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Mini Review

Is the Innate Immune Response Involved in the Transient Protection Provided by Spike-Based COVID-19 Vaccines?

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Introduction

Recently, some regional and/or national governments have suggested the need of three-monthly application of COVID-19 vaccines to keep optimal protection. This suggestion is given mainly by the now clear waning immunity that has been observed with SARS CoV-2 Spike-based vaccines, believed to be responsible for outbreaks in countries with >70% vaccinated population and supported by several studies from different countries [1].

Beyond the evident safety questions that multi-application rise considering the side effects already reported [2], and the mid- and long-term adverse effects that are still under investigation in clinical trials [3], it is quite intriguing that such schedule of application is required when Spike-specific cellular and humoral responses elicited by vaccination have been reported to last up to at least 12 months [4]. In this work by *Bertoletti et al.,* it is shown that the neutralizing antibody response reaches a plateau 30 days after the second BNT162b2 dose, whereas Spike-specific T cells, that are smaller than those induced in infected individuals with severe disease, peak 5 days after the second dose and decay almost to pre-second dose basal levels in less than 40 days. In clear contrast, the transient protection provided by this vaccine has a constant negative slope initiating 10 days after the second dose and reaching <40% performance in less than 200 days [1]. Thus, the transient protection provided by this vaccine seems not to follow neither neutralizing antibody nor Spike-specific T cell dynamics, because the former reaches the plateau when protection starts to fall constantly, whereas the latter falls near basal levels >60 days before transient protection reaches <40% performance. Moreover, it is intriguing that despite Spike-based vaccines are expected to elicit similar immune responses to Spike protein, and therefore to SARS CoV-2, the dynamics of transient protection provided by different vaccines is very different, with behaviors apparently separated by vaccine type [RNA or adenoviral vector] [1]. These findings raise the question of whether this transient vaccine-provided protection could be associated with other mechanisms beyond B and T cell responses to Spike protein, since SARS CoV-2 Spike structure-function features may limit their efficacy.

It is well known that SARS CoV-2 Spike protein has a furin cleavage site, that is not present in 2003 SARS CoV, which is presumably relevant for human transmission and disease outcome. This cleavage site mediates >80% Spike cleavage in an in vitro model [5]. Furin is an extracellular protease but also an intracellular active one that may be localized at the Endoplasmic Reticulum-Golgi Intermediate Compartment [ERGIC], where most viral particles are assembled. Thus, Spike protein can be processed by furin prior to viral exit from the cell. This in turn could pre-activate or sensitize Spike fusion micromachine, modify its conformation during viral cell exit pathway and/or modify viral tropism [5]. Moreover, it has been shown that Spike S1 domain is shed after furin cleavage [6], a proteolytic molecular mechanism that is common for plasma membrane molecules [7]. These structure-function considerations raise the possibility that furin cleavage acts as a bypass for the activation of the membrane fusion mechanism and/or that it may help the virus to evade the immune response as it has been suggested [6]. Thus, it is possible that Spike neutralizing antibodies have a limited benefit to block SARS CoV-2 infection. On the other hand, specific T cells generated by full-length, proline-modified Spike could also be limited by its intracellular shedding either at

proteolytic processing and/or its presentation in HLA. In addition, the delay, property of T cell recognition of infected cells and the downregulation of interferon response by SARS CoV-2 in infected cells could also constrain the efficacy of their protection, as it has been demonstrated [8].

With this panorama, the question that emerges is what other mechanisms could be behind the transient protective effect of COVID-19 Spike-based vaccines? One possibility is that beyond the immune response against a xenoprotein such as Spike, vaccine components or viral vectors elicit transient immune responses that protects individuals against infection. It is already known that mRNA carrier Lipid Nanoparticles [LNP] are highly inflammatory [9], they have long been known to induce autophagy [10], and that other vaccine components are well-known immunogens. Indeed, the innate immune response has been shown to control SARS CoV-2 infection through the Mannose-Binding Lectin [MBL] pathway [11], and the innate immune response is activated by LNP [9]. The involvement of the innate immune response could be the reason why these vaccine strategies have not and will not allow to reach herd immunity as expected, even with vaccination levels >70%, despite they provide a transient protection, that decays with a constant negative slope. In this contexture, it turns out that the appropriate and required comparative control to test vaccine efficacy is not the unvaccinated group nor a saline placebo group or treatment without a xenoprotein, as it has been done by the manufacturer of BNT162b2 vaccine [12]. Rather, the control group requires a scrambled RNA, or other well-known control xenoprotein, with ~1300 amino acids inoculated with the same vaccine components, to rule out that a transient, unspecific response mediates the protective role.

If this could be the case, then the efforts to fight this pandemic with these vaccines should be reconsidered, as suggested by experts of the WHO, who declared them unlikely to be appropriate or sustainable, and requiring different characteristics [13]. Chiefly, if a chronic unspecific inflammatory state by three-monthly vaccination is required to achieve the so-called optimal protection by these vaccines, that could increase the risk to develop other diseases. Finally, in this scenario, no mandatory vaccines should be approved until this possibility is clearly ruled out.

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Conflict of Interest

None.

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