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Review

Review: N1-methyl-pseudouridine (m1Ψ): Friend or foe of cancer?

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ABSTRACT

Due to the health emergency created by SARS-CoV-2, the virus that causes the COVID-19 disease, the rapid implementation of a new vaccine technology was necessary. mRNA vaccines, being one of the cutting-edge new technologies, attracted significant interest and offered a lot of hope. The potential of these vaccines in preventing admission to hospitals and serious illness in people with comorbidities has recently been called into question due to the vaccines' rapidly waning immunity. Mounting evidence indicates that these vaccines, like many others, do not generate sterilizing immunity, leaving people vulnerable to recurrent infections. Additionally, it has been discovered that the mRNA vaccines inhibit essential immunological pathways, thus impairing early interferon signaling. Within the framework of COVID-19 vaccination, this inhibition ensures an appropriate spike protein synthesis and a reduced immune activation. Evidence is provided that adding 100 % of N1-methyl-pseudouridine (m1Ψ) to the mRNA vaccine in a melanoma model stimulated cancer growth and metastasis, while non-modified mRNA vaccines induced opposite results, thus suggesting that COVID-19 mRNA vaccines could aid cancer development. Based on this compelling evidence, we suggest that future clinical trials for cancers or infectious diseases should not use mRNA vaccines with a 100 % m1Ψ modification, but rather ones with the lower percentage of m1Ψ modification to avoid immune suppression.

1. Introduction

When the COVID-19 pandemic broke out in early 2020, there was an immediate need for COVID-19 vaccines. Creating new vaccine technologies was necessary to increase vaccine effectiveness and decrease production time [1]. mRNA vaccines, one of the cutting-edge new technologies, attracted a lot of interest and offered a lot of hope [2,3]. Fast development and manufacturing speeds were made possible by this technique, which were crucial capabilities that could be successfully employed in biotechnological and therapeutic scenarios [4]. The manufacturing of mRNA vaccines can be completed in a matter of days or weeks as opposed to months or years required for the manufacture of, for example, attenuated or inactivated viruses [5]. It is possible to achieve this using in vitro transcription of mRNA, in which nearly any mRNA sequence may be generated from a DNA template [6,7]. Additionally, an mRNA vaccine would give the cell-specific instructions for using cytoplasmic translation to create a desired immunogenic protein [8]. The development of mRNA therapies, like other nucleic acid-based

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treatment methods, has been hampered by several delivery challenges. Before arriving at the ribosomes, an RNA molecule, for example, may be destroyed by ribonucleases or captured by endosomes [9]. A further obstacle in the mRNA delivery is related to the RNA crossing biological membranes due to its negatively charged phosphodiester backbone [10].

This problem was resolved by encasing the RNA in a wrap made of lipid nanoparticles (LNPs) and guiding it to the ribosomes. These lipids were explored as delivery systems for RNA to mammalian cells decades ago [11–13]. In addition to the aforementioned delivery difficulties, therapeutic mRNA faced at least two other significant obstacles: When administered to animals, in vitro transcribed (IVT) mRNA would: 1) be susceptible to nuclease breakdown; and 2) induce innate immunogenicity comparable to that experienced when infected by a pathogen [14]. Pseudouridine (Ψ), a widely recognized RNA alteration that can be utilized to substitute uridine in the IVT mRNA, provided a solution to these problems. It has been shown that Ψ inclusion increases RNA stability while concurrently dampening the anti-RNA immune response [15,16]. Since it was shown that the Ψ-modification could help mRNA to avoid innate immune responses [16], a search for Ψ-derivatives with the enhanced characteristics was conducted. As a result, it was discovered that N1-methyl-Ψ (m1Ψ) decreased the functionality of innate immune sensors, and performed properly (and even better than Ψ) when tested in several basic human cells. In mice, m1Ψ enhanced the translational efficiency and lowered the cytotoxicity of modified mRNA delivered intramuscularly and through the skin [17].

2. The role of pattern recognition receptors in cancer

Pattern recognition receptors (PRRs) were discovered in 1990 [18], and their roles in stimulating cells of the innate and adaptive immune systems have been at the center of attention of many researchers since that time [19]. For this work, Jules A. Hoffman and Bruce A. Beutler were awarded The Nobel Prize in Physiology or Medicine 2011, along with the acknowledgment of the contributions of Ruslan Medzhitov and Charles A. Janeway Jr. Germline-encoded receptors, or PRRs, are essential for both the immune system's defense against infections and the development of cancer [20]. Retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), Toll-like receptors (TLRs), and DNA sensors are the five families that constitute PRRs [21]. PRRs identify RNA, DNA, and structural proteins from bacteria, viruses, fungi, and parasites, in addition to the pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharides (LPS), flagellin, and lipoproteins [21]. Furthermore, they can recognize the internal damage-associated molecular patterns (DAMPs) released during necrosis, apoptosis, or cellular stress. Examples of these include heat shock proteins (HSPs), extracellular matrix proteins generated during tissue damage, and the chromatin-associated protein high-mobility group box 1 (HMGB1) [22]. PRRs' identification of DAMPs/PAMPs causes immune cell activation and transient expression of pro-inflammatory genes [20].

3. mRNA vaccination impairs the RIG-I signaling pathway: implications for cancer development

Cytoplasmic PRRs known as RLRs are capable of identifying both internal and viral double-stranded RNAs. The DEXH box RNA helicases RIG-I, melanoma differentiation-associated gene 5 (MDA5), and RIG-I-like receptor LGP2 (also known as ATP-dependent RNA helicase DHX58) are the three members of the RLRs family that have been discovered at this point [20]. Through their Caspase Activation and Recruitment Domains (CARD), they initiate a signaling process. Type-I interferons (IFN) and pro-inflammatory cytokines are secreted as a result of their downstream signaling activating the essential transcription factors IFN regulatory factor (IRF)-3/7 and Nuclear factor kappa B (NF-κB) [20]. RLR activation has been shown to have anti-tumor properties in recent investigations [23]. By promoting the signal transducer and activator of transcription 1 (STAT1) expression and the transcription of various genes linked to Type-I and type-II IFN induction, RIG-I activation can inhibit the growth of leukemia cells [24]. The connection between innate and adaptive responses has been emphasized by the recent emergence of the hypothesis that type-I IFN signaling participates in the induction of the anti-tumor T cell response [25,26]. For example, Type-I IFN-independent autophagy and apoptosis can be triggered in melanoma cells by activating RIG-I and MDA5 [27].

When MDA5 and RIG-I interact with their ligands, their attachment to the mitochondrial membrane adaptor protein, the mitochondrial antiviral signaling (MAVS) protein activates a mechanism that ultimately leads to the nuclear translocation of the transcription factors NF-κB and IRF-3 as well as the production of Type-I IFN [28]. In the meantime, their collaboration sets off a different signaling mechanism that is not dependent on the tumor suppressor p53. Rather, this pathway leads to the activation of the pro-apoptotic BCL-2 family member NOXA, as well as mitochondrial apoptosis via caspase-9 and the apoptotic protease activating factor-1 [27].

