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STATE-OF-THE-ART PAPER

New Targets to Treat the Structural Remodeling of the Myocardium

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Classical therapy of heart failure is based on treatment of its pre-disposing/triggering factors and of the neurohumoral activation secondary to the deterioration of cardiac function. A new view is emerging that proposes the direct intervention on the pathological structural remodeling of the myocardium as part of heart failure therapy. In fact, in conditions of chronic injury, the cardiomyocytic and the noncardiomyocytic components of the myocardium undergo a series of structural lesions (i.e., cardiomyocyte growth and death, inflammation, alterations of collagen matrix, and microvascular rarefaction) that are governed by a complex interplay of mechanisms. Our increasing knowledge of the role of these mechanisms in remodeling enables us not only to better understand how our more successful therapies work but also to explore novel therapies for the future. In this paper, we will examine recent insights from experimental and pilot clinical studies that have provided new targets for interventions to prevent or reverse inflammation, alterations of collagen matrix, and cardiomyocyte death. (J Am Coll Cardiol 2011;58:1833–43) © 2011 by the American College of Cardiology Foundation

The concept of cardiac remodeling was initially created to describe the changes in the anatomy of the left ventricle that occur after myocardial infarction. Today, myocardial remodeling is used to describe a variety of changes in the biophysiology of the cardiomyocyte, the volume and composition of cardiomyocyte and noncardiomyocyte compartments, and the geometry and architecture of the left ventricular (LV) chamber that occur in response to myocardial infarction, pressure or volume overload, cardiomyopathic states, and exposure to infectious or cardiotoxic agents (1). Myocardial remodeling results from modifications that are not necessarily adaptive to the initial insult, but pathologic and potentially self-perpetuating in a progressive vicious circle (2). Myocardial remodeling may result in alterations of cardiac energetics, compromise of intramyocardial perfusion, deterioration of both diastolic and systolic function, and propensity for arrhythmias (1). Therefore, myocardial remodeling is a key determinant of the clinical course and outcome of a number of cardiac diseases evolving with chronic heart failure (HF) (Fig. 1).

HF has become a major clinical and public health challenge. Since conventional strategies for the treatment of HF are still largely based on targeting its causes and its neurohumoral consequences, a broader perspective may be useful for the development of novel medical therapies to prevent or even reverse myocardial remodeling and reduce the burden of HF. In this conceptual framework, gene expression profiling (microarray) studies have identified gene cluster expression profiles that may be involved in the structural remodeling of the myocardium. Genes associated with remodeling were largely those involved in cardiomyocyte hypertrophy and death, inflammation, alterations of collagen matrix, and microvascular rarefaction (3,4). Since the antiremodeling effects of current pharmacological (5) and device-based (6) measures to treat HF have been recently reviewed, this article will focus on experimental and clinical studies that have provided new therapeutic targets. In addition, given that novel therapies for cardiomyocytic hypertrophy (7) and microvascular rarefaction (8) have been addressed recently elsewhere, the insights for new interventions on myocardial inflammation, fibrosis, and cardiomyocyte death will be considered in this article. This said, it is necessary to remark that HF is a clinical syndrome that necessarily reflects a diversity of patterns of structural myocardial remodeling both in qualitative and quantitative terms

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Abbreviations and Acronyms

HF = heart failure
IGF = insulin-like growth factor
IL = interleukin
LV = left ventricular
microRNA = micro-ribonucleic acid
MMP = matrix metalloproteinase
NF = nuclear factor
PCP = procollagen type I carboxy-terminal proteinase
TGF = transforming growth factor
TLR = toll-like receptor
TNF = tumor necrosis factor

(Table 1) (9–11). As a consequence, the impact of the different therapeutic strategies here reviewed on the components of myocardial remodeling requires a critical and cautious approach.

Inflammation

Upon activation of the innate immune system by cardiac injury, several inflammatory mediators are released and inflammatory cells are attracted to the myocardial site of injury (12). All these humoral and cellular factors have distinct functions in the remodeling process. For instance, cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α are involved in cardiomyocyte apoptosis and activation of matrix metalloproteinases (MMPs) that can degrade the physiological collagen scaffold of the myocardium (13,14) (Fig. 2). The resulting collagen fragments exert potent pro-inflammatory actions, while MMPs can also process cytokines and chemokines altering their biological activity (14). Conversely, whereas neutrophils release oxidants and proteases also involved in apoptosis and collagen degradation, monocytes/macrophages stimulate fibroblast- and myofibroblast-mediated synthesis and deposition of collagen fibers contributing to the development of myocardial fibrosis (15) (Fig. 2).

Although several studies have shown raised levels of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 in the circulation of patients with HF (16), the results of large clinical trials based on anticytokine therapy for patients with HF have been largely disappointing due to either neutral or negative findings (17,18). In this regard, there are several fundamental issues to be dealt with. Is inflammation in HF the same as in conditions such as cancer or rheumatoid arthritis, in terms of cytokines and their dependent pathways activation, despite differences in the degree of inflammation? And more importantly, does inflammation have the same impact among different HF etiologies and in the different stages of evolution? If inflammation pathways are redundant in HF, theoretically it is not sensible to focus intervention on individual cytokines rather than on the cytokine network. Therefore, much work is needed to clarify the physiological role of both individual cytokines and cytokine networks, in different stages of HF, due to different etiologies, and compared with other known inflammatory diseases.

