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NOVEL HYPOTHESIS

COVID-19 vaccination can occasionally trigger autoimmune phenomena, probably via inducing age-associated B cells

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1 | AGE-ASSOCIATED B CELLS

Age-associated B cells (ABCs) constitute a CD11c$^+$ T-bet$^+$ B-cell population that expands continuously with age in healthy individuals,[1] but also displays a premature accumulation in cases of autoimmune and/or infectious diseases.[2-5] In autoimmune settings, ABCs are implicated in the production of autoreactive immunoglobulin G,[2] the enhanced antigen presentation to T cells, and the formation of spontaneous germinal centers.[6,7] T-bet, which is a transcription factor highly expressed in ABCs, is considered to be the master regulator of all these processes,[8] although new data suggest that its expression may not be required for the generation of functional ABCs.[9]

In humans, the ABC subset is also known as double-negative (DN) B cells because of the lack of immunoglobulin D and CD27 memory marker expression.[10-12] DN B cells have been further divided into two subgroups, based on the expression of the follicular homing marker CXCR5.[13] More specifically, the CXCR5$^+$ cells (DN1) are expanded in elderly healthy individuals and lack T-bet expression, whereas the CXCR5$^-$ cells (DN2) express T-bet and are more marked in autoimmune diseases (mostly systemic lupus erythematosus).[10,11,13] The DN2 cells are hyperresponsive to Toll-like receptor 7 (TLR7) signaling, so are poised to generate autoreactive antibody-secreting plasmablasts.[13] In general though, their role in the development of autoimmunity remains elusive.

2 | AUTOIMMUNE PHENOMENA FOLLOWING COVID-19 VACCINATION

Autoimmune disease flares and new-onset disease following coronavirus disease 2019 (COVID-19) vaccination have recently been reported.[14,15] In general, all these cases appeared rare and most of them were moderate in severity and had an excellent resolution of inflammatory features, with the use of corticosteroids alone[14,15] (indicating that COVID-19 vaccines are actually safe). The use of TLR7/8 and TLR9 agonists, as adjuvants of the available mRNA and DNA severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines, may be the trigger of these post-vaccination autoimmune/inflammatory phenomena,[14] as it is well known that both TLR7 and TLR9 are involved in the generation and amplification of autoreactive immune responses.[16]

In more detail, the adjuvanticity of COVID-19 vaccines depends—to a large extent—on the intrinsic adjuvanticity of mRNA or DNA, which respectively stimulate the innate immune system through endosomal and cytoplasmic RNA/DNA sensors such as TLRs.[17] The stimulation of TLR7 and TLR9 might be expected to produce elevated levels of type I interferon and so upregulate interferon-stimulated genes[16,17] that contribute to the pathogenesis of a number of rheumatic diseases.[18]

3 | POTENTIAL INDUCTION OF ABCs BY COVID-19 VACCINATION

Apart from autoimmune diseases, ABCs/DN B cells also expand in infectious diseases—including COVID-19,[4,5,19,20] usually having either an exhausted or anergic phenotype.[21] Moreover, circulating DN B cells increase in numbers after vaccination against influenza virus in healthy individuals.[22] Considering all these facts, we believe that there is a strong possibility for ABCs/DN B cells to be induced by COVID-19 vaccines and then be involved in the autoimmune phenomena that (may) follow.

Our knowledge regarding the role of TLR7 and TLR9 in determining the fate of ABCs,[23] in conjunction with the fact that agonists that bind to these two receptors are used as adjuvants in the available mRNA and DNA COVID-19 vaccines,[14,17] further strengthens our hypothesis. To be more specific, we note that TLR7 and/or TLR9 stimulation, after antigen internalization via B-cell receptor, leads pre-immune B cells to an ABC-poised status.[23] Signals from interferon-γ or interleukin-21 determine the ABC phenotype.[24] Otherwise, especially when TLR9 is engaged but no further signals exist, the cell is led to apoptosis.[23,24] In general, ABC generation is based on the synergistic triggering of B-cell receptor, TLR7, and interferon-γ or interleukin-21 receptors.[3,23,24]

4 | CONCLUSIONS

In this article, we discuss the probability of ABC-mediated autoimmunity (flare or new-onset) following COVID-19 vaccination. We find it important to mention here that, according to observations from a new study, the frequencies of DN B cells decrease in previously SARS-CoV-2-infected individuals after their vaccination against the aforementioned virus,[25] indicating that vaccine response counters the infection-induced production of potentially pathogenic B cells. At first glance, the results of that study seem to oppose our hypothesis. However, we want to make it clear that we do not call into question the safety of COVID-19 vaccines (besides, the data derived from participants in observational studies[14,15] clearly suggest that rheumatic disease flares and new-onset disease following COVID-19 vaccination are uncommon, mild to moderate in severity, and in most cases are treated with oral corticosteroids) and we propose an ABC-induction only in the rare cases that autoimmune phenomena occur after the vaccination, as ABCs are indissolubly associated with autoimmunity.[2,3,7,8,11-13] Furthermore, it is wise to keep in mind that ABC-induction and as a result the estimation of ABC percentages are affected by various parameters, such as the age of the individual,[1,26] the ethnicity (as these cells are more marked in African-American people),[13,27] and of course the interval between vaccination and cell counting.

Taking into account the prognostic and/or diagnostic potential of ABCs in rheumatic diseases,[28] we believe that the enumeration of these cells could enable better management of people to be vaccinated (especially those with autoimmune/rheumatic history, as some of the post-vaccination flares described were severe).[14] Such an approach may determine the most proper vaccination time-points for these people and so bring the least side effects and the most effective therapeutic benefits.[29]

AUTHOR CONTRIBUTIONS

Conceptualization and Writing-Original Draft: Athanasios Sachinidis.

Critical Revision and Supervision: Alexandros Garyfallos.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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