Aging and Longevity
The IGF-1 Enigma
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IGF-1 belongs to the insulin family of peptides and acts as a growth factor in many tissues and tumors. Locally acting isoform of IGF-1 targeted to skeletal muscle enhances muscle growth and differentiation, prevents age-related muscle atrophy, and potentiates regeneration after injury.1,2 Similarly, cardiac restricted expression of IGF-1 increases the formation of ventricular myocytes, attenuates myocyte death, and delays the development of an aging myopathy.3,4 In the heart, the IGF-1–IGF-1 receptor system induces division of cardiac stem cells (CSCs), upregulates telomerase activity, hinders replicative senescence, and preserves the pool of functionally competent CSCs.5,6 After muscle injury, IGF-1 promotes the activation, mobilization, and differentiation of satellite cells which, together with the recruitment of bone marrow progenitor cells, contribute to skeletal muscle regeneration in old animals.1,2 Spontaneous repair of damaged muscle typically occurs in young animals and is severely impaired with age. Importantly, heart failure leads to a catabolic state characterized by a progressive loss in skeletal muscle mass and the appearance of cardiac cachexia in the late stages of the disease. This information formed the basis of the study by Schulze et al7 published in the current issue of Circulation Research.

The dramatic problem of skeletal muscle wasting with chronic heart failure has become a common clinical reality. Cardiac decompensation is a disease of the elderly, which has reached endemic proportion with the progressive increase in average lifespan of the population in the Western world.7 Unfortunately, muscle atrophy cannot easily be reversed, and the pharmacology is palliative at best. Similarly, strategies aiming at the reconstitution of muscle mass with systemic administration of growth factors or potential implementation of cell therapy are in an infancy stage. The work of Schulze et al has addressed this major pathological condition with a novel molecular–genetic approach based on the recognition of a signaling pathway that involves the ubiquitin–proteasome complex.6 Remarkably, the upstream positive modulator of the muscle-specific ubiquitin ligase atrogin-1/MAFbx has been identified in the Foxo transcription factors (Figure 1). Upregulation of Foxo opposes the synthesis of muscle proteins,8 which is, however, counteracted by a selective muscle isoform of IGF-1 through phosphorylation of Foxo by Akt and inhibition of Foxo transcriptional activity.6 In both skeletal muscle and heart, IGF-1 activates the PI3-kinase pathway that in turn phosphorylates Akt targeting several molecules promoting cell growth and survival.9 Prevention of cell death and induction of cell replication are the ultimate goal of cell therapy; the former attenuates the extent of injury, and the latter determines the degree of structural and functional recovery.

The IGF-1–IGF-1 receptor system plays an important role not only in skeletal and cardiac muscle disease but also in organism development. Homozygous deletion of IGF-1 in mice does not preclude embryonic and fetal formation of organs but offspring body weight is 45% of wild-type littermates, suggesting that IGF-1 controls >50% of body mass.10 More dramatic are the effects of targeted disruption of the IGF-1 receptor gene. Generalized organ hypoplasia with respiratory failure occurs, and these defects lead invariably to death at birth.10 Paradoxically, mutation of the homologue of insulin–IGF-1 receptor, daf-2 in nematodes or Inr in fruit flies, delays aging and extends maximum lifespan in these lower eukaryotes.11 Attenuation of insulin/IGF-1 signaling results in upregulation of DAF-16 which activates a variety of genes implicated in longevity and inhibits selective life-shortening genes.12 Conversely, as elegantly demonstrated by Schulze et al,6 overexpression of muscle IGF-1 interferes with Foxo, which is the mammalian homolog of DAF-16, and inactivation of Foxo has a powerful positive therapeutic impact on skeletal muscle growth and cachexia. How important these differences are in distal effectors of insulin/IGF-1 between invertebrates and mammals is difficult to appreciate, but caution against the tendency to translate results in worms and flies to human beings. Restoration of IGF-1 levels in elderly individuals by hormone-replacement therapy has significant health benefits.13

The molecular mechanism underlying the increased lifespan in long-lived daf-2 mutants is largely mediated by the enhanced expression of enzymes that protect and repair oxidative damage.12 Reactive oxygen species (ROS) are formed in several compartments of the cells, but ~90% of intracellular oxidants is generated within the mitochondria. Strong reductions in IGF-1 signaling in C. elegans results in a quiescent state of diapause called dauer, which corresponds to a nonfeeding stress-resistant larval state.11 Most importantly, nearly 35% of nematodes with modest decreases in daf-2 become extremely lethargic and dauer-like and lose spontaneous motility. In both cases, oxidative stress is minimal and longevity may be dictated by the metabolic switch.14 This possibility is consistent with the well-established para-
The increased in lifespan, albeit modest, of mice heterozygous for the deletion of the IGF-1 receptor is restricted to the female cohort, and the lack of evidence in males remains unexplained. Similarly, the few hour increase in survival of transgenic mice after the injection of paraquat to induce oxidative damage is a weak argument in favor of the oxidative stress leading to cellular senescence and death. Whether a similar mechanism is operative in skeletal muscle is currently unknown. But, if this were the case, it could contribute to the prevention of muscle atrophy observed by Schulze et al in chronic heart failure.6

