Researchers discover cause, develop pharmacological treatment for reducing retinitis pigmentosa vision loss

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"AdipoR1 is one of the principal enzymes that regulate ceramide content in the eye," says first and co-corresponding author Dominik Lewandowski, Ph.D., postdoctoral scholar at the UCI School of Medicine. "Ceramide accumulation is detrimental for the retina and has been associated with non-syndromic retinitis pigmentosa. Our study showed that this imbalance could be effectively targeted pharmacologically by inhibiting two of the three ceramide generation pathways." Credit: School of Medicine / UCI

Researchers from the University of California, Irvine have discovered that the absence of Adiponectin receptor 1 protein (AdipoR1), one of the principal enzymes regulating ceramide homeostasis in the retina, leads to an accumulation of ceramides in the retina, resulting in progressive photoreceptor cell death and ultimately vision loss. The team also found that a combination of desipramine and L-cycloserine reduced lowered ceramide levels, which protected photoreceptors, helped preserve the retina's structure and function, and improved vision.

The study, titled "Inhibition of ceramide accumulation in AdipoR1$^{-/-}$ mice increases photoreceptor survival and improves vision," was published this month in the *Journal of Clinical Investigation Insight*.

Study findings show that ceramide imbalance damages the neural retina and retinal pigmented epithelium, accompanied by a significant reduction of electroretinogram amplitudes, decreased retinoid content in the retina, reduced cone opsin expression and massive inflammatory response. A buildup of ceramides in the retina, likely due to insufficient ceramidase activity, led to photoreceptor death. When treated with the desipramine and L-cycloserine combination, ceramide levels were lowered, which helped preserve photoreceptors in mice. The team also observed improved daylight vision in the L-cycloserine treated mice, and

that prolonged treatment significantly improved electrical responses of the primary visual cortex to visual stimuli.

"Although AdipoR1 is found in multiple organs, the highest levels are found in the eye and brain, suggesting its critical importance in these neural tissues. Our study results highlight the significance of AdipoR1 ceramides in the retina, and show that pharmacological inhibition of ceramide generation can provide a therapeutic strategy for patients suffering from retinitis pigmentosa or AdipoR1-related retinopathies," said Krzysztof Palczewski, Ph.D., Donald Bren Professor of Ophthalmology at the UCI School of Medicine and co-corresponding author.

Degeneration of photoreceptor cells and retinal pigment epithelium is the underlying cause of several progressive retinal diseases. Many of these conditions have only minimally effective or no treatment options. New therapeutic approaches are urgently needed to combat these disorders and reduce vision loss.

Ceramides are essential for eukaryotic cell membrane stability and act as potent signaling molecules in inflammation, cell cycle arrest, cell death and heat shock response pathways. Ceramide imbalance has also been found in cancer, Alzheimer's disease, type 2 diabetes, multiple sclerosis, cardiovascular disease and non-alcoholic fatty liver disease.

"Noninvasive pharmacological treatment is more easily achieved in humans than gene therapy," said first and co-corresponding author Dominik Lewandowski, Ph.D., postdoctoral scholar at the UCI School of Medicine. "Our proposed pharmacological strategy might become broadly applicable to other neurodegenerative conditions related to high ceramide levels."

More information: Dominik Lewandowski et al, Inhibition of

ceramide accumulation in AdipoR1-/- mice increases photoreceptor survival and improves vision, *JCI Insight* (2022). DOI: 10.1172/jci.insight.156301