Combination of factor H mutation and properdin deficiency causes severe C3 glomerulonephritis.

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Abstract

Factor H (fH) and properdin both modulate complement; however, fH inhibits activation, and properdin promotes activation of the alternative pathway of complement. Mutations in fH associate with several human kidney diseases, but whether inhibiting properdin would be beneficial in these diseases is unknown. Here, we found that either genetic or pharmacological blockade of properdin, which we expected to be therapeutic, converted the mild C3 GN of an fH-mutant mouse to a lethal C3 GN with features of human dense deposit disease. We attributed this phenotypic change to a differential effect of properdin on the dynamics of alternative pathway complement activation in the fluid phase and the cell surface in the fH-mutant mice. Thus, in fH mutation-related C3 glomerulopathy, additional factors that impact the activation of the alternative pathway of complement critically determine the nature and severity of kidney pathology. These results show that therapeutic manipulation of the complement system requires rigorous disease-specific target validation.

Identifier

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