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Novel Coronavirus Covid-19 Genetics, the Determining Factor for Vaccine Development

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ABSTRACT: Novel coronavirus covid -19 has emerged as a pandemic in the world. Although vaccines have been developed, scientists all over the world are struggling to find a vaccine 100 percent effective against it. Clinical trials are going in vivo using mouse models. In view of the above scenario the present article illustrates the genetics of the novel virus which is an essential factor for determining a vaccine against it. By studying the genetics of a virus we know the different proteins coded by it. These proteins especially the spike protein in the case of coronavirus are used for designing vaccines. Strategy is to combine the coronavirus spike protein with adjuvants: small molecules added to a vaccine to boost the recipient's immune response. Apart from that we can also design RNA vaccines using SARS-CoV-2 RNA. Here also, adjuvants may help enhance the immune response when such vaccines are administered to older populations and may reduce the amount of RNA needed in each vaccine.

There is a hidden reservoir of viruses in animals and they can spill over occasionally into human population. Covid -19 caused by coronavirus (SARS-CoV-2) is a Public Health Emergency of International Concern. Coronaviruses are so named because they look like halos (coronas) when viewed under the electron microscope. They are found almost everywhere. They are the second leading cause of the common cold after rhinoviruses. The first coronavirus was isolated in 1937. Some infect humans and others circulate among animals, including camels, cats and bats. The first human coronavirus was cultured in the 1960s from nasal cavities of people with the common cold. Coronaviruses can easily cross the species barrier and infect humans with high fatality.

There are 4 major categories of coronaviruses denoted by Greek letters alpha, beta, delta and gamma. Out of these alpha and beta coronaviruses are known to infect humans. There are seven known human coronaviruses i.e. HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV (Severe acute respiratory syndrome), MERS-CoV (Middle East respiratory syndrome), and now SARS-CoV-2.

SARS-CoV-2 belongs to the family *Coronaviridae* and genus *Betacoronavirus*. It possesses a single strand, positive sense RNA genome ranging from 26-32 kilobases in length (1). Among the positive-strand RNA virus, coronavirus have the highest frequency of recombination. They combine the genetic information from different sources when a host is infected with multiple coronaviruses. Coronaviruses mutate and change at a high rate, resulting in havoc for both diagnostic detection as well as therapy (vaccine).

Phylogenetic analysis of 2019-nCoV showed that the virus belongs to the subgenus *Sarbecovirus*. Bat-derived coronaviruses fell in basal positions in the subgenus *Sarbecovirus*, with SARS-CoV-2 most closely related to bat-SL-CoVZC45 and bat-SL-CoVZXC21 (2).

Structural similarities have been formed between the receptor-binding domains of SARS-CoV and SARS-CoV-2. Therefore, we suggest that SARS-CoV-2 might use ACE2 as the receptor which is a receptor for SARS-CoV, despite the presence of amino acid mutations in the SARS-CoV-2 receptor-binding domain (3).

The replication process in coronaviruses involves a 2-step replication mechanism. Majority of RNA virus genomes contain a single open reading frame (ORF) which is then translated as a single polyprotein that is then catalytically cleaved into smaller functional viral proteins, but coronaviruses can contain up to 10 separate ORFs. Replicase, the biggest one of these ORFs, which alone is twice the size of many other RNA viral genomes is translated by most ribosomes. Then the replicase gene encodes a series of enzymes which use the rest of the genome as a template to produce a set of smaller, overlapping messenger RNA molecules, that are then translated into the structural proteins -- the building blocks of new viral particles.

The genome organization of SARS-CoV-2 was shown to be similar to the related bats and human coronavirus. The open reading frames (ORFs) from 5' to 3' is as follows: 5' UTR; ORF1ab with 16 non-structural proteins (nsp) 1-16



including RNA polymerase RNA dependent nsp12; Helicase nsp13 and 3'-to-5' exonuclease nsp14; S surface spike protein; E envelope protein; M membrane protein and N nucleocapsid protein There are also at least 6 predicted ORFs as hypothetical proteins with no associated function(4-6).

New insights and concepts about the genetics of SARS-CoV-2 are being adopted and implemented daily. Recently Tang et.al and GISAD database in the SARS-CoV-2 portal defined three subtypes: S, G and V, according to nucleotide variants that produce amino acid changes. These changes are located in ORF8 L84S; S (spike protein) D614G and nsp3 G251V, in the nucleotide position 28144, 23403 and 3471 respectively for S, G and V, according to the reference sequence NC_045512.2.(7,8).

As far as infecting the host genome is concerned the spike protein on the surface of the viral particle plays key roles in the binding of the cell receptor and membrane fusion (9, 10), by which the host range is firmly determined (11). In a study from China, the infection risk of non-human-origin coronavirus was evaluated for early warning and good performance was achieved. The main limitation was that only viral spike proteins were used to build the prediction model and social factors, such as traffic conditions, population size, and citizens habits in daily life, were not involved(12).

The virus undergoes a strong immunologic pressure in humans, and may thus accumulate mutations to outmaneuver the immune system (13). These mutations could result in changes in viral virulence, infectivity, and transmissibility (14). Therefore, it is imperative to investigate the pattern and frequency of mutations occurred. Aside from the pathogen, microbiota in the lung is associated with disease susceptibility and severity (15). Alterations of lung microbiota could potentially modify immune response against the viral and secondary bacterial infection (16, 17). Thus, understanding the microbiota, which comprises bacteria that could cause secondary infection or exert effects on the mucosal immune system, might help to predict the outcome and reduce complications(18).

The entire human population generally lacks immunity to SARS-CoV-2 and hence is susceptible to the novel virus. A 100 percent effective vaccine is the need of the hour. This review provides deep insights regarding the genetics of novel coronavirus which will facilitate in the designing of spike protein and RNA based vaccines which might eliminate this pandemic.

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