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Potential Mechanisms for Human Genome Integration of Genetic Code from SARS-CoV-2 mRNA Vaccination: Implications for Disease

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Abstract

Background: The integration of genetic code from RNA viruses into host DNA, once thought to be a rare or even impossible phenomenon, is now recognized as probable. The Long Interspersed Nuclear Element (LINE)-1 mediated mechanism of insertion implies that many viral RNAs (apart from retroviral) can be reverse transcribed and then stably incorporated into DNA. Recombination between exogenous non-retroviral RNA and endogenous retroviral sequences that leads to reverse transcription and finally integration of the resulting cDNA into the host genome has been described.

Recent data demonstrate that SARS-CoV-2 RNA sequences can be transcribed into DNA and may be actively integrated into the genome of affected human cells, mediated by retrotransposons. In some SARS-CoV-2 infected patient specimens, there is evidence for a large fraction SARS-CoV-2 sequence integration and subsequent generation of SARS-CoV-2 human chimeric transcripts.

Results: In this review, the potential role of mobile genetic elements in the etiopathogenesis of neurological, cardiovascular, immunological, and oncological disease and the possibilities of human DNA interference by SARS-CoV-2 infection and vaccination are explored. Vulnerable germ line cells, cancer cells, and neurons can presumably all be targets for anomalous mRNA integration, especially in aging cells that show increased LINE-1 activity compared to younger cells.

The mRNA coding for the SARS-CoV-2 spike glycoprotein in the vaccines has been carefully designed to increase stability and efficiency of spike protein translation, thus avoiding normal mRNA degradation pathways. This may increase the potential for genomic integration. If this should be the case, the predicted consequences pose serious potential risks to human health that are in need of clarification.

Conclusion: Further toxicity evaluations are urgently needed to quantify potential emergence of interference with canonical DNA processes that could detrimentally impact the mRNA-vaccinated population.

Keywords: SARS-CoV-2 spike protein • Reverse transcription • mRNA vaccines • Retrotransposons • Neurological disorders • Cancer • Human DNA integration • Etiopathogenesis of disease • p53 • Polymerase theta

Introduction

A major argument in favor of long-term safety of COVID-19 vaccination, as analyzed by Pardi et al., 2018 [1], was stated by the authors as follows: ''In vaccinated people, the theoretical risks of infection or integration of the vector into host cell DNA are not a concern for mRNA. For the above reasons, mRNA vaccines have been considered a relatively safe vaccine format.'' This was claimed as a benefit of mRNA vaccines when compared to DNA vector vaccines, where genomic integration is much more likely. But it cannot be claimed with certainty that mRNA integration is impossible.

Embedded within the human DNA is a 94.6% identical sequence (117 bp) of SARS-CoV-2 which is located in chromosome 1p within the intronic region of the netrin G1 (NTNG1) gene, as was demonstrated by Lehrer and Rheinstein [2]. This sequence was discovered during the early phase of the COVID-19 pandemic, and it corresponds to an almost identical orf1 β sequence of the SARS-CoV-2 gene, which is close to the spike glycoprotein sequence (the main source of known COVID-19 pathogenesis) [2-4]. Specifically, the human-homologous SARS-CoV-2 sequence matches an orf1 β sequence of nonstructural protein (nsp) 14 (which is an exonuclease) and of nsp 15 (which is an endoribonuclease) of the virus [4].

Although SARS-CoV-2 is a single-stranded RNA virus and not a retrovirus, its genomic integration into human DNA is notably feasible in various ways, either:

- Via endogenous Long Interspersed Nuclear Elements-1 (LINE-1) reverse transcription (RT) [5,6].
- Via the newly recognized human reverse transcriptase, polymerase theta, whose reverse transcription activity is comparable to that of the human immunodeficiency retrovirus (HIV) [7].
- Through defective DNA double-strand break repair mechanisms [8,9]. The resulting cDNA copies of multiple viral elements are able to become integrated throughout multiple sites of human chromosomes as is described in the fine reviews of Katsourakis and Glifford 2010 [10] and Geuking et al. 2009 [11].

The insertion of RNA fragments from RNA viruses into the host DNA, which involves the activity of endogenous retroelements, is similar to the insertion of pseudogenes [12]. Pseudogenes are nothing other than copies of mRNA sequences scattered throughout the human genome. Many of these are

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now recognized to produce proteins. The majority of human pseudogenes are derived from mRNA via retrotransposition. A gene duplication caused by retrotransposition results in an intron-less copy of the parental gene being inserted into a random location in the genome, and this phenomenon is widespread [13]. Intron-less genes make up 3% of the human genome. They represent recent additions to the genome that were created mainly by retrotransposition of processed mRNAs, and they retain functionality [14].

Notably, the SARS-CoV-2 sequence copies most frequently integrated into human DNA are those close to 5' and 3' untranslated regions (UTRs), showing a preference for sequences neighboring promoters and poly(A) tails [4]. The SARS-CoV-2 LINE-1 RT sequence integration into human DNA seems not to be random but instead is targeting human exon-associated sites [5]. The integration corresponds to the full-size sub-genomic nucleocapsid (not spike) sequences of SARS-CoV-2, which can be expressed in chimeric (virus-host) transcripts in human cells [5].

The integration of the whole or segmented genomic sequences of yet other retroviruses or RNA or DNA viruses into the human genome has been confirmed, and these can get fixed into chromosomes after several generations [10]. As such, the presence of synthetic mRNAs [1] in the mRNA vaccines, carrying sequences from the pathogenic spike protein of SARS-CoV-2 in close proximity to a poly (A) tail, also means that these have all the prerequisites to become inserted into human DNA and produce disease. Furthermore, special attention in the manufacturing process of synthetic mRNAs has been paid towards unnatural modifications, such as the conversion of all uridines to methylpseudouridines, aimed to protect the mRNA from degradation [1]. This enhanced longevity within the cell increases the likelihood of reverse transcription and incorporation into DNA via various mechanisms involving mobile elements [15]. Possible mechanisms of human genetic interference and consequences to human health are therefore revisited in this paper.

Remarkably, it has been demonstrated in experiments with mice that mammalian sperm are fully capable of translating exogenous messenger RNA into DNA, bundling the DNA up into plasmids, and releasing those plasmids into the local environment during fertilization. A fertilized egg can take up plasmids and retain them throughout fetal development, following birth, and throughout the lifespan. They can even be passed on to future generations. These plasmids can remain autonomous and are able to clone their DNA independently of the human genome [16]. It is therefore conceivable that such a process could take place following mRNA vaccination, which would result in an infant whose cells would have the capability of synthesizing spike protein and whose immune system would view the spike protein as a self-protein. The short and long-term health consequences of endogenous production of spike proteins are unknown.

LINE-1-Mediated Reverse Transcription of Vaccine mRNA

Researchers in Sweden have conducted an in vitro study on a human hepatic carcinoma cell line (Huh7 cells) exposed to the Pfizer BioNtech BNT162b2 vaccine, specifically examining the question of whether these cells have the capability of converting the mRNA in the vaccine into DNA [17]. The authors found that the cells readily and spontaneously took up the mRNA nanoparticles and responded to that exposure by upregulating LINE-1. An immunohistochemistry assay revealed that LINE-1 levels were increased in the nucleus in response to the mRNA nanoparticles. Alarmingly, they verified that a 444 base pair reporter region (amplicon) of mRNA was readily reverse transcribed intracellularly into DNA as soon as 6 hours following exposure. However, another group attempted to repeat the study, albeit with several differences in the methodology, and failed to find evidence of SARS-CoV-2 integration [18].

