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COVID-19 vaccines: modes of immune activation and future challenges

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The new vaccines against SARS-CoV-2 are novel in terms of specificity, their wide dissemination across the global population and the inclusion of newly licensed mRNA platforms. We discuss here how the approved vaccines trigger innate immunity to promote durable immunological memory and consider the future implications of protecting populations with these vaccines.

The global SARS-CoV-2 pandemic has caused significant loss of life, profound disruption to lives and livelihoods, and widespread economic, sociological and psychological damage. Severe COVID-19 involving acute respiratory distress syndrome (ARDS), multi-organ failure and death remains the most serious threat from infection, but long-term sequelae from mild disease have also been reported. The high transmissibility, presence of asymptomatic carriers and emergence of new variants have had a prolonged effect on the global population for the past year and counting. Vaccination constitutes the most promising path back to 'normal life'; here, we discuss how the newly approved vaccines can mobilize innate and adaptive immune responses, implications for their durability, and ongoing and future challenges for protecting the population.

Approved vaccine formulations

Significant advances in cutting edge vaccine technologies over the past decade have resulted in two main types of SARS-CoV-2 vaccines now being approved for emergency use — an unprecedented achievement in modern medical science. The approved vaccines developed by Pfizer and Moderna use mRNA technology and lipid nanoparticle (LNP) delivery systems, while the approved formulations by AstraZeneca, Johnson and Johnson and Gam-COVID-vac (Sputnik V) contain DNA delivered within non-replicating recombinant adenovirus (AdV) vector systems[1–4]. Both the mRNA and AdV vaccines encode production of the SARS-CoV-2 spike (S) protein, which is the primary target for neutralizing antibodies generated from natural infection and for therapeutic monoclonal antibodies[1]. To date, results from the phase III clinical trials showed that both the Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273) mRNA vaccines achieved 90–95% efficacy in protecting against COVID-19 (REFS[1,2]), while the AdV vaccines (ChAdOx1 nCoV-19) and Gam-COVID-vac (Sputnik V) showed protection at a slightly lower efficacy (average 70% and 91%, respectively)[3,4]. Both vaccine types generate significant neutralizing antibody titres and virus-specific T cell responses as measured in blood 2–4 weeks post inoculation[5,6]. These trials, which collectively involved more than 100,000 participants, provide compelling rationale for expedient and widespread vaccination of the global population. While the AdV vaccine platform has been licensed for Ebola, the mRNA vaccine platform represents a newly licensed formulation. Thus, we still have much to learn about how these vaccines mobilize the immune response, the durability of protection and how to further optimize them to protect against new variants, strains and disease manifestations.

Triggering innate and adaptive responses

To stimulate adaptive immunity, a vaccine requires a pathogen-specific immunogen as well as an adjuvant — the latter stimulates the innate immune system and provides the necessary second signal for T cell activation. An optimal adjuvant stimulates innate immunity without inducing systemic inflammation that could elicit severe side effects. For mRNA vaccines, the mRNA can serve as both immunogen (encoding the viral protein) and adjuvant, owing to intrinsic immuno-stimulatory properties of RNA. Upon entry into cells, single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA) are recognized by various endosomal and cytosolic innate sensors that form a critical part of the innate immune response to viruses. Endosomal Toll-like receptors (TLR3 and TLR7) bind to ssRNA in the endosome, while components of the inflammasome such as MDA5, RIG-I, NOD2 and PKR bind to ssRNA and dsRNA in the cytosol, resulting in cellular activation, and production of type I interferon and multiple inflammatory mediators[7] (FIG. 1). The current vaccines contain purified, in vitro-transcribed single-stranded mRNA with modified nucleotides to reduce binding to TLR and immune sensors, thus limiting excessive production of type I interferon and its inhibitory function on cellular translation (see REF.[7]). The LNP carrier further protects the mRNA, can target delivery to lymphatics and promote protein translation in lymph

