The Role of the Small GTPase ARF6 in Mediating Oxidative Stress-Induced Senescence in the Retinal Pigment Epithelium

Lu, Samuel (School: Rowland Hall- Lincoln Street Campus)

Age-related macular degeneration, or AMD, is a progressive degeneration of the retina that causes significant central visual impairment, impacting nearly 20 million elderly adults in the United States. Degeneration and dysfunction of the retinal pigment epithelium (RPE), a supportive monolayer of cells positioned between the retina and the choroid, is commonly seen in patients with AMD. Due to high metabolic activity and constant light exposure, RPE is very prone to oxidative stress, which is a common driver of cellular senescence in the aging process. ARF6 is a small monomeric GTPase associated with neurodegenerative diseases, but its role in AMD is unknown. This project investigated the role of ARF6 in oxidative stress-induced senescence in RPE cells using an in vitro model. Wild-type (WT), ARF6Q67L(constitutively active), and ARF6T27N(dominant negative) were introduced into ARPE-19 cells using adenoviral vectors. The cells were subsequently treated with oxidizing hydrogen peroxide to simulate aging in human eyes. Level of senescence was determined with immunofluorescence of pH2A.X(phosphorylated Histone 2A.X), a common cell senescence marker. ARF6Q67L was found to markedly increase the number of pH2A.X foci and signal intensity, while ARF6T27N showed a significant decrease in the number of foci and total intensity, suggesting that the dominant negative form can antagonize RPE senescence, while the constitutively active form can amplify RPE senescence. These findings provide evidence that ARF6 activity influences the oxidative stress-induced senescence in RPE cells, and identifies ARF6 as a potential therapeutic target in the future development of AMD treatments.

Awards Won: