An imbalance of human complement regulatory proteins CFHR1, CFHR3 and factor H influences risk for age-related macular degeneration (AMD).

Fritsche LG, Lauer N, Hartmann A, Stippa S, Keilhauer CN, Oppermann M, Pandey MK, Köhl J, Zipfel PF, Weber BH, Skerka C (2010) An imbalance of human complement regulatory proteins CFHR1, CFHR3 and factor H influences risk for age-related macular degeneration (AMD). *Hum Mol Genet* 19(23), 4694-4704. PubMed

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Projects

Interaction of complement proteins and acute phase proteins in inflammatory processes
Details

Abstract

A frequent deletion of complement factor H (CFH)-related genes CFHR3 and CFHR1 (ΔCFHR3/CFHR1) is considered to have a protective effect against age-related macular degeneration (AMD), although the underlying mechanism remains elusive. The deletion seems to be linked to one of the two protective CFH haplotypes which are both tagged by the protective allele of single nucleotide polymorphism rs2274700 (CFH:A473A). In a German cohort of 530 AMD patients, we now show that protection against AMD conferred by ΔCFHR3/CFHR1 is independent of the effects of rs2274700 and rs1061170 (CFH:Y402H). This suggests a functional role of CFHR1 and/or CFHR3 in disease pathogenesis. We therefore characterized the CFHR3 function and identified CFHR3 as a novel human complement regulator that inhibits C3 convertase activity. CFHR3 displays anti-inflammatory effects by blocking C5a generation and C5a-mediated chemoattraction of neutrophils. In addition, CFHR3 and CFHR1 compete with factor H for binding to the central complement component C3. Thus, deficiency of CFHR3 and CFHR1 results in a loss of complement control but enhances local regulation by factor H. Our findings allude to a critical balance between the complement regulators CFHR3, CFHR1 and factor H and further emphasize the central role of complement regulation in AMD pathology.

Identifier

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