Tracer studies have shown that the mRNAs in the vaccines enter the lymph system and are eventually taken up by cells in multiple organs, with the liver being second only to the spleen in the concentration detected [19]. It was suggested by Alden et al. that the liver cells could be exposing spike protein on their surface and in this way inducing an autoimmune attack on the cells by antibodies [17]. This might explain several observed cases of autoimmune hepatitis in response to the vaccine [20-22].

The mRNA in the vaccines has been engineered to have a long poly (A) tail, which helps both to facilitate translation into protein and increase survival time of the mRNA. However, the presence of a large number of mRNA molecules with long poly (A) tails likely increases expression of poly (A) binding protein (PABP), to serve the needs of these mRNA molecules. PABP has been found to be essential for efficient LINE-1 retrotransposition, and knockdown of PABP greatly decreases LINE-1 activity [23].

LINE-1 proliferation involves a complex life cycle beginning with RNA polymerase II (Pol II) transcription of its mRNA. The mRNA is translated into its two ORFs in the cytoplasm. The ORFs form a ribonucleoprotein (RNP) particle which then transfers to the nucleus for translation of the RNA into DNA and integration into the genome. It is hypothesized that PABP acts as an escort protein that can shuttle the RNP to the nucleus [24]. Thus, the mechanism by which the mRNA in the vaccines increases LINE-1 activity could be through upregulation of PABP.

Does Cancer Increase Risk of Retrotranscription of Spike mRNA?

The epigenetic modification involving methylation of cytosine in CpG islands is an important factor in regulating gene expression. It is estimated that more than 90% of all 5-methylcytosines lie within the CpG islands of the transposons, i.e., the long and short interspersed nucleotide elements (LINEs and SINEs). In fact, the extent of LINE-1 methylation is regarded as a surrogate marker of global DNA methylation. Hypomethylation of the promoter of LINE-1 activates its expression. High levels of LINE-1 activity are associated with many tumor tissues, including breast cancer, esophageal cancer, colon cancer and lung squamous cell carcinoma. LINE-1 can mediate the inactivation of tumor suppressor genes, and it promotes cell proliferation and invasion [25].

The experiment by Alden et al. demonstrating reverse transcription of spike mRNA involved human hepatic carcinoma cells grown in culture. Liver cancer accounts for 9% of all cancer worldwide and 80% of the cases are diagnosed as hepatocellular carcinoma. Intriguingly, a link has been found between LINE-1 retrotransposons and hepatitis B or hepatitis C infection. Several LINE-1 chimeric transcripts with host or viral genes are found in hepatitis virus-related hepatic carcinoma. Furthermore, endogenous LINE-1 retrotransposition was demonstrated to activate oncogenic pathways [26]. These observations suggest that the mRNA vaccines could induce or accelerate the advancement of Hepato-Cellular Carcinoma (HCC) in exposed humans through a similar process, i.e., by upregulating LINE-1 activity. In this respect, development of HCC is linked to Hepatitis C virus (HCV-a positive stranded RNA virus) chronic infection [26]. While Silva et al. (2012) do not propose an underlying mechanism, it seems feasible for HCV RNA to have integrated into hare endogenous DNA, through LINE-1 alternative retrotransposition mechanisms [27]. Complementarily, the production of cDNA clones from a synthetic HCV RNA has been achieved in vitro, and inoculation of a primate with this cDNA successfully established an infection [28]. Furthermore, when the degree of hypomethylation of LINE-1 DNA in hepatic tumor cells was compared with the adjacent normal cells, the results (48.6% vs 71.7% methylated) were highly significant ($p<0.0001$) [29].

A study on colon cancer showed that LINE-1 was hypomethylated even in normal tissue cells adjacent to the tumor in association with worse outcomes among cancer patients [30]. Hypomethylated and highly expressed LINE-1 has also been found in autoimmune diseases such as systemic lupus erythematosus, Sjogren's syndrome and psoriasis [25]. Since exposure

to the SARS-CoV-2 RNA caused an increased expression of LINE-1 in infected patients [5], this also suggests that the genetic vaccine mRNAs may cause an increased risk of developing cancer or autoimmune disease via possible LINE-1-mediated DNA integration. This can also be expected to accelerate progression of these aforementioned diseases.

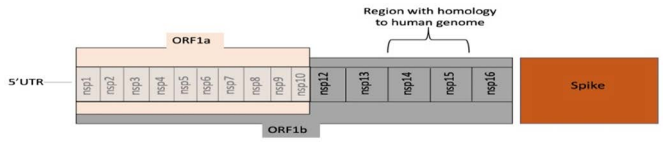

Figure 1. Illustration of the segment of the SARS-CoV-2 genome that is nearly identical to a human gene sequence. Adapted from Figure 2, Rastogi et al., 2020 [31].

The Mobile Genetic Elements and Neurological Disease Etiopathogenesis

The segment of SARS-CoV-2 that is nearly identical to a human gene sequence is within nsp14 and nsp15 in the viral genome, with only nsp16 (a 904 bp sequence) separating it from the spike protein sequence, as schematized in Figure 1 [1,4]. This segment is embedded within the orf1 β of SARS-CoV-2. Other viral ORFs, encoded as endogenous elements, are expressed as mRNAs in human cells [10]. The human genomic sequence that is homologous to the SARS-CoV-2 genome is located within the NTNG1 gene [2,4]. Importantly, disturbances of neuronal development associated with genetic anomalies within the NTNG1 and NTNG2 genes are proving responsible for the pathophysiology of schizophrenia [31-33].

A plethora of RNA-binding proteins are critically involved in transcription control [34]. Even though only a small fraction of the synthetic RNA gets into cells, the presence of synthetic mRNA in vaccines even at concentrations as low as 30 ug and 100 ug (a minimum of 40 trillion synthetic mRNA molecules) may produce RNA-protein-binding complexes that control transcription and may cause epigenetic dysregulation [35]. For example, this is important when the binding protein can be the topoisomerase 3 β (with biological properties to control mental, aging and neurodevelopmental functions), as this specific enzyme forms a highly conserved and medically important complex with yet another protein, Tudor-domain containing 3 (TDRD3) [36]. This powerful complex may interact with histones, single-stranded RNA, DNA, translation factors, and polymerase II. This may cause non-physiological neurodevelopment and aging defects in humans [36].

During studies to discover SARS-CoV-2 and human protein-protein relationships, 332 interactions of high confidence were revealed between the two species [1]. These interactions actually demonstrated the promising efficacy of chloroquine and an antipsychotic drug haloperidol against SARS-CoV-2. Nevertheless, these numerous protein-protein interactions complicate even more the possible protein expression of SARS-CoV-2 sequences in human DNA and their interactions through Human Endogenous Retroviral, Alu and LINE-1 genomic DNA-encoded reverse transcriptases and other human endogenous proteins [37]. Such interactions have been shown to have severe consequences in neurological diseases [38].

