normal circumstances or mildly stressed conditions (such as short periods of nutrient depletion), autophagy degrades non-essential proteins and selectively removes damaged organelles to preserve the integrity of the cardiomyocyte. In addition, autophagy has been shown to antagonize apoptotic death and preserve cardiomyocyte mitochondria [116,197].

Mice deficient of lysosome-associated membrane protein 2 (LAMP2), an essential protein for autolysosome formation, manifest impaired autophagy with accumulation of autophagosomes, resulting in cardiomyopathy and HF [198,199]. Cardiomyocytes that lack ATG5 and/ or ATG7 are susceptible to HF triggered by pressure overload or adrenergic stress [174,200]. Ultrastructural analyses of cardiac muscle silenced of ATG5 or ATG7 reveal irregular sarcomeric structures and misshapen mitochondria [178]. Similarly, these isolated cardiomyocytes exhibit increased cell death and worsened hypertrophy in the settings of epinephrine or phenylephrine challenge. These findings suggest that maintenance of a constitutive baseline level of autophagic flux is required for normal cardiomyocyte cellular structure and function, a notion which is consistent with observations in other cell types [192].

There continues to be debate as to whether autophagy is harmful or helpful in the context of HF. With time, however, a consensus is emerging that autophagic flux can be either beneficial or detrimental, depending on the context, proximal trigger, and extent of activation. Work is presently under way to determine the extent to which these changes are quantitative (too much or too little) versus qualitative (autophagy that targets specific cellular elements) [150].

In a model of severe pressure overload-induced HF, Zhu et al. reported that cardiomyocyte autophagy increases in a model of severe TAC and remains chronically elevated, leading to amplified hypertrophic growth and increased rates of functional decline [201]. Cardiomyocyte-specific over-expression of Beclin-1, a protein involved in early and late autophagic flux events, triggered higher levels of stress-induced autophagy and worsened pathological remodeling and survival [201]. Conversely, Beclin-1 haploinsufficient mice manifest decreased levels of autophagy and diminished pathological remodeling [198,201].

At the same time, there is evidence that stimulation of autophagy may rescue pressure overload-induced cardiac hypertrophy and dysfunction via increases in autophagy and mTOR regulation [202]. Nakai et al. reported that autophagy levels are decreased in TAC hearts at 1 week [203]. They also reported that tamoxifen-inducible cre-recombinase-driven silencing of ATG5 in cardiomyocytes leads to an amplified hypertrophic response after TAC. In line with this, several studies have reported that rapamycin, an inhibitor of the autophagy-suppressive mTOR complex 1 and numerous downstream processes, rescues afterload-induced cardiac hypertrophy and can decrease mortality and prolong longevity [184,204]. Together, these data suggest that autophagic dysregulation, whether it is excessive or insufficient, is detrimental in load-induced HF.

4. Linking Ca^{2+} with autophagy and apoptosis

Ca^{2+} handling, intracellular recycling by autophagy, and programmed cell death by apoptosis are each essential to normal cardiac function, and each is perturbed in disease. Thus, it comes as little surprise that these three fundamental processes are mechanistically linked. That said, these links are only recently being uncovered (Fig. 4).

Apart from its role in EC coupling, Ca^{2+} is an important second messenger than governs a wide range of signaling pathways [205]. Basal Ca^{2+} levels in cardiomyocytes during

diastole are ≈100 nM, and this equilibrium is perturbed in multiple disease states [40,206,207]. For example, mdx mice (a mouse model for Duchenne muscular dystrophy) develop cardiomyopathy at 12–20 months of age reminiscent of that seen in patients [208]. Coincident with this, age-dependent increases in cytosolic Ca^{2+} are observed in adult cardiomyocytes from mdx mice, reaching ≈400 nM at 1 year [207]. As described above, HF is characterized by increases in diastolic Ca^{2+} concentration in the cytosol due to alterations in SR (leaky RyR2/reduced SERCA) and sarcolemmal Ca^{2+} fluxes (increased entry). In addition, altered localization of calsequestrin-2, a major Ca^{2+} buffer protein in the SR, likely contributes [209]. Persistent elevation of cytosolic Ca^{2+} or spontaneous Ca^{2+} release unrelated to systole (e.g. sparks) will activate Ca^{2+} dependent signaling pathways under basal conditions with a variety of downstream effects.

