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Review Series

Recently, low — but abnormal — rates of cardiomyocyte apoptosis have been observed in failing human hearts. Genetic and pharmacological studies suggest that this cell death is causally linked to heart failure in rodent models. Herein, we review these data and discuss potential therapeutic implications.

Death begets failure in the heart

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Introduction

Heart failure is a heterogeneous syndrome that can result from primary cardiomyopathies or, more commonly, myocardial infarction, hypertension, and valvular heart disease, among other disorders. The prevalence of heart failure has increased dramatically as modern therapies have reduced the mortality of acute myocardial infarction. However, current treatments for heart failure are woefully inadequate, and the availability of hearts for transplantation is severely limited. Even those therapies that successfully target biologically relevant pathways (e.g., β-adrenergic receptor blockers, angiotensin-converting enzyme inhibitors) become less effective with time (1). These limitations underscore the need for understanding the biology of heart failure at the most fundamental level.

The underlying cause of heart failure has remained an enigma since this syndrome was first described by Richard Lower in 1669 (2). Multiple mechanisms have been proposed, including desensitization of β-adrenergic receptor signaling (3), dysregulation of excitation-contraction coupling (4, 5), alterations in cytoskeletal proteins (6), myosin isoform switches (7), and dysfunctional energy utilization (8, 9), all topics covered elsewhere in this series. Indeed, these mechanisms have been implicated in the progressive loss of contractile function in heart failure. On the other hand, there is a longstanding notion that heart failure involves not only myocyte contractile dysfunction, but also cell “drop-out.” The loss of myocytes would be predicted to decrease contractility and promote slippage of muscle bundles, wall thinning, and dilatation — the archetypical changes observed in heart failure.

In this review, we first discuss the evidence that cardiomyocyte death plays a mechanistic role in heart failure and go on to consider how this mechanism may provide a target for novel therapies.

Central apoptosis pathways

Cell death can occur by apoptosis, necrosis, or perhaps autophagy. A framework has been described for apoptosis, a highly regulated cell suicide process that is hard wired into all metazoan cells (10). Much less is known about necrosis, although recent work suggests that this form of cell death may be actively regulated and is not necessarily accidental (11, 12). Autophagy is an important recycling process in which macromolecules are degraded in the lysosome so that their components can be used as energy substrates by the cell (13). Whether autophagy functions as a death process remains controversial (11, 14).

Apoptosis is mediated by 2 evolutionarily conserved central death pathways: the extrinsic pathway, which utilizes cell surface death receptors; and the intrinsic pathway, involving mitochondria and the ER (Figure 1) (10). In the extrinsic pathway, death ligands (e.g., FasL) initiate apoptosis by binding their cognate receptors (15). This stimulates the recruitment of the adaptor protein Fas-associated via death domain (FADD), which then recruits procaspase-8 into the death-inducing signaling complex (DISC) (16–18). Procaspase-8 is activated by dimerization in this complex and subsequently cleaves and activates procaspase-3 and other downstream procaspases (19).

In contrast to the extrinsic pathway that mediates a specialized subset of death signals, the intrinsic pathway transduces a wide variety of extracellular and intracellular stimuli including loss of survival/trophic factors, toxins, radiation, hypoxia, oxidative stress, ischemia-reperfusion, and DNA damage. Although a myriad of peripheral pathways connect these signals with the central death machinery, each ultimately feeds into a variety of proapoptotic Bcl-2 proteins that possess only Bcl-2 homology domain 3 (BH3-only proteins) and the proapoptotic multidomain Bcl-2 proteins Bax and Bak (20). These proteins undergo activation through a diversity of mechanisms to trigger the release of mitochondrial apoptogens, such as cytochrome *c*, into the cytoplasm (21–27). Once in the cytoplasm, cytochrome *c* binds Apaf-1 along with dATP. This stimulates Apaf-1 to homo-oligomerize and recruit procaspase-9 into the multiprotein complex called the apoptosome (28–39). Within the apoptosome, procaspase-9 is activated by dimerization, after which it cleaves and activates downstream procaspases. Bid, a BH3-only protein, unites the extrinsic and intrinsic pathways: following cleavage by caspase-8, Bid’s C-terminal portion translocates to the mitochondria and triggers apoptogen release (40–42).

The extrinsic and intrinsic pathways are held in check by a variety of endogenous inhibitors of apoptosis. FLICE-like (Fas-associated death domain protein-like-interleukin-1–converting enzyme–like) inhibitory protein (FLIP), whose expression is highly enriched in striated muscle, binds to and inhibits procaspase-8 in the DISC (43). Antiapoptotic Bcl-2 proteins, such as Bcl-2 and Bcl-x_L, inhibit mitochondrial apoptogen release through biochemical mechanisms that are still incompletely understood (10). Ku-70 and humanin bind Bax and block its conformational activation and translocation to the mitochondria (44, 45). X-linked inhibitor of apoptosis (XIAP) and related proteins that contain baculovirus inhibitor of apoptosis repeats bind to and inhibit already activated caspases-9, -3, and -7, as well as interfering with procaspase-9 dimerization and activation (46–50). Each of these inhibitors act on circumscribed portions of either the extrinsic or intrinsic pathway. In contrast,

Nonstandard abbreviations used: ARC, apoptosis repressor with a CARD (caspase recruitment domain); BH3, Bcl-2 homology domain 3; DISC, death-inducing signaling complex; FADD, Fas-associated via death domain; Gαq, α subunit of Gq; IP3R, inositol 1,4,5-triphosphate receptor; XIAP, X-linked inhibitor of apoptosis.

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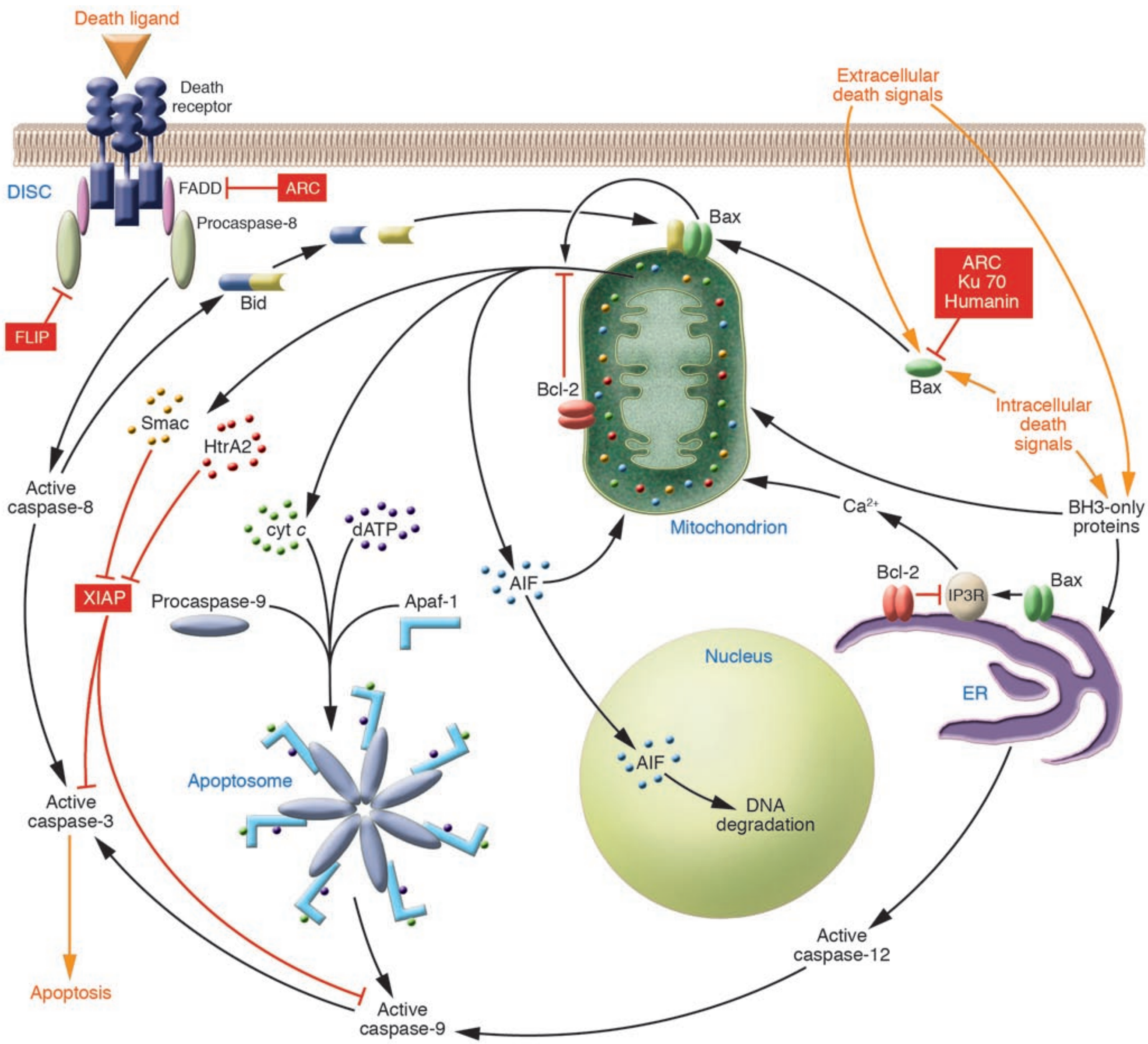