Conversely, an improvement in the understanding of the underlying mechanisms involved in clinical responses to anti-inflammatory agents is required. This is illustrated by data from a recent review of the potential beneficial mode of action of pentoxifylline, a putative TNF-α inhibitor in HF (19). In their review, the investigators showed that several trials have reported improved clinical outcome after pentoxifylline treatment, but without a concordant effect on TNF-α modulation, suggesting that these beneficial effects may not necessarily occur through TNF-α inhibition, but

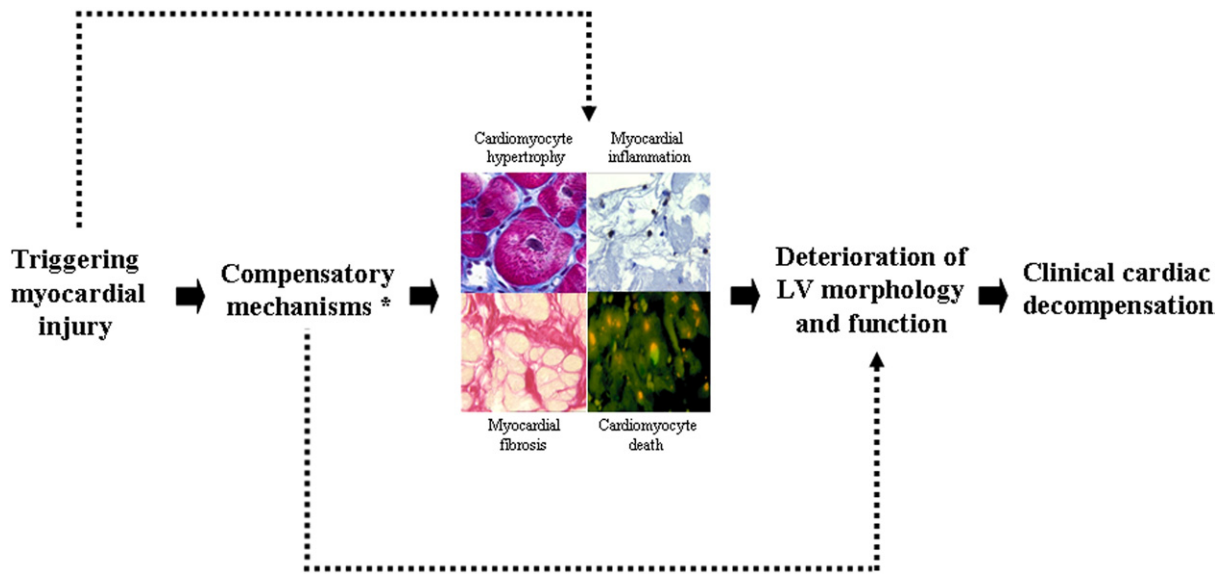

Figure 1 Pathogenesis of Heart Failure

The lesions responsible for myocardial remodeling are critically involved in the deterioration of left ventricular (LV) morphology and function that leads to clinical cardiac decompensation. *Neurohormonal mechanisms activated to maintain the pumping capacity of the heart initially compromised by the triggering injury.

Table 1 Heterogeneity of Myocardial Structural Remodeling in Different Cardiac Diseases at Heart Failure Stage

Disease	Inflammation	Fibrosis		Collagen Scaffold	Cardiomyocyte Death		
		Reactive	Reparative	Disruption	Apoptosis	Necrosis	Autophagy
Hypertensive heart disease	+	++		+	++		
Ischemic heart disease	+/++	+	+++	++	+	+++	+
Dilated cardiomyopathy	+/++	+	++	+++	++	+	+
Myocarditis	+++	+++	(+)		++		+
Diabetic cardiomyopathy	++	+++	+		++	+	+
Aortic valve stenosis	+	+++		+	+++		

Semiquantitative score of the severity of the lesions: + = low; ++ = moderate; +++ = high. Parentheses indicate that the information about the presence of reparative fibrosis in myocarditis is contradictory. Elaborated with information reviewed in Graham et al. (9), Dorn (10), and Jiang and Liao (11).

may be mediated by other subtle effects on arterial vasculature. Therefore, future basic and clinical research based on anti–TNF-α therapy should establish the best type of currently available antagonists (e.g., the fusion protein etanercept, and the monoclonal antibodies infliximab, adalimumab, certolizumab, and golimumab), the optimal dosage, which subgroups of chronic HF to treat, and the putative molecular mechanisms involved in clinical changes before any firm conclusions regarding efficacy can be drawn.

Novel potential therapeutic options to reduce inflammation in chronic HF are emerging from pre-clinical discoveries. For instance, pentraxin 3, a molecule produced by monocytes, macrophages, and vascular and fibrogenic cells in response to IL-1β and TNF-α (20), seems to counteract the detrimental effects of these cytokines and exert anti-remodeling actions in the ischemic injured heart (21). Moreover, TG100-115, a compound that inhibits the catalytic domain of the enzyme PI3Kγ/δ, a crucial component of signal transduction controlling the recruitment of white blood cells from the blood stream into tissues (22), has been shown to exert cardiac protective effects in animal models of ischemia/reperfusion (23). Intervention on the downstream mannose-binding lectin complement-activating pathway, which has been recently reported to be increased in the left