In a recent study, Knabl et al. [29] investigated changes in the immune response in three distinct categories of people: those who had received the BNT162b2 mRNA vaccination after contracting the beta SARS-CoV-2 variant, those who had contracted the infection without having received any prior vaccinations, and uninfected people who had received the BNT162b2 vaccine. The vaccinated hospitalized cohort showed a more than twofold rise in the ATP-dependent RNA helicase DHX58 (also known as ATP-dependent helicase LGP2) expression, according to the authors' findings. MDA5 and RIG-I expression, on the other hand, was not significantly increased [29].

It is well recognized that LGP2 inhibits IFN synthesis by blocking the RNA-activated cytoplasmic RIG-I pathway [30,31]. Importantly, suppression of LGP2 increases interferon beta (IFNβ) expression and enhances the death of tumor cells [32]. Researchers found that in the majority of the 14 types of human cancer cells with different origins, there was a relationship between radiotherapy resistance and LGP2 expression [32]. In subsequent investigations, it was found that the proportion of cells that are resistant to cytotoxicity increased when elevated levels of LGP2 was observed, preventing radiotherapy-induced apoptosis. In contrast, LGP2 depletion increased the cytotoxic effects of radiation. The reason behind the over two-fold increase in the LGP2 expression in the hospitalized cohort of vaccinated individuals was not explained by Knabl et al. [29]. We hypothesize that this increase is related to the impairment in IFN signaling, further compromising anti-tumor responses.

According to one of the limited research findings in this field, modified nucleotide-containing RNA molecules interfere with the RIG-I-like innate immune activation pathway's initial signaling, while m1Ψ-containing RNA attaches to RIG-I but is unable to trigger the traditional RIG-I conformation changes that are associated with strong innate immune responses [33]. The disruption of the RIG-I signaling pathway by m1Ψ constitutes a positive outcome for COVID-19 vaccine success by dampening the anti-RNA immune response [15,16]. However, avoiding immune detection of the mRNA by adding m1Ψ favors a greater spike protein synthesis but, in contrast, it might induce immune suppression that could favor the reactivation of quiescent bacterial, viral, or fungal infections, as well as perhaps enabling the unrestrained multiplication of cancer cells [34]. In this regard, a recent investigation found totally opposite results in IFN responses when evaluating the effects of non-modified vaccines vs. vaccines modified with m1Ψ [35], and these relevant findings will be described below.

4. m1Ψ use in COVID-19 mRNA vaccines

m1Ψ was added in 2020 to Pfizer-BioNTech's COVID-19 mRNA candidate vaccine (Comirnaty® or BNT162b2), which codes for the

entire transmembrane spike (S) protein of SARS-CoV-2 [36]. A significant amount of m1Ψ-modified SARS-CoV-2 (COVID-19) spike mRNA was generated by extensive IVT. After demonstrating a favorable safety record and 95 % protection from the disease after a two-inoculation protocol (intramuscular injection), the Pfizer vaccine became the first mRNA vaccine to be fully licensed against COVID-19 [37,38]. The accepted method for assessing new vaccines has been disease-specific: is it clinically effective against the virus being vaccinated against, and does it develop antibodies or cellular immunity to protect against it? This view is dissipating as epidemiological [39,40] and immunological [41–43] studies have shown that vaccines can have both positive and negative non-specific effects (NSEs), also referred to as heterologous or un-targeted outcomes. Simply put, vaccination may affect diseases from which it is not designed to prevent [44,45].

5. Is m1Ψ a friend or foe of cancer?

The creators of the mRNA vaccines against SARS-CoV-2 have emphasized only the positive aspects related to the addition of m1Ψ: it was critical to diminish the disintegration of this synthesized mRNA as well as its immunogenicity to avoid an overly aggressive immune response. However, important investigations performed during this pandemic have demonstrated that mRNA-based and inactivated vaccines temporarily disrupt IFN signaling [46–49]. It is important to reveal here that in 2017, Pepini et al. [46] warned that the innate immune response stimulated by RNA vaccines may have both positive and negative effects. Although systemic Type-I IFN induced by PRRs may enhance the adaptive immune response, it may also prevent the production of antigens encoded by self-amplifying vaccines and impede RNA replicon amplification, which would decrease the vaccine efficacy [46]. According to their findings, a self-amplifying mRNA (SAM) vaccination triggered a rapid inflammatory reaction as shown by the overexpression of many IFN-stimulated genes (ISGs). SAM sensors include cytoplasmic RLRs in non-immune cells and endosomal TLR7 in immune cells. Additionally, they found that when IFN-α/β signaling was absent, there was an increase in both immunogenicity and SAM antigen generation, indicating that lowering early Type-I IFN responses could enhance the potency of RNA vaccines [46].

5.1. In a melanoma model, the non-modified mRNA vaccine produced strong Type-I interferon-dependent anti-tumor immunity

Following mRNA transfection, the main cytokines produced by dendritic cells (DCs) constitute antitumor innate immune responses, specifically type- I IFN, which play a crucial role in antigen presentation and T cell development toward cytolytic effector cells [50]. Sittplangkoon et al. [35] found that a modified vaccine with m1Ψ elicited lower DC activation, whereas a non-modified vaccine produced a greater DC activation.

Using the ovalbumin antigen (OVA) mRNA-LNP platform, researchers examined the impacts of various m1Ψ percentages integrated into mRNA on the immunogenicity and anti-cancer effects in a B16 murine melanoma model [35]. They showed that OVA expressing mRNA encapsulated into a LNP (OVA-LNP) significantly increased the IFN-I synthesis and the developmental process of DCs, and that these effects were negatively correlated with rising percentages of m1Ψ modification, that is, the higher the percentage of modification with m1Ψ, the lower the production of IFN-I. More significantly, non-modified OVA-LNP dramatically decreased tumor expansion and increased survival in the B16-OVA murine melanoma model. In contrast, OVA-LNP with m1Ψ modification increased tumor growth and decreased survival. Specifically, all of the animals that were injected with OVA-LNP that had not been modified survived until the end of the 31-day experiment, whereas only half of the animals that were given OVA-LNP with a 100 % m1Ψ modification survived [35].The Programmed Cell Death protein 1 (PD-1) exhaustion indicator on the T cells of vaccinated animals was also examined [35].

When activated, PD-1 specifically interferes with the T cell receptor-mediated effector activities, resulting in T cell dysfunction or exhaustion [51]. While animals receiving non-modified OVA-LNP experienced an increase in the PD-1^+ $CD4^+$ T cells, those who were injected OVA-LNP with m1Ψ modification of 100 % exhibited a significant increase in PD-1^+ $CD8^+$ T cells [35]. It is interesting to note that interferon gamma (IFN-γ) has been shown to suppress the expression of PD-1 on $CD8^+$ T cells, with a consequential increase in anti-tumor cytotoxicity [52].

In contrast, PD-1 high expressing $CD8^+$ cells were strongly activated (expressing the highest level of granzyme B), but they also displayed a non-functional phenotype, with reduced ability to secrete IFN-γ and a poor clinical outcome for patients with head and neck cancer [53], colorectal cancer [54], melanoma [55], prostate [56], breast [57,58], and gastric cancer [59]. Exhausted $CD8^+$ T cells can therefore allow cancer growth, whereas a decrease in the number of PD-1^+ $CD8^+$ T cells after treatment was linked with an increased likelihood of surviving [60–62].

