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Cell fusion as a link between the SARS-CoV-2 spike protein, COVID-19 complications, and vaccine side effects

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Abstract

A distinctive feature of the SARS-CoV-2 spike protein is its ability to efficiently fuse cells, thus producing syncytia found in COVID-19 patients. This commentary proposes how this ability enables spike to cause COVID-19 complications as well as side effects of COVID-19 vaccines, and suggests how these effects can be prevented.

Keywords: cell fusion, syncytia, cell hybrids, viruses, coronaviruses, SARS-CoV-2, COVID-19, fusogens, blood coagulation cascade, thrombosis, cancer, vaccines, neurological complications.

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A hallmark of severe COVID-19 is the abundance of syncytia, the products of fusion between two or more cells in the lungs of patients.[1–3] These syncytia have been attributed to the ability of spike, a protein encoded by SARS-CoV-2, to fuse cells to each other, and prompted a search for drugs that could prevent this cell fusion. Recently, Braga and colleagues[3] identified a set of already approved drugs that prevent spike-induced cell fusion and inhibit TMEM16F, a protein that has two activities.[4] One, a calcium-activated ion channel, regulates chloride secretion, while the other, a lipid scramblase, relocates phosphatidylserine (PS) to the cell surface in a process known as PS externalization.

PS externalization is required for cell fusion in many systems,[5,6] which explains why inhibiting a scramblase prevents the formation of spike-induced syncytia. However, Braga and colleagues have concluded that although PS externalization "is required for plasma membrane fusion, chloride secretion might have relevance in COVID-19 pathogenesis".[3] This assumption, that the scramblase activity merely helped to identify the ion channel as a potential therapeutic target, reflects a common opinion that syncytia produced in the body by infectious viruses are inconsequential.

To evaluate this assumption let us consider how cell fusion and syncytia it produces might be involved in COVID-19.

Terminology and abbreviations

Cell fusion: a process of merging two or more cells into one by merging their plasma membranes.

Fusogen: an agent, often a protein such as SARS-CoV-2 spike, capable of fusing cellular membranes. Viral fusogens fuse the viral envelope to the plasma membrane of the target cell and can fuse plasma membranes of adjacent cells to each other.

Syncytium (plural **syncytia**): a multinucleated cell produced by the fusion of two or more cells. The term comes from Greek *syn* "together" and *kytos* "box, or cell".

Heterokaryon: a syncytium produced from more than one cell type, say, a pneumocyte fused to an epithelial progenitor or a leukocyte.

Homokaryon: a syncytium produced from cells of the same type, as would be the case with the fusion of two or more pneumocytes.

Cell hybrid: Mononuclear offspring of syncytia, produced once a syncytium undergoes mitosis. For example, hybridomas are made by fusing leukocytes with plasmacytoma cells to obtain hybrids that produce monoclonal antibodies.

PS (phosphatidylserine): the most abundant anionic (negatively charged) membrane lipid. In live cells, PS is actively moved to the cytoplasmic side of plasma membrane.

Scramblases: Proteins, such as TMEM16F, that randomize, or scramble, the asymmetric distribution of PS across the membrane, a process known as **PS externalization**.

Cell fusion as a trigger of the blood coagulation cascade

Discovering syncytia in COVID-19 patients led to a suggestion that "the fusogenic properties of the MERS-CoV- and SARS-CoV-2-infected cells might be linked to the pathogenesis of thrombosis,"[2] a major complication of COVID-19.[7,8]

What could this link be?

I would like to suggest two candidates: the scramblase activity associated with spike-induced cell fusion,[3] and cell death.

Several observations suggest that the scramblase activity induced by spike[3] may be able to cause thrombosis.

First, PS externalization resulting from scramblase activity not only enables cell fusion but also controls the rate limiting steps of the blood coagulation cascade [9–11] (Fig. 1).