Figure 1
In the extrinsic pathway, ligand binding induces death receptors to recruit FADD, which recruits procaspase-8. Within this complex (DISC), procaspase-8 dimerizes and activates. Caspase-8 proteolytically activates procaspase-3, which cleaves cellular proteins causing cell death. In the intrinsic pathway, extracellular and intracellular stimuli signal to the mitochondria through a variety of BH3-only proteins (e.g., Bid) and through Bax, which translocates to and inserts into the outer mitochondrial membrane. Bax and Bak (not shown) stimulate the release of cytochrome *c* (cyt *c*) and other apoptogens. Once released, cytochrome *c* binds Apaf-1 along with dATP. This triggers oligomerization of Apaf-1 and recruitment of procaspase-9. Within this complex (apoptosome), procaspase-9 dimerizes and activates. Caspase-9 proteolytically activates procaspase-3. Caspase-8 also cleaves Bid, and its C-terminal fragment translocates to the mitochondria, where it activates Bax and Bak stimulating apoptogen release. FLIP binds and inhibits procaspase-8 in the DISC. ARC binds Fas, FADD, and procaspase-8, inhibiting DISC assembly. ARC, Ku-70, and Humanin bind Bax and inhibit its conformational activation and translocation. Bcl-2 and Bcl-x_L (not shown) inhibit mitochondrial apoptogen release. XIAP binds and inhibits activated caspase-9 and -3. Once cytoplasmic, the mitochondrial apoptogens Smac and HtrA2 bind XIAP, displacing and disinhibiting caspases. HtrA2 also has a serine protease activity that cleaves XIAP (not shown). AIF translocates to the nucleus and, in conjunction with a presumed endonuclease, mediates large-scale DNA fragmentation. A subset of intrinsic pathway death signals stimulate the ER, possibly through BH3-only proteins. This causes the release of intraluminal Ca^{2+} into the cytoplasm, which is mediated by Bax and Bcl-2 through the IP3R. Ca^{2+} translocates to the mitochondrial matrix and stimulates opening of the mitochondrial permeability transition pore in the inner membrane (not shown), which indirectly results in apoptogen release. The ER pathway may also activate procaspase-12, which can cleave and activate procaspase-9 independently of apoptosome formation (see text).

apoptosis repressor with a CARD (ARC), which is expressed preferentially in striated muscle and some neurons, antagonizes both central apoptosis pathways (51). The extrinsic pathway is inhibited by ARC's direct interactions with Fas, FADD, and procaspase-8, which prevent DISC assembly, while the intrinsic pathway is inhibited by direct binding and inhibition of Bax (51–53).

