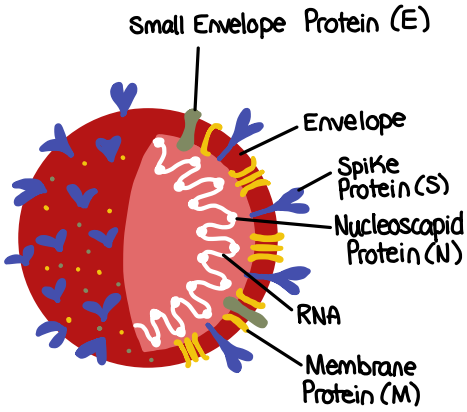
# CHAPTER 13~ GENES & COVID-19 SUSCEPTIBILITY IN HUMANS

## INTRODUCTIONS

- Coronaviruses are a group of RNA viruses which cause diseases in mammals & birds, such as respiratory tract infections, which generally range from mild to lethal
  - -Mild illness in humans include some cases of the common cold
  - -More lethal varieties can cause SARS MERS & COVID-19
- Most recent common ancestor of all coronaviruses is estimated to have existed as recently as 8000 BCE some model place it as far back as 55 million years or more
  - -Implies long term co-evolution w/ bat & avian species
- Coronavirus disease 2019 is a contagious disease caused by sever acute respiratory syndrom coronavirus 2
  - -The structural proteins of SARS-CoV-2 include membrane glycoprotein (M), envelope protein (E), nucleocapsid protein (N) & the spike protein (S)
- Viral component that attaches to the host receptor via the ACE2 receptors which is an enzyme on the surface of many cell types which generates small proteins by cleaving the larger protein angiotensinogen which that then go on to regulate functions in the cell
  - -SARS-CoV-2 infects people of all ages
    - ↳Evidence suggest risk to 2 groups of people
      - ① Older people
      - ② Those w/ underlying medical conditions




## HOW DOES SARV-CoV-2 INFECT HUMANS

- Virus' surface spike protein mediates SARS-CoV-2 entry into cells by binding the ACE 2 receptor in humans through its receptor binding domain & is proteolytically activated by human protease
- Cell entry of SAR-CoV-2 is preactivated by proprotein convertase furin, reducing its dependence on target cell protease for entry
  - -Effective @ cell entry & infection
- ACE 2 receptor protein is present in many cell types & tissues including the nose, mouth, lungs, heart, blood vessels, kidneys, liver & gastrointestinal tract.
- ACE assists in modulating the activities of a protein called angiotensin (ANG II) which increases blood pressure & inflammation, thereby increasing damage to blood vessel lining & promotes various types of tissue injury.
- ACE 2 converts ANGII to other molecules effectively counteracts the effects of ANG II such as inflammation & cell death.
- When SARS-CoV-2 virