Antibody-Dependent Complement Responses toward SARS-CoV-2 Receptor-Binding Domain Immobilized on “Pseudovirus-like” Nanoparticles

Many aspects of innate immune responses to SARS viruses remain unclear. Of particular interest is the role of emerging neutralizing antibodies against the receptor-binding domain (RBD) of SARS-CoV-2 in complement activation and opsonization. To overcome challenges with purified virions, here we introduce “pseudovirus-like” nanoparticles with ∼70 copies of functional recombinant RBD to map complement responses. Nanoparticles fix complement in an RBD-dependent manner in sera of all vaccinated, convalescent, and naïve donors, but vaccinated and convalescent donors with the highest levels of anti-RBD antibodies show significantly higher IgG binding and higher deposition of the third complement protein (C3). The opsonization via anti-RBD antibodies is not an efficient process: on average, each bound antibody promotes binding of less than one C3 molecule. C3 deposition is exclusively through the alternative pathway. C3 molecules bind to protein deposits, but not IgG, on the nanoparticle surface. Lastly, “pseudovirus-like” nanoparticles promote complement-dependent uptake by granulocytes and monocytes in the blood of vaccinated donors with high anti-RBD titers. Using nanoparticles displaying SARS-CoV-2 proteins, we demonstrate subject-dependent differences in complement opsonization and immune recognition.