This may be even more important for patients already infected with SARS-CoV-2 who then receive the spike protein sequences in mRNA vaccines and have already reverse-transcribed SARS-CoV-2 sequences scattered throughout sensitive organs such as the central nervous system [1,4,5]. This may be highly consequential for those patients who also suffer from pre-existing neurodegenerative diseases [38]. Already, there are emerging reports regarding COVID-19 mRNA vaccination association with acceleration of Parkinson's disease [39,40] and prion disease [41].

Recent investigations reveal the persistent presence in the blood up to 15 months post infection of SARS-CoV-2 spike S1 subunit (S1) that is able to cross the blood brain barrier, likely within exosomes, in patients suffering from post-acute sequelae of SARS-CoV-2 infection [42]. However, this finding requires further investigations as to whether the S1 protein itself is persistently carried by non-classical CD14lo, CD16+ monocytes for a long period of time, or if instead the S1 presence is the result of endogenous DNA production, as the possibility of whole virus persistence in cells has been excluded in this study [42]. Retrotransposition may also explain the enduring presence of both mRNA and spike protein in lymph node germinal centers up to 60 days post-vaccination [43].

Does the Spike Protein Enhance Risk to Prion Disease via LINE-1?

The Gag polyprotein is a protein that is present in all retroviruses. It is an essential nucleic-acid-binding protein that supports virion assembly and facilitates reverse transcription and integration into the host DNA. The human prion protein, PrP, is also a nucleic-acid-binding protein, and it has been discovered that PrP can act as a chaperone to facilitate reverse-transcriptase-mediated cDNA synthesis, in a way that is very similar to the role of the Gag protein. In fact, a seminal paper published in 2020 by Lathe et al. proposed that toxicity of the misfolded PrP^{SC} (SC refers to "scrapie," the prion disease that affects sheep) involves another player, and that that other player is most probably the endogenous retroelement, LINE-1. Furthermore, these authors provide strong evidence that PrP facilitates the export of LINE-1 mRNA together with PrP itself into exosomes [44]. Lathe et al. wrote: "The most likely (natural) form of the transmissible agent is, arguably, an exosome-like phospholipid particle that also contains PrP and RNAs, notably retroelement RNAs or fragments thereof" [44].

It has now been well established that prion infectivity is spread along nerve fibers [45]. The infectivity often begins in germinal centers in the spleen and lymph nodes, and misfolded PrP shows up in these germinal centers long before disease manifestation in the brain. It has been proposed that exosomes released by immune cells in the spleen carry misfolded PrP to the brain along nerve fibers such as the vagus nerve, as reviewed in [19]. Such exosomes would likely induce an inflammatory response in the nerve fibers during their transport, leading to conditions such as Guillain Barre disease.

Human T cells, B cells, monocytes and dendritic cells all express PrP, and expression is upregulated in response to activation [46]. The mRNA vaccines are carried into the spleen by dendritic cells, where the complex process that induces antibody production ensues. This involves activation of the B cells and T cells, which logically would upregulate PrP expression. The study by Alden et al. showed that liver cancer cells upregulate expression of LINE-1 in response to transfection with the spike mRNA [17]. It is likely that something similar would transpire in the immune cells in the spleen.

These arguments suggest that the mRNA vaccines could induce the release of exosomes from immune cells in the germinal centers containing variable amounts of the spike protein, the mRNA for the spike protein, and/or PrP complexed with LINE-1 mRNA. Delivery of such exosomes to the brain would induce neuroinflammation possibly leading to prion disease and other neurodegenerative diseases. The nerve fibers themselves would also plausibly become inflamed due to exposure to these loaded exosomes. This also invites the possibility of LINE-1 conversion of spike protein mRNA into DNA within neurons that take up the exosomes, with unknown consequences.

Complex genomic mosaicism is a feature of neurons in the brain and is increased in the context of Alzheimer's disease [47]. Mosaicism can be induced in the neural genome via retrotransposons, particularly LINE-1 [48]. Direct evidence of this comes from experiments involving retrotransposition of a human LINE-1 in transgenic mice, which resulted in neuronal somatic mosaicism [49]. Notably, individual neurons in Alzheimer's brain have many copies of the amyloid precursor protein (APP) [47], and this is likely due

to activation of LINE-1. APP duplication is a causal factor in early-onset Alzheimer's disease [50]. These observations lay the groundwork for the possibility that COVID-19 vaccination, with lipid nanoparticle delivery of mRNA coding for the spike protein, even further enhances the complex genomic mosaicism of neuronal cells.

mRNA SARS-CoV-2 Vaccination can Cause Interference with Human Genomic DNA like Other Viral RNAs

RNA molecules have the ability to spontaneously modify their sequences and, even when fragmented, to direct the synthesis of their respective copies [51]. RNA recombination [52] and transmissibility via sperm [16] or via metathesis reactions to the next generation of cells is one of the major obstacles to overcome in mRNA technology application for infectious disease vaccination [1]. Long Terminal Repeats (LTRs) within Human Endogenous Retroviruses (HERVs) [37,53] contain the necessary sequences of promoters, enhancers, and poly(A) tail signals to reverse transcribe a foreign RNA sequence to a dsDNA and thereafter, as for the SARS-CoV-2 RNA, to integrate multiple fragments into various human chromosomes [1,4,7].

The LTRs therefore have all the necessary machinery, apart from necessary enzymes for reverse transcription [7] and integration into human DNA, to code for viral envelope, nucleocapsid and matrix capsid [38] and potentially produce new recombinant viral particles having chimeric (host and viral) sequences. Similar chimeric sequences were detected in cell lines infected with SARS-CoV-2 [5]. In addition, since LINE-1 retrotransposons are amplified during early embryonic life [54], this constitutes likelihood for circulating dendritic cells derived from hematopoietic stem cells and reproductive cells (oocytes and sperm cells) to be affected. This is true even with small dosages of mRNAs in vaccines, where long-lived SARS-CoV-2 spike protein RNA sequences could be reverse transcribed upon entering the cell, and subsequently be encoded into germ-line libraries. This can cause additional production of spike protein sequences beyond those initially intended by endogenous expression [1]. In this respect the assembly of virions carrying chimeric SARS-CoV-2 sequences is a probable long-term consequence [5,7]. Also, functional insertions within the HERV sequences, other than evolutionarily driven [10], can awaken the otherwise epigenetically silenced HERV and LTR genes. Of foremost concern is that these can become active and play a causative role in autoimmunity, tumorigenesis and other disease progressions [55].

By this kind of DNA interference, which is highly plausible with SARS-CoV-2 mRNA sequences [1,4,5], regions of DNA like those of HERV-K (using the lysine (K) tRNA) called HERV-K human mouse mammary tumor virus like-2 (HML-2) regions, and HERV-W (using the tryptophan (W) tRNA) sequence elements [56], can also be awakened [53,55].

Such a phenomenon has already been proven for other non-retroviral RNA viruses [10] as well as other coronavirus sequences [4]. The HERV-K (HML-2) region alone contains more than 90 provirus segments scattered throughout the whole of transcriptionally active human DNA, and these can be carcinogenic, triggering melanomas and teratocarcinomas [57]. These unfortunate genetic events can happen simply by disturbing natural anti-cancer host defense mechanisms, developed over millions of years from co-evolution of host and viral genetic material exchange and dissemination throughout the human genome as a line of health defense [57].

