Introduction

Genes, Oxidative Stress, and Aging

The free radical theory of aging was first introduced by Denham Harman as a logical albeit speculative biological explanation for the age-related loss of function observed in most species. Today this theory has garnered widespread empirical support and become one of the major mechanistic explanations underlying aging and senescence, particularly when mitochondrial sensitivity to reactive oxygen species and the resultant changes were integrated into it. This understanding, developed by many people working with a variety of different systems, has enhanced our understanding of the role which the genes play in the aging process. The several articles gathered here do, when taken together, provide important new and/or confirming data which extends our knowledge of the genetic mechanisms involved in aging.

Much extraordinary work has been done with the nematode, *C. elegans*. Shuji and Yoko Honda (p.177) show that there are at least two separate mechanisms involved in the organism's longevity response to oxidative stress. The first mechanism depends on mutations in the well-known *age-1* gene (a PI3K homologue) that up-regulates the expression of certain antioxidant defense genes associated with resistance to oxidative stress (*sod-3* and *cat-1*). Such resistance can also be generated by a short-term exposure to hyperoxia. This treatment extends life span slightly but significantly by increasing the expression of various *sod* isoforms, thereby enhancing the defences against oxidative stress. Understanding the details underlying these different mechanisms of gene regulation will be an important component of our ability to eventually modulate this antioxidant defense system.

In my own lab, my collaborators and I have previously shown that the up-regulation of various antioxidant defense genes (particularly *CuZnSOD*, *MnSOD*, *catalase*, and others) bear an intimate, perhaps even causal, relationship to the delayed onset of senescence and extended longevity characteristic of our long lived strains. Steven Buck and I now show (p. 149) that the up-regulation of these antioxidant defense genes is itself dependent on a concurrently altered metabolism necessary to provide the cofactors necessary to the increased activity of the several different antioxidant defense genes. It is interesting to note that different selected strains not only activate different antioxidant defense genes but also have strain-specific supporting metabolic alterations. It will be interesting to determine whether certain metabolic alterations are more effective in supporting extended longevity than others.

Recent work has suggested that much of the damage associated with aging may be due to the effects of inflammation, and this 'inflammatory hypothesis of aging' has been formally proposed as a subset of the free radical theory of aging. Continuing their work in this area, Hae Young Chung and his colleagues (p. 161) nicely demonstrate in their work that NF-6B is up-regulated in aging rats as a result of a significant decrease in the cytosolic I6B\$ component. Such older animals show age-related increases in a number of pro-inflammatory enzymes and cytokines, particularly following a mild proinflammatory stimulus. Much of the loss of function associated with aging may arise from a chronic inflammation of certain systems resulting from a loosening of NF-6B regulation. These findings suggest possibilities for future interventions.

Prof M. A. Yoo and her colleagues (p. 185) have investigated the age-related changes in the innate immune system of *Drosophila*. They demonstrate that the animal's ability to mount an effective immune response to foreign bacteria decreases in a typical age-associated pattern, indicating that the loss of function in this system must also be considered as one of the age-related losses of function in this model system. Most interestingly, they have shown that the normal functioning of the innate immune system in this organism is dependent on a functioning antioxidant defense system. Flies deficient for XDH, and thus under higher levels of oxidative stress, had an impaired inducibility of some but not all immune system genes. Their work effectively brings the fly's innate immune system into the number of physiological systems adversely affected by the aging animal's gradual loss of resistance to oxidative stress.

Christopher Driver (p.171) presents an interesting hypothesis in which he suggests that the increased production of reactive oxygen species observed in many aging models may depend on the presence or absence of various specific factors, particularly those involving cytosolic calcium or other signaling molecules. If correct, then this interpretation of the literature suggests the possibility that the production of reactive oxygen species may be reduced by pharmacological agents that block the factors that increase their production by the cell rather than by altering the patterns of gene expression in the cell. The importance of this speculative model lies in its apparent explanatory power, a feature which should encourage its empirical testing by different labs. The model's most interesting prediction is that some presently existing neurologically active drugs may also have a significant impact on aging; a finding which is generally consistent with recent reports of pharmacologically based extensions of longevity in the fly and worm model systems.

Taken together, these several papers nicely illuminate the ubiquitousness of the loss of function brought about by reactive oxygen species, its involvement in the aging process, the complexity of the organism's defensive responses, and the manner in which a loss of function in one area spreads outward and affects other physiological systems. A pessimist might see the inevitability of such events; an optimist might see potential sources for effective intervention in the aging process. In any event, these papers stimulate our imagination and make us wonder again about the nature of the aging process.

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