Evaluation of serum sphingolipids and the influence of genetic risk factors in age-related macular degeneration.

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Abstract

Sphingolipids are bioactive molecules associated with oxidative stress, inflammation, and neurodegenerative diseases, but poorly studied in the context of age-related macular degeneration (AMD), a prevalent sight-threatening disease of the ageing retina. Here, we found higher serum levels of hexosylceramide (HexCer) d18:1/16:0 in patients with choroidal neovascularization (CNV) and geographic atrophy (GA), two manifestations of late stage AMD, and higher ceramide (Cer) d18:1/16:0 levels in GA patients. A sensitivity analysis of genetic variants known to be associated with late stage AMD showed that rs1061170 (p.Y402H) in the complement factor H (CFH) gene influences the association of Cer d18:1/16:0 with GA. To understand the possible influence of this genetic variant on ceramide levels, we established a cell-based assay to test the modulation of genes in the ceramide metabolism by factor H-like protein 1 (FHL-1), an alternative

splicing variant of CFH that also harbors the 402 residue. We first showed that malondialdehyde-acetaldehyde adducts, an oxidation product commonly found in AMD retinas, induces an increase in ceramide levels in WERI-Rb1 cells in accordance with an increased expression of ceramide synthesis genes. Then, we observed that cells exposed to the non-risk FHL-1:Y402, but not the risk associated variant FHL-1:H402 or full-length CFH, downregulated ceramide synthase 2 and ceramide glucosyltransferase gene expression. Together, our findings show that serum ceramide and hexosylceramide species are altered in AMD patients and that ceramide levels may be influenced by AMD associated risk variants.

Beteiligte Forschungseinheiten

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