Second, a deficiency of TMEM16F, the scramblase identified by Braga and colleagues, is responsible for Scott syndrome, a bleeding disorder,[12] suggesting that this scramblase is involved in blood clotting.

Third, viral infections cause thrombosis primarily by triggering the assembly of what is called the fuse that triggers blood coagulation cascade.[13,14] This fuse, also known as extrinsic tenase, is formed by Tissue Factor (TF) and Factor VIIa on the outer surface of the cellular membrane enriched externalized PS[11] (Fig. 1). The combination of PS, TF, and calcium ions can increase Factor VIIa activity by a remarkable five to eight orders of magnitude.[15,16]

Fourth, TF and its regulation have been considered potential targets for COVID-19 therapy.[17,18] TF is regulated by controlling its expression, by tissue factor pathway inhibitor (TFPI), and by priming TF through a process known as de-encryption. The primary candidate for the de-encrypter is ex-

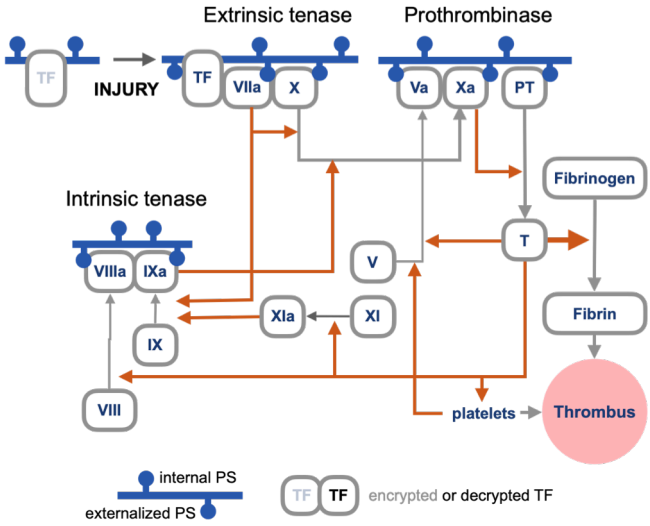

Figure 1. An outline of the blood coagulation cascade

Blood coagulation cascade is a network of proteases, their precursors, cofactors, cells, enzymes, feedbacks, and feed-forwards whose complexity and still unresolved questions make this outline by necessity rudimentary, with the primary goal to illustrate where the proteins that require binding to externalized PS (phosphatidylserine) for activation are in the network.

Most proteins involved in coagulation are called factors and are labeled by Roman numerals, such as Factor X or FX (hence enzymes that process FX are *tenases*). For simplicity, in this cartoon the letter F is omitted. Activated factors are labeled with an a, as in FXa. Orange arrows represent proteolytic activity, grey arrows show a transition between forms. Blue horizontal lines represent a cellular membrane with the cell surface facing down. Accordingly, the pinheads of externalized PS also face down. Note that most PS is actively relocated to face the cytoplasm unless the cell dies or the distribution is randomized by lipid scramblases.

As discussed in the text, the primary trigger of coagulation induced by viral infections is the extrinsic tenase (top left), which is a complex of TF (Tissue Factor) and FVIIa assembled on externalized PS in the presence of calcium ions. This tenase produces FXa to activate enough thrombin to generate the components of the intrinsic tenase, which increases the production of FXa, and, consequently, of thrombin, which generates enough fibrin to make a thrombus, a meshwork of polymerized and cross-linked fibrin with entrapped blood cells, primarily platelets, which is large and stiff enough to obstruct a blood vessel.

Note that TF is encrypted and so is unable to activate FVIIa, until it is de-encrypted by externalized PS (reviewed in ref. 10).

ternalized PS.[10] How PS externalization is induced in TF-expressing cells is unclear. [11]

The syncytial tenase hypothesis. The synergy of TF and externalized PS in activating FVIIa, and the report that spike-induced syncytia externalize PS,[3] together suggest a hypothesis that these syncytia can be a platform for assembling extrinsic tenase capable of triggering the blood coagulation cascade (Fig. 2).