Potential for Inducing Oncogenesis and Metastasis: The Role of Stem Cells

To obtain optimum results of protein expression during development of an intradermal delivery technology with synthetic mRNAs, at a minimum a 900 bp macromolecule sequence was needed [58]. The average molecular weight of ribonucleotide monophosphates is 339.5 g/mol (MW) [59]. This makes the doses of 30 μg and 100 μg of synthetic mRNA vaccines at first glance seem extremely low to be capable of genetic interference within human cells [58]. For non-dividing cells, it seems that the risk of insertional mutagenesis is low [58]. However, the synthetic mRNAs, even within minutes post-vaccination, rapidly disseminate from the injection site to the neighboring draining network of lymph nodes [60]. The widespread niches of lymph nodes throughout the whole organism contain quiescent undifferentiated precursor stem cells receiving proliferation signals under stress conditions, and hence mitotic division of these cells is elevated [61].

Human hematopoietic stem cells (HSCs) have an overwhelming capacity for accelerated mitotic division that confers their enhanced ability to transform into cancer stem cells. In fact, it was due to their unique capabilities to regenerate and form resemblances of ex vivo tissues that the whole of RNA editing technology was built to serve curative purposes [62]. Notably, the RNA editing of HSCs pursued in the laboratory is passed robustly and with high frequency from parental HSCs into the next generations of cells that then become cancerously modified stem cells. Given the highly complex and meticulously organized regulatory features within the nucleus of HSCs of the lymphatic system [53], and given both the epigenetic and transcriptional dysregulation the synthetic mRNA could induce within the HSC niche environment described previously, it is reasonable to consider the possibility that the synthetic mRNA associated with these vaccinations could induce pathological changes in that regulatory network [61].

RNA editing (epigenetic modifications and post-transcriptional regulation) is a highly sensitive process, errors within which can establish malignancy in stem cells. Stem cells have a highly vulnerable orchestration of genetic events in response to both intrinsic (within the cell) and extrinsic (out of the cell) factors [62]. Also, the emergence of malignancy from previously healthy stem cells has been proven to be easily induced by endogenous microRNA (miRNA) interference (epitranscriptomic regulation) during mRNA editing [62]. Additionally, as the stimulation of activation, differentiation and proliferation is a common task for immune cells and other stromal cells located in lymph nodes [61], the risk of DNA interference or epigenetic disturbance by even one synthetic mRNA macromolecule entering the cell cannot be excluded.

Potential for Spike Protein Induction of Oncogenic Signaling via JAK/STAT3 Pathway

A case can easily be made that a stem cell in a lymph node is vulnerable to oncogenesis through the influence of the spike glycoprotein, which is being obligatorily produced from the mRNA in the vaccine. Many studies have shown that the spike protein alone is capable of inducing overexpression of the pro-inflammatory cytokine interleukin-6 (Il-6) [63-65]. This cytokine in turn induces tyrosine phosphorylation of STAT3, which then migrates to the nucleus to induce an inflammatory response [63].

In the nucleus, STAT3 binds to and activates promoters of a broad panel of genes encoding proteins that induce cellular proliferation, a key step towards tumorigenesis [66]. Hyperactivation of STAT3 occurs in many types of cancer, including acute myeloid leukaemia, multiple myeloma, and solid tumors of the bladder, bone, breast, brain, cervix, colon, oesophagus, head-and-neck, kidney, liver, lung, ovary, pancreas, prostate, stomach, and uterus [66].

The JAK/STAT3 pathway has been shown to promote the conversion of human pre-leukemia stem cells into acute myeloid leukemia stem cells. The mechanism involves activation of enzymes that deaminate adenosine in double-stranded RNA, converting it to inosine. This class of enzymes is called the adenosine deaminase acting on RNA (ADAR) enzymes, and they are strongly linked to cancer [67]. They induce an A-to-I transformation in double-stranded RNA that ultimately results in a missense encoding of

adenosine as guanidine. Priming of Il-6 through a recent mRNA vaccine could accelerate the mutation rate in the spike protein mRNA during a subsequent active infection with SARS-CoV-2, directly through upregulation of ADAR enzymes by pro-inflammatory cytokines [68]. It has been demonstrated that the administration of convalescent plasma to an immune-compromised patient results in the rapid emergence of novel strains in that patient [69]. It can be anticipated that a vaccinated immune-compromised individual, when infected with SARS-CoV-2, would also be a host for rapid viral evolution, due to the persistent exposure of the virus to ineffective antibodies induced by the vaccine. This could explain the rapid emergence of resistant variants of SARS-CoV-2 in recent months, following an aggressive vaccination initiative at the population level.

A-to-I editing of double-stranded RNA is a post-transcriptional regulatory mechanism that plays an important role in cancer. A major place where A-to-I editing takes place is the 3'-UTR region of mRNA molecules. Importantly, such editing leads to a shortening of the 3'-UTR segment, and this often results in the removal of binding sites for miRNAs that suppress protein synthesis. In this respect, such editing increases protein expression of the affected gene, often leading to carcinogenesis [70].

The HSCs have the potential to differentiate and become literally any kind of cell in the mature organism, and the not-sufficiently-guided genetic interference of stem cells may lead to diseases such as hematopoiesis disorders as well as cancer [71]. Lymph-circulating tumor cells are commonly present in patients with diagnosed malignancies. The presence of these cells does not, of course, depend upon an established diagnosis and should be expected to be found in patients with an undiagnosed malignancy as well. The presence of these cells confers a clinically important metastatic potential as compared to the blood-circulating malignant cells that have escaped from primary tumors, and this process can be augmented by any RNA interference. As the synthetic mRNAs tend to disperse and accumulate in regional lymph nodes [60] and the lymph-circulating malignant cells have a stem cell cycle mosaic of proliferation [55,62] and use the entire lymphatic system to travel, then the risk of augmented metastatic potential can also be considered as elevated in these cases [71].

Spike Protein, Inflammation, Syncytia, DNA Damage and Senescence

It was long thought that only germ cells express LINE-1, but this has turned out not to be true. In addition to transformed cells, many types of somatic cells express LINE-1, and it is upregulated under stressed conditions such as oxidative stress [72]. Expression of LINE-1 in human cells can lead to cancer via DNA double strand breaks. In laboratory experiments, exposure of cells grown in culture to LINE-1 ORF2 alone induced double strand breaks [73].

In a cleverly designed laboratory experiment, Meyer et al. explored the notion that exposure of the pulmonary epithelium to the spike protein can lead to the release of mediators that drive endothelial dysfunction [74]. These researchers demonstrated that spike-transfected human A549 epithelial cells released inflammatory molecules that are characteristic of a Senescence-Associated Secretory Phenotype (SASP), along with a 3-fold increase in Reactive Oxygen Species (ROS). Furthermore, ROS levels were increased approximately 2-fold in endothelial cells exposed to the culture medium taken from the spike-producing A549 cells compared to empty plasmid-transfected control cells. Hence, endothelial cells respond to signaling from spike plasmid-transfected epithelial cells through a "bystander senescence response" that can lead to endothelial damage via a paracrine process. Cellular senescence was also associated with an increased level of endothelial adhesion molecules promoting leukocyte tethering to the vascular wall. Such tethering is a first step towards leukocyte extravasation and subsequent tissue invasion and inflammation.

