

RPE TISSUE-SPECIFIC FACTOR H DELETION INDUCES AMD-LIKE FEATURES

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Age-related macular degeneration (AMD) is a central vision-threatening disease, and its development is significantly associated with the Y402H variant in the complement factor H (Cfh) gene. Cfh is a soluble glycoprotein, and a negative regulator of complement activation. It is secreted by retinal pigment epithelium (RPE), liver and immune cells among others, but to date it is unclear whether the origin of the Cfh is of importance in regulating the alternative complement pathway and eye homeostasis.

Here, Cfh^{flx/flx} mice were crossed with Best1-cre mice, with the Best1 promoter providing RPE-specific expression of the Cre recombinase, inducing an RPE-specific deletion of loxP flanked Cfh. Cfh(RPE)^{-/-} mice on a mixed C57BL/6 and 129 background exhibited 95% Cre-positive RPE cells in immunostained cryosections. qPCR revealed a concomitant decrease of 95% in Cfh mRNA. Compared to Cfh total knockout mice, Cfh(RPE)^{-/-} animals preserved an intact complement system, with normal levels of circulating Cfh, C3 and Cfb, as well as sub-RPE deposition of the C3-breakdown product iC3b, as also seen in AMD patients. C5b-9 deposition was elevated in cryosections of 6 month old Cfh(RPE)^{-/-} mice, and western blotting analysis of RPE and choroid protein revealed higher Cfh levels compared to controls. F4/80 and CD206 immunostaining revealed sub-RPE accumulation of activated macrophages in 6 month old Cfh(RPE)^{-/-} animals compared to controls. Increased autofluorescence was visualised in 12 month old Cfh(RPE)^{-/-} mice using a micron III, and yellow, drusen-like deposits were evident in fundus imaging relative to wild type and Cre controls. RPE-selective Cfh loss thus manifests in AMD-like changes and may provide insight into the source of secreted Cfh as target for therapeutics.

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