Preventing Adverse Remodeling and Rupture During Healing After Myocardial Infarction in Mice and Humans

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Abstract

Adverse ventricular remodeling during the healing phase after acute myocardial infarction (MI) continues to be an important problem that impacts adult cardiology practice. Most clinicians and cardiovascular researchers recognize that significant left ventricular (LV) remodeling occurs during infarct healing, and optimal healing is critical for survival with a favorable outcome. Over the last 3 decades, several laboratories have been actively searching for specific molecular targets that may lead to the development of therapies and strategies to optimize postinfarct healing, prevent adverse remodeling, and improve clinical outcome. Others search for markers of adverse LV remodeling so as to identify high-risk patients for therapy. However, specific therapy to optimize healing and prevent adverse post-MI remodeling is currently lacking. Optimal medical therapy after MI may not be so optimal yet. Hearts continue to enlarge after MI, and heart failure is a growing burden.

Inflammation and extracellular matrix remodeling are 2 key components of healing and LV remodeling after MI. Several proinflammatory cytokines, including interleukin-6 (IL-6), are consistently upregulated in the infarct zone after experimental MI. The 3 members of the superfamily of IL-6 cytokines (IL-6, cardiotrophin-1, and leukemia inhibitory factor) share a common 130-kDa glycoprotein (gp130) receptor subunit for activation of their signaling pathways. All IL-6 cytokines are potent activators of signal transducer and activator of transcription 3 (STAT3). The IL-6 receptor binds the IL-6 ligand and the gp130 subunit, which in turn mediates signal transduction via 3 major downstream pathways (ie, Janus kinase/signal transducer and activator of transcription JAK/STAT, Src-homology tyrosine phosphatase–signal transduction protein–extracellular signal-regulated kinase [SHP2-Ras-ERK], and phosphatidylinositol 3-kinase-dependent [PI3/Akt]; Figure). After activation, negative-feedback mechanisms regulate gp130 signaling. IL-6 is produced by various cells, including cardiomyocytes, fibroblasts, and inflammatory cells, in the infarct border zone in animals and humans. It has been implicated in myocardial stunning and decreased contractility. Cardiotoxin-1 and leukemia inhibitory factor act through the JAK/STAT pathway induced by gp130 to mediate cardiac hypertrophy and antiapoptosis. Transgenic overexpression of IL-6 and the IL-6 receptor results in hypertrophy and antiapoptosis. It has been suggested that these 3 responses (reduced contractility, hypertrophy, and antiapoptosis) might favor survival of myocardium in the border zone. Increased IL-6 in the infarct border zone is associated with LV enlargement. However, the muting of IL-6 in mice did not affect MI size, LV function, remodeling, or survival compared with wild-type mice, which suggests compensatory upregulation.

Other experimental evidence indicates that STAT3, the major downstream molecule of IL-6, transduces stress signals from the plasma membrane to the nucleus, which leads to changes in gene transcription. Activation of the JAK-STAT signaling pathway in ischemia-reperfusion is cardioprotective via transcriptional activation of cytoprotective genes. Decreased STAT3 is involved in hypertrophy, ischemic-reperfusion injury, myocardial capillary growth, interstitial matrix deposition, and heart failure. A large body of evidence suggests that increased STAT3 is cardioprotective, whereas decreased STAT3 is harmful. STAT3 activation is thought to be beneficial in MI, ischemic preconditioning, and pressure overload and to promote cardiomyocyte survival, hypertrophy, and cardiac angiogenesis. Decreased STAT3 in patients with dilated cardiomyopathy is thought to mediate the development of heart failure. Deletion of STAT3 abolishes the ischemic preconditioning–induced decrease in infarct size and results in increased inflammation and fibrosis, as well as heart failure.

Many studies in humans have suggested that elevated plasma levels of IL-6 may provide a useful prognostic marker of poor outcome in patients with unstable angina, acute MI, and heart failure and that they correlate with progression of heart failure. Circulating IL-6 levels correlate with LV dysfunction and progression of heart failure. Additionally, the rise in circulating IL-6 levels is associated with a parallel decrease in plasma levels of the IL-6 receptor, which is also consistent with involvement of IL-6 in inflammation after MI. However, levels of IL-6 are low in myocardium of patients with dilated cardiomyopathy, which suggests a dysregulation of the IL-6–gp130-STAT3 signaling pathway. Other evidence suggests that increased local and circulating levels of cardiotoxin-1 appear to play a role in LV remodeling in patients with hypertension and dilated cardiomyopathy. Although IL-6 has been implicated in adverse remodeling and heart failure previously, the mechanisms were unclear. Because IL-6 activates gp130, high IL-6 is associated with adverse post-MI remodeling, and activation of gp130 was found to be cardioprotective experimentally, there was a real need to explain this apparent discrepancy.

