Tetanus vaccination generates antigen-specific bone marrow long-lived plasma cells (LLPC), which provide safeguards for decades and have a serologic half-life of 10 years. Humoral immunity provided by influenza vaccines is short-lived and typically wanes within 4–6 months. However, natural infection provides long-lasting immunity, as shown in elderly adults who maintained neutralizing antibodies to the 1918 Spanish influenza virus nearly 90 years after the primary infection. In this study, the United States authors investigated whether individuals vaccinated with the mRNA COVID-19 vaccines could generate the bone marrow LLPC specific to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein. They measured antibody-secreting cells (ASC) specific for influenza, tetanus, or SARS-CoV-2 in both LLPC (CD19-) and non-LLPC (CD19+) subsets in the bone marrow.

The term ASC refers to all antibody-secreting cells, including early-minted ones (plasmablasts) of which some progressively mature into LLPC, and more mature (plasma cells). After vaccination, most of the ASC released from secondary lymph nodes undergoes apoptosis unless they finally reach the specialized bone marrow survival niches filled with mesenchymal stromal cells and myeloid cells. These new arrivals can further differentiate into a mature, long-lived phenotype LLPC (CD19- CD138+) that produces neutralizing antibodies.

About the study

Samples of bone marrow aspirates were obtained from healthy adult donors vaccinated with

Tdap (tetanus-diphtheria-pertussis), influenza, or COVID-19 primary and booster vaccines. ASC specific for influenza, tetanus, or SARS-CoV-2 were measured in both, LLPC (CD19-) and non-LLPC (CD19+) subsets within the bone marrow up to 33 months after vaccination. These findings were compared with well-known long-lived responses such as tetanus- or influenza-specific ASC. They also verified these results by using multiplex bead binding assays of secreted antibodies in the supernatants of cultured ASC.

Results

21 bone marrow aspirate samples were taken from 19 healthy adult donors who received the Tdap (tetanus-diphtheria-pertussis), influenza, or COVID-19 primary and booster vaccines. Bone marrow aspirates were obtained between 1.5 and 33 months after the SARS-CoV-2 mRNA vaccination.

There was an abundance of SARS-CoV-2-specific ASCs in the short-lived plasma cell compartment of the bone marrow, but these cells were largely excluded from the LLPC compartment as early as two months and up to almost three years after immunization. This phenomenon was in stark contrast to the influenza- and tetanus-specificities inherent to bone marrow LLPC. At 33 months after the vaccination, ASCs specific for SARS-CoV-2 remained excluded from the LLPC compartment of the bone marrow.

All individuals were found to have ASC specific for influenza, tetanus, and SARS-CoV-2 in at least one bone marrow ASC compartment. However, only influenza- and tetanus-specific ASC were readily detectable in the LLPC, whereas SARS-CoV-2 specificities were mostly excluded. It is noteworthy that ASCs specific for SARS-CoV-2 were mostly excluded from the LLPC in five patients with PCR-proven history of infection or vaccination. The ratios of non-LLPC: LLPC for influenza, tetanus, and SARS-CoV-2 were 0.61, 0.44, and 29.07, respectively.

These specificities were further validated by using multiplex bead binding assays of secreted antibodies in the supernatants of cultured ASC. The IgG ratios of non-LLPC: LLPC for influenza, tetanus, and SARS-CoV-2 were 0.66, 0.44, and 23.26, respectively.

The authors discussed possible reasons for the exclusion of SARS-CoV-2 specificity from the bone marrow LLPC compartment and the inability of mRNA vaccines to induce necessary precursor programs to fully mature into the bone marrow LLPC. According to them, the lack of a sustained antibody response could be due to the unstable nature of the mRNA and the transient expression of the S protein during induction. Considering that both the mRNA and Ad vector vaccine platforms induce strong germinal center reactions and interactions with T

follicular helper cells, the mechanisms underlying their failure to generate LLPC are more puzzling. This suggests dysfunction in the maturation process in the bone marrow microniche. The authors also think that the limited duration of the neutralizing antibody responses could be due to the structural nature of the S protein itself.

Other immunologists also commented on these findings. Some speculated that SARS-CoV-2's surface features might offer an answer. As B cells carry Y-shaped receptors that attach to viral surface proteins of the pathogen, if both branches of the Y bind to the same pathogen proteins, they trigger a phenomenon called "cross-linking," which spurs B cells to transform into LLPCs. Electron microscopy showed that SARS-CoV-2 spikes are about 25 nanometers apart, and some authors believe that this is too distant for a single B cell receptor to readily bind to two at once. As a result, B cells don't become cross-linked, and LLPCs don't develop. However, others are more skeptical that spacing impacts significantly a vaccine's durability. (Cohen J. Why does COVID-19 vaccine protection quickly wane? Science 2024; 386 (6719). https://www.science.org/doi/epdf/10.1126/science.adt9019

Other immunologists think that mRNA vaccines lead to immune refocusing, where suboptimal antibodies are induced against immune subdominant or immune-recessive epitopes on the S protein. This unnatural, weak, and aberrant stimulation of the adaptive immune system does not induce LLPC specific to SARS-CoV-2. On the other hand, barely detectable LLPCs specific for SARS-CoV-2 have a completely different cause in unvaccinated individuals who have had one or more SARS-CoV-2 infections. The innate immune system of healthy, unvaccinated individuals is usually able to largely control the virus so that only a weak stimulation of the adaptive immune system is required to ultimately eliminate the virus. As the immune escape pandemic continued to evolve and the innate immune system of unvaccinated individuals became better trained, the contribution of their adaptive immune system to controlling the virus remained relatively small. Consequently, immunological memory was insufficiently triggered to generate significant amounts of LLPCs specific for SARS-CoV-2.
https://www.voiceforscienceandsolidarity.org/scientific-blog/poor-insights-on-what-stimulates-long-lived-antibody-production-could-spur-false-hope-for-better-covid-19-vaccines

Conclusion

This study showed that people who received repeated doses of vaccine, and in some cases also became infected with SARS-CoV-2, largely failed to make special antibody-producing cells called LLPC in the bone marrow. This resulted in the rapid waning of serum antibodies.

These results provided important insights into how the mRNA vaccines fail to induce the necessary ASC precursors with programs required to mature into LLPC.

Journal Reference

Nguyen, D.C., Hentenaar, I.T., Morrison-Porter, A. *et al.* SARS-CoV-2-specific plasma cells are not durably established in the bone marrow long-lived compartment after mRNA vaccination. *Nat Med* (2024). (Open Access) https://doi.org/10.1038/s41591-024-03278-y