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Lipid Signaling in the Retina: A Druggable Target?

Editorial

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Retina tissue has comparably high levels of lipids and a number of these lipids are highly relevant to inter- and intracellular signaling. Based on both clinical findings and evidence from animal models of retinal diseases, lipids have been implicated in the pathogenesis of age-related macular degeneration (AMD) and diabetic retinopathy (DR) [1- 4]. Of particular interest are studies that show a direct involvement of diets modifying lipid intake and lipid metabolism with retina pathology [2, 3]. For AMD, a disease with age as a predisposing factor and a major cause of vision loss for patients older than 65 [5], lipid pathology was detected early on as a characteristic of the disease, specifically abnormal amounts and types of lipids were found in macular deposits and implicated in structural changes leading to pathology [1]. In particular, retinal pigment epithelium (RPE) cells, which are involved in lipid signaling and express high levels of lipid binding proteins, control the metabolic activity of the retina and are affected early in AMD disease development [6-8]. Functional impairment of RPE cells is tightly linked to pathological changes in lipid signaling and is regarded as an early event in AMD disease pathogenesis [1, 9]. Genetic evidence from clinical studies points towards a direct involvement of key enzymes in lipid metabolism and lipid signaling in AMD development, but at the same time also opens up the possibility to identify novel drug targets as well as drugs specifically directed towards modifying aberrant lipid signaling or metabolism [7, 8, 10].

A related area that has received significant attention both clinically as well as from a basic science research perspective is signaling resulting from the development and disease causing activity of advanced lipid peroxidation end products. These compounds, potential antigens for autoimmune responses involved in AMD, have been implicated in AMD pathogenesis and have been linked to AMD pathology both mechanistically as well as phenotypically [9, 11-13]. Such observations, as well as a number of animal models that have taken advantage of clinical observations and findings to model AMD pathogenesis and the AMD disease phenotype, has led to the development of dietary supplementation strategies to prevent or at least temporarily attenuate the progression of AMD [14]. These strategies involve lipid signaling in several respects: Based on the finding that advanced lipid peroxidation end products play a key role in the development of AMD they focus on approaches to limit oxidative stress directly and indirectly. They also make effective use of lipophilic components such as vitamin E and beta-carotene to specifically address lipid signaling pathways and altered lipid oxidation [13, 14].

In parallel, diabetic retinopathy (DR), a major complication of both type 1 and type 2 diabetes affecting a large majority of diabetic patients, is strongly modulated if not in part caused by systemic dyslipidemia [15, 16]. In animal models, a direct involvement of lipid signaling and oxidative stress in the pathogenesis of DR was found with the potential of intervention emerging [17, 18]. Similar findings were made on the clinical side implicating abnormal lipid metabolism and lipid signaling in the pathogenesis and disease progression of DR [4, 19-21]. In this area, initial progress has been made clinically with respect to DR therapy when restoring lipid metabolism and thereby attenuating aberrant lipid signaling [22].

As research into the lipid composition of the retina and associated metabolic pathways continues [23, 24] and is being linked to other signaling pathways controlling DR pathogenesis, such as insulin signaling, additional insights into mechanisms and phenotypes of DR, such as a significant decrease in docosahexaenoic acid content, become available and open up the possibility of novel drug targets and therapies [4, 15, 25-27]. As these studies in the areas of lipid metabolism and lipid signaling progress, their involvement in additional signaling pathways, such as NF-κB signaling and changes in adhesion molecule expression during inflammation, becomes apparent and has the potential to result in the development of additional therapeutic innovations and drug delivery strategies [4, 15, 28].

In sum, both basic as well as clinical research have identified numerous direct and indirect lines of evidence connecting retinal disease with abnormal lipid signaling and lipid metabolism. While this is highly instructive for our understanding of complex and chronic retinal diseases that take many years to develop, it has also

shown great potential to help the field identify new drug targets and therapies for diseases with a significant socio-economic burden, such as AMD and DR [29, 30].

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