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COMMENTARY

SARS-CoV-2 vaccination in the context of original antigenic sin

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ABSTRACT

Immunological memory is the ability of the adaptive immune system to ensure a persistent protective effect after immunization. However, it can also be a limitation to building a sufficient level of protective antibodies specific to new mutations of the virus. It is imperative to bear this phenomenon (called "original antigenic sin") in mind and make every effort to overcome its inherent pitfalls when updating current and designing new vaccines.

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The current vaccination campaign against SARS-CoV-2 seems to be finally successful in at least slowing, if not containing, the spread of the COVID-19 pandemic. At present, the main problem with coping with this global epidemiological challenge is the risk of inadequate protection against novel mutations or variants of SARS-CoV-2, as suggested by the results of several Phase III clinical trials conducted in various regions of the world, where the emergence of new virus mutations has been shown to reduce the protective effect of the currently available vaccines. These new coronavirus variants are most likely to evade more often and more readily the specific immunity afforded by vaccination, a fact essentially impacting the success rate of the vaccination campaigns ongoing across the world. This is exemplified by the success rates of completed vaccination series with the Janssen COVID-19 Vaccine reported from the United States (72%), Brazil (68%) and South Africa (64%) or the rates achieved in individuals receiving the AstraZeneca COVID-19 Vaccine in the United Kingdom (70%) and Brazil (58%).[1,2] These early data from different geographic regions highlight the need for redesigning the currently approved vaccines to better fit the ever-changing epidemiological landscape, that is, the specific viral strains currently circulating around the world.

This task may seem to be an easy one, since re-vaccination or booster vaccination is a common health-care policy tool used to restore or, possibly, enhance specific immunity, and has been employed successfully in all routine annual influenza re-vaccination programs. However, this strategy in the context of the current pandemic may be hindered by a phenomenon first desribed by Thomas Francis, Jr. in the 1953, just in connection with regular influenza vaccination, and referred to as original antigenic sin.[3,4]

Briefly, the antibody-mediated immunity achieved post-vaccination may not be fully specific to a distinct antigen variant contained in the vaccine since the antigenic determinants may be shared across various strains of the respective types or subtypes of the viral pathogen as is the case with influenza. This has been conclusively documented in geographic serology surveys showing one's history of response after influenza vaccination.[5] While inducing specific antibodies targeting antigens contained in the vaccine, i.e., neuraminidase and hemagglutinin, a new vaccination series also raised the levels of antibodies specific to antigens produced in response to previous vaccination or influenza. Moreover, the rate of production of the original antibodies could be significantly faster.[6] Original antigenic sin only applies to antibodies because the antigen-specific affinity of B cell receptors alters subsequent exposures to their cognate antigens while the specificity of T-cell clones never does.[7]

This gives rise to a situation whereby the targeted and desirable response to new variants of the influenza virus types and subtypes is suppressed whereas a response to previously recognized heterovariants of influenza virus that share the same antigenic determinants with the new ones is preferred.[8] Similarly, vaccination with a nonavalent human papillomavirus (HPV) vaccine resulted in significantly decreased levels of antibodies specific to five new genotypes in individuals previously immunized with the quadrivalent HPV vaccine compared with those receiving the nonavalent HPV vaccine first.[9] Should this stimulation elicit high levels of antibodies against the previous variant, original antigenic sin may be offset by crossed reactivity provided that different strains of the subtype in question share high amounts of the same or similar epitopes, as demonstrated by outcomes of a study of vaccination with influenza A virus subtype H5N1.[10]

Regrettably, current data about the emergence of novel SARS-CoV-2 variants suggest progressive divergence of the novel lines from the original ones. In this context, original antigenic sin may reduce the efficacy of vaccines based on modified superficial structures of SARS-CoV-2. Aware as we are of the same scenario observed after vaccination

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against flavivirus infections (tick-borne encephalitis, yellow fever or dengue fever), it is now clear that any future vaccination against SARS-CoV2 should take into account this immune mechanism.[11] It was just the naturally acquired or post-vaccination immunity, which was actually original antigenic sin, hindering the development of new specific immunity to tick-borne encephalitis post-vaccination.[12] The same mechanism may work the other way round as individuals vaccinated against yellow fever showed appreciably lower seroresponse rates after recovery from a heterologous flavivirus-borne disease (Zika virus).[13]

Given the above, it is most appropriate – when scheduling booster vaccination or even re-vaccination – to carefully monitor the seroresponse of those vaccinated since a reduced immune response to new SARS-CoV-2 variants at the expense of an enhanced response to original variants could in fact result in inadequate protection of those vaccinated against the current virus variants. Hence, the extremely high levels of specific anti-SARS-CoV-2 antibodies achieved by vaccination, which – as indicated by the most recent data – tend to persist for months post-vaccination, should serve as a warning sign.[14,15] In addition, it is not yet obvious if the robust vaccination-induced response of T cells can compensate for original antigenic sin to afford a sufficient level of protection against the new SARS-CoV-2 variants.

Most current COVID-19 vaccines are designed to incorporate the dominant viral antigen of the SARS-CoV -2, i.e., the S-protein. If the updated vaccines against the new mutations were based on the same type of antigen protein (S-protein only), the effect of original antigenic sin could be strengthened as mentioned above in the case of vaccination with the nonavalent HPV vaccine. We can only speculate that if the vaccine contained more antigenic components (such as the common influenza vaccine with hemagglutinin and neuraminidase), the chances of overcoming original antigenic sin would have been increased. Therefore, it is obvious to consider multicomponent vaccines which, in addition to the S-protein, could also contain nucleocapsid or envelope proteins of SARS-CoV-2.

As suggested by a recent observation in naturally immunized individuals receiving two doses of the Pfizer COVID-19 (Comirnaty) vaccine, original antigenic sin may pose a problem in future research and development of vaccines.[16] While the first dose of the vaccine was able to raise the preexisting levels of functional and specific antibodies, these either failed to change or even declined after the second dose (virus-neutralizing antibodies), and the same applied to the levels of antigen-specific antibody-secreting cells. As this observation was made in only a small group of 13 subjects with naturally acquired immunity against SARS-CoV-2, who had rather average or below-average levels of the antibodies assessed, one may expect an enhanced effect of original antigenic sin after new vaccination against COVID-19 in those with manyfold higher antibody levels after complete immunization.

The reason for writing this opinion is to give the reader an idea of the comprehensive nature of the immunity system on the one hand, and its potential limitations on the other. As original antigenic sin is one of the latter, it is imperative to bear this concept in mind in these difficult times and make every effort to overcome its inherent pitfalls when updating current and designing new vaccines.

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