

SARS-CoV-2 mRNA vaccination sensitizes tumors to immune checkpoint blockade

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A recent paper in *Nature* shows that SARS-CoV-2 mRNA vaccination within 100 days of beginning immune checkpoint inhibitor immunotherapy improves survival of cancer patients by systemically inducing Type I interferons, suggesting that an off-the-shelf cancer vaccine that potently stimulates innate immunity may not need to be customized to contain tumor-associated antigens to be effective.

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy, but only about 20% of solid tumors respond to current treatments. Some patients with advanced cancers that do not respond or develop resistance to conventional or targeted therapies can be cured by immunotherapy. These results have galvanized cancer immunologists to figure out ways to increase the range of tumors that respond to immunotherapy. However, recent clinical studies of combinations of ICIs or of ICIs with other drugs have been disappointing. New therapeutic approaches that target other pathways by which tumors evade immune detection and elimination or that reengineer the immunosuppressive tumor microenvironment (TME) are needed. One of the most effective ways to identify new therapeutic strategies is to characterize the molecular and immunological characteristics that distinguish ICI-responsive and -unresponsive cancer patients.

A surprising recent study in *Nature*¹ found that advanced cancer patients vaccinated within 100 days of receiving ICIs with the BioNTech-Pfizer or Moderna SARS-CoV-2 mRNA vaccines were much more likely to be cancer-free and to survive 3 years after their treatment began (Fig. 1). This observation was initially made in patients with non-small cell lung cancer (NSCLC) and melanoma, two of the most ICI-responsive cancers. High tumor cell expression of PD-L1, the ligand of the checkpoint receptor PD-1, is a biomarker for ICI responsiveness. The tumors of NSCLC patients vaccinated with the SARS-CoV-2 vaccines before they received ICI were more likely to express high levels of PD-L1 than those from patients who were unvaccinated or vaccinated > 100 days before or after beginning immunotherapy. This association extended beyond NSCLC and melanoma. When the authors analyzed all cancer patients at MD Anderson from 2020 to 2023 whose tumors were examined for PD-L1, which included many patients whose cancers are not approved for ICI, they found that those who received COVID vaccines within 100 days of their biopsy were more likely to express PD-L1 highly and also had significantly better survival.

The striking and unexpected clinical association of better cancer outcomes and ICI responsiveness with mRNA vaccination against a viral antigen unrelated to cancer antigens (the SARS-CoV-2 Spike protein) prompted the authors to investigate potential mechanisms underlying improved tumor

control. The SARS-CoV-2 mRNA vaccines are unusually highly immunogenic and often cause a limited flu-like illness that reflects their induction and secretion of antiviral and inflammatory cytokines and chemokines that recruit immune cells to sites of infection and activate them to orchestrate a potent adaptive immune response to the vaccine antigen. In this study, a handful of healthy donors were given the Moderna Spikevax vaccine and their plasma was analyzed for hundreds of immune cytokines. Not surprisingly, interferon (IFN)- γ and IL-6 were the first increased cytokines 6 h post vaccination and were followed by a surge of multiple cytokines that peaked at 24 h and returned almost to baseline a week later. Most striking amongst them was IFN- α , which increased 100–1,000 fold, but the sharply increased cytokines also included other Type I IFNs, IFN- γ , the IL-1 receptor antagonist, and other inflammatory cytokines and chemokines, and their blood cells showed signs of systemic activation with widespread PD-L1 expression in myeloid and dendritic cells (DCs) and expression of activation markers on NK and T cells. PD-L1 is an IFN-stimulated gene.

