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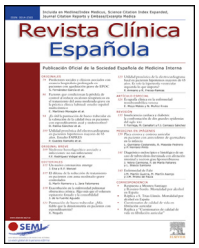

EDITORIAL

Possible effect of the ''original antigenic sin'' in vaccination against new variants of SARS-CoV-2☆

Posible efecto del «pecado antigénico original» en la vacunación frente a las nuevas variantes del SARS-CoV-2

In 1960, Francis[1], studying the response to flu revaccination, observed that those who were revaccinated presented with a lesser immune response than those who had not previously been vaccinated. He proposed the term ''original antigenic sin'' (OAS) for this phenomenon in which, after a second exposure to a different antigen variant of the same virus, the immune system responded with antibodies of a lesser intensity and specificity.

This phenomenon, also called ''Hoskins' paradox'' or ''negative interference,'' means that with another vaccination for a virus that uses strains which are antigenically different, the immune system basically responds with the already-present antibodies (immunological laziness) and, to a lesser extent, with new antibodies induced by the new vaccine, decreasing the protective efficacy of the second vaccine[2,3]. In this manner, the immunological footprint left by the first contact with the virus will determine future responses to it, given that it will be fixed by the first immune response[1].

OAS increases through vaccination with low doses of an antigen, as memory B cells sequester the immunogens which activate new B cells, despite the fact that the latter have a high affinity and capacity for antibody production when faced with the new antigen[3]. Thus, OAS could determine the immune evasion of new antigenic variants in people who have already had the infection or have previously been vaccinated against another variant. This negative effect has already been observed in other viral infections apart from the flu, such as dengue virus and human papillomavirus[2–4].

We must study the possible effect of OAS in depth during the process of revaccination against new variants of SARS-CoV-2[5]. It has be proposed that antigenic distance could explain the way in which efficacy of vaccines may be related to prior vaccination. Indeed, vaccines with distant antigenic variants may not be controlled by the prior immune response, which would have created immune ''imprinting'' that would determine the initial formation of antibodies against the first recognized variant[6].

In revaccination, the immune system uses the initial imprinting and simply modifies the B cell clonotypes, adapting them to the new antigen. This phenomenon would leave individuals with a limited, pre-established immune response such that revaccination would produce an immune response that is always lesser than what is induced by first contact with the virus[7]. This phenomenon would not be a problem if the immunological memory produced neutralizing antibodies against new vaccine antigens. However, it would be a problem if they were non-neutralizing antibodies, such as those induced by human coronaviruses other than SARS CoV-2[5].

Lessler et al.[8] have proposed an alternative hypothesis to OAS that they call ''antigenic seniority'' to explain the lesser immune response following revaccination. This hypothesis establishes the existence of a dominant antibody response as a consequence of repeated exposures to the same antigens more so than the existence of an immune imprinting against the first viral antigen. However, it does not seem that in the case of human coronaviruses, repeated exposure determines this type of response[5,9].

Due to the constant genetic evolution of SARS-CoV-2—both natural and due to pressure from the human immune system—it is possible that in the near future, we may have to revaccinate the population against variants that become predominant[9]. In this context, it is to be expected that OAS would hinder achieving adequate protection, favoring the spread of the virus despite mass vaccination. Thus, the selection of a similar antigenic variant already recognized by a large part of the population for a new vaccine could lead to the following consequences:

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a) The induction of back-boosting, that is obtaining increased protective immunity in response to a second stimulation of the memory B cells as a consequence of the presence of common antigens or antigens shared between them.
b) Obtaining a non-protective immune response due to the induction of non-neutralizing antibodies in response to the new antigenic variant.
c) Use of a multiantigenic vaccine that could mask the protective immune response (antigen masking) against some viral components if any of them had previously been detected by the immune system[6].

To evaluate the efficacy of revaccination and the possible impact of OAS on SARS-CoV-2, a clinical trial has been started in individuals vaccinated with the mRNA-1273 vaccine. Two possibilities are going to be studied: in one, individuals will only receive one dose of the new vaccine adapted to the South African variant (mRNA-1273.351) and in the other, one dose of the combination of mRNA-1273 + mRNA-1273.351[10]. The results will provide information on the role of prior antigen imprinting on the quantity and quality of the immune response to the new genetic variant of SARS-CoV-2.

At this time, it is very difficult to forecast the possible impact of OAS on future revaccinations against SARS-CoV-2, but we must begin to analyze it and find a way to improve the antigen presentation of the new variants of this virus.

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Conflicts of interest

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