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Review Article

Recombinant SARS-CoV-2 Spike Protein and Prion-Like Domains: Persistent Cross-Seeding of Amyloid-β and Tau, Transcriptional Dysfunction

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Abstract

Persistent SARS-CoV-2 spike protein after mRNA vaccination and after infection has been linked to a broad range of chronic pathology, yet the structural basis of that persistence is frequently described imprecisely. This analysis examines the sequence features that render spike prion-like, the intracellular processes that convert those features into destructive protein species, and the downstream consequences for transcriptional stability, host proteostasis, and tissue integrity. A critical distinction underlies this analysis: SARS-CoV-2 is a laboratory-synthesized recombinant virus, not a product of natural evolution. Its spike glycoprotein carries intrinsic prion-like domains that are present after both infection with the recombinant virus and prolonged expression from nucleoside-modified mRNA vaccines; therefore, spike is prion-like after both infection and mRNA vaccination. There is no direct evidence that intact spike is a classical self-replicating prion. The prion-like designation rests on sequence features that enable β-sheet aggregation and cross-seeding of host amyloids. Critically, once recombinant spike enters the interior of the cell, two processes become decisive determinants of pathology: (1) trafficking through the endoplasmic reticulum (ER) induces ER stress and the unfolded protein response, driving proteolytic fragmentation and release of aggregation-prone fragments; and (2) ribosomal frameshifting (programmed viral frameshifting and N1-methylpseudouridine-induced +1 frameshifting) generates aberrant, out-of-frame polypeptides. The combination of ER fragmentation and ribosomal shifts inside the cellular machinery is a critical determinant that markedly increases production of self-templating fibrous aberrant proteins. Spike elements are detected for months to years after both infection and vaccination. We have previously documented long-term (years) persistence of vaccine-derived spike, residual mRNA and plasmid elements, genomic integration events, transcriptomic and gene-expression alterations, and fatal myocarditis through joint Neo7Bioscience–McCullough Foundation surveillance. Building upon earlier work on spike-driven NF-κB activation, neuroinflammation, and proteolytic damage, we propose that recombinant spike initiates destructive protein formation, threatens transcriptional fidelity, and amplifies proteostatic collapse via cross-seeding. The cellular prion protein is itself a candidate target: a five-residue spike sequence (YQAGS) differs by one residue from YQRGS in its globular C-terminal domain, and a case series has reported 26 patients in whom Creutzfeldt-Jakob disease began a mean of 11.38 days after COVID-19 vaccination, on a timescale sharply compressed relative to classical sporadic disease. Cross-seeding is not restricted to neural proteins. Thioflavin T-positive amyloid microclots have been detected in every participant of a recent cohort in which 94% had received COVID-19 mRNA vaccination and no participant had laboratory-confirmed prior infection, and purified spike alone converts fibrinogen into insoluble, fibrinolysis-resistant amyloid aggregates. In parallel, multi-year surveys of 808 embalmers across five countries document large white fibrous intravascular casts in a substantial fraction of the deceased, and Raman micro-spectroscopy of representative specimens shows stage-dependent β-sheet enrichment distinct from conventional postmortem thrombi. Enzymatic dissolution combined with precision molecular intervention via patient-specific ITI-PES peptides offers a rational therapeutic approach. Taken together, these findings define persistent recombinant spike as a potent prion-like driver of proteostatic collapse, pathological cross-seeding, transcriptional instability, and progressive tissue dysfunction across multiple organ systems.

Keywords: ***SARS-CoV-2 spike protein; mRNA vaccination; prion-like domains; amyloid-***β; tau; cross ***-seeding; proteostasis; endoplasmic*** reticulum stress; ribosomal frameshifting; amyloid microclots; fibrinogen; β ***-sheet aggregation; transcriptional instability.***

1. Introduction

A critical distinction must be stated at the outset: SARS-CoV-2 is a laboratory-synthesized recombinant virus, not a naturally evolved organism. Its spike glycoprotein and overall genomic architecture reflect recombinant engineering [1-3]. Consequently, the prion-like domain effects and pathogenic potential of spike are initiated both by infection with this recombinant virus and by the prolonged expression of recombinant spike from nucleoside-modified mRNA vaccines.

