Ionotropic Stress and Integrin
Another Link to Myocardial Remodeling

Saraswati Pokharel, Umesh C. Sharma

Cardiac remodeling is an adaptive response to chronically increased wall stress. Adaptive remodeling of the myocardium, caused either by increased workload or ionotropic stress, requires mediators for the communication of cardiac cells with their surrounding extracellular matrix. Integrins are likely candidates that transduce increased mechanical force into the intracellular biochemical signals. In this issue of Hypertension, Krishnamurthy et al report a potential role of myocardial β1-integrin in the adaptive and maladaptive remodeling that occurs in isoproterenol-induced left ventricular hypertrophy. To place the findings of this study in context with emerging studies regarding myocardial remodeling and the progression to left ventricular failure, a brief review of the biology of β1-integrin with respect to myocardial hypertrophy and remodeling is presented here.

Integrins are heterodimeric cell-surface receptors composed of α and β subunits that function as adhesive and signaling molecules, as well as mechanotransducers. In noncardiac cells, it has been demonstrated that integrins respond to abnormal strain in a manner similar to that which would be found during pressure or volume overload in the heart. Integrins are expressed in various types of cells, including leukocytes, endothelial cells, vascular smooth muscle cells, fibroblasts, and myocytes. Previously, integrins were considered as the structural protein essential for maintaining the integrity of the cell–matrix interaction. Emerging studies have established the role of integrins in signal transduction cascades involved in cell migration, proliferation, and growth. β1-Integrin is a dominant subunit expressed in the heart, which is shown to participate in the hypertrophic response of cardiac ventricular myocytes.

The study by Krishnamurthy et al provides some unique insights into the potential role of integrin in left ventricular remodeling and function. This study used β-adrenergic stimulus to induce cardiac stress in wild-type and β1-integrin–deficient mice and examined β1-integrin function with respect to left ventricular remodeling and failure. In integrin-deficient mice, β-adrenergic receptor stimulation failed to increase myocardial fractional shortening and ejection fraction. These findings were associated with increased cardiomyocyte apoptosis. It is often speculated that progressive deterioration of left ventricular function in heart failure is because of ongoing loss of viable cardiomyocytes. Although these findings created considerable enthusiasm, some skepticism still remains as to whether cardiomyocyte apoptosis plays an important role in the progression of heart failure.

The data presented by Krishnamurthy et al regarding the putative role of β1-integrin in left ventricular remodeling and function are provocative in several ways. First, increased levels of β1-integrin were identified in mice after β-adrenergic receptor stimulation. Second, β1-integrin–deficient mice that received isoproterenol infusion for 4 weeks had higher levels of matrix metalloproteinase-2 and matrix metalloproteinase-9. Earlier, these investigators have demonstrated that matrix metalloproteinase-2 interferes with the phosphorylation of focal adhesion kinase that mediates survival signals of β1-integrin and activates c-Jun N-terminal kinase–dependent myocyte apoptosis. Activation of c-Jun N-terminal kinase is suggested to play a role in the activation of the mitochondrial death pathway of apoptosis in cells of cardiac and noncardiac origin. The authors observed greater increase in c-Jun N-terminal kinase activation in β1-integrin–deficient mice after isoproterenol infusion. Taken together, these studies suggest that increased matrix metalloproteinase-2 expression and activity may induce cardiac myocyte apoptosis in β1-integrin–deficient mice via the involvement of the c-Jun N-terminal kinase–dependent mitochondrial pathway.

In addition to their antiapoptotic effects, integrins are shown to mediate stretch-dependent matricellular response in chronic pressure overload. Integrins associate with signaling molecules in the focal adhesion complex, which act both as a signaling device and a connection to cytoskeleton. On stimulation, integrins interact with transducing molecules like P125 focal adhesion kinase, of which the amino-terminal domain binds to the intracellular domain of β1- and β3-integrins, whereas its carboxyterminal binds to the SH2 and SH3 domains of several proteins involved in focal adhesion assembly and signal transduction. Ionotropic stress or mechanical stretch leads to the activation of the integrin-linked focal adhesion complex and phosphorylation of focal adhesion kinase at various tyrosine residues.
Phosphorylation of focal adhesion kinase activates the c-Src signaling system and induces the production of connective tissue growth factor, which promotes ECM synthesis. This signal transduction mechanism has been implicated in the matricellular response to mechanical stretch. Therefore, the critical role of integrin in the cardiac remodeling processes is becoming recognized, and a simplified summary of some of the important pathways involved in integrin signaling is shown in the figure.

Although these studies are associative, they do emphasize a protective role of β1-integrins in β-adrenergic receptor–stimulated apoptosis and adverse cardiac remodeling. These findings suggest that integrin is important for physiologically “intact” β-adrenergic receptor–induced cardiac load and injury in cardiomyocytes and fibroblasts. As suggested by the authors, further research to elucidate the mechanisms that shift the balance from apoptosis to cell survival during chronic β-adrenergic stimulation may have important clinical implications to counteract the detrimental effects of chronic adrenergic overstimulation.

**Source of Funding**

U.C.S. is a recipient of the American Heart Association Greater Mid-West Fellowship (2006).

**Disclosures**

None.

**References**
