Molecular principles for docosahexaenoic acid (DHA) retention specificity and cell function in the nervous system

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The molecular mechanisms of selective docosahexaenoic acid (DHA) enrichment in the nervous system (e.g. photoreceptors, synaptic membranes and dendrites) have remained incompletely understood. We uncovered a novel function of an integral membrane protein (IMP) as necessary for photoreceptor cell (PRC) survival. We found that this protein mediates DHA retention in retinal pigment epithelial (RPE) and photoreceptor cells. We created IMP KO mice by retroviral gene trapping and also by homologous recombination, which resulted in photoreceptor degeneration. In situ hybridization shows that IMP occurs in photoreceptor/RPE cells, whereas no signal appears in mice devoid of IMP. Thus, we discovered that ablation of IMP leads to: a) photoreceptor cell degeneration, drastically attenuated electroretinograms, and a severely and early impaired retinol visual cycle; b) a flecked retina resembling human fundus albipunctatus with unchanged vasculature; c) activated macrophages beneath the RPE, autofluorescence in RPE and macrophages, and undigested photoreceptors in RPE; d) TUNEL-positive cells in the photoreceptor nucleus; e) specific reduction of retinal DHA, since arachidonic acid was unchanged; f) overexpression or silencing of IMP in human RPE cells leads to enhanced or decreased DHA uptake, respectively; and g) absence of photoreceptor cell-specific very long chain polyunsaturated fatty acids (VLC-PUFAs), along with unchanged ELOVL4 abundance.

We thereby demonstrate that IMP is a novel molecular switch that selectively and specifically controls DHA lipidome in RPE and photoreceptor cells by modulating DHA retention and conservation, and is required for photoreceptor-specific elongation to VLC-PUFAs. Since the photoreceptor DHA lipidome comprises endogenous cell survival responses, mimicking them to counteract early stages of retinal degenerative diseases will lead to a therapeutic paradigm shift.

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