



Coronavirus (COVID-19) Infections and Vaccines

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Abstract

The virus that causes COVID-19, is SARS-CoV-2, was confirmed a common virus on March 11th 2020. With over 50 million cases and 1.2 million deaths around the world, Thus, the race to develop a COVID-19 vaccine is an urgent global imperative. There are over 165 vaccine candidates being developed, with 33 in various stages of clinical testing. COVID-19 has brought unprecedented society level attention on a truly global scale into antibody and vaccine science and technology. Billions of people are now aware of antibodies, therapeutic, protective and diagnostic and vaccine design, manufacturing and clinical trial design. COVID-19 has impacted every single country on the planet with currently 68 million confirmed infections and 1.5 million deaths. These numbers will continue to increase until natural immunity, improved therapeutic interventions, vaccines or a combination of all three succeed. Vaccines are a reality – clinical management has started. Interventional antibodies are in late stage trials. This COVID event is simply the biggest medical and economic threat in modern history and antibody and vaccine science is at its core. This review discuss the infection cycle by COVID-19 immune defense mechanisms that can be harnessed to develop novel vaccines that present durable protection against COVID-19.

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Introduction**The virus that causes COVID-19**

Coronaviruses are relatively large enveloped, single-stranded, positive-sense RNA viruses (~30 kb). Their membrane has a crown-like appearance, due to its decoration with glycoprotein 'spikes' [1]. In particular, the β -coronavirus family includes Severe Acute Respiratory Syndrome (SARS) virus (SARS-CoV), Middle East respiratory syndrome (MERS) virus (MERS-CoV), and the COVID-19 causative agent SARS-CoV-2 [2,3]. The 5' two-thirds of the SARS-CoV-2 genome encodes two poly proteins, pp1a and pp1ab, collectively termed the replicase. These poly proteins are cleaved into 16 non-structural proteins including RNA-dependent RNA polymerase (RdRp) by two essential viral proteases, 3C-like protease (3CLpro) and papain-like protease (PLpro). In the 3' one-third of the SARS-CoV-2 genome, like oth-

er β -coronavirus, encodes four essential structural proteins and a set of accessory proteins, which can all interfere with the host innate immune response [4,5]. These structural proteins are [6]: 1) Spike (S) glycoproteins – represent the largest structures of the virus and are essential for the entry into host cells. 2) Small Envelope (E) proteins - are only present in small quantities and most likely function as ion channels, not necessarily needed for viral replication but essential for pathogenesis. 3) Membrane/Matrix (M) proteins – are the most abundant proteins in the virus structure and are responsible for viral membrane curvature and binding to the nucleocapsid. 4) Nucleocapsid (N) proteins – bind to the viral RNA genome and ensure the maintenance of the RNA in a 'beads-on-a-string' conformation.



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The infection cycle by COVID-19

A cellular receptor expressed in the lungs, arteries, heart, kidneys, and the intestine is angiotensin-converting enzyme 2 (ACE2). Angiotensin-converting enzyme 2 binds to the viral (S) protein and constitutes the cellular entry receptor for SARS-CoV-2 into their human host [7]. The S protein is cleaved into two subunits, S1 and S2, by an extracellular protease. While S1 binds to ACE2, S2 is further cleaved and activated by the host surface-associated transmembrane protease serine 2 (TMPRSS2) [8]. These actions result in host-viral membrane fusion and the release of the RNA genome into the host cell cytoplasm. Firstly, the host translational machinery is hijacked for the translation of the polyproteins and the essential viral proteases. The polyproteins (pp1a and pp1ab) are cleaved into 16 non-structural effector proteins by 3CLpro and PLpro allowing them to form the replication complex together with the RNA-dependent RNA polymerase, which synthesizes a full-length negative RNA strand template [1,6]. This is used to replicate the complete RNA genome and generate the individual sub-genomic mRNA templates needed for the translation of the viral structural and accessory proteins. The newly synthesized structural and accessory proteins are then trafficked from the ER through the Golgi apparatus, after which new virions assemble in budding Golgi vesicles [6]. Finally, the mature SARS-CoV-2 virions are exocytosed and released from the host cell into the surrounding environment to repeat the infection cycle [2].

COVID-19 antigens are also presented to tissue residing Antigen-Presenting Cells (APCs) such as macrophages, which in turn can produce a range of pro-inflammatory cytokines including IL-1, IL-4, IL-5, IL-8, MCSF, CXCL-10, and TNF- α [2,9]. In some cases, these cytokines proliferate an enhanced, unbalanced, and devastating pro-inflammatory response in the host

COVID-19 vaccine development

Currently, scientists around the world are exploring all the potential strategies to develop an efficient vaccine against SARS-CoV-2. Most vaccine candidates for COVID-19 aim to induce neutralizing antibodies against the viral Spike (S) protein, preventing uptake via the human ACE2 receptor and thereby blocking infection [10,11,12]. A striking feature of this COVID-19 vaccine development landscape is the diversity of technology platforms being evaluated, including: 1) Live attenuated vaccines: Use a modified 'live' SARS-CoV-2 virus with reduced virulence (e.g. codon deoptimization or a mutated E protein [13]). This strategy can induce a quick and strong immune response but can be dangerous for immunosuppressed persons. 2) Recombinant protein-based vaccines: Use SARS-CoV-2 proteins (e.g. S protein) to elicit an immune response in the host. Commonly used in combination with an adjuvant for improved immunogenicity. 3) DNA vaccines: Use plasmid DNA to express antigens of SARS-CoV-2 for efficient delivery into the host cells. There are currently no approved DNA vaccines for humans. A) mRNA vaccines: Encodes a SARS-CoV-2 antigen and uses a system such as a liposome for delivery into the host. There are currently no approved mRNA vaccines for humans.

The majority superior vaccine candidates for COVID-19 that have moved into human safety and efficacy clinical trials (I and II), include an mRNA-based vaccine developed by Moderna

(NCT04283461) and an adenovirus type 5 viral vector-based vaccine developed by CanSino Biologicals (NCT04341389). Additionally, adjuvants such as AS03 and MF59 are being explored in recombinant S-protein based SARS-CoV-2 vaccines, to enhance immunogenicity and make lower doses possible, enabling vaccination of a wider population of people. A successful vaccine must produce both specific and, efficient neutralizing antibodies against SARS-CoV-2. Importantly, previous experience in the development of vaccines against SARS and MERS indicates the potential for damaging and unwanted immune enhancement effects. Therefore, careful and thorough testing is needed before the release of a global COVID-19 vaccine.

Conclusion

The majority people rise an effective immune response against SARS-CoV-2 with re-infection cases still considered rare. Nevertheless, reports have suggested that the viral-clearing antibody response of asymptomatic/mild cases of COVID-19 wanes rather rapidly (< 90 days). Consequently, these individuals may be at risk to re-infection. Therefore, there remains a great need to develop our understanding of the host immune response against SARS-CoV-2 for the development of an effective and long-lasting vaccine strategy.

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