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Editorial article

# Immunology in COVID-19; more than diagnosis of infection or the basis of vaccination☆

## Inmunología en COVID-19; mucho más allá del diagnóstico de la infección o de la vacunación

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Over the last year and a half of the pandemic, the entire population has become familiar with: the importance of having a qPCR (direct detection gold standard technique) for the diagnosis of SARS-CoV-2 infection (severe acute respiratory syndrome coronavirus-2); antibodies; the concepts of immunisation.

Despite all this ïntensive training¸ many imprecise concepts remain (especially those associated with the immune response and immunisation).

These concepts have often been propagated by different specialists, and maybe we, the immunologists, have not been able to explain them properly (or we have not been listened to properly). This has led to the perpetuation of misconceptions, such as relying solely on the diagnosis of IgM or IgG detection in SARS-CoV-2, talking about protection based only on antibodies, and the vaccination of those who are already immunised. In this commentary we want to focus on analysing the most basic concepts that have been used extensively, and not always accurately, throughout this pandemic.

The serological tests provide information about humoral immunity, but they are not a specific marker of infection. A positive IgM result for SARS-CoV-2 does not always equate to an acute or recent infection, as this positive IgM may persist for months in the absence of detectable viral load. As with other infections, the serological tests are very useful for the screening, but should only be used for diagnosis when there is no option of accessing the direct detection technique, such as qPCR.[1] The presence of IgG does not indicate that the infection has passed, but it does indicate that the immune response has continued its course.

Another concept to clarify is the role of innate immunity. In the SARS-CoV-2 infection, the innate immune response is the first line of defense, and it is essential for both viral containment as well as the development of hyperinflammation conditions associated with the most severe symptoms. Its molecules include cytokines, of which the type-1 interferons (IFN) for example (IFN-⟨, IFN-® and others such as the IFN-⟧) are the paradigm and, in the group of cellular components, it is the NK cells that can eliminate the virus-infected cells.[2] In general, the type-1 IFNs occur in the infected cells themselves, and they are a mechanism of intrinsic immunity in almost every cell in the body. There are several type-1 IFNs, but in the SARS-CoV-2 infection, the IFN-⟨ and the IFN-⟧ seem to play a central role[3] in infection control: a few intrinsic defects and autoantibody blockages have been linked to some of the more serious cases.

Associated with innate immunity is the concept of trained immunity, by which the innate system can improve with ẗrainingf̈rom previous contacts. Epigenetics is one of the most clearly implicated mechanisms and, in the case of SARS-CoV-2 infection, it may be responsible for some of the good responses to the infection and the asymptomatic or quasi-asymptomatic conditions which, it is worth remembering, are (fortunately) the most common conditions for the majority of healthy individuals.

SARS-CoV-2 is a virus and, as such, an intracytoplasmic pathogen, and in most of the responses to intracellular pathogens, it is the cytotoxicity (death of the infected cell) that will achieve its elimination. Together with the NK cells, the specific cytotoxic response of the adaptive immunity has cytotoxic T cells as the main effector element for eliminating the virus. The T cells response also coordinates the humoral response, as it enables the B cells to develop and enhance specific antibodies against the viral surface proteins. It is true that these antibodies can block the interaction with the cell receptor, preventing the entry of new infectious cells (this function is performed by what is called 'neutralizing antibodies') and preventing viral spread[4] but they do not eliminate the infection. They block the spread and eliminate viruses in the extracellular spaces (especially IgA in secretions); however, it is the T cells that are able to eliminate an established infection.

Fortunately, for the control of this pandemic, in almost all patients, memory generation induces protection against a second infection. This fact, which has been evidenced in both immunisation generated by natural infection and vaccine-induced immunisation, is inherent in the immune memory of the adaptive or specific immune response and is the basis for lasting protection. Together

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with the antibodies there is the involvement of the memory B cells and, in a lesser known but essential way, the memory CD4+ or CD8 + T cells.[5] The reality is that there is no immune memory without T cells, and although it is not common, there may be immune memory without antibodies or B cells. In fact, antibodies are not detected in all infected patients, especially in less severe forms of the disease[6] or, of course, in some people with genetically based humoral immunodeficiencies that also resolve the infection. In contrast, the CD4+ and CD8 + T cell response is detected in almost all patients recovering from COVID-19.

The T cell response may be the first sign of an immune response to SARS-CoV-2, which appears before the antibody response.[6,7] While adaptive cellular immunity is critical for resolving the infection, it also plays a relevant role in the development of severe disease, with the characteristic hyperinflammatory phase.

Post-vaccination immunisation develops protection by an equivalent mechanism, in which the T cell response is and should be critical. However, the focus regularly (including leading scientific articles) continues to be centered on the evaluation of SARS-CoV-2 protection solely by the antibodies, when we know that it is the T cells that actually eliminate the virus and protect us against possible reinfections. This is understandable given the greater simplicity of the evaluation of the antibodies and their direct relationship with the T cell response, but it is evident that it is a surrogate marker for the real protective response.

