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Microcirculatory Inflammation: A Key Driver of Adverse Reactions to mRNA-Containing COVID-19 Vaccines

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Abstract: The mRNA-based COVID-19 vaccines, Pfizer-BioNTech's Comirnaty and Moderna's Spikevax, were successfully deployed to help control the SARS-CoV-2 pandemic, and their updated formulations continue to be recommended for protecting high-risk populations. One widely discussed aspect of these vaccines is their uniquely broad spectrum and increased incidence of adverse events (AEs), collectively referred to as post-vaccination syndrome (PVS). Although PVS is rare, the high number of administered doses among healthy individuals has resulted in a substantial number of reported vaccine-related injuries. A prominent manifestation of PVS is multisystem inflammation, hypothesized to result from systemic transfection of organ cells with genetic instructions for a toxin, the spike protein (SP)-, delivered via pro-inflammatory lipid nanoparticles (LNPs). In this review, we focus on endothelial cells in the dense microcirculatory networks of various organs as primary sites of transfection and PVS. We outline the anatomical variations of the microcirculation contributing to the individual variability of symptoms and examine the molecular and cellular responses to vaccine nanoparticle exposure at the endothelial cell level with a focus on the pathways of a sustained cascade of toxic and autoimmune processes. A deeper understanding of the mechanisms underlying mRNA-LNP-induced PVS and AEs at the cellular level is critical for improving the safety of future vaccines and other therapeutic applications of this groundbreaking technology.

Keywords: lipid nanoparticles; blood vessels; Comirnaty; Spikevax; COVID-19; microcirculation; immune response; innate immunity; adaptive immunity

1. Introduction

The mRNA-containing lipid nanoparticle (mRNA–LNP)-based COVID-19 vaccines, Pfizer's Comirnaty and Moderna's Spikevax, played a crucial role in mitigating the severity of SARS-CoV-2 infections and saving lives during the pandemic. Since their introduction, >5 billion doses were administered worldwide, and despite the subsiding of the pandemic, these vaccines remained the primary tool for maintaining immunity against circulating SARS-CoV-2 variants. However, as of May 2025, the CDC has revised its recommendations, limiting the use of COVID-19 mRNA vaccines and number of boosters mainly to high-risk populations. Several countries and regions had already restricted their use, partly due to the declining threat of the virus, and partly in response to increasing concern over the uniquely broad spectrum and relatively high incidence of adverse events (AEs)

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compared to traditional vaccines [1]. However, as of May 2025, the CDC has revised its recommendations, limiting the use of COVID-19 mRNA vaccines and boosters mainly to high-risk populations. Several countries and regions had restricted their use earlier, partly due to the declining threat of the virus, and partly in response to increasing concern over the uniquely broad spectrum and relatively high incidence of adverse events (AEs) compared to traditional vaccines.

Although such AEs are statistically rare on an individual basis (officially reported at 0.03–0.5%) [1], the vast scale of global vaccination campaigns has resulted in a significant absolute number of vaccine-related injuries. These adverse outcomes have been collectively described as post-vaccination syndrome (PVS) [2-7], a newly recognized condition affecting millions worldwide, including individuals with persistent health issues or disabilities that may qualify as an iatrogenic orphan disease [1]. In some cases, simultaneous inflammation of multiple organs can occur, leading to a highly lethal condition known as multisystem inflammatory response syndrome.

The objective of this review is to investigate the role of endothelial cells (ECs) within the microcirculation as a likely primary site of vaccine-induced injury. A better understanding of these processes is essential for improving the safety, and thereby the future success, of mRNA–LNP platform technology, not only for vaccination but for other therapeutic purposes.

2. The mRNA–LNP-induced Inflammatory Complications and their Root Cause

Table 1 shows a list of organs whose inflammation was reported in the publicly available 3-month safety surveillance report of Pfizer [8]. The advantage of using these data is that the list of AEs likely excludes symptoms caused by SARS-CoV-2 infection, as the vaccine had not been administered to infected individuals. Also, the list was compiled from data in 52 countries, arguing against bias. The list was compiled by AI searching in the report for words containing the ”itis” tag, and then screening out the redundant entries with a qualifying term, such as “acute, chronic, (auto)immune, immune-bacterial”, etc). Thus, the list does not distinguish among inflammatory conditions due to bacterial, viral infections or autoimmune attack, acute or chronic inflammations, it just shows that essentially all organs can be inflicted with a form of inflammation starting sometimes within 3 months after vaccination.

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Table 1. Inflammatory complications associated with immunization with mRNA-LNP vaccines.

