Pivotal discoveries in age-related macular degeneration

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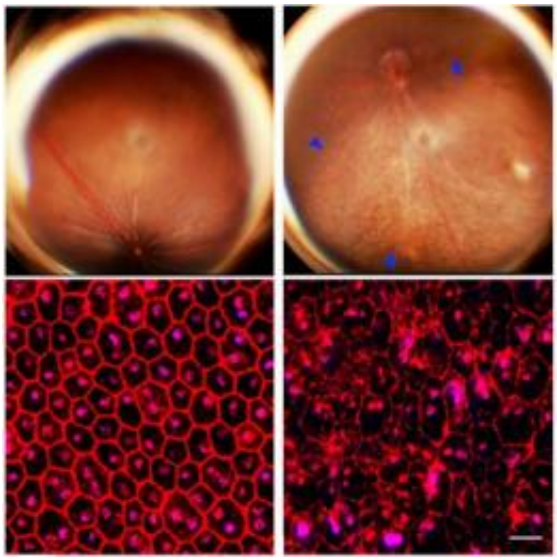

Geographic atrophy is induced by DICER1 reduction as seen in the retinal photograph (top right, blue arrowheads). This is prevented by blocking Alu RNA (top left). Flat mount pictures show that the degeneration of the RPE cells induced by DICER1 reduction (bottom right) is prevented by blocking Alu RNA (bottom left). Credit: Ambati Laboratory/University of Kentucky

A team of researchers, led by University of Kentucky ophthalmologist Dr. Jayakrishna Ambati, has discovered a molecular mechanism implicated in geographic atrophy, the major cause of untreatable blindness in the industrialized world.

Their article, "DICER1 Deficit Induces Alu RNA Toxicity in Age-

Related Macular Degeneration," was published online by the journal *Nature* on Feb. 6.

Concurrent with this discovery, Ambati's laboratory developed two promising therapies for the prevention of the condition. This study also elaborates, for the first time, a disease-causing role for a large section of the human genome once regarded as non-coding "junk DNA."

Geographic atrophy, a condition causing the death of cells in the retina, occurs in the later stages of the "dry type" of macular degeneration, a disease affecting some 10 million older Americans and causing blindness in over 1 million. There is currently no effective treatment for geographic atrophy, as its cause is unknown.

Ambati's team discovered that an accumulation of a toxic type of RNA, called Alu RNA, causes retinal cells to die in patients with geographic atrophy. In a healthy eye, a "Dicer" enzyme degrades the Alu RNA particles.

"We discovered that in patients with geographic atrophy, there is a dramatic reduction of the Dicer enzyme in the retina," said Ambati, professor and vice chair of the Department of Ophthalmology and Visual Sciences and the Dr. E. Vernon and Eloise C. Smith Endowed Chair in Macular Degeneration Research at the UK College of Medicine. "When the levels of Dicer decline, the control system is short-circuited and too much Alu RNA accumulates. This leads to death of the retina."

Alu elements make up a surprisingly large portion — about 11 percent by weight — of the human genome, comprising more than 1 million sequences. However, their function has been unknown, so they have been called "junk" DNA or part of the "dark" genome. The discovery of Alu's toxicity and its control by Dicer should prove of great interest to other researchers in the biological sciences, Ambati says.

Ambati's team developed two potential therapies aimed at preventing geographic atrophy and demonstrated the efficacy of both approaches using laboratory models. The first involves increasing Dicer levels in the retina by "over-expressing" the enzyme. The second involves blocking Alu RNA using an "anti-sense" drug that binds and degrades this toxic substance. UK has filed patent applications for both technologies, and Ambati's group is preparing to start clinical trials by the end of this year.

Response from the scientific community has been enthusiastic.

"These findings provide important new clues on the biological basis of geographic atrophy and may provide avenues for intervention through preventing toxic accumulation of abnormal RNA products," said Dr. Paul Sieving, director of the National Eye Institute.

"Ambati's latest research provides important mechanistic insights in geographic atrophy, and identification of this novel pathway may result in new therapeutic targets for a major cause of blindness," said Dr. Napoleone Ferrara, a member of the National Academy of Sciences and Lasker-DeBakey awardee who is a researcher at Genentech.

This work has "widespread implications" for future study, said Dr. Stephen J. Ryan, president of the Doheny Eye Institute and member of the Institute of Medicine.

"The authors have opened an important line of research with real possibilities for future therapeutic intervention for patients with geographic atrophy," Ryan said.

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