Naturally occurring C3-convertase antibodies: a Nef precursor?

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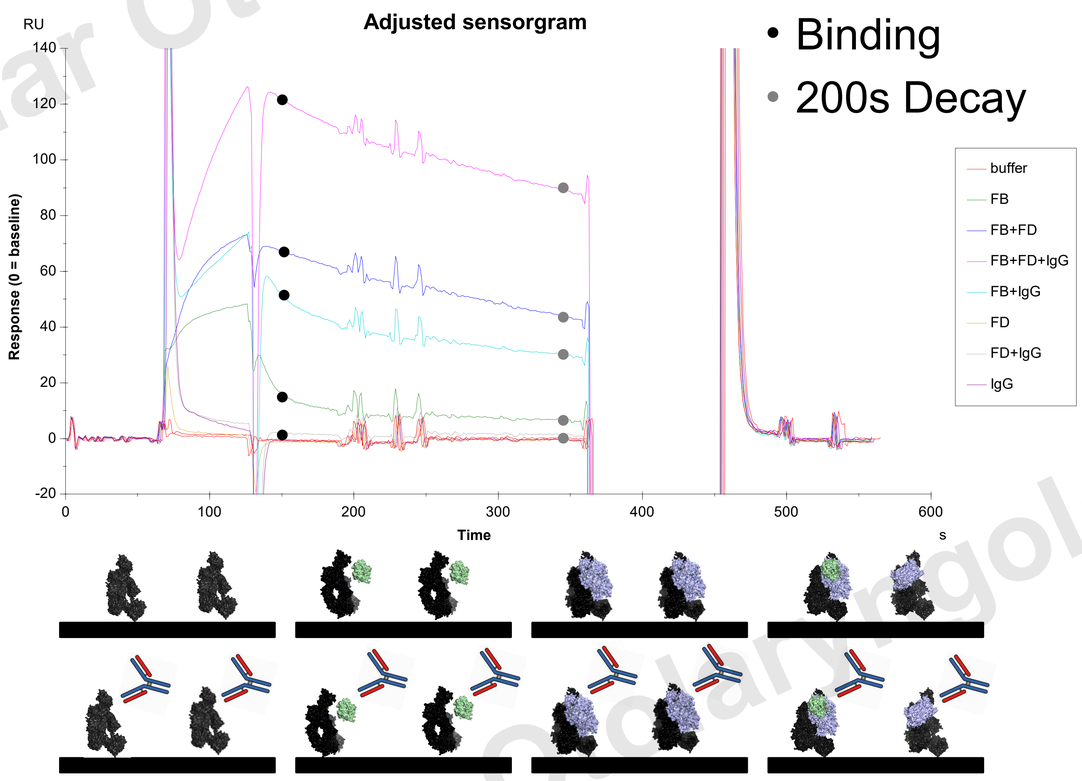
Introduction

Pathogenic autoantibodies that bind to and dysregulate the C3-convertase (C3bBb) are called Nephritic Factors (Nefs). Nefs are identified in ~80% of C3 Glomerulopathy patients.[1] Why these antibodies arise is unknown, and there is no consensus on whether analogous antibodies exist in the normal population. We developed a specificity assay to test antibody binding to C3bBb and C3-proconvertase (C3bB) by surface plasmon resonance to explore the prevalence of C3-convertase binding antibodies in the normal population

Methods

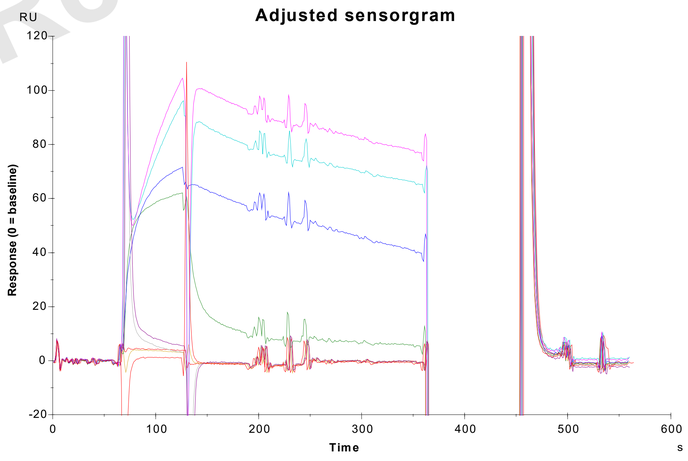
IgG from 30 normal donors were tested as well as Nef-containing positive control IgG and an anti-C4b sham control IgG. With C3b as a ligand, specific binding for each sample was determined using diverse sample preparations: purified normal human (NH) IgG alone, FB alone, FB with NH IgG, FD alone, FD with NH IgG, FB+FD, and FB+FD with NH IgG. Binding was measured following injection and after 200 seconds of dissociation. Normalized Decay (ND) was calculated by the following equation: ND= (RU at 200s)/(RU at 0s).

