Introduction

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This special issue of AGE is devoted to recent studies of long-lived mice. Over the past 10 years, several spontaneous mutations and experimentally produced genetic modifications have been reported to cause significant extension of longevity in laboratory stocks of mice. Careful investigation into these special cases of extended longevity can reveal mechanisms that modulate the rate of aging in mammal and may apply to humans.

Drs. Boylston, DeFord, and Papaconstantinou report results of examining profiles of gene expression in two long-lived hypopituitary mutants. They include much previously unpublished data in their article, and identify several mechanisms that are likely to account for the extended longevity of these animals. Their findings link alterations in signaling and metabolic pathways to longevity.

Dr. Brown-Borg focuses on stress resistance as a potential mechanism of increased longevity of dwarf mice. Her data relate the endocrine phenotype of these mutants to reduced generation of reactive oxygen species, enhanced antioxidant defenses, and reduced oxidative damage, thus placing the increase in lifespan of dwarf mice in the context of current views on cellular mechanisms of aging.

Dr. Ikeno and his colleagues use histopathological studies to determine whether long-lived mutant mice die from the same causes as wild-type animals and to compare the effects of these mutations with the effects of caloric restriction. His studies elucidate various elements of the complex interplay between aging and cancer.

Dr. Forshee addresses the issues of brain aging and preservation or loss of cognitive

functions in animals with reduced growth and/or IGF-1 levels in the circulation. Her findings provide evidence of the surprising coexistence of reduced activity of the somatotrophic axis and preservation of the “youthful” capacity for learning and memory in long-lived mutant and gene knockout mice.

Dr. Sun presents data on local expression of IGF-1 in the hippocampus, a brain region critical for memory formation. Divergent changes in peripheral and hippocampal IGF-1 levels may explain some of the paradoxical findings in the study of cognitive function in long-lived dwarf mice.

Dr. Coschigano discusses characteristics of growth hormone receptor knockout (GHRKO) mice with emphasis on the suspected mechanisms of their extended longevity. These animals offer a unique opportunity to study the roles of GH and IGF-1 in aging since their GH signaling is selectively disrupted. This avoids many of the difficulties in the interpretation of findings obtained from Ames and Snell dwarf mice, two GH-deficient mutants that also lack prolactin and thyrotropin.

Drs. Carrière, Liu, and Hekimi report findings from a recently produced new type of long-lived mouse. These animals are most intriguing, since the “longevity gene” involved is not directly related to either pituitary hormone secretion or altered insulin signaling, which are probably involved in mediating the effects of the somatotrophic axis on aging.

Drs. Schriener and Linford report their success in extending the lifespan of a mouse by overexpression of an antioxidant enzyme, catalase.

Although there have been several reports of increasing the longevity of “lower” invertebrate animals using this approach, previous attempts to alter the lifespan of mice by mutations affecting expression of antioxidant enzymes have not been successful.

Before closing, we would like to express our gratitude to the authors who agreed to contribute

to this special issue. Thanks to their efforts, we can present the readers of AGE with this review of some of the most exciting developments in the study of mammalian longevity genes.

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