A further complication to Fig. 1 is the adaptive immune resistance to the antitumor immune response that some tumor phenotypes may develop. Instead of Type-I and II interferons suppressing PD-1, expression of the ligand PD-L1 is induced by cancer cells or other aberrant cells in the tumor microenvironment. This allows cancer cells to evade T cell recognition despite the IFN signaling pathways. In mutated melanoma cells PD-L1 is mostly regulated by IFN gamma signaling [63]. The PD-L2 ligand is also induced, but by both IFNγ and IFNβ signaling. If IFN signaling is also impaired by m1Ψ modified mRNA vaccines, then immune recognition and suppression of cancer cells will be even more impaired than by either pathway alone [63].

5.2. In a melanoma model, non-modified OVA-LNP vaccine prevents metastases to the lung

Macrophages are multipurpose cells that participate in various tasks including removing dead cells, favoring inflammation, presenting antigens, and reconstruction of injured tissue [64,65]. Macrophages are diverse cells with a range of phenotypes and roles. Macrophages have the ability to polarize and differentiate into M1 or M2 cells in response to changes in the microenvironment [66–68]. Immune cells known as M1 macrophages play a role in inducing particular immune and inflammatory responses [69,70]. M2 macrophages, on the other hand, are anti-inflammatory cells that inhibit effector T cells through interleukin 10 (IL-10) release [71].

Being the prevailing phenotype in tumor-associated macrophages, the M2 phenotype plays an essential role in stimulating tumor growth, invasion, and metastasis [68,72]. The endothelium can become more vulnerable to invasion by tumor cells when M2 macrophages produce proteases, like matrix metalloproteinases, which can disrupt the basement membrane surrounding the endothelium [66,73]. M2 macrophages also stimulate angiogenesis through the production of vascular endothelial growth factors [74]. According to these processes, M2 macrophages play a major role in tumor invasion and metastasis, which typically result in a less favorable clinical outcome for both humans and mice [75,76]. Significantly, it was recently demonstrated that tumor-associated M2 macrophages can have their polarization reversed to the M1 phenotype, thus preventing tumor metastasis by blocking IL-10 signaling [77].

The question of whether the non-modified OVA-LNP vaccine triggers an immune reaction against lung metastases in a melanoma model was also investigated by Sittplangkoon et al. [35]. To create lung metastasis, intravenous injections of B16F0-OVA cells were used. B16-F0 is a cell line isolated from the skin of a mouse with melanoma. Mice were intramuscularly inoculated with two doses (10 μg/dose) on days 4 (dose 1) and 8 (dose 2) after tumor cell administration of either: 1) OVA-LNP (100 % m1Ψ modification); phosphate-buffered saline (PBS); or a not related antigen that encoded mRNA-LNP (PR8HA-LNP). The amount of

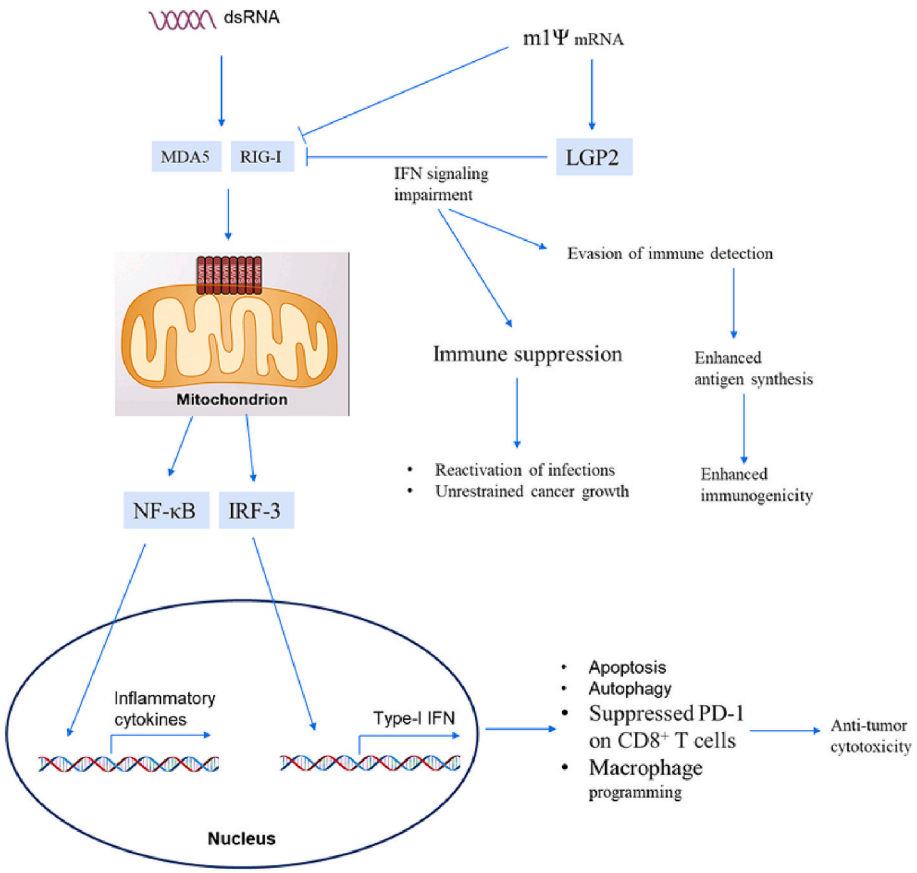

Fig. 1. Schematic representation of the potential effects of 100 % m1Ψ modified mRNA vaccines on RIG-I-like receptors (RLRs). Suppression of RLR function may induce the desired evasion of immune detection to ensure that the vaccine genetic content is successfully translated into immunogenic antigen, but the suppressed pathways are also known to play key roles in cancer development surveillance, potentially eliciting undesired non-specific effects.

lung nodules was recorded, and lung metastasis was evaluated on day 18. Nodule growth was inhibited only by non-modified OVA-LNP, according to the results. 100 % m1Ψ-modified OVA-LNP, on the other hand, failed to inhibit lung metastasis with similar numbers of lung tumors as the not-related antigen (PR8HA-LNP) or PBS control (Fig. 2). This finding emphasizes the beneficial impact of strong anti-tumor innate immunity, including metastasis, on antigen-specific non-modified mRNA-LNP [35]. Altogether, the study provided indirect evidence showing that modified mRNA vaccines with 100 % m1Ψ impair IFN-I synthesis and negatively affect survival in the B16-OVA murine melanoma model [35]. It is important to mention that the authorized COVID-19 mRNA vaccines contain 100 % of such an m1Ψ modification.

Interestingly, IFN alpha (IFN-α) (a Type-I IFN) reprograms M2 macrophages to the M1 phenotype, inhibiting tumor growth and metastasis [78]. Conversely, M2 macrophages facilitate invasion, proliferation, and migration as well as apoptosis inhibition of glioma cells (the commonest and deadly tumor of the central nervous system), thus promoting immune escape [79]. Regarding COVID-19 vaccines, even though the BNT162b2 vaccination effectively produced cellular and humoral immunity against SARS-CoV-2, it waned at six months and also reduced IFN-α and IFN-γ levels [49]. We propose that the reduction of IFN-α and IFN-γ levels after BNT162b2 vaccination could favor a shift from M1 to the M2 phenotype, thus promoting cancer growth and metastasis.

