Review

Autoimmune Inflammatory Reactions Triggered by the COVID-19 Genetic Vaccines in Terminally Differentiated Tissues

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Abstract: As a result of the spread of SARS-CoV-2, a global pandemic was declared. Indiscriminate COVID-19 vaccination has been extended to include age groups and naturally immune people with minimal danger of suffering serious complications due to COVID-19. Solid immuno-histopathological evidence demonstrates that the COVID-19 genetic vaccines can display an off-target distribution in tissues that are terminally differentiated, triggering autoimmune reactions. These include the heart and brain, which may incur *in situ* production of spike protein eliciting a strong autoimmunological inflammatory response. Due to the fact that every human cell which synthesizes non-self antigens becomes inevitably the target of the immune system, and since the human body is not a strictly compartmentalized system, accurate pharmacokinetic and pharmacodynamic studies are needed in order to determine precisely which tissues can be harmed. Therefore, our article aims to draw the attention of the scientific and regulatory communities on the critical need of bio-distribution studies for the genetic vaccines against COVID-19, as well as of rational harm-benefit assessments by age group.

Keywords: COVID-19; genetic vaccines; adverse reactions; autoimmunity; immunohistochemistry; spike protein

1. Introduction

As a result of the spread of SARS-CoV-2, a global pandemic was declared by the WHO. The worldwide response to the outbreak was strong and monolithic, focused on mass and indiscriminate vaccination using novel genetic platforms. Invoking emergency regulatory pathways to expediate market introduction, and the inherent public trust in traditional vaccines (based on inactivated or attenuated viruses), facilitated the use of lowered regulatory standards of safety and efficacy and circumvention of critical pharmacodynamic, pharmacokinetic and genotoxicity tests typical for drugs and gene therapies. Thus, billions of people were vaccinated despite a paucity of data regarding bio-distribution or bio-persistence in humans, which only emerged from independent research or Freedom of Information disclosures after the administration of billions of doses. The speed at which the genetic vaccines were developed, manufactured and released was presented to the public as an achievement made possible by the scientific prowess of the pharmaceutical industry working in partnership with global governments for the greater

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good. However, in the words of the recently retired head of vaccine R&D at Pfizer, Dr. Kathrin Jansen: "*We flew the aeroplane while we were still building it*" (Kingwell, 2022). This "achievement" involved scientific imprudence that must be subject to increased scrutiny as mounting safety signals, negative vaccine efficacy and immune escape continue to accumulate.

2. Survey methodology

In this review we addressed the issue of the off-target distribution exhibited by the genetic vaccines against COVID-19, with a particular focus on the immunohistochemistry findings emerged from histopathological studies.

3. The immunization mechanism of the genetic vaccines

Many medical doctors and scientists currently recommending the COVID-19 genetic vaccines are ignoring fundamental immunological mechanisms and are underestimating the potential autoimmune consequences. Even Pfizer does not fully understand how their vaccine works as Senior Vice President for Vaccine Clinical R&D Dr. William Gruber stated at FDA's VRBPAC meeting of June 15th, 2022: "*we don't have a complete understanding of the nature of the way that the vaccine works in terms of producing immune response*" ("Web-Conference Silver Spring, Maryland 20993," 2022). The genetic vaccines against COVID-19 that were authorized for emergency use in the USA and in the European Union are the mRNA vaccines (produced by Pfizer/BioNTech and Moderna) and the adenoviral vector vaccines (produced by AstraZeneca and J&J/Janssen) (CDC, 2020; "Safe COVID-19 vaccines for Europeans | European Commission"). These vaccines contain genetic information that hijacks human host cell machinery to synthesize the spike protein of SARS-CoV-2 and present it on the surface of cells as the immunogen (Mascellino et al., 2021). Most likely, once translated by the ribosomes, the spike protein gets processed by the Golgi apparatus, and presented to the immune system in two ways: i) as the entire protein displayed on the cellular membrane, which can be recognized by B cells and T-helper cells; and/or ii) as protein fragments loaded on the major histocompatibility complex I (MHC I) (Mascellino et al., 2021; Polykretis, 2022).