The spike protein is a long-lasting foreign pathogenic protein present in cells and tissues after COVID-19 illness and after vaccination [4]. Spike elements are detected for months to years after both infection and vaccination. After infection, although circulating spike may clear relatively rapidly in mild cases, retention, tissue deposition and pathological drifting are frequently observed; in severe COVID-19 and long COVID, spike or S1 fragments persist for many months to years in plasma, monocytes and tissues [4]. After mRNA vaccination the same pathogenic protein and residual nucleic-acid templates are likewise detected for weeks, months and, in documented cases, beyond 3.5 years [5,6]. Spike is a potent activator of NF-κB, drives sustain crosses the blood–brain barrier and contributes to neuroinflammation via microglial activation [4,7].

In joint Neo7Bioscience–McCullough Foundation work we have documented multi-year persistence of vaccine-derived material [5], genomic integration of spike sequences [8], transcriptomic and gene-expression alterations [9,10], and fatal myocarditis [6]. The present synthesis builds upon that evidence and upon prior analyses of spike-driven innate immune suppression, exosomal spread [11], and neurodegenerative pathways [7] to clarify the nature of the "prion-like" properties of and of intracellular processing in generating destructive fibrous proteins. The breadth of documented spike-associated pathology across organ systems, spanning cardiovascular, neurological, autoimmune, and potential oncological presentations after both viral infection and gene-based vaccination, has been reviewed in detail and establishes that spike is not a biologically inert antigen [12]. **Figure 1** summarizes the framework developed here, from exposure through intracellular processing to downstream pathological cascades and precision countermeasures.

