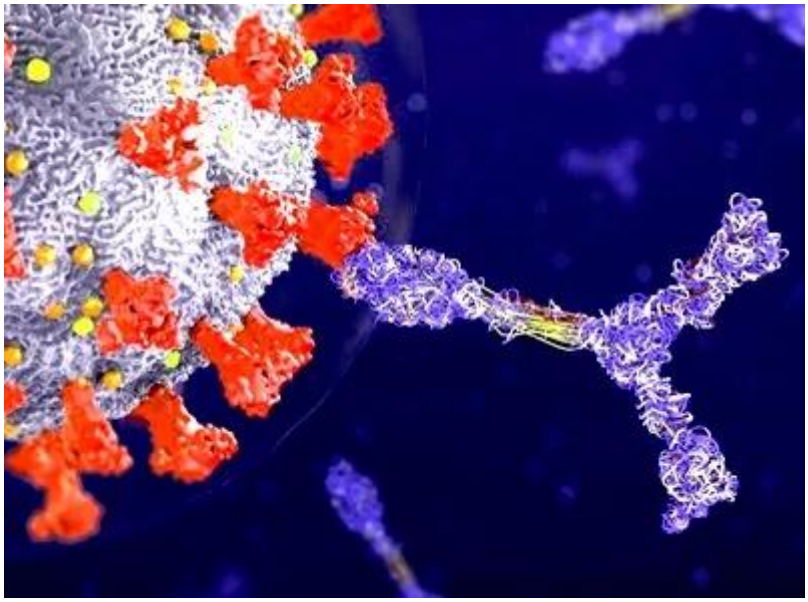
BNT162b2 (Pfizer- BioNTech) and mRNA 1273 (Moderna) vaccines were the first messenger RNA (mRNA)-based vaccines ever approved. In both vaccines, an mRNA sequence determines the structure and assembly of the immunogen, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) glycoprotein. Previous studies have found that the immunoglobulin G (IgG) response after two doses of the mRNA COVID vaccines consists mainly of the proinflammatory subclasses IgG1 and IgG3. Shortly after two doses of vaccine (either Comirnaty or mRNA-1273), subclasses IgG1 and IgG3 were predominant, IgG2 responses were rare, and IgG4 responses were nearly undetectable. However, German researchers emphasized that the longitudinal evolution of the four IgG subclasses (IgG1, IgG2, IgG3, and IgG4) in response to mRNA vaccination—particularly their long-term development after the second and the third dose—has not yet been analyzed. Therefore, in this study, they longitudinally monitored the IgG response in two independent cohorts of healthcare workers vaccinated with two or three mRNA COVID-19 vaccines. They aimed to investigate whether the mRNA COVID vaccination increases the proportion of IgG4 specific for SARS-CoV-2.

The authors pointed to limited investigations on the role of vaccine-induced IgG4 in infectious diseases. Interestingly, in the VAX003 trial that developed the vaccine against human immunodeficiency virus (HIV), repeated protein immunization resulted in higher levels of IgG2 and IgG4 specific for HIV gp120. In the RV144 trial, prime-boost immunization with a canarypox vector (ALVAC-HIV) increased levels of HIV- specific IgG3 antibodies that enhanced effector functions such as antibody-dependent cellular phagocytosis and cellular cytotoxicity. In contrast, vaccine-induced IgG4 antibodies inhibited the same effector functions. IgG4 is the least abundant IgG subclass, with some unique structural and functional features. IgG antibodies are described as a “blocking” and “anti-inflammatory” antibody that cannot activate antibody-dependent immune effector responses. Some previous studies reported that after COVID-19 vaccinations, some patients developed IgG4-related disease, a systemic immune-mediated fibro-inflammatory disease characterized by elevated serum levels of IgG4, an abundant infiltration of two or more affected organs with IgG4-positive plasma cells, and fibrosis of affected organs.
https://discovermednews.com/two-case-reports-of-igg4-related-disease-after-anti-sars-cov-2-vaccination/



About the Study and Results

The researchers longitudinally monitored the IgG response in serum samples from two independent cohorts of healthcare workers vaccinated with two or three mRNA COVID-19 vaccines. The results showed that repeated immunization with the mRNA COVID-19 vaccines increased levels of the IgG4 antibody against SARS-CoV-2 S protein and IgG4-switched memory B cells. The induction of IgG4 antibodies was not observed after immunization with adenovirus vector-based COVID vaccines.

Five to seven months after the second immunization with the mRNA COVID-19 vaccines, noninflammatory IgG4 antibodies were detected in about half of the serum samples. Importantly, IgG4 has not been found in any sample at earlier time points.

After the third immunization with the mRNA COVID-19 vaccines, IgG4 levels increased significantly and became detectable in almost all vaccine recipients. Specifically, IgG4 serum levels increased from 0.04% shortly after the second vaccination to 19.27% late after the third vaccination.

The levels of all other IgG subclasses decreased during the same period.

Also, in parallel with higher proportions of anti-S protein IgG4 antibodies, antibody-mediated phagocytic activity and complement deposition decreased in sera after the third immunization.

Flow cytometry and single-cell sequencing of memory B cells specific for the SARS-CoV-2 S

protein, isolated after the second and third vaccination, confirmed the presence of a substantial number of SARS-CoV-2 S protein-reactive IgG4-switched B cells. In contrast, IgG3-positive clones were hardly detectable.

The authors emphasized that they could not formally rule out *de novo* class switching to IgG4 immediately after the booster vaccination. However, the rapid increase of IgG4 antibodies and the presence of IgG4 antibodies against the SARS-CoV-2 S protein in the serum at this time support the idea that booster immunization reactivated already-present IgG4 memory B cells.

Conclusion

In this study, Irrgang et al. were the first to report an increase in the proportion of SARS-CoV-2 S protein-specific noninflammatory IgG4 antibodies and IgG4-switched memory B cells in adults, starting after the second and increasing further after the third mRNA COVID vaccination. The authors stressed that the induction of antiviral IgG4 antibodies is a rarely described phenomenon, regardless of the underlying mechanism.

There are important questions about the functional consequences of this phenomenon. Further research is needed to clarify the specific immunological mechanisms driving this response and to evaluate whether an IgG4-driven antibody response affects further viral infections and booster vaccinations. The authors believe these questions are relevant for future immunization campaigns against SARS-CoV-2 and new mRNA-based vaccines against other pathogens.

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