



## Commentary

# Retinal disease: How to use proteomics to speed up diagnosis and metabolomics to slow down degeneration

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Photoreceptors in mammalian retinas are non-dividing and terminally differentiated. Expression of non-functional or toxic proteins can lead to irreversible loss of photoreceptors and blindness. Gene therapy to express a normal protein can be used to treat certain types of blinding diseases and using stem cells to replace photoreceptors or CRISPR to repair mutant genes also are becoming feasible. However, those treatments will be expensive and gene therapy will have to be unique for each of the hundreds of genes linked to retinal degeneration [1].

An alternative approach, that may require less specificity, is to make photoreceptors generally more robust so they degenerate slower. If blindness could be delayed, patients could remain asymptomatic during their lifetime. A therapy that makes photoreceptors more robust could be inexpensive, e.g., a diet or supplement that is initiated early before there is substantial damage. This would require a diagnostic tool that uses biomarkers to identify candidates for therapy early before they experience blindness. Wert et al. [2] report a new diagnostic strategy in *EBioMedicine* that fits these criteria. They also describe how a nutritional supplement can slow a common type of retinal degeneration, retinitis pigmentosa.

Screening blood for systemic biomarkers can be straightforward, but biomarkers released from a degenerating retina are diluted substantially when they enter the circulation. Fortunately, the retina is adjacent to the vitreous, which is accessible for biopsy. The vitreous

is a transparent gelatinous extracellular matrix between the retina and the anterior eye. For the past decade Vinit Mahajan and his colleagues have been exploring the composition of the vitreous proteome [3]. Wert et al. used methods they developed to compare vitreous proteomes from 2 patients with advanced retinitis pigmentosa (caused by mutations in PDE6, a gene encoding a phototransduction protein) to vitreous proteomes from 2 subjects with normal retinas. They identified many proteins with substantial fold changes and statistical significance. A striking example was fatty acid synthase (FASN), which was ~30 fold more abundant in vitreous from the degenerating eyes. The study showed differences between vitreous from normal and degenerating eyes, but the small sample size and the single time point in the course of degeneration limited further interpretation.

To get statistical power sufficient to identify vitreous biomarkers, Wert et al. then performed the same types of analyses on a mouse model of rod degeneration also linked to PDE6. They quantified proteins from retinas and from vitreous at the onset of degeneration, at the peak of degeneration and after degeneration was complete, each with substantially more statistical power than was possible in the human studies. Overall, the analyses revealed a striking re-distribution of proteins between the retina and vitreous. As degeneration progressed retinas lost photoreceptor proteins, which then appeared in the vitreous. These proteins, many of which have roles in phototransduction or energy metabolism, were present in the vitreous even at the earliest time point. They are potential biomarkers that could be detected in vitreous biopsies signaling the onset of photoreceptor degeneration.

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One protein that leaked from degenerating mouse retinas to the vitreous was fatty acid synthase, which also was detected in the human studies. This led Wert et al. to ask whether perturbing fatty acid metabolism could influence rod degeneration in PDE6-deficient mice. They raised mice on a ketogenic diet (6:1:1 fat:protein:carbohydrate) starting at the day of weaning, p21. The ketogenic diet partially preserved photoreceptor nuclei, but it did not influence visual sensitivity. Wert et al. recognized that substantial degeneration already had occurred by p21 so they explored nutritional factors that can be fed to dams and reach the pups via milk.  $\alpha$ -ketoglutarate was the most effective one they tested. It increased both the number of photoreceptor nuclei and the electrical responses to light. The mechanism by which  $\alpha$ -ketoglutarate has this effect is not known yet, but Wert et al. showed that  $\alpha$ -ketoglutarate is taken up by the retina and that it influences the distributions of retinal metabolites.

Wert et al. are not reporting a cure for retinitis pigmentosa, but their findings do show that nutrients can influence metabolism in ways that slow degeneration. Analogous strategies are being pursued in cancer research, where nutrition-based therapies interfere selectively with cancer cell growth [4]. Gene therapies for retinal degeneration that enhance glycolytic metabolism [5], mTOR activity [6] or glucose transport [7] in rods or cones can delay blindness in mice. Continued investigations of the metabolic needs of photoreceptors [8–10] may reveal how  $\alpha$ -ketoglutarate slows degeneration and they may help to identify additional metabolic fuels that enhance the resilience of photoreceptors.

## Declaration of Competing Interest

The authors declare no conflicts of interest.

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