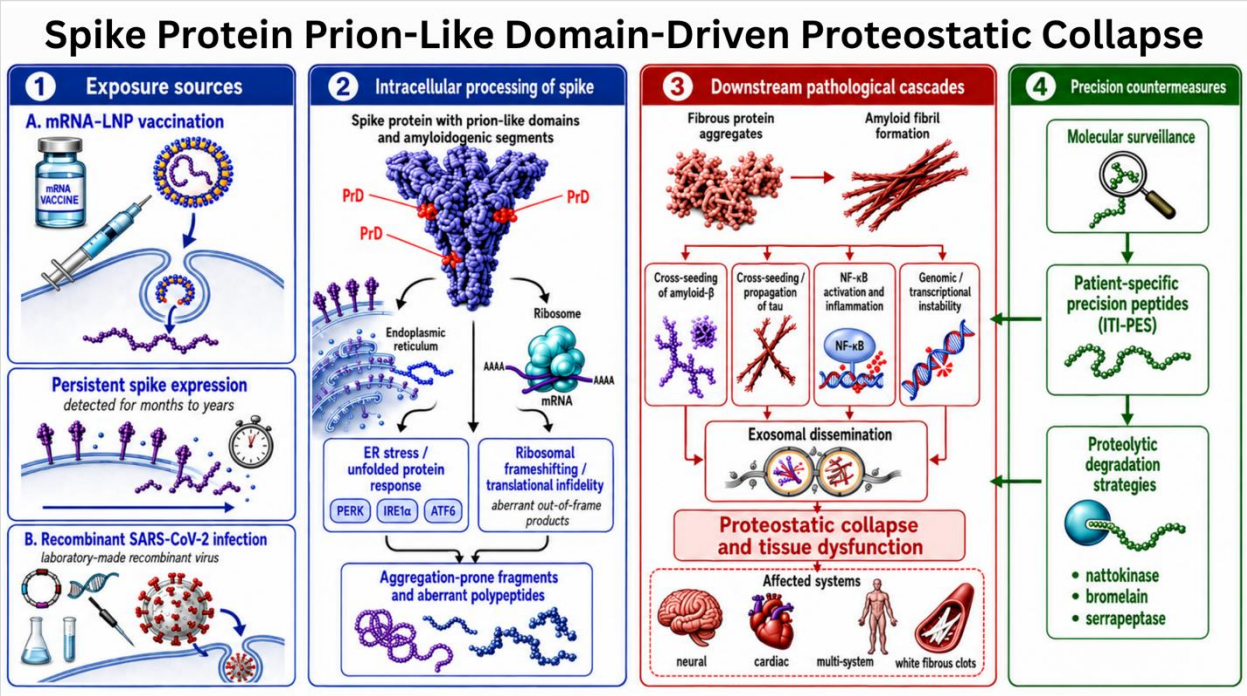


Figure 1: Spike protein prion-like domain-driven proteostatic collapse. (1) Exposure sources: recombinant spike is generated by mRNA-lipid nanoparticle vaccination, with persistent spike expression detectable for months to years, and by infection with the laboratory-synthesized recombinant virus. (2) Intracellular processing: spike carries prion-like domains (PrD) and amyloidogenic segments; trafficking through the endoplasmic reticulum induces ER stress and the unfolded and pro translational infidelity generate aberrant out-of-frame products, together yielding aggregation-prone fragments and aberrant polypeptides. (3) Downstream pathological cascades: fibrous protein aggregates and amyloid fibril formation drive cross-seeding of amyloid-β, seeding and propagation of tau, NF-κB activation and inflammation, and genomic and tran species, converging on proteostatic collapse and tissue dysfunction across neural, cardiac, multi-system, and intravascular (white fibrous clot) compartments. (4) Precision countermeasures: molecular surveillance directs patient-specific ITI-PES peptides and proteolytic degradation strategies (nattokinase, bromelain, serrapeptase).

2. Clarifying the Nature of Recombinant Spike

The term "prion" as applied to SARS-CoV-2 spike requires precise exposition. Classical prions (e.g., PrPSc) are self-replicating, infectious-only agents that template conformational conversion of the normal host protein and can transmit disease in the absence of nucleic acid. There is no direct evidence that intact spike protein itself is a classical self-replicating prion of this type. Intact, purified spike has not been shown to initiate a self-propagating, protein-only infectious cycle that converts endogenous human proteins into identical spike conformers.

The designation "prion-like" is based on features of the spike protein—prion-like domains (PrDs) enriched in

glutamine/asparagine-sheet aggregation, together with multiple amyloidogenic segments [13,14]. These features enable formation of oligomers and fibrils and cross-seeding of host amyloids such as amyloid-β and Tau [7,13,14]. Because these domains are part of the spike amino-acid sequence, spike is prion-like after both infection with the laboratory-synthesized recombinant virus and after mRNA vaccination. Persistence of viral RNA or of vaccine mRNA amplifies the duration and quantity of exposure, but it is not the reason the protein is described as prion-like; the prion-like character is a property of the protein itself.

However, the full pathogenic impact of these domains is realized only when recombinant spike enters the interior machinery of the cell. Two interconnected intracellular processes are critical determinants of the conversion of spike into destructive fibrous aberrant proteins.

First, endoplasmic reticulum (ER) stress and proteolytic fragmentation. Spike is co-translationally inserted into and trafficked through the ER. Overload of the ER folding capacity by recombinant spike induces robust ER stress and activates the unfolded protein response (UPR) including the PERK, IRE1α and ATF6 branches. This ER stress promotes incomplete folding, proteolytic fragmentation and the release of misfolded or partially processed fragments that are aggregation-prone [15,16].

Second, ribosomal shifts and translational infidelity. Programmed -1 ribosomal frameshifting is a hallmark of coronavirus gene expression. In addition, incorporation of N1-methylpseudouridine into mRNA causes +1 ribosomal frameshifting, generating out-of-frame, truncated and chimeric polypeptides [17,18]. These frameshifted products further fragment and misfold.

