Commentary

Insulin-like growth factor-1 in myocardial tissue: interaction with tumor necrosis factor

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Abstract

Insulin-like growth factor (IGF)-1 is a well characterized growth factor that plays a role in the regulation of myocardial structure and function. Using an *ex vivo* murine model, Davani and coworkers, in this issue of *Critical Care*, demonstrate that IGF-1 confers cardiac protection against ischemia via mitochondria-dependent mechanisms. Those investigators used the ratio of mitochondrial to nuclear DNA to demonstrate that IGF-1, which prevents reduction in this ratio during reperfusion, provides cytoprotection. This commentary also reviews mechanisms of IGF-1 function and provides a graphic representation of IGF-1 signaling mechanisms in potential crosstalk relations with mediators of inflammation in the heart (specifically tumor necrosis factor-α).

Keywords heart, inflammation, injury, ischemia, signaling

Introduction

Insulin-like growth factor (IGF)-1 is a well characterized growth factor for a variety of cells and plays a role in the regulation of myocardial structure and function. There is evidence that IGF-1 improves cardiac performance and muscle survival in heart subjected to ischemia/reperfusion [1,2]. Therefore, elucidating the IGF-1 signaling pathways, especially in relation to cell survival, may help to promote the potential use of IGF-1 in the treatment of heart disease.

Using an *ex vivo* murine model, Davani and coworkers [1], in this issue of *Critical Care,* demonstrate that IGF-1 confers cardiac protection from reperfusion injury via mitochondria-dependent mechanisms. Because of its vital role in myocardial energy production, the quantity of functional mitochondria is essential to myocardial activity and health. Davani and coworkers propose that the ratio of mitochondrial DNA (mtDNA) to nuclear DNA (nDNA), which is increased during ischemia and reduced with reperfusion, is a very sensitive marker of cardiac injury. They then use the mtDNA : nDNA ratio to demonstrate that IGF-1, which prevents the reduction in mtDNA : nDNA ratio that occurs during reperfusion, confers myocardial cytoprotection. The mtDNA : nDNA ratio emphasizes the importance of mitochondria-related mechanisms in reperfusion injury, and it also provides a novel reference for evaluating cardiac injury.

Insulin-like growth factor-1 mediated cell survival in myocardial tissue

Insulin-like growth factor-1 signaling pathways in myocardial tissue

Two distinct forms of cell death, namely necrosis and apoptosis, are involved in the survival effect of IGF-1 in the cardiovascular system. IGF-1 not only inhibits necrosis via

IGF = insulin-like growth factor; IRS = insulin receptor substrate; mtDNA = mitochondrial DNA; nDNA = nuclear DNA; PI3 = phosphoinositol-3; TNF = tumor necrosis factor.

preservation of mitochondrial function, specifically by inhibiting membrane permeability and cytochrome C release in mitochondria, but also it reduces apoptosis through the inhibition of death signals generated by mitochondria [3].

IGF-1 survival signals are mediated by binding to its receptor, the type 1 IGF receptor. This receptor is a heterotetramer containing cytosolic substrates (insulin receptor substrate [IRS], Shc, and Gab-1), which serve as docking proteins for downstream events. It has been demonstrated that IGF-1 mediated survival correlates with the activation of the protein kinase Akt, and this pathway was disrupted by applying wortmannin, a specific inhibitor of phosphoinositol-3 (PI3)-kinase, in different models of cardiac ischemia [4,5]. Moreover, the antiapoptotic effects of IGF-1 are abolished if Akt activation is suppressed during ischemia/reperfusion injury in transgenic mouse hearts that over-express IGF-1 [6]. Recent studies revealed that IGF-1 induced myocardial protection from ischemia/reperfusion injury is associated with attenuated Bax induction and caspase 3 activation [3,7]. There is also evidence that P70 S6 kinase is involved in the survival signal of IGF-1 in H9c2 cells, and a PI3-kinase→Akt→P70 S6 kinase pathway exists in cardiomyocytes [8].

However, IGF-1 induced myocardial protection cannot be explained by the PI3-kinase/Akt pathway alone. In addition to inhibition of Bax expression, the protective effect of IGF-1 is associated with the inhibition of C-jun N-terminal protein kinase activation [9]. Moreover, Yamashita and coworkers [6] showed that inhibition of p38 mitogen-activated protein kinase activation was accompanied by suppression of Akt activation during ischemia/reperfusion in the IGF-1 transgenic heart.

