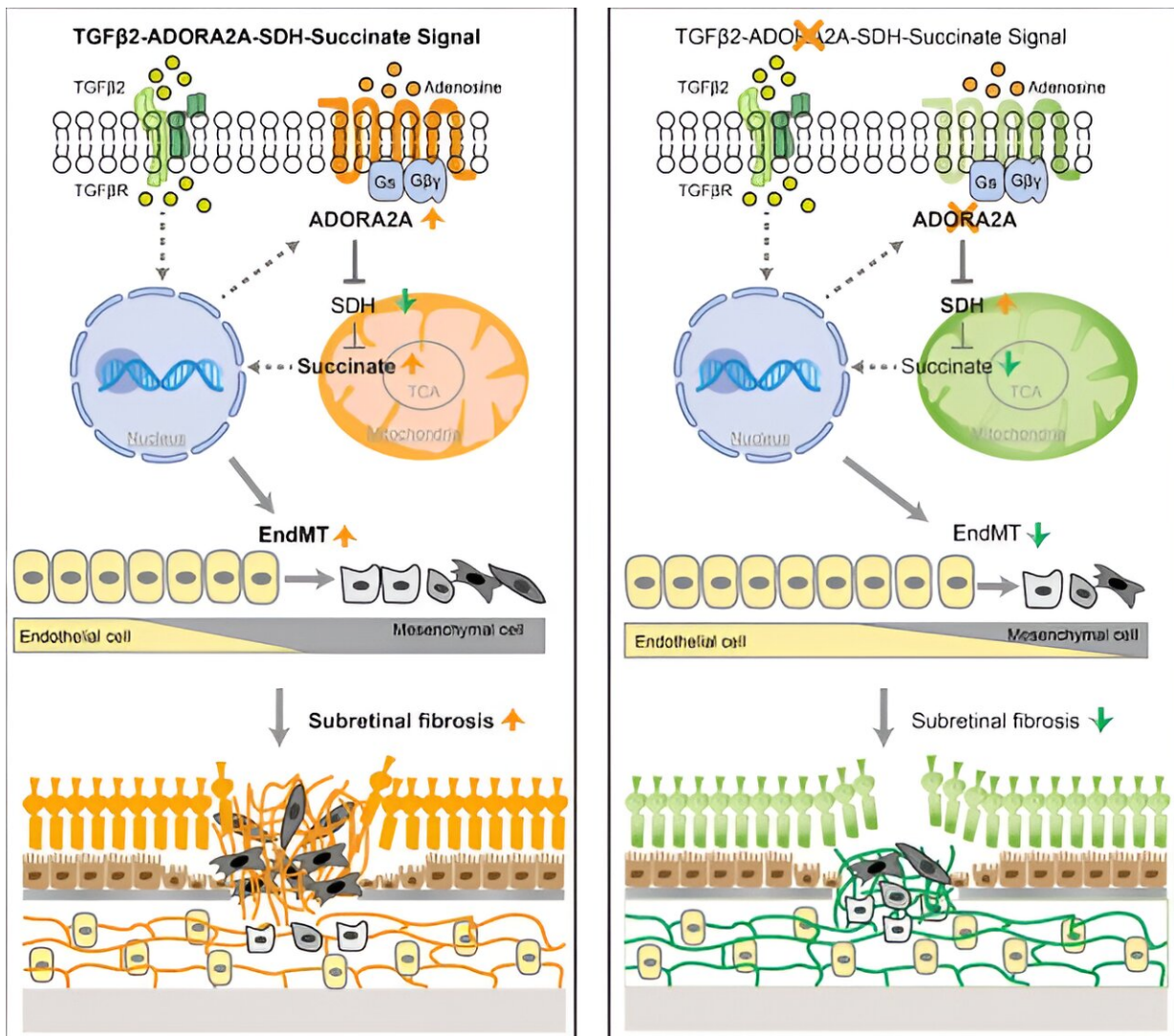


Scientists identify new treatment target for leading cause of blindness

May 2 2024



Schematic diagram illustrating the role of ADORA2A-mediated SDHB-succinate signaling in EndMT and the subsequent subretinal fibrosis. Credit: *Science Translational Medicine* (2024). DOI: 10.1126/scitranslmed.adk3868

Medical College of Georgia scientists report that a gene previously implicated in the development of atherosclerotic lesions in coronary arteries could be key to understanding why many people don't benefit from the most used therapy for neovascular age-related macular degeneration (AMD), a leading cause of blindness.

