Complement Factor H-Related 5-Hybrid Proteins Anchor Properdin and Activate Complement at Self-Surfaces.

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Abstract

C3 glomerulopathy (C3G) is a severe kidney disease for which no specific therapy exists. The causes of C3G are heterogeneous, and defective complement regulation is often linked to C3G pathogenesis. Copy number variations in the complement factor H-related (CFHR) gene cluster on chromosome 1q32 and CFHR5 mutant proteins associate with this disease. Here, we identified CFHR5 as a pattern recognition protein that binds to damaged human endothelial cell surfaces and to properdin, the human complement activator. We found the two N-terminal short consensus repeat domains of CFHR5 contact properdin and mediate dimer formation. These properdin-binding segments are duplicated in two mutant CFHR5 proteins, CFHR2-CFHR5Hyb from German patients with C3G and CFHR5Dup from Cypriot patients with C3G. Each of these mutated proteins assembled into large multimeric complexes and, compared to CFHR5, bound damaged human cell surfaces and properdin with greater intensity and exacerbated local complement activation. This enhanced surface binding and properdin recruitment was further evidenced in the mesangia of a transplanted and explanted kidney from a German patient with a

CFHR2-CFHR5Hyb protein. Enhanced properdin staining correlated with local complement activation with C3b and C5b-9 deposition on the mesangial cell surface in vitro. This gain of function in complement activation for two disease-associated CFHR5 mutants describes a new disease mechanism of C3G, which is relevant for defining appropriate treatment options for this disorder.

Beteiligte Forschungseinheiten

Infektionsbiologie Peter F. Zipfel Mehr erfahren

Leibniz-HKI-Autor*innen



Qian Chen

Details



Andrea Hartmann

Details



Christine Skerka

Details



Peter F. Zipfel

Details

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