FHR3 Blocks C3d-Mediated Coactivation of Human B Cells.

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Abstract

The autoimmune renal disease DEAP-HUS (deficient for complement factor H- related (CFHR) genes and autoantibody positive form of hemolytic uremic syndrome) is characterized by the presence of autoantibodies specific for the central complement regulator, factor H, combined with a homozygous deficiency in CFHR3 and CFHR1. As both FHR3 and FHR1 bind to C3d and iC3b, which are ligands for complement receptor type 2 (CR2/CD21), the aim of the present study was to examine whether FHR3-C3d or FHR1-C3d complexes modulate B cell activation. Laser scanning microscopy and automated image-based analysis showed that FHR3, but not FHR1 or factor H, blocked B cell activation by the BCR co-receptor- complex (CD19/CD21/CD81). FHR3 bound to C3d, thereby inhibiting the interaction between C3d and CD21 and preventing co-localization of the co-receptor-complex with the BCR. FHR3 neutralized the adjuvant effect of C3d on B cells as shown by inhibited intracellular CD19- and Akt phosphorylation in Raji cells, as well as Ca^{2+}-release in peripheral B cells. In cases of CFHR3/CFHR1 deficiency, the FHR3 binding sites on

C3d are occupied by factor H, which lacks B cell inhibitory functions. These data provide evidence that FHR3, which is absent in patients with the autoimmune form of DEAP-HUS, is involved in B cell regulation.

Beteiligte Forschungseinheiten

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