Efficient cell killing usually requires neutralization of inhibitory pathways as well as activation of effector mechanisms. This is best illustrated in mammalian cells by the ability of sympathetic neurons to withstand the usual toxic effects of direct intracellular injection of cytochrome *c*, a resistance attributable to XIAP (54). In most cell types, XIAP's tonic inhibition of caspases is relieved by the release of the mitochondrial apoptogens Smac/DIABLO and Omi/HtrA2, which directly bind XIAP, thereby displacing caspases (23–25). In addition, Omi/HtrA2 has a serine protease activity that cleaves XIAP, resulting in its irreversible inhibition (55).

Recently, the endoplasmic reticulum has been recognized as an important organelle in the intrinsic pathway. In addition to its role in cellular responses to traditional ER stresses, such as misfolded proteins, this organelle appears to be critical in mediating cell death elicited by a subset of stimuli originating outside of the ER, such as oxidative stress (56). Similar to their roles in transducing upstream signals to the mitochondria, BH3-only proteins appear to relay upstream death signals to the ER (57). The death signal output from the ER can take several forms. First, certain death stimuli increase cytoplasmic Ca^{2+} concentrations, a process controlled by Bax and Bcl-2 in the ER membrane through interactions between Bcl-2 and the inositol 1,4,5-trisphosphate receptor (IP3R), an ER Ca^{2+} release channel (56, 58). Increased cytoplasmic Ca^{2+} can result in Ca^{2+} overloading of the mitochondrial matrix and opening of the mitochondrial permeability transition pore. This, in turn, can lead to permeabilization and depolarization of the inner mitochondrial membrane, gross mitochondrial swelling, rupture of the outer mitochondrial membrane, and apoptogen release (59). The relevance of this mechanism may be dependent on cell context and stimulus, however, as apoptogen release in some instances of apoptosis is limited to much more subtle features of mitochondrial remodeling (60). A second ER death output is activation of procaspase-12 (61). Procaspase-12 can be activated through the intrinsic ER machinery (62) or cleavage by calpain, which can, in turn, be activated by elevations in cytoplasmic Ca^{2+} (63). Once activated, caspase-12 can translocate to the cytoplasm and cleave and activate procaspase-9 independently of apoptosome formation (64). This mechanism may provide a means by which the ER can carry out the distal steps in the intrinsic pathway independently of mitochondria. Although knockout mice have uncovered an essential role for procaspase-12 in ER stress-induced apoptosis (61), the applicability of this mechanism to humans is less clear due to procaspase-12 polymorphisms in some populations that encode nonsense mutations (65).

Lessons from myocardial ischemia-reperfusion

The significance of these apoptotic pathways in cardiomyocytes is most clearly revealed in the context of ischemia-reperfusion, a model characterized by a robust burst of apoptosis over a limited time frame (66, 67). Ischemia-reperfusion activates both the extrinsic and intrinsic pathways. Moreover, a variety of genetic studies indicate that both pathways play critical roles in the genesis of ischemia-reperfusion–induced myocardial infarction. Thus, a loss of function mutation in the death receptor Fas (*lpr* mouse) results in a 64% decrease in cardiomyocyte apoptosis and a 63% decrease in infarct size following ischemia-reperfusion in vivo (68). The source of death ligands during ischemia-reperfusion may be the heart cells (myocytes or nonmyocytes) themselves, as transudates from isolated perfused wild-type hearts contain FasL, TNF-α, and TNF-related apoptosis-inducing ligand (TRAIL) in the reperfusion phase (69). Similarly, infarct size following ischemia-reperfusion is reduced by 53% in mice lacking Bid, and this is accompanied by reduced cardiac dysfunction (70). These data implicate the extrinsic pathway in cardiomyocyte apoptosis and suggest that the Bid connection between the extrinsic and intrinsic pathways is important for efficient killing in this model. Additional genetic data underscore the importance of the intrinsic pathway in cardiomyocyte apoptosis following ischemia-reperfusion. Myocardial overexpression of Bcl-2, an antiapoptotic protein that inhibits cytochrome *c* release, reduces infarct size by 48–64% (71, 72). Likewise, cardiac-specific expression of either of 2 independent procaspase-9 dominant negative alleles decreases infarct size by 53% and 68%, with amelioration of cardiac functional abnormalities (70). These data provide proof of concept that cardiomyocyte apoptosis is a causal component of ischemia-reperfusion injury.

