The Soluble Interleukin 6 Receptor Takes Its Place in the Pantheon of Interleukin 6 Signaling Proteins
Phenoconversion of Cardiac Fibroblasts to Myofibroblasts

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The cardiac stroma provides tensile strength binding muscle cells and serves as structural scaffolding in the presence of continuous cyclic changes in mechanical tension. The principal stromal cell types are fibroblasts, but this designation belies their diversity and topographical differentiation from organ to organ, including the heart. For example, skin fibroblasts and vascular smooth muscle cells share the expression of desmin and are thereby distinguished from virtually all other fibroblasts and myofibroblasts, including those in heart. The term “fibroblast” designates a highly heterogenous group that exhibits distinct differentiated phenotypes in different tissues. The implications of these fundamental differences are unclear. Furthermore, the study of fibroblast and myofibroblast biology in specific organs is important; however, in the context of the heart it is a relatively understudied area. Recent work has revealed that ventricular fibroblast activation and cardiac fibrosis may be primary events in ventricular remodeling rather than occurring as secondary responses to cardiomyocyte injury. Thus, the traditional role of cardiac fibroblast as a secondary disease modifier has been called into question recently, and the need to establish the specific behavior and expression patterns of genes that characterize cardiac myofibroblasts is becoming apparent.

Hypertension is marked by the development of cardiac fibrosis, and it is well established to contribute to increased risk of cardiovascular events, which can be partially alleviated with appropriate treatment. The interstitium of healthy heart is populated by cardiac fibroblasts, which can effect a slow turnover of fibrillar collagens and other matrix proteins. Fibroblasts respond to both mechanical loading and/or transforming growth factor-β1 stimulation by phenoconverting to contractile and hypersecretory myofibroblasts. Thus, an essential step in the onset of cardiac fibrosis is the cardiac ventricular fibroblast conversion to myofibroblastic phenotype. Myofibroblasts are the primary mediators of wound healing in the damaged ventricle, and we have demonstrated previously that they are the dominant cell type in the infarct scar. The relevance of investigating the biology of these cells in hypertrophied hearts is high, because they contribute to cardiac fibrosis and matrix remodeling through the elevated production of fibrillar and nonfibrillar collagens, as well as focal adhesion–associated proteins, respectively. Although a number of laboratories have reported on this in vitro phenoconversion in primary cells and have described a number of cytokines that are associated with this conversion and subsequent remodeling of the cardiac extracellular matrix, the cytokines of the interleukin (IL)-6 superfamily are also known to influence matrix remodeling and cardiac fibrosis.