Three conditions would need to be met by this mechanism to cause clinically significant thrombosis. First, syncytia should express TF, which is likely because endothelial cells express TF during viral infections,[8] while the lungs are abundant in other cell types that express this protein.[10] Second, syncytia should come in contact with blood, which can happen if syncytia are formed within a blood vessel, or if blood vessels become leaky, a condition common in viral infections, including COVID-19.[19] Finally, the tenase activity should be sufficiently abundant to trigger the coagulation cascade. What this tipping point is would depend on the number and size of syncytia, which will be defined by the extent of infection, as well as on the coagulation state of a patient.

Thrombosis by death. The second hypothesis suggests that syncytia formed by cells lining a blood vessel might contribute to thrombosis merely by dying because by sloughing off they would uncover a patch of the thrombogenic basement membrane with a surface area equal to that of many mononuclear cells. Because even a single 20-micron fiber of collagen, the main component of the basement membrane, is sufficient to trigger platelet-dependent clotting,[20] the patch exposed by dying syncytium that is made of more than several cells might be large enough to produce a thrombus.

Given that even one thrombus can cause problems or even death, the potential contribution of syncytia to COVID-19 thrombosis by either mechanism could be clinically relevant.

SARS-CoV-2 may be able to engage either mechanism both locally, by fusing infected cells, and remotely.

Thrombosis at a distance. SARS-CoV-2 spike, like other viral fusogens, can fuse cells in two ways (Fig. 2). To fuse from within, the virus makes an infected cell produce viral components, including spike, which is transported to the plasma membrane. Once there, spike can fuse the infected cell to an adjacent cell that has a spike receptor. Another mechanism, fusion from without, is executed by viral particles or lipid vesicles studded with spike that serve as a bridge between two cells.[21,22] This means that extracellular vesicles that are pro-

duced in COVID-19 patients[23] may be able to form syncytia and thus cause thrombosis even in tissues that are not infected with the virus.

Inflammation and fibrosis. Besides mediating blood clotting, the coagulation cascade interrelates with signaling pathways that regulate inflammation, fibrosis, and some other conditions associated with COVID-19.[24] Therefore, if syncytia produced by spike trigger the blood coagulation cascade, this activity would contribute to COVID-19 beyond inducing thrombosis.

Cell fusion and SARS-CoV-2 variants of concern

While spike can fuse viruses to cells and cells to each other, the underlying mechanisms of these two activities are not identical. For example, sera from convalescent COVID-19 patients neutralize fusion of the virus to cells but fail to prevent the fusion of cells.[22] Likewise, modifying the spike of SARS-CoV, which causes severe acute respiratory syndrome, to enable maturation of this protein by furin, a protease that also processes SARS-CoV-2 spike, increases the ability of SARS-CoV to fuse cells manyfold with little effect on virus-cell fusion.[25] Finally, a single mutation in a porcine coronavirus spike enables this protein to cause cell-cell fusion at barely detectable amounts without affecting the ability of the virus to infect.[26]

These observations mean that some SARS-CoV-2 variants can differ in the incidence of cell fusion and thus its consequences, including the ability to persist in the body by using cell-to-cell transmission,[27] a mechanism also used by HIV.[28,29] This prediction is consistent with the report that novel SARS-CoV-2 variants of concern have mutations associated with a gain in syncytia formation.[30]

The pain of (con)fused neuronal networks

Neurological manifestations, including pain, are common in COVID-19 patients.[31] While SARS-CoV-2 is likely to contribute to these symptoms in multiple ways, short-circuiting neuronal networks by fusing neurons can explain not only how some