Depletion of SR Ca^{2+} stores not only perturbs Ca^{2+} cycling and contractile performance, it may also trigger additional responses, such as activation of the unfolded protein response (UPR) and cell death pathways, as well as autophagy impairment. For example, pharmacological inhibition of SERCA using thapsigargin activates the UPR, demonstrating that SR Ca^{2+} levels and the UPR are interconnected [210]. Activation of UPR has been reported in TAC-induced hypertrophy [211] and may be involved in HF progression [212]. The UPR comprises three major cascades: protein kinase RNA-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring protein 1α (IRE1α). Together, these pathways modulate gene expression, apopto-sis, autophagy, metabolism, and other events [213]. Ultimately, activation of the UPR serves to restore SR homeostasis by suppressing translation of new proteins, facilitating chaperone-mediated protein processing, and promoting degradation of excess protein. If SR homeostasis cannot be restored, the UPR will ultimately trigger apoptotic cell death.

We reported recently that over-expression of Xbp1s (downstream of IRE1α) blocks I/R injury, diminishing infarct size and preserving contractile function [214]. Conversely, activation of CHOP (downstream of PERK) exacerbates I/R injury [215]. Moreover, we and others have shown that Xbp1s levels are increased in failing human hearts (pre-LVAD) relative to the levels observed after mechanical unloading with a left ventricular assist device (post-LVAD) [214]. This correlates with reported improvements in Ca^{2+} handling and contraction force/kinetics observed after mechanical unloading [216]. We suggest that, similar to the hyperinsulinemic state in patients with type 2 diabetes or elevated BNP/ANF levels in HF, increased abundance of Xbp1s may function as a compensatory response, serving to mitigate injury [214]. In addition, there is evidence that higher levels of Xbp1s observed in settings of cardiac stress may regulate miRNAs, SERCA, and NCX, promoting beneficial angiogenesis and suppressing pathological remodeling [217–219].

Ca^{2+}-dependent regulation of cell death pathways, both apoptosis and necrosis, occurs at multiple levels. As discussed, calpains are Ca^{2+}-activated proteases linked to both apoptosis and necrosis [220]. Ca^{2+} overload after myocardial I/R injury increases calpain activation, and inhibition of calpains reduces infarct size [221,222]. Calpain activation is associated with pro-caspase 3, poly-ADP ribose polymerase and AIF cleavage, as well as apoptosis (reviewed in [220]). Similarly, cleavage of pro-caspase-3 and procaspase-9 is governed by Ca^{2+} [223].

HF is associated with mitochondrial dysfunction, which leads to ROS accumulation, elevations in inflammatory markers, increased apoptosis, and impaired autophagy [197,224–226]. As described earlier, perturbations in Ca^{2+} homeostasis can trigger MPTP opening and consequent loss of mitochondrial membrane potential, as well as activation of the intrinsic apoptosis cascade via release into the cytoplasm of cytochrome C, AIF and Smac/DIABLO. Furthermore, Bcl-2 and Bax are reported to regulate mitochondrial Ca^{2+} distribution and permeability, and pathological cardiac hypertrophic stress can promote Bcl-2/Bax-driven Ca^{2+} dysregulation and apoptosis initiation [227,228]. Recently, it has been proposed that RyR2 Ca^{2+} leak promotes mitochondrial Ca^{2+} overload and ROS production in HF, which may contribute to mitochondrial dysfunction and cell death [17].

Links between Ca^{2+} and autophagy are less well established. Using the Ca^{2+} phosphate method of DNA transfection in HEK293-T cells, increases in autophagy related to Ca^{2+}, involving Beclin 1 and ATG5, were first described [229]. Elevations in intracellular Ca^{2+} triggered by other means (e.g. ionomycin, ATP, thapsigargin) in MCF-7 cells are associated with activation of CaMKII-beta and AMPK and rerepression of mTOR inhibition [230].

Recently, a role for Ca^{2+} in governing autophagy has been highlighted that involves the Ca^{2+}-specific ion channel polycystin-2 (PC2) [231]. By forming a multiprotein ion channel complex with polycystin-1 (PC1), PC2 participates in the function of primary cilia. There, these proteins respond to a variety of extracellular cues, transducing them into changes in intracellular Ca^{2+} [232]. Changes in conformational shape triggered by shear stress on primary cilia lead to activation of the PC1/PC2 complex and consequent changes in intracellular Ca^{2+} levels [232]. Now, very recent evidence suggests that PC2-dependent changes in Ca^{2+} may be important in driving autophagosome formation (unpublished observations). In particular, we have amassed evidence that cardiomyocyte-specific silencing of the PKD2 gene, which codes for PC2, elicits impaired accumulation of autophagosomes and LC3 lipidation, independent of AKT or AMPK activity (unpublished observations). Furthermore, PC2 co-immunoprecipitates with the essential autophagosome initiation protein Beclin 1, and PC2 localizes to the ER. Together, these findings suggest that dysregulated PC2, acting to impair Ca^{2+} handling and autophagic flux, may participate in the pathogenesis of HF.