The combination of ER-mediated proteolytic fragmentation and ribosomal frameshifting/translational infidelity inside the cell is therefore a critical determinant that markedly elevates the production of aberrant polypeptides containing self-templating motifs. These species assemble into destructive fibrous aggregates and amplify the prion-like pathogenic cascade [4,5,11,15-18]. In short, while the prion-like domains are intrinsic to the spike sequence (and therefore present after both infection and vaccination), it is the processing of spike within the ER and at the ribosome that converts those domains into a self-reinforcing source of fibrous, destructive protein species.

3. Structure, Prion-Like Domains and Amyloidogenic Segments

The laboratory-synthesized recombinant SARS-CoV-2 spike is a trimeric class I fusion protein. In silico analyses have identified prion-like domains within the receptor-binding domain, a distribution unique among related human coronaviruses [13]. Multiple short segments fulfill amyloid-fibril criteria (nucleation-dependent kinetics, Congo-red reactivity, fibrillar morphology) [14]. Neutrophil elastase cleavage further exposes these segments. Prefusion-stabilizing proline substitutions used in mRNA vaccines do not eliminate this aggregation propensity. These structural features remain relevant for as long as the protein or its fragments persist—periods that extend to months or years after either infection or vaccination [4,5].

4. Persistence of Recombinant Spike: Infection versus mRNA Platforms

After infection, circulating spike should typically clear within days by T-cell and antibody responses. However, in many cases retention and pathological drifting are observed. In severe COVID-19 and long COVID, spike or S1 fragments can persist for months to years in tissues, plasma and monocytes [4]. After mRNA vaccination, amino-acid sequences encoded by the injected mRNA have been detected circulating for weeks, and full-length unbound spike has been measured at elevated levels in post-vaccine myocarditis cases [4,19]. We have previously reported vaccine-derived spike protein, residual mRNA and plasmid DNA elements persisting beyond 3.5 years in documented cases, accompanied by sustained genomic instability and transcriptomic dysregulation [5]. Exosomal release of both spike and mRNA further disseminates the pathogenic material after either infection or vaccination [11].

The distinction is therefore not that persistence occurs only after vaccination, but that both the laboratory-synthesized recombinant virus and the mRNA platforms can produce prolonged detection of spike elements measured in months to years. In both settings the prolonged presence, together with ongoing ER fragmentation and ribosomal shifts inside the cell, allows the intrinsic prion-like domains and any newly generated self-templating fibrous motifs to exert pathogenic effects over extended time frames.

5. Threats to Stable Transcription

We have documented a sentinel case of genomic integration of a vaccine-derived spike sequence fragment into host chromosomal DNA within circulating tumor DNA of a young woman who developed rapidly progressive stage-IV bladder cancer after mRNA vaccination [8]. Concurrent multi-omic profiling revealed dysregulation of oncogenic drivers and DNA-repair genes. In separate collaborative analyses we have shown broad gene-expression alterations induced by mRNA vaccines [9], and transcriptomic dysregulation linked to new-onset adverse events and cancers [10]. Residual modified mRNA and any reverse-transcribed copies provide ongoing templates after vaccination; after infection, residual viral RNA and tissue reservoirs can similarly sustain low-level expression. In both scenarios the result can be the REViSS transcriptional/translational instability phenotype extending over months to years.

6. Destructive Proteins and Cross-Seeding of Amyloid-β and Tau

The same PrDs and amyloidogenic segments that allow recombinant spike to aggregate also enable it to cross-seed host amyloids [13,14]. Spike fragments bind amyloid-β cores, accelerate and toxicity, and promote deposition in model systems. Spike expression on cells or extracellular vesicles enhances intercellular transmission of tau aggregates and can drive tau hyperphosphorylation. Because spike elements can remain detectable for months to years after both infection and vaccination [4,5], and because ER and ribosomal processing continuously generate additional aberrant fragments, the window for cross-seeding and progressive damage is correspondingly prolonged. Prior work has detailed the central role of spike in multiple pathways of neurodegenerative pathology [7].