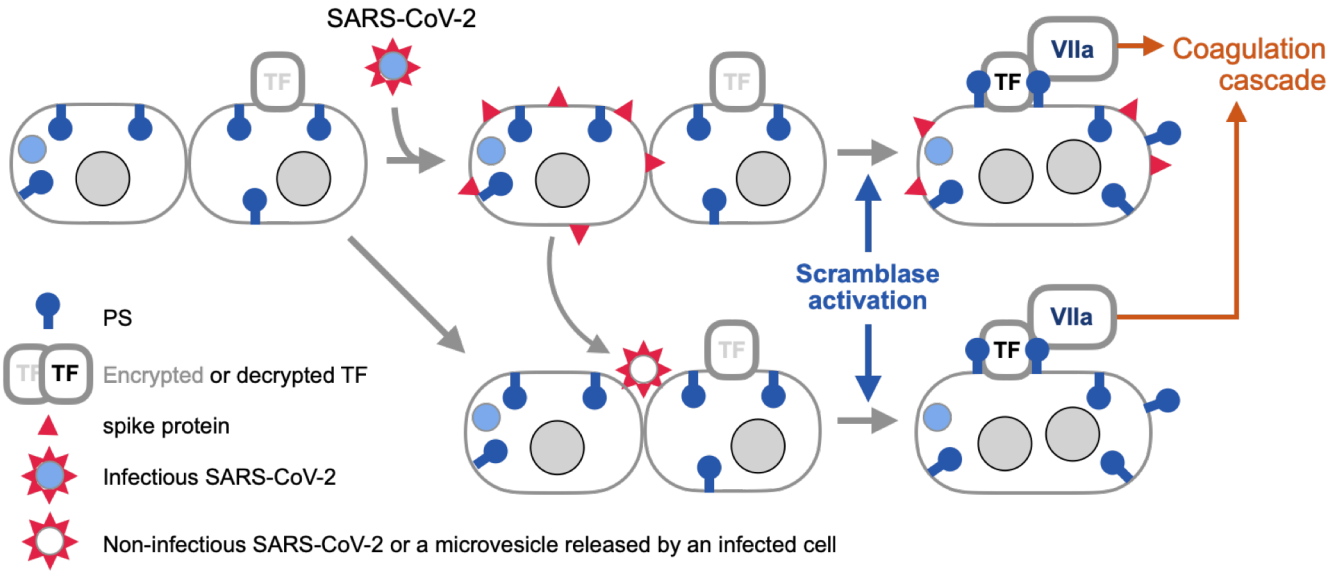

Figure 2. Syncytia induced by SARS-CoV-2 spike as a platform for triggering blood coagulation cascade. SARS-CoV-2 is covered by an envelope, which is fused to the cell membrane by spike once this protein is activated by binding to one of its receptors and processed by a membrane protease (both are not shown for simplicity). The infected cell produces viral components, including spike. Now, spike can fuse the membrane of the host cell with the membrane of an adjacent cell if that cell also has a spike receptor. Braga and colleagues[3] found that spike-induced cell fusion is associated with activation of TMEM16F, a scramblase that externalizes PS. This commentary proposes that PS externalized by spike enables the formation of the extrinsic tenase (Fig. 1), the key trigger of blood coagulation cascade during viral infections.

SARS-CoV-2 spike can also fuse cells if the virus is not infectious, or even if spike is incorporated into membrane vesicles,[22] like extracellular vesicles released by infected cells. This mechanism is known as fusion from without[21], as the viral particle or a vesicle provides a bridge between the membranes. Because syncytia produced by this mechanisms are not infected with SARS-CoV-2 in this case, their origin may be difficult to trace.

Note that TF is encrypted, meaning that it is unable to activate FVIIa, until it is de-encrypted by externalized PS (reviewed in ref. 10).

neurological symptoms emerge but also why they last after the infection is cleared.