Does myocyte apoptosis occur during heart failure?

In contrast to ischemia-reperfusion, heart failure is characterized by very low — but abnormal — levels of cardiomyocyte death that persist for months to years. Questions have been raised as to whether myocyte loss in heart failure occurs primarily by apoptosis (73, 74). Thus far, however, this issue is unresolved, as only indirect markers have been used to characterize types of cell death. The most rigorous data demonstrate apoptosis rates of 0.08–0.25% in patients with end-stage dilated cardiomyopathy compared with 0.001–0.002% in controls (73, 75, 76). But is it reasonable to believe that rates this low could have a detectable impact on the pathogenesis of heart failure?

Does cardiomyocyte apoptosis play a causal role in heart failure?

This issue was addressed directly using transgenic mice with heart-restricted expression of a procaspase-8 fusion protein, whose dimerization and activation could be induced by administration of a drug (Figure 2) (77). Not surprisingly, within hours of acutely activating caspase-8, these transgenic mice died due to extensive cardiac damage. Interestingly, however, transgenic mice that never received the dimerizing drug died spontaneously over 2–6 months of a profound dilated cardiomyopathy. In contrast, longevity and cardiac function were normal in mice that expressed lower levels of the transgene protein and mice that expressed similar levels of an identical transgene protein except for a point mutation in the catalytic cysteine of the caspase. The explanation for the cardiomyopathy in the high-expressing inducible caspase-8–transgenic mice proved to be low rates of cardiomyocyte apoptosis: 0.023% as compared with 0.002% in controls. These data demonstrate that very low, albeit abnormal, rates of cardiomyocyte apoptosis are sufficient to cause lethal dilated cardiomyopathy. Given that the rates of cardiomyocyte apoptosis in patients with end-stage dilated cardiomyopathy are 5- to 10-fold higher than those in this transgenic model (73, 75, 76), myocyte apoptosis may also play a causal role in human heart failure. To test whether apoptosis is required for the development of cardiomyopathy in this model, a broad-spectrum caspase inhibitor was administered systemically starting before cardiac decompensation. Caspase inhibition abrogated cardiac dilatation and markedly ameliorated contractile dysfunction. These experiments provide direct evidence that low levels of cardiomyocyte apoptosis may be a causal component of heart failure.

Support for the importance of cardiomyocyte apoptosis in heart failure is also provided by another, more physiological model (Figure 2). Gq transduces humoral (e.g., angiotensin II) and mechanical stimuli that are important in cardiac hypertrophy (78). Myocardial overexpression of the α subunit of Gq (Gαq) bypasses the need for stimulus and elicits cardiac hypertrophy and dilated cardiomyopathy (79–81). This phenotype is accompanied by cardiomyocyte

