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LETTER TO THE EDITOR

Immune response against viral infections and nucleic acid-based vaccines

To the editor,

We read with interest the letter by Polykretis,[1] which summarized some basic immunological principles in relation to COVID-19 vaccines. However, the terminologies the author uses to describe the types of vaccines and targets of immune response are in our view misinforming and have basic errors.

The author uses the term 'traditional vaccine' in a confusing way by stating that the traditional vaccines do not induce human cells to produce viral proteins. Traditional vaccines include both live and non-live vaccines,[2] and subcutaneous inoculation of smallpox (variola) virus was the oldest known procedure for the prevention of more severe disease for centuries. Variolation was replaced by the inoculation of cowpox (vaccinia) virus as a safer method, which later led to use of 'vaccination' as a general term for the immunization procedure aiming different diseases. These methods used viruses collected from patients or animals, which resulted in development of an 'attenuated' and usually localized form of the disease by intracellular production of viral proteins to induce an immune response; therefore, both methods were more traditional than the inactivated and toxoid vaccines.[3,4]

We also consider the term 'genetic vaccine', used by the author for nucleic acid-based mRNA and DNA vaccines and viral vector-based vaccines, misleading. The efficiency of all live (original or attenuated) viral vaccines requires that their DNA or mRNA sequences are translated in the infected human cells by the target cell's protein synthesis machinery. They thus induce an immune response in the same way as viral infections themselves. If using a microbial genetic code for inducing protein synthesis in our cells will be enough to name these vaccines as 'genetic vaccines', we may need to re-classify all viral infections as 'genetic diseases' due to their shared mechanisms of inducing an immune response.

When it comes to the discussion on different immune response to vaccination, Polykretis nicely outlines the different pathways that come into play. However, we object to the definition of the immune response to the COVID-19 spike protein following mRNA vaccination as an 'autoimmune reaction'. Autoimmunity, by definition, would refer to a reactivity against a self-antigen, primarily due to problems with the self-tolerance mechanisms. An immune response specifically directed against a viral protein cannot be termed an 'autoimmune reaction'; or the mere definition of self and non-self would have to be redefined. Of course, immunity to self can translate into autoimmunity, such as the induction of cross-reactive antibodies due to molecular mimicry, or exacerbation of an existing autoimmune condition as a result of strong type 1 interferon response, following viral infections or vaccinations, but target antigens for organ damage in those cases are still self, and these immune responses are different from the immune responses against cells expressing viral antigens.

mRNA vaccines use the genetic code of one or more of the viral proteins, which are involved in the disease pathogenesis and recognized as the main target to develop a protective immune response. Nucleic acid-based vaccines mimic the viral infection itself, but since these vaccines cannot replicate, the induction of viral protein synthesis by their nucleic acid sequence is limited in terms of duration and involved tissues. Regulatory guidelines are not yet established for the novel mRNA vaccine platforms, and neither EMA, nor FDA consider them as 'gene therapy medicinal products' or 'gene therapy products', respectively. Because of the previously performed studies conducted with the identical components of the delivery systems, no specific biodistribution studies were requested by the authorities.[5] Limited number of studies with the lipid nanoparticles of the mRNA COVID-19 vaccines, accessed through the European Medicines Agency (www.ema.europa.eu) documents (EMA/707383/2020 Corr.1 and EMA/15689/2021 Corr.1), reveal that there was no unexpected biodistribution. In addition to the administration site and draining lymph nodes, lipid nanoparticle's biodistribution in rodents mainly targets liver, but nanoparticles could be detected in all tissues at very low levels compared with the plasma. It should be kept in mind that the dose of vaccine used in rodents for the toxicology studies is 300–1000 times higher than the human dose,

and the innate immune response induced by the vaccine differs in rodents compared with the vaccine response in humans.[6] In humans, mRNA vaccines activate an IL-1-driven immune response, and it is amplified by the lipids in the delivery systems.[6] However, these vaccines induce higher amounts of anti-inflammatory IL-1Ra compared with IL-1 in mouse leukocytes and reduce toll-like receptor signalling, which result in no strong inflammatory response despite 1000-fold higher doses, and this difference affects the distribution and clearance of vaccine content.[6]

Currently, the biodistributions of the different mRNA vaccines are not well characterized in humans; however, the extent and amount of its distribution cannot be compared with the viral disease itself. Therefore, the adverse effect profile associated with mRNA vaccines was quite similar to the profile associated with COVID-19, but occurring at very low frequencies.[7,8] There are no data suggesting that these adverse events are associated with the direct cytopathic effects of the immune response due to vaccine-associated expression of viral proteins. Overall COVID-19 vaccines are accepted as safe, and most of the adverse effects associated with COVID-19 vaccines are mild and self-limiting.[8,9] Despite the relative enrichment of some adverse effects in mRNA and vector-based vaccines compared with the inactivated vaccines, all important adverse events including myocarditis, pericarditis, cardiac arrhythmias, thrombocytopenia and thromboembolism were found to be at much greater frequencies following SARS-CoV-2 infection compared with the frequencies observed following COVID-19 vaccinations.[9]

Several different mechanisms contribute to the development of disease manifestations, and hyperinflammatory response is responsible for most pathological events leading to the worse outcomes. Recent studies documented the role of infection of alveolar macrophages and monocytes with the uptake of antibody-opsonized SARS-CoV-2 virus by Fcγ-receptors, which results in pyroptosis and systemic inflammation.[10] Antibodies against viral antigens contribute to the induction macrophage infection, and it has been shown that antibodies leading to hyperinflammatory response target mainly the nucleocapsid protein. On the contrary, mRNA COVID-19 vaccines induce the production of antibodies against only the spike protein, and anti-spike antibodies did not promote antibody-mediated enhancement by the infection of monocytes and macrophages. Hence, this feature of the vaccines provides a better safety profile compared to the immune response observed in course of the disease by producing beneficial neutralizing antibodies, which reduce the infection risk and prevent the development of worse clinical outcomes without causing a hyperinflammatory response.[10]

The mRNA-based vaccine technologies are rapidly evolving, and better pharmacokinetic and biodistribution studies will be helpful for the development of much safer and effective vaccines. On the contrary, with their conditional approval and widespread use, these vaccines helped saving millions of lives.[10] In the future, the efficacy and safety of these novel vaccines should be continuously assessed by weighing the risks related to the vaccines and the risks associated with the disease causing an outbreak.

CONFLICT OF INTEREST

Both authors declare that neither they nor their family members or spouses have a conflict of interest relevant to the content of this letter.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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