1. Aortitis	38. Lupus encephalitis	75. Noninfectious myelitis	112. Respiratory syncytial virus bronchiolitis
2. Arteritis	39. Lupus endocarditis	76. Noninfective encephalitis	113. Respiratory syncytial virus bronchitis
3. Arthritis	40. Lupus enteritis	77. Noninfective encephalomyelitis	114. Retinal artery embolism
4. Bronchitis	41. Lupus hepatitis	78. Noninfective oophoritis	115. Retinal vasculitis
5. Bronchitis viral	42. Lupus myocarditis	79. Ocular vasculitis:	116. Rheumatoid arthritis
6. Capillaritis	43. Lupus myositis	80. Oculofacial paralysis	117. Rheumatoid scleritis
7. Cervicitis	44. Lupus nephritis	81. Oesophagitis	118. Rheumatoid vasculitis
8. Cholangitis	45. Lupus pancreatitis	82. Optic neuritis	119. Schizencephaly scleritis
9. Colitis	46. Lupus pneumonitis	83. Optic perineuritis	120. Schonlein henoch purpura nephritis
10. Cystitis	47. Lupus vasculitis	84. Osteomyelitis	121. Segmented hyalinising vasculitis
11. Dermatitis	48. Lymphocytic hypophysitis	85. Palisaded neutrophilic granulomatous dermatitis	122. Silent thyroiditis
12. Dermatomyositis	49. Mastocytic enterocolitis	86. Pancreatitis	123. Sle arthritis
13. Encephalitis	50. Medicaldevice site vasculitis	87. Panencephalitis	124. Spondylitis
14. Encephalomyelitis	51. Meningitis	88. Papillophlebitis	125. Spondyloarthritis
15. Enteritis	52. Meningitis aseptic	89. Parainfluenzae viral laryngo-tracheobronchitis	126. Stoma site thrombosis
16. Enteritis leu	53. Meningitis herpes	90. Paraneoplastic dermatomyositis	127. Subacute endocarditis
17. Enterocolitis	54. Meningoencephalitis	91. Pericarditis	128. Takayasu's arteritis
18. Gastritis	55. Meningoencephalitis herpetic	92. Pericarditis lupus	129. Thromboangiitis obliterans
19. Glomerulonephritis	56. Meningomyelitis	93. Peritoneal fluid accumulation	130. Thrombophlebitis
20. Hepatitis	57. Meningomyelitis herpes	94. Peritonitis	131. Thrombophlebitis migrans
21. Herpes zoster	58. Mesangioproliferative glomerulonephritis	95. Pharyngitis	132. Thrombophlebitis septic
22. Ileitis	59. Microscopic polyangiitis	96. Pneumonia viral	133. Thrombophlebitis superficial
23. Infected vasculitis	60. Mononeuritis	97. Pneumonitis	134. Thyroiditis
24. Infusion site vasculitis/thrombosis	61. Myasthenic myelitis	98. Poems syndrome	135. Tracheobronchitis
25. Interstitial granulomatous dermatitis	62. Myelitis	99. Polyangiitis	136. Tracheobronchitis mycoplasmal
26. Juvenile idiopathic arthritis	63. Myelitis transverse	100. Polyarteritis nodosa	137. Tracheobronchitis viral
27. Juvenile polymyositis	64. Myocarditis	101. Polyarthritis	138. Tubulointerstitial nephritis and uveitis syndrome
28. Juvenile psoriatic arthritis	65. Myocarditis post infection	102. Polychondritis	139. Ulcerative keratitis
29. Juvenile spondyloarthritis	66. Myositis	103. Polymyositis	140. Urticarial vasculitis
30. Keratitis	67. Nephritis	104. Proctitis	141. Uveitis
31. Laryngeal rheumatoid arthritis	68. Neuritis	105. Pseudovasculitis	142. Vaccination site vasculitis
32. Leukoencephalitis	69. Neuritis cranial	106. Pyostomatitis	143. Varicella zoster gastritis
33. Leukoencephalomyelitis	70. Neuromyelitis optica pseudo relapse	107. Radiculitis	144. Varicella zoster oesophagitis
34. Lichen planus	71. Neuromyelitis optica spectrum disorder	108. Rash pruritic	145. Vasculitis
35. Lichen sclerosus	72. Neuropathy peripheral	109. Rasmussen encephalitis	146. Vasculitis gastrointestinal
36. Limbic encephalitis	73. Neutropenic colitis	110. Renal arteritis	147. Vasculitis necrotising
37. Lupus cystitis	74. Nodular vasculitis	111. Renal vasculitis	

The similar kinetics of vaccine-induced inflammatory AEs listed in Table 1 (developing within days or much later, in months after vaccination) and numerous commonalties in these illnesses, such as the association with reactivation of certain viral strains (Table 2), point to a common, very fundamental immune abnormality or combination of abnormalities. A recent comprehensive hypothesis on this conundrum attributes the phenomenon, at least in part, to plausible consequences of inherent structural and functional properties of the mRNA–LNP platform [1, 9]. The design challenges include ribosomal synthesis of the SP, which fundamentally alters antigen processing and presentation; extensive chemical modification of the mRNA, rendering SP translation poorly controllable; the use of a proinflammatory, fusogenic aminolipid in the LNP, which promotes widespread systemic distribution and transfection of non-target cells to produce a toxin; the chemical stabilization of the SP, despite its known pluritoxicity; the choice of LNP lipid composition with reduced nanoparticle stability in aqueous environments; the PEGylation of the LNP surface, despite PEG's known immune reactivity and immunogenicity; and recombinant production of the mRNA,

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which carries a risk for DNA contamination. These features collectively predispose to collateral tissue damage caused cytotoxic T cell and complement-mediated autoimmune responses. Although nucleoside modifications (e.g., pseudouridine substitution) of the mRNA reduce recognition by innate immune sensors, such as TLR3, TLR7, TLR8, and retinoic acid-inducible gene I (RIG-I) [10-14], residual activation of innate immunity by the modified mRNA via RIG-I-like receptors, under certain conditions, remains an open question [15].

Table 2. Virus strains whose reactivations may be associated with inflammatory AEs of mRNA vaccines.

Strains	References
Cytomegalovirus (CMV)	[16, 17]
Epstein-Barr virus (EBV)	[18]
Herpes simplex virus (HSV)	[19-21]
Varicella Zoster virus (VZV),	[22, 23]

Given the multicausal and multiorgan nature of vaccine-induced inflammation, numerous pathological processes are likely involved. This review focuses on microcirculatory inflammation as a central driver of inflammatory AEs. The task is complicated by tissue-specific differences in microcirculatory structure and function, as described below.

Components and Unique Organization of Microcirculation Across Tissues

The microcirculation refers to the smallest blood vessels in the body (below ~200 micrometer), including arterioles, capillaries, and venules which collectively responsible for gas and nutrient exchange, waste removal, and immune surveillance at the tissue level. Some morphological features of cells in the microcirculation are illustrated in Figure 1.