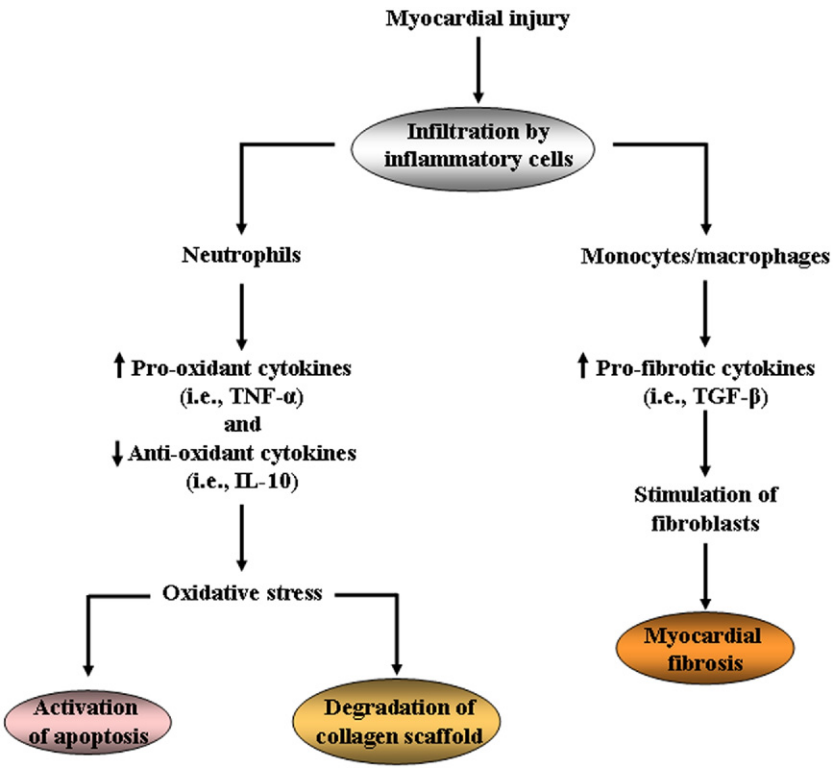

Figure 2 Schematic of Pathways

Schematic representation of the pathways through which myocardial inflammation may facilitate the development of other lesions that characterize myocardial remodeling (i.e., apoptosis and fibrosis). IL = interleukin; TGF = transforming growth factor; TNF = tumor necrosis factor.

ventricle of mice with experimentally-induced myocardial infarction and continuous up-regulation of the IL-6 activated gp130/STAT3 signaling pathway (24), may represent a novel therapeutic target to tackle inflammation after cardiac injury. Although data from pre-clinical studies suggest that inhibition of toll-like receptor 4 (TLR4) may be a novel therapeutic strategy for myocardial remodeling associated with ischemic HF (25), this may not be a promising therapeutic avenue because TLR4 inhibition may lead to a functional loss of the innate immune mechanisms, and, thus, the global prognosis may not be improved.

Targeting the vicious inflammation-oxidative stress cycle can be another approach to interfere with the remodeling effects of inflammation. Recently, it has been proposed that maintenance of an optimal balance between 2 of the major cytokines that are demonstrably connected to oxidative stress, the pro-inflammatory TNF-α and the anti-inflammatory IL-10, may be of crucial importance in mitigating both inflammation and oxidative stress processes leading to myocardial remodeling and HF (26) (Fig. 2). The finding that patients with advanced HF exhibit a low IL-10:TNF-α ratio in blood (27) adds further support to this notion. In this regard, it has been reported that treatment with recombinant IL-10 inhibits TNF-α–dependent inflammation and oxidative stress, and attenuates myocardial remodeling and LV dysfunction in a murine model of HF (28).

Although the influence of inflammatory pathways on cardiomyocyte survival is a matter of controversy, it offers a window of therapeutic opportunity. Indeed, the nuclear factor (NF)-κB super family of transcription factors has been implicated in the regulation of the life-death switch in many cell types, including cardiomyocytes (29). Whereas it has been shown that NF-κB is cardioprotective during acute hypoxia and reperfusion injury (30), prolonged activation of NF-κB appears to be detrimental and to promote HF by eliciting signals that trigger chronic inflammation through enhanced production of cytokines including TNF-α, IL-1, and IL-6, leading to endoplasmic reticulum stress responses and cell death (31). Although the underlying mechanisms that account for the multifaceted and differential outcomes of inflammation on cardiac cell fate are presently unknown, it has been proposed that therapies designed to modulate NF-κB activity in the heart temporally and spatially hold promise for mitigating both inflammation and aberrant cardiomyocyte death after injury (32).

In summary, as recently proposed by an expert group of the Heart Failure Association of the European Society of Cardiology (33), several requirements need to be accomplished by future studies in the field of anti-inflammatory therapies for HF to establish their usefulness and safety (33). In particular, a more careful and precise patient selection for upcoming clinical trials of anti-inflammatory agents in HF, as well as more fundamental pre-clinical studies including better animal models are recommended.

