Post-Liver Transplant C3G with Highly Elevated Factor H Autoantibodies

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Introduction

Factor H (FH) is the key negative regulator of the alternative pathway (AP), both in the circulation and on the cell surface. Autoantibodies to FH (FHAAs) can be found in patients with complement-mediated rare renal diseases like atypical hemolytic uremic syndrome (aHUS) and C3 Glomerulopathy (C3G). The presence of FHAAs is often associated with homozygous deletion of the \textit{CFHR1} gene. Due to the presence of highly homologous sequences in this genomic region, the deletion of both copies of the \textit{CFHR3–CFHR1} genes is a very common structural copy number variation in the human genome.

We present a unique case wherein a post-liver transplant recipient developed C3G secondary to acquired deficiency of FHR1. FHAAs do not stabilize C3 convertase on the cell surface. The presence of FHAAs is often associated with syndromes (aHUS) and C3 Glomerulopathy (C3G).

Patient

A 30-year-old male underwent a liver transplant at age 20 for auto-immune hepatitis. A few years later, he was diagnosed with declining renal function. A weak FHL1 band is seen. FHL1 is an alternate spliced FH version, which contains first 7 SCR.

Methods

1. Complement biomarkers were quantified using a customized panel that employs a battery of ELISAs, RIDs and hemolytic assays.
2. Autoantibodies to FH, FB, FI, CR1, C3 convertase (C3Nefs) and C5 convertase (C5Nefs) were measured by ELISAs or cell based methods.
3. Total IgG was isolated using a Melon Gel. IgG3 and IgG1/2/4 fractions were separated using Protein A. IgG1/2/4-\(\kappa\) was further absorbed using PureProteome Lambda Ig Binder Magnetic Beads.
4. Completed assays included:
   a) A fluid-phase C3 convertase assay (FPC3CA)
   b) A cell-based C3 convertase activity assay
   c) A cell-based cofactor activity assay
5) AP Dysregulation in the Fluid Phase

Figure 1. FHRI expression in patient and controls. Western blotting shows no circulating FHRI in the patient. FHRI is produced by the liver, implying that the recipient has acquired FHRI deficiency. A weak FH1L band is seen. FH1L is an alternate spliced FH version, which contains first 7 SCR.

Table 1. Isotypic ELISA

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<td>FHAAs</td>
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<td>FBAAs</td>
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FHAAs is an IgG1 and FBAAs is an IgG3.

4) Epitope Mapping

Figure 3. Epitope mapping. FHAAs binds to the N-terminus (SCRs 1-4) of FH, while FBAAs targets the Bb portion of FB.

Conclusion

Here we present a case of acquired FHRI deficiency that led to the generation of high levels of FHAAs. Functional analyses show that these FHAAs impair the DAA and CA of FH. FHAAs do not stabilize C3 convertase on the cell surface. The role of FBAAs in the disease in this case is unclear.

This case highlights a causal relationship between deficiency of FHRI and FHAAs. Importantly, when FHRI is absent, auto-antigenicity to FH can be induced even after maturation of the immune system.

(Supported in part by National Institutes of Health R01 DK110023)