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New study represents major breakthrough in macular degeneration

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University of Kentucky researchers, led by Dr. Jayakrishna Ambati, have made an exciting finding in the "dry" form of age-related macular degeneration known as geographic atrophy (GA). GA is an untreatable condition that causes blindness in millions of individuals due to death of retinal pigmented epithelial cells.

The paper, "ERK1/2 Activation is a Therapeutic Target in Age-Related Macular Degeneration" appears in the current online issue of the premier journal Proceedings of the National Academy of Sciences.

Ambati, professor of physiology, and professor and vice chair of ophthalmology and visual sciences at UK, is a leader in the field of macular degeneration research. Previous research from the Ambati laboratory published in the journal Nature showed that in human eyes with geographic atrophy there is a deficiency of the enzyme DICER1, leading to accumulation of toxic Alu RNA molecules in the retinal pigmented epithelium. Another paper published in the journal Cell showed that when these RNAs build up in the eye they trigger activation of an immune complex known as the NLRP3 inflammasome. In turn, this leads to the production of a molecule known as IL-18, which causes death of retinal pigmented epithelial cells and vision loss by activating a critical protein known as MyD88. Importantly, Ambati and colleagues found evidence that activity of the inflammasome, IL-18, and MyD88 were all increased in human eyes with GA. They then showed that blocking any of these components could prevent retinal degeneration in multiple disease models. The researchers are excited that blocking these

pathways could herald a new potential therapy for GA, for which there is no approved treatment.

In the current paper, the authors show that Alu RNA, which increases following DICER1 deficit, activates a family of enzymes known as extracellular-signal-regulated kinases (ERK) 1/2. ERK 1/2, which are also known as classical mitogen-activated protein kinases (MAPKs), were found to be increased in the RPE of human eyes with GA and shown to be key mediators of RPE cell death. This work further defines the mechanisms of cell death in human GA and identifies a new therapeutic target for the dry form of AMD.

Provided by University of Kentucky