Alterations of Collagen Matrix

Although fibrosis is commonly found in the setting of the ischemic scar (i.e., reparative or replacement fibrosis), there is increasing recognition of diffuse interstitial and perivascular myocardial fibrosis (i.e., reactive fibrosis) occurring either in regions remote to the infarct or as a separate entity in a variety of conditions in the absence of infarct, including hypertensive heart disease, diabetic cardiomyopathy, hypertrophic cardiomyopathy, and idiopathic dilated cardiomyopathy (34). Whereas reparative fibrosis may contribute to preserve LV morphology and systolic function (i.e., preventing adverse geometric remodeling) (35), reactive fibrosis is thought to contribute to the deterioration of LV function (i.e., impairing the mechanical properties of the left ventricle during diastole) and electrical activity (i.e., facilitating arrhythmogenesis) (36). Because of space limitations, we will focus our attention on pathologic myocardial fibrosis. Given the dynamic nature of the myocardial collagen network, fibrosis can be viewed as the result of the unbalance between the enhanced synthesis of collagen types I and III and unchanged or reduced collagen degradation (34).

In the clinical setting, some data with drugs used for standard therapy of cardiac diseases support the notion that myocardial fibrosis can be targeted with beneficial clinical impact. In small clinical studies performed in hypertensive patients with histologically proven myocardial fibrosis, it has been shown that treatment with the angiotensin-converting enzyme inhibitor lisinopril was able to reduce the extent of myocardial fibrosis, and that this effect was associated with improved LV diastolic dysfunction (37). Similarly, treatment with the angiotensin-II receptor blocker losartan diminished myocardial fibrosis, and this was accompanied by a decrease in LV stiffness (38). Additionally, in hypertensive patients with clinical HF, treatment with the loop diuretic torasemide in addition to standard therapy, which was able to reduce myocardial fibrosis, improved New York Heart Association functional class in these patients (39). Data from the RALES (Randomized Aldactone Evaluation Study) and EPHESUS (Eplerenone Heart Failure Efficacy and Survival Study) studies support a beneficial role for mineralocorticoid receptor antagonists on extracellular matrix turnover, as assessed by circulating biomarkers of collagen metabolism, with a positive impact in post-infarct remodeling and clinical outcome (reviewed in [40]).

The synthesis of fibrillar collagen is regulated by myofibroblasts (41). The origin of myofibroblasts is unclear but may result from growth factor-mediated (e.g., transforming growth factor [TGF]-β, platelet-derived growth factor) and hormone-mediated (e.g., endothelin-1, angiotensin II, aldosterone) differentiation of resident fibroblasts or recruitment of microvascular pericytes or endothelial cells, as well as from progenitor stem cells present in the circulation or in the heart itself (41). For instance, it has been recently reported that TGF-β released by inflammatory cells induces the transdifferentiation of fibroblasts to myofibroblasts and

the subsequent synthesis and deposition of collagen in the myocardium of patients with HF and preserved ejection fraction (42). In this regard, compounds that act at the level of the TGF-β heteromeric receptor may be a useful approach to interfere with the fibrotic process. In fact, in an experimental rat model of myocardial infarction, treatment with a TGF-β type I receptor inhibitor significantly reduced TGF-β activity, leading to the attenuation of myocardial remodeling and LV dysfunction (43). Conversely, a synthetic peptide from TGF-β type III receptor (betaglycan) has been shown to inhibit TGF-β–dependent signaling pathway and collagen type I synthesis in cardiac fibroblasts, as well as to prevent myocardial fibrosis in rats with spontaneous hypertension (44).

Collagen types I and III are secreted by myofibroblasts as procollagen type I and III precursors having N-terminal and C-terminal propeptides that are cleaved to yield the triple helical monomers (45) (Fig. 3). The enzyme procollagen type I carboxy-terminal proteinase (PCP) is a neutral, calcium-dependent proteinase responsible for the cleavage of the carboxy-terminal propeptide of procollagen type I (45) (Fig. 3). In addition, PCP stimulates extracellular activation of the enzyme lysyl oxidase that controls the formation of covalent cross-links between collagen type I molecules to form insoluble stiff collagen type I fibrils (45) (Fig. 3). Evidence from experimental and clinical studies shows that the excess of PCP and lysyl oxidase is associated with an increase in myocardial collagen type I synthesis, cross-linking, and deposition observed in different cardiac diseases (46). Of interest, recent findings show that these alterations are associated with impaired diastolic function and reduced exercise tolerance in patients with HF and preserved ejection fraction (47). In this regard, it has been reported that, in contrast to the addition of furosemide, the addition of torasemide to standard HF therapy reduced the excess of PCP and lysyl oxidase, as well as the exaggerated cross-linking and deposition of collagen fibers present in the myocardium of patients with HF (48,49).

Other emerging possibilities to act therapeutically on myocardial fibrosis involve micro-ribonucleic acids (microRNAs) and stem cells. Altered regulation (mostly up-regulation) of a number of specific microRNAs related to myocardial fibrosis has been found in animal models of LV hypertrophy and failure, and in human end-stage HF (50). The first successful antagomir treatment of myocardial fibrosis and HF in a murine pressure overload model using specific miR-21 antagonists (51) paved the way for microRNA manipulation as a novel treatment strategy to prevent and treat LV fibrosis, hypertrophy, and failure. Conversely, direct injection of human stem cells—in particular, mesenchymal stem cells—into ischemic rat myocardium decreased fibrosis, and that resulted in the prevention of systolic and