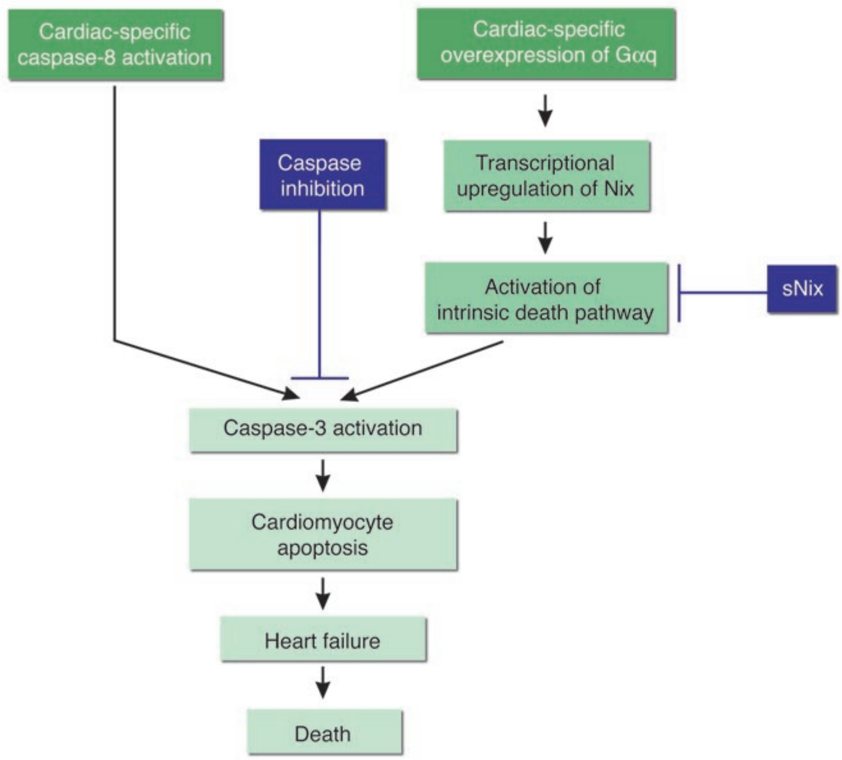

Figure 2
Cardiomyocyte apoptosis plays a mechanistic role in murine heart failure models. Cardiac-restricted expression of a conditional caspase-8 transgene indicates that low, but abnormal, levels of cardiomyocyte apoptosis (0.023% vs. 0.002% in controls) are sufficient to cause a lethal dilated cardiomyopathy. Similarly, cardiac-specific expression of $G\alpha q$ induces the transcriptional activation of the BH3-only–like protein Nix, which results in cardiomyocyte apoptosis and dilated cardiomyopathy. The latter is severely exacerbated and lethal during pregnancy. Caspase inhibitors or expression of sNix, an antiapoptotic Nix splice variant, ameliorate cardiomyopathy in these models. In addition, caspase inhibition and sNix decrease mortality in the $G\alpha q$ peripartum cardiomyopathy model.

apoptosis, which is mediated by the transcriptional induction of Nix/BNip3L, a BH3-only–like protein (82). In addition to this baseline cardiomyopathy, 30% of pregnant $G\alpha q$-transgenic mice exhibit fulminant lethal heart failure accompanied by further increases in apoptosis. Inhibition of apoptosis, either through expression of sNix, an antiapoptotic Nix splice variant (82), or administration of a broad-spectrum caspase inhibitor (83), markedly decreases the severity and mortality of the $G\alpha q$ peripartum cardiomyopathy.

Hemodynamic overload is a unifying stimulus in multiple forms of heart failure. Several studies provide evidence that inhibition of cardiomyocyte apoptosis lessens the severity of cardiomyopathy resulting from hemodynamic overload. Overexpression of Bcl-2 (84) or ARC (85) inhibits cardiomyopathy induced by prior myocardial infarction. Conversely, loss of a basal survival mechanism can exacerbate cardiomyopathy induced by hemodynamic overload. This is illustrated by a study on mice with ventricular-restricted deletion of gp130 (86), a component of the receptor for several prosurvival cytokines that induces the STAT-dependent transcription of Bcl-x_L (87). While these mice are normal at baseline, they develop lethal heart failure following aortic constriction. Taken together, these and other studies (88, 89) demonstrate a mechanistic role for cardiomyocyte apoptosis in heart failure.

What pathways mediate cardiomyocyte apoptosis in the failing heart?

Although the fundamental blueprint for cell death signaling has been highly conserved over more than a billion years of evolution, the precise molecular events — especially upstream ones — are often specific to cell type and/or death stimulus. Relevant stimuli in heart failure probably include stretch (90), ROS (91), β_1-adrenergic agonists (92, 93), angiotensin II (94), proinflammatory cytokines (95), cytoskeletal abnormalities (96), and drugs such as anthracyclines (97), although the relative importance of these stimuli in the most common instances of heart failure has not yet been established. Likewise, with the exception of the angiotensin II → $G\alpha q$ → Nix and gp130 → STAT → Bcl-x_L pathways noted above, little is known about the connections between the myriad of upstream signaling pathways and the central death machinery. Moreover, the pathophysiological significance of some upstream events is poorly understood. For example, strong evidence implicates telomere dysfunction as a cause for myocyte apoptosis in heart failure (98–100). However, it remains unclear whether telomere uncapping represents an abortive attempt by cardiomyocytes to reenter the cell cycle or a response to the activation of multiple stress pathways.

Even the importance of each of the central death pathways in heart failure needs to be better defined. For example, while both intrinsic and extrinsic death pathways play significant roles in ischemia-reperfusion injury, little is known about the importance of the extrinsic pathway in heart failure. Similarly, although the ER pathway is known to be activated in failing human hearts (101), the extent to which it plays a mechanistic role in cardiomyocyte demise remains to be determined. The study of mice harboring mutations in various components of the central death machinery, which has been so informative with respect to understanding ischemia-reperfusion injury, should be useful in addressing some of these questions.

Potential therapeutic targets and future questions

We have described experimental evidence showing that cardiomyocyte apoptosis is a causal component of ischemia-reperfusion injury and heart failure in rodent models. If this paradigm extends to humans, it follows that prevention or inhibition of myocyte death may provide a novel therapeutic approach to these most common and lethal heart syndromes. How might inhibition of cardiomyocyte apoptosis be achieved in a clinical setting?

We will limit our comments to small molecule therapies, which, at present, are the most practical options. In general, receptors and enzymes constitute the molecules most amenable to pharmacological manipulation. Several receptor/enzyme pathways influence survival in cardiomyocytes. In fact, β-adrenergic receptor antagonists and inhibitors of the angiotensin II axis (angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists) are already mainstays in the treatment of heart failure. The extent to which the salutary effects of these agents are attributable to their inhibition of apoptosis is not known. Although β_1-selective adrenergic receptor blockers are used primarily to avoid extracardiac side effects, this approach is also consistent with observations that β_1-adrenergic receptors activate death pathways in cardiomyocytes, which are opposed by β_2-adrenergic receptors (102, 103).

The serine-threonine kinase Akt is a central molecule in several receptor-mediated survival pathways in cardiomyocytes. Akt inhibits apoptotic signaling at multiple levels including phosphorylation of the BH3-only protein Bad (104, 105), IKKβ (a proximal kinase that activates NF-κB signaling) (106), the proapoptotic transcription factor Foxo3a (107), and perhaps procaspase-9 (108, 109). Akt can be activated in cardiomyocytes by receptor tyrosine kinase ligands, such as IGF-1 (110, 111), and by exogenously administered thymosin β4 (112). IGF-1 and Akt have been demonstrated to reduce cardiomyocyte apoptosis and infarct size following ischemia-reperfusion and prolonged ischemia (111, 113–117). In addition, cardiac-restricted expression of an IGF-1 transgene has beneficial effects on cardiac remodeling following myocardial infarction (114) and in a genetic model of cardiomyopathy (118), although interpretation of these studies is complicated by the fact that myocardial IGF-1 expression was present in the mice beginning in the fetus, which resulted in baseline increases in the number of cardiomyocytes (119). Interestingly, growth hormone, which increases serum IGF-1 levels, was shown in a small clinical study to improve clinical and functional parameters in patients with idiopathic dilated cardiomyopathy (120). Although questions remain concerning the deleterious effects of Akt on the heart (121), the data discussed here raise the possibility that IGF-1 may ameliorate heart failure through inhibition of cardiomyocyte apoptosis. Similarly, activation of the gp130 → STAT → Bcl-x_L survival pathway with ligands such as cardiotrophin-1 (CT-1) may provide an alternative means of achieving this end (122).