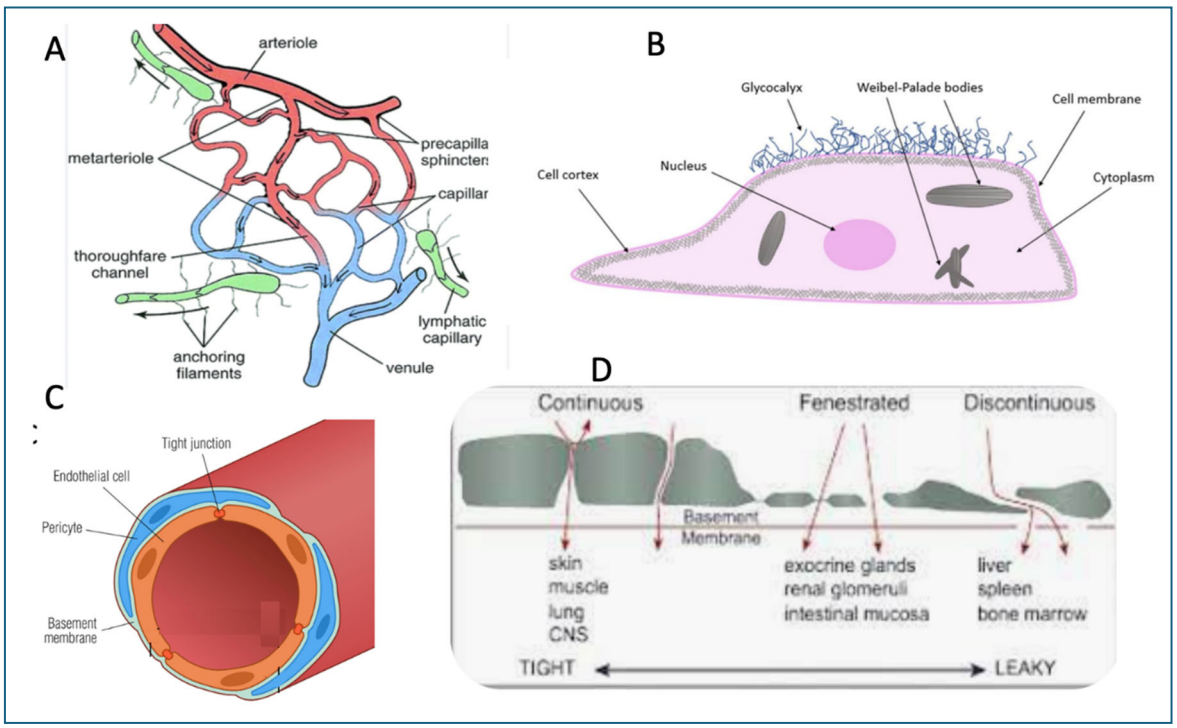

Figure 1. (A) Schematic representation of microcirculation. The arterioles and venules are bridged by a network of capillaries. Some of the precapillary arterioles have sphincter-like structures, whereas the capillaries have pericytes to control blood flow through the network system [24]. In the interstitial space dead-end lymphatic capillaries are anchored to the underlying tissue by filaments. (B) ECs composed of a plasma membrane with surface receptors, a cytoskeleton that maintains shape and enables signal transduction, cell junctions for barrier

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function, and organelles like the nucleus, mitochondria, and endoplasmic reticulum to support metabolism, protein synthesis, and regulatory functions. The glycocalyx is a thin, gel-like layer of glycoproteins and glycolipids that coats the surface of ECs, playing a crucial role in vascular permeability, mechanotransduction, and protection against shear stress and inflammation. (C) Cross-section of a capillary in peripheral nerves, illustrating the spatial arrangement of structural components such as the ECs, basal lamina, pericytes, and tight junction. (D) the three types of capillaries; continuous (tight junctions), fenestrated (pores in ECs), and discontinuous (large gaps between cells), each specialized for different organ systems.

Endothelial cells (Fig 1B), which line the inner surface of all blood vessels, play a pivotal role in maintaining vascular homeostasis by regulating blood flow by modifying the tone of underlying smooth muscle, barrier function, coagulation, and immune cell trafficking, and so on. A crucial component of the ECs is the glycocalyx, a gel-like, carbohydrate-rich layer that lines the luminal surface of endothelial cells and other cell types. It is composed mainly of glycoproteins, proteoglycans (e.g., syndecans, glypicans), and glycosaminoglycan chains such as heparan sulfate and hyaluronic acid. It acts as a selective permeability barrier, sensing and modulating shear stress signaling, and preventing adhesion of leukocytes and platelets under physiological conditions (10). The connections among ECs can be continuous (tight junctions), fenestrated (pores in ECs), and discontinuous (large gaps between cells), each specialized for different organ systems (Figure 1C and D).

4. Endothelial Cells in the Frontline of Vaccine-Induced Inflammation

The ECs are particularly responsive to inflammatory stimuli and are often the first point of contact for systemically circulating immune mediators and nanoparticles, including mRNA-LNPs. Damage to the glycocalyx, and, hence, endothelial integrity, can precipitate secondary cascades such as coagulation, C activation, immune cell infiltration, all of which contribute to various pathophysiological states, including inflammation, sepsis, ischemia-reperfusion injury, and vascular complications related to infections and vaccinations [25]. The manifestations of symptoms and illnesses vary widely across organs, reflecting not only differences in immune responses but also organ-specific anatomical factors, discussed below.

5. Distinctive Microcirculatory Architectures Across Organs and Their Impacts on Vaccine-Induced Inflammations

Although all organs share a fundamental microvascular blueprint, the microcirculatory networks vary significantly in the density of the capillary network (Fig 1A), endothelial subtypes (Figure 1B), tightness of intercellular junctions (Figure 1C), and capillary fenestration type (Figure 1D). Likewise, the local regulatory mechanisms that involve adjacent tissue cells, such as pericytes in nerve fibers, smooth muscle cells, precapillary sphincters, or other resistance mechanisms that govern blood flow in accordance with the functional demands on blood supply [26]. These structural and functional variations render the microcirculation a highly specialized, tissue-specific interface between the bloodstream and parenchymal cells. Consequently, they critically influence the nature and extent of inflammatory responses. In particular, the localization or systemic spread of the SP is strongly governed by the microanatomy of the vasculature in the affected organs.

For example, the heart's microcirculation is uniquely organized, characterized by an exceptionally dense capillary network providing nearly a one-to-one capillary fiber ratio allowing fast diffusion of and exchange of gases and nutritional molecules (Figure 2A). The surface cardiomyocytes are covered with the epicardium, the inner layer of pericardium. The pericardium contains pericardial fluid, which can also be affected by inflammation [27-29]. The anatomical proximity, involving a high-density capillary network within the microcirculation, provides a structural basis for the frequent co-occurrence of pericarditis and myocarditis, a condition referred to as myopericarditis [30-32].

