

THE IGF SYSTEM AND LONGEVITY

C. Conover (P)

Mayo Clinic, 200 First Street SW, Rochester, MN 55905

A reduction in insulin-like growth factor (IGF)-I signaling has been associated with an increase in longevity and delayed onset of age-related disorders in diverse species. The IGF system is complex with ubiquitous ligands and with IGF receptors present on virtually all cells. However, IGF binding proteins (IGFBPs) and IGFBP proteases ultimately determine ligand availability and, hence, response. Our overall hypothesis is that the aging process is regulated, at least in part, by a specific protease, so-called pregnancy-associated plasma protein-A (PAPP-A), which degrades inhibitory IGFBP-4 thereby increasing IGF-I bioavailability without a change in IGF-I expression. The corollary to this is that PAPP-A deficiency, by decreasing local IGF availability and receptor signaling, would result in increased longevity. To test this hypothesis, we generated PAPP-A knock-out mice. These mice are born as proportional dwarfs due to impaired IGF-II bioavailability during early embryogenesis. Otherwise, these mice appear healthy and show normal post-natal growth. We found that this suppression of PAPP-A expression through genetic manipulation results in the extension of lifetime survival of these mice by 30-40% in both males and females. This was not associated with alterations in serum glucose, insulin, IGF-I or growth hormone levels, and dietary intake was not significantly different between PAPP-A knock-out mice and wild-type littermates. These data indicate that the PAPP-A knock-out mouse is a valuable new model for investigating molecular issues of aging that relate to IGF-I signaling, and point to PAPP-A as a possible drug target with potential to regulate longevity and age-related diseases by moderate restraint of IGF signaling.