It is well established that lysosome acidification depends critically on Ca^{2+} exchangers interacting with V-ATPases [233]. Release of lysosomal Ca^{2+} can be induced by Bafilomycin A1 (BafA1), an inhibitor of V-type ATPases, resulting in loss of the pH gradient and suppression of further Ca^{2+} uptake [234]. Importantly, BafA1 is also an established inhibitor of autophagic flux [235]. Alterations in cytosolic Ca^{2+} in failing hearts likely alter lysosomal Ca^{2+} gradients, impairing lysosome function and impacting autophagic flux. Moreover, lysosome Ca^{2+} signaling regulates the activities of both calcineurin and TFEB, a key regulator of lysosomal biogenesis and autophagy [236].

Interplay between autophagy and ER stress has been described under physiological conditions [237]. In several forms of cardiac pathology, including HF, the UPR is activated [238]. Normally, accumulation of unfolded proteins within the ER triggers dissociation of an inhibitor chaperone, named GRP78, from PERK and IRE1. However, continued

accumulation of unfolded protein can lead to dysfunctional UPR signaling with ultimate activation of apoptosis. It has been suggested that GRP78 is essential in mediating the UPR and Ca^{2+} signaling, as GRP78 can inhibit type 1 cell death induced by ionomycin (a well known apoptosis-inducing Ca^{2+} ionophore) [239,240]. Alternatively, alterations in the abundance of SERCA protein have been shown to have a role in apoptosis, as thapsigargin, which blocks SERCA, leads to decreased Ca^{2+} levels and subsequent apoptosis triggered by ER stress [241,242]. Ceramide dysregulation during Ca^{2+} overload is suggested to induce ROS production, further worsening Ca^{2+} release and leading to increased levels of apoptosis [243,244].

The ER is a major storage and trafficking site for Ca^{2+} and chaperone proteins essential for proper Ca^{2+} handling and protein folding. In particular, the balance between SERCA-dependent Ca^{2+} entry and Ca^{2+} leak is essential to maintain ER homeostasis [245]. A significant body of evidence suggests that the ER's role in cellular stress and cell death is related to Ca^{2+} and intricate control of autophagy and apoptosis cascades [246–248]. In addition, Ca^{2+}-mediated ER chaperones, such as calreticulin, are involved in protein folding, such that dysregulation of Ca^{2+} leads to alterations in chaperone capacity, triggering cellular stress [249,250].

Depending on the circumstance, cellular demise can be initiated by Ca^{2+} release from the ER via multiple mechanisms, leading to Ca^{2+}-driven mitochondrial cell death [247,251]. However, IP_3 receptor-mediated Ca^{2+} delivery to mitochondria can help sustain ATP levels by regulating oxidative phosphorylation, in turn promoting cell survival [249,252]. Clearly, governance of Ca^{2+} signaling within the cardiomyocyte is central to guiding the cell toward survival or death.

As mentioned previously, Bax and Bak are factors that play a significant role in ER Ca^{2+}-mediated apoptosis. Specifically, rapidly increasing Bax releases Ca^{2+} from the ER, driving an increase in Ca^{2+} within mitochondria with subsequent release of cytochrome c [112,113,253]. Likewise, deficiency of Bax and Bak leads to reduction of ER Ca^{2+} release even in the face of IP_3-receptor signaling to increase Ca^{2+}. In part due to their proximity to the ER, Bax and Bak can also negatively affect Bcl-2 and Bcl-XL's roles in ER Ca^{2+} regulation. During times of ER stress, Bax/Bak may engage IRE1α leading to UPR activation; subsequent resolution of this can occur via Bax/Bak neutralization by Bcl-2 or Bcl-XL [254,255]. In relation to Ca^{2+}, the protective anti-apoptotic actions of Bcl-2 derive from its lowering of IP_3-driven ER Ca^{2+} levels [256,257].

