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Letter to the Editor

Do COVID-19 RNA-based vaccines put at risk of immune-mediated diseases? In reply to "potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases"

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To the Editor,

I read with great interest the article by Vojdani et al. [1], concerning the hypothesis of a molecular mimicry mechanism between the nucleoprotein/spike protein of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and self-antigens. Viruses are notoriously involved in the pathogenesis of autoimmune diseases [2], and the authors reasonably conclude that such a cross-reactivity might lead to the development of immune-mediated disorders in COronaVirus Disease-19 (COVID-19) patients in the long term. The authors also suggest that a similar scenario might take place following COVID-19 vaccination.

Vaccine-associated autoimmunity is a well-known phenomenon attributed to either the cross-reactivity between antigens or the effect of adjuvant [3]. When coming to COVID-19 vaccine, this matter is further complicated by the nucleic acid formulation and the accelerated development process imposed by the emergency pandemic situation [4]. Currently, lipid nanoparticle-formulated mRNA vaccines coding for the SARS-CoV-2 full-length spike protein have shown the highest level of evidence according to the efficacy and safety profile in clinical trials, being therefore authorized and recommended for use in the United States and Europe. Although the results from phase I and II/III studies have not raised serious safety concerns [5], the time of observation was extremely short and the target population not defined. Reported local and systemic adverse events seemed to be dose-dependent and more common in participants aged under 55 years. These results presumably depend on the higher reactogenicity occurring in younger people that may confer greater protection towards viral antigens but also predispose to a higher burden of immunological side effects.

The reactogenicity of COVID-19 mRNA vaccine in individuals suffering from immune-mediated diseases and having therefore a pre-existent dysregulation of the immune response has not been investigated. It may be hypothesized that immunosuppressive agents prescribed to these patients mitigate or even prevent side effects related to vaccine immunogenicity.

Besides the mechanism of molecular mimicry, mRNA vaccines may give rise to a cascade of immunological events eventually leading to the aberrant activation of the innate and acquired immune system.

RNA vaccines have been principally designed for cancer and infectious diseases. This innovative therapeutic approach is based on the synthesis of RNA chains coding for desired antigenic proteins and exploits the intrinsic immunogenicity of nucleic acids. In order to avoid degradation by RNases, RNA can be encapsulated in nanoparticles or liposomes, which deliver the cargo inside target cells following a process of endocytosis. mRNA is then translated into immunogenic proteins by cell ribosomal machinery [6].

However, prior to the translation, mRNA may bind pattern recognition receptors (PRRs) in endosomes or cytosol. Toll-like receptor (TLR) 3, TLR7 and TLR8 are able to recognize chains of double-stranded (ds) RNA or single-stranded (ss)RNA in endosomes, while retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) may detect short and long filaments of dsRNA in the cytosol. The final result is the activation of several pro-inflammatory cascades, including the assembly of inflammasome platforms, the type I interferon (IFN) response and the nuclear translocation of the transcription factor nuclear factor (NF)-kB [7].

Importantly, the up-regulation of these immunological pathways is widely considered to be at the basis of several immune-mediated diseases, especially in genetically predisposed subjects who have an impaired clearance of nucleic acids [8]. This could particularly hold true in young female individuals, due to the over-expression of X-linked genes presiding over the antiviral response and the stimulatory effect played by estrogens on the immune system. The X chromosome hosts several genes involved in the immune response, including *TLR7* and *TLR8* genes, and about 10% of microRNAs indirectly controlling the activation of the immune system [9].

Therefore, young and female patients who are already affected or predisposed (*e.g.* immunological and serological abnormalities in absence of clinical symptoms, familiarity for immune-mediated

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diseases) to autoimmune or autoinflammatory disorders should be carefully evaluated for the benefits and risks of COVID-19 mRNA vaccination. According to epidemiological data, these subjects may develop the infection asymptomatically or pauci-symptomatically and it is worth noting that, in line with the article of Vojdani et al. [1], the presence of autoreactive cells and autoantibodies cross-reacting against SARS-CoV-2 epitopes may even turn naturally protective towards the infection. Until proven otherwise, the administration of a nucleic acid vaccine may instead put these individuals at risk of unwanted immunological side effects by either sensitizing the PRRs or generating cross-reactive cell clones and antibodies. Moreover, COVID-19 mRNA vaccine might differently stimulate myeloid or plasmacytoid dendritic cells (DCs), generating an unbalance in the downstream cytokine pathways that play a crucial role in autoimmunity and autoinflammation [3].

Modifications in nucleoside and nanoparticle composition through a proper manufacturing may help to prevent some of these drawbacks. For instance, the substitution of uridine with pseudouridine was shown to reduce immunogenicity and type I IFN production while enhancing the synthesis of viral antigenic proteins [10]. A strong type I IFN response may, in fact, negatively affect the vaccine efficacy by suppressing the process of mRNA translation [10]. However, type I IFNs play a beneficial role in strengthening the antiviral response, as they favor the maturation of DCs, the CD8+ T cell-mediated cytotoxicity and the secretion of several cytokines, like interleukin (IL)-12 and IL-23 [11]. Notably, polymorphisms in the genes encoding these cytokines or their receptors have been associated with the susceptibility to autoimmune diseases [12]. Additionally, an excessive production of type I IFNs may result in the breakdown of the immunological tolerance and, therefore, in autoimmunity [10].

Lipid components may also dictate the type and intensity of the immune response, by enhancing the production of IFN-γ, IL-2 and tumor necrosis factor (TNF)-α with the subsequent activation of both CD4+ and CD8+ T lymphocytes. Although this is not the case of the authorized COVID-19 mRNA vaccines, future formulations containing adjuvant like TLR agonists [13] may exacerbate pre-existing autoimmune or autoinflammatory disorders and should therefore be discouraged in this cohort of patients.

Given the current state of the art, my view is that individuals with a dysfunctional immune response should receive the COVID-19 mRNA vaccine only if the benefits of this approach clearly outweigh any risks and after a careful evaluation case by case.

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Declaration of Competing Interest

The author has no competing interests to declare.

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