Complement-mediated renal diseases: genotype-phenotype and inhibition studies

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Abstract

Background
Renal diseases can be associated with excess complement activation related to complement
gene variants or circulating autoantibodies. These diseases include atypical hemolytic uremic
syndrome, a form of thrombotic microangiopathy, or C3 glomerulopathy/membranoproliferative glomerulonephritis. Both diseases can progress to
kidney failure requiring dialysis or transplantation. Complement inhibition with eculizumab, a
very costly antibody against C5, is effective in atypical hemolytic uremic syndrome and in
some, but not all, cases of C3 glomerulopathy. There is therefore a need for alternative and less
costly treatments.

Aims
• To identify complement mutations in renal diseases and correlate genotype to phenotype
• To investigate the effect of factor D inhibition on complement activation

Methods
Genetic analysis of patients with complement-mediated renal disease was performed by Sanger
or next generation sequencing. Bioinformatics was performed using genome databases and
complement mutations identified. The phenotype of patient mutations was studied using patient
sera and mutant constructs applying complement activation assays such as hemolysis, binding
and degradation assays and release of soluble C5b-9. The effect of factor D inhibition was
evaluated.

Preliminary results
Three factor B mutations found in patients with atypical hemolytic uremic syndrome and
membranoproliferative glomerulonephritis were assessed. One was found to be a gain-of
function mutation. An additional factor B gain-of function mutant construct was evaluated, and
the excessive activity of both gain-of function mutants was effectively decreased by a factor D
inhibitor. The one gain-of function mutation in factor B was thoroughly evaluated in the
kindred of the proband assessing other affected and unaffected carriers of the mutation in
several generations and the extended family in order to identify the founder in which the
mutation originated. Likewise, genetic variants in factor H-related 5 will be assessed for their
phenotype. Genetic variants in complement mutations associated with atypical hemolytic uremic syndrome and C3 glomerulopathy/membranoproliferative glomerulonephritis will be described in a large Nordic cohort.

**Significance**

Complement mutations will be described, and the phenotype of factor B and factor H-related 5 mutations evaluated. Furthermore, the thesis will highlight the effect of factor D inhibition on factor B mutations in complement-mediated renal diseases.

**References**