There is growing evidence that IFN-I, either directly or indirectly, modulates T cells to improve antitumor T cell immunity [25,26]. IFN-I stimulates T cells directly to halt ineffective responses, and it also indirectly affects T cell priming by increasing co-stimulatory molecules on antigen-presenting cells. IFN-I also increases IFN-γ release, which directly stimulates immune cells. Previous research demonstrated that failures in antigen cross-presentation to CD8+ T cells prevented highly immunogenic tumor cells from being eliminated by DC-specific knockout model for INF-I receptors ($Ifnar^{-/-}$ mice). This evidence clearly shows that IFN-I can boost T cell immunity through DCs [25]. In response to the non-modified mRNA vaccine, researchers found robust proof that IFN-I, either directly or indirectly, is necessary to initiate an anti-tumor response [35].

5.3. The effects of modified vs. unmodified mRNA vaccines on Toll-like receptors (TLRs)

The class of PRRs with the best description is made up of toll-like receptors, which are the mammalian homologs of the drosophila toll protein. These receptors (TLRs) detect foreign antigens, also known as PAMPs, which originate from bacteria or viruses [80]. Furthermore, mounting data suggests that TLRs are linked to several chronic inflammatory illnesses brought on by infection, which can result in the development of cancer [81,82] and that the tumorigenic inflammatory response is frequently triggered by downstream TLR signaling pathway molecules. It has been found that numerous tumor cells, tissues, or tumor cell lines express certain TLRs at high levels. It is possible that TLR4 expression on tumor cells either directly or indirectly enhances tumor progression because TLR4 is overexpressed in inflammation-associated colorectal neoplasia in humans and mice, and TLR4-deficient mice are significantly protected from colon carcinogenesis [83]. An immunohistochemistry analysis conducted on 81 patients with diffuse large B-cell lymphoma revealed a significant correlation between tumor associated macrophages and TLR4, suggesting that TLR4-induced inflammation could be the cause of macrophage accumulation in the tumor microenvironment [84]. In this sense, the immune system's

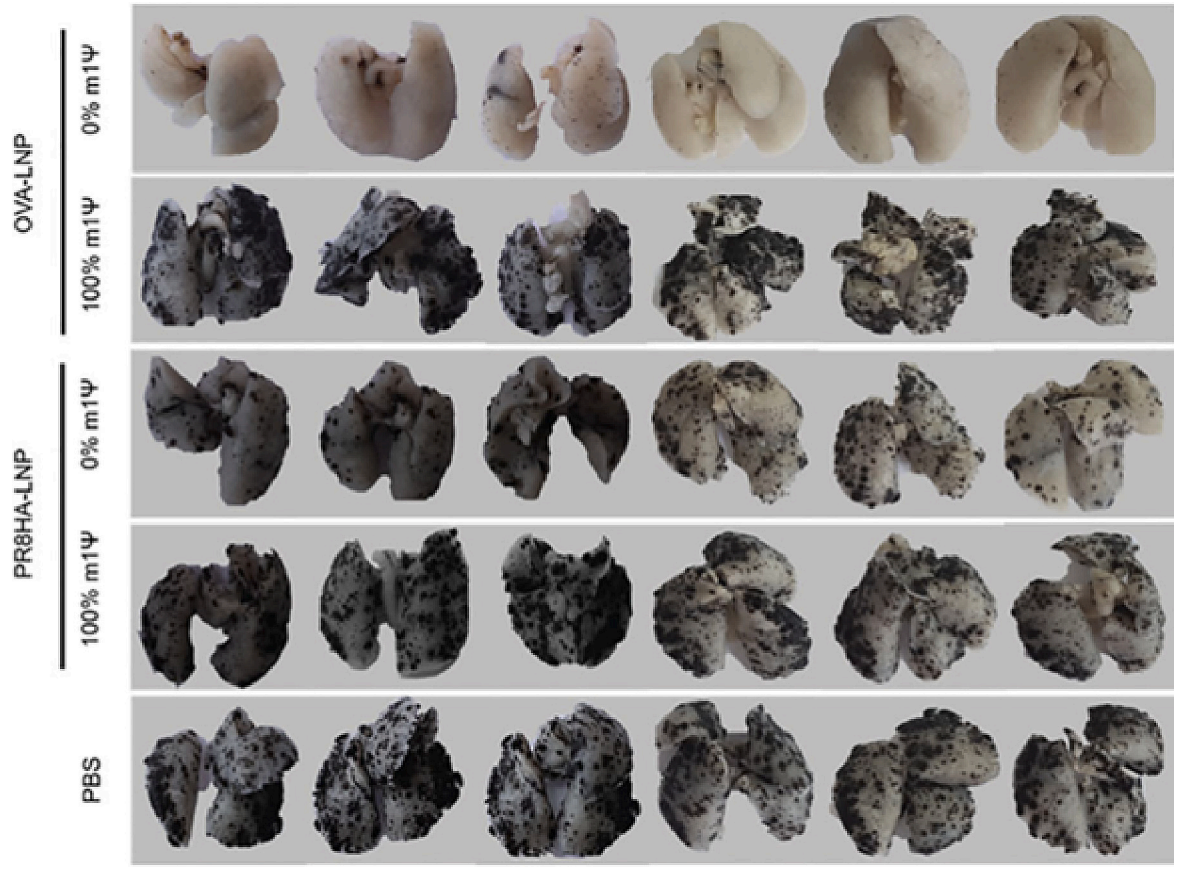

Fig. 2. Unmodified mRNA-LNP immunization prevents B16F0-OVA melanoma from metastasizing to the lungs. In opposition, modified OVA-LNP (with 100 % m1Ψ) did not show any suppression of lung metastasis with the same number of lung nodules as the unrelated antigen (PR8HA-LNP) or PBS control. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY).
Source: [35].

detection of these TLRs is critical for controlling cancer progression.

IRFs, NF-κB, and mitogen-activated protein kinases (MAPKs) are among the signaling pathways that TLRs trigger to produce a variety of cytokines that are essential in many pathologies, including cancer. RNA specifically signals via human endosomal TLR3, TLR7, and TLR8, but the integration of modified nucleosides into the RNA molecule disables TLR activity [16]. Conversely, it has been demonstrated that non-modified mRNA itself presents adjuvant activity by attaching and triggering the innate immune system sensors, primarily TLRs 3, 7, and 8 [85]. It was shown by Karikó et al. [16] that adding modified nucleosides, such as m1Ψ, decreased TLR activity. We believe that this is a double-edged sword because, while it prevents mRNA degradation and enhances the synthesis of the spike protein, it impairs TLR signaling, posing a greater challenge for the immune system to use these receptors to mount an adequate anti-tumor response (Fig. 3).

On the other hand, the significant therapeutic advantages of non-modified mRNA vaccines may result from TLR7 and TLR8 receptor activation, which then triggers the release of pro-inflammatory cytokines through the phosphorylation of IRF-5, which is dependent on the myeloid differentiation primary response protein 88 (MyD88) [86]. IRF-5 is indispensable in the polarization of M1 macrophages [87], which are capable of phagocyting and releasing pro-inflammatory cytokines like IL-6, IL-12, IL-23, and tumor necrosis alpha (TNF-α), as well as reactive nitrogen and oxygen species. These cytokines then foster the cytotoxicity of CD8+ T cells and NK cells. Furthermore, in response to STAT1 signaling, M1 macrophages release chemokine ligand 9 (CXCL9), CXCL10, and CXCL15, which attract cytotoxic T lymphocytes (CTLs) to the tumor environment [88]. Furthermore, lung metastasis is inhibited by an increase in M1-like macrophages [89].