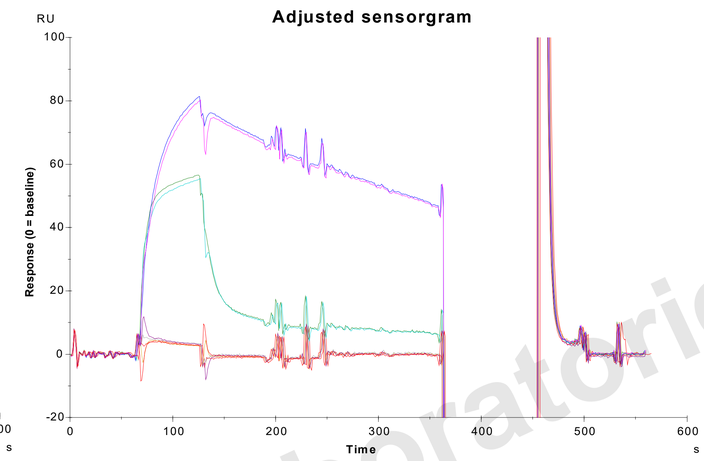


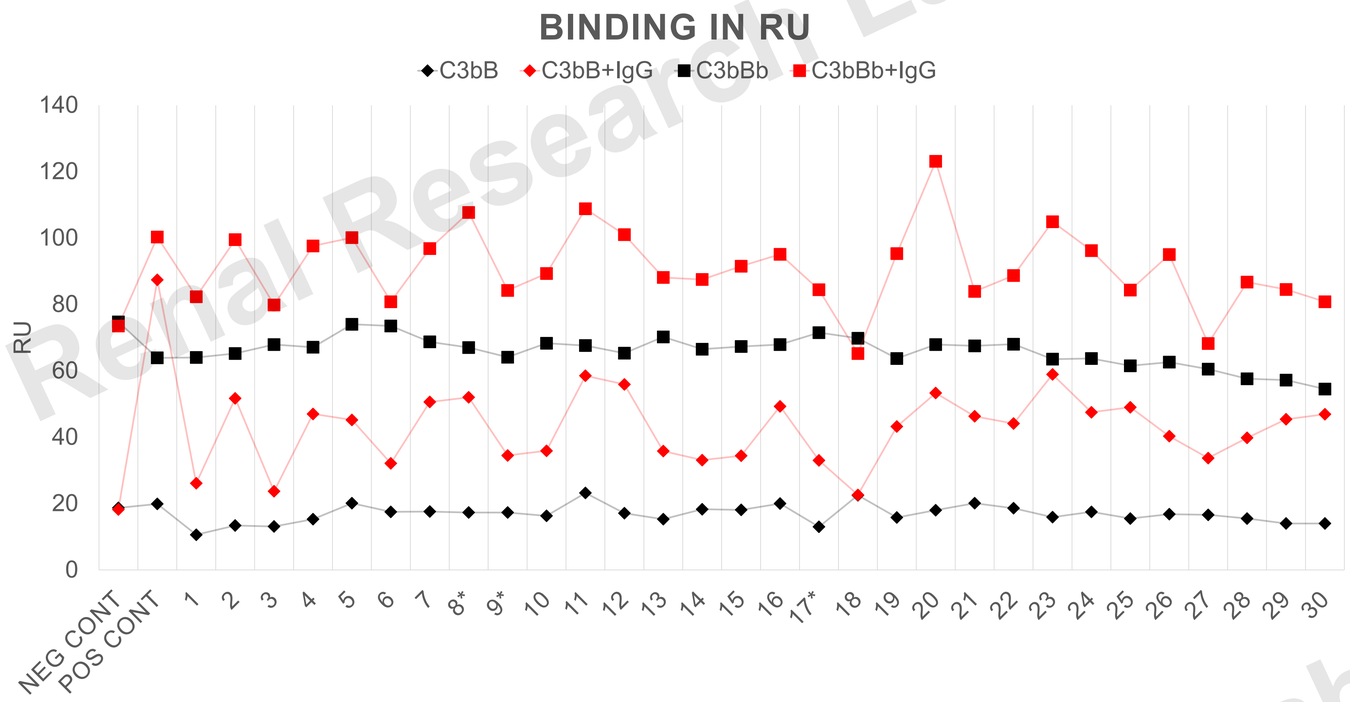
- Binding
- 200s Decay

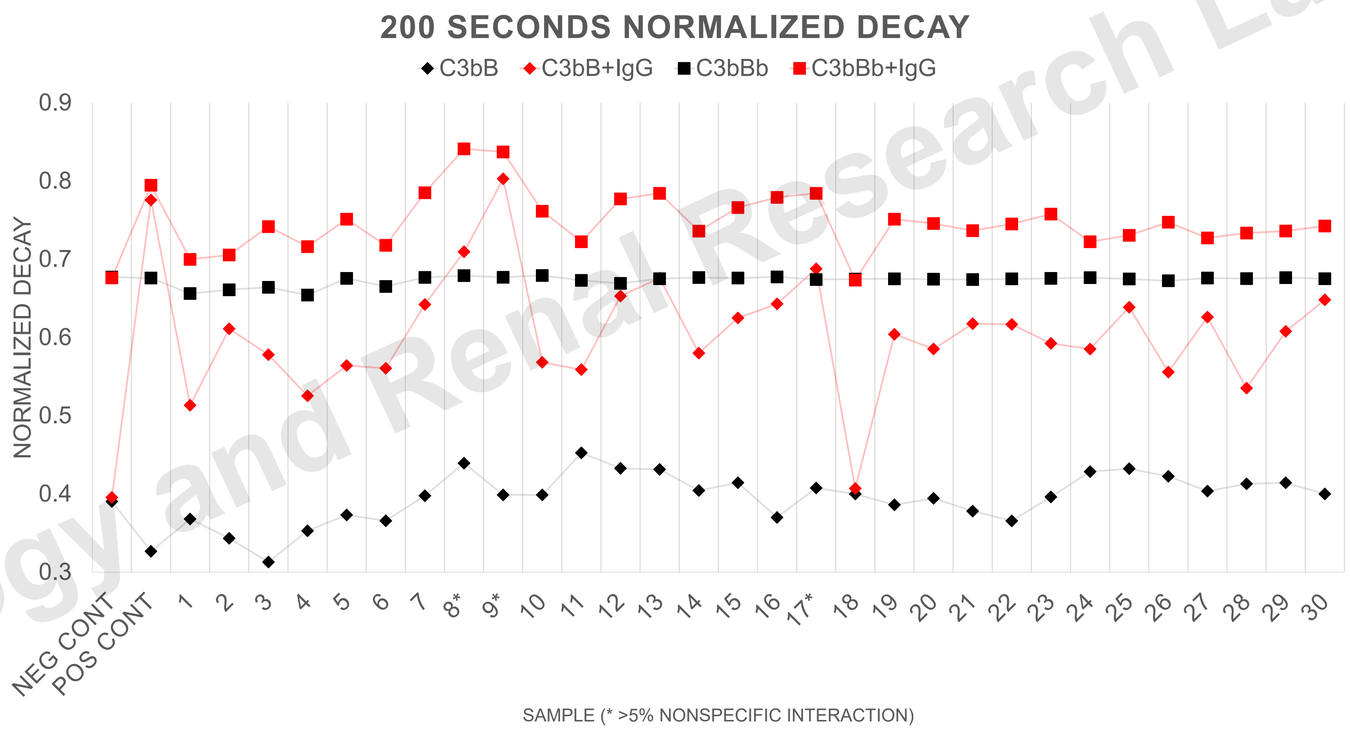
Results

Anti-C4b antibody demonstrated no binding and no stabilizing effect on C3bB or C3bBb. The Nef positive control displayed no nonspecific binding (IgG alone or FD+IgG) but had significant binding to and stabilization of C3bB and C3bBb. One NH sample replicated the negative control results while 86.7% of NH samples matched the Nef's specificity for C3bB and C3bBb. However, the stabilization of these samples was less than the Nef control.









Conclusions

Our data suggests that autoreactive C3bB and C3bBb antibodies are highly prevalent in the normal population, but they lack the degree of stabilization seen with the Nef control. Considering the different kinetics and the lack of disease in the donor population, these antibodies are technically not Nef. We prefer a C3-Convertase autoantibodies (C3CAbs) nomenclature. C3CAbs in normal sera may inform next steps in determining the origin of the pathogenic version of these antibodies (Nef) in C3G

References

1.Clinical Journal of the American Society of Nephrology, 7**:** 265-274, 2012 10.2215/cjn.07900811