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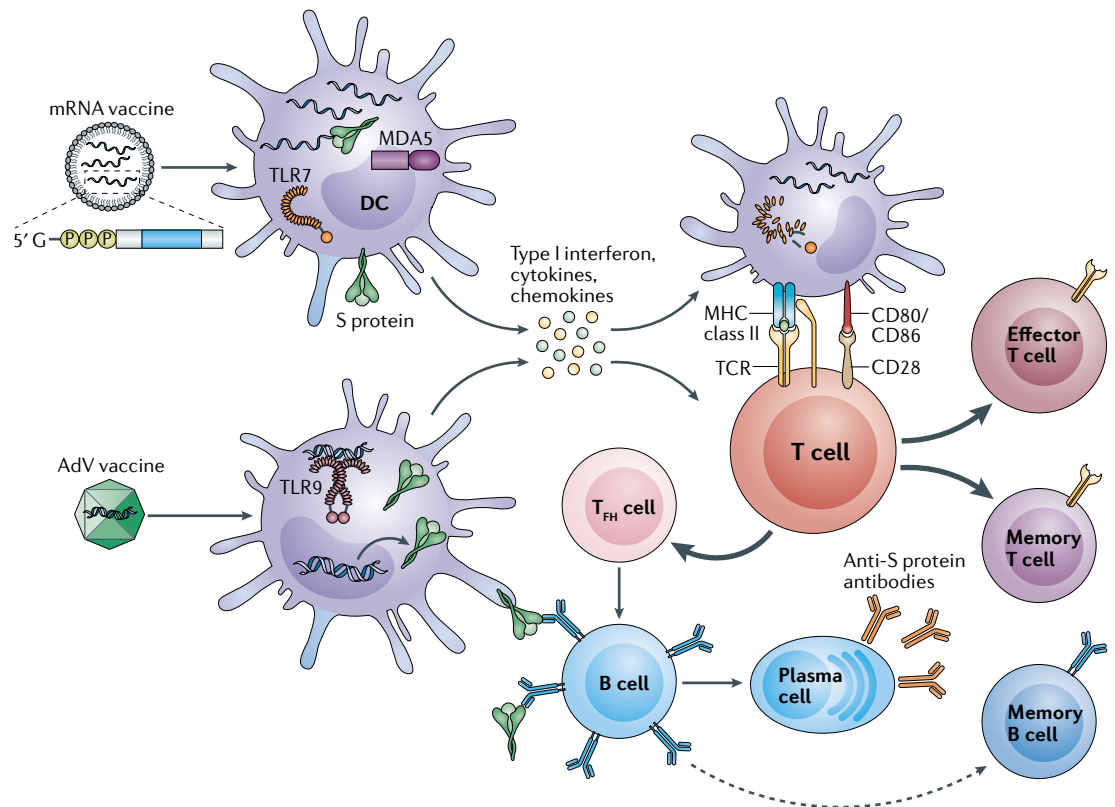✉e-mail: teijaro@scripps.edu; df2396@cumc.columbia.edu

Fig. 1 | **How mRNA and adenovirus vector vaccines elicit immunity to SARS-CoV-2.** The two vaccine formulations —
mRNA encoding the SARS-CoV-2 spike (S) protein encapsulated in lipid nanoparticles or adenovirus (AdV) vectors
encoding the S protein — gain entry into dendritic cells (DCs) at the injection site or within lymph nodes, resulting in
production of high levels of S protein. In addition, innate sensors are triggered by the intrinsic adjuvant activity of the
vaccines, resulting in production of type I interferon and multiple pro-inflammatory cytokines and chemokines. RNA
sensors such as Toll-like receptor 7 (TLR7) and MDA5 are triggered by the mRNA vaccines, and TLR9 is the major
double-stranded DNA sensor for the AdV vaccine. The resultant activated DCs present antigen and co-stimulatory
molecules to S protein-specific naive T cells, which become activated and differentiated into effector cells to form
cytotoxic T lymphocytes or helper T cells. T follicular helper (T_{FH}) cells help S protein-specific B cells to differentiate
into antibody-secreting plasma cells and promote the production of high affinity anti-S protein antibodies. Following
vaccination, S protein-specific memory T cells and B cells develop and circulate along with high affinity SARS-CoV-2
antibodies, which together help prevent subsequent infection with SARS-CoV-2. TCR, T cell receptor.

nodes (LNs)[7]. Once in the LN, the LNP is engulfed
by dendritic cells (DCs), which subsequently produce
and present the antigen to T cells for activation of the
adaptive immune response.

