Cardiac extracellular matrix: a dynamic entity

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Understanding the regulation of the extracellular matrix of the heart is essential to understanding the chronic changes in heart function in disease states such as hypertension, heart failure, and diabetes. This understanding relies on overturning the concept that the extracellular matrix of the heart is inert. As a structural protein, the major role of collagen, a major component of the extracellular matrix, was considered as replacement of necrotic myocytes. This concept was derived from early research on the heart that logically emphasized an understanding of the properties of cardiomyocytes, the cells that develop force. Nutrient supply and waste product removal from these myocytes required detailed investigations of the vasculature of the heart so that studies on the extracellular matrix started relatively late. Pioneering studies on the extracellular matrix by Borg, Caulfield, and Robinson in the late 1970s and early 1980s identified a complex fibrillar collagen network in the heart. The complex physiological role of the extracellular matrix includes connecting myocytes, aligning contractile elements, preventing overextending and disruption of myocytes, transmitting force, and providing tensile strength to prevent rupture (22). Excessive collagen clearly is detrimental to cardiac function. Weber and colleagues (22) have shown convincingly that collagen deposition can be controlled by hormones such as angiotensin II and aldosterone. Chronic activation of the renin-angiotensin system is associated with the appearance of inflammatory cells and fibroblasts in the perivascular space, preceding the changes to the vasculature, leading to a perivascular fibrosis (20). Infarct tissue, predominantly collagen, is not inert but is dynamic, living tissue that is cellular, vascularized, metabolically active, and contractile (18, 21).

The extracellular matrix is a complex mixture of collagen fibrils, elastin, cells including fibroblasts (6) and macrophages, macromolecules such as glycoproteins, and glycosaminoglycans together with other molecules such as growth factors, cytokines, and extracellular proteases. In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Bouzeghrane and colleagues (2) have hypothesized that fibrillin is also a constituent of the myocardium interstitium that is regulated during the development of cardiac fibrosis. This glycoprotein is deficient in Marfan’s syndrome, a severe autosomal dominant trait affecting the cardiovascular system, eyes, skeleton, dura, lungs, skin, and integument caused by mutations of the fibrillin-1 gene (FBN1). Death frequently results from dissection or rupture of the ascending aorta. Deficient fibrillin-1 content has been implicated in the matrix disruption of patients with bicuspid aortic valve by triggering matrix metalloproteinase production (9). Bouzeghrane and colleagues (2) have shown that fibrillin is abundant throughout the rodent myocardium as thin fibers that cross over the perimyocardium and around arteries. Fibrillin increased in the interstitium and accumulated in microscopic scars after the induction of cardiac fibrosis by angiotensin II or deoxycorticosterone acetate. Furthermore, angiotensin II and transforming growth factor-β1 enhanced the synthesis of fibrillin by cardiac fibroblasts. These results strongly suggest that fibrillin is an important component of the extracellular matrix of the myocardium that is upregulated during the development of cardiac fibrosis.

This study has used rodents to suggest potentially important changes in human disease. Are these findings unique to the rodent heart and thus not relevant to the human heart, especially in chronic cardiovascular disease? Of course this can only be answered by appropriate studies on human myocardium, especially in patients with chronic hypertension or heart failure. However, previous studies showing that angiotensin-converting enzyme (ACE) inhibitors prevented or reversed cardiac fibrosis in angiotensin II-infused or deoxycorticosterone acetate-treated rats (4, 19) have been confirmed by elegant studies in patients treated with lisinopril (3). This strongly suggests that the human heart will show similar responses in the extracellular matrix to the rodent heart.

The demonstration of fibrillin throughout the normal myocardium suggests a unique role for this component of the matrix, possibly to transmit force from myocytes to the extracellular matrix. One potential role would be the regulation of the stiffness or compliance of the heart. Collagen is a well-known regulator of myocardial stiffness, and cross-linking of the collagen strands is a key determinant (16). Bioengineering research could provide the necessary insights into the role of fibrillin as it has with the role of collagen in the mechanical function of the heart (8, 10, 12). These studies have developed three-dimensional representations of cardiac muscular architecture to investigate issues such as force development, electrical activation throughout the myocardium, and shear properties. Although these studies have emphasized the role of the collagen network, the techniques would also be useful to define the role of fibrillin in cardiac function in both normal function as well as in pathophysiological states such as cardiac fibrosis. The definition of perivascular fibrillin deposition suggests that vascular function may also be regulated by changes in fibrillin deposition, possibly changing vascular stiffness and endothelial function.

The molecular trigger for the increased expression of fibrillin is unknown. One suggestion would be reactive oxygen species such as superoxide or its product hydrogen peroxide formed by the action of superoxide dismutase. Both angiotensin II and endothelin, the hormones increased following angiotensin II infusion or deoxycorticosterone acetate-salt administration (7, 14) in the rat models used in this study, stimulate production of superoxide by NADPH oxidase (13). Superoxide stimulated collagen production by cardiac fibroblasts (17); tempol, a superoxide dismutase mimic, or losartan, an AT1 receptor antagonist, prevented NADPH-generated superoxide production and aldosterone-induced fibrosis (11). An increased endothelin-1 concentration acting through ET-A receptors has
been shown to be a major cause of the hypertrophy and fibrosis in the deoxycorticosterone acetate-salt hypertensive rat because these changes could be prevented by administration of the selective ET-A receptor antagonist A-127722 (1). In deoxycorticosterone acetate-salt hypertensive rats, the impaired vasodilator responses to acetylcholine were decreased following suppression of superoxide formation by sesamin (15).

The increased fibrillin deposition in cardiac fibrosis suggests this process as a potential target for therapeutic intervention in chronic cardiovascular disease. Many interventions have been shown to decrease collagen production or increase collagen breakdown (5); it seems logical to determine whether these interventions are selective for collagen or also apply to fibrillin expression or deposition. Possibly the most useful interventions for control of collagen deposition involve inhibition of the actions of either angiotensin II or endothelin. Selective agents, especially the ACE inhibitors as well as AT1 and ET-A receptor antagonists, are now widely available for these studies. The use of these inhibitors and antagonists would also help define the pathophysiological consequences of an increased fibrillin expression and deposition.

In summary, Bouzeghrane and colleagues (2), by showing the presence of fibrillin in rodent hearts and its upregulation in models of cardiac fibrosis, have demonstrated the dynamic complexity of the extracellular matrix. Furthermore, they have added a potential target molecule for the understanding and modification of cardiac function in both the normal and diseased heart.

REFERENCES