These results are consistent with those of another study that investigated the response of cultured bronchial epithelial and endothelial cells to spike-protein transfection, which also demonstrated that the cells responded with increased ROS levels triggering an inflammatory response and ultimate apoptosis [75].

A remarkable series of papers by a large team of researchers in China have demonstrated indisputably that the spike protein causes cells that have ACE2 receptors (such as the pulmonary epithelial cells) to form multinucleated giant cells, known as syncytia, via cell-cell fusion [76-78]. This cell fusion response depended upon protease-dependent cleavage of the spike protein into S1 and S2, and further cleavage of the S2 subunit at the S2' site [77]. These syncytia eventually succumb to cell death by pyroptosis, enhancing the inflammatory response.

Furthermore, multiple micronuclei were detected within the syncytia, and these micronuclei were associated with γH2Ax (H2Ax with phosphorylated Ser139), a highly precise and very early marker for DNA damage [78]. These authors wrote: "Together, these results suggest that the syncytial micronuclei are the sites succumbing to genomic instability and DNA damage." [78] The increase in γH2AX detection due to spike protein expression in A549 epithelial cells is accompanied by an increase in $p16^{INK4A}$ tumor suppressor and p21 oncogenic proteins [74]. The fact that the spike protein also induces upregulation of LINE-1 should raise concern for the potential for reverse transcription of spike protein mRNA in the context of the formation of syncytia invoking DNA damage repair mechanisms.

The so-called "cGAS-STING DNA sensing pathway" is an important biological pathway that responds to Cytoplasmic Chromatin Fragments (CCF) and activates a type-I interferon response. Cyclic GMP-AMP synthase (cGAS) is the DNA sensor that then causes the endoplasmic reticulum protein, stimulator of interferon genes (STING), to trigger the interferon response. It was demonstrated that the cGAS-STING pathway was a key player in the induction of the type I interferon response in cells transfected with spike protein [77]. The authors of a perspective article on the cGAS-STING pathway wrote: "While short-term inflammation triggered by the CCF-cGAS-STING pathway is required for immune clearance of senescent cells, chronic inflammation mediated by SASP is destructive, resulting in tissue damage and even tumorigenesis." [79] A review paper with the provocative title, "DNA Damage-How and Why We Age?" argued that excessive activation of the DNA repair mechanism due to persistent DNA damage may be the primary cause of accelerated aging and the associated diseases [80].

DNA Repair Mechanisms: An Active Role for Polymerase Theta

Normally, when a cell is infected with a virus, it immediately launches type I interferon signaling upon detection of viral RNA. One of the important consequences of the subsequent signaling cascade is the upregulation of the tumor-suppressor gene p53. P53 induces cell cycle arrest upon detection of double-strand DNA breaks, thus protecting the cell from severe genetic defects during replication and thus is tumor-suppressing. Multiple DNA repair strategies are available to repair the breaks so that replication can resume. P53 also arrests viral replication, thus slowing production of multiple copies of the virus to further the spread of infection [81]. Any DNA Double-Strand Break (DSB) opens up the opportunity for a chromosomal translocation, where the two fragmented pieces re-attach to different chromosomes. This can result in both missing genes and extra genes, which can profoundly disrupt chromosomal integrity, causing a progression towards cancer. Thus, it is imperative to repair the break before these potentially catastrophic genetic alterations can take place.

Gene editing is a technology that gives scientists the ability to change an organism's DNA by altering, removing, or inserting genetic sequences at a specific location in a genome. The most well-known gene editing technology is CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats-

CRISPR-associated protein 9). This technology is borrowed from a bacterial capability to combat bacteriophages. CRISPR sequences, originating from bacteriophages, are found in half of sequenced bacterial genomes and in nearly 90% of genomes from archaea [82]. Cas9 uses CRISPR sequences as a guide to recognize and cleave specific strands of DNA that are complementary to the strand in the CRISPR sequence.

While CRISPR/Cas9 is considered to offer precision control over the location in the DNA sequence that is modified, this has turned out to not always be true. The technology begins by introducing a DNA double-strand break, and it relies on standard cellular methods to repair the break. Eukaryotic cells have acquired multiple mechanisms to repair DNA breaks, depending on the stage of the cell cycle. So-called homologous recombination (HR) is very accurate, but it depends on the availability of a DNA template as a guide, which is only available during the later G2 and M stages. Non-homologous end-joining (NHEJ) comes into play during earlier stages of the cell cycle (G0, G1 and S). Its repair process is more prone to introducing transcription errors. A third repair mechanism, termed Microhomology-Mediated End Joining (MMEJ), has only been recognized as an alternative mode of repair in the past few years [83]. It involves first annealing two microhomologous regions of the two broken strands, and then filling in the gaps through DNA synthesis using a DNA polymerase. A significant part of the original sequence gets removed through this process, and thus it is an error-prone solution.

Polymerase theta (PolΘ) is an important DNA repair enzyme involving double-strand DNA breaks using MMEJ, also known as "synthesis-dependent end joining" and "theta-mediated end joining." As outlined above, the method causes the insertion of additional sequences at joining sites as well as deletions-so-called "indels." It is not expressed in most tissues, with tumors being the notable exception. It is upregulated in association with many cancers, including stomach, lung, and colon cancers, breast cancer and ovarian cancer, and its overexpression is a prognosis for poor clinical outcomes [84]. PolΘ is a key driver of genome evolution and of CRISPR/Cas9-mediated mutagenesis [85].

We hypothesize that the mRNA vaccines coding for spike protein set up a situation in a transfected cell, particularly one that is in a proliferative state, that could be highly susceptible to severe chromosomal aberrations. Because the technology involves extensive modifications to the original viral mRNA to conceal its viral source, it achieves a "stealth" entry into the cell without provoking a normal type I interferon response [86]. The cell immediately launches efficient translation of the mRNA to produce abundant amounts of spike protein. The spike protein causes severe DNA damage, including double-strand breaks, as described previously. This genetic stress does launch a type I interferon response, but it is delayed such that significant damage takes place before p53 is sufficiently upregulated. Furthermore, DNA-damage induced interferon β is directly implicated in cell senescence and inhibition of stem cell function associated with accelerated aging [87].

A paper aptly titled, "Repair of G1 induced DNA double-strand breaks in S-G2/M by alternative NHEJ" showed, using CRISPR technology to disable p53, that DNA breaks introduced during G1 could later be repaired by polΘ, after the cell cycle had advanced to S-G2/M phase [88]. By disabling the less promiscuous NHEJ repair pathway, they allowed the cell cycle to progress after the break had occurred, leading to the generation of multiple aberrant chromosomal rearrangements while promoting overall cell survival. Importantly, G1-induced broken DNA ends generate chromosomal translocations at a high frequency during the S-G2/M phases, indicating that the broken DNA ends have lost the ability to reconnect during cell cycle progression. Notably, PolΘ is unable to repair DNA breaks during G1 phase [88]. As stated by W. Feng et al., "Pol Θ/TMEJ addiction is associated with increased levels of replication-associated DSBs, regardless of the initial source of damage" [89]. This implies that excessive DNA damage induces upregulation of polΘ. This suggests that cancer cells and proliferating immune cells transfected with the spike protein would suffer from an accelerated rate of genetic mutations, leading to cancer progression.

