Study reveals mechanisms of dry age-related macular degeneration

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University of Kentucky researchers led by Dr. Jayakrishna Ambati, professor and vice-chair in the Department of Ophthalmology and Visual Sciences at the University of Kentucky, have made revealing discoveries about the precise mechanisms of retinal pigmented epithelium (RPE) death in the late stages of age-related macular degeneration (AMD). The findings were released last week in the

Proceedings in the National Academy of Sciences (PNAS).

Geographic atrophy, an advanced form of dry AMD characterized by death of the RPE, causes untreatable blindness in millions worldwide. Previous studies from the Ambati lab reported in the journals *Nature* and *Cell* showed that RPE death in dry AMD is due to a deficiency in the enzyme DICER1, which leads to accumulation of toxic Alu RNA molecules, which in turn activate an immune platform called the inflammasome.

However, until now, the precise mode of RPE death in AMD was unresolved. The current study, led by Younghee Kim, Ph.D., and Nagaraj Kerur, Ph.D., both postdoctoral Fellows from the Ambati lab, implicates the involvement of Caspase-8 as a critical mediator of RPE degeneration. This latest finding implicates apoptosis as the cell death pathway induced by Alu RNA, and these findings could lead to new potential therapeutic targets for dry AMD.

Ambati was recently honored with the NIH Director's Pioneer Award for Research Discovery for a newly discovered type of DNA. He and his team focus on the mechanisms that control cell death and vascular growth which have led to fundamental insights into the factors that lead to development of AMD. They are planning to start clinical trials for dry AMD.

More information: "DICER1/Alu RNA dysmetabolism induces Caspase-8–mediated cell death in age-related macular degeneration." *PNAS* 2014 ; published ahead of print October 27, 2014, DOI: 10.1073/pnas.1403814111

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