Profibrotic Effects of Angiotensin II in the Heart: A Matter of Mediators

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In response to mechanical and/or metabolic stress the myocardium undergoes structural remodeling involving cardiomyocyte hypertrophy and interstitial and perivascular fibrosis. Cardiomyocyte hypertrophy includes an increase in contractile and embryonic protein content, which appears largely on the activation of transcription of the corresponding cardiac genes that encode these proteins. Myocardial fibrosis is the result of the exaggerated deposition of collagen types I and III fibers as a consequence of the predominance of the synthesis over the degradation of collagen molecules. Myocardial remodeling is accompanied by a progressive decline in cardiac function over time, which underlies the pathogenesis of heart failure in patients with chronic cardiac conditions.

It is now accepted that a number of systemic and locally expressed factors have key roles in the process of myocardial remodeling. One of these factors is angiotensin II (Ang II). Whereas the role of Ang II in cardiomyocyte hypertrophy is well established, emerging experimental and clinical evidence is providing support for the notion that this peptide induces myocardial fibrosis. Several potential pathways may mediate the profibrotic effects of Ang II on the heart. On the one hand, a number of findings indicate that the interaction of Ang II with the Ang II type-1 (AT1) receptor located in cardiac fibroblasts results in induction of fibroblast hyperplasia, activation of collagen biosynthetic pathways, and inhibition of collagen degradative pathways. On the other hand, more recent findings suggest that fibrosis may represent the reparative response to myocardial inflammation induced by Ang II through the interaction with AT1 receptors present in cells from the cardiac microvasculature.

Whatever the pathway is, available data indicate that the profibrotic effect of Ang II results from synergistic cooperation between this peptide and other profibrotic factors. For instance, the ability of Ang II to stimulate fibroblasts and alter the metabolism of fibrillar collagen may be mediated by transforming growth factor-β, endothelin-1, and plasminogen activator inhibitor-1. In addition, several lines of evidence point to osteopontin as a critical mediator of the proinflammatory and profibrotic cardiac effects of Ang II. First, monoclonal antibodies directed against osteopontin have been found completely to block the stimulatory effects of Ang II on cultured rat cardiac fibroblasts. Second, elevated osteopontin mRNA expression has been detected in the hypertrophied and fibrotic left ventricle in rat models characterized by high myocardial Ang II concentrations such as the Ren2 rat, rats with renovascular hypertension, and spontaneously hypertensive rats with heart failure. Third, myocardial inflammation and fibrosis have been associated with the expression of osteopontin in coronary walls of rats with Ang II/salt-induced hypertension. Fourth, Matsui et al. report in this issue of Hypertension that mice lacking osteopontin do not develop myocardial fibrosis in response to Ang II-induced hypertension. Finally, human myocardium with extensive fibrosis and cardiomyocyte hypertrophy have shown substantial immunoreactivity for osteopontin.

Osteopontin is a cell-secreted adhesive glycoprophosphoprotein found as a component of the extracellular matrix in a diversity of tissues. Osteopontin binds to integrin receptors (αβ3, αβ5, αβ1) to regulate cell responses and is also a ligand for certain variant forms of CD44 receptor (v6 and/or v7), through which it acts as a chemoattractant factor for various cell types, notably monocytes/macrophages. In addition, it has been shown that osteopontin interacts with fibronectin and collagen, which suggests a possible role in matrix organization and stability.

Osteopontin expression is induced in cardiovascular cells in response to a number of stimuli, including cytokines, growth factors, and hormones. Cell culture studies have shown that Ang II stimulates osteopontin mRNA expression in cardiac cells, including fibroblasts and microvascular endothelial cells. Reactive oxygen species and activation of members of the mitogen-activated protein kinase superfamily would mediate this effect. In addition, Ang II has been shown to increase osteopontin mRNA expression in fresh samples of human myocardium. Interestingly, it has been shown that myocardial osteopontin expression is markedly attenuated in Ang II–infused rats treated either with adrenalectomy or with the selective aldosterone blocker eplerenone. These preliminary findings are partly confirmed by data reported by Matsui et al. in this issue showing that eplerenone does tend to decrease the cardiac osteopontin mRNA level in wild-type Ang II–infused mice. Thus, aldosterone may mediate the stimulatory effect of Ang II on cardiac osteopontin, providing additional support to the proposal that aldosterone activation of cardiac mineralocorticoid receptors critically contributes to cardiac damage induced by Ang II.
In summary, although blood pressure dependent effects of Ang II are difficult to separate from blood pressure independent effects in most studies, including the present one by Matsui et al., this peptide emerges as an important determinant of the fibrotic response of the myocardium to injury. Data reviewed in this commentary illustrate the complex network of mediators and interactions potentially involved in Ang II–induced myocardial fibrosis. Osteopontin seems to play a central role in this network and, thus, may be considered as a target for possible therapeutic strategies aimed to block the development of myocardial fibrosis and, in turn, to prevent heart failure in chronic cardiac diseases.

References