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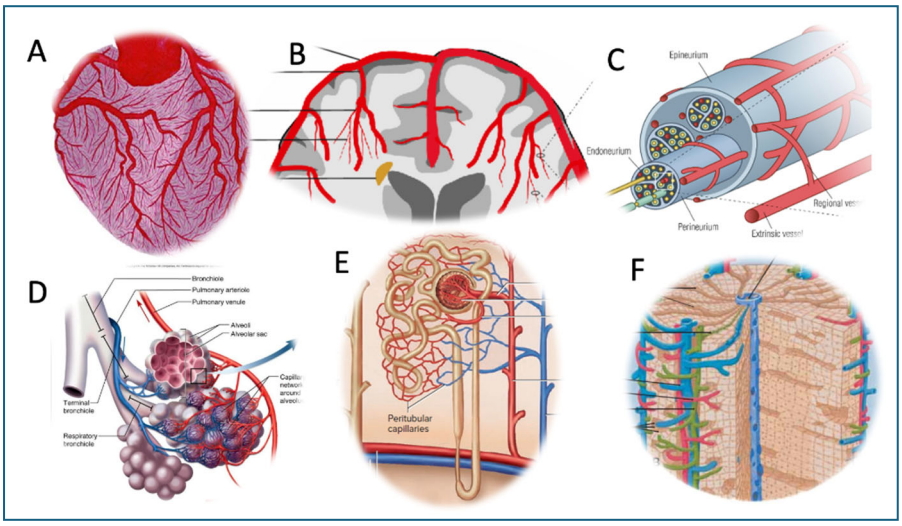

Figure 2. Special features of the microcirculation in major organs of the human body. Schematic representations synthesized from publicly available figures (Google Images).

In the brain, ECs in non-fenestrated capillaries are connected by tight junctions, forming the blood–brain barrier, which strictly regulates molecular and cellular trafficking (Figure 2B). This anatomical configuration is consistent with the emergence of localized inflammatory processes, underlying epileptic, cognitive and other focal AEs, for example optic neuritis, Guillain–Barré syndrome, facial paresis, etc. [33]. The localized, restrained inflammation also helps explain the functional neurological disorders which are characterized by neurological symptoms without detectable abnormalities upon imaging with MRI or CT [33-35]. The situation is similar in the spinal cord, for example in transverse myelitis, which entails localized motor, sensory, and autonomic dysfunction.

In peripheral nerves, the endoneurium, which encases the individual nerve fibers (axons) along with their myelin sheath, contains an extensive network of capillaries also with tightly bound ECs (Fig 2C). Here, too, the inflammatory signals spread locally, along the axons and the perineurial and epineurial tissue, leading to demyelinating neuritis of different afferent or efferent nerves.

In the lung, the microcirculation comprises an extensive and highly permeable capillary network that lies in close association with the alveolar epithelium (Figure 2D). This anatomical arrangement facilitates the transmission of inflammatory signals to both type I squamous epithelial cells and type II secretory cells, leading to widespread inflammatory involvement of the respiratory tissue. Consequently, typical manifestations of vaccine-induced inflammatory adverse events in the lung include alveolar infiltrates accompanied by respiratory distress, such as dyspnea, chest tightness, and hypoxia. [36, 37].

In the kidney, the microcirculation consists of two distinct capillary networks: glomerular capillaries, which form high-pressure filtration units, and peritubular capillaries, which surround the renal tubules and facilitate selective reabsorption and urine concentration within the nephron (Fig 2E). Inflammation of the ECs in both types of capillaries explain the nephrotic syndrome characteristic of vaccine injury, manifested in acute onset edema, hypoalbuminemia, and heavy proteinuria [38, 39].

In the liver, the microcirculation is organized into sinusoidal capillaries with a discontinuous endothelium, allowing free distribution of inflammatory mediators among the blood and hepatocytes. Accordingly, the symptoms of vaccine-induced hepatitis reflect common hepatocyte dysfunction, manifested in acute cholestatic liver injury (biliary obstruction), abdominal pain, pruritus, fever, fatigue, anorexia, nausea and vomiting, laboratory deviations, occasionally fatal outcome in patients with preexisting liver disease [40-44].

Given this diversity of AEs in different organ systems, the impact of endothelitis must be tissue-specific, likely responsive to targeted anti-inflammatory therapies.

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6. The Journey of mRNA-LNPs from the Deltoid Muscle to the Sites of Inflammations

Intramuscular injection of mRNA–LNP-based vaccines is generally associated with immediate interaction with antigen-presenting cells (APCs) and other immune cells at the injection site and within the draining lymph nodes. These locations are considered the primary sites for T and B cell priming and have remained the central focus of most narratives concerning the immune mechanisms of mRNA-based vaccines [45-48]. However, it is well established that LNPs injected intramuscularly rapidly distribute throughout the body, reaching various non-immune organs and cell types, many of which can take up the nanoparticles.

Three main mechanisms have been proposed to explain how mRNA-LNPs gain access to the blood. One is an accidental, direct injection into a small vessel. Because the standard immunization protocol does not require aspiration or needle retraction prior to injection [49], inadvertent intravenous administration and fast entry of vaccine into the brachial vein may occur, particularly in regions with dense capillary networks, such as the deltoid muscle. Second, entry via the lymphatic system [50], which may start through the blind-ended portions of lymphatic vessels, which are leaflet-like endothelial structures that open in response to increased interstitial pressure (Fig 1A). The 300 μL bolus of vaccine can transiently and locally raise tissue pressure above the typically low pressure within lymphatic vessels, promoting nanoparticle entry. Once inside the lymphatic network, rhythmic contractions and relaxations of the lymphatic walls propel the nanoparticles centrally through valve-separated chambers and lymph nodes [51-54]. High-speed video lymphoscintigraphic measurements showed the velocity of lymph flow in the ~2-9 mm/s range, which implies that the vaccine nanoparticles reach the ductus lymphatics from the deltoid muscle, enter the lymph into the vena cava (Figure 3), and distribute in the microcirculation of different organs within about an hour [55, 56]. Importantly, lymphatic vasomotion, and, hence, the pumping activity of lymph microvessels, are delicately controlled by endothelial nitric oxide and prostaglandins [57].