That fusing neurons can cause neurological problems has been considered in other virus-induced diseases. In animals, severe neurological symptoms of pseudorabies, a disease also known as mad itch, have been linked to the ability of pseudorabies virus to electrically couple the activity of neurons by fusing their axons.[32,33] How such coupling could also contribute to the loss of smell, a common symptom of COVID-19, can be gleaned from experiments in the nematode *C. elegans* in which fusing two functionally different chemosensory neurons impaired chemosensation.[34]

In humans, the fusion between neurons and glial cells, which surround neuronal bodies, has been proposed to explain the origin and persistence of the neuropathic pain that can last for months after the acute phase of herpes zoster (shingles).[35] This fusion has been detected in a patient affected by shingles, [36] confirmed in a human xenograft model of this disease, [37] and accidentally discovered in an unrelated mouse model in which cortical neurons were infected with a retrovirus pseudotyped with VSV-G, the fusogen of vesicular stomatitis virus.[38] Whether the fusogens of human endogenous retroviruses (HERV), whose expression has been associated with various neurological disorders, function as pathogens of these diseases by fusing cells, as has been suggested,[39] is yet to be determined.[40,41] Together, these observations mean that abnormal neuronal fusion induced by viral proteins is not restricted to a particular fusogen or to certain neurons.

Can SARS-CoV2 spike fuse neurons in the human body? Spike has been detected in the brain of deceased COVID-19 patients,[42] although how abundant SARS-CoV2 can be in the nervous system is still debated.[43,44] However, considering how efficiently SARS-CoV2 spike fuses cells[22] and how intricate neuronal networks are, the chance that spike can disrupt them by fusing some of their components does not seem to be negligible, as a recent report also convincingly argues by demonstrating that spike can fuse neurons in brain organoids.[45] If spike retains this activity in the brain, it would be not difficult to envision how neuronal anastomoses created by cell fusion can contribute to cognitive disturbances associated with COVID-19[31].

Such short-circuits may last for some time after a viral infection clears because the mechanisms that can repair them by “disconnecting” the anastomosed neurons or replacing them may be inefficient or inexistent.

Syncytia and other products of cell fusion are heterogeneous abnormal cell types with emergent properties.

Syncytia made by exogenous viruses are abnormal by definition because cell fusion in the body is normally restricted to a handful of physiological processes, such as fertilization, myogenesis, and the formation of osteoclasts, the cells that remodel bones.[6,46]

What is known about the mechanisms of physiological fusion – which is much less that one would expect given its function in the body – gives the impression that these mergers are planned and rehearsed down to the very last detail to ensure that only the right cells fuse at the right time and place and that, with the exception of fertilization and stem cell fusion, the resulting syncytia do not attempt to proliferate.

These sophisticated mechanisms, however, are overridden by many infectious viruses, including SARS CoV-2, which fuse cells randomly as long as the cells carry a cognate receptor.[6,47] This randomness means that cell fusion induced by infectious viruses is a violent event that forcefully unites two or more finely tuned and specialized systems that just happened to be next to each other but may be quite different in their functions, gene expression patterns, cell cycle stage, age, activation status, and other features.

For example, in the lungs of COVID-19 patients, SARS-CoV-2 infects, and can thus fuse, multiple cell types: ciliated cells in the airway, alveolar type 2 pneumocytes, and epithelial progenitors among others.[1] What are the properties of, say, a syncytium that is made up of a pneumocyte with an epithelial progenitor? What happens if a leukocyte or another cell that carries one of spike receptors[48] joins in? Moreover, SARS-CoV-2 may not be the only virus that makes syncytia in COVID-19. For example, HERV-W ENV, the inactive fusogen of an endogenous retrovirus,[49] was detected in the leukocytes of COVID-19 patients at concentrations that exceeded that in the cells from healthy donors by orders of magnitude.[50] If SARS-CoV-2 also induces expression of related HERV ENVs, includ-

ing fusogenic syncytin-1,[51] the number of cell types involved in cell fusion would increase even further. However, even without this potential boost, it is likely that COVID-19 patients have populations of diverse abnormal syncytia.