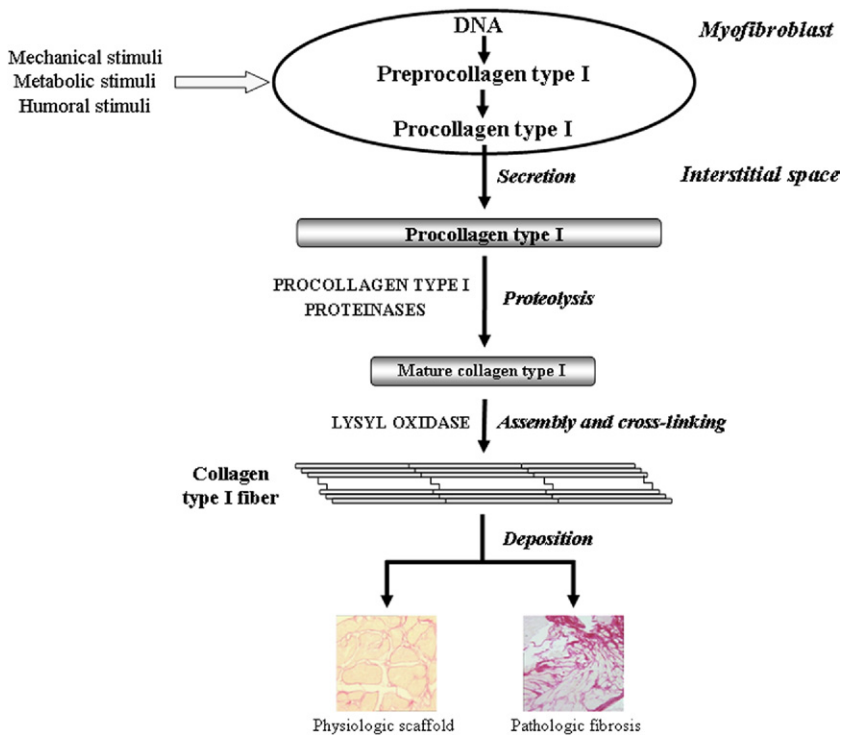

Figure 3 Schematic of Extracellular Steps

Schematic representation of the extracellular steps involved in the generation and deposition of collagen type I fibers in normal conditions (leading to the formation of the myocardial collagen scaffold) and pathologic conditions (leading to myocardial fibrosis). DNA = deoxyribonucleic acid.

diastolic LV dysfunction without evidence of myocardial regeneration (52). Additionally, stem cell transplantation significantly attenuated the increase in cardiac expression of collagen types I and III, and TGF-β in the infarcted myocardium (53). Because stem cells express a number of molecules involved in the biogenesis of extracellular matrix such as adrenomedullin, thymosin-β, thymocollagenase, MMPs, serine proteases, and their inhibitors, it has been suggested that transplanted stem cells can inhibit fibrosis through paracrine actions (54). However, the understanding of the underlying mechanisms, delivery, specificity, and potential toxicity of such microRNAs and stem cells needs to be improved to consider their future therapeutic applicability.

It is important to mention that there are clinical conditions in which excessive degradation of the physiologic cardiac collagen scaffold (i.e., endomysial and perimysial collagen) coexists with pathologic collagen deposition or fibrosis. For instance, in post-myocardial infarction, activation of myocardial MMP-2 and MMP-9 has been documented and demonstrated to be involved in collagen scaffold degradation, LV dilation, and compromise of cardiac systolic function (55). In addition, an association between myocardial MMP-1 up-regulation and reduction of collagen scaffold has been reported in hypertensive patients with LV dilation and systolic HF (56). Furthermore, administration of glucocorticosteroids and nonsteroidal anti-inflammatory drugs during the acute post-myocardial infarction period has been shown to result in increased infarct-associated MMP levels and activity, increased thinning of the infarct zone, greater degrees of infarct expansion, and LV dilation and dysfunction (57,58). In this regard, although earlier proof-of-concept pre-clinical studies of nonselective MMP inhibitors had yielded promising results in preventing post-myocardial remodeling, data from the PREMIER (Prevention of Myocardial Infarction Early Remodeling) study failed to confirm them (59). In the PREMIER study, patients with LV ejection fraction $<$40% after an ST-segment elevation myocardial infarction were randomly assigned within 48 h after their infarction to receive either a broad MMP inhibitor (PG-116800) or placebo and were followed up for 90 days to evaluate the effects on LV volumes measured by echocardiography. No significant benefit was found. This disappointing finding may be a result of better reperfusion and medical therapy with angiotensin-converting enzyme inhibition and beta-blockade, or simply, as the researchers suggest, a too-small dose of the inhibitor agent to elicit a clinically measurable response.

Despite this failure, recent discoveries of oxidative/nitrosative activation and phosphorylation of MMPs, as well as novel non–matrix-related intracellular and extracellular targets of MMPs, give hope for the development of newer MMP inhibitors (60). In addition, a potential new mechanism of MMP inhibition through recombinant matricellular proteins (i.e., nonstructural glycoproteins that regulate interactions between cardiac cells and extracellular matrix) can be advanced. In fact, it has been reported that increased levels of the matricellular protein thrombospondin-2 reduce MMP-2 activity per se by scavenging of the MMP-thrombospondin-2 complex through the lipoprotein-related protein receptor (61).

In summary, the therapeutic modulation of myocardial collagen matrix must be designed to restore the equilibrium between the synthesis and degradation of collagen to both preserve the physiologic cardiac collagen matrix and prevent or eliminate the pathologic accumulation of fibrotic tissue. In addition, the strategies designed to reach this aim should provide cardiac-specific targeting to maintain tissue structure and preserve tissue repair in other organs.