A study published in 2021 revealed the unexpected discovery that PolΘ is capable of reverse transcribing RNA into DNA [7]. In fact, PolΘ exhibits a significantly higher velocity and fidelity of deoxyribonucleotide incorporation on RNA versus DNA. It can undergo a remarkable structural transformation in order to maintain productive interactions on DNA/RNA templates. It can accommodate a full RNA-DNA hybrid within its active site, and efficiently transcribe template ribonucleotides into DNA, thus promoting RNA-based DNA repair. PolΘ appears to be unique among human polymerases in its ability to reverse transcribe RNA, with an efficiency equivalent to that of the retroviruses. It is therefore possible that PolΘ can reverse transcribe vaccine-transfected mRNA into DNA and integrate it into the genome at DNA break sites. All of these considerations are summed up in the flow chart shown in Figure 2.

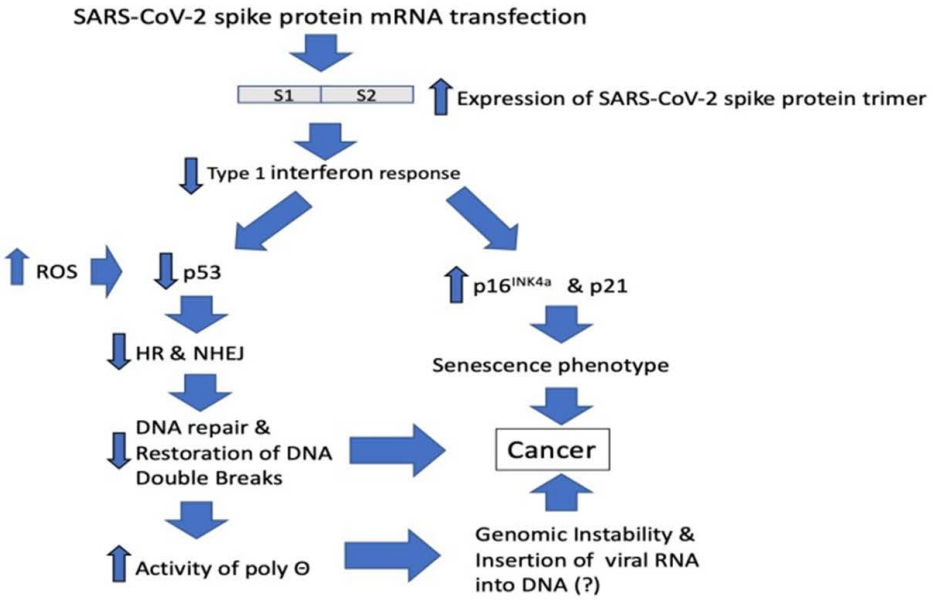

Figure 2. Schematic of sequence of events hypothesized to play out in response to cellular uptake of the mRNA sequences in the SARS-CoV-2 mRNA vaccines, particularly for cells with an active cell cycle.

DNA Break Repair Mechanisms: When RNA meets DNA

It was postulated long ago that, apart from retroviruses that have the capability to become inserted into human DNA by reverse transcription, the genetic material of all other RNA viruses cannot become inserted into DNA under any circumstance [1]. However, experimentally, this has long been proven not to be the case. In 2009, Geuking et al. showed that an otherwise unwarranted genetic recombination could occur between the lymphocytic choriomeningitis RNA virus and the endogenous intra-cisternal A-type (IAP) retrotransposon, and that this led to reverse transcription of the exogenous viral RNA [11]. This exogenous RNA was finally inserted by means of its complementary DNA into the recipient DNA, together with the IAP element. Since this important finding, as the authors declared, it became warranted to properly investigate any potential interaction with retroviral elements before RNA viruses could be used therapeutically to insert new genetic material. Retroelements are active remnants of the RNA-to-DNA world transition that occurred millions of years ago on earth. The active interaction of all RNA viral genetic elements with eukaryotic DNA is now a readily occurring phenomenon sustaining human biodiversity [15].

Compounding the problematic potential of viral or vaccine mRNA integration into host cell DNA is the potential destructive impact of the spike protein itself on DNA. Double-stranded DNA breaks are a severe type of DNA damage, and they carry the greatest risk of initiating a malignant transformation in affected cells' progeny. BRCA1/2 and p53 orchestrate highly complex DNA repair processes specifically directed toward repair of dsDNA breaks [90].

The potential for double-strand DNA breaks brought about by the spike protein seems compelling, given the evidence of micronuclei and syncytia formation in exposed fibroblasts [76-78]. G1 and G2/M checkpoint malfunctioning is coupled with the subnuclear inhibition of the formation of BRCA1 and 53BP1 foci [9,91]. An in vitro study has shown that the S2 subunit of the spike protein interacts with both BRCA and p53, suggesting that it could interfere with their anti-cancer function [92]. The cells affected by SARS-CoV-2 spike protein continue with their mitotic division with unresolved DNA breaks in chromosomes [93]. This creates a serious case of recombinogenic events as the cells continuously undergo transcription and replication, where the formation of co-transcriptional R loops is imminent if not regular [8].

Recently published literature on SARS-CoV-2 spike protein driven cellular and tissue injury reveals a large number of COVID-19 vaccine injury syndromes [35,40,41,94-104]. Many of these injuries can be expected if the mechanisms described in this paper are taking place. Figure 2 summarizes our findings by describing multiple ways that mRNA in SARS-CoV-2 vaccines may induce pathology in dividing human cells. There is strong evidence that the spike protein itself induces DNA damage and subsequent DNA repair mechanisms. It also causes increased expression of LINE-1, which is capable of converting the mRNA to DNA. Chimeric transcripts can emerge from the processes that ensue in the nucleus. RNA-protein complexes derived from the vaccine mRNA lead to unpredictable sequelae. These processes combined suggest exposure to mRNA coding for the Spike protein is potentially oncogenic, particularly in those who already have polymorphisms in p53 and or BRCA as well as those with latent or manifest malignancy.

