

Antigen Presentation of SARS-CoV-2 mRNA Vaccines

Subjects: **Cell Biology**

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Infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causes Coronavirus Disease 2019 (COVID-19), which has reached pandemic proportions. A number of effective vaccines have been produced, including mRNA vaccines and viral vector vaccines, which are now being implemented on a large scale in order to control the pandemic. The mRNA vaccines are composed of viral Spike S1 protein encoding mRNA incorporated in a lipid nanoparticle and stabilized by polyethylene glycol (PEG). The mRNA vaccines are novel in many respects, including cellular uptake and the intracellular routing, processing, and secretion of the viral protein. Because of space restrictions, viral vector vaccines not discussed in detail. The antigen presentation routes in MHC class I and class II, in relation to the induction of virus-neutralizing antibodies and cytotoxic T-lymphocytes, will be reviewed. In rare cases, mRNA vaccines induce unwanted immune mediated side effects. In rare cases, the mRNA-based vaccines may lead to an anaphylactic reaction. This reaction may be triggered by PEG. The intracellular routing of PEG and potential presentation in the context of CD1 will be discussed.

mRNA vaccine

viral vector vaccine

Spike protein

antigen presentation

polyethylene glycol

platelet factor 4

thrombosis

1. Introduction

The high morbidity and mortality rate of coronavirus disease of 2019 (COVID-19) has triggered the rapid development of vaccines against its causative agent, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) ^{[1][2]}. Vaccines remain the most effective way to eliminate and control the COVID-19 virus. As of September 27, 2021, nearly 6 billion doses of highly effective vaccines have been administered (World Health Organization) ^[3]. The two major categories of SARS-COV-2 vaccines are messenger RNA-based (mRNA) vaccines and viral vector vaccines that both target the Spike protein of the virus ^[4]. Worldwide, the most used mRNA vaccines are those of Pfizer/BioNTech (BNT 162b2) and Moderna (mRNA-1273). The most frequently used viral vector vaccines are the ones of Oxford/AstraZeneca (ChAdOx 1 nCoV-19) and Jansen/Johnson and Johnson (Ad26.COV2:S), as well as the Sputnik-V and CanSino vaccines.

Both mRNA vaccines as well as viral vector based vaccines or SARS-COV2 have turned out to be highly effective for protection against mild and severe COVID-19 cases. After vaccination, cytotoxic T-cells are activated and high levels of (IgG and IgA) antibodies against the Spike protein are generated that show virus-neutralizing capacity in laboratory settings ^{[5][6][7]}.

This entry describes the pathways, outside and inside of the cell, that lead to the presentation of Spike protein peptides to the immune system. Both the classical antigen presentation route via MHC class I to cytotoxic T cells (CD8+) and via MHC class II to T helper cells (CD4+), as well as the antigen-presenting routes for presentation to non-conventional T cells will be reviewed.

2. SARS-CoV-2 mRNA Vaccine Antigen Presentation

T cells only can recognize antigens when presented by molecules of the major histocompatibility complex (MHC). MHC molecules consist of an α chain, associated with $\beta 2$ microglobulin (MHC class I) or of an α chain and β chain (class II). MHC class I present antigens which are produced intracellularly, and this includes viral peptides which are synthesized by virus infected cells. MHC class I is expressed by all cells of the body. Cytotoxic T cells (also known as CD8+ T cells), can recognize antigens presented in MHC class I, and upon differentiation can kill the virus-infected cells [8][9]. MHC class II molecules are expressed by the so-called professional antigen-presenting cells (dendritic cells, macrophages, and also B-lymphocytes) and present viral peptides to CD4+ T cells, the helper cells for CD8+ T cells, B cells, and other cells of the immune system (Figure 1) [9]. For activation of B cells, the B cell receptor (membrane immunoglobulin) can recognize and interact with either soluble or cell-bound antigens, but it does not require antigen presentation in MHC class I or II. However, the antibody response of B cells to protein antigens is dependent on T helper cells, in particular follicular helper T cells [10]. Next to MHC class I and II, non-conventional antigen presenting molecules exist which will be discussed below.

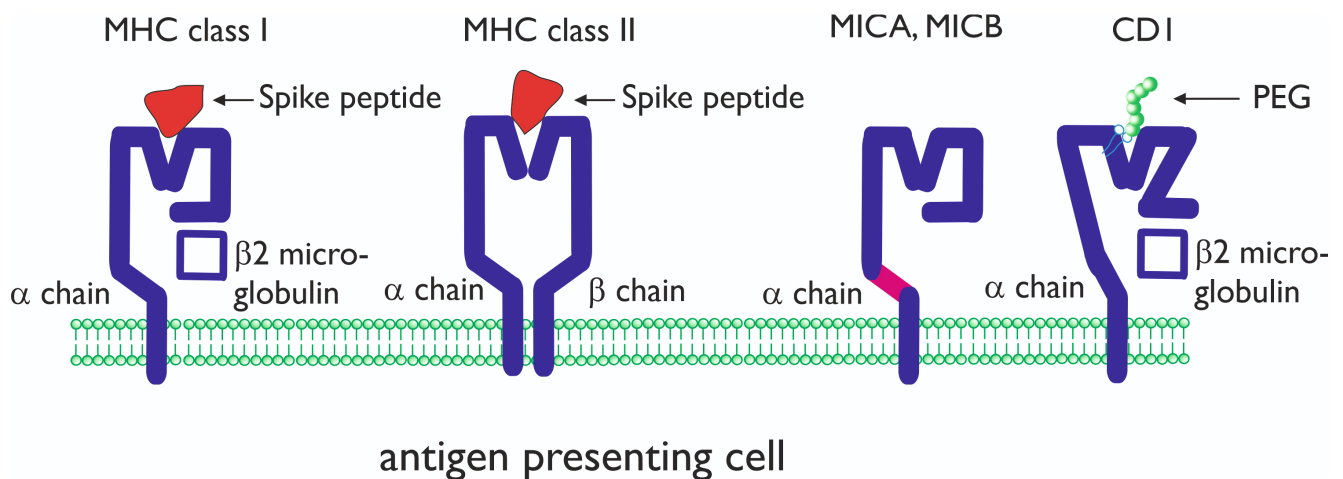


Figure 1. Schematic presentation of conventional and non-conventional antigen-presenting molecules major histocompatibility complex (MHC) class I and class II. The molecules are shown with (different) Spike peptides in the antigen-presenting groove. MHC class I-related molecules A and B (MICA, MICB) and CD1 are non-conventional antigen-presenting molecules consisting of a single α chain. CD1 is composed of an α chain, associated with $\beta 2$ microglobulin. CD1 can present lipid antigens and (potentially) lipid-bound polyethylene glycol (PEG).

2.1 SARS-CoV-2 vaccines

DNA or RNA vaccines are delivered through the use of viral vectors (such as an adenovirus: another (harmless) virus with a nucleic acid of the virus that you are vaccinating for encoded in the genome) or non-viral delivery systems (e.g., using electroporation or lipid nanoparticles to enter cells) [\[11\]](#).

The mRNA vaccines against SARS-CoV-2 Spike protein were developed by Moderna and Pfizer/BioNtech in record time, with the first vaccinations occurring less than a year after this novel coronavirus was sequenced [\[12\]](#)[\[13\]](#)[\[14\]](#)[\[15\]](#). Even though mRNA vaccines appear to be simple (consisting of a lipid envelope surrounding mRNA molecule encoding for the antigen protein of interest), hard work has gone into optimizing the safety and efficacy profiles by the pioneering work of multiple research, thereby enabling this success story.

2.2 Uptake, processing, and antigen presentation

The mechanism of action of an mRNA vaccine is very similar to the mechanism of viral infection. Through the use of the translational machinery of the host cells, the mRNA is translated into proteins. These proteins may undergo post-translational modification and either function within the cell or be secreted. Proteasomes degrade cytoplasmic proteins, thus generating antigenic peptide epitopes that are transported to the ER and loaded onto MHC class I molecules ([Figure 2](#)). MHC class I can present these peptides on the surface of the cell for specific CD8+ T cells. Alternatively, the secreted exogenous proteins can be taken up by professional antigen-presenting cells, either residing in the tissue or draining lymph nodes, and then be processed and presented in MHC class II [\[16\]](#). In mRNA-vaccinated individuals (BNT162b1), T-cells can be detected to be secreting interferon- γ upon in vitro restimulation with SARS-CoV-2 peptides, which confirms the induction of CD4+ Th-cells through MHC class II [\[17\]](#). Professional antigen-presenting cells also can present exogenous antigens, which are processed via alternative intracellular routing and presented via MHC class I (cross-presentation) [\[18\]](#)[\[19\]](#).

