HUMAN FACTOR H-RELATED PROTEIN 5 BINDS TO PENTRAXIN 3 AND THE EXTRACELLULAR MATRIX AND MODULATES COMPLEMENT ACTIVATION

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Introduction: Factor H (FH) is known as a main regulator of complement activation. By contrast, the physiological roles of the FH-related proteins are poorly understood. Genetic studies implicated human factor H-related protein 5 (CFHR5) in the glomerular diseases atypical hemolytic uremic syndrome, dense deposit disease and CFHR5 nephropathy. Furthermore, the CFHR5 protein was identified in glomerular immune deposits in diseased kidneys. Weak complement regulatory activity of CFHR5 and competition for C3b binding with the complement inhibitor FH were reported, but its physiological function remains unclear. The aim of the current study was the further functional characterization of CFHR5.
Methods: Interaction of CFHR5 with pentraxin 3 (PTX3), C-reactive protein and extracellular matrix was analyzed by ELISA and Western blot. FH cofactor activity was measured by analyzing C3b cleavage by Western blot. Assembly and activity of alternative pathway C3 convertase and complement activation in serum were analyzed by ELISA.
Results: Binding of native CFHR5 to PTX3 was detected from human plasma and the interaction was characterized using recombinant proteins. The binding of PTX3 to CFHR5 is of approximately twofold higher affinity compared to that of FH. PTX3 binding was not mediated via the C-terminal CFHR5 domains. PTX3 binding to CFHR5 was significantly reduced in buffer lacking calcium ions and at lower pH. A disease-associated mutant CFHR5 bound less PTX3. Binding of PTX3 to CFHR5 resulted in increased C1q binding. On the other hand, CFHR5 dose-dependently inhibited FH binding and its cofactor activity on PTX3, the short pentraxin C-reactive protein and the extracellular matrix *in vitro*. In addition, CFHR5 supported alternative pathway C3 convertase (C3bBb) formation via C3b binding and triggered alternative pathway complement activation.
Conclusions: CFHR5 may locally enhance complement activation via interference with the complement inhibiting function of FH, by enhancement of C1q binding and by direct activation of the alternative pathway, thereby contributing to glomerular disease.

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