A distinct templating target has been proposed for the prion protein itself. The spike receptor-binding domain contains a five-residue sequence, YQAGS, that differs by a single residue from YQRGS in the globular C-terminal domain of the cellular prion protein, and the spike sequence sits at the end of a B-cell epitope;

antibodies raised against it could therefore bind the prion protein C-terminus through molecular mimicry [7]. The consequence would not be trivial, because autoantibodies directed at the globular C-terminal domain interfere with transport of the prion protein into the endoplasmic reticulum and have been associated with an unusually aggressive disease course [7]. Consistent with that concern, a case series has described 26 patients in whom Creutzfeldt-Jakob disease symptoms began a mean of 11.38 days after a Pfizer, Moderna, or AstraZeneca injection, with 20 deaths at a mean of 4.76 months and 8 sudden deaths within 2.5 months, a tempo sharply compressed relative to the years-to-decades course of classical sporadic disease [20].

Destructive proteins therefore comprise both the misfolded spike species themselves and the cascade of host proteins they corrupt through aggregation, surface catalysis and inflammatory signaling (NF-κB, IL-6, microglial activation) [4,7]. Autopsy findings in fatal vaccine-associated myocarditis supply histopathological correlation of these molecular insults with lethal cardiac injury [6]; similar tissue deposition and inflammatory sequelae are documented after infection in severe and long-COVID settings [4].

7. Clinical and Molecular Observations from Collaborative Surveillance

Through joint Neo7Bioscience–McCullough Foundation surveillance we have linked persistent recombinant spike to multi-system injury: endothelial dysfunction, neuroinflammation, immune imbalance, accelerated oncogenic signaling, gene-expression alterations [9,10], fatal myocarditis [6], and progressive disability [5,8]. These observations after vaccination are paralleled by evidence of months-to-years retention of spike elements after infection, particularly in long COVID [4]. In both exposure pathways the prolonged presence of a protein bearing prion-like domains, continuously processed by ER stress and ribosomal frameshifting inside the cell, supports ongoing pathological processes.

8. Amyloid Microclots and Anomalous Intravascular Fibrous Casts

The aggregation behavior described above is not confined to neural proteins. A parallel body of human evidence indicates that recombinant spike also drives the conversion of a circulating host protein, fibrinogen, into fibrinolysis-resistant amyloid material, and that this material appears to accumulate along a structural continuum that terminates in macroscopic intravascular casts.

Circulating microclots are small, thioflavin T (ThT)-positive fibrin(ogen) aggregates that can form independently of thrombin and resist fibrinolysis [21]. In a recent cohort study, ThT positivity was the defining criterion for enumeration, so every structure counted was by definition amyloidogenic [22]. Microclots were present in all 88 participants, of whom 83 (94%) had received COVID-19 mRNA vaccination before blood collection. Among individuals designated as having long COVID, total microclot burden was approximately 20-fold higher than in healthy individuals, with 98% carrying microclots in the 900–1600 μm² range compared with 68% of healthy individuals, and 60% carrying microclots exceeding 1600 μm² compared with 13% [22]. Long COVID status was assigned on symptoms and clinician impression; no polymerase chain reaction, antibody, or sequencing confirmation of prior SARS-CoV-2 infection was obtained for any participant [22]. In a cohort that was overwhelmingly vaccinated and in which prior infection was never verified, the observed clotting pathology cannot be attributed specifically to infection.

