Trimeric S Glycoprotein of SARS-CoV Induces High-titer Neutralizing Antibodies that Block Virus Binding to the ACE2 Receptor

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Severe acute respiratory syndrome is caused by a novel coronavirus (SARS-CoV) and represents a serious emerging human infectious disease. An intensive search is underway to develop a safe and efficacious vaccine. The Spike (S) glycoprotein is a major target of the host neutralizing antibody response. We therefore analysed whether native purified trimeric S glycoprotein was capable of inducing a neutralizing antibody response. We found that as early as 30 minutes post-entry into the ER, high-mannosylated S assembles into trimers prior to acquisition of complex *N*-glycans in the Golgi. Trimeric S has native antigenicity and fold as demonstrated by reactivity with IgG from SARS patient sera and binding to the ACE2, an entry receptor of SARS-CoV. Trimeric S protein could be effciently produced and immunopurified from mammalian cells infected with a recombinant Semliki Forest Virus vector. When injected in mice with Alum adjuvant trimeric S protein induces a TH2-based antibody response in mice directed against denatured or native S-protein and SARS-CoV-infected cells. High-titers of SARS-CoV neutralizing antibody are detected in animals immunized and boosted with trimeric S protein. Titers drop within a month following the last immunization but stabilize at a constant and high level. Neutralizing antibody titers are significantly higher than those observed in patients with SARS. Neutralizing sera block S-protein binding to the ACE2 receptor suggesting inhibition of receptor binding as the major mechanism of neutralization. Future studies need to assess the protective capacity and the potential immunopathological side effects of neutralizing antibodies in a relevant animal model that reproduces SARS-CoV induced pathology and/or disease.