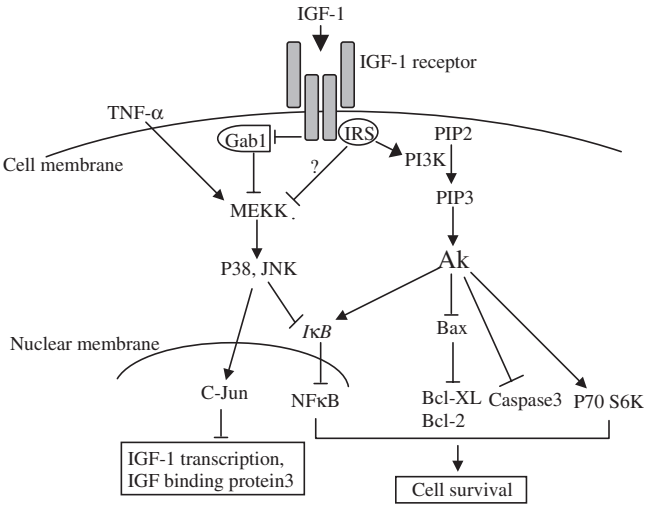
Therefore, IGF-1 receptor binding serves as an extracellular signal to stimulate its intracellular substrate IRS, which leads to activation of PI3-kinase. The products of the PI3-kinase reaction then activate Akt. Activated Akt kinase plays a crucial role in antiapoptosis by modulating different signal downstream events (Fig. 1).

Insulin-like growth factor-1 and tumor necrosis factor

Tumor necrosis factor (TNF)-α is a proinflammatory cytokine that has been implicated in the pathogenesis of cardiovascular disease. Myocardial TNF-α is an autocrine contributor to myocardial contractile dysfunction and cardiomyocyte death in ischemia/reperfusion injury, sepsis, chronic heart failure, viral myocarditis, and cardiac allograft rejection [10].

Accumulating evidence shows that crosstalk of TNF-α and IGF-1 signaling pathways may modulate biologic functions in cardiovascular tissue. Patients with chronic heart failure exhibit an inverse relationship between IGF-1 and TNF levels [11]. Drugs that increase the concentration of TNF-α decrease IGF-1 concentration in the rat heart [12]. It has been demonstrated that TNF-α suppresses IGF-1 mRNA expression and upregulates IGF-binding protein 3 [13]. Moreover, TNF-α attenuation of IGF-1 may be involved in phosphorylation of the c-Jun pathway [14]. On the other hand, it has been suggested that the cytoprotection associated with IGF-1 is correlated with downregulation of nuclear factor-κB activation induced by TNF-α [15].

Figure 1



Model of insulin-like growth factor (IGF)-1 mediated signal transduction pathways to regulate cell survival in myocardial tissue. IRS, insulin receptor substrate; JNK, C-jun N-terminal protein kinase; MEKK, mitogen-activated protein kinase kinase kinase; NFκB, nuclear factor-κB; PI3, phosphoinositol-3; PIP, phosphoinositol-4-phosphate; TNF, tumor necrosis factor.

IGF-1 is important for the growth and survival of cardiovascular tissue. However, long-term IGF-1 treatment downregulates the expression of Gab1 associated with MEKK3, which enhances TNF-induced c-Jun and nuclear factor-κB activation, as well as adhesion molecule expression in endothelial cells [9]. Long-term IGF-1 treatment thus leads to hypersensitivity to TNF-mediated signaling events.

Effects of insulin-like growth factor-1 on myocardial function

IGF-1 is not only an important survival factor for the heart, but it also plays a role in improving cardiac function. IGF-1 has been shown to improve perfusion pressure and left ventricular compliance in ischemia/reperfusion by decreasing interstitial edema, preserving the myocardial tissue lattice, and protecting mitochondrial integrity [1]. IGF-1 mediated protection of cardiac contractility may be involved in the PI3 kinase pathway and in activation of protein kinase C [16]. IGF-1 induces increases in intracellular calcium [17] and myofilament calcium sensitivity, both of which improve cardiac contractility [16].

Conclusion

IGF-1 is an important growth factor for the survival and function of the heart. Accordingly, much focus has been given to IGF-1 as a potential therapeutic agent. Indeed, it has been shown that IGF-1 has a cytoprotective effect in different models of cardiac ischemic injury. However, the role of IGF-1 in cardiovascular disease is still not clear. Recent evidence suggests that long-term exposure to IGF-1 may actually be detrimental to the heart. It is clear that further investigation of the IGF-1 signaling network is needed before its clinical application can be declared.

Competing interests

None declared.

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