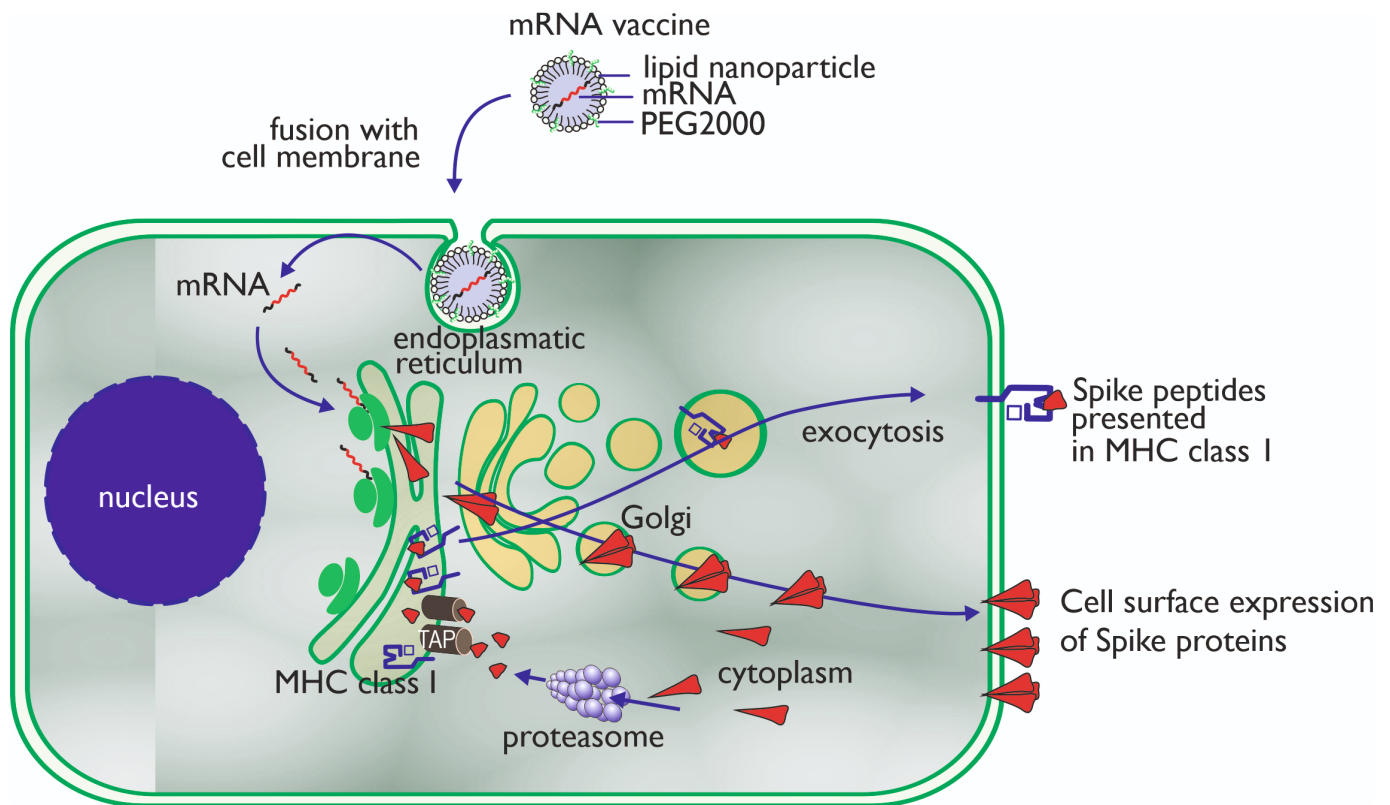


Figure 2. Uptake, processing, and MHC class I presentation of Spike proteins encoded by an mRNA vaccine.

There are multiple advantages to using mRNA-based vaccines over traditional vaccines. mRNA vaccines combine the simplicity, safety, and focused immunogenic properties of subunit vaccines with the favorable immunological properties of live viral vaccines. mRNA vaccines are molecularly defined to encode only the specific antigen of interest and no other excess information. This means that in the case of a SARS-CoV-2 vaccine, the mRNA does not encode the entire virus, but only the S-protein. This greatly reduces the complications associated with biological vaccine production (such as genetic variability). An important benefit of RNA-based vaccines is the enormous flexibility of vaccine design and production. The antigen encoding sequence (the ORF) can be easily modified at specific locations or codon optimized to improve translation or engineered to guide the antigen to the desired intracellular compartments to improve antigen presentation. Modifications such as point mutations, deletions, or the removal of glycosylation sites could all potentially affect antigenicity, immunogenicity, and overall vaccine efficacy. Moreover, next to additions to the coding sequence, the half-life of mRNA, the pharmacokinetics of protein expression (such as magnitude and duration), and immunogenicity are all available for fine-tuning via modifications of, for example, the 5' and 3' UTRs and optimization of the length of the poly-A tail [20]. The mRNA could also be tailored in such a way to provide potent adjuvant stimuli to the innate immune system by direct activation of RNA-specific receptors, which may reduce the need for additional adjuvants [21].