JNK, an important stress mediator protein, can phosphorylate and inhibit Bcl-2's protective anti-apoptotic effect by dysregulating Ca^{2+} in the ER [258,259]. This phosphorylated Bcl-2 in unable to bind and inactivate pro-apoptotic factors (of the BH3 family), and can lead to increased ER Ca^{2+} release, subsequently causing excess Ca^{2+} uptake and mitochondrial Ca^{2+}-driven apoptosis [259,260]. Furthermore, during ER stress, CHOP-driven increases in pro-apoptotic Bim can antagonize Bcl-2 and Bcl-XL, limiting its mitochondrial and cytoprotective roles [261,262].

With time, our understanding of the interactions between ER stress, autophagy and apoptosis continues to grow. For instance, Beclin-1, typically thought of simply as an essential autophagy protein involved at the nucleation stage, has been demonstrated to engage the anti-apoptotic factor Bcl-2 in the ER, leading to inhibition of starvation-induced autophagy [263–265]. When there is pathological accumulation of misfolded proteins or dysregulation of Ca^{2+} levels, ER stress-induced autophagy is activated via IRE1α as part of the UPR. Then, together with TRAF2, JNK activation ensues [266,267]. To support further the UPR's antagonism of misfolded proteins, particularly when ER capacity is overwhelmed, induction of autophagy takes place, assisting elimination of pathologic proteins. Although ERAD is recognized as the predominant cellular mechanism for removal of unfolded proteins in the context of ER stress, a diversity of studies has shown that autophagy can be potently activated by ER stress [268–270]. The UPR interactions between PERK/elF2α lead not only to ATG12 activation, but PERK also drives an increase in other ATG genes via ATF4 [271,272]. Furthermore, XBP-1 splicing can activate Beclin-1, leading to increased autophagy [273]. Recently, it was reported that JNK-mediated phosphorylation of Bcl-2 facilitates its release of Beclin-1, thereby allowing autophagy to proceed [274,275]. The essential autophagy protein ATG12 can also bind and inhibit Bcl-2 family proteins, leading to increased apoptotic cell death [276,277].

Further evidence for Ca^{2+}'s role in regulating autophagy arises from modulators, such as ionomycin and thapsigargin, that lead to mTOR inhibition and blockage of autophagic flux with autophagosome accumulation [248,278]. Particularly, ER Ca^{2+} release activates AMPK and CaMKII pathways to stimulate autophagy via mTOR inhibition [279–281]. Alternatively, ER Ca^{2+} release also may activate protein kinase C (PKC), thereby leading to autophagy activation in an mTOR-independent fashion [282,283]. Clearly, there appear to be multiple mechanisms that drive the interplay between Ca^{2+}, autophagy, apoptosis, and ER stress.

Although much of the discussion focuses on HF stemming from systolic dysfunction, the contributions of apoptosis and autophagy may differ significantly in HFpEF. For instance, there exists evidence that in obesity-induced type 2 diabetes mellitus, increased apoptosis and mitochondrial dysfunction contribute to worsening diastolic dysfunction. Further, eplerenone, a mineralocorticoid antagonist, decreased apoptosis, as evidenced by decreases in caspase-3 activation, TUNEL staining, and nuclear pyknosis [284]. However, the distinction between therapeutically regulating apoptosis in diastolic versus systolic HF is difficult to delineate; there may be beneficial effects on systolic function, as well as diastolic function, such that the salutary effects are multifactorial and difficult to separate definitively. In a study evaluating models of systolic and diastolic HF, it was suggested that adenoviral knockdown of BNIP3 (which harbors the pro-apoptotic BH3 domain) rescued cardiac volume and function and that these benefits derive from decreases in myocardial apoptosis, ER stress, and attenuation of mitochondrial fragmentation [285]. It is important to recognize, however, that BNIP3 has important roles in mediating mitochondrial cell death by regulating ion channels affecting Ca^{2+} flux between the ER and mitochondria. Therefore, it is possible that BNIP3 knockdown helps balance ER Ca^{2+} content, mitigating mitochondrial damage and reducing apoptosis, subsequently improving both systolic and diastolic function [286].

In a high salt model of diastolic HF, it was reported that miR-208a decreased apoptosis and increased anti-apoptotic factors, resulting in blunted increases in hypertrophic markers (β-MHC) and cardiac mass, and improvements in diastolic function [287]. In PAH-induced diastolic HF, it was found that autophagy is overactive, contributing to pathological remodeling and cell death. However, treatment with dehydroepian-drosterone, a metabolic intermediate in the biosynthesis of the androgen and estrogen sex steroids, restored autophagy back to baseline levels, resulting in improved diastolic functional parameters (e.g. end-diastolic pressure) [152]. Aging is also clearly associated with diastolic dysfunction, as stiffening of the cardiac ventricles occurs over time; in particular, NAD^+-dependent class III histone deacetylases (sirtuins) and ATG protein signaling appear to become impaired with age, contributing to an imbalance and inhibition of basal autophagic flux [288,289]. Caloric restriction and starvation lead to increases in autophagy, and many studies have indicated that caloric restriction blunts the decline in both diastolic and systolic function with age [290,291]. Thus, there exist multiple similarities and differences between autophagy and apoptosis in the regulation of cardiac function, whether it be diastolic or systolic.