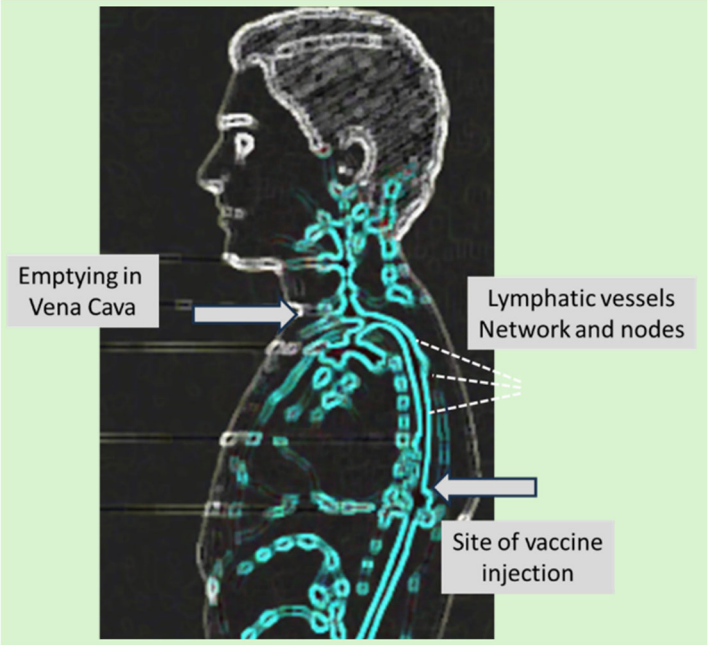

Figure 3. Lymphatic passage of mRNA-LNP from the deltoid muscle to blood.

The third option for LNP entry into the circulation is reversal of the enhanced permeation and retention (EPR) phenomenon [58], whereby nanoparticles re-enter the blood from the extracellular space through regions of increased permeability in inflamed tissues.

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As for the extent and kinetics of systemic biodistribution of mRNA-LNPs, Pfizer Australia's preclinical study reported that 2.8% of a radioactive lipid marker remained in the plasma of rats 15 minutes after intramuscular injection of Comirnaty-equivalent LNPs, with plasma levels peaking between 1 and 4 hours [59]. Over a 48-hour period, the LNPs were primarily distributed to the liver, adrenal glands, spleen, and ovaries [59]. Low-level (<2%) radioactive signals were also detected in 12 additional organs [59, 60].

The endothelial lining of blood vessels constitutes the first biological barrier to the systemic distribution of mRNA–LNPs, raising the question, what portion of the endothelial surface can be accessed by the LNPs. One approximation addressing this question is the LNP/EC ratio, i.e., the number of LNPs interacting with one EC. The 30 μg mRNA in each Comirnaty injection, taken together with the number of mRNA molecules in each fully loaded LNP to be in the low single digits [61-65], furthermore approximately 3% of the LNPs entering in blood over a few hours after the deltoid injection, the 2.05×10^{-8} moles of injected mRNA, or 1.23×10^{16} mRNA molecules translates to ~2xE^{14} fully loaded LNPs reaching the blood within hours. This is about 300-fold higher than the estimated $6x10^{11}$ EC in a 70 kg human, based on the measurements of blood vessel surface areas and endothelial cell dimensions [66]. Although obviously, the individually variable muscular leakage kinetics and rapid uptake of LNPs by the liver and spleen rapidly modify this number, in theory, the vaccine-induced endothelial activation and inflammation can potentially affect the entire vascular system.

7. The Pathophysiology and Diagnosis of Vaccine-Induced Vasculitis

Table 2. shows the types and symptoms of vasculitis classified according to the size of the blood vessels affected. Based on the proportional relationship between LNP uptake and capillary surface area, most vasculitis symptoms are associated with inflammation of small vessels, which collectively provide the largest endothelial interface (Table 3). Nevertheless, the inflammatory diseases involving tissue compartments enriched in medium- and large-sized blood vessels have also been documented to display distinct clinical features (Table 3).

Table 3. Vasculitis types and symptoms classified according to the size of the blood vessels affected.

Vessel Size	Types of Vasculitis	Typical Symptoms
Small	• Microscopic polyangiitis (MPA) • Granulomatosis with polyangiitis (Wegener's) • Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) • IgA vasculitis (Henoch-Schönlein purpura) • Cryoglobulinemic vasculitis • Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis) • Cutaneous leukocytoclastic vasculitis • Leukocytoclastic vasculitis • ANCA*-associated vasculitis	• Vasodilation • Increased vascular permeability • Leukocyte adhesion, margination and transmigration • Endothelial activation and dysfunction • Microthrombus formation • Pain • tissue hypoxia/ischemia • lactate accumulation, acidosis
Medium	• Polyarteritis nodosa (Kawasaki disease) • ANCA-associated vasculitis	• Skin ulcers • Abdominal pain • Mononeuritis multiplex • Hypertension

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Large	• Giant cell arteritis • Takayasu arteritis	• Headache • Visual disturbances • Jaw claudication • Limb claudication • Elevated ESR/CRP

*ANCA, anti-neutrophil cytoplasmic antibodies.

The diagnosis of vasculitis-related illnesses on organ level remains challenging. The nonspecific symptoms, such as fever, fatigue, rash, may not pin down the organ affected just as the inflammatory markers (e.g., CRP) and autoimmune indicators (e.g., ANCA, ANA) in blood or cerebrospinal fluid. Imaging studies, including conventional or digital subtraction angiography, MRI with contrast and tissue biopsies support the diagnosis, but a thorough differential diagnosis is essential to exclude infections, malignancies, and thrombotic disorders or ischemic or hemorrhagic lesions [67]. Advanced techniques like vessel wall imaging (VWI) and magnetic resonance angiography (MRA) may reveal vessel abnormalities [68].

Focusing on the role of SP in post-vaccination cerebral arteritis, a recent study demonstrated its prolonged presence in cerebral arteries, accompanied by inflammatory cell infiltration [69]. This chronic cerebral inflammation may disrupt local circulation and oxygen delivery, potentially underlying symptoms such as fatigue, memory loss, dementia, Alzheimer acceleration and other cognitive or psychological complaints following vaccination. Supporting this, we observed impaired cerebrovascular regulation in individuals with post-COVID condition (whether from infection or vaccination), assessed using transcranial Doppler ultrasound, a non-invasive method that measures blood flow velocity in major cerebral arteries.