Cardiomyocyte Death

The loss of functional cardiomyocytes involved in the progression from cardiac injury to symptomatic HF can be attributable to various modalities of cell death, including apoptosis, necrosis, and autophagy, that are interconnected by common cellular pathways at multiple points (62) (Fig. 4). Although the significance of the contribution of apoptotic cell death to myocardial remodeling continues to be debated, associations of apoptosis with LV wall thinning and chamber dilation, and deterioration of systolic performance have been found in experimental models and clinical studies (10). Whereas completely executed apoptosis leads to cardiomyocyte death and reduction of functioning cardiomyocyte mass, the potential also exists for activation of upstream apoptotic steps only leading to compromise of adenosine triphosphate production and diminished functional efficiency of viable cardiomyocytes (10) (Fig. 4). Therefore, the notion has emerged that apoptosis inhibition is likely to be a necessary adjunct to cardiomyocyte regeneration in the global strategy of "myocardial salvage" (62).

Whereas some studies have shown that direct caspase inhibition reduces the acute loss of myocardium in various animal models, other studies indicate that caspase inhibition might not be able to completely inhibit apoptosis, likely because apoptosis can be induced in the ischemic-hypoxic injured heart lacking caspase activation by caspase-independent pathways (63). Nevertheless, regarding alternative potential antiapoptotic therapies indirectly related to caspase inhibition for which some proof of principle exists, it is worth considering that UCF-101 (a small-molecule inhibitor of the mitochondrial Omi/HtrA2 serine protease released into the cytoplasm during induction of apoptosis, that in turn promotes caspase activation) rescues cardiomyocytes and restores LV dysfunction after ischemia/reperfusion injury in the rat heart (64).

As in the case of fibrosis considered in the preceding text, emerging evidence has shown that microRNAs and factors released from stem cells play a role in regulating apoptosis in the heart, suggesting that they can be therapeutic targets for apoptosis-related cardiac diseases (65,66). For instance, overexpression of miR-320 has been shown to enhance

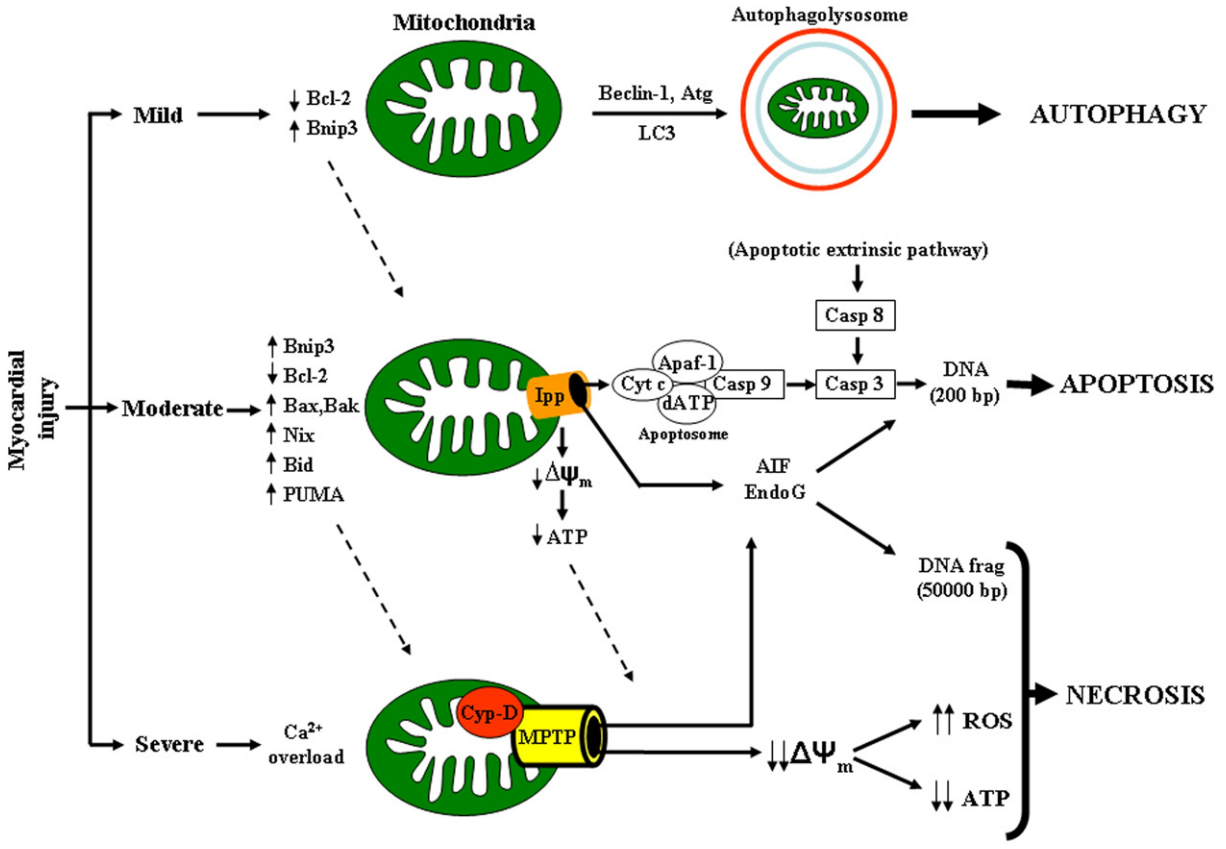

Figure 4 **Mechanisms and Potential Relationships Among Autophagy, Apoptotic, and Necrotic Pathways**