Recent studies in mice have indicated that p53 activation by overexpression of p44 leads to premature organism aging by an adaptive compensatory response characterized by upregulation of the IGF-1–IGF-1 receptor system.26,27 p44 is a short isoform of p53 with a truncation of the amino-terminal of p53. Because Mdm2 binds to the amino-terminal of p53, p44 is no longer modulated by Mdm2. The unusual role of p53 in accelerating the aging process through the IGF-1 signaling pathway is at variance with findings concerning the impact of IGF-1 on p53. IGF-1 phosphorylates the amino terminal of p53 and, thereby, the expression of Mdm2. Mdm2 binds to p53 leading to the formation of Mdm2–p53 inactive complexes and inhibition of p53 function.25

The postulated negative role of IGF-1 in life expectancy contrasts with the positive effects of IGF-1 on skeletal muscle atrophy and cardiomyocyte loss as a function of age in mice. Some clues to this conundrum are found in the study of Schulze et al. IGF-1 increases the anabolism of skeletal muscle cells and attenuates the ubiquitin–proteasome pathway and, therefore, muscle catabolism and the formation of oxidative products with heart failure.8 Similarly, IGF-1 decreases oxidative damage in the myocardium with aging2 and diabetes in vivo and hyperglycemia in vitro (PA, unpublished data, 2005). IGF-1 prevents downregulation of the uncoupling protein-3 with hyperglycemia, interfering with the generation of ROS,28 and can repair oxidative DNA damage by homologous recombination.29 Importantly, IGF-1 de-
crease baseline production of ROS and prevents DNA damage, irreversible growth arrest and apoptotic death of adult CSCs (Figure 2), and a similar phenomenon may be operative in skeletal muscle stem cells.1

The short lifespan in lower organisms such as the C. elegans and the Drosophila is linked to the loss of regenerative capacity of somatic tissues in adulthood.30 Dying cells cannot be replaced, and this results in a rapid and progressive decline in organ function. Conversely, cell turnover by activation and commitment of resident progenitor cells remains active in mammals, and old damaged cells that accumulate with time can be replaced by new, younger, better functioning cells. IGF-1 potentiates cell turnover and regeneration in susceptible cells including CSCs5 and satellite cells.1,2 Skeletal muscle and myocardial regeneration mediated by IGF-1 activation and growth of satellite cells and CSCs delays the onset of heart failure and its complications in mammals.1,2,4–6 However, the impact of IGF-1 on aged terminally differentiated cells is more complex and only partially understood. The growth stimulating IGF-1 signals may be substituted by metabolic insulin signals31 that enhance oxidative stress and might trigger the endogenous cell death pathway.

In summary, the postulated aging effects of IGF-1 are not clear. Human studies indicate that increased levels of IGF-1 are characterized by a decreased incidence of heart failure and mortality in elderly individuals.32,33 This impact of IGF-1 on the human heart may be operative at the level of the CSC compartment where primitive cells continue to renew themselves and give rise to committed progenies. Similarly, the skeletal muscle–specific IGF-1 isoform may counteract the decline in mass and functional performance with old age and ventricular decompensation, protecting the pool of satellite cells which effectively replace senescent dying cells.1,2,6 Together, these observations support the hypothesis that well-preserved functional CSCs and skeletal muscle satellite cells maintain the youth of the heart and skeletal muscle opposing aging effects and disease states. Extreme caution has to be exercised in the translation of results in simple postmitotic organisms to large mammals and particularly human beings in which the life and death of most somatic organs is regulated by a stem cell compartment.

Acknowledgments

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References


Figure 2. Cardiac progenitor cells and reactive oxygen species. A and B, Baseline formation of hydroxyl radicals (green) in isolated c-kit positive progenitor cells in the absence (A) and in the presence (B) of IGF-1 at 100 ng/mL. Hydrogen peroxide, 100 μmol/L, markedly increases the generation of hydroxyl radicals (C) which is significantly reduced by IGF-1 (D). Nuclei are stained by Syto17 (red).

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