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In this issue of Circulation, Hilfiker-Kleiner and coworkers address the possible causative role of increased IL-6 in inflammation, adverse remodeling, and heart failure after MI. They hypothesized that physiological activation of gp130 might be protective after MI, whereas the disturbed balance of downstream signaling pathways due to gp130 point mutation might be detrimental. They performed a comprehensive series of experiments with genetic, molecular biology, and pharmacological inhibition in logical sequence with a focus on IL-6 and STAT3 and addressed the potential mechanisms. The group has published reports on IL-6 previously. Here, they used cardiomyocyte-specific gp130Y757F mutant mice with disturbed signaling of the common IL-6 receptor gp130 to form ligand-specific receptor subunits. The IL-6–gp130 receptor complex activates the 3 downstream signaling pathways (JAK/STAT, Ras-Raf [signal transduction protein-signal transduction protein downstream to Ras]-MEK/ERK, and PI3K/Akt) in response to pressure overload or myocardial infarction. B, Tyrosine phosphorylation of JAKs and recruitment of STAT proteins to the gp130 receptor. STAT complexes then translocate to the nucleus and activate transcription. Genes transcriptionally upregulated by STAT3 include SOCS proteins-1 and -3, which interact with the kinase domain of JAK proteins or cytoplasmic phosphotyrosine residue (phospho-Tyr759) of the receptor, resulting in inhibition of STAT protein phosphorylation and negative-feedback regulation of STAT activation. The gp130 receptor–mediated signaling promotes cardiomyocyte survival, induces hypertrophy, and modulates cardiac extracellular matrix and function. CT-1 indicates cardiotrophin-1; LIF, leukemia inhibitory factor; IL-6R, IL-6 receptor; MEK, MAPK/ERK kinase; MAPK, Mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; ECM, extracellular matrix; P, phosphate; PI3K/AKT, phosphatidylinositol 3-kinase-dependent; SOCS, suppressor of cytokine signaling; TYK2, tyrosine kinase 2. Adapted from Figure 1 in Fisher and Hilfiker-Kleiner with kind permission of Springer Science+Business Media. Copyright © 2007, Springer Berlin/Heidelberg.

There were 5 main findings. First, the selective cardiomyocyte-restricted mutant mice had normal cardiac function and morphology at 3 months of age, comparable to that of their nonmutant littermates. Second, MI in the mutant mice resulted in sustained cardiac inflammation, increased LV rupture rate, heart failure, and higher mortality. Third, these adverse effects in the mutant mice were associated with prolonged and enhanced activation of STAT3 and increased expression of IL-6 and complement-activating mannose-binding lectin C (MBL-C). Fourth, pharmacological inhibition of the complement system with cobra venom factor reduced inflammation, prevented LV rupture, and improved cardiac function in the mutant mice. Fifth, selective genetic reduction of STAT3 restricted to cardiomyocytes in Y757F mutant mice produced stronger effects by preventing upregulation of IL-6, complement activation, and sustained inflammation, thereby lowering the post-MI LV rupture rate, heart failure, and mortality. These results nicely demonstrate that high levels of IL-6 may increase adverse LV remodeling and heart failure after MI because of impaired downregulation of...
gp130-mediated STAT3 activation in young mice. Importantly, the findings suggest a potential causative role of increased IL-6 serum levels in impaired downregulation of gp130-STAT3 activation, thereby promoting post-MI inflammation, adverse remodeling, LV rupture, and heart failure.

The findings are important and provocative because the same laboratory previously suggested that STAT3 is protective after acute MI or ischemia, albeit with more transient upregulation.14–18 Others have suggested that cytokines may have different effects in acute MI and the subsequent healing phase. Here, the authors suggest that sustained gp130-STAT3 activation and signaling after MI is deleterious in Y757F mutant mice. They also explain why increased IL-6 and therefore increased gp130 activation can be harmful during the healing phase of subacute MI. Importantly, their findings implicate impaired downregulation of STAT3 activation.

At least 8 points deserve mention. First, proteins and molecules may exert different effects in acute and subacute phases of MI. This is especially the case with cytokines and appears to apply here. Second, both acute and subacute phases of MI are highly dynamic processes, with a ‘soup’ of different cytokines, proteins, molecules, and cells being activated and deactivated in timed sequence. This has profound implications for therapy to optimize healing and prevent adverse remodeling in the acute and subacute phases of MI. Third, the authors were careful to analyze infarct and molecular data in mice matched for infarct size that survived 14 days, to avoid the confounding effect of significant deaths that occurred between 5 and 10 days after MI. Nevertheless, the findings in the Y757F, STAT3<sub>1null</sub> and Y757F mutant mice are impressive. Fourth, infarct-size was expressed as percent LV rather than percent risk area, and the larger infarct size in Y757F mice at 2 weeks refers to infarct-size and most likely reflects infarct-scar expansion rather than increased myocardial damage. Fifth, evidence of collagen fragmentation is consistent with adverse remodeling and an increased rupture rate. The increase in matrix metalloproteinase-1 and -13 but not tissue inhibitor of metalloproteinases-1 was the likely cause of infarct-scar expansion. Sixth, the steady increase in MBL-C mRNA in Y757F mice over 2 weeks after MI is consistent with increased inflammation; however, the finding of increased IL-6 serum levels in impaired downregulation of transcription factor group (with inhibition of the complement system) compared with controls in Y757F mice with MI is consistent with the notion that prolonged activation of STAT3 and inflammation are detrimental after MI. Eighth, although ruptures during subacute MI are common in mice and could be prevented, they are rare in humans. Further studies are needed to determine whether targeting the IL-6/gp130/STAT3 pathway may be a potential approach to prevent adverse remodeling and improve healing in subacute MI.

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