C3-glomerulopathy autoantibodies mediate distinct effects on complement C3- and C5-convertases.

Zhao F, Afonso S, Lindner S, Hartmann A, Löschmann I, Nilsson B, Ekdahl KN, Weber LT, Habbig S, Schalk G, Kirschfink M, Zipfel PF, Skerka C (2019) C3-glomerulopathy autoantibodies mediate distinct effects on complement C3- and C5-convertases. *Front Immunol* 10, 1030.

Abstract

C3 glomerulopathy (C3G) is a severe kidney disease, which is caused by defective regulation of the alternative complement pathway. Disease pathogenesis is heterogeneous and is caused by both autoimmune and genetic factors. Here we characterized IgG autoantibodies derived from 33 patients with autoimmune C3 glomerulopathy. Serum antibodies from all 33 patients as well as purified IgGs bound to the in vitro assembled C3-convertase. Noteworthy, two groups of antibodies were identified: group 1 with strong (12 patients) and group 2 with weak binding C3-convertase autoantibodies (22 patients). C3Nef, as evaluated in a standard C3Nef assay, was identified in serum from 19 patients, which included patients from group 1 as well as group 2. The C3-convertase binding profile was independent of C3Nef. Group 1 antibodies, but not the group 2 antibodies stabilized the C3-convertase, and protected the enzyme from dissociation by Factor H.

Also, only group 1 antibodies induced C3a release. However, both group 1 and group 2 autoantibodies bound to the C5-convertase and induced C5a generation, which was inhibited by monoclonal anti-C5 antibody Eculizumab in vitro. In summary, group 1 antibodies are composed of C3Nef and C5Nef antibodies and likely over-activate the complement system, as seen in hemolytic assays. Group 2 antibodies show predominantly C5Nef like activities and stabilize the C5 but not the C3-convertase. Altogether, these different profiles not only reveal a heterogeneity of the autoimmune forms of C3G (MPGN), they also show that in diagnosis of C3G not all autoimmune forms are identified and thus more vigorous autoantibody testing should be performed.

Beteiligte Forschungseinheiten

Infektionsbiologie Peter F. Zipfel Mehr erfahren

Leibniz-HKI-Autor*innen

Sara Afonso

Details

Andrea Hartmann

Details

Susanne Lindner

Details

Ina Löschmann

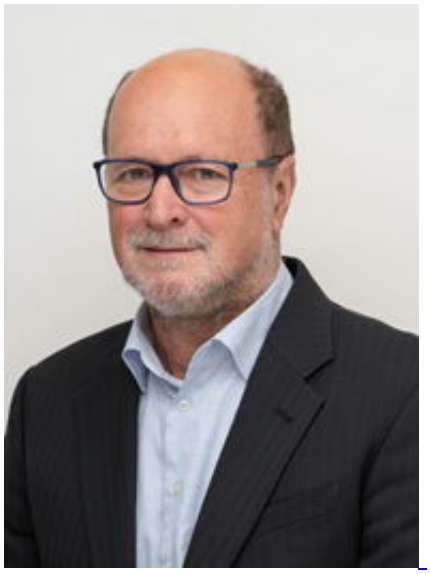
Details

Christine Skerka

Details

Fei Zhao

Details



Peter F. Zipfel

Details

Identifier

doi: 10.3389/fimmu.2019.01030

PMID: 31214159