AIF = apoptosis-inducing factor; Apaf = apoptosis protease-activating factor; Atg = autophagy-related genes; ATP = adenosine triphosphate; Casp = caspase; Cyp-D = cyclophilin-D; Cyt c = cytochrome c; dATP = deoxyadenosine triphosphate; DNA = deoxyribonucleic acid; Endo-G = endonuclease-G; frag = fragmentation; Ipp = ion-permeable pore; MPTP = mitochondrial membrane transition pore; PUMA = p53 up-regulated modulator of apoptosis; ROS = reactive oxygen species; $\Delta\Psi_m$ = inner mitochondrial membrane potential.

apoptosis in cardiomyocytes, whereas knockdown of miR-320 or in vivo treatment with antagomir-320 can attenuate apoptosis and reduce infarct size upon ischemia/reperfusion (67). Additionally, some experimental data suggest that factors released by stem cells in infarcted hearts (i.e., IL-10, osteopontin, and clusterin) may reduce adverse remodeling and enhance cardiac recovery (68,69).

Although a significant proportion of necrotic deaths are passive, evidence has emerged that necrosis can also be regulated and thus therapeutically interfered with (70). For instance, cyclosporine A, which inhibits necrosis by blocking the mitochondrial permeability transition pore, has been shown to reduce infarct size in the mouse (71). In a small study of 58 patients with acute ST-segment elevation myocardial infarction, cyclosporine A, administered immediately before angioplasty/stenting, significantly reduced creatine kinase release and infarct size by magnetic resonance imaging during the first 5 days (72). Although this pilot study suggests that cyclosporine A may reduce infarct size in human ST-segment elevation myocardial infarction treated with reperfusion, the numbers are too small to draw any firm conclusions, and evaluation of cardiac function and long-term follow-up are needed. Finally, necrostatin-1, also an inhibitor of the mitochondrial membrane transition pore and thus protector of the mitochondrial integrity and function, is able to decrease infarct size in experimental models of ischemia/reperfusion (73,74).

Several observations indicate that constitutive autophagy in the heart under physiological conditions is a homeostatic mechanism for maintaining cardiomyocyte size and global cardiac structure function. The controversy arises when considering the role of autophagy in myocardial infarction because it has been described to be protective during ischemia but detrimental during reperfusion (75). Similarly, although failing human hearts exhibit an increased number of autophagosomes, suggestive of increased autophagy (76,77), further examination of the details of this process is necessary to evaluate whether autophagy plays a protective or a deleterious role in heart failure, thus making premature any attempt to target it therapeutically.

Because cumulative evidence unquestionably points to the mitochondria as arbiters of the different cardiomyocyte

death pathways (Fig. 4), mitochondria-targeted interventions aimed to the preservation of mitochondrial integrity and function remain a focal point of ongoing research in the therapeutic modulation of cell death. Currently, most efforts along these lines focus on preventing the mitochondrial oxidative damage that arises from ischemic or hypoxic conditions (78). Additionally, a number of signal transduction studies have proven that mitochondrial integrity can be enhanced by kinases involved in cell survival, in particular Akt kinase or PKB (79). In this conceptual framework, the connection between insulin-like growth factor (IGF)-I signaling, Akt, and mitochondrial protection (80) points to IGF-I as a potential therapeutic candidate. This is further supported by the clinical observation that in studies of patients with HF, IGF-I levels are low and correlate with the severity of LV systolic dysfunction (81,82). However, no studies have investigated yet the actions of direct IGF-I supplementation in HF patients. Additionally, recent evidence has been provided on a novel strategy to preserve mitochondrial function and cardiomyocyte death by down-regulation of the protein Nogo-A, which cardiac expression is elevated in experimental models of dilated cardiomyopathy and in humans with end-stage HF (83).

In summary, apoptosis, necrosis, and autophagy may coexist in a variety of relationships (i.e., in parallel and in series, with either up-stream of the other). Should this scenario bear out, it would necessitate a careful investigation of the contribution of each type of cell death to myocardial remodeling. In addition, this possibility has potential therapeutic implications, as drugs that inhibit one pathway may shift death to another (e.g., caspase inhibitor shifting death receptor-induced apoptosis to necrosis) (62).

Future Directions

Findings from recent experimental studies suggest that gene therapy may have a place in myocardial remodeling. For instance, cardiac-specific replenishment of local vascular endothelial growth factor (84) or hypoxia-inducible factor 1-α (85) restores microvascular homeostasis, repairs myocardial remodeling, and improves LV function in rodents with diabetic cardiomyopathy independently of systemic metabolic changes. Conversely, it has been recently reported that long-term cardiac pro–B-type natriuretic peptide gene delivery prevents myocardial remodeling and improves LV function in rats with hypertensive heart disease, these effects being independent of blood pressure changes (86). However, researchers continue to investigate new genes and combinations of genes and approaches that combine gene and cell therapy, and to develop novel expression vectors and delivery systems.

Small molecule histone deacetylase inhibitors block myocardial remodeling in animal models, suggesting an unforeseen potential for these classes of compounds for the treatment of HF. Indeed, chronic treatment of spontaneously hypertensive rats with valproic acid (87) and deoxycorticosterone acetate-salt hypertensive rats with suberoylanilide hydroxamic acid (88) reduced myocardial expression of IL-1β and TNF-α, which correlated with suppression of interstitial fibrosis and reduction of LV hypertrophy. Nevertheless, several pre-clinical questions remain to be answered before histone deacetylase inhibitors can move toward clinical testing for treating HF.

