Insulin-like growth factor-1 (IGF-1) plays a role in the regulation of myocardial structure and function. IGF-1 is capable of improving cardiac muscle survival, growth, calcium signaling, and differentiation. Among various actions of IGF-1 on heart, the ability of IGF-1 to counteract apoptosis of cardiomyocytes has drawn significant attention in recent years. IGF-1 suppresses myocardial apoptosis and improves myocardial function in various models of experimental cardiomyopathy. Compared with other growth factors, the survival effect of IGF-1 on myocardium is rather unique.

More Than Just Phosphoinositol-3’-Kinase and Akt

Using an ex vivo model of perfused heart isolated from IGF-1 overexpressing transgenic mice, the study by Yamashita et al6 in this issue of Circulation Research demonstrated that disrupting the activation of Akt abolished the antiapoptotic effects of autocrine/paracrine IGF-1 during ischemia/reperfusion injury. Activation of p38 mitogen-activated protein (MAP) kinase has been previously implicated in myocardial injury during ischemia/reperfusion. These investigators confirmed previous studies that blocking p38 MAP kinase reduced myocardial apoptosis in wild-type heart. However, in this study, inhibiting p38 MAP kinase activation was accompanied by significant suppression of Akt activation during ischemia/reperfusion and increased apoptosis in the IGF-1 transgenic heart. The authors concluded that, on inhibiting p38 MAP kinase activation, the reduction of Akt activation in the transgenic myocardium disrupted the spatial balance between p38 MAP kinase and Akt activation and thus triggered more apoptosis during ischemia/reperfusion. In this study, inhibition of p38 MAP kinase was achieved with chemical inhibitor SB203580. One may argue that chemical inhibitors are not impeccably specific; thus the attenuation of Akt activation by SB203580 might have been attributable to cross-inhibition. Furthermore, we cannot completely exclude the possibility that other signaling kinases could have been cross-inhibited. In another study that also used perfused heart to study ischemia/reperfusion, the same dose of SB203580 inhibited activation of c-Jun N-terminal kinase (JNK) by ≈35%. Because JNK could have been activated during ischemia/reperfusion, the contribution of JNK to modulation of apoptosis in this transgenic model remains to be clarified.

Activation of p38 MAP kinase has been consistently observed during ischemia and reperfusion, conditions that induce myocardial apoptosis and injury. But p38 kinase is also activated during preconditioning, a condition that is known to reduce myocardial apoptosis on additional ischemia insult. How p38 differentially regulates myocardial injury and protection and how p38 modulates the complex proapoptosis/antiapoptosis signaling in cardiomyocyte has not yet been satisfactorily studied so far. The phospho-p38 antibodies used in the study by Yamashita et al6 interact with both phosphorylated p38α and phosphorylated p38β. Present data suggest that the functional properties of p38 isoforms are somewhat different; p38α aggravates induction of myocardial apoptosis, whereas p38β promotes myocardial growth response. It will be interesting to explore the roles of different p38 isoforms during apoptosis induction in the transgenic mice. Regardless of whether cross-inhibition by SB203580 had occurred or how different p38 isoforms were regulated, this study clearly illustrates the importance of assessing signal pathways as a network and not as a single pathway.

Unique Music Made by Common Instruments

More and more data indicate that the spatial balance and crosstalk of different signaling pathways may modulate biological functions. Take IGF-1, for example; we now know that the survival effects of IGF-1 involve activation of the phosphoinositol-3’ (PI3)-kinase/Akt pathway in cardiac muscle. Although many growth factors can activate PI3-kinase/Akt in the heart, most growth factors do not suppress cardiac muscle apoptosis. Furthermore, IGF-1 needs both PI3-kinase and the extracellular signal–regulated kinase pathway to send out its messengers to suppress apoptosis. Most growth factor/hormone receptors use some components of the same intracellular signaling molecules, such as PI3 kinase, MAP kinases, signal transducers and activators of transcription, G proteins, and protein kinase C, but each growth factor has its own unique biological actions. Unique actions can be executed with a pool of common signaling molecules, just as different music can be played with the same set of instruments. Perhaps the uniqueness is attained by differences in the spatial balance in each signaling pathway, the timing of activation in each pathway, the subcellular location where the messengers were recruited and activated, and the traffic in the signaling network. We should not discount the importance of PI3-kinase/Akt in myocardial survival, because activation of
PI3-kinase or Akt alone is sufficient to partially suppress cardiomyocyte apoptosis. But these data do suggest that IGF-1 receptor orchestrated more pathways than just PI3-kinase to suppress activation of apoptosis in heart.