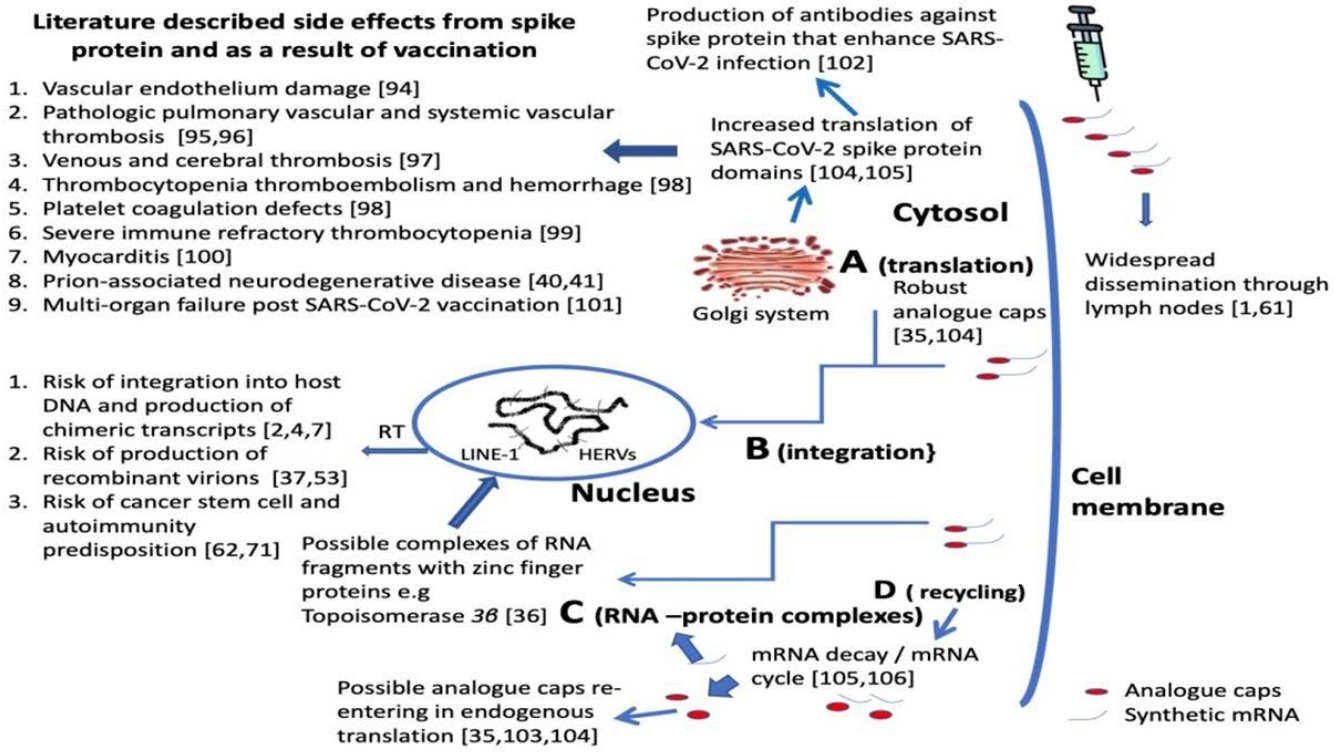

Figure 3. Multiple ways that mRNA in SARS-CoV-2 vaccines may induce pathology and genetic side effects in dividing human cells and the organism. (A) Spike protein translation. The enhanced translating spike protein mRNAs result in serious side effects, verified in publications, (B) Genomic integration; The LINE-1, polymerase theta and HERV reverse transcriptase autonomous retrotransposons can possibly reverse transcribe within more vulnerable dividing cells (stem cells in lymph nodes) and produce chimeric sequences of host and virus spike protein fragments and new virions. Genetic disturbance of otherwise silent HERVs may produce neurodegenerative disorders and cancer. (C) Recycling; Continuous mRNA decay and recapping may re-allocate robust analogue caps to endogenous mRNAs. (D). RNA-Protein complexes; Fragments of spike protein mRNAs may form protein complexes with endogenous nucleases to produce DNA interference. LINE-1: Long Interspersed Nuclear Elements 1; HERVS: Human Endogenous Retroviruses; RT: Reverse Transcription.

Retrotransposon Association and Types of Neurological Disorders Diagnosed as a Consequence of SARS-CoV-2 mRNA Vaccination

Amongst the family of Transposable Elements (TE), also known as "jumping genes," the subfamily of retrotransposons contains the clinically important categories of Long Terminal Repeat (LTR) and non-LTR transposons. The LTR retrotransposons, also known as endogenous retroviruses (ERVs), account for 8% of the human genome (HERVs) and are actively participating in the etiopathology of multiple sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) and Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) [38]. LINE-1s are autonomous non-LTR transposons that contribute to 17% of the human genome and participate in the molecular pathogenesis of neurologic disorders [105-108]. Both HERV and LINE-1 transposons work in a "copy-and-paste" fashion and have an RNA intermediate in the process of their amplification, and this can cause disease in humans by integrating into genes. The spectrum of neurologic disorders caused by LINE-1 insertions into DNA throughout the human life span is wide, ranging from autism, psychosis and schizophrenia, to Alzheimer's disease [109].

Aicardi-Goutieres syndrome (AGS) is a genetic disease that presents as severe encephalitis in infancy, associated with lymphocyte infiltration into the brain and elevated type I interferon levels in cerebrospinal fluid. It causes demyelination of motor neurons, and usually results in severe mental and physical handicaps and premature death.

Research has investigated the contribution of retrotransposons to the etiopathogenesis of AGS, which often arises when 3'→5' repair exonuclease 1 (TREX1) becomes mutated [110]. The normal function of TREX1 is that of an antiviral DNAse that consumes single stranded and double stranded DNA and thus prevents type I interferon associated inflammatory responses. The researchers investigated the source of interferon activation in AGS and found that the amount of DNA isolated from the hearts of TREX1 knockout mice was 32-fold increased as compared to the DNA isolated from wild type mice. TREX1 knockout mice die prematurely from circulatory failure caused by inflammatory myocarditis [111]. Amongst the TREX1 deficient DNA sequences, retroelements were highly over-represented, and the researchers identified 25 different retroelements, a mixture of LINE-1, ERVs, and short interspersed elements (SINEs), showing that both LTRs and non-LTRs accumulate in this neurologic disorder. The authors suggested that this accumulation of retrotransposon single-strand DNA was the primary source of toxicity [110].

Additionally, activation of HERVs has been reported to take place by the exogenous retroviruses HTLV-1 and HIV-1. Both HERV-W and HERV-K are transactivated by HTLV-1 Tax protein in T cells [56]. Especially in astrocytes, the HERV-W sequence is indirectly activated by HIV Tat protein, which acts as an endogenous retrovirus, via Toll like Receptor 4 (TLR4) and through induction of NF-κB and TNF-α pathways [112].

In a preprint paper, it was observed that mRNA vaccination coding SARS-CoV-2 spike protein did not stimulate an increase in the interferon response in AGS [113]. However, and surprisingly, a case study, involving an AGS patient who presented with post-COVID-19 generalized panniculitis, showed that SARS-CoV-2 RNA, specifically spike protein RNA, can induce a type I interferon response in AGS [114]. In this AGS case, no virus particles could be detected by electron microscopy in biopsies from lesions, and the IgG positivity to SARS-COV-2 confirmed an immune response to spike protein [115]. This implies that the spike protein, by inducing increased expression of LINE-1, can cause symptoms of AGS via increased presence of single-strand LINE-1 DNA.

A growing number of cases in the peer-reviewed literature describe diagnosed neurologic disorders as a consequence of SARS-CoV-2 mRNA vaccination. These are categorized respectively as LINE-1 and HERV retrotransposon-associated diseases according to [38,109], and selected cases for each category are presented in Table 1. Moreover, an increasing series of cases of Functional Neurologic Disorder (FND) are being diagnosed as an immediate causal effect of SARS-CoV-2 mRNA vaccination [116,117]. FNDs are due to "functional" rather than "structural" disruption of brain networks and this can cause severe disability in sufferers, whose numbers are increasing worldwide [118].