5. Conclusions and perspective

HF is a multifaceted syndrome, ever growing in individual and societal impact. It is characterized by profound dysregulation in Ca^{2+} handling and homeostasis, coupled with alterations in autophagy-driven catabolism and programmed cell death. Recent insights have unveiled novel links among these three biological processes. Indeed, recent studies highlight that these events are tractable by means with potential therapeutic relevance, such as small molecule HDAC (histone deacetylase) inhibitors. Further advances, building on these new discoveries, hold significant promise to afford benefit with clinical impact.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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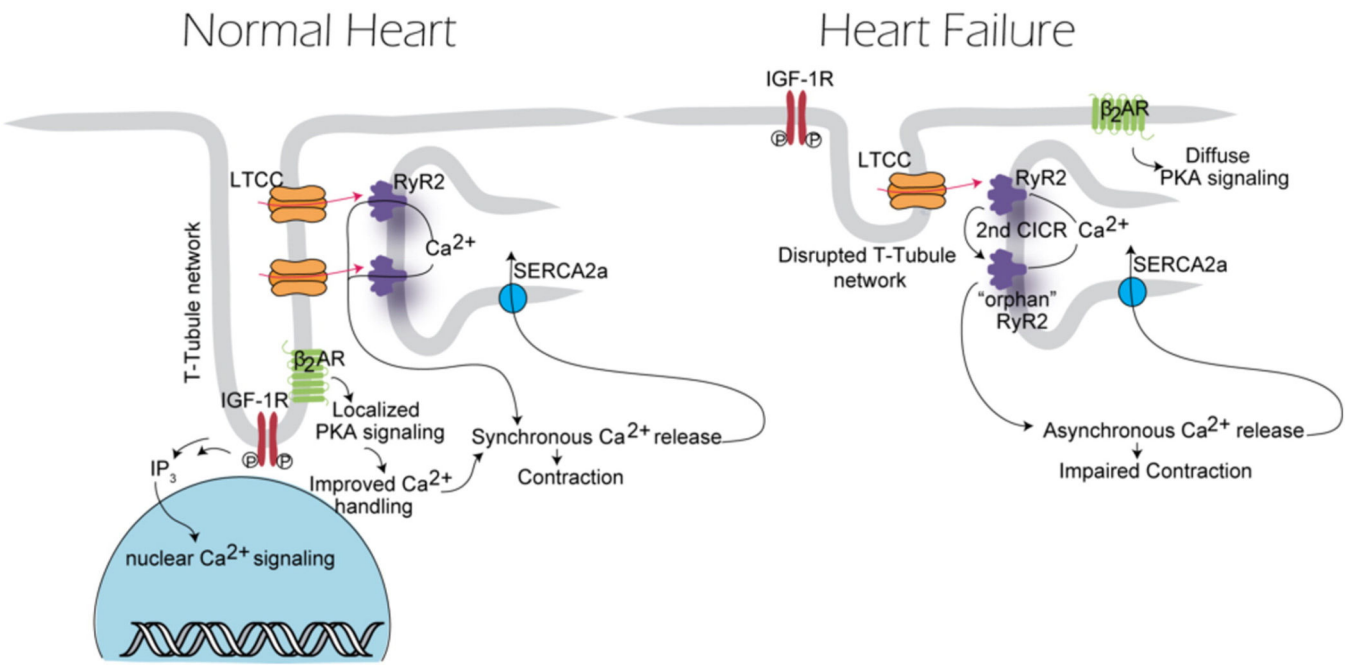

Fig. 1.

Disruption of t-tubule network in HF. In failing cardiomyocytes, there is progressive deterioration of t-tubule architecture, impeding the normal propagation of action potentials into the cardiomyocyte core. It has been proposed that “orphan” RyR2 are located outside the junctional cleft, triggering a second wave of CICR that perturbs synchronicity during systole and diastole. As these orphan RyR2 are located distant from the dyads, they are activated late, contributing to impaired contractile performance. Distorted t-tubule architecture may also impair signaling elicited by catecholamines and growth factors.

