

OXIDATIVE AND GENETIC ORIGINS OF AGE-RELATED CATARACT

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Age-related cataract (ARC) is the major cause of blindness in the developing world. The majority of humans 75 years old or older in the U.S. will require treatment, often lens replacement, for this condition. There is evidence that ARC is at least partly produced by oxidative damage to both the lens fibers and their predecessor lens epithelial cells. However, most studies supporting this concept have been carried out with mice or other mammals that receive oxidative insults of external origin (U.V., X-irradiation), including oxidative agents per os or parenterally. We have avoided the above treatments and have examined the rate and degree of ARC development over lifespan in untreated mice of determined genetic backgrounds, where we have localized 3 quantitative trait loci (QTL) that influence the rate and degree of ARC in 4-way cross mice. We have also examined the influence of indigenous oxidative damage in mice in which specific native antioxidant enzymes have been either knocked out or reinforced by transgenic modification. These enzymes include catalase, glutathione peroxidase-1, and Mn superoxidase (SOD2). We have also examined ARC in the long-lived, oxidative stress-resistant GHRKO dwarf mouse. We conclude that the development of ARC in the mouse is strongly influenced by specific but as yet unclassified genetic alleles and by internally generated oxidative damage that is responsive in vivo to antioxidant enzymes. We will provide evidence, also for the mechanism of the cataract development.