

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 forms the basis of the study by Schulze et al\(^6\) published in 2005; 97: 411–414.)

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 \(\approx 90\%\) 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-
Targeted mutation of the p66<sup>shc</sup> gene decreases the formation of ROS, increases the resistance to oxidative stress, and prolongs life by 30% in mice. This constitutes the first demonstration that a gene can modify the formation and effects of ROS on survival and maximum lifespan in mammals. By multiple pathways, p53 increases the intracellular concentration of ROS. The adaptor protein p66<sup>shc</sup> constitutes a powerful effector that links p53 to oxidative stress. In the absence of p53, the ability of p66<sup>shc</sup> to modulate the elevation of intracellular oxidants and induce cell death is lost.<sup>22</sup> p66<sup>shc</sup> possesses a unique N-terminal domain that becomes phosphorylated at Ser 36 when cells are exposed to oxidative stress. Phosphorylated p66<sup>shc</sup> inhibits the activity of the forkhead family of transcription factors (Foxo), leading to the reduced transcription of forkhead target genes such as the antioxidants superoxide dismutase and catalase.<sup>23</sup> Additionally, a fraction of intracellular p66<sup>shc</sup> is located within the mitochondria where it binds to the heat shock protein, Hsp70. This inert complex is activated and dissociated on oxidative stress, leading to a marked decrease in mitochondrial membrane potential and increased transmembrane permeability and ROS formation.<sup>22</sup> In this regard, it has recently been shown that overexpression of catalase targeted to the mitochondria expands median and maximum lifespan in mice.<sup>24</sup>

IGF-1 downregulates p53 and Bax and upregulates Bcl2 in cardiomyocytes.<sup>25</sup> p53 is a potent stimulant of Ang II formation which, in turn, increases cytosolic calcium and 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.<sup>6</sup>

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.<sup>26,27</sup> 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.<sup>25</sup>

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.<sup>8</sup> Similarly, IGF-1 decreases oxidative damage in the myocardium with aging<sup>2</sup> 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,<sup>28</sup> and can repair oxidative DNA damage by homologous recombination.<sup>29</sup> 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 CSCs\(^5\) 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 signals\(^31\) 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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