All nucleated cells display the MHC I on their membranes, which present endogenous antigens, derived from the proteasomal degradation of intracellular proteins, to $CD8^+$ T lymphocytes (Rock, Reits & Neefjes, 2016; Kotsias, Cebrian & Alloatti, 2019). This mechanism enables the immune system to continuously monitor the proteosynthetic activity of all nucleated cells, in order to identify whether a cell is producing mutant, viral and/or non-self proteins, in general. The MHC II displays fragments of exogenous antigens that have been phagocytized throughout the body to $CD4^+$ T lymphocytes, and it is found on the membranes of professional antigen-presenting cells (APCs) (Rock, Reits & Neefjes, 2016; Kotsias, Cebrian & Alloatti, 2019). When the immune system recognizes a viral antigen as foreign, it triggers an inflammatory reaction which leads to the death of the antigen-presenting cell (Rock, Reits & Neefjes, 2016; Kotsias, Cebrian & Alloatti, 2019). Consequently, the genetic vaccines, by inducing human cells to synthesize a viral protein, intrinsically rely on an autoimmune reaction mediated by T-cells to elicit an immune response.

4. Bio-distribution beyond the injection site

Considering that every cell that synthesizes viral proteins is perceived as a threat by the immune system and killed, it becomes crucial to determine the exact bio-distribution of the genetic vaccines within the organism (Polykretis, 2022). Some authors pointed out the need for accurate pharmacokinetic and pharmacodynamic assessments (Doshi, 2021; Merchant, 2021; Cosentino & Marino, 2022; Polykretis, 2022; Blaylock, 2022). However, despite the fact that pharmacokinetic studies are a fundamental part of drug safety assessment, according to European Medicines Agency policy, they are generally not required for vaccines (Doshi, 2021). Thus, the classification of these platforms as traditional

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vaccines was used to justify such evaluations to be skipped. It is well known that even traditional vaccines can cause the immune system to target its own cells throughout the immunization process. However, there are some major differences between the genetic vaccines and the traditional vaccines for which the bio-distribution evaluation is not "generally required". As discussed by Polykretis and McCullough, the vaccines based on inactivated or killed viruses mainly involve presentation to APCs that phagocytose virus particles and present viral antigens to the immune system (Polykretis & McCullough, 2022). Such cells, which undergo a continuous turnover, perform this specific function within the organism, making them somewhat expendable. The vaccines based on attenuated viruses result in the infection of a small number of human cells in order to trigger an immune response.

A bio-distribution study performed by Pfizer on rats and submitted to drug regulatory agencies, first released by Japan's Pharmaceuticals and Medical Devices Agency (PMDA), showed that the lipid nanoparticles (LNPs) containing the mRNA accumulate beyond the injection site, mainly in the liver, the adrenal glands, the spleen, the ovaries and other tissues ("https://phmpt.org/wp-content/uploads/2022/03/125742_S1_M4_4223_185350.pdf"). There is additional evidence that genetic vaccines can persist in the blood; Fertig et al. discovered that vaccine-associated synthetic mRNA stays in the bloodstream for at least two weeks following injection with BNT162b2 (Fertig et al., 2022). Notably, blood samples from children and young adults who developed post-mRNA vaccination myocarditis revealed the presence of circulating free spike protein (Yonker et al., 2023). Exosomes with spike protein have been detected in blood on day 14 after vaccination and increased after the booster dose, lasting until four months (Bansal et al., 2021). Due to the principles of chemical kinetics and passive diffusion, the prolonged persistence of the genetic material encoding the spike protein in the systemic circulation could enable it to reach even distant tissues. In support of this, the vaccine mRNA was detected even in secretions, such as breast milk (Hanna et al., 2022). Furthermore, it is noteworthy that the vaccine mRNA can persist in the lymph nodes up to 8 weeks (Röltgen et al., 2022), instead of "few days" as stated initially by the CDC (Sanders, 2022).