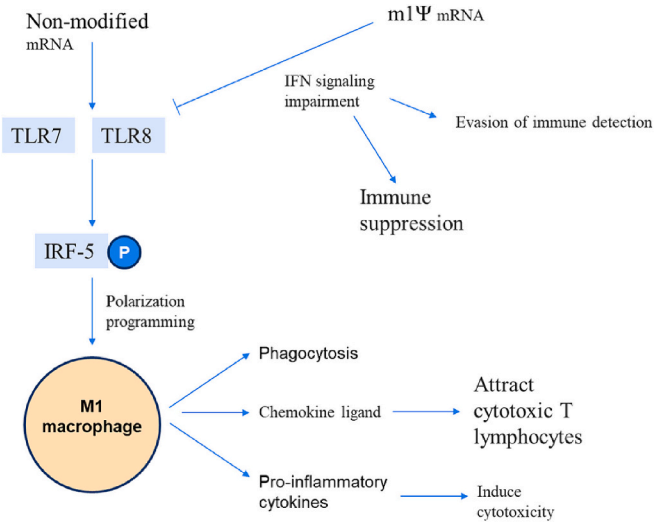

Fig. 3. Schematic representation of the potential effects of 100 % modified vs. unmodified mRNA vaccines on Toll-like receptors (TLRs). In a similar fashion to suppression of innate immune functions observed with RLRs, suppression of TLRs could also negatively impact proper anti-cancer surveillance by impacting induction of M1 macrophage polarization.

6. Additional mechanisms associated with m1Ψ translation

6.1. Imperfect translation of m1Ψ mRNA leading to the synthesis of different proteins as opposed to uniform production of the spike protein

Surprisingly little is known about how ribonucleotide alteration influences protein synthesis, especially for translation of therapeutic IVT mRNAs, considering their widespread use. A new investigation found that during mRNA translation, m1Ψ dramatically increases +1 ribosomal frame-shifting [90]. The process of mRNA translation is a strictly regulated and strongly conserved method of protein synthesis. Even with sophisticated protein quality control mechanisms, amino acid deficiency in melanoma causes aberrant proteins to be produced via ribosomal frame-shifting [91]. This mechanism occurs when translating ribosomes shift reading frames at specific locations, producing multiple proteins [92]. Ribosomal frame-shifting has been discovered in many cancer cell types and viruses, but not in most normal cells [91].

In recent work, no evidence was found that frame-shifted proteins in humans derived from BNT162b2 vaccination are linked to short-term unfavorable effects. However, the authors warned that antigen presentation of +1 frame-shifted protein could activate T cells that target host cells [90]. In our opinion, that could lead to autoimmunity. In addition, it has been discovered that melanoma cells induce ribosomal frame-shifting as an evasion mechanism through the generation of neo-antigens and the presentation of abnormal *trans*-frame peptides [93]. Therefore, the possibility that these aberrant peptides could also stimulate cancer development cannot be ruled out.

6.2. Modified mRNA can alter the duration of antigen production and thus induce IgG4 production

It was first assumed that the vaccine mRNA enclosed in LNPs would remain confined at the inoculation location and quickly degrade. However, several reports showed that mRNA and LNPs can enter the circulation and accumulate in a variety of distant tissues [94]. The majority of intravenously delivered LNPs predominantly pass through and accumulate in the liver. LNPs are endocytosed when endogenous apolipoprotein E (ApoE) adsorbs onto their surface and interacts with the low-density lipoprotein receptor (LDLR) on hepatoma and hepatocyte cells [95].

To investigate repeat dose toxicity, in a nonclinical GLP-compliant study, adult Wistar rats were administered BNT162b2 as intramuscular injections on three occasions, a week apart. 3 different doses were given: 10, 30, and 100 μg [96]. Examination confirmed the presence of microscopic vacuolation of portal hepatocytes, an indicator of hepatocellular injury. This was thought to be linked to the hepatic distribution of the pegylated lipid in the LNP and was reported to be fully addressed by the end of the study's 3-week recovery period. The effects of LNPs on Wistar rats with less healthy livers before administration were not investigated [96]. El Sammak et al. [97] used positron emission and computer tomography (PET/CT) to study vaccine-associated hypermetabolic lymphadenopathy (VAHL). 49 of 57 patients with VAHL had increased anti-spike titers 15–21 days after the 2nd dose of the Pfizer-BioNTech COVID-19 vaccine [97].

In 2023, a retrospective study showed statistically significant higher fluorine 18 (18F) fluorodeoxyglucose (FDG) uptake in vaccinated vs. non-vaccinated patients [98]. Uptake was elevated in both axillary lymph nodes and myocardium for up to 180 days after the second booster. These findings are consistent with persistent presentation of a spike protein antigen [98]. In another study, Turner et al. [99] found that 12 weeks after primary vaccination, all participants in their study tested positive for spike protein binding germinal center B cells. Findings were confirmed by spike staining and biotinylation [99]. The primary function of the 5′ cap is to prevent uncontrolled destruction of cytoplasmic mRNAs since the XRN family of 5′-3′ exoribonucleases rapidly breaks down uncapped or partially capped transcripts [100]. The addition of a 5′-cap [m7(3′OMeG) (5′) ppp (5′) (2′OMeA) pG, also known as trinucleotide "cap 1"] to the mRNA COVID-19 vaccines was a significant modification which served to prevent the RNA from degrading [101].

By not being rapidly degraded, the mRNA from the vaccines could continue to produce the spike protein for a longer time (up to 187 days) according to a recent study [102]. Other works have shown that repeated mRNA vaccination elicits the production of IgG4 antibodies [103–116]. It has been proposed that elevated IgG4 levels may protect by blocking the effects of IgE, which is similar to what happens during effective allergen-specific immunotherapy and preventing immune over-activation, i.e., the cytokine storm [105]. In previous work we hypothesized that the observed rise in IgG4 levels following multiple mRNA vaccinations is an immune tolerance mechanism to the spike protein, which could permit unopposed SARS-CoV2 infection and replication by inhibiting natural antiviral responses rather than a protective mechanism [117]. In addition, IgG4s are also involved in many pathologies, including cancer. We suggest that increased IgG4 production derived from repetitive mRNA vaccination could induce cancer development in susceptible individuals (in press).

6.3. m1Ψ modified mRNA promotes G4 quadruplex and R-loop formation, thus leading to transfected cell genome instability

Guanine-cytosine (GC) enrichment in m1Ψ modified mRNA promotes the formation of non-B secondary structures, such as G4 quadruplexes and R-loops [118]. G4's are formed from stacked guanine tetrads that are stabilized by Hoogsteen hydrogen bonds (Fig. 4). They have a role in cancer by inducing DNA damage, replication stress and impairment of regulation of transcription and translation - leading to both genomic and epigenetic instabilities. G4's also contribute to the stability of R-loop/G4 hybrids [119].

An R-loop is a triple-stranded nucleic acid structure made up of a displaced DNA strand and a DNA: RNA hybrid. R-loops are widely distributed throughout genomes and play a major physiological role. They are essential for controlling DNA replication, histone and DNA modifications, and gene expression (Fig. 5). Numerous investigations have revealed that R-loops are involved in basic biological functions in a range of organisms. Ironically, even though they perform important roles for biological processes, they can also exacerbate genome instability and damage to DNA. R-loops are associated with several human diseases, such as autoimmune diseases, cancer, and neurological disorders [120]. A recent study found that 47 % of BNT162b2 mRNA-compatible transcripts created R-loops, compared to 12.5 % of transcripts from the SARS-CoV-2 spike gene [121].

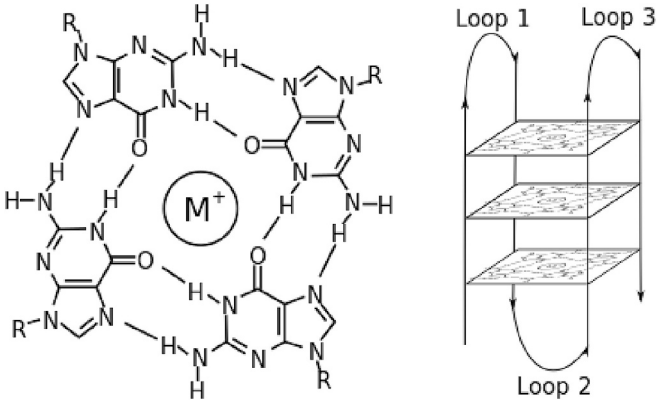

Fig. 4. Example of a (mini) G-quadruplex, showing one layer and the full stacked structure. This file is licensed under the Creative Commons Attribution-Share Alike 2.5 Generic license: https://creativecommons.org/licenses/by-sa/2.5/deed.en.
Reprinted from G-quadruplex.jpg by [119].

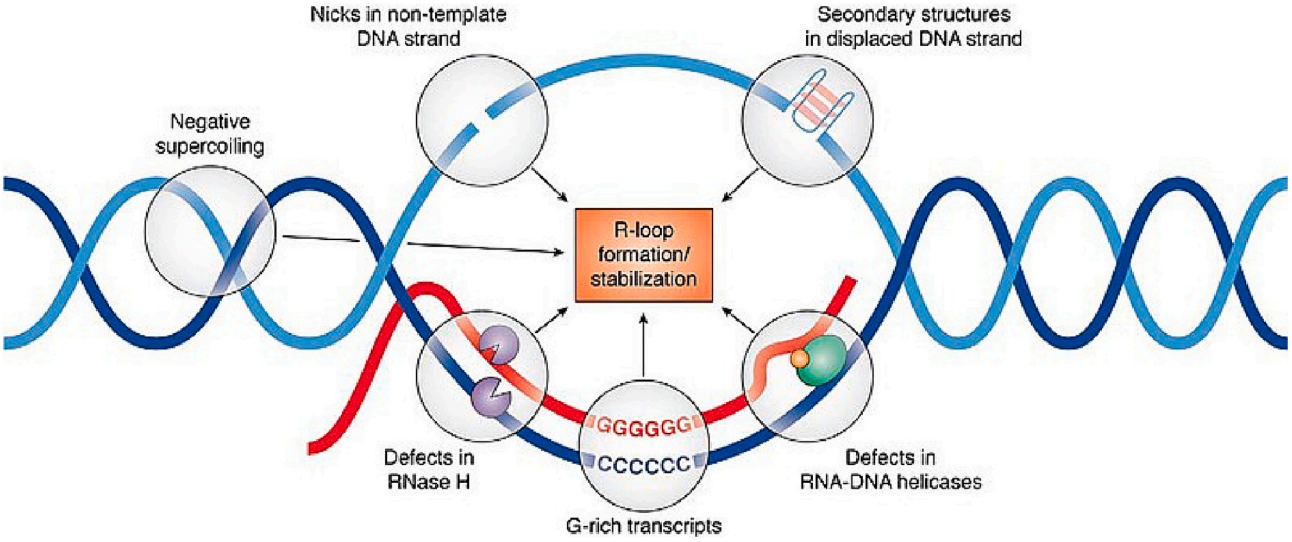

Fig. 5. Inverse supercoiling encourages the creation of R-loops. Topoisomerases halt negative supercoiling, which prevents the creation of R-loops. A snip on the non-template strand downstream of a promoter reduces the efficiency of DNA reannealing, favoring the nucleation of an R-loop. The R-loop structures can also be stabilized by secondary structures in DNA. The RNA transcript's G-clusters promote the creation of R-loops. An increase in R-loop formation is also caused by deficiencies in anti-R-loop factors such as RNA-DNA helicases and RNase H. This file is licensed under the Creative Commons Attribution-Share Alike 4.0 International license: https://creativecommons.org/licenses/by-sa/4.0/deed.en.
Reprinted from R-loop promoting factors.jpg [120].

6.4. Epigenetic crosstalk

According to a recent in silico study, base pairing between the nucleotide sequences of coding and noncoding genes and the COVID-19 BNT162b2 mRNA vaccine may create epigenetic interactions in human recipient cells. These computational findings suggest that the epigenetic environment of recipient cells may be more significantly impacted by the COVID-19 mRNA vaccine than by the effects of the spike gene during natural infection, especially concerning pathways linked to inflammation or cancer [121].

Transcripts with sequence complementarity to the BNT162b2 mRNA vaccine were predicted to interact with human proteins like Adipocyte Enhancer-Binding Protein (AEBP1), Noradrenergic Imidazoline-1 receptor protein (Nischarin), and Cysteine Rich Hydrophobic Domain 1 (CHIC1), which are linked to both proliferative and autoimmune pathways, in greater quantities than the virus gene [122–125]. The spike RNA gene of SARS-CoV-2 and the BNT162b2 mRNA vaccine, which encodes the S protein, do not possess the same complementarity pattern, and they may potentially lead to epigenetic discrepancies of the targeted genes and cause long-term complications [121].

7. Discussion

The COVID-19 pandemic's impact caused an unprecedented level of biomedical research community participation, which made it possible for the fastest vaccine production process in history [36]. Using mRNA vaccines has a number of benefits over other platforms. This platform combines the well-defined composition and safety of killed or subunit vaccines with the immunological properties of live attenuated vaccines, including endogenous antigen expression and T cell induction [126]. At provisional analysis, Pfizer-BioNTech's BNT1262b2 and Moderna's mRNA-1273 both demonstrated excellent vaccination effectiveness rates of 95 % and 94.5 %, respectively [37,127]. Additional advantages are a quick research cycle, ease of industrialization, an uncomplicated production method, adaptability to new variants, and the ability to boost immunity [128]. The modified nucleobase (m1Ψ) aids in protecting mRNA vaccines from the immune system, minimizing the amount of unfavorable immunological stimulation they cause [15,16].

However, this vaccine-induced immune suppression could have unintended consequences. In the reviewed literature, we have found that m1Ψ from mRNA vaccines impair the RIG-I and TLR signaling pathways, thus blocking IFN Type-I synthesis. These are unexpected findings. It is obvious that Karikó and her colleagues did not anticipate the possibility that adding m1Ψ to mRNA to avoid an excessive inflammatory response, could make people susceptible to other pathogens and allow cancer growth by suppressing the immune system. We believe that this could constitute a negative non-specific effect of mRNA vaccines that requires further thorough verification. In Table 1 we have summarized the main findings from the work of Sittplangkoon et al. [35]. These researchers discovered that m1Ψ-mRNA-modified vaccines induced completely opposite results to those produced by non-modified vaccines (Table 1).