Pantheon of IL-6 Receptor Proteins

Indeed, the IL-6 cytokine superfamily of ligands has received a great deal of attention during the past decade, and the biology of their signaling is becoming clearer. IL-6, in particular, is widely acknowledged to play an important role in systemic inflammation. The gp130 glycoprotein is a common receptor component for the transduction of signal to a number of these cytokines and has been labeled the “promiscuous” receptor. Thus, gp130 homodimers and heterodimers (with LIFR, OSMR, and WSX-1) subserve a majority of the IL-6 family of cytokines, including cardiotrophin 1 (CT-1), oncostatin M, IL-27, and leukemia inhibitory factor (LIF), among others. Because this receptor is a likely poster child for redundancy within cellular function, investigators have struggled for more than a decade to unravel the high specificity of signaling when coupled with different binding partners. The gp130 is indispensable to its receptor partners. Notably, the gp130 homodimer is associated with many diverse functions within the related group of associated cytokines that it serves and seems to be a powerful participant of both health and disease in the heart muscle, particularly in association with the IL-6 signal. Although it is a required member of IL-6 signal transduction, it does not actually participate in the ligand binding. The most likely reason for the subtle control over a range of IL-6 effects reported in the literature resides in the complexity of its receptor system. For example, gp130 is known to interact with a number of soluble and membrane-bound receptors, including soluble IL-6R (sIL-6R), as well as membrane-bound IL-6R (Figure) and IL-11R. In keeping with the theme of complexity and overlapping roles of this ligand family, other members of the IL-6 superfamily are known to affect the behavior of fibroblasts and myofibroblasts. For example, migration and activation of cardiac fibroblasts are known to be influenced by...
CT-1.\textsuperscript{15} Unlike the effect of many cytokines, CT-1 is known to exert a significant antifibrotic stimulus in heart myofibroblasts (using procollagen I C-terminal peptide secretion normalized for cell number), but it may function as a relatively strong “homing” signal in the postmyocardial infarction heart.\textsuperscript{15} Thus, an integrated signal from many cytokines may be required for wound healing and in initiation of cardiac fibrosis. A recent surge of investigation has established IL-6 as a pleiotropic cytokine that regulates a number of cellular functions, many of those through Janus Kinase–Signal Transducer and Activator of Transporting (JAK-STAT) activation. A novel mouse knockout study shows that ablation of this cytokine using IL-6\textsuperscript{-/-} mice led to ventricular dilatation, elevated interstitial collagen deposition, and a marked increase in discoidin domain receptor (DDR2)–positive fibroblasts versus values from wild-type mice.\textsuperscript{12} Furthermore, a recent article by Kobara et al\textsuperscript{13} highlights the requirement of IL-6 for left ventricular remodeling after myocardial infarction in mice. In that work, IL-6R was immuno-suppressed in postmyocardial infarction Balb/c mice using the MR-16 antibody, and it was shown that these mice were protected from loss of contractile function, cardiomyocyte hypertrophy, and interstitial fibrosis in the heart remote to the site of infarction. Collectively, this newly available evidence establishes a connection between IL-6–mediated proliferation of fibroblasts and of cardiac fibrosis; many questions as to the specificity of IL-6 receptor activation in cardiac fibroblasts remained unclear, and until very recently, the significance of the sIL-6R receptor was unknown in the context of function of these cells.

In the present issue of \textit{Hypertension}, Meléndez et al\textsuperscript{16} provide data to underscore a fascinating development in the area of IL-6 signaling. This group found that the sIL-6R receptor is required to allow the transduction of IL-6 and, in their experimental conditions, facilitates the conversion of cardiac fibroblasts to myofibroblasts. Currently, how gp130 and LIFR mediate differential signaling for both CT-1 and LIF is unclear and requires further investigation.

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\caption{Participation of sIL-6R in IL-6 transduction in cardiac fibroblasts. sIL-6R binds IL-6 and gp130. gp130 participates in the signal transduction of all of the IL-6 superfamily cytokines, including CT-1 and LIF. The current article by Meléndez et al\textsuperscript{16} highlights the importance of sIL-6R in cardiac fibrosis, including the phenoconversion of fibroblasts to myofibroblasts. sIL-6R is required for the conversion of fibroblasts to myofibroblasts. Currently, how gp130 and LIFR mediate differential signaling for both CT-1 and LIF is unclear and requires further investigation.}
\end{figure}
effects may depend on recruitment of the soluble IL-6R (Figure). Indeed, whether sIL-6R is present or absent from a system may determine the net effect of IL-6 on cells, particularly in cardiac fibroblasts. Thus, sIL-6R may serve to control IL-6 signaling via its own bioavailability. It would be worthwhile to determine whether input of both membrane-bound IL-6R and sIL-6R is required for maximal stimulation of collagen deposition and whether both affect the rate of appearance of myofibroblasts. Finally, one may speculate as to whether a novel parallel system operates in the signaling of other related cytokines, such as CT-1 or LIF, both ligands use the gp130/LIFR heterodimer. This notwithstanding, Meléndez et al\textsuperscript{16} have provided a novel contribution with this latest article, which begins to clarify the diversity of effects of IL-6 in heart.

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**References**


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