Peroxisomal beta-oxidation deficiency in RPE leads to RPE degeneration and loss of retinal function

Kocherlakota S.[1], Das Y.[1], Swinkels D.[1], Fransen M.[2], Baes M.[1]

[1] *Laboratory of Cell Metabolism, KU Leuven, Leuven, Belgium.*
[2] *Laboratory of Lipid Biochemistry and Protein Interactions, KU Leuven, Leuven, Belgium*

Keywords: peroxisomes, RPE, multifunctional protein 2, retinal degeneration.

Abstract

Patients with peroxisomal beta-oxidation deficiency often present with visual abnormalities[1]. A mouse model lacking Multifunctional Protein 2 (MFP2), which is the central enzyme of peroxisomal beta-oxidation, showed a clear degeneration in the retina: shortened photoreceptor outer segments (POS), death of photoreceptors, increased retinal distress, protrusion of the retinal pigment epithelium (RPE) cells into the photoreceptor layer, and loss of their characteristic hexagonal shape. This was accompanied by reduced visual acuity and function.

To understand the origin of the loss of RPE integrity, we generated a mouse model with RPE-specific *Mfp2* inactivation (*Best1-Mfp2* knockout). These mice also showed a loss of RPE hexagonal shape and RPE protrusion into the photoreceptors, similar to the global knockouts, but no general shortening of POS, nor any death of photoreceptors. In addition, they displayed increased retinal distress and reduced visual function, which suggests that the peroxisomal beta-oxidation of the RPE is crucial for the maintenance of the neural retina.

Loss of RPE65, a marker of mature RPE, and increased immunoreactivity for PCNA (a protein expressed only in proliferating cells) indicate that RPE cells are dedifferentiating in *Mfp2*$^{-/-}$ mice.

Together, our results show that peroxisomal beta-oxidation in the RPE is crucial to maintain the integrity of this cell layer, and indirectly of the neural retina.

References

[1] Das Y. et al. (2019), Peroxisomal Disorders and Retinal Degeneration, Bowes Rickman C et al. (eds) Retinal Degenerative Diseases. Advances in Experimental Medicine and Biology, vol 1185: 317-321

[*]**Corresponding author: sai.kocherlakota@kuleuven.be**