The AdV vaccines also contain inherent adjuvant
properties, although these reside with the virus par-
ticle that encases the DNA encoding the immuno-
gen. Following injection, AdV particles target innate
immune cells like DCs and macrophages and stim-
ulate innate immune responses by engaging multiple
pattern-recognition receptors including those that bind
dsDNA — in particular TLR9 — to induce type I inter-
feron secretion[8]. Unlike AdV vectors, mRNA vaccines
do not engage TLR9, but both vaccine formulations
converge on the production of type I interferon (FIG. 1).
Type I interferon-producing DCs and other cells that
have taken up the vaccine-derived nucleic acids encoding
the S protein can deliver both an antigenic and inflam-
matory signal to T cells in LNs draining the injection site.
This activates S protein-specific T cells and mobilizes
adaptive immunity against SARS-CoV-2 (FIG. 1).

The ability of mRNA and AdV vaccines to promote
intracellular production of S protein along with innate
immune responses should prime both CD8^{+} and CD4^{+}
T cells to differentiate into effector and memory sub-
sets. In particular, vaccine-driven production of type I
interferon promotes differentiation of CD4^{+} and CD8^{+}
effector T cells producing inflammatory and cytotoxic
mediators, and CD4^{+} T follicular helper (T_{FH}) cells,
which promote B cell differentiation into antibody-
secreting plasma cells (FIG. 1). Both the mRNA and AdV
vaccines require two doses spaced 3–4 weeks apart to
promote optimal protection and have been associated
with mild to moderate side effects, including injection
site pain, transient fever and chills, which can be aug-
mented with the second dose. This secondary enhance-
ment of the inflammatory response can derive from
short-term changes to innate cells like macrophages
through a phenomenon called 'trained immunity'[9],
and/or from activation of memory T cells and B cells
generated from the initial injection. Type I inter-
feron has been shown to amplify T cell memory and

promote B cell differentiation and survival, suggesting vaccine-associated inflammation in the booster can further promote generation and perpetuation of long-term immunological memory.

Durability and future challenges

Preclinical and early results from human trials show that both vaccines generate anti-S protein IgG and virus-specific neutralizing antibody responses for several months post-vaccination[5,6], while the T cell data remain to be fully elucidated. This short-term durability is likely sufficient for curtailing the spread of SARS-CoV-2 and beginning the path back to normalcy. However, the global pervasiveness of SARS-CoV-2 along with the emergence of S protein variants could potentially limit vaccine efficacy. Eradication of SARS-CoV-2 from the population may prove challenging, owing to reservoirs within individuals who are not vaccinated and/or in other animal species. New vaccine formulations containing the variant S sequences and additional SARS-CoV-2 proteins could be generated, and annual or semi-annual SARS-CoV-2 vaccines could be given for persisting strains and/or seasonal variants. The mRNA vaccine formulation is ideally suited for repeat or modified vaccination as different mRNAs containing mutant S proteins can be rapidly synthesized and included within the LNP carrier. By contrast, the AdV vector formulation generates AdV-specific immunity, which can limit efficacy of repeated boosters owing to immune-mediated clearance of the vector.

The unprecedented mass and simultaneous vaccination of the global population will undoubtedly reveal heterogeneity in vaccination responses and some individuals may not generate robust antibody responses or be protected. Immunity to respiratory viruses can be mediated by tissue-resident memory T (T_{RM}) cells that are established in the lung during the initial infection and retained as non-circulating populations that mediate protective responses in situ upon viral re-challenge[10]. T_{RM} cells can be generated from site-specific vaccination with attenuated viral vaccine formulations[10]. It would be interesting to determine whether intranasal delivery of mRNA vaccines can promote T_{RM} cells and protection in the lung. The development of self-replicating mRNA vaccines (which mimic viral replication) may also enhance protective T cell immunity. Such alterations in formulation and delivery route could be used to optimize the vaccines according to immune status and age.

In conclusion, the SARS-CoV-2 pandemic has accelerated the licensing of promising vaccine formulations that provide hope for fortifying our immune systems against the current and future emerging pandemics.

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