3. Antigen Presentation of SARS-CoV-2 Vaccine Additives

3.1. Unconventional Antigen Presentation Molecules

In the allergic reactions to mRNA vaccination, which occur as rare but serious adverse events, IgE antibodies to PEG have been implicated. The frequency of anaphylaxis after injection is approximately 11.1 in 1 million for the Pfizer/BioNTech vaccine [22]. The CDC in the USA reported 21 cases of anaphylaxis out of 1.8 million doses administered. For the Moderna vaccine, the CDC reported 2.5 cases per million doses administered [23]. AstraZeneca has also shown some cases of anaphylaxis. According to the European Medicines Agency, 41 out of 5 million people vaccinated with AstraZeneca showed possible signs of anaphylaxis. Jansen has also shown few hypersensitive reactions [24].

The mechanisms behind these anaphylactic reactions are still unknown; however, a hypersensitivity reaction to either polyethylene glycol (PEG) in the mRNA vaccines or to polyoxyethylene-sorbitan-20-monooleate (polysorbates 80) in the virus-vectored vaccines could be the vaccine components triggering the hypersensitive reaction.

Previous studies on vaccine-associated anaphylaxis showed that additives such as gelatin, egg protein, latex, or polysorbate 80 all can elicit hypersensitive reactions in susceptible persons [25]. Case studies have shown that patients with a known allergy for PEG also can be hypersensitive to polysorbate based on cross-reactivity between the two compounds [26].

3.2. Hypersensitivity and PEG Antigen Presentation

It is difficult to understand why some people have an allergic response to PEG and why others do not. Previous studies have indicated that induction of hypersensitivity does depend on the dosage, the route of administration, as well as the molecular weight of PEG used [27]. Numerous cosmetic products such as toothpaste contain PEG, and therefore, everyone is continuously exposed to PEG. Many drugs are conjugated to PEG (PEGylated) to increase their half-life and efficacy [28]. It has been shown that PEGylated drugs, such as doxil, can lead to hypersensitivity reactions, especially in the case of high molecular weight PEG administered intravenously [29].

3.3. Antigen Presentation of PEG

PEG, which is obviously not a peptide, would have to be presented through an alternative, non-MHC pathway. A possible pathway would be CD1 antigen presentation. CD1 is a protein (family) related to the non-polymorphic and MHC class I molecules. CD1 proteins are able to present (its own and foreign lipid antigens) to T lymphocytes. Group 1 (CD1a-c) and 2 (CD1d) CD1 proteins are expressed on the cell surface and function as antigen-presenting molecules. Group 3 (CD1e) is only expressed extracellularly and is involved with the processing and editing of lipids for presentation by the other CD1 isoforms. Although structurally related (see **Figure 1**), a difference between MHC class I and CD1 is that the inner surface of CD1 is covered with hydrophobic residues, and the α helices differ as well. There is a deeper antigen-binding groove in CD1 (which differs per CD1 isoform).

3.4. Thrombosis and Vaccine-Induced Thrombocytopenia (VITP)

Vaccines have some mild to moderate side effects, with some seen in the clinical trials of COVID-19 vaccine development, in which thousands of volunteers have participated, and some rare cases of anaphylaxis occurred [22]. Thrombotic side effects were initially reported for recombinant genetic vaccines and have raised concerns about the safe use and development of vaccines [30]. One of the severe events in COVID-19 infection is coagulopathy leading to various thrombotic complications and even death [31]. Similar to COVID-19/SARS-CoV-2 infection-induced immune thrombocytopenia (ITP) [32], ITP post-vaccination is a possible adverse effect. The vaccine adverse event reporting system (VAERS) has documented over 160 cases (June 2021) of thrombosis or thrombocytopenia as an adverse effect of mRNA vaccines [33]. The European Medicines Agency (EMA) has reported at least 169 cases (4 June 2021) of cerebral venous sinus thrombosis (CVST) and 53 cases of splanchnic vein thrombosis (SVT) among 34 million recipients of the ChAdOx1 nCoV-19 vaccine. The increasing numbers of rare adverse events are not surprising, as vaccination numbers are constantly increasing. However, the pathogenesis or etiology of these adverse effects is not completely clear, but could be partly based on abnormal antigen processing or presentation.

4. Conclusions

Both mRNA-based as well as viral vector vaccines with the genetic information for the SARS-CoV-2 Spike protein have turned out to induce an efficient humoral and cellular immune response. The design of these vaccines ensures that the antigens are presented to CD4+ T cells in MHC class II and to CD8+ T cells in MHC class I. The role of unconventional T cells, and the presentation of vaccine antigens to these unconventional T cells, is not completely understood at the moment. The benefits of vaccination in preventing COVID-19 must be emphasized, which far outweigh the risks of (severe) adverse events [29]. However, in rare cases, immune mediated side effects are observed, particularly hypersensitivity reactions including anaphylaxis. Delineation of the molecular mechanisms underlying these adverse effects will be required to reduce the incidence and to develop adequate testing and treatment modalities.

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