IGF-1 Overexpression Rescues the Failing Heart

Allen M. Samarel

Congestive heart failure (CHF) is a syndrome affecting nearly 5 million Americans with 550,000 new cases diagnosed annually. Despite recent advances in pharmacological therapy, the enormity of the clinical problem has stimulated cardiovascular scientists to test a variety of new and provocative hypotheses that may ultimately prove useful in CHF prevention and treatment. One such novel approach is addressed by Welch et al in this issue of Circulation Research. They tested the hypothesis that insulin-like growth factor-1 (IGF-1), a peptide growth factor involved in cardiomyocyte proliferation, differentiation, and cell survival, can positively affect CHF progression in a transgenic mouse model of dilated cardiomyopathy. The study provides new and important information about the cellular mechanisms leading to ventricular remodeling and also adds to the current controversy regarding the roles of cardiomyocyte apoptosis and regeneration in the pathogenesis of CHF.

What's Wrong With the TOT Mouse?

Welch et al make use of two previously characterized transgenic mouse lines in a selective crossing experiment. Dilated cardiomyopathy was modeled by overexpression of the cytoskeletal protein tropomodulin, to produce homozgyous animals (tropomodulin-overexpressing transgenic [TOT] mice) with many of the features of human idiopathic dilated cardiomyopathy. Tropomodulin is an actin-binding protein that associates with the pointed ends of actin filaments. This occurs late in the process of myofibrillogenesis and is thought to be responsible for maintaining the final length of thin filaments in mature, striated myofibrils. Sussman and coworkers have previously shown that tropomodulin overexpression in cultured cardiomyocytes produces shortened actin filaments and myofibrillar degeneration, whereas antisense downregulation of tropomodulin produced abnormally long actin filaments at the cell periphery. Thus, it might seem surprising that TOT cardiomyocytes are elongated, with a markedly increased length-to-diameter ratio. Cardiomyocyte elongation is a feature common to many other forms of eccentric ventricular remodeling, in which end-diastolic chamber dimension is increased. The mechanisms regulating cardiomyocyte shape are largely unknown, but these observations suggest a dissociation of the factors that regulate sarcomere length from those that regulate cell length.

Recent studies have shown that cardiomyocyte shape may be controlled by signaling pathways common to, as well as distinct from, those that regulate myofibrillar protein gene expression and sarcomere assembly. For instance, overexpression of constitutively active PKCe in cultured cardiomyocytes induced the load-independent, serial assembly of sarcomeres without a substantial increase in total protein mass. Overexpression of constitutively active MEK5 produced a similar phenotype and induced eccentric cardiac hypertrophy that progressed to dilated cardiomyopathy and sudden death in transgenic mice. It seems unlikely that the cardiomyocyte shape change alone was sufficient to produce the constellation of abnormalities present in TOT mice. Nevertheless, increased cell length without a concomitant increase in cell diameter may prevent cardiomyocytes from developing adequate force to compensate for the extent of chamber dilatation.

TOT mice display tropomodulin overexpression, abnormal [Ca2+]i handling, and altered signal transduction before the development of severe myofibrillar degeneration. Thus, the cardiomyopathy must be caused by relatively subtle alterations in sarcomeric structure and function. In this regard, the actin cytoskeleton should be viewed not only as the scaffold for myosin motors to generate force, but also as a component of the cellular machinery that senses mechanical load. Exactly how cardiomyocytes perceive increased load (in this case, increased systolic and diastolic wall stress) and transduce these mechanical signals into altered gene expression, sarcomeric assembly, and cell survival remains the subject of intense investigation. Mechanical stress increases cardiomyocyte [Ca2+]i via increased Ca2+ influx through both stretch-activated and voltage-gated Ca2+ channels. Stretch-activated and L-type Ca2+ channels are in turn influenced by the integrity of the actin cytoskeleton and its coupling to the extracellular matrix via integrins. Thus, it is conceivable that tropomodulin overexpression results in ventricular remodeling primarily via a defect in [Ca2+]i handling brought about by disruption of the actin-based cytoskeleton. In favor of this hypothesis is the fact that inhibition of the Ca2+/calmodulin-dependent phosphatase calcineurin prevented the development of dilated cardiomyopathy in TOT mice and in 2 other mouse models with defective sarcomeric proteins. Welch et al provide convincing evidence that TOT overexpression ultimately induces cardiomyocyte apoptosis. The responsible mechanisms were not fully explored, but like other features of the hypertrophic/dilated phenotype, apoptosis likely results at least in part as a consequence of dysregulated neurohormonal and mechanochemical signaling. Circulating and locally released norepinephrine, angiotensin II, and endothelin I are all markedly increased as a consequence of the heart failure state, and profound activa-

