FHR5 Binds to Laminins, Uses Separate C3b and Surface-Binding Sites, and Activates Complement on Malondialdehyde-Acetaldehyde Surfaces.

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Projects

The role of complement in autoimmune disease
Details

Characterization of Complement Factor H Related Protein 5 (CFHR5)
Details

Abstract

Factor H related-protein 5 (CFHR5) is a surface-acting complement activator and variations in the CFHR5 gene are linked to CFHR glomerulonephritis. In this study, we show that FHR5 binds to laminin-521, the major constituent of the glomerular basement membrane, and to mesangial laminin-211. Furthermore, we identify malondialdehyde-acetaldehyde (MAA) epitopes, which are exposed on the surface of human necrotic cells (Homo sapiens), as new FHR5 ligands. Using a set of novel deletion fragments, we show that FHR5 binds to laminin-521, MAA epitopes, heparin, and human necrotic cells (HUVECs) via the middle region [short consensus repeats (SCRs) 5-7]. In contrast, surface-bound FHR5 contacts C3b via the C-terminal region (SCRs8-9). Thus, FHR5 uses separate domains for C3b binding and cell surface interaction. MAA epitopes serve as a complement-activating surface by recruiting FHR5. The complement activator FHR5 and the complement inhibitor factor H both bind to oxidation-specific MAA epitopes and FHR5 competes with factor H for binding. The C3 glomerulopathy-associated FHR21-2-FHR5 hybrid protein is more potent in MAA epitope binding and activation compared with wild-type FHR5. The implications of these results for pathology of CFHR glomerulonephritis are discussed. In conclusion, we identify laminins and oxidation-specific MAA epitopes as novel FHR5 ligands and show that the surface-binding site of FHR5 (SCRs5-7) is separated from the C3b binding site (SCRs8-9). Furthermore, FHR5 competes with factor H for binding to MAA epitopes and activates complement on these modified structures.

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