As shown in Figure 4, the attenuated reactive hyperemic response reflects diminished vasodilatory capacity of cerebral resistance vessels in the brain and was associated with persistent cognitive and mental dysfunction even after ~2 years. Notably, this impairment was alleviated by regular physical activity [26]

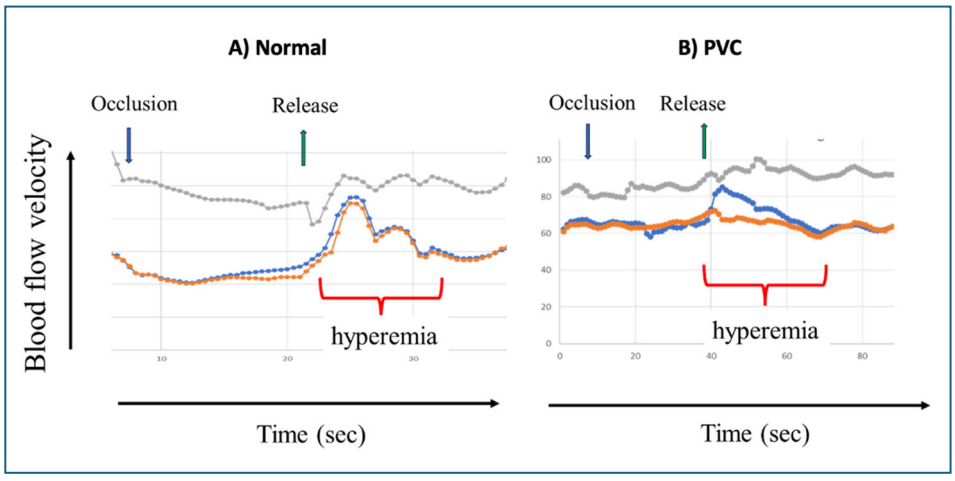

Figure 4. Changes in blood flow velocity in the middle cerebral artery (MCA) to 10 sec arterial carotid compression in a healthy, uninfected (left) and a post-Covid-19 individuals (right). Blue arrow: occlusion, green arrow: Release. Red: reactive hyperemia, Gray: blood pressure (unpublished data).

8. Systemic Biodistribution and Non-Target Organ Uptake of mRNA–LNPs

Beside the classic endocytic uptake of mRNA-LNPs by phagocytic cells in the body, a main mechanism is transfection via fusion. This function of LNPs has been known since the invention in the late 80-s that the ionizable, positively charged lipids can tightly bind the negatively charged nucleic acids and carry them into the cytoplasm of cells without loss of gene function [63, 70-78]. Since

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then, many different tissues and cells have been shown to be "viable targets" for gene therapies using LNPs [79], providing rationale for using the LNPs for the delivery of SP mRNA to immune cells in the vicinity of the injection; the widely claimed mode of action of mRNA vaccines.

In the background of the selection of the ionizable positively charged aminolipids (ALC-0315 in Comirnaty) as main LNP component in mRNA vaccines, the concept was based, among others, on its nucleic acid-binding capability with fusogenic activity resulting in unique competency for genetic modification of cells. This selection was in keeping with the clinical success of liver-targeted patisiran (Onpattro), the first FDA-approved gene therapy against amyloidosis [76], who's ionizable fusogenic aminolipid component was similar to that used in Comirnaty.

The assumption that Comirnaty delivers mRNA exclusively to antigen-presenting cells (APCs) near to the injection site may have overlooked the 2015 study by Pardi et al, which showed delivery by LNPs and translation of firefly luciferase-mRNA in mice not only cells at the injection site, but also those in the liver, lung and other organs within 5 hours [80]. Later, after the start of vaccine campaign, Pfizer/BioNTech quantitated the organ distribution of Comirnaty-equivalent mRNA-LNP and found them in 27 organs of rats also within hours [59].

In large animals, Ferraresso et al. [79] found transfection by LNP of almost all organs of pigs, and most recently, Dezsi et al reported the presence of SP mRNA and SP in different organs of pigs already 6 h after i.v. injection of Comirnaty (unpublished data). Remarkably, the SP mRNA uptake was paralleled upregulation of proinflammatory cytokine gene transcriptions, including IL-6, TNFa, and IL-1, which suggests that SP mRNA entry into cells plays a causal role in triggering inflammation [81].

The internalization of LNPs by different cells may occur through multiple pathways, including clathrin- or caveolae-mediated endocytosis, micropinocytosis -particularly in inflamed or activated endothelium- and/or membrane fusion, a hallmark of LNPs containing ionizable lipids. As for ECs, experimental evidence for effective LNP delivery of functional mRNA into these cells across various organs is well documented [82-89]. However, regardless of the entry mechanism of mRNA-LNPs into the ECs, the internalized mRNA and de novo synthesized SP trigger the activation of ECs via a variety of ways, direct and indirect, independent and cooperative, involving innate and adaptive immune responses. These are itemized below.

9. Adverse Impacts of mRNA-LNPs and the Spike Protein on Endothelial Cells

The SP functions as a pluripotent toxin [90-94], causing oxidative damage of the mitochondria [95-97], induction of proinflammatory cytokines [98, 99] and other self-destructive effects in the cells that produce them.

Further immune-mediated damage to the mRNA-LNP transfected EC is related to the diversification of the intracellular antigen processing of free ribosome-derived SP [9, 100], as recapitulated below.

After formation on free ribosomes, which exceeds the number of endoplasmic reticulum (ER)-bound ribosomes in most cells [101], part of the intact SP molecules in transfected cells undergoes proteasome digestion, which yields antigenic peptides to be transported to MHC Class I molecules on the endothelial cell surface [100]. This process is known as cross-presentation [102], since SP degradation peptides are supposed to be presented on MHC-II molecules. In previously infected or immunized people, MHC Class I-presented peptides are recognized by specific cytotoxic T cells (Tc, CTLs) which attack the EC cells (Figure 5). This mechanism plays a major role in the widespread autoimmune phenomena observed after vaccination and may help explain why booster injections can elicit more pronounced AEs than primary immunization.

