SIZE, STRESS, AND AGING

Richard A. Miller (P)

University of Michigan

Small size and extended life span are typically found together in dogs, mice, and horses, and short people are cancer resistant. Mice with low levels of early-life IGF-I live longer than those with higher IGF-I levels. What are the connections, at the cell and tissue level, between low IGF-I levels and retardation of aging, cancer, and other late-life diseases? Recent studies show that fibroblast cell lines derived from the long-lived mutant Snell dwarf mouse are resistant, in culture, to multiple forms of lethal stress, including the oxidative agents peroxide and paraquat, the toxic heavy metal cadmium, heat, the DNA alkylating agent MMS, and ultraviolet light irradiation. Similar results are seen using cell lines from the Ames dwarf mutant and from mice lacking the growth hormone receptor, both of which, like the Snell dwarf, have low levels of IGF-I during postnatal life. These findings suggest that perhaps low levels of IGF-I in early life trigger developmental pathways that produce a permanent (or at least long-lasting) state of stress resistance in fibroblast cells. Fibroblasts from Snell dwarf mice show five other properties of interest: (a) they are resistant to UV light-induced inhibition of RNA polymerase; (b) they are resistant to metabolic quiescence induced by low glucose concentrations; (c) they are resistant to some, but not all, inhibitors of the mitochondrial electron transport chain; (d) they are particularly sensitive to agents that block protein processing in the ER and Golgi apparatus; and (e) they generate unusually low levels of heat shock protein HSP70 after serum withdrawal. Furthermore, Snell dwarf fibroblasts are resistant to the apoptotic crisis and spontaneous transformation induced by continuous long-term culture in standard conditions, i.e. culture in 20% O_2; this last observation may provide a clue to the life-long cancer resistance of the Snell dwarf mouse.

Collaborators: Andrzej Bartke, John Kopchick, Scott Leiser, Scott Maynard, Shin Murakami, Amir Sadighi Akha, Adam Salmon. *Support: National Institute on Aging, and Ann Arbor DVA Medical Center.*