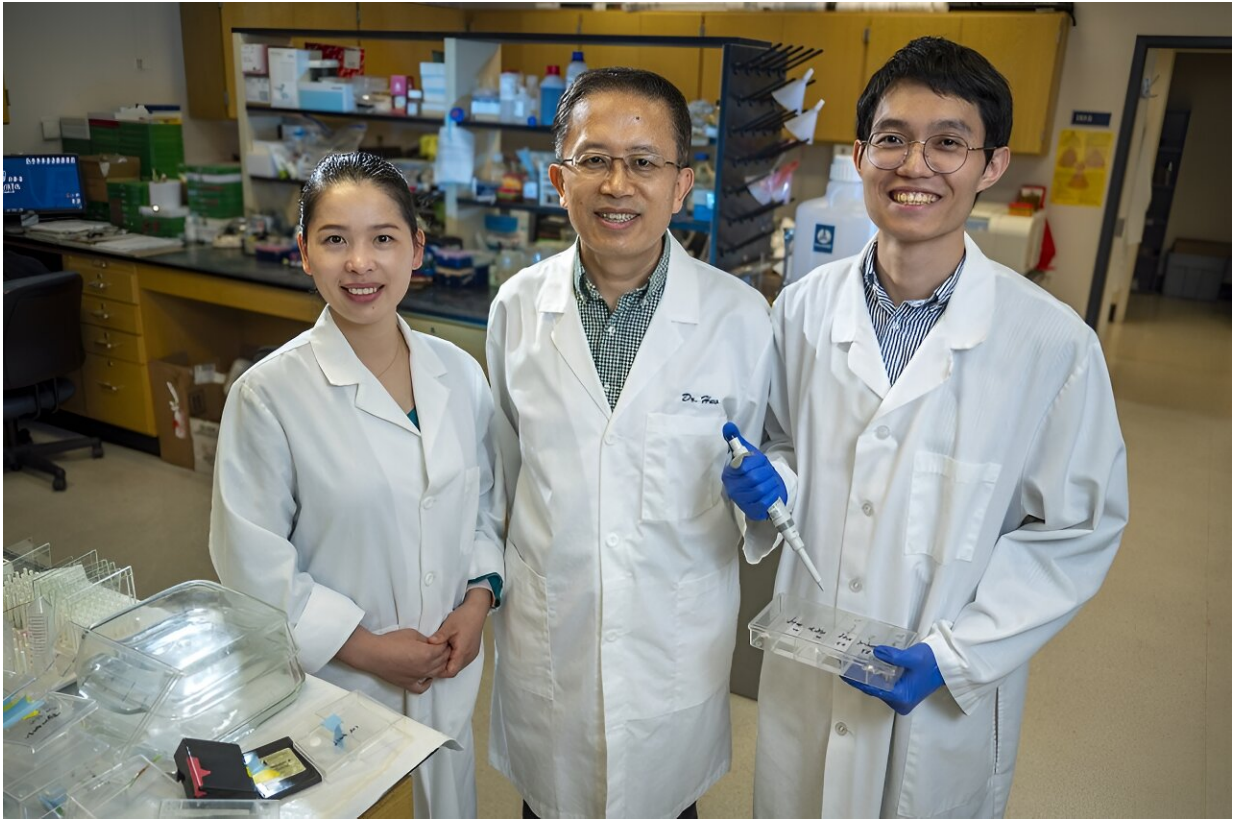
AMD is a condition characterized by abnormal blood vessel growth in the back of the eye. It is highly prevalent in the elderly and people with diabetes, obesity, and many other chronic metabolic diseases. Excessive vascular growth damages the macula, the part of the eye that translates light into image signals.

Anti-VEGF therapy, which blocks [vascular endothelial growth factor](#) and keeps excessive blood vessel growth at bay, is usually the first line of defense.

But that treatment only works well for around a third of patients suffering from this form of AMD, says Dr. Yuqing Huo, MD, Ph.D., the Director of the Vascular Inflammation Program at MCG's Vascular Biology Center. "The reason is that the excess vasculature is often accompanied by the growth of fibroblast cells," he says.

Collagen and many other proteins produced by these fibroblast cells accumulate outside of the vascular cells and eventually lead to fibrosis or scarring in the eye. This keeps the excess vasculature from being suppressed by anti-VEGF treatments.

"We show, for the first time in this study, that many fibroblast cells are actually produced by these excessive [endothelial cells](#). We must find a way to prevent this from happening," Huo says.



Drs. Qihua Yang, Yuqing Huo and Yongeng Cai. Credit: Michael Holahan, Augusta University

He and his team believe the answer lies in targeting the adenosine receptor 2A (Adora2a)—a G-protein-coupled adenosine receptor found in high levels in the brain, immune cells, and blood vessels.

Adora2a has been reported to be crucial in modulating inflammation, myocardial oxygen consumption, and coronary blood flow. Adenosine, a metabolite produced by cells under conditions of stress, injuries, and lack of oxygen, can activate Adora2a to protect our body from injury.

But in excess, adenosine can lead to excessive blood vessel growth. In

their current research, Huo and his colleagues found a high-level or persistent adenosine-activated Adora2a signal could transform endothelial cells, the luminal cells of the vasculature, into activated [fibroblast cells](#) and, eventually, cause fibrosis. Huo and his colleagues hypothesize that blocking this receptor can prevent that from happening.

Using genetically engineered mice that develop fibrosis in the backs of their eyes, researchers delivered an Adora2a agonist (KW6002), which binds to the receptor and blocks its function.

"We also studied mice that had Adora2a removed from only the vascular endothelial cells," says Qihua Yang, Ph.D., a postdoctoral fellow with Huo and the first author on this study. "All of these mice demonstrated decreased fibrosis in the eye." These [novel findings](#) were reported and recently selected as the cover image for *Science Translational Medicine*.

"We have previously demonstrated that blocking Adora2a can reduce excessive blood vessel growth, which happens in the early stages of AMD," says Yongfeng Cai, Ph.D., a postdoctoral fellow in Huo's lab and a member of the research team. They now have an eye toward generating an antibody that could recognize Adora2A.

"The antibody could be delivered via an injection to the back of the eyes, an approach often used in eye clinics, to block the activation of adenosine to Adora2A," Huo says.

"An antibody could really block both excessive blood vessel growth, the early stage of AMD, and fibrosis, the late stage of AMD. Our findings indicate that blocking Adora2a can certainly target multiple stages of this disease, which might be much more efficient than current treatments."

More information: Qihua Yang et al, Inactivation of adenosine receptor 2A suppresses endothelial-to-mesenchymal transition and inhibits subretinal fibrosis in mice, *Science Translational Medicine* (2024). [DOI: 10.1126/scitranslmed.adk3868](https://doi.org/10.1126/scitranslmed.adk3868)

Provided by Medical College of Georgia at Augusta University

Citation: Scientists identify new treatment target for leading cause of blindness (2024, May 2) retrieved 21 June 2024 from <https://medicalxpress.com/news/2024-05-scientists-treatment.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.