Aging and Longevity
The IGF-1 Enigma
Piero Anversa

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 forms the basis of the study by Schulze et al6 published in Circulation Research,2005;97:411-414.)

The molecular mechanism underlying the increased lifespan in long-liveddaf-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 indaf-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-

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The increase 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 deleterious effects of IGF-1 receptors on oxidative stress response and life expectancy. In the Western world, women live several years longer than men do and have a reduced incidence of heart failure, but the underlying cause for this difference in lifespan between genders 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.

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. 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.

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.

Importantly, the female heart is more resistant to aging effects than the male heart and has an enhanced expression and nuclear localization of Akt, powerful survival factor and distal effector of IGF-1. Animal models with deficiencies in IGF-1 are complicated by the concurrent alterations in growth hormone or hypopituitarism, which result in multiple endocrine defects and developmental abnormalities. These confounding factors make the dwarf mice inappropriate for the assessment of the role of IGF-1 in biological aging and lifespan.
creases 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 and the operative in skeletal muscle stem 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.

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References


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