What are the properties of abnormal syncytia? The properties and the fates of syncytia produced by infectious viruses in the body remain practically unknown. However, observations made in experimental systems and by studying physiological syncytia provide some clues. One of them is that syncytia can become abnormal not only by combining distinct features of parental cells that are not found together in normal cell types, but also by having emergent properties that appear to result from reconciling distinct gene expression patterns underlying different cell types.[52,53]

For example, fusion of human bronchial epithelial cells to human multipotent stromal cells resulted in cells that appeared epithelial but failed to function properly because the two ion channels required to maintain bronchial and alveolar fluid balance were impaired due to changes in gene expression: one protein lacked a subunit, the other was improperly expressed.[54] Likewise, bone marrow-derived cells fused to hepatocytes in a mouse model of chronic liver damage yielded cells that differed in their gene expression patterns from both parental types and, unexpectedly, expressed cytokines and genes involved in neurotransmission and in the TGF-β pathway.[55] In an extreme case illustrating an enigmatic phenomenon called extinction, fusion of hepatoma cells to fibroblasts silenced hundreds of genes specific to either parental cell type, thus producing dedifferentiated cells.[56] Even fusion of cells belonging to the same cell type can produce syncytia with new properties, as happens with osteoclasts, which resorb bone better than their mononuclear precursors.[57]

Given the outlined examples, it is not unreasonable to envision that some syncytia created by SARS CoV-2, associated viral infections, or induced endogenous viruses can produce cytokines or other signaling factors capable of deregulating tissue homeostasis either locally or even systemically, as happens in COVID-19 during cytokine storms.[24] These cells might also become sanctuaries for the virus, as has been reported for HIV[28,29], or by evading or corrupting immune surveillance, perhaps by fusing to immune cells.

Cell fusion and neoplasia

While the published reports on COVID-19 discuss large syncytia, as these cells are the most noticeable products of cell fusion due to their size and numerous nuclei (thus often called multinucleated giant cells), they are not the only outcome of cell fusion. Cell fusion can produce binuclear or trinuclear cells, which are often more abundant in experimental systems than large syncytia but could go unnoticed in human tissues. Even if noticed, they may not be attributed to cell fusion because distinguishing them reliably from binuclear cells produced by failed mitosis in human tissues may be difficult or impossible with available tools.[58]

A syncytium, especially if it has only two or three nuclei, can also enter mitosis to produce mononuclear daughter cells. These syncytia are commonly multipolar and thus are prone to producing aneuploid cells with chromosomal aberrations, adding another layer of abnormal features to the offspring of cell fusion.[59,60] Such abnormalities may be particularly significant to COVID-19 patients with neoplastic lesions because chromosomal aberrations contribute to tumor progression.[61,62]

Another potential concern comes from a long-standing model that cell fusion, particularly fusion induced by viruses, contributes to cancer development, progression, metastasis, recurrence, dormancy, and acquired drug resistance (reviewed in: [39,63–65]). This model has been supported by recent reports of cell hybrids in human cancers,[58,66] by multiple observations in animal models (reviewed in: [39,65,67,68]), by findings that human cells can be made cancerous through cell fusion,[59,69,70] and by comparing the evolution of tumors and cell hybrids.[71] However, whether any neoplastic hybrids found in humans[58] are made by viral fusogens, as has been suggested[72–74], is yet to be determined. Nonetheless, out of an abundance of caution, it may be reasonable to monitor the incidence and progression of neoplastic lesions in COVID-19 patients closely, as has been proposed.[75]

This incomplete list of mechanisms that cell fusion can use to produce diverse abnormal cells, including neoplastic, suggests that drugs that target cell fusion, such as those identified by Braga and colleagues[3], might also be useful for preventing potential neoplastic consequences of COVID-19. These drugs, as we about to discuss, can also be

useful for preventing side effects of some COVID-19 vaccines.