The work of Sittplangkoon et al. [35] is of seminal relevance since it demonstrated that adding 100 % m1Ψ to the mRNA vaccine in a melanoma model stimulated cancer growth and metastasis. The implications of their results are especially important in the context of the current pandemic caused by SARS-CoV-2. Due to the health emergency, in 2021 the use of mRNA vaccines containing 100 % m1Ψ was authorized [129]. The need to quickly have an effective vaccine did not allow

Table 1
For all parameters evaluated, a modified mRNA vaccine with m1Ψ elicited completely opposite results to those induced by a non-modified vaccine.

Modified mRNA vaccine with 100 % m1Ψ	Non-modified vaccine
Enhances translation efficiency by inhibiting type-I interferon signaling	Reduces translation efficiency but increases type-I interferon production
Increases tumor growth	Reduces tumor growth
Decreases survival	Increases survival
Does not activate the endosomal toll-like receptor 7/8 (TLR7/8)	Activates the endosomal toll-like receptor 7/8 (TLR7/8)
Induces polarization to the macrophage M-2 phenotype, which promotes lung metastasis	Induces polarization to the macrophage M-1 phenotype, which inhibits lung metastasis
Elicits lower dendritic cells activation	Elicits more efficient dendritic cells activation
Induces an increase in PD-1$^+$ CD8$^+$ T cells	Induces an increase in PD-1$^+$ CD4$^+$ T cells

Adapted from: [35].

long-term studies to be carried out on the possible adverse effects of this type of vaccine.

When m1Ψ was incorporated into COVID-19 mRNA vaccines, innate immune sensors' activity was reduced, and mRNA's translational capability was enhanced [15,17]. While this was a significant step toward the success of the COVID-19 vaccines, Type-I IFN-dependent antitumor immunity was adversely affected by such mRNA modification due to modified paracrine signaling pathways. Therefore, there is a possibility that mRNA-based COVID-19 vaccines could facilitate cancer growth and metastasis, and for this reason, it is urgent to investigate it. It is important to clarify here that mRNA vaccines do not cause cancer; but they could stimulate its development (Fig. 6). There is pathologically a distinction to be made between the agents that initiate and promote tumors and malignant conversion vs. those that also/instead promote cancer progression [130]. We are more concerned with experimental and clinical data with regard to the latter.

Cancer is a highly complex disease that can be activated by a variety of internal and external factors. Infectious pathogens are known to play a role in oncogenesis, and viral infection is responsible for an incidence of 15 % of cancer cases in humans [131]. In a review article, the authors recently suggested that infection with SARS-CoV-2 may increase the probability of developing cancer [132]. Nevertheless, although a large percentage of the literature supports a positive association between COVID-19 severity and cancer progression, the unfavorable results were primarily ascribed to the comorbidities—obesity, active smoking, and advanced age—that cancer patients exhibited [133]. Furthermore, it is important to take into consideration the numerous recent cases describing cancer disappearance during or following SARS-CoV-2 infection. These cases encompass a wide range of cancer types, including Hodgkin lymphoma, multiple myeloma, acute leukemia, cutaneous T cell lymphoma, colorectal cancer, and follicular lymphoma [134]. After an extensive search, we found that, in total, 21 cancer cases were associated with remission after SARS-CoV-2 infection and 3 with remission after mRNA vaccines (2 from Pfizer and 1 case from Moderna), potentially further supporting our hypothesis that mRNA vaccines could be associated with cancer development due to m1Ψ modification of the mRNA genetic code [134–136]. A recent work proposed a similar hypothesis: "certain COVID-19 vaccines may generate a pro-tumorigenic milieu (i.e., a specific environment that could lead to neoplastic transformation) that predisposes some (stable) oncologic patients and survivors to cancer progression, recurrence, and/or metastasis" [137].

Like any medical treatment, vaccines are not exempt from inducing adverse effects. Recognizing this possibility will expand the current vaccination paradigm and could enable the development of better and safer vaccines. Sittplangkoon et al. [35] discovered that the use of non-modified mRNA elicits a robust immune response against malignant tumors and prevents metastasis, unlike modified vaccines in which 100 % of m1Ψ was added. More experimental research is urgently needed to confirm these findings in other cancer models, like lung, pancreatic, colorectal cancer, and lymphoma. Of note, the first documented case of B-cell lymphoblastic lymphoma in a BALB/c mouse after intravenous high-dose mRNA COVID-19 vaccination (BNT162b2) was recently published [138]. At 14 weeks of age, one animal (out of 14) experienced spontaneous death with significant organ hypertrophy and disperse cancerous infiltration of multiple organs (liver, kidney, lung and spleen) by lymphoid cancer two days after booster vaccination (i.e., 16 days after prime) (Fig. 7). BALB/c have a typical medium lifespan of 17–20 months and typically exhibit a relatively low incidence of tumor pathology [139].

Immuno-histochemical examination revealed organ sections compatible with a B-cell lymphoblastic lymphoma phenotype [138] Although the authors "explicitly indicated the lacking evidence for causality between mRNA vaccination and the observed lymphoma", several separate cases of development, growth, worsening, and spontaneous regression of T cell lymphoma have been reported in humans after mRNA-based SARS-CoV-2 vaccination [134,140–145].

Considering the body of published research works, we suggest that until it is demonstrated that mRNA vaccines do not promote the development of cancer, clinical trials using 100 % modified mRNA vaccines with m1Ψ should not be carried out. We propose a moratorium on use with human subjects due to the precautionary principle that the potential benefit of modified mRNA vaccines achieving desired immunogenic humoral response might not outweigh the benefit of inducing innate immune responses seen with non-modified mRNA vaccines. In terms of achieving immunological response to a foreign antigen, the COVID-19 vaccines were effective, albeit not for an extensive time due to SARS-CoV-2 virus immune escape from neutralizing antibodies. However, these are significant biological effects induced by m1Ψ-modified genetic content that are not fully understood due to the limitation of time to investigate these effects before approval of mRNA COVID-19 vaccines.

In the Pfizer clinical trial, Polack et al. [37] assessed the safety and efficacy of two 30-μg doses of BNT162b2 only, administered intramuscularly 21 days apart, as compared with placebo. Adults 16 years of age or older who were healthy or had stable chronic medical conditions, including but not limited to human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus infection, were eligible for participation in the trial. Key exclusion criteria included a medical history of COVID-19, treatment with immunosuppressive therapy, or diagnosis with an immunocompromising condition, so, cancer patients were no included.

The analysis of some of the published reports suggests that a deeper understanding needs to be obtained by the scientific community with regards to how the m1Ψ-modified genetic content of candidate vaccines could influence cancer progression due to suppression of the immunological response [46–49], especially innate immunity. Similarly, quantification of antigen should gain further insight to confirm if either a non-modified mRNA vaccine or one with a lower percentage of m1Ψ

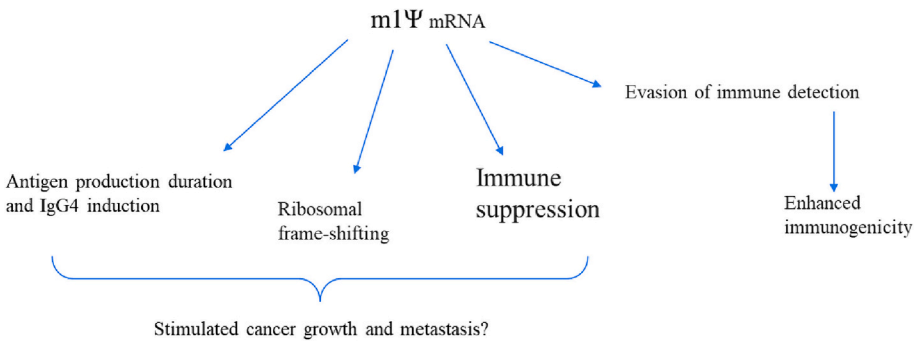

Fig. 6. Evasion of immune detection by a 100 % m1Ψ-modified mRNA elicits desired enhanced immunogenicity, but also could potentially cause additional downstream effects that unwittingly could be contributing to undesired stimulation of cancer growth and metastasis in afflicted individuals with either initial stages of cancer development or those already receiving cancer treatment.

