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Letter to Editor

PEGylated COVID-19 vaccines and cell-cell fusion

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We read with interest the recent paper Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis by Trougakos et al. published in Trends in Molecular Medicine on April 20, 2022, suggesting that the COVID-19 vaccines based on microRNA (mRNA) technology could trigger rare but potentially life-threatening adverse effects (AEs) by eliciting the expression of full-length spike (S) protein in human tissues and organs. This hypothesis is in line with our own observations and those of others, regarding the S antigen-mediated cell-cell fusion and potential pathology [1-3].

The SARS-CoV-2 virus is marked by the presence of a polybasic cleavage site at the S1/S2 junction capable of forming syncytia by fusing host cells into multinucleated structures. For example, minute amounts of S2 antigen can activate the human fusion machinery, engendering large hybrid cells that are not reversed by the COVID-19 vaccines [4]. This may explain the reports of rare syncytia-based AEs, including giant cell myocarditis, documented in some Pfizer-BioNTech and Moderna -1273 recipients [4,5]. Moreover, the S2 protein of SARS-CoV-2 virus can activate human endogenous retroviruses (HERVs), especially type W, that encodes for the physiological placental fusogen syncytin-1, a superantigen, associated not only with cell-cell fusion but also with the "cytokine storm", hyperinflammatory-type responses [6](Figure 1).

Exploitation of arginine (Arg), a physiological muscle fusogen, is another SARS-CoV-2-mediated mechanism of syncytia formation by hijacking human furin to activate the fusion machinery. For example, the triple-Arg insert at the S2 furin cleavage site (FCS), reminiscent of other syncytia forming pathogens, including HIV and anthrax, suggest that Arg is commonly utilized by viruses to induce cell-cell fusion. In a recent paper, we discussed HERV activation and Arg exploitation as possible causes of neurodegenerative disorders, a model in line with Trougakos et al. spike hypothesis [1](Figure 1).

Cell-cell fusion is a physiological or pathological process in which one or more adjacent cells merge their plasma membranes, cytoplasm, nuclei, and intracellular organelles to form multinucleated hybrid structures that often exhibit novel and emerging properties. Under normal circumstances, cell-cell fusion occurs during fertilization, placentation, and myoblasts/osteoclasts formation, as well as in the central nervous system (CNS) where astrocytes engender neuron-supporting syncytia. Several viruses, including SARS-CoV-2, have developed the ability to exploit human physiological fusogens and generate an optimal milieu for replication and immune evasion. Indeed, as cell-cell fusion requires externalization of phosphatidylserine (ePS) and activates the cellular senescence program, an iron-rich, apoptosis-resistant phenotype, viruses likely thrive by hijacking host fusogens [7].

Aside from eliciting the expression of S protein, mRNA vaccines may engender syncytia through their adjuvant, polyethylene glycol (PEG), an established chemical fusogen [8](Figure 1). As PEG has never been a component of an approved vaccine, its exact interaction with syncytia-forming viruses is unexplored at the present time [9]. In addition to its fusogenic properties, PEG transiently increases the permeability of blood brain barrier (BBB), and PEGylated nanoparticles are routinely used as vehicles for CNS drug delivery, suggesting that mRNA vaccines can access human brain [10]. These PEG properties may explain the rare neuropsychiatric AEs of mRNA vaccines that are unrelated to PEG anaphylactic complications [11]. Aside from merging cells, PEG was reported to reconnect severed axons as well as fuse herpes simplex virus type 1 (HSV-1) with host cell membranes, highlighting potential

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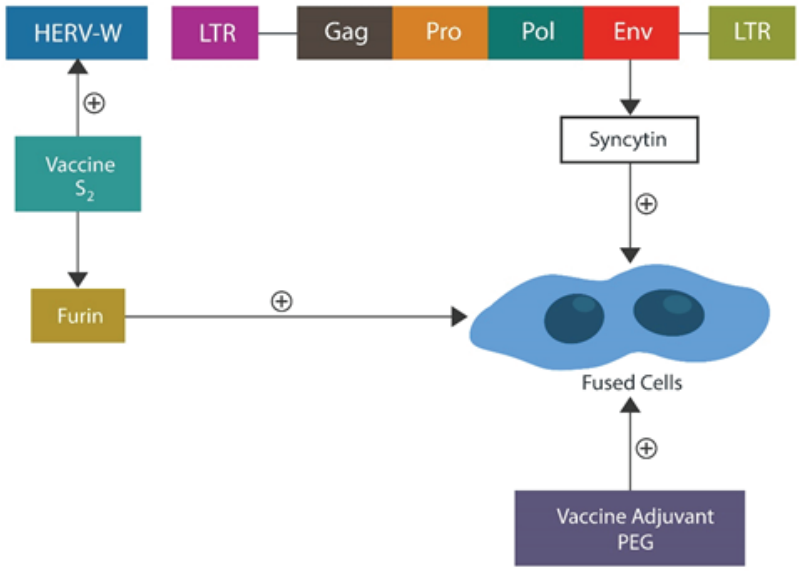

Figure 1. *COVID-19 mRNA vaccines promote the expression of viral S protein (S1 and S2) on host cells. Upon being processed by the human furin, S2 activates the HERV-W, ancestral retroviruses embedded in human DNA. HERV-W is comprised of one or two long terminal repeats (LTRs), gag, pol and env genes. The env gene encodes for syncytin-1, a physiological placental fusogen, that under pathological circumstances can aberrantly fuse cells, generating the rare vaccine adverse events (AEs), such as giant cell myocarditis. Furin is activated by the double arginine (Arg) insert at S2, the proline-arginine-arginine-alanine motif. Arg, a physiological muscle fusogen that merges myoblasts, may be usurped by the vaccine or viral S2, contributing to pathological syncytia. The vaccine adjuvant PEG, used for stabilization and delivery purposes, is an established chemical fusogen that increases BBB permeability, facilitating the formation of pathological brain syncytia.*

avenues of CNS pathology, especially in combination with the highly fusogenic S protein. For example, dysfunctional PEG may trigger neuropathology by aberrantly fusing neurons and/or axons, short-circuiting the CNS networks as demonstrated in humans with varicella-zoster (shingles) or animals with pseudorabies infection [12].

Taken together, COVID-19 mRNA vaccines induce the expression of viral S protein in host cells, possibly promoting cell-cell fusion, as indicated in rare AEs. The PEG adjuvant in mRNA vaccines, an established chemical fusogen, was never a component of approved vaccines previously therefore, its exact interaction with viral fusogens is currently unknown. Thus, more studies are needed to evaluate the spectrum of rare interactions at the molecular level, and whether PEG is the ideal vaccine component.

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