One of the few published studies that has evaluated the vaccine response by determining not only humoral but also cellular immunity in kidney transplants is the paper by Cucchiari et al. This study included 41 patients who, after immunisation with the mRNA vaccine-1273 (developed by Moderna & NIH), did not have an antibody response, but did have specific cellular immunity to SARS-CoV-2 and should therefore be considered immunised, that is with vaccine response.[8,9]

Another topic that has generated debate is vaccination in those who have been infected with SARS-CoV-2. What does vaccination bring to this group? Will they have a better immune response in case of reinfection? Will someone who has been infected and not vaccinated be better protected than someone who has been infected and subsequently vaccinated? One of the arguments for vaccinating those who have already passed COVID-19 was not knowing how long the ñaturalp̈ost-infection immunisation could last. But what we know up to now, from data about other similar infections (SARS-CoV-1 and MERS) and, above all, from the recent demonstration of long-lived plasma cells[10] together with the already defined memory T cells, is that the protective capacity can develop over decades, which for some people means that they may have lifelong protection. Although it cannot be confirmed until the corresponding time has elapsed, this is the most plausible hypothesis, although surprisingly the opposite hypothesis is often defended.

In relation to the immune memory, a notable aspect is the concept of hybrid immunity. This refers to the combination of natural immunity against SARS-CoV-2 together with the vaccine-generated immunity, in which the memory B cells and the CD4 + T cells generate an increased antibody response and wider crossover protection against viral variants.[11]

However, vaccination of infected people or revaccination seems more like a proposal based on understandable socio-political caution in the face of problems from new pandemic waves, as well as economic interests related to these vaccines, rather than a clear health need based on specific scientific data. As mentioned previously, the detection or not of circulating IgG antibodies should not be the real argument for this action. Controlled studies that go beyond the antibodies may or may not demonstrate the real convenience of revaccinations.

The concept of post-immunisation protection should be considered as the dichotomy of whether to ḧave itör n̈ot have it. Although quantifiable aspects exist (antibodies or cell numbers), the adaptive protection will depend on whether the individual has a cellular memory response to SARS-CoV-2 and will be protected against reinfection.[12,13]

The authorised vaccines have proved to be up to 95% effective in preventing the laboratory-confirmed infection for a few months after vaccination[14,15]. This level of protection is not significantly different from the 89–95% protection that has been estimated after a natural infection.[16,17] This protection does not mean that the individual in contact with infected people cannot show the re-entry of the virus in the form of qPCR: but rather the protection indicates that a poor evolution of the disease will not develop.

Associated with natural or post-vaccination immunisation is the level of reduction in transmissibility. In recent months it has been proven that although it is not a total reduction, it is an obvious one. The reduced capacity of local immunity production (evidenced by IgA antibodies) of the systemic vaccines compared to natural immunisation may be related to a better capacity to reduce transmissibility among those who have had this n̈atural immunisation, although the data have not been confirmed so far. This reduced transmissibility provides evidence in favour of vaccines that act on the mucous membranes, to be approved in the not-too-distant future.[18] They could provide a clear reduction in transmissibility, which is necessary for the definitive control of the pandemic.

Regarding the protection of immunity against new variants, it should be noted that these variants are related to the area of interaction of the cell receptors, and they do not nullify the protection that the T cells may develop against other more conserved areas. B cells have a process called T cell-dependent somatic hypermutation, which is the capacity to acquire new specificities so as to adapt more quickly to the new variant,[19] although initially there are no preformed antibodies. In this regard, the impact of SARS-CoV-2 variants on CD4+ and CD8 + T cell reactivity in convalescent COVID-19 donors and in mRNA vaccine receptors has been evaluated, and it has shown an insignificant impact of the variants in the global responses of CD4+ and CD8 + T cells.[20]

A current issue under discussion is whether to vaccinate a third dose or the complete regimen, to at-risk groups, such as immunocompromised patients including those transplanted and elderly people who have not developed cellular immunity and therefore have no humoral immunity either. This is an important aspect to consider, as these risk groups that have not developed immunisation, not only have a higher risk of serious infection, but could also have a longer viral replication, which would facilitate the emergence of new viral mutations. In those at-risk groups whose underlying condition cannot be changed (underlying disease, treatment, or age), adding a third dose in a "heterologous" way (that is, with a vaccine other than the one used primarily) could be the best suited, as it would allow for additional options in a situation of failure and limit antivector immunogenicity where appropriate.[21]

Current evidence does not show the need for generalised use of booster vaccinations in populations that have received an effective primary vaccination regimen. Although the benefits of primary vaccination against SARS-CoV-2 clearly outweigh the risks, we could potentiate the onset of autoimmune phenomena (such as myocarditis, Guillain-Barré syndrome) or alloimmune phenomena (in transplant patients), if new doses are given beyond the primary vaccination without clearly establishing the necessary length of time between doses and without a thorough prior scientific and epidemiological assessment of a possible benefit.[22]

Finally, since this is a pandemic and, as its name suggests, it is not a problem inherent in just one continent or state, we should focus today on achieving so-called ḧerd immunity, quantified at levels of 80–95% of the population, which would convert the infection's

capacity of transmissibility into being irrelevant. Before revaccinating those who are already immunised (by studying the persistence of specific cells, rather than erroneously focusing on determining antibody levels), it is more important to reach this population coverage worldwide to reduce the likelihood of new variants that may leave us without the protection of immunisation. No one can and should not forget the very low distribution of this immunisation in developing countries, especially on the African continent, and the risk of restarting another pandemic.

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