Cell fusion and COVID-19 vaccines

The majority of available COVID-19 vaccines, including all four vaccines authorized in the United States and the European Union, work by expressing spike in the cells of the injected individuals. They do so either by infecting the cells with an adenovirus carrying a spike gene (AstraZeneca[76] and Janssen[77] vaccines) or by transfecting them with a spike mRNA (Pfizer[78] and Moderna[79] vaccines). Once expressed, spike is recognized by the immune system as a foreign antigen, triggering an immune response to the protein and thus to SARS-CoV-2.

Considering spike as an antigen might distract from the fact that the primary activity of this protein is to fuse biological membranes, which is why spike expressed in cells can fuse them into syncytia. This fact raises two questions that have yet to be asked despite all the attention and scrutiny that spike has received[80]: Does spike fuse any cells if expressed by the vaccines? And, does this fusion, should it occur, have any unwanted consequences?

Given that spike expressed by SARS-CoV-2 fuses cells in COVID-19 patients,[1,2] that spike expressed by viral vectors or by transfection fuses human cells in the dish,[22,81,82] and that spike fuses cells even if expressed in undetectable amounts,[22] it is reasonable to presume, until proven otherwise, that spike does fuse some cells in the injected individuals.

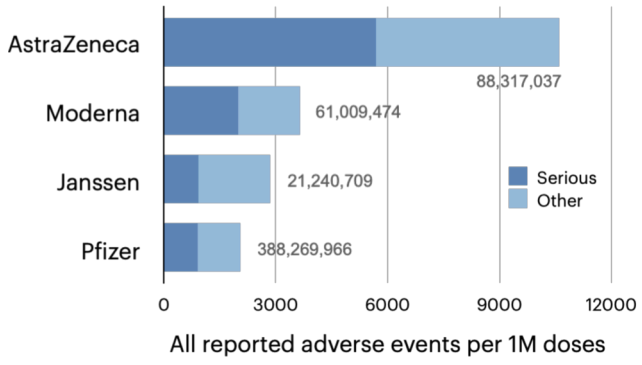

Figure 3. The incidence of suspected vaccine complications recorded in the European Database Of Suspected Adverse Drug Reactions Reports (EudraVigilance)[109] as of August 6, 2021. The numbers of doses administered by that date, and shown next to the bars. were taken from: https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab

Could this fusion be pathogenic?

If cell fusion induced by expression of spike contributes to COVID-19 complications, as this and previous reports[1,2] have suggested, then expressing spike by other means, including those used by the vaccines, should be expected to have similar effects. The puzzling case of the AstraZeneca vaccine is consistent with this possibility.

An unexplained feature of this vaccine is the highest incidence of reported complications among the four vaccines[83,84] (and Fig. 3), including a series of thrombotic complications[85,86] that permanently suspended the AstraZeneca vaccine in a number of countries and has delayed its authorization in the United States.[87] These complications have been ascribed to antibodies elicited by adenoviruses against platelet factor 4,[88,89] to the alternative splicing of spike,[90] and to the binding of adenoviruses or spike to platelets.[80,89] However, the proposed mechanisms still need to fully explain why thrombotic events have also been reported for mRNA vaccines, albeit at a lower incidence[83,91] why they can occur within days after vaccination,[83] why they are as rare as they fortunately are, why the AstraZeneca vaccine has a higher incidence not only of thrombosis but also of some other complications[83], and, finally, how these complications can be prevented.

