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Ocular drug discovery: New targets and mechanisms for age-related macular degeneration

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Age-related macular degeneration (AMD) is a leading cause of blindness worldwide. The lack of adequate AMD animal models and poorly understood pathogenesis have greatly hindered our progress in therapeutic development. To address these shortcomings, this project was designed to examine how retinal redox dysregulation leads to AMD and characterize glutaredoxin 2 (Grx2), a mitochondrial thiol redox regulating enzyme, knockout mice as a new animal model for AMD. We found that Grx2 KO mice developed age-dependent retinal degenerative pathology. By 12-month of age, Grx2 null mice showed ~50% decrease in a-wave and ~30% decline in b-wave amplitude (n=8, P<0.01). Histological analysis revealed extensive RPE lesions, including RPE atrophy, vacuolation, hyper- and hypo-pigmentation, sub-RPE deposits, and loss of tight junction integrity. Age-dependent lipofuscin accumulation was also observed in Grx2 KO mice. Furthermore, Grx2 KO mice demonstrated increased marker of mitochondrial oxidative damage including PSSG accumulation. In conclusion, Grx2 plays a critical role in maintaining the mitochondrial redox homeostasis in the aging retina. Grx2 deficiency causes PSSG accumulation and sensitizes RPE cells to age-related oxidative damage, leading to RPE degeneration and photoreceptor damage. As a new animal model for AMD, Grx2 KO mice will provide new insights into pathogenesis and therapeutics of AMD. Grx2 may serve as a new therapeutic target for AMD and the Grx2 activating drugs may be used to treat AMD.

Biography

Hongli Wu has completed her PhD from Peking University and Postdoctoral studies from the University of Nebraska-Lincoln. She is the Assistant of Pharmaceutical Sciences at the University of North Texas Health Science Center. She has published more than 25 papers in reputable journals.

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