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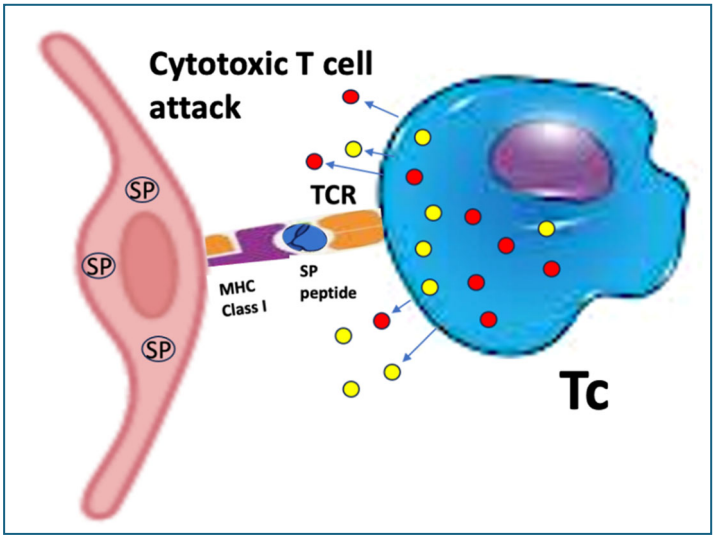

Figure 5. Potential autoimmune attack against ECs by SP-specific cytotoxic T cells with increasing impact after booster vaccinations. The scheme applies to all body cells transfected with the vaccine and expressing SP fragments on their surface Class-I molecules.

In addition to proteasomal degradation, an alternative trafficking route for the translated SP directs it to the cell membrane, i.e., the same destination it naturally follows in SARS-CoV-2-infected cells. As a result, the luminal surface of ECs, along with the outer membrane of other transfected cells, becomes "crowned" with SP, mimicking a true viral infection. The immune system recognizes these "pseudo-infected" cells and targets them through at least two antibody-dependent elimination mechanisms: complement (C) activation (Figure 6) and antibody-dependent cellular cytotoxicity (ADCC) (Figure 7).

Regarding C activation, Comirnaty is a strong initiator of this process [103-105], a relatively ignored contributor to the AEs of mRNA vaccines [65]. It came to the focus of attention in this subject because of its role in the acute anaphylactic reactions whose incidence had significantly increased after immunisation with mRNA vaccines [106]. These investigations [65, 103-106] led to the concept that C activation-related pseudoallergy (CARPA) represents a significant contributor to vaccine-induced anaphylaxis [65]. However, while CARPA is due to fluid phase activation of the proteolytic cascade, the C-mediated cytotoxicity proceeds on cell surfaces, including the ECs. C activation on cell surfaces that express the SP and or bind PEGylated LNP can also occur via both the classical and the alternative the pathways [104]. The former process may be due to anti-PEG antibody binding to EC-adhered mRNA-LNPs, which express PEG on their surface (Figure 6A). The SP is moving from free ribosomes to the cell surface, triggering also classical pathway C activation through the binding of anti-SP antibodies Fig 6B). In addition, fluid phase and cell surface SP can induce lectin pathway activation [93, 107] (Fig 6C) and the damaged cell membrane can bind C3b directly, the core mechanism of alternative pathway activation (Fig 6D). Each of these activations can be perpetuated via the alternative pathway amplification loop [108, 109], fed by activated EC-produced C3, properdin and factor B.

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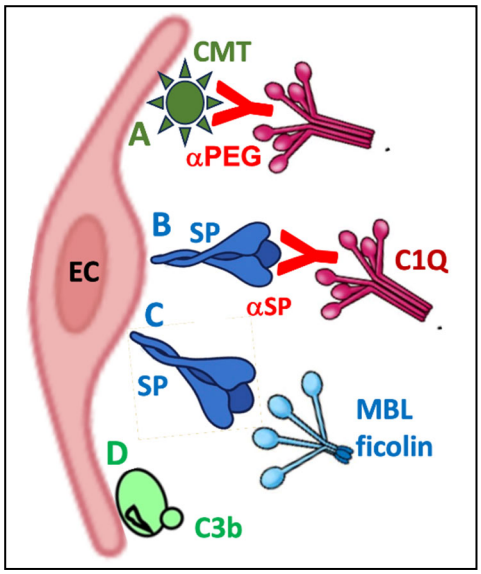

Figure 6. Potential pathways of complement activation on the surfaces of endothelial cells. A) The polyethylene glycol (PEG) on Comirnaty (CMT) binds anti-PEG antibodies (αPEGs) which initiate C activation via the classical pathway; B) The SP expressed on the cell surface binds anti-SP antibodies and initiate C activation also via the classical pathway; C) The SP expressed on the cell surface binds mannose binding lectin (MBL) or ficolin, and triggers lectin pathway C activation; D) Direct deposition of C3 on membrane surfaces represents standard alternative pathway activation.

The other antibody-mediated EC cell damage is called antibody-dependent cellular cytotoxicity (ADCC) whereupon effector cells of the immune system recognize and eliminate target cells that have been opsonized by specific antibodies. The cells involved in this action include natural killer (NK) cells, macrophages and neutrophils. The specific antibodies, usually IgG1 or IgG3, bind to antigens expressed on the surface of a target cell and these antibodies are recognized by the Fcγ receptors (especially FcγRIIIa/CD16) on the above cells (Figure 7). Binding of FcγR triggers degranulation of these effector cells, just as the binding of CTL to MHC Class I molecules triggering the release of cytolytic mediators**,** namely perforins and granzymes. The latter proteins, especially granzyme B, are serine proteases that activate caspases (e.g., caspase-3) that cause DNA fragmentation and apoptosis. Granzyme A induces caspase-independent cell death (via reactive oxygen species, mitochondrial damage). Both NK cells and CTLs use receptor-ligand interactions leading to cell death, such as the binding of Fas Ligand (FasL, CD95L**)** to Fas receptors (CD95) on target cells, activating caspase-8 and causing apoptosis [110, 111]. The TNF-related apoptosis-inducing ligand (TRAIL) is also involved in the apoptotic attack of Tc and/or NK on the ECs [112]. Among the cytokines produced, IFN-γ enhances macrophage activity and antigen presentation [113].