The authors turned to manipulable mouse models of immunologically cold lung cancer (Lewis lung cancer, LLC) and melanoma (B16F0) to identify what immune responses are important in tumor immune control after vaccination. A homegrown Spike mRNA-lipid nanoparticle (LNP) vaccine was given intramuscularly at the same time as anti-PD-1 to mice bearing small subcutaneous tumors or orthotopic LLC lung tumors. Like the human cancers, tumors in mice treated with the Spike mRNA-LNP vaccine plus anti-PD-1 were strongly suppressed compared to those in mice that were untreated or received only the vaccine or anti-PD-1 or were treated with recombinant IFN- α . Importantly, tumor control was abrogated by antibodies to the Type I IFN receptor, suggesting that Type I IFN signaling was necessary, though maybe not sufficient, for vaccine-induced immune protection. Consistently, one day after vaccination, plasma IFN- α was > 1 ng/mL only in mice treated with the vaccine with or without anti-PD-1, but not in those given just anti-PD-1 or empty LNPs, and the macrophages and DCs in their spleens and tumor-draining lymph nodes were highly activated with highly expressed PD-L1. Blocking the IL-1 receptor (IL-1R), in contrast, did not dampen tumor control by the vaccine plus anti-PD-1, even though IL-1/IL1R signaling may play a key role in the effectiveness of the vaccine against SARS-CoV-2². Inflammatory cytokines, such as IL-1, IL-6 and TNF α , were induced at comparable levels by LNPs that did not contain any RNA, but the Type I IFN response required mRNA cargo.

Treatment of tumor-bearing mice with the mRNA-LNP vaccine plus anti-PD-1 also dramatically increased the numbers of activated CD8⁺ T cells systemically. In fact, the

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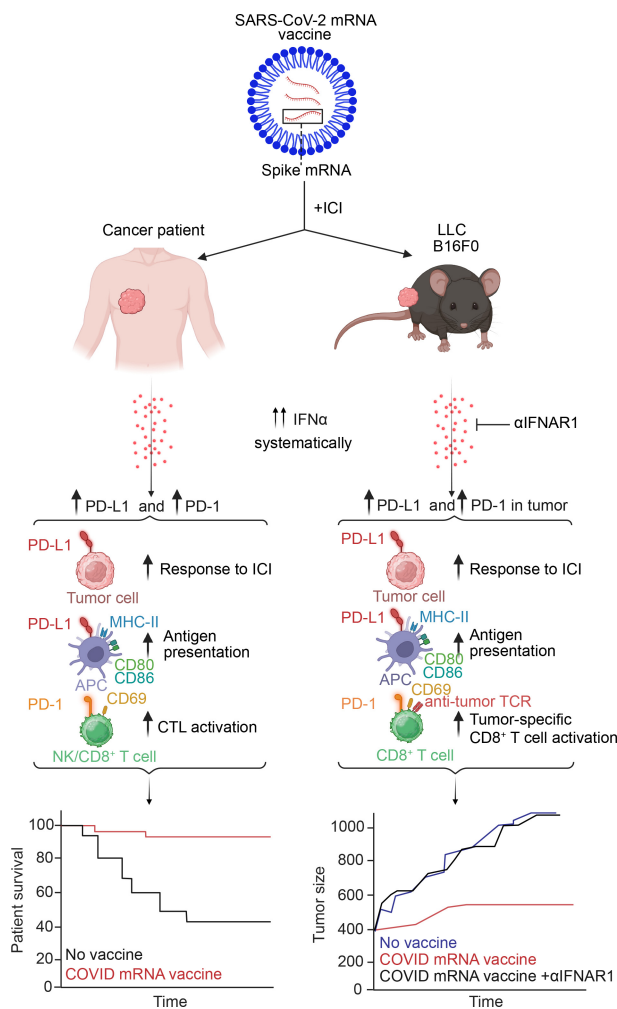


Fig. 1 SARS-CoV-2 mRNA vaccination sensitizes tumors to immune checkpoint blockade. Griffin *et al.*¹ retrospectively found that cancer patients, bearing a variety of immunologically cold tumors, responded better to ICI if they received a SARS-CoV-2 mRNA vaccine within 100 days of starting ICI. The vaccine increased plasma IFN- α . Tumors and circulating APCs (monocytes and DCs) showed increased PD-L1⁺ and circulating CD8⁺ T cells and NK cells were more activated and expressed PD-1. The mechanism behind tumor protection was examined in mice bearing immunologically cold LLC or melanoma (B16F0), which were similarly protected when they were vaccinated with a SARS-CoV-2 mRNA vaccine at the same time they were started on ICI therapy. Vaccinated mice showed a sizeable increase in tumor-infiltrating tumor-specific CD8⁺ T cells. Tumor protection in mice depended on Type I IFNs since it was blocked by an antibody to the Type I IFN receptor (IFNAR1).

