Lab grown 'mini eyes' unlock understanding of blindness in rare genetic condition

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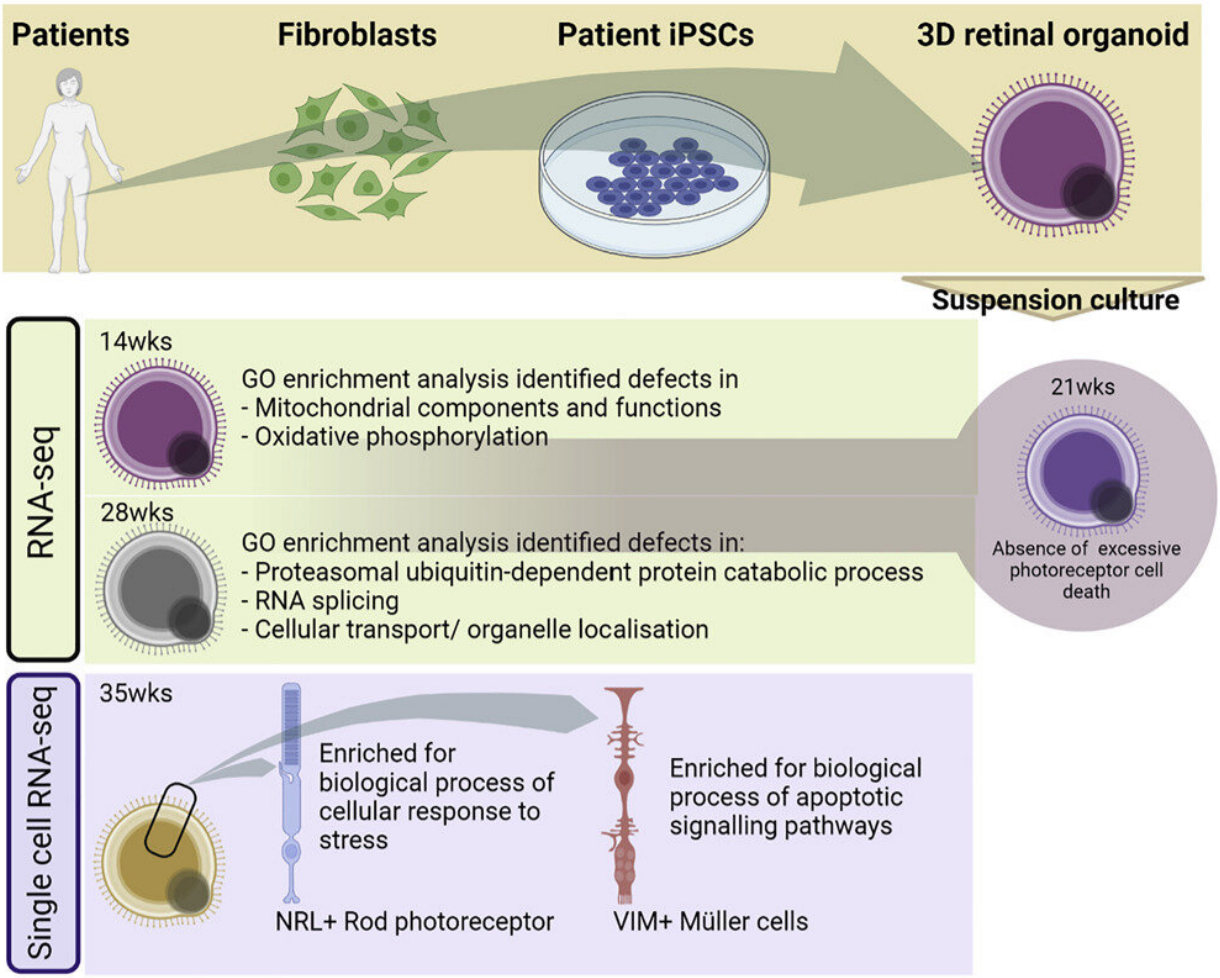

Graphical abstract. Credit: *Stem Cell Reports* (2022). DOI: 10.1016/j.stemcr.2022.09.006

Researchers at UCL Great Ormond Street Institute of Child Health (UCL GOS ICH) have grown "mini eyes," which make it possible to study and better understand the development of blindness in a rare genetic disease called Usher syndrome for the first time.

The 3D mini eyes, known as organoids, were grown from stem cells generated from skin samples donated by patients at Great Ormond Street Hospital for Children (GOSH). In a healthy eye, rod cells—the cells which detect light—are arranged in the back of the eye in an important region responsible for processing images called the retina. In this research, published in *Stem Cell Reports*, the team found that they could get rod cells to organize themselves into layers that mimic their organization in the retina, producing a mini eye.

These mini eyes are an important step forward because previous research using animal cells couldn't mimic the same sort of sight loss as that seen in Usher syndrome.

Usher syndrome is the most common genetic cause of combined deafness and blindness, affecting approximately three to ten in 100,000 people worldwide. Children with Type 1 Usher syndrome are often born profoundly deaf, while their sight slowly deteriorates until they are blind by adulthood.

Although cochlear implants can help with hearing loss, there are currently no treatments for retinitis pigmentosa, which causes vision loss in Usher syndrome. While this research is in early stages, these steps towards understanding the condition and how to design a future

treatment could give hope to those who are due to lose their sight.

The mini eyes developed in this research allow scientists to study light-sensing cells from the human eye at an individual level, and in more detail than ever before. For example, using powerful single cell RNA-sequencing, it is the first time researchers have been able to view the tiny molecular changes in rod cells before they die.

Using the mini eyes, the team discovered that Müller cells, responsible for metabolic and structural support of the retina, are also involved in Usher syndrome. They found that cells from people with Usher syndrome abnormally have genes turned on for stress responses and protein breakdown. Reversing these could be the key to preventing how the disease progresses and worsens.

As the mini eyes are grown from cells donated by patients with and without the genetic "fault" that causes Usher syndrome, the team can compare healthy cells and those that will lead to blindness.

Understanding these differences could provide clues to changes that happen in the eye before a child's vision begins to deteriorate. In turn, this could provide clues to the best targets for early treatment—crucial to providing the best outcome.

Dr. Yeh Chwan Leong, Research Associate at UCL GOS ICH and first author said, "It's difficult to study the inaccessible tiny nerve cells of the patient's retina as they are so intricately connected and delicately positioned at the back of the eye. By using a small biopsy of skin, we now have the technology to reprogram the cells into stem cells and then create lab-grown retina with the same DNA, and therefore same genetic conditions, as our patients."

Professor Jane Sowden, Professor of Developmental Biology & Genetics

at UCL, and senior author, said, "We are very grateful to patients and families who donate these samples to research so that, together, we can further our understanding of genetic eye conditions, like Usher syndrome."

"Although a while off, we hope that these models can help us to one day develop treatments that could save the sight of children and young people with Usher syndrome."

The mini eye model for eye diseases could also help teams understand other inherited conditions in which there is the death of rod cells in the eye, such as forms of retinitis pigmentosa without deafness. Additionally, the technology used to grow faithful models of disease from human skin cells can be used for a number of other diseases—this is an area of expertise at the Zayed Centre for Research into Rare Disease in Children at UCL GOS ICH.

Future research will create mini eyes from more patient samples, and use them to identify treatments, for example by testing different drugs. In the future, it may be possible to edit a patient's DNA in specific cells in their eyes to avoid blindness.

More information: Yeh Chwan Leong et al, Molecular pathology of Usher 1B patient-derived retinal organoids at single cell resolution, *Stem Cell Reports* (2022). DOI: 10.1016/j.stemcr.2022.09.006

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