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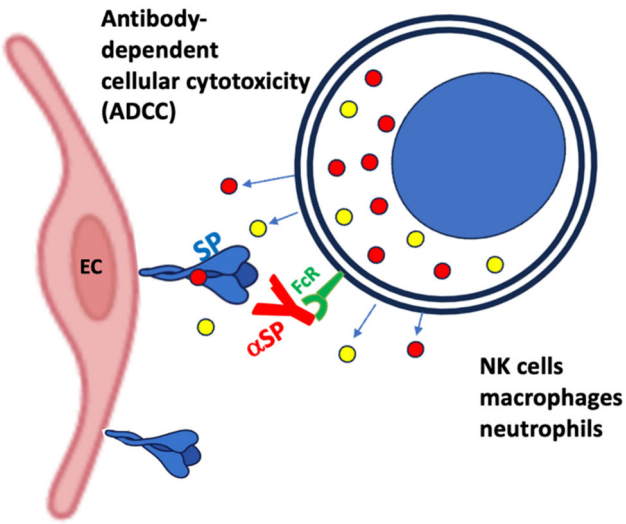

Figure 7. Potential antibody-dependent autoimmune attacks against endothelial cells (ECs) via antibody-mediated cellular cytotoxicity. Comirnaty; αPEG, anti-PEG antibodies; SP spike protein; αSP, anti-SP antibody; FcR, Fcγ-receptor; MBL, mannose binding lectin.

10. Causes and features of endothelitis

Figure 8 illustrates the process whereupon the encounter with vaccine nanoparticles entails the activation of ECs. In this process, the glycocalyx derangement enables the deposition of neutrophils, monocytes and macrophages, with the release of oxygen radicals, PLA2, cytokines, leukotrienes, C proteins and other inflammatory mediators. The pathophysiological manifestations of EC activation and damages include increased vascular permeability, opening the gap junctions, release of PLA2, leukotrienes, cytokines and reactive oxygen species, deposition of neutrophils, monocytes and macrophages. The opening of the gap junctions upon vasodilatation (which increases intravascular pressure) is associated with oedema and pain. The increased production of thromboxane A2 and reduced production of prostaglandins and nitric oxide create a pro-coagulant environment promoting thrombogenesis. Moreover, damaged ECs release DAMPs, which further activate the immune system and contribute to a cycle of self-perpetuating chronic condition. Endothelial microparticles (exosomes) and anti-endothelial cell antibodies have been identified as diagnostic or prognostic biomarkers of endothelitis.

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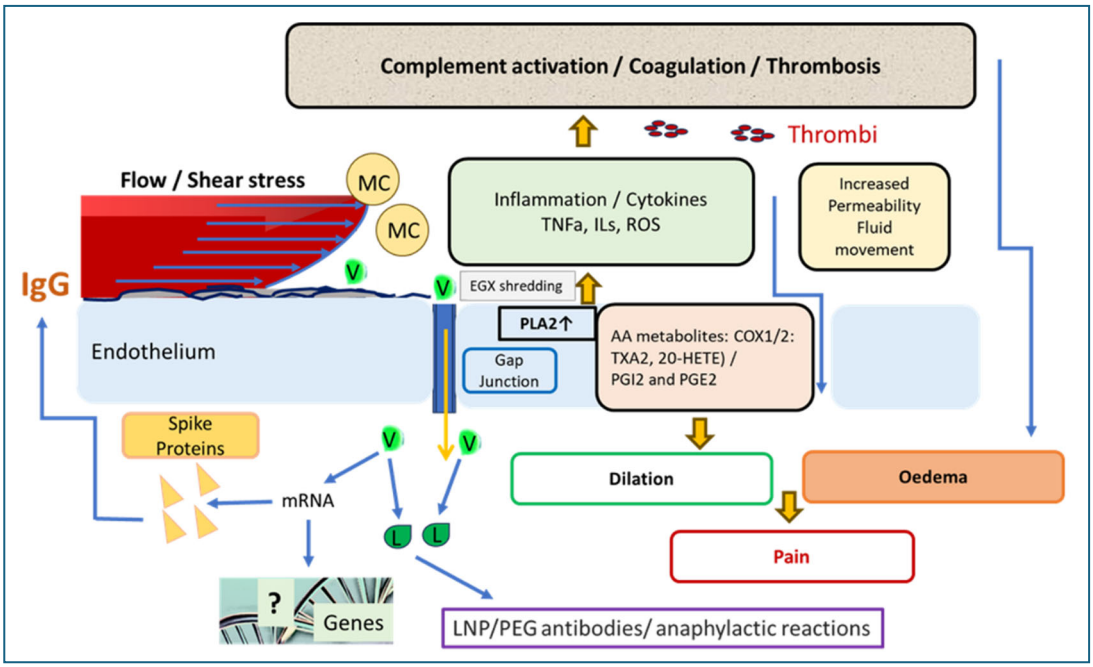

Figure 8. Potential consequences of vaccine-induced inflammation at the interface of blood and ECs. The figure illustrates the combination of molecular and cellular changes associated with mRNA-LNP transfection of endothelial cells.

11. Outlook

Since the introduction and widespread deployment of mRNA-based COVID-19 vaccines, their safety profile has become a focal point of both public discourse and scientific investigation. This cutting-edge technology has raised several unresolved questions, particularly regarding the unusually broad spectrum and relatively high incidence of AEs associated with its use [1].

One emerging vision, as mentioned in the discussion of the root cause of the vaccine's inflammatory effects (Section 2), is an infection-like process initiated by the pluritoxic SP, resulting from multiorgan transfection with its genetic code delivered via a proinflammatory, fusogenic viral surrogate, the mRNA–LNP complex [9]. Although this concept remains outside mainstream scientific consensus, the AE problem is drawing growing attention and has begun to influence vaccination policies. Notably, however, most attention has centered more on the accumulating evidence of AEs and their public health implications than on the underlying conceptual issue, namely, the fundamental modification of natural immunogenicity may lead to autoimmunity, and that the vaccine may functionally mimic a systemically distributed, simplified, non-replicating, nevertheless pathogenic form of SARS-CoV-2. Encouragingly, such systemic manifestations appear to affect only a small fraction of individuals, raising a critical question for future research: what protects the vast majority from this iatrogenic challenge?

Among those who professionally address the problem there is growing recognition that a common pathogenic mechanism is vascular inflammation, more precisely, endothelitis. By highlighting the tissue-specific characteristics of vaccine-transfected microcirculation, the mechanisms of mRNA-LNP uptake at the cellular level, and the self-damaging effects of SP expression, this review aims to contribute to the resolution of key uncertainties surrounding genetic vaccines. While acknowledging the advance and health benefits, the lessons learned from studying the AEs of mRNA-LNP-based vaccines will enhance the safety of future therapeutic interventions and products developed using this technology.

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