5. A role for exosomes

One mechanism by which the mRNA and the spike protein could be distributed throughout the body is via extracellular vesicles, particularly exosomes. A study preceding the release of the mRNA vaccines found that human cells exposed to mRNA nanoparticles were able to release fully intact mRNA molecules into exosomes, and that these exosomes could be taken up by recipient cells that then synthesized fully functional protein from the mRNA code (Maugeri et al., 2019). Furthermore, an *in vitro* study demonstrated that human cells transfected with the mRNA nanoparticles coding for spike protein released the spike protein into exosomes that could then be taken up by microglia in the brain, triggering an inflammatory response (Mishra & Banerjea, 2021). In studies on biodistribution, very high concentrations among organs are found in the spleen. Immune cells in germinal centers in the spleen release exosomes as an essential step in antibody production (Fernández-Messina et al., 2020). Exosomes protect their mRNA cargo from degradation, and, furthermore, they not only travel freely via the vasculature and the lymphatic system, but they also navigate nerve fibers. From the spleen along the splanchnic and the vagus nerves, exosomes could reach the heart, the liver and the brain (Seneff et al., 2022).

Exosomal transport of genetic material also plays an important role in reproductive tissues such as the testes, where a phenomenon known as Sperm-Mediated Gene Transfer (SMGT) has been demonstrated. This is the process by which genetic material from somatic cells in males can be passed on to progeny in an inheritable mosaic fashion, at low copy number, without needing to be stably integrated into the genome (Pittoggi et al., 2006; Spadafora, 2008, 2017; Parrington, Coward & Gadea, 2011). Recently, SMGT was

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observed after gene therapies were injected directly into the brain of male mice prior to mating with about a third of embryos inheriting the transgene (O'Brien et al., 2020). The LNPs that deliver the genetic vaccines also act as exosomes, delivering the genetic code for the spike protein to the testes and ovaries. Thus, not only SMGT should be a concern, but the spike protein mediated immune gonadal attack could also compromise fertility.

6. Histopathological data

Strong histological evidence from biopsies and autopsies have demonstrated that the vaccine-derived spike protein was synthesized in terminally differentiated tissues (Baumeier et al., 2022; Schwab et al., 2022; Mörz, 2022). Baumeier et al. detected the vaccine-derived spike protein on the cardiomyocytes of 9 out of 15 patients with clinical suspicion of myocarditis (which were negatively tested for SARS-CoV-2), proving that the viral protein has been synthesized in the heart tissue and suggesting an autoimmune response due to vaccination (Baumeier et al., 2022). Schwab et al. describe the histopathological findings from standardized autopsies performed on 25 people who had passed away unexpectedly and within 20 days from vaccination (none of the deceased persons had SARS-CoV-2 infection prior to vaccination) (Schwab et al., 2022). Both the aforementioned studies support the idea that vaccine-induced myocardial inflammation was a consequence of excessive T-lymphocytic infiltration, predominantly $CD4^+$ T-cells, which are the main drivers of autoimmunological myocardial injury. Mörz described the expression of the vaccine-derived spike protein in the brain and the heart of a patient who developed multifocal necrotizing encephalitis upon vaccination with BNT162b2 (Mörz, 2022). Immunohistochemistry also revealed the expression of the vaccine-encoded spike protein in the vesicular keratinocytes and the endothelial cells in the dermis (Yamamoto et al., 2022).

7. Additional causes of inflammation

A series of neurological disorders, including chronic inflammatory demyelinating polyneuropathy (CIDP) and multiple sclerosis (MS), have been firmly diagnosed and attributed to mRNA based COVID-19 vaccination (Reinfeld et al., 2021; Finsterer, 2022; Toljan et al., 2022; Singh et al., 2022). Although routine clinical diagnostic measures cannot confirm the presence of vaccine-derived spike protein in these cases, the Long Interspersed Nuclear Element-1 (LINE-1) and the Human Endogenous Retroviral (HERV) mediated insertion mechanisms could be responsible for the translation of the spike protein within the affected neural tissues (Kyriakopoulos et al., 2022). Additionally, the mechanisms of p53 overexpression due to the spike protein toxicity in neurons has been recently revealed (Kyriakopoulos et al.). Dysregulated levels of p53 are strongly associated with the emergence of a dysregulated inflammatory response and development of autoimmunity (Fierabracci & Pellegrino, 2016).