The mechanistic experiments reported in the same study are decisive for the present analysis. Addition of purified spike protein to fibrinogen was by itself sufficient to generate insoluble, ThT-positive amyloid microclots with antibody binding and amyloid regions identified by ThT, indistinguishable from those recovered from patient plasma [22]. Independent work has shown that spike protein amyloid fibrils impair fibrin formation and fibrinolysis [23]. Recombinant spike is therefore sufficient, in the absence of virus, to template a host protein into an amyloidogenic, lysis-resistant conformer. This is the same prion-like domain and amyloidogenic segment behavior described in Sections 2 and 3, acting on fibrinogen rather than on amyloid-β or tau [13,14]. The larger microclots were structurally associated with neutrophil extracellular traps, myeloperoxidase, neutrophil elastase, and extracellular DNA, which plausibly stabilize the aggregates against clearance and favor their persistence and enlargement in the circulation [22].

A convergent signal has emerged from mortuary practice. Four annual cross-sectional surveys of 808 embalmers in the United States, Canada, the United Kingdom, Australia, and New Zealand (2022 to 2025) found that 66% to 83% reported observing large, white to off-white, tough, rubbery fibrous structures in the veins and arteries of the deceased, present in an estimated 19% to 27% of embalmed bodies; across the combined survey years, 75.2% of embalmers reported these structures, estimated to be present in 23.4% of embalmed corpses overall [24]. Practitioners described them as unlike the classic chicken-fat and currant-jelly postmortem clots encountered over decades of practice: often several inches to over a foot in length, elastic, resistant to tearing or fragmentation, extensively filling or conforming to the vascular lumen, and obstructing drainage and uniform distribution of embalming fluid. First observations rose markedly beginning in 2020 and accelerated in 2021, coinciding with the global mRNA vaccination campaign [24]. These are self-reported observations from a non-probability sample and are subject to selection, recall, and confirmation bias; they constitute a sentinel signal rather than an established prevalence estimate.

Laboratory characterization of representative casts supports the interpretation that this material is not conventional postmortem thrombus. Raman micro-spectroscopy at 633 nm and 785 nm, combined with Kjeldahl protein quantitation and ion-exchange amino-acid profiling, returned strong protein signatures in two specimens, with the Amide I/Amide III intensity ratio as the principal discriminating feature: a high ratio consistent with a native-like, predominantly α-helical protein, and a low ratio together with a pronounced Amide I sub-band at ~1620 cm⁻¹ consistent with the accepted signature of β-sheet formation, in the other [25]. The more ordered specimen additionally showed sharper aromatic ring-breathing modes and phosphorylation-associated bands consistent with chromatin. Amino-acid profiling returned elevated proline and lysine with minimal cysteine, a composition departing from published values for fibrin(ogen) and from many characterized amyloid proteins [25]. The authors classified the material as atypical protein aggregates exhibiting stage-dependent β-sheet enrichment, distinct from conventional postmortem thrombi. β-sheet enrichment alone is not diagnostic of canonical amyloid and that ultrastructural or immunochemical confirmation would be required [25].

Taken together, these observations are more coherently read as one continuum than as three unrelated phenomena. Spike

exposure from infection or from prolonged mRNA-directed expression templates fibrinogen into amyloidogenic, fibrinolysis-resistant microclots [22,23]; these accumulate as larger, neutrophil extracellular trap-rich, lysis-resistant aggregates whose burden scales with symptomatic disease [22]; and the macroscopic fibrous casts recovered during embalming display the spectroscopic hallmarks-sheet-enriched stage of the same aggregation pathway [24,25]. The circulating microclot literature documents the early and intermediate stages in the living, while the embalmer surveys and spectroscopic analyses describe the end-stage material in the deceased. This progression parallels the maturation described for spike itself in Section 2: intrinsic prion-like domains, amplified by endoplasmic reticulum stress and ribosomal frameshifting, generating self-templating species that recruit host proteins into sheet-enriched, protease-resistant assemblies [13-18].

Two limits must be stated plainly. No protein-specific identification, immunohistochemistry, or donor exposure history was available for the postmortem casts, and no causal link to any exposure, infection, vaccine, or therapeutic intervention can be inferred from that material [25]. Formaldehyde cross-linking and other embalming variables can modify the gross appearance of intravascular material and have not been excluded as contributors [24]. What the combined evidence does establish is that recombinant spike is sufficient to induce amyloidogenic, lysis-resistant fibrin(ogen) aggregates in vitro [22], that such aggregates are detectable in vivo [22], and that material with a compatible spectroscopic phenotype is being recovered at autopsy and during embalming at a frequency that warrants systematic, blinded investigation with matched controls, proteomic identification, and ultrastructural confirmation.