Although manipulation of receptor-mediated upstream pathways is attractive because of their accessibility, this approach can be confounded by redundancy and complicated by undesirable pleiotropic effects. These issues provide a strong rationale for interventions that focus directly on the central death pathways. Where in the central death pathways would inhibition of cardiomyocyte apoptosis be most efficiently achieved? Both central death pathways converge on caspases. Broad-spectrum caspase inhibitors reduce infarct size by 21–52% and decrease cardiac dysfunction following ischemia-reperfusion (123–125, S1). Caspase inhibitors have also been shown to ameliorate cardiac dysfunction and/or inhibit mortality in the caspase-8 and Gαq models of dilated cardiomyopathy discussed above (77, 83). These effects of caspase inhibition correlate with inhibition of cardiomyocyte death, which suggests that the benefit of these agents results from their antiapoptotic properties. Recently, however, caspases have been demonstrated to cleave cardiac contractile proteins and at least 1 cardiac transcription factor (S2–S4). This raises the possibility that caspase inhibitors may also preserve cardiac function independently of their effects on cell death.

The efficacy of caspase inhibitors in these settings poses important questions. Caspase activation in cardiomyocytes occurs after mitochondrial damage and the release of apoptogens. Moreover, as in many systems, cytochrome *c* release in the myocardium is unaffected by caspase inhibition (S5). Given these mitochondrial abnormalities, it is curious that caspase inhibitors exert such marked improvement on disease pathogenesis. Whether their beneficial effects result from inhibiting upstream caspases, the release of other apoptogens (such as apoptosis-inducing factor and endonuclease G, whose translocation appears to be caspase dependent; refs. S6, S7), or other yet-to-be-described mechanisms remains to be determined.

Another example of a small molecule that antagonizes the central death machinery is UCF-1, an inhibitor of the serine protease activity of Omi/HtrA2 (S8). Unexpectedly, UCF-1 markedly inhibits cardiomyocyte apoptosis and reduces infarct size following ischemia-reperfusion by maintaining XIAP levels (S9). These data indicate that relief of inhibitory pathways is critical for apoptosis to proceed in cardiomyocytes and suggest that strategies built around maintaining inhibition may be cardioprotective.

Despite the efficacy of postmitochondrial inhibition of apoptosis in these examples, an even more effective strategy may be to intercept apoptotic signaling upstream of the mitochondria. While a premitochondrial approach might be limited by redundancy, it offers the important advantage of preventing mitochondrial dysfunction. In fact, cells lacking both Bax and Bak, either one of which is required for upstream death signals to gain access to the mitochondria, exhibit long-term protection against multiple noxious stimuli (S10, S11). Premitochondrial inhibition may require drugs that interfere with interactions between BH3-only (e.g., Bid) and multidomain proapoptotic Bcl-2 proteins (e.g., Bax and Bak) (Figure 1). Another attractive possibility is provided by the endogenous inhibitor ARC. ARC would provide premitochondrial inhibition of both extrinsic and intrinsic pathways and preserve mitochondrial function (51, S12). In addition, the relatively restricted expression pattern of endogenous ARC (52) may offer a means to avoid potential carcinogenic effects of diffuse long-term inhibition of apoptosis. A major outstanding issue is how best to exploit endogenous ARC as a therapeutic agent.

Conclusions

Our understanding of the significance of myocyte loss during heart failure has increased substantially since this phenomenon was initially observed by cardiac pathologists. Molecular and genetic studies demonstrate clearly that cardiomyocyte apoptosis is a critical process in the pathogenesis of heart failure in rodent models. If this paradigm extends to humans, apoptosis will be a logical target for novel therapies. Despite success in establishing a mechanistic link between apoptosis and heart failure, our knowledge of the precise molecular mechanisms that regulate cell death specifically in this syndrome remains rudimentary. An understanding of these mechanisms will be indispensable for the rational design of future antiapoptotic therapies.

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