Table 1. Selected LINE-1 and HERV associated neurologic disorders diagnosed as a conclusive consequence of SARS-CoV-2 mRNA vaccination.

Selected LINE-1-associated neurological disorders diagnosed as a consequence of SARS-CoV-2 mRNA vaccination. (See: Suarez et al., 2018 [109])		
Disease diagnosed	**Short clinical presentation and description of cases**	**Reference**
Psychosis starting immediately after first mRNA dose and worsening after the second mRNA dose	31 year old male with anxiety and moderate leukocytosis. Asymptomatic prior to mRNA vaccination. MRI: Hyperintensities in the left, subcortical and periventricular white matter.	Reinfeld et al., 2021 [124]
Acute psychosis with catatonic features after encephalitis starting immediately after the first dose of mRNA vaccine	21 year old female suffering from anti-N-methyl-D-aspartate (NMDA) receptor encephalitis after mRNA vaccination. Anxiety and hypochondriacal delusions.	Flannery et al., 2021 [125]
Acute mania with psychotic features one day after the first dose of mRNA vaccination	42 year old male with increased psychomotor activity, anxious and dysphoric. Loosening of associations, persecutory and reference delusions and lack of insight. Young mania rating scale (YMRS): 45. C-reactive protein: 4.2 mg/dL and white blood cell count: 8.8 mg/dL	Yesilkaya et al., 2021 [126]
Manic symptoms, suicidal attempt and thoughts of extinction immediately after the second dose of mRNA vaccination.	57 year old male, anxious, dysphoric with increased psychomotor activity. Nihilistic delusions with no insight. YMRS score: 42. No previous history of psychiatric disease.	Yesilkaya et al., 2021 [126]
Selected HERV-associated neurological disorders diagnosed as a consequence of SARS-CoV-2 mRNA vaccination (See: Kury et al., 2018 [38])		
Disease diagnosed	**Short clinical presentation and description of cases**	**Reference**
Chronic inflammatory demyelinating polyneuropathy (CIDP) initiated 3 months post the second dose of mRNA vaccine.	66 year old female with progressive lower extremity and bilateral arm weakness, 3 months post the second mRNA vaccination. Hyporeflexia, numbness and tingling in bilateral upper extremities, poor oral intake, weight loss, overall gradual loss of strength. Pain. Decreased motor strength, absent deep tendon reflexes in both lower extremities. Guillain-Barre syndrome was considered and ruled out. Electrodiagnostic findings consistent with CIDP. Firm diagnosis was based on serum and urine immunofixation revealing presence of IgG kappa monoclonal protein.	Singh et al., 2022 [127]

Multiple Sclerosis (MS) with symptoms initiated the first day post a single dose of mRNA vaccination.	29 year old female with acute onset of left leg weakness and numbness on the first day post mRNA vaccination that developed paresthesia in her right arm after one week. Marked hyperlexia in upper and lower left extremities with diminished vibratory sensation in the left leg. MRI and CSF examination diagnosed MS.	Toljan et al., 2022 [128]
Multiple sclerosis with symptoms initiated 3 days post the first mRNA vaccination that worsened immediately after the second dose of mRNA vaccine.	37 year old male with developing paresthesia in the left arm. Urinary urgency and gait imbalance. Left arm hyperlexia and right sided internuclear ophthalmoplegia. MRI diagnosed MS.	Toljan et al., 2022 [128]
Progressive neurodegeneration leading to MS with symptoms initiated approximately one month post the second dose of mRNA vaccine.	41 year old healthy male with progressive paraparesis and difficulty initiating voiding two months after the second mRNA dose. He developed acute onset right hemiparesis with right facial drop. First MRI was suggestive for demyelinating disorder and inconclusive for stroke. Later MRI, serum and CSF examinations excluded systemic autoimmunity and infection and were conclusive for MS diagnosis.	Toljan et al., 2022 [128]
Central Nervous System (CNS) inflammation leading to progression of already diagnosed stable MS	A series of 7 cases with stable MS where MRI showed active CNS demyelination of the optic nerve, spinal cord and brain. Symptoms included gait instability, visual loss, limp weakness and sphincter disturbance.	Khayat-Khoei et al., 2022 [129]
Multiple sclerosis with symptoms initiated after 5 weeks of the second mRNA vaccination	43 year old female who developed distal right arm weakness and right periorbital and palatal numbness. Ipsilateral knee flexor and hip flexor weakness. CSF analysis and MRI were conclusive for MS diagnosis.	Toljan et al., 2022 [128]

The most intriguing findings of Multiple Sclerosis (MS) and chronic inflammatory de-myelinating polyneuropathy (CIDP) development due to SARS-CoV-2 mRNA vaccination are probably the most important to suggest HERV activation due to epigenetic dysregulation [119,120]. SARS-CoV-2 spike protein is known to induce a pro-inflammatory response via TLR4 activation [121-129]. Similarly, HERV-W env protein pathogenically activates TLR4 on oligodendroglial precursor cells, which results in impairment of differentiation of these cells and subsequent lack of capacity to repair myelin. This leads to demyelinated and degenerated axons, as found in MS [38].

Conclusion

Recent discovery of SARS-CoV-2 genome integration through a mechanism involving LINE-1 or polymerase theta raises great concern regarding possible unwanted durable incorporation of spike protein sequences into the human genome. Moreover, the series of case reports describing diagnosed neurologic disorders, having as a sole common causality factor the SARS-CoV-2 mRNA vaccination, undoubtedly highlights the potential association of retrotransposon activation to the emergence of these diseases. Human DNA interference by synthetic mRNAs in vaccines is more than simply a theoretical possibility. Reverse transcription of code from COVID-19 vaccine mRNA has been demonstrated in human hepatoma cell lines, although confirmation of the result by an independent group is needed.

Since their encoded sequences are specific for SARS-CoV-2 spike protein, and these can also be integrated into human DNA, the resulting pathogenesis due to molecular vaccination requires an explicit evaluation through genotoxicity research. In addition to the pathogenic potential of endogenously (DNA) encoded spike proteins, we have shown that activation of the cellular enzymatic networks that carry out this DNA integration entail their own distinct and multifaceted pathogenic potential. These risks are expected to be highest in specific vulnerable populations, namely individuals during the developmental phase (children) and patients suffering from malignancy, autoimmune disease, cardiovascular and neurological disease, and genetic disorders. We recognize that it is speculative to suggest that vaccine mRNA could initiate the broad range of pathological events we describe. However, given the extensively documented potential for both endogenous (human retroviral) and exogenous (viral) RNA to trigger these events, relevant investigations are urgently needed, especially considering the large number of individuals who have been administered one or more mRNA products coding for the SARS-CoV-2 spike protein.

Ethical Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Supporting Data

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

AK, GN and SS all contributed substantially to the writing of the document. AK, PM, GN, and SS all participated in multiple revisions. GN prepared Figure 1. AK and SS prepared Figures 2 and 3. AK prepared Table 1. All authors have read and approved of the final version of the manuscript.

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In memory of Mrs Rodamanthi Kyriakopouloy BA BSc.

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