IGF-1 as a Cardiac Drug

Most scientists agree that IGF-1 is an important survival factor for the heart. However, whether IGF-1 has any clinical application in cardiomyopathy is not clear. The uncertainty surrounding the clinical applications of IGF-1 stems from the data derived from growth hormone trials in patients with heart failure and IGF-1 trials in patients with diabetes. The biological actions of growth hormone are in part mediated through upregulation of IGF-1 production in tissues and organs. An initial uncontrolled study of growth hormone therapy in patients with severe heart failure produced some exciting results. However, a sustained benefit of growth hormone was not found in larger and better-designed trials.

Although clinical trials that used lower doses of IGF-1 to treat younger patients with diabetes reported nearly no adverse reaction, chronic treatment with high doses of IGF-1 in older patients with diabetes is associated with edema, jaw tenderness, arthralgias, tachycardia, and orthostatic hypotension. These side effects probably were caused by excessive IGF-1 (ie, acromegaly) and vasodilatation. Pharmaceutical companies have accordingly decided not to develop IGF-1 as a cardiac drug because of the side effects and inconsistent growth-hormone efficacy. However, there are reasons to believe that their decision may have been premature.

The growth hormone heart failure trials were carried out in patients with relatively advanced cardiomyopathy. If the major biological actions of IGF-1 in adult heart involve myocardial protection and survival, the best therapeutic opportunity for IGF-1 or growth hormone should be during early stages of cardiomyopathy. Moreover, growth hormone effects may not be equal to IGF-1 effects, because in addition to inducing IGF-1 production, growth hormone can bind to specific cell-surface growth hormone receptors and trigger its own specific signaling. Therefore, both growth hormone receptor signaling and IGF-1 receptor signaling contribute to the biological actions of growth hormone. A lack of therapeutic efficacy with growth hormone does not necessarily attest to an ineffectiveness of IGF-1 therapy for cardiomyopathy.

How to Use a Double-Edged Sword?

Several lines of evidence suggest that chronic exposure to excessive IGF-1 may not be a good thing for the heart. When growth hormone and IGF-1 were injected to achieve supra-physiological levels over a prolonged period of time, cardiac hypertrophy inevitably occurred. Patients with acromegaly, who have high levels of circulating IGF-1, often suffer from cardiomyopathy. On the other hand, hypopituitary patients with low IGF-1 levels also can exhibit myocardial dysfunction. IGF-1 seems to be a double-edged sword; neither too much nor too little IGF-1 is good for the heart. In future IGF-1 trials on cardiomyopathy, it might be prudent to first test its efficacy and safety in patients with heart failure and low circulating IGF-1 levels.

An alternative to IGF-1 therapy will be genetic or chemical manipulation of IGF-1 signaling pathways in myocardium. As shown in the study by Yamashita et al., disrupting the homeostasis of the IGF-1 signaling network may lead to cardiac muscle death. Mismatch of intracellular signaling pathways contributes to the development of many human diseases, and cardiomyopathy is no exception. Dysregulation of extracellular signal–regulated kinase, p38 MAP kinase, JNK, protein kinase C, and other signaling pathways has been found in various models of cardiomyopathy. Detailed studies into the relationship between the antiapoptosis signaling network of IGF-1 receptor and the dysregulation of myocardial signaling in cardiomyopathy may provide new windows of therapeutic opportunities. Increased efforts to study the mechanisms of IGF-1 receptor signaling network in healthy and diseased heart are warranted; we need to know more.

References


**Key Words:** insulin-like growth factor-1  ■ phosphoinositol-3’-kinase  ■ Akt  ■ apoptosis  ■ heart
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