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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

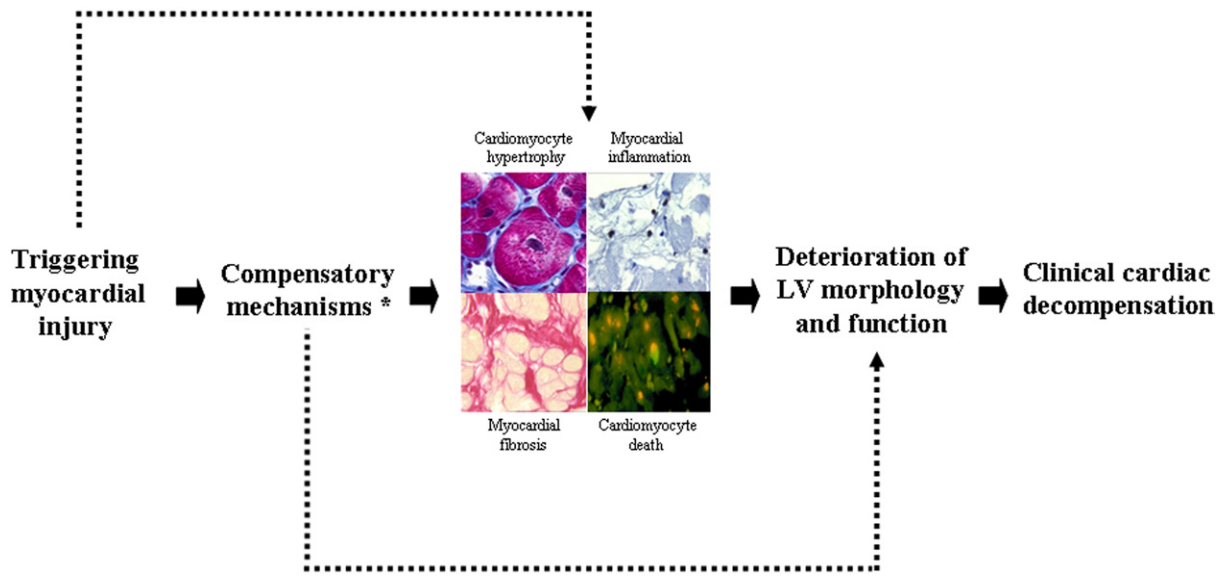

Figure 1 Pathogenesis of Heart Failure

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.