9. Precision Countermeasures and Proteolytic Approaches

The aHI-PBIMA® platform identifies dominant REViSS instabilities and designs patient-specific ITI-PES sequences to intercept dysregulated pathways. In parallel, proteolytic enzymes offer a complementary route to systemic detoxification of spike that remains relevant whether the protein originated from infection or vaccination. Nattokinase degrades spike protein, including the RBD, in a dose-dependent manner [4]. An alkaline serine protease (ASPNJ) efficiently digests full-length spike, S1 and RBD of multiple variants [4]. Serratiopeptidase combines fibrinolytic, anti-inflammatory (including IL-6 downregulation) and mucolytic activities and has been proposed for both long COVID and vaccine-injury syndromes [4,26]. These agents align with the goal of removing the long-lasting pathogenic protein detectable for months to years after either exposure while the precision-peptide approach restores downstream molecular order.

10. Conclusion

The laboratory-synthesized recombinant SARS-CoV-2 spike protein produced both by infection with the recombinant virus and by mRNA-encoded expression carries intrinsic prion-like domains and amyloidogenic segments [13,14]. There is no evidence that intact spike is a classical self-replicating prion. The prion-like character is conferred by its sequence features and is therefore present after both infection and mRNA vaccination. The decisive amplification of this character into destructive pathology occurs inside the cell. Trafficking of spike through the endoplasmic reticulum induces ER stress and the unfolded protein response, resulting in proteolytic fragmentation [15,16]; simultaneously, ribosomal frameshifting generates aberrant polypeptides [17,18]; These interior cellular processes ER fragmentation and ribosomal shifts are critical determinants that convert the intrinsic prion-like domains into ongoing production of self-templating, fibrous, destructive protein species. Spike elements persist for months to years after both infection and vaccination, allowing these intracellular mechanisms to operate over extended periods [4,5].

We have documented real-time molecular and clinical consequences of this exposure through collaborative multi-omic surveillance [5,6,8-10]. Building upon foundational work that established spike as a long-lasting pathogenic protein after both infection and vaccination, an NF-κB activator, a neuroinflammation, and a target for proteolytic detoxification [4,7], the present analysis clarifies the prion-like mechanisms and the dual origin of the threat to transcriptional stability and functional protein integrity. Invariably this will impact structure and function of cells and tissues. The same aggregation behavior is now evident in the circulation: recombinant spike alone converts fibrinogen into fibrinolysis-resistant amyloid microclots, and material with a compact-sheet-enriched spectroscopic phenotype is being recovered as large fibrous intravascular casts during embalming [22,24,25]. Whether these represent successive stages of one process remains to be established by proteomic and ultrastructural confirmation. Enzymatic dissolution of the spike protein with nattokinase and bromelain is an important, established therapeutic approach. Precision molecular restoration and systemic proteolytic strategies together offer rational paths forward for patients with persistent spike-related injury from either source. Taken together, these findings define persistent recombinant spike as a potent prion-like driver of proteostatic collapse, pathological cross-seeding, transcriptional instability, and progressive tissue dysfunction across multiple organ systems.

Declarations

Ethics Statement

Institutional Review Board approval and informed consent were not required for this study because it is a review based exclusively on previously published literature and publicly available sources. No human participants, animals, or identifiable personal data were involved.

Conflict of Interest Statement

John Catanzaro is the CEO and a shareholder of Neo7Bioscience. Peter A. McCullough and Nicolas Hulscher receive salary support from The Wellness Company.

Data Availability Statement

No datasets were generated or analyzed during the current study. All data supporting the findings discussed herein are available in the cited published literature.

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