frequency of potentially tumor-reactive splenic CD8⁺ T cells that bound to any of 6 tetramers carrying melanoma-associated antigenic peptides increased dramatically; they also expressed PD-1 and other activation markers both in the spleen and the tumor. Moreover, the proportion of tumor cells in vaccinated mice expressing PD-L1 also tripled to a mean of ~60%, a level that predicts ICI responsiveness. The expansion of activated CD8⁺ T cells and of tetramer-labeled T cells was abrogated by anti-IFNAR1 and did not occur in mice that were treated with IFN- α plus anti-PD-1, again suggesting that IFNs are required but may not be sufficient for vaccine-related protection. Because the total proportion of tumor-associated antigen-reactive CD8⁺ T cells in the tumor was at most ~10% while the proportion of PD-1⁺ T cells in the tumor was about 6 times that, most of the activated tumor-infiltrating CD8⁺ T cells are likely to be bystander cells whose T cell receptors do not recognize a tumor antigen. Since CD8⁺ T cells

that recognize non-tumor antigens were not analyzed as controls and CD8⁺ T cell functionality (killing, cytokine secretion) was not assessed, it is unclear whether the vaccine helped induce functional T cells, preferentially activated tumor-specific T cells or nonspecifically activated non-naïve CD8⁺ T cells that had previously seen antigen.

It may not be so surprising that the SARS-CoV-2 mRNA vaccine had such a profound effect on antitumor immunity and the ability to respond to ICI. The more a vaccine looks like a pathogen, the more likely it is to stimulate IFNs and inflammation, and mRNA vaccines, composed of RNAs encapsulated in a lipid envelope, resemble RNA viruses. The mRNA vaccine's resemblance to viruses led to a potent innate immune danger signal, not just locally but also systemically, that reached the faraway tumor, its draining lymph nodes and lymphoid secondary structures throughout the body. An innate immune danger signal, in addition to antigen and co-stimulation, is needed to activate both functionality and memory of CD8⁺ T cells, the final effector cells that eliminate the tumor and are key to successful immunotherapy. Functionality and memory are critical for effective anti-tumor immunity. The control flu and pneumococcal vaccines, which contain inactivated virus or pneumococcal polysaccharides, respectively, didn't provide any added protection in vaccinated cancer patients. The flu vaccine stimulates the same types of IFNs and inflammatory cytokines, but at lower levels³, while pneumococcal vaccines engage a different innate sensing program⁴, which is probably why they failed to increase immune control of the tumor.

This work challenges a long-standing assumption in cancer immunotherapy — that vaccines must encode tumor-specific antigens to be therapeutically meaningful. It raises the exciting possibility that cancer vaccines may not need to be personalized to present tumor neoantigens predicted by the specific mutations in a patient's cancer, which would greatly reduce the cost, expedite the time to vaccination, and could possibly effectively increase tumor immunity and response to ICI in patients whose tumors have low mutational burden. Already off-the-shelf RNA-lipoplex cancer vaccines that target non-mutated tumor-associated antigens or HPV viral antigens, being developed by U. Sahin and his colleagues at BioNTech, when administered intravenously, have been shown to activate antigen-presenting cells (APCs) systemically to expand functionally active antitumor CD8⁺ T cells to reject aggressive and advanced tumors in mice⁵. Cancer vaccines modeled on what worked in mice are in late-phase clinical trials for melanoma, NSCLC and head and neck cancer, and show hints of effectiveness in previously treated, advanced cancer patients⁶. Other intriguing cancer vaccination studies in mice bearing colorectal or melanoma cancer cell lines make a strong case that intravenous vaccination is much more effective than subcutaneous, intradermal, or intramuscular vaccines at eliciting potent antitumor immunity that remodels the TME to eliminate a class of suppressive macrophages, induces high systemic levels of Type I IFNs and functional CD8⁺ T cells^{7,8}. Those studies used self-assembling nanoparticles or a chimpanzee strain of an attenuated adenovirus to express cancer neoantigens and showed that protection depended on Type I IFNs, eliminating immunosuppressive macrophages and activating antigen-specific T cells. The need for intravenous vaccination likely depends on how immunogenic the vaccine is, since the COVID-vaccinated patients in the current study were all vaccinated intramuscularly. Since the induc-