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Circulation Research is available at http://www.circresaha.org
DOI: 10.1161/01.RES.0000015425.11187.19

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tion of their Gq-coupled receptors is sufficient to induce apoptosis via stimulation of the mitochondrial death pathway. Other mechanisms, including anoikis as a direct consequence of cytoskeletal disruption may also contribute to progressive myocyte loss, wall thinning, and chamber dilatation. Although the relative contribution of apoptosis to human CHF progression remains controversial, transgenic mouse models in which apoptosis is a prominent feature have demonstrated its dramatic potential for chamber remodeling. In the present study, Welch et al demonstrate a 4-fold increase in the number of TUNEL-positive nuclei from an undefined number of TOT hearts at an undefined time point during the development of CHF. Although these data are certainly suggestive of a causative role in ventricular remodeling, a much more detailed analysis of the regional and temporal development of apoptosis will be required to convince those skeptical of its role in CHF progression.

IGF-1 to the Rescue

Welch et al now describe a dual-hemizygous mouse line (TIGFO mice) generated by selective breeding of TOT mice with hemizygous IGF-1-overexpressing mice. IGF-1 mediates many of the effects of growth hormone on cardiovascular structure and function and has been shown to promote cardiomyocyte hyperplasia and hypertrophy, improve contractility, and inhibit apoptosis (for review, see Ren et al). IGF-1 overexpression in TIGFO animals prevented or reduced virtually every abnormality associated with tropomodulin expression. It is curious, however, that the authors did not analyze tropomodulin expression itself in TIGFO animals, to ensure that the improvements in structure and function were not the result of a nonspecific reduction in transgene expression. Similarly, a detailed analysis of the sarcomeres in TIGFO cardiomyocytes was not performed to identify which ultrastructural features were affected by IGF-1 overexpression and which were not. Nevertheless, the improvement in chamber geometry and global ventricular function provides additional evidence for a potential therapeutic benefit of IGF-1 (and by inference, growth hormone itself) on the failing heart, regardless of the initial cardiac insult.

Cardiomyocyte Apoptosis and Regeneration

Adult, hemizygous IGF-1 mice have enlarged hearts, with a progressive increase in cardiomyocyte cell number, but with normal cell volume and normal or even supernormal indices of cardiomyocyte contractility. These data suggest that prolonged stimulation of cardiomyocyte IGF-1 receptors induces a significant proportion of cardiomyocytes to remain in the cell cycle postnatally. IGF-1 enhances cardiomyocyte hyperplasia during the fetal period, but cardiomyocyte hypertrophy, rather than hyperplasia, was seen in transgenic mice overexpressing a constitutively active form of phosphoinositide 3-kinase, a major downstream effector of the IGF-1 receptor signaling pathway. Whether nontransgenic, TOT, IGF, or TIGFO cardiomyocytes continue to divide was not specifically addressed in the present study, but was implied by the persistent expression of Ki67, a nuclear marker of replicating cells. Ki67 was found in approximately 0.2% of nontransgenic cardiac cells. Tropomodulin expression alone reduced the number of Ki67-positive nuclei, whereas IGF-1 overexpression significantly increased this number in both IGF and TIGFO hearts. These measurements were performed by analysis of tissue sections rather than isolated cardiomyocytes, so identification of cardiomyocyte nuclei cannot be unequivocally assured. Nevertheless, these provocative findings support other data by the Anversa group that challenges the widely held view that the heart is a postmitotic organ, at least with respect to the ability of adult cardiomyocytes to replicate in vivo. They suggest that ventricular remodeling represents, in part, an imbalance between the rate of cardiomyocyte cell loss and the rate of cardiomyocyte regeneration. Further investigation and confirmation by other laboratories will be required to prove that (1) the Ki67-positive cells are indeed cardiomyocytes; (2) they are capable of cytokinesis; and (3) they are generated from dividing cardiomyocytes or, alternatively, from migrating progenitor cells that are induced to proliferate and differentiate by localized, myocardial overproduction of IGF-1.

Summary

Regardless of the ultimate mechanisms involved, Welch et al add to the growing body of data supporting the benefit of IGF-1 as a prophylactic and interventional treatment for CHF. Issues regarding modes of delivery and local versus systemic effects of the hormone must be resolved, but an agent that promotes cardiomyocyte survival while improving contractile performance would be a welcomed addition to our standard therapy for CHF patients.

References


Keywords: growth hormone ■ apoptosis ■ cardiac regeneration
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Circ Res. 2002;90:631-633
doi: 10.1161/01.RES.0000015425.11187.19

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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