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PRIMARY eyecare

Stanford Medicine researchers build an eye 'aging clock'

In this Primary Eyecare we share a story about a new technique Stanford Medicine researchers and their collaborators developed for studying eye fluid, which led them to a way of measuring ocular aging, and suggested new avenues for treatment of many common eye diseases.

The scientists looked at nearly 6,000 proteins present in the aqueous humour and found that they could use 26 of them to predict aging. Using artificial intelligence, they developed an eye-aging "clock," indicating which proteins accelerate aging in particular eye diseases. They also found that some cells commonly targeted in treatment are not the ones most involved in disease, encouraging a reevaluation of therapies.

Professor Vinit Mahajan is the senior author of the report published in Cell, October 2023, and Julian Wolf, MD, a postdoctoral scholar in Mahajan's lab, is the lead author of the paper. They believe that their findings provide one of the best connections ever made between disease states and accelerated aging in the eye.

The research team developed a technique for tracing expression of multiple protein origins - TEMPO. By tracing proteins to a type of cell where the RNA that creates the proteins resides the team sought to better understand which cellular processes contribute to various eye diseases. Using eye fluid from 46 healthy patients, Mahajan and his team trained an AI algorithm to predict the age of the patient. They then fed the algorithm the nearly 6,000 proteins present in the fluid to see if a subset of these proteins could predict the patient's age. They found 26 that could do so when used as a group.

Liquid biopsies were also taken from the aqueous humour of patients with three types of eye diseases: diabetic retinopathy, retinitis pigmentosa, and uveitis; who were locally anaesthetised during surgery. Comparing the diseased eye fluid with the healthy fluid, they found that patients with diseased eyes had proteins that indicated a higher age: 12 years older in patients with early-stage diabetic retinopathy, 31 years in those with late-stage diabetic retinopathy, 16 years in retinitis pigmentosa patients and 29 years in uveitis patients.

They also also found that the cells responsible for indicating increased age were different with each disease: vascular cells in late-stage diabetic retinopathy, retinal cells in retinitis pigmentosa and immune cells in uveitis.

Since some cells commonly targeted in current treatments are not the ones most involved in disease, the findings encourage a reevaluation of therapies.

For example, diabetes drugs commonly target blood vessel cells because they become leaky with disease, but the researchers found the big increase in proteins from healthy to late-stage diabetic retinopathy is in macrophages. The researchers also found that some cells had showed accelerated aging before symptoms appeared, suggesting the treating the molecular pathway early might possibly prevent disease damage before it becomes irreparable. Targeting both aging and disease cells could make treatment more effective, Mahajan said, because the two appear to act separately but simultaneously to damage the eye.

Mahajan anticipates that researchers will apply the TEMPO technique and aging clock to other organ fluids such as liver bile and joint fluid. The hope is that by knowing these biomarkers, researchers will run more successful clinical trials because they will have a more refined look into the cellular processes driving disease. Currently, 90% of drug candidates tested in mice models or human cells fail in clinical trials.

'Knowing the cells driving disease and aging may increase chances of success, Mahajan said. "At the molecular level, patients present different manifestations even with the same disease. With a molecular fingerprint like we've developed, we could pick drugs that work for each patient."

Citation:

Liquid-biopsy proteomics combined with AI identifies cellular drivers of eye aging and disease in vivo. Julian Wolf, Ditte K. Rasmussen, Young Joo Sun, Jennifer T. Vu, Elena Wang, Camilo Espinosa, Fabio Bigini, Robert T. Chang, Artis A. Montague, Peter H. Tang, Prithvi Mruthyunjaya, Nima Aghaeepour, Antoine Dufour, Alexander G. Bassuk, Vinit B. Mahajan, Published:October 19, 2023001:https://doi.org/10.1016/j.cell.2023.09.012

Credits:

Researchers from the Aarhus University in Denmark, University of Minnesota, Retina Consultants of Minnesota, University of Calgary, University of Iowa and Veterans Affairs Palo Alto Health Care System contributed to the work.

The study was made possible by Stanford researchers affiliated with the Byers Eye Institute who created a biobank of eye fluid collected in the operating room.

Image: Pexels Photo 6224724; RONE

And in other news: The story of the optometrist, the 'lumpy-bumpy' optic disc, and the $10 million gift

When he was around 7-8 years old), Sam Hickman was undergoing an annual eye exam and his optometrist noticed that his optic nerves had the "lumpy-bumpy" telltale sign of optic disc drusen.

Tiny deposits of calcium phosphate fill the hole where the optic nerve connects the eyes to the brain. The deposits can cause peripheral vision loss, extra blind spots and, in some cases, blindness, though severe vision loss is rare.

Hickman, now 24, can see his computer screen fine, though he has a hole in his vision, in the center-left part of his right eye. He notices it when he looks at something far away. The disease scares him: there is no treatment, the disease is often progressive.

"Not only is there no chance my eyes will get better," Hickman said, "but there's a very good chance they'll get worse. It's hard to think that there's a ticking time bomb on my vision."

With little research to date, scientists still do not know what causes ODD, why and when it progresses, and how to meaningfully treat it. But now, having received a $10 million gift from an anonymous donor last year to open what is believed to be the world's first optic disc drusen center, Stanford Medicine researchers hope to make major advances in understanding and treating the condition.

"It's an amazing opportunity to make a huge difference in vision restoration," said Liao, a neuro-ophthalmologist at Stanford Health Care and director of the Center for Optic Disc Drusen, at Stanford's Byers Eye Institute.

Source: Stanford Medicine News Centre

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