A growing body of evidence supports the hypothesis that autocrine and paracrine mechanisms, mediated by factors released by the resident cardiac cells, could play an essential role in cytoprotection, angiogenesis, and extracellular matrix turnover in the remodeled myocardium (89). The recent demonstration that chemically or genetically activated cardiac cells may release molecules to protect tissue against mechanical, ischemic, or metabolic injury provides a potential route to achieve the delivery of specific molecules produced by these cells for innovative therapy of the remodeled myocardium.

Recent evidence suggests that glucagon-like peptide-1 and the exenatide analogue AC 3174 exert antiremodeling and cardioprotective effects in animal models of myocardial infarction (90) or hypertensive heart disease (91), these effects being independent of changes in systemic hemodynamics and glucose metabolism. Hence, pharmacology of glucagon-like peptide-1 (e.g., glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors) may represent a novel approach for the treatment of myocardial remodeling in cardiac diseases associated with diabetes mellitus or not.

Mechanical circulatory support provided by LV assist devices and electromechanical synchronization provided by cardiac resynchronization therapy have been shown to regress myocardial remodeling (e.g., inflammation, fibrosis, and apoptosis) and to improve LV geometry, contractile function, and hemodynamic parameters in HF patients (92,93). These promising findings should inspire further research to better understand the mechanisms responsible for both myocardial remodeling and its regression in this particular setting.

Conclusions

In spite of a substantial improvement in outcomes in the past 2 decades, we continue to face significant challenges in treating patients with HF. Because conventional medical strategies for the treatment of HF do not correct the underlying cause (i.e., remodeling of the myocardial structure that reduces viable or functional myocardial tissue), there is a necessity to focus on new strategies that target mechanisms responsible for some of the cellular and tissue lesions characteristic of the remodeled myocardium. We realize that a large number of studies on these novel strategies were not discussed in this brief review because our only intention was to highlight a selected group of topics that were more recently identified or that were consistent with the theme at hand (Table 2). In addition, although

Table 2 Summary of Emerging Targets and Potential Therapeutic Agents to Treat Structural Myocardial Remodeling

Alteration	Target	Therapeutic Agent	Reference No.
Inflammation			
	TNF-α	Pentoxifylline, pentraxin 3, IL-10	(10,21,28)
	IL-1β	Pentraxin 3	(21)
	PI3Kγ/δ	TG100-115	(23)
	IL-6 gp130/STAT3	Cobra venom factor derivatives?	(24)
	TLR4	Molecules targeting TLR4 (e.g., statins, vitamin D3)	(25)
	NF-κB	Inhibitors (e.g., lactacystin)	(32)
Alterations of collagen matrix			
	Renin-angiotensin system	ACEIs or ARBs	(37,38)
	Aldosterone	Spironolactone or eplerenone	(40)
	TGF-β_1	Receptor antagonists	(43,44)
	PCP/PCPE	Torasemide	(48)
	LOX	Torasemide	(49)
	miR-21	AntagomiR-21	(51)
	MMPs	Several inhibitors	(59,60)
		Thrombospondin-2	(61)
	Several	Stem/progenitor cells	(52–54)
Cardiomyocyte death			
	Mitochondrial Omi/HtrA2	UCF-101	(64)
	Nogo-A protein	Several inhibitors	(83
	miR-320	Antagomir-320	(67)
	Akt protein	Stimulants (e.g., IGF-1)	(80)

ACEI = angiotensin-converting enzyme inhibitor; Akt = protein kinase B; ARB = angiotensin receptor blocker; IGF = insulin-like growth factor; IL = interleukin; IL-6 gp130/STAT3 = interleukin-6 glycoprotein 130/signal transducer and activator of transcription 3; LOX = lysyl oxidase; MMP = matrix metalloproteinase; NF-κB = nuclear factor-kappa B; Omi/HtrA2 = serine-protease Omi/HtrA2; PCP/PCPE = procollagen type I carboxy-terminal proteinase/PCP enhancer; PI3Kγ/δ = phosphoinositide-3 kinase gamma/delta; PTP = permeability transition pore; TGF = transforming growth factor; TLR = toll-like receptor; TNF = tumor necrosis factor.

significant insight and hypothesis generation regarding myocardial remodeling have been gained through the use of animal models, the physiological differences between the cardiovascular systems of animals and humans, with respect to myocardial remodeling and LV dysfunction, are an important consideration. In particular, an important challenge in translating the observations from pre-clinical studies into clinical treatment strategies relates to clinical studies being designed on top of established pharmacological therapy, whereas most experimental studies test novel interventions without concomitant drug regimens such as anti–renin-angiotensin system drugs. In addition, because HF is a complex, multifactorial syndrome consisting of many overlapping phenotypes, the dynamic and heterogeneous nature of myocardial remodeling cannot be captured by a simplified pathophysiologic view, and as a consequence, its therapy cannot be considered under a reductionist approach. Nevertheless, data here reviewed provide essential information for identifying potential novel targets, and their potential drawbacks, and are thus required for developing novel treatment strategies to prevent or reverse myocardial remodeling that leads to LV dysfunction and HF.

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