The presence of free spike protein in the blood (Ogata et al., 2021; Cognetti & Miller, 2021; Boschi et al., 2022) constitutes an additional source of hazard since it may dysregulate the renin-angiotensin system via ACE2 binding (Bellavite, 2021; Angeli et al., 2022), and could cause endothelia-platelet interactions (Perico et al., 2022), harming the cardiovascular system.

8. Conclusions

Numerous studies report the onset of autoimmune reactions following COVID-19 vaccination (Gadi et al., 2021; Watad et al., 2021; Bril et al., 2021; Portuguese et al., 2021; Ghielmetti et al., 2021; Vuille-Lessard et al., 2021; Chamling et al., 2021; Clayton-Chubb et al., 2021; Minocha et al., 2021; Elrashdy et al., 2021; Garrido et al., 2021; Chen et al., 2022; Fatima et al., 2022; Mahroum et al., 2022; Finsterer, 2022; Garg & Paliwal, 2022; Kaulen et al., 2022; Kwon & Kim, 2022; Ruggeri, Giovanellla & Campennì, 2022). The histopathological data provide indisputable evidence that demonstrates that the genetic vaccines exhibit an off-target distribution, causing the synthesis of the spike protein and thus triggering autoimmune inflammatory reactions, even in tissues which are terminally differentiated

and subject to symptomatic damage (Baumeier et al., 2022; Mörz, 2022; Schwab et al., 2022). Despite the fact that the mechanisms of the antigen processing and presentation and the consequences for cells synthesizing viral proteins are largely known and have been characterized for decades (Kotsias, Cebrian & Alloatti, 2019), the genetic vaccines were rolled out in the absence of accurate bio-distribution and bio-persistence evaluations in humans, and the vast majority of the scientific community accepted that without concern. Indeed, page 20 of Pfizer's non-clinical overview submitted to FDA in 2021 stated: "*no RNA or protein metabolism or excretion studies will be conducted*" ("BNT162b2 Module 2.4. Nonclinical Overview"). Further, the question posed by VRBPAC member Dr. Jay Portnoy on June 15th, 2022 regarding the number of cells producing spike protein, and the amount and persistence of spike protein production after mRNA dosing was dismissed as "*academic*" by Pfizer representative Dr. William Gruber ("Web-Conference Silver Spring, Maryland 20993," 2022). A similar question asked by ACIP's Dr. Pablo Sanchez on June 23rd, 2022 was answered by the Moderna representative: "*The spike protein availability, I believe, is on the order of days, but like less than a week. But I will confirm that with our tox folks as well*" (*June 23, 2022 ACIP Meeting - Votes*, 2022). To our knowledge, this has not been made available.

Moreover, the guidance against performing autopsies, ostensibly to limit viral transmission, implemented by many countries worldwide during the pandemic, severely limited the ability to gather more clinical information regarding direct evidence of injuries in tissues which may have led to vaccine-related deaths (Salerno et al., 2020). The association of COVID-19 vaccination with the development of serious cardiovascular complications, especially amongst the younger and healthier age groups, has been widely recognized (Mansanguan et al., 2022; Yonker et al.; "Myocardial Inflammation/Myocarditis After COVID-19 mRNA Booster Vaccination. presentation at ESC Congress 2022"). In a growing number of studies, it has been determined upon autopsy that vaccine-induced conditions were the cause of death (Choi et al., 2021; Schwab et al., 2022). In general, the potential risks of genetic vaccines that induce human cells to become targets for autoimmune attack cannot be fully assessed, without knowing the exact distribution and kinetics of LNPs and mRNA, as well as the production and pharmacokinetics of the spike protein. Since the human body is not a strictly compartmentalized system, this is a matter of serious concern for every current or future genetic vaccine which induces human cells to synthesize non-self antigens. In fact, for terminally differentiated tissues, the loss of cells results in irreversible damage with a potentially fatal prognosis. In conclusion, in light of the undeniable evidence of off-target distribution, the administration of genetic vaccines against COVID-19 should be halted until accurate pharmacokinetic, pharmacodynamic and genotoxicity studies are performed, or they should only be delivered in circumstances when the benefits greatly outweigh the risks.

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