tion of a strong systemic Type I IFN response seems to be key for antitumor efficacy, the intravenous route of administration (or alternatively, more potent adjuvants) might be the key to more effective cancer vaccines.

A word of caution is warranted. Inflammation is a double-edged sword in cancer that can enhance antitumor efficacy but also promote carcinogenesis and malignancy⁹. Which effect dominates depends on many factors, including the tumor type and stage, whether the inflammation is acute or chronic, and how severe it is. In fact, a recent study using a genetically engineered mouse model of *Her2*-driven dormant breast cancer showed that influenza or mouse-adapted SARS-CoV-2 infection caused IL-6-dependent awakening of tumor dormancy and metastasis¹⁰. IL-6 is induced by Type I IFNs and was prominently induced by the mRNA-LNP vaccines. The finding that SARS-CoV-2 infection increased metastatic recurrences in dormant tumors in mice prompted an analysis using the UK Biobank of long-term cancer survivors (5–10 years out with no apparent cancer), which showed that SARS-CoV-2 infection significantly increased cancer-related deaths. Although inflammation can foster malignancy, immunoprotection by innate immune activation induced by an mRNA vaccine will likely dominate over cancer exacerbation in the setting of already developed cancer. There is likely a sweet spot for the optimal amount of inflammation to potentially activate innate immunity to sculpt the TME to be more inflamed and immunostimulatory and generate cytotoxic and long-lived T cells, but avoid unacceptable clinical toxicity.

Despite the strength of the clinical correlations, mechanistic and vaccine design questions remain, which can be worked out more comprehensively in mouse models. While the authors demonstrate that mRNA vaccines induce a transient, Type I IFN-dominated innate immune program that activates APCs and primes tumor-reactive CD8⁺ T cells, the downstream immune circuitry may be complex. Additional factors besides Type I IFNs may be needed to shape the antitumor response, including other innate immune pathways and chemokine programs that transform the TME and promote the recruitment and activation of cytotoxic lymphocytes, especially since IFN- α treatment could not substitute for the vaccine in mice. Fully characterizing the effect of mRNA-LNP vaccines on the tumor and TME using powerful and unbiased multiomic and spatial transcriptomic and proteomic tools will undoubtedly help to identify the key changes in the tumor-

infiltrating immune cells and pathways that control the most effective vaccine responses. Future studies leveraging existing genetic models, such as mice deficient in specific pattern-recognition receptors or cell types, or more clinically relevant tumor models especially with more advanced disease, could help clarify how mRNA vaccines trigger danger-sensing networks in the tumor setting and investigate in more detail how varying the vaccine parameters (RNA modifications, nature of the antigen, lipid composition), dosing schedule and route of administration affect tumor control. The immunostimulatory properties of the LNP lipids, the LNPs and comparison of mRNA-LNPs with attenuated live viral or bacterial vaccines or other constructs merit closer attention. Although Type I IFNs are well recognized to promote effective antitumor immunity, not much is known about whether IFN- γ or more inflammatory pathways and cytokines, which can be more immunogenic but also more toxic, could be induced to improve tumor control.

COMPETING INTERESTS

The authors declare no competing interests.

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ADDITIONAL INFORMATION

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