Combating drug resistance in age-related macular degeneration

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An international team of researchers led by Baylor College of Medicine and Houston Methodist has discovered a strategy that can potentially address a major challenge to the current treatment for choroidal

neovascularization (CNV), an aggressive form of age-related macular degeneration, the leading cause of irreversible blindness in the elderly.

Anti-vascular endothelial growth factor (anti-VEGF) has revolutionized the treatment for CNV; however, up to one-fourth of all treated patients are unresponsive to this treatment and about one-third of the responders become resistant to it after repeated administration over time.

Working with a mouse model they developed, the researchers found that combining apolipoprotein A-I binding protein (AIBP) with anti-VEGF overcomes anti-VEGF resistance and effectively suppresses CNV. The findings open the possibility of reducing anti-VEGF resistance in patients in the future. The study appears in the journal *Communications Biology*.

Addressing resistance to anti-VEGF treatment has been challenging. For instance, developing strategies to overcome the resistance has been limited by a poor understanding of its mechanism and the absence of suitable animal models.

"Various combination therapies have been explored in clinical trials. For example, targeting PDGF (Fovista) or the angiopoietin pathway. However, no major breakthrough has been reported. In fact, a phase III trial combining anti-VEGF and PDGF failed to demonstrate improved efficacy," said co-corresponding author Dr. Yingbin Fu, associate professor and Sarah Campbell Blaffer Endowed Chair of Ophthalmology at Baylor.

A new approach to combat anti-VEGF resistance

Fu joined forces with Dr. Longhou Fang, associate professor of cardiovascular sciences at Houston Methodist DeBakey Heart and Vascular Center and co-corresponding author of this work.

The inspiration for their study came from previous work suggesting that macrophages may play a role in anti-VEGF resistance and that increased cholesterol accumulation in macrophages may promote CNV. Such cholesterol accumulation also has been associated with the formation of abnormal new blood vessels invading the retina. These vessels leak, which promotes inflammation and rapid photoreceptor (light-detecting cells) damage.

In addition, Fu, Fang and their colleagues, as well as other researchers, had reported that AIBP promotes the removal of cholesterol from endothelial cells and macrophages, two cell types that are involved in the development of CNV.

"Together, these observations suggested the possibility that AIBP might help overcome anti-VEGF resistance and effectively suppress CNV," Fu said.

Developing an animal model to assess new approach to overcome anti-VEGF resistance

To test their hypothesis, the researchers developed a model of anti-VEGF resistance by combining advanced age with laser delivery in mice. As they became older, the mice showed increased resistance to anti-VEGF treatment that correlated with increased intracellular cholesterol accumulation in macrophages.

The researchers tested the effect of AIBP and anti-VEGF in disease progression in this mouse model.

In young mice that were about eight weeks old, both AIBP and anti-VEGF were equally effective in controlling disease progression. In intermediate age mice, which were about eight months old or the

equivalent of middle-aged people, macrophages showed increased cholesterol accumulation. In this group, anti-VEGF treatment was less effective when compared with younger mice, but the AIBP treatment was as affective controlling the disease.

The oldest group of mice, which was about 18 months old or the equivalent of senior people, showed highest cholesterol accumulation inside macrophages and were resistant to anti-VEGF treatment. Interestingly, AIBP alone also did not inhibit CNV, but the combination of AIBP with anti-VEGF overcame the anti-VEGF resistance and robustly suppressed laser-induced CNV by 47 percent.

This study also has increased our understanding of the mechanism underlying anti-VEG resistance. The researchers provide strong evidence that the accumulation of cholesterol in old macrophages plays a central role in anti-VEGF resistance because the old mice became responsive to anti-VEGF treatment when macrophages were chemically depleted. Fu, Fang and colleagues propose that the beneficial effect of AIBP is likely due to both its ability to enhance cholesterol removal from macrophages and its anti-inflammatory function.

Clinical implications

"Our findings encourage us to test the combination therapy of AIBP and anti-VEGF in clinical trials to determine whether it can help patients with the condition," Fu said. "The projected number of people with age-related macular degeneration is 196 million in 2020 and 288 million in 2040. There is great interest in novel therapies for this devastating condition."

Co-author Dr. James Handa, Chief of the Retina Division at the Wilmer Eye Institute, Johns Hopkins School of Medicine said, "Age-related macular degeneration has multiple factors that contribute to its

development; therefore, future treatments that target multiple pathways, such as what we describe here, may lead to more effective outcomes."

"As a cardiovascular scientist, my research is centered on cholesterol metabolism and angiogenesis, the formation of new blood vessels. My team has been collaborating with Dr. Fu for several years in developing AIBP as a potential treatment for age-related macular degeneration," Fang said. "Our studies show that AIBP can be a promising therapy for the treatment of CNV. Compared to the standard anti-VEGF therapy, AIBP targets multiple causes of age-related macular degeneration by correcting the adverse profiles associated with aging. The discovery that the combination therapy can overcome anti-VEGF resistance shows the power of multidisciplinary research."

More information: Lingping Zhu et al, Combination of apolipoprotein-A-I/apolipoprotein-A-I binding protein and anti-VEGF treatment overcomes anti-VEGF resistance in choroidal neovascularization in mice, *Communications Biology* (2020). DOI: 10.1038/s42003-020-1113-z

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