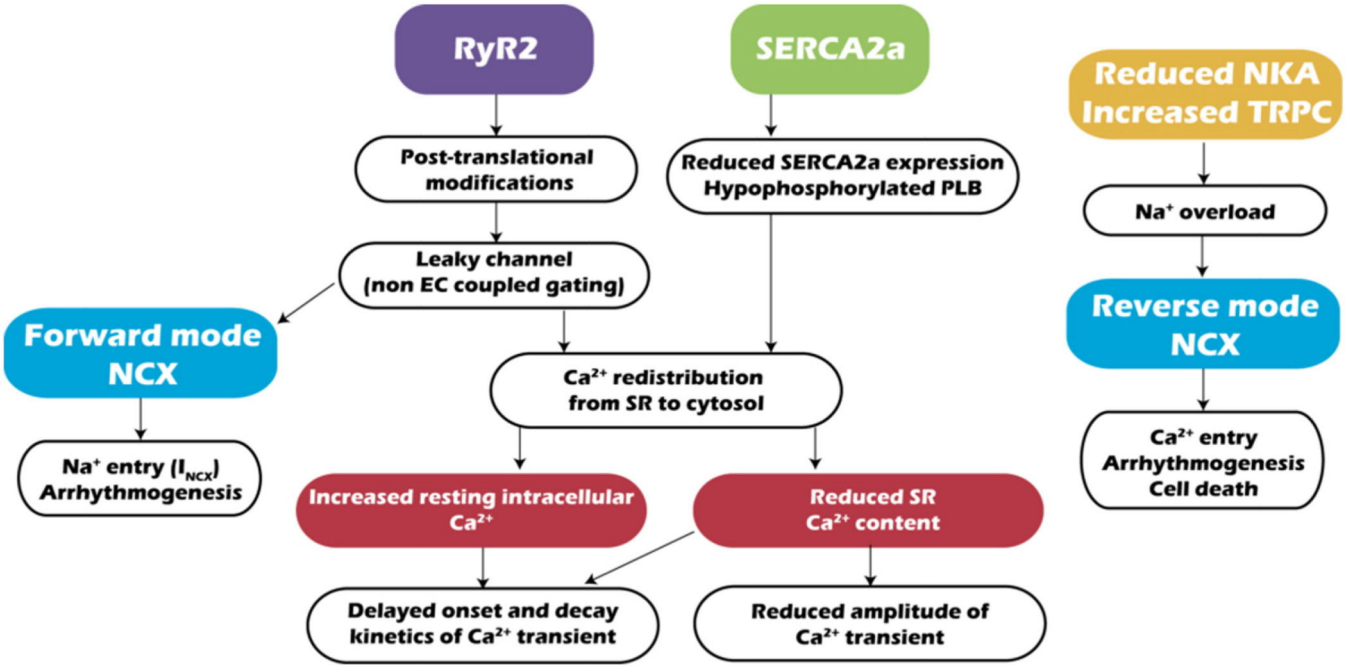

Fig. 2.

Ca^{2+} mishandling in HF. Alterations in RyR2, SERCA2a, NCX, Na^+/K^+ ATPase (NKA) and TRPC channels lead to impaired Ca^{2+} and Na^+ handling, which negatively impacts the contractibility of failing cardiomyocytes. NKA: Na^+/K^+ ATPase.

