Docket #: S18-556

Metabolites Delay Retinal Degeneration

Stanford researchers have discovered that dietary metabolites, specifically alpha-ketoglutarate, are able to delay retinal degeneration to treat blinding retinal diseases regardless of the type of retinal condition. Scientists found these metabolites were able to slow down retinal degeneration through a common pathway, independent of gene mutations (approximately 200 known genes involving retinal degeneration) to help delay vision loss for millions of patients. One prime example is Retinitis Pigmentosa (RP), the most common cause of hereditary blindness in developed countries for which there is no available therapy.

Researchers used proteomics to identify metabolic pathways that were affected during retinal degeneration in mice and found that oral delivery of alpha-ketoglutarate was shown to provide significant visual rescue of the rods, cones, and inner retina through at least one month of age in a preclinical model of RP (retinitis pigmentosa). Further, dietary supplementation with B vitamins and a ketogenic diet was found to improve photoreceptor cell survival in some cases.

This discovery has the potential to address an unmet clinical need to treat retinal degeneration disorders such as, but not limited to retinitis pigmentosa, Usher syndrome, Alport's syndrome, Kearns-Sayre, abetalipoproteinemia, McLeod syndrome, Bardet-Biedl syndrome, neurosyphilis, toxoplasmosis and Refsum's disease. Continued research to test additional metabolite derivatives including delivery and dosing methods will refine therapeutics to target ocular disease.

Figure

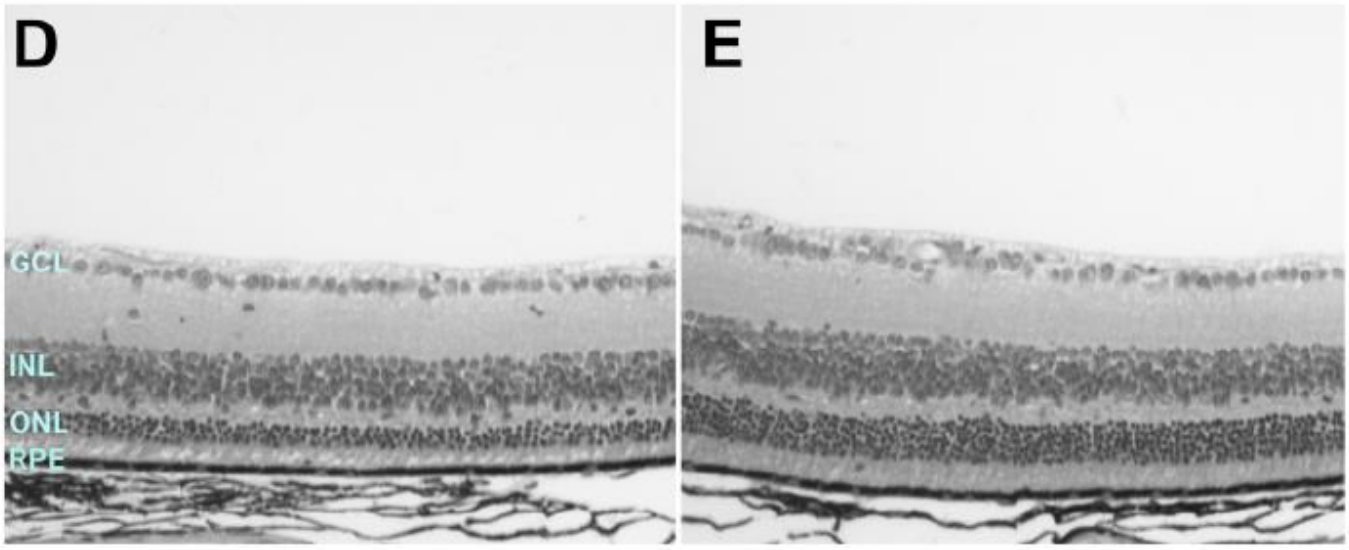

Figure explanation: Oral delivery of alpha-ketoglutarate rescues visual function and photoreceptor cell survival in a preclinical model of autosomal recessive retinitis pigmentosa (arRP). Electroretinography and histological analysis were performed at P28. (D) Mice without treatment of oral alpha-ketoglutarate showed a greater loss of the outer nuclear layer (ONL) and inner and outer segments of the photoreceptor cells in comparison to (E) Mice treated with alpha-ketoglutarate. GCL, ganglion cell layer; INL, inner nuclear layer; RPE, retinal pigment epithelium. Magnification: 10X.

Stage of Development

- Continued research with mouse models to test other metabolite derivatives including doses and ocular delivery methods to avoid systemic side effects

Applications

- **Treatment for retinal and neurological degenerative diseases** such as:
  - Retinitis pigmentosa (RP), a progressive neurodegenerative disease, is the most common cause of hereditary blindness in developed countries
  - Usher syndrome, Alport's syndrome, Kearns-Sayre syndrome, abetalipoproteinemia, McLeod syndrome, Bardet-Biedl syndrome, neurosyphilis, toxoplasmosis, and Refsum's disease

Advantages

- **Unmet medical need:** No current therapy delays retinal degeneration

- **Oral supplementation with alpha-ketoglutarate alone provided (at one month):**
  - Significant visual rescue of rods, cones, and inner retina visual responses
  - Significant visual rescue of the ONL and the inner/outer segments of the photoreceptors noted on histological analysis
- **Dietary supplementation with B vitamins and a ketogenic diet (at one month)** -- found to improve photoreceptor cell survival in some cases

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