If spike-induced cell fusion is pathogenic, as this commentary argues, then the unfortunate ranking of the AstraZeneca vaccine becomes predictable because it is the only out of the four vaccines that makes the wild type, fully fusogenic spike,[76,92] delivering it with a vector optimized to express “very high levels” of the protein.[93]

Spike used in the other three vaccines has been made less fusogenic, apparently fortuitously, while optimizing spike as an antigen. To improve the immune response, the developers[76,77,79] have stabilized spike structure by two mutations that suppress a conformational change triggered by binding to ACE2.[94,95] Because this change is involved in spike activation,[48] suppressing it has also inhibited cell fusion in a tissue culture assay by several fold.[77] Two additional mutations introduced in the Janssen vaccine decreased this incidence in the same assay further[77] by altering the site recognized by furin, a protease that contributes to spike activation by cleaving it into two subunits.[48]

Whether these additional mutations remain as effective in the human body is unclear, as other proteases can replace furin[96,97] and because this cleavage may be not required.[98] However, since the abundance of these proteases varies among human tissues,[97] altering the furin site might affect the incidence of some complications. None of the developers mutated the S2' site, whose cleavage exposes the fusion peptide, the part of viral fusogens that penetrates the target membrane.[99]

These observations suggest a relationship between the fusogenicity of spike proteins and the reported incidence of side effects. Is this relationship accidental or causal?

A causal relationship entails two testable predictions:

First, complementing vaccination with drugs that prevent spike-induced cell fusion should reduce the incidence of complications. A number of approved drugs that have such activity, including hotly debated ivermectin,[100–102] have been already identified by Braga and colleagues.[3]

Second, vaccines that use recombinant spike fragments[103] or other derivatives of spike that are not fusogenic without any doubt should have fewer complications than vaccines that express fully or partially fusogenic spike. Vaccines that use inactivated SARS-CoV2 (currently Sinopharm[104] and Sinovac[105]) would have an intermediate incidence of complications because inactivated viruses can still fuse cells from without (Fig. 2), although without the capacity to express spike the incidence of syncytia is limited by the number of injected viral particles. This prediction is consistent with safety reports for vaccines that use inactivated virus[106,107] but further studies, and having all current and future vaccines tracked by publicly accessible databases of suspected vaccine complications, like VAERS[108] in the United States and EudraVigilance[109] in Europe, would provide a larger set of data to evaluate, as has been done to compare the AstraZeneca and Pfizer vaccines[83].

The hypothesis that cell fusion mediates some vaccine complications needs to be tested because the scale of COVID-19 vaccination calls for an abundance of caution, which hardly implies overlooking the primary activity of the antigen, and because the proposed hypothesis applies to other fusogenic proteins that one might want to express in the human body to prevent a viral infection or another disease. For example, a number of such vaccines are already in Moderna's pipeline.[110] Evaluating the potential consequences of cell fusion early in vaccine development might help to prevent avoidable side effects.

If vaccines cause vaccine complications by inducing cell fusion, one might ask, why then are these complications so rare, diverse, and overlap with those observed in COVID-19? Perhaps, as has been suggested,[111] the outcome of vaccination depends on how a vaccine is injected. If, as intended, the vaccine stays strictly intramuscular, the syncytia it creates may be inconsequential as they stay at the site of injection and die in due course. However, if a vaccine spreads systemically because it is accidentally injected into a blood or lymphatic vessel, or for other reasons, the outcome would depend on which cells, where, and in what numbers begin to express spike and thus acquire the ability to fuse. For example, the fusion of endothelial cells to each other or to other cells carrying a spike receptor, including platelets[112] and pericytes[113], could result in thrombosis, while the fusion of neurons may lead to neurological manifestations. Some complications caused by cell fusion may be specific to a particular vaccine or to COVID-19 because the tropisms of adenoviral vectors, mRNA-carrying lipid particles, and SARS-CoV-2 overlap but are not identical.[48,114,115] A contributing factor could be a predisposition of some individuals to cell fusion by viral fusogens, which is difficult to evaluate at this time because cell fusion regulation in general and the regulation of cell fusion induced by viruses in particular is still largely a *terra incognita*.

In summary, this author hopes that the discovery of syncytia in COVID-19 patients will help to dissect cell fusion and its consequences, both in health and in disease, by making more researchers aware of this fascinating yet often overlooked process. After all, we tend to notice only what we expect to see.

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CONFLICTS OF INTEREST

I declare no conflicts of interest.

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