Abstract

The study of peripheral retina: morphological, molecular, clinical and imaging aspects

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Understanding vision, identifying unknown sources of ocular diseases and developing new treatment modalities requires widening our understanding about previously unidentified constituents of the retina. Studying the peripheral retina makes sense only in comparison to central area and any segregation attempt limits our understanding in full-picture. An innovative path is to embrace a systematic process from molecular level through aspects of morphology to clinical usability which involves patient-friendly diagnostic tools such as in-vivo imaging modalities.

Tubulin Polymerization Promoting Protein (TPPP) is a disordered moonlighting protein with a zinc-binding site that may display different functions according to cellular and subcellular localisation or interacting molecules. It has been characterised as an oligodendrocyte specific protein in the brain, where TPPP regulates the dynamics and stability of the microtubule network by its bundling and acetylation enhancing activities. This can be modulated by the binding of zinc to TPPP. In neurodegenerative disorders, TPPP was found in neuronal inclusions of the brain. TPPP was detected in few different tissues including the retina, with no further characterisation. Given the common embryonic development of both the brain and the retina and high-quality and better imaging options in retina than brain scans, research for new hallmark proteins in the retina is relevant. Furthermore, characterising new molecule may help in understanding the complexity of neurocircuitry of vision and site of eventual disease.

In this study, evidence is provided for the first time for the expression and localization of TPPP in the zinc-rich layer of the retina both in peripheral and central areas and in a subclass of amacrine cells, ganglion cells, as well as in the oligodendrocytes in the optic nerve. Localization of TPPP was established by confocal microscopy using calbindin and synaptophysin as markers of specific striations in the inner plexiform layer (IPL) and presynaptic terminals respectively. Immunogold staining and electron microscopy imaging identified the presence of TPPP in postsynaptic nerve terminals in striations S1, S3 and S5 in the IPL both in mice and human eyes, highlighting the specificity and abundance of TPPP to the zinc-rich synaptic layer of the retina, the IPL. Molecular level in vivo imaging targeting TPPP is not yet possible, however the inner retina including the IPL proved to be an excellent candidate for retinal layer changes tracked by ocular coherence tomography (OCT).

The clinical and imaging study was set up to identify aspects regarding the thickness of the IPL in association with zinc homeostasis, the modulator of TPPP. Our study has found that zinc serum concentration inversely correlates with the thickness of the IPL-GCL complex. Furthermore, patients with lower concentration of zinc in serum tend to have thicker inner retina layers and vice versa. These findings open new prospective and emerge further experimental studies in order to evaluate whether the fine architecture and physiology of the inner retina has the potential to benefit from oral zinc supplementation and gain therapeutic relevance through modulating molecules such as TPPP.