

Review

# IGF-I is a matter of heart

Ole Saetrum Opgaard, Ping H. Wang \*

*Departments of Medicine, Biological Chemistry, Physiology and Biophysics, Center for Cardiovascular Hormone Research, University of California, Medical Science I, Room C240, Irvine, CA 92697, USA*

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## Abstract

An intriguing relationship between IGF-I action and cardiac function has been noted for some time, but exactly how IGF-I modulates myocardial function remained obscure. Recent research shed novel insight into potential mechanisms of IGF-I actions in cardiac muscle. New discoveries help elucidate the role of IGF-I signaling in protecting cardiac muscle against injuries, and support potential therapeutic roles for IGF-I in cardiomyopathy. Multiple actions of IGF-I has been described in cardiac muscle cells, including the well-documented anti-apoptosis effect and the newly emerged action on cardiac muscle regeneration. Furthermore, interplay between heat shock protein and IGF-I receptor signaling has been identified and this new paradigm might be involved in the development of diabetic cardiomyopathy. This article reviews recent research findings and outlines potential therapeutic implications of IGF-I in heart failure.

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## 1. Introduction

Age-related and other structural changes of the heart, including alterations secondary to myocardial infarction, often cause a progressive decline in cardiac function that ultimately can lead to congestive heart failure. These changes were previously considered to be largely irreversible, an assumption based on the belief that cardiac myocytes were unable to regenerate [1]. A potential new approach to treatment of congestive heart failure is emerging from the observation that insulin-like growth factor-I (IGF-I) appears to prevent and/or delay the decline of myocardial function and death of cardiomyocytes [2]. Even more intriguing is the recent concept of myocardial stem cells able to regenerate in the adult heart, and the observation that IGF-I appears to be an important stimulant for this regeneration [3]. Recent data derived from patients also suggest that IGF-I may

be used to stratify the risk of heart failure [4]. This mini-review will focus on evidence supporting potential therapeutic roles for IGF-I in diseases affecting the myocardium.

## 2. IGF-I prevents death of cardiac myocytes

In myocardial ischemia/reperfusion injury, myocardial infarction, and heart failure, there is often myocyte loss, although a later increase in myocardial mass may occur through compensatory myocyte hypertrophy and/or increased deposition of collagen in the interstitium [5]. In addition to acute myocyte necrosis after ischemic injury, evidence has accumulated that programmed cell death (apoptosis) is a key contributor to myocyte loss, accompanying many forms of myocardial disease and even occurring during normal aging in the absence of identifiable necrosis [6].

It has been demonstrated in different tissues that IGF-I can prevent apoptosis and prolong cell survival

\* Corresponding author. Tel.: +1 949 8246981; fax: +1 949 8242200.  
E-mail address: [phwang@uci.edu](mailto:phwang@uci.edu) (P.H. Wang).

[7–9], and the IGF-I receptor has been proposed to be a central regulator of mammalian lifespan [10]. Inhibition of cardiomyocyte loss through suppression of cell death pathways may represent a strategy to prevent heart failure, and it has been shown that IGF-I decreases myocyte apoptosis after myocardial infarction in mice [11], in ischemia-reperfusion injury in rats [12], and in cultured rat cardiomyocytes [13]. The anti-apoptotic actions of IGF-I can be observed at physiological concentrations, while other growth factors seem unable to suppress apoptosis of cardiac muscle cells, even at pharmacological levels [13].

Activation of the IGF-I receptor leads to stimulation of several phosphorylation cascades that regulate a wide array of biological effects [14]. Two major IGF-I signaling pathways have been well established. One involves sequential activation of Ras, Raf-1, Mek, and ERK, and activation of this pathway has been linked to cell growth and proliferation. The other involves activation of phosphatidylinositol 3-kinase (PI 3-kinase) and Akt, and this pathway has been linked to cell metabolism, growth, and anti-apoptotic responses [15]. IGF-I activates both MAP-kinase and PI 3-kinase pathways in cardiac muscle [16–19], and it has been shown that the PI 3-kinase – Akt pathway, promotes survival of cardiac myocytes both in vitro and in vivo, and protects cells from reperfusion injury in vivo [20,21].

### 3. Regenerative potential of human adult cardiac myocytes

The traditional view that the adult myocardium represents a terminally differentiated organ with no regenerative potential [1] has been challenged recently by new data showing that cardiac stem cells exist in adults, and that these cells may be the source of myocardial renewal in both animals and humans [22,23]. Human studies have demonstrated a subpopulation of cardiac myocytes that are not terminally differentiated; these myocytes appear able to re-enter the cell cycle and undergo nuclear mitotic division early after myocardial infarction. Of note was the observation that the number of cycling myocytes was significantly larger in the zone bordering an infarct than in the distant myocardium [24].

The prevalence of left ventricular hypertrophy and congestive heart failure increases with age, even in individuals without hypertension or clinically apparent cardiovascular disease [25], although more extensive telomere erosion, cellular senescence, and myocyte cell death characterize aged diseased hearts [26]. While previous autopsy studies have suggested that the increase in myocardial mass was due solely to myocyte hypertrophy and/or increased amount of collagen [5], more recent analyses of postmortem human hearts have demonstrated a significantly increased number of myocytes in

patients with congestive heart failure [27]. Furthermore, studies of human hearts from autopsy and explanted hearts have confirmed that mitotic myocardial cells are present in the human myocardium [28]. Of even greater interest, a nearly 10-fold increase in the number of mitotic cells was measured in human end-stage ischemic hearts and in idiopathic dilated cardiomyopathy compared to control hearts [28]. Furthermore, in patients with aortic stenosis, intense new myocyte formation resulting from the differentiation of cells with stem-cell markers was seen [29]. Their number increased >13-fold, supporting the existence of cardiac stem cells that amplify and commit to the myocyte lineage in response to increased workload [29].

The origin of cardiac stem cells, whether permanently residing in the myocardium or taken up from the general circulation/bone marrow, seems unclear [30,31]. Interestingly, in cases of sex-mismatched cardiac transplants in humans, the female hearts in the male hosts had a significant number of Y positive myocytes and coronary vessels, suggesting a peripheral origin of these cells [30].

### 4. IGF-I promotes regeneration of human myocardial cells

There are several lines of evidence that IGF-I plays an important role in regeneration of cardiac myocytes. Culture studies of adult rat myocytes have documented that added IGF-I activates DNA synthesis [32]. In IGF-I transgenic mice, experiments have shown that cardiac stem cell division is induced via the IGF-I receptor, and is accompanied by enhanced telomerase activity, delayed senescence, and preservation of a reservoir of functionally competent cardiac stem cells [33].

Recent results in humans and animals have provided evidence that myocyte replication does occur under physiological and pathological conditions in the heart, and IGF-I seems to promote the expression of growth-related genes, DNA replication, myocyte nuclear mitotic division, and cell division [3]. Regarding cardiac myocyte hypertrophy independent of hyperplasia, it remains possible that growth factors other than IGF-I are involved, in part because IGF-I deficiency did not prevent development of pressure overload hypertrophy in mice [34]. In this regard, pretreatment with the growth hormone secretagogue, growth hormone-releasing peptide 2, protected selectively against the diastolic dysfunction of myocardial stunning in rabbits, while this effect was not seen after treatment with growth hormone itself – despite causing a significant increase in IGF-I levels [35].

Although cardiac myocytes do divide in the adult heart, the magnitude of regeneration is far below the extent of myocyte death in the failing heart. However, IGF-I may provide an opportunity to enhance myocardial repair after myocardial injury.

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