Nature Reviews Endocrinology | Published online 14 Oct 2016; doi:10.1038/nrendo.2016.174

METABOLISM

Nampt deletion blinds mice

Disruption of nicotinamide adenine dinucleotide (NAD^+) biosynthesis could be an early step in retinal dysfunction, according to a new study conducted in mice.

Retinal dysfunction results from many diseases, such as diabetic retinopathy and age-related macular degeneration; however, the shared pathological mechanisms are unclear. Mutations affecting the biosynthesis of NAD^+, an important coenzyme and electron carrier, have previously been associated with inherited blinding diseases. Jonathan Lin and colleagues, therefore, investigated whether decreased levels of NAD^+ lead to retinal degeneration.

The team generated mice that lacked nicotinamide phosphoribosyltransferase (the rate-limiting enzyme in the dominant mammalian pathway of NAD^+ synthesis , which is encoded by *Nampt*), specifically within photoreceptors. These *Nampt*-deficient mice had retinal atrophy by 6 weeks of age and disrupted electroretinography readings, both of which could be rescued by injection of the NAD^+ precursor nicotinamide mononucleotide. Interestingly, several mouse models of retinal degeneration, including streptozotocin-induced diabetic retinopathy and light-induced retinal dysfunction, had lower retinal NAD^+ levels than healthy controls.

The team also examined cultured photoreceptor-like cells treated with the Nampt inhibitor FK866, and detected a decreased reductive capacity compared with untreated cells. This effect was not seen in retinal pigment epithelium cells, suggesting a distinct susceptibility in photoreceptor cells. Furthermore, the FK866-treated photoreceptor cells exhibited hyperacetylation of mitochondrial proteins, potentially resulting from a reduction in SIRT3 activity, which could be an important contributor to mitochondrial dysfunction.

"NAD^+ intermediates may have therapeutic efficacy against a broad range of retinal diseases," concludes Lin. "We are very excited about these translational possibilities."

Charlotte Ridler

ORIGINAL ARTICLE Lin, J. B. *et al.* NAMPT-mediated NAD^+ biosynthesis is essential for vision in mice. *Cell Rep.* http://dx.doi.org/10.1016/j.celrep.2016.08.073 (2016)
FURTHER READING Garten, A. *et al.* Physiological and pathophysiological roles of NAMPT and NAD metabolism. *Nat. Rev. Endocrinol.* **11**, 535–546 (2015)