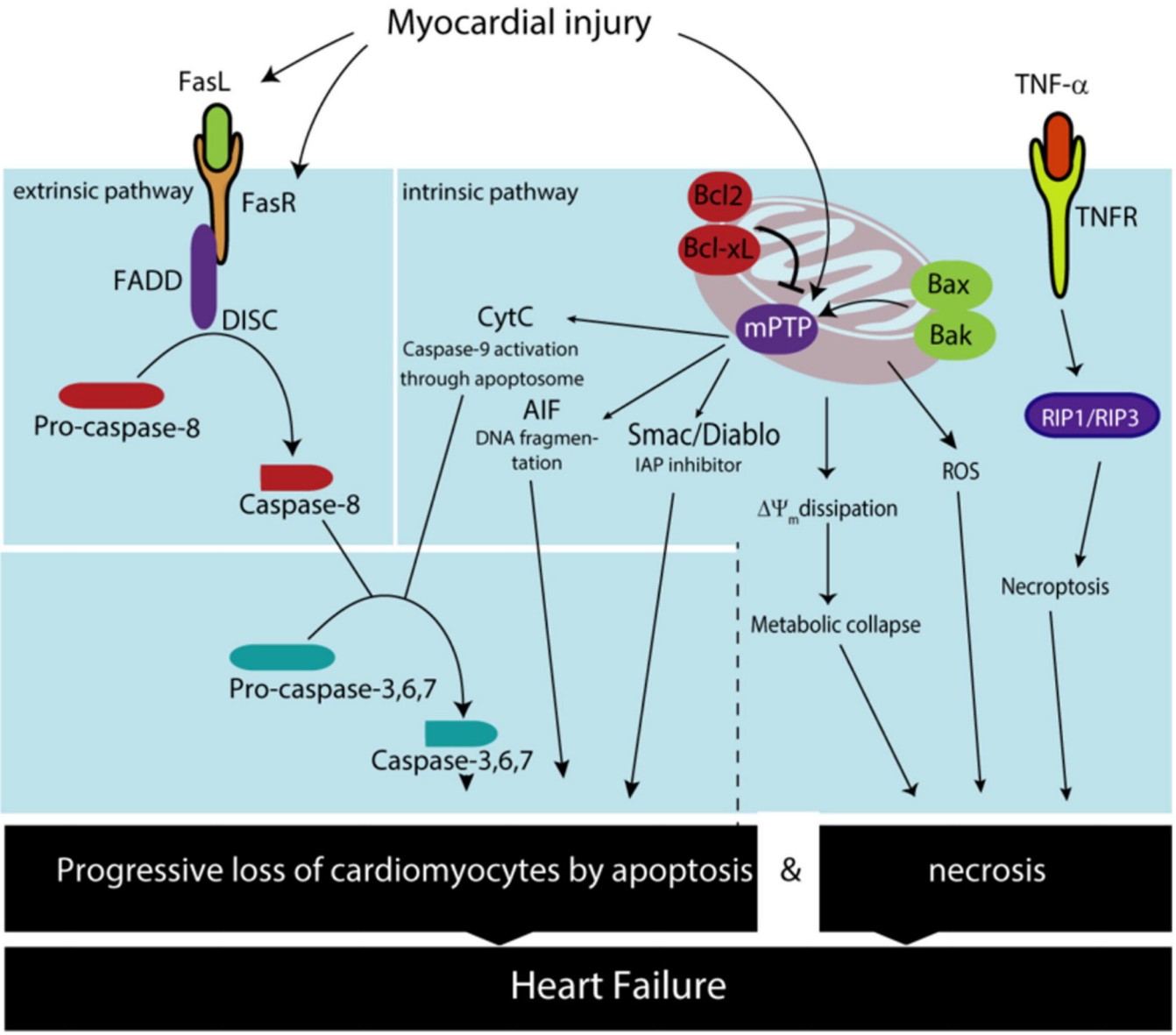

Fig. 3.

Increased levels of apoptosis and necrosis are observed during HF. Activation of both the extrinsic and intrinsic apoptotic pathways have been described in HF. Activation of FasR leads to caspase-8 activation and extrinsic pathway activation. On the other hand, mitochondrial permeabilization leads to cytochrome C, AIF and Smac/Diablo release, which triggers the intrinsic pathway. Similarly, mitochondrial Ca^{2+} overload leads to mitochondrial membrane potential dissipation (ΔΨm) and ROS production, which ultimately trigger necrosis. In addition, regulated necrosis or necroptosis has emerged as another source for cell death in HF through activation of RIP1/RIP3. Over time, cardiomyocyte death results in a decreasing abundance of functional cardiomyocytes in the failing heart, which further deteriorates cardiac function.

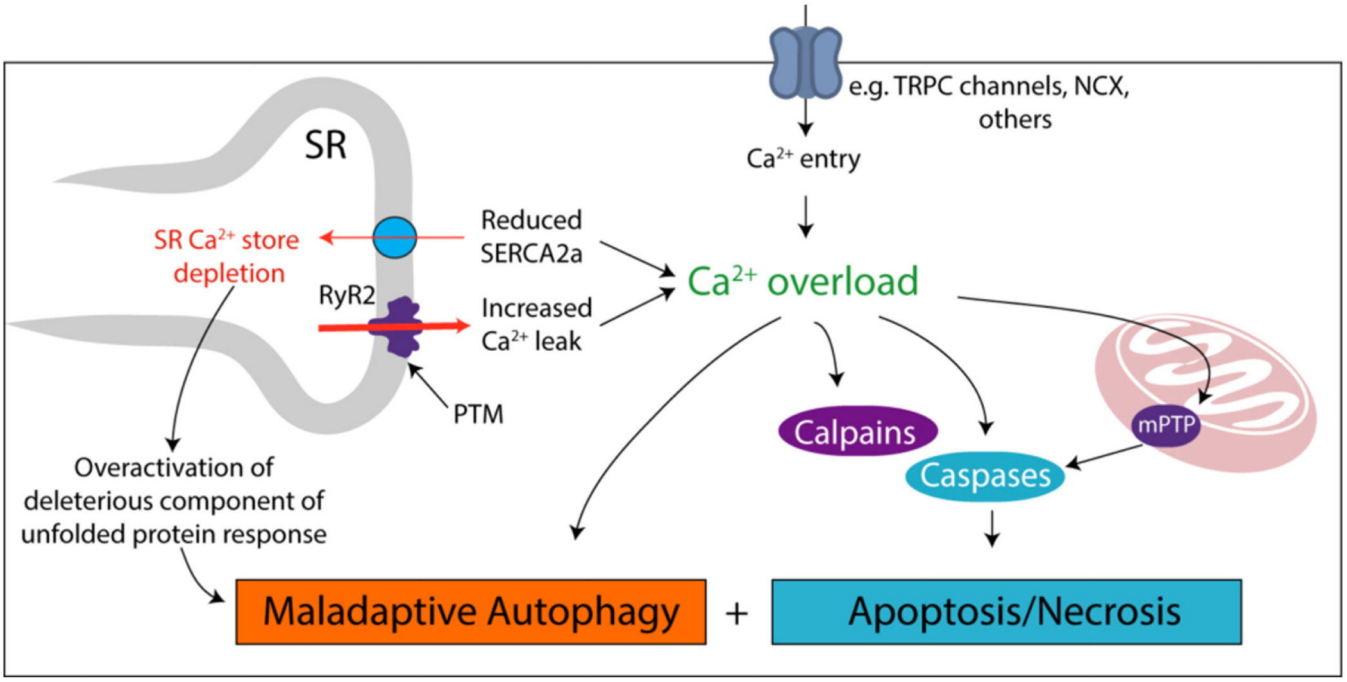

Fig. 4.

Relationships among disordered Ca^{2+} homeostasis, autophagy, necrosis and apoptosis in HF. It is generally accepted that depletion of SR Ca^{2+} stores, coupled with rises in cytosolic Ca^{2+}, perturb EC coupling and elicit changes in cellular signaling events. Post-translational modifications (PTM) of RyR2 and reduced SERCA activity redistribute SR Ca^{2+} to the cytosol. Increased cytosolic Ca^{2+} also triggers pathways that contribute to cardiac muscle wasting. Activation of apoptotic pathways (e.g. calpains, caspases, or mPTP opening) has been extensively related to Ca^{2+} dysregulation, and there is some evidence pointing to altered autophagic signaling as well.

Table 1

Summary of current hypotheses explaining HF progression.

Hypothesis	Description	Reviewed in
Impaired EC coupling	Alterations in Ca^{2+}-handling and cardiomyocyte ultrastructure lead to impaired Ca^{2+} cycling that impinge on both systolic and diastolic function. Ca^{2+} overload might trigger mitochondrial dysfunction and cell death	[13,14,18,209]
Alterations in sarcomeric proteins	Switch in myosin, actin, troponin, tropomyosin, and titin isoforms	[292,293]
Adrenergic system	Increased adrenergic signaling in HF	[294]
Renin-angiotensin-aldosterone axis	Increased activity of this axis leads to maladaptive hypertension and HF development	[295–297]
Epigenetic modification and noncoding RNAs	Modifications in gene expression associated with cardiac remodeling and HF progression	[298,299]
Innate immunity	Increased inflammation in HF patients related to left ventricular remodeling and dysfunction	[300]
Reactive oxygen species	Activation of unfolded protein response, apoptosis and senescence	[301]
Nitric oxide (NO)	NO insensitivity. Increased ROS leads to peroxynitrite formation and deficient NO-cGMP-PKG activity. Impairment in LV function and endothelial dysfunction	[302]
Changes in autophagic flux	Increased autophagic activity correlates with hypertrophic and HF progression	[192]
Mitochondrial dysfunction	Reduced mitochondrial function, increased ROS production and diminished ATP production	[85,291]
Increased cell death	Necrosis, apoptosis and autophagy contribute to progressive reduction and remodeling in cardiomyocytes in failing hearts	[116,303]