The form and function of the heart is determined by the dynamic interaction of both intra and extracellular signals. During normal growth of the neonatal heart myocytes undergo hypertrophy in response to variety of signals including changes in blood pressure. The number of fibroblasts also increase and the collagens and connective tissue is formed. The coordination of these signals and cell interactions result in a heart that is adapted to adult function. However, in response to a changing environment, eg, hypertrophy, infection, or failure, the normal coordination of between these signals becomes disrupted and leads to detrimental cardiac remodeling. Understanding the sources of these signals and their relationship to the myocyte and nonmyocyte populations of the ventricular wall would seemingly be an important key to understanding and regulating the adaptive processes that lead to altered cardiac function and potentially catastrophic failure.

It is well documented that the adaptive processes of cardiac remodeling are linked to dynamic myocyte-fibroblast interactions or cross-talk, including the expression of cytokines, ECM, as well as mechanical and electrical signals. Whereas the myocyte population remains relatively stable, the fibroblasts, as in neonatal life, appear to change dramatically during hypertrophy and injury. Of the various aspects of myocardial remodeling that have been explored in infarction, hypertrophy or congestive failure, most have centered on the changes in the extracellular compartment milieu, principally analyzing the changes in the amount of collagen and fibrosis. Correlative investigations have described the increases and alterations in the amount of collagen with changes in wall stiffness and altered function. For example, it is fundamentally understood that collagen is organized into fibrillar structures which can associate with the myocardial cell surface by which they exert mechanical effects. But how this happens, how it is regulated and how altered biomechanical properties adversely affect myocardial remodeling remain important but unresolved questions.

Answers to these questions were pursued in the article by Oka et al. They found that an adhesive protein called periostin was strongly upregulated before and during remodeling processes. They also determined that levels of periostin expression correlated with the amount of collagen produced. They reasoned that understanding more about how periostin contributed to fibroblast-myocyte interactions could seemingly provide important new understanding on pathological remodeling in the heart and possible new targets for therapy. These authors clearly demonstrate that by genetically manipulating the expression levels of periostin they can affect the extent of scar formation associated with infarctions and hypertrophic growth. They also consider the cell specificity of periostin secretion and conclude that periostin is normally associated with fibroblasts. Previous studies indicated that periostin might be expressed by myocytes but these studies were equivocal as in vitro studies using neonatal myocytes are rarely free of fibroblasts.

Periostin appears to be a unique extracellular protein secreted by fibroblasts that is upregulated following injury to the heart or changes in the environment. It has the ability to associate with other critical ECM regulators such as TGF-β, tenascin, and fibronectin, and as demonstrated by Oka and colleagues, periostin is a critical regulator of fibrosis by altering the deposition and attachment of collagen. These experiments combined with those reported by Norris et al showing that periostin regulated collagen fiber diameter and crosslinking, further suggest mechanisms by which periostin could regulate the mechanical properties of the heart wall would be by directly binding to fibrillar and nonfibrillar proteins of the extracellular matrix.

Oka et al also provide important data that periostin can also modify adhesion between myocytes and fibroblasts which they suggest may modify wall stiffness or biomechanical properties depending on whether its expression is stimulated or downregulated. Periostin is often thought of as another adhesion protein because of its homology to Drosophila fasciclin proteins. But is periostin just another adhesion protein? The genetic and physiological findings of Oka et al and other recent reports indicate that periostin appears to interact with multiple cell-surface receptors, especially integrins, to signal changes in gene expression through Akt or PI3 kinase pathways. The contextual nature of its functions as reported by Oka et al are consistent with a dynamic role for periostin in contact-signaling between fibroblasts and cardiomyocytes that can modify adhesion as well as regulate collagen formation and fibrosis.

Significantly, when periostin was knocked out, animals had a much reduced fibrosis, which resulted in aneurysm and rupture of the ventricular wall, especially if subjected to changes in hemodynamic pressure or to a heart attack. Conversely, overexpression of periostin in the heart protected...
from rupture in infracted regions. This suggests that down-regulating periostin could benefit a patient experiencing a remodeling disease, but if periostin is to be used as a therapeutic target, it might have to be given in a dose dependent manner that would not prevent formation of a collagen scar but rather limit its size. These data, point to the importance of analyzing remodeling as a multiple component process which includes populations of cardiac myocytes and fibroblasts, several ECM components, and the organization of the collagen network. Again, this point was emphasized in the periostin null mice that experienced ventricular rupture, indicating that the quantitative amount of periostin (and perhaps other ECM components) is critical to the physiological result.

To summarize, the Oka article confirms that periostin is made by mesenchymal derived cells and that expression of periostin following injury or environmental perturbations can alter normal physiological interactions between fibroblasts and myocytes that can affect collagen, fibrosis and scar mechanics. Thus, by regulating extracellular or matricellular components, such as periostin, there is realistic potential for controlling the onset and/or progression of myocardial remodeling.

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None.

**References**

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