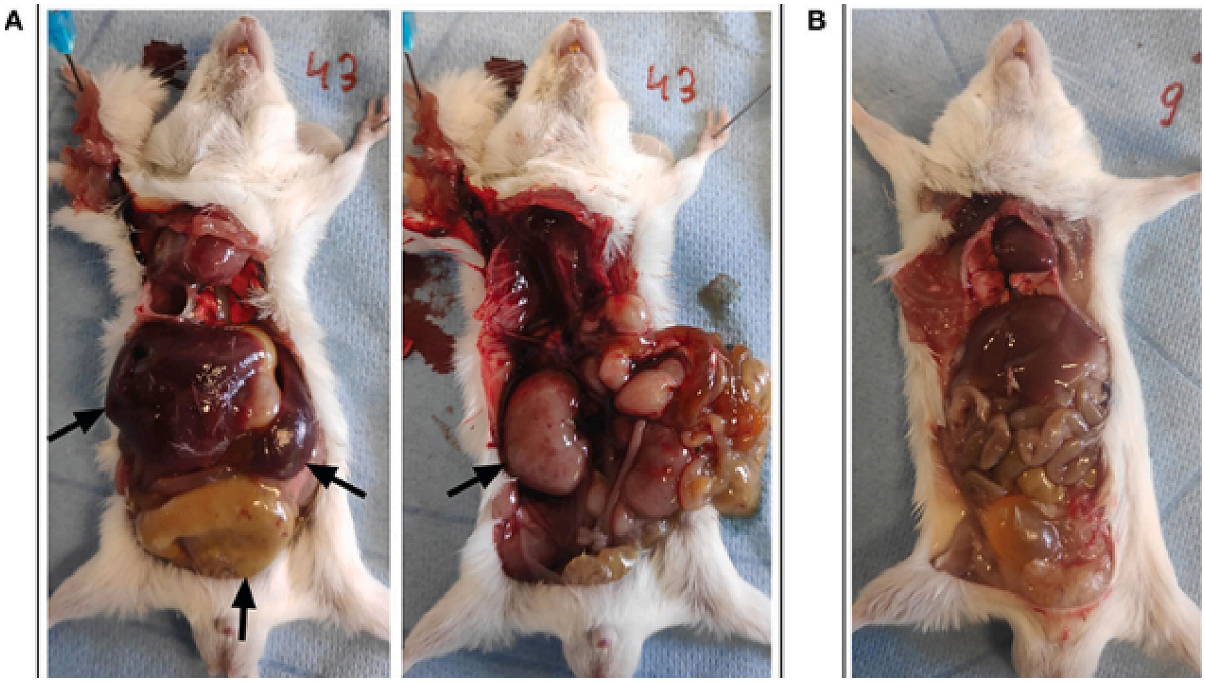

Fig. 7. Organs were examined during a necropsy after a spontaneous death, which revealed lymphoid neoplasm two days after booster vaccination with BNT162b2. (A) At necropsy, several of the animal's primary organs, including the liver, kidneys, spleen, and intestines (black arrows), showed disproportionate hypertrophy. (B) A reference animal with a typical morphology. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution, or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice.
Source: [138].

modification could be safer and thus preferred substitute for antigen presentation.

The main limitation of this review is that, to date, there are few reports associating the use of m1Ψ in mRNA vaccines with cancer development, making the relationship between cause and effect difficult to determine. Precisely for this reason, it is urgent to carry out long-term studies in the animal model to verify or refute such a possibility, especially given the long asymptomatic latency periods typical of many cancers. In the analysis by Nadler & Zurbenko [146], 35 of 44 patients, representing 89 % of cases, had cancers that progressed without detection for 10 years or longer. Furthermore, according to a recent Austrian nationwide study [147], a fourth dose did not prevent COVID-19 deaths in older adults. Thankfully, the death toll was small, but it was higher than those who had received three doses and those who had not received the vaccination. In terms of preventing COVID-19 mortality, the relative vaccination effectiveness (rVE) of four versus three vaccine doses was −24 % (95 % confidence interval: −120 to 30). Not a single person under 40 passed away from COVID-19. Residents of nursing homes accounted for a sizable fraction of all cause deaths as well as the bulk of COVID-19 deaths. In terms of infection prevention, the fourth dose shielded recipients during the first three months; nevertheless, six months later, the number of infections increased relative to the group that received the three doses [147].

During the massive vaccination campaign, it has been frequently stated: the benefits outweigh the risks. In our opinion, that was true with the first 2 doses, as hospitalizations and deaths were shown to decrease [148–151]. However, after the third dose, the risk exceeds the benefits, especially for the elderly and immunocompromised individuals, so health authorities should re-evaluate the real usefulness of continuing to administer boosters.

Glossary

AEBP1	Adipocyte Enhancer-Binding Protein
ApoE	Apolipoprotein E
CARD	Caspase Activation and Recruitment Domains
CHIC1	Cysteine Rich Hydrophobic Domain 1
CLRs	C-type lectin receptors
CTLs	cytotoxic T lymphocytes
CXCL	chemokine ligand
DAMPs	damage-associated molecular patterns
DCs	dendritic cells
FDG	fluorodeoxyglucose
HMGB1	high-mobility group box 1
HSPs	heat shock proteins
IFNβ	interferon beta
IFN-γ	interferon gamma
IL-10	interleukin 10
IRF	interferon regulatory factor
ISGs	interferon-stimulated genes
LDLR	low-density lipoprotein receptor
LGP2	laboratory of genetics and physiology 2
LNPs	lipid nanoparticles
LPS	lipopolysaccharides
m1Ψ	N1-methyl-pseudouridine
MAPKs	mitogen-activated protein kinases
MDA5	melanoma differentiation-associated gene 5
MyD88	myeloid differentiation primary response protein 88
NF-κB	nuclear factor kappa B
Nischarin	Noradrenergic Imidazoline-1 receptor protein
NLRs	nucleotide-binding oligomerization domain (NOD)-like receptors
OVA	ovalbumin antigen
PAMPs	pathogen-associated molecular patterns
PD-1	Programmed Cell Death protein 1
PR8HA-LNP	cancer antigen: A/PoRico/8/1934
PRRs	pattern recognition receptors
RLRs	retinoic acid-inducible gene I (RIG-I)-like receptors

SAM	self-amplifying mRNA vaccine
STAT1	signal transducer and activator of transcription 1
TLRs	toll-like receptors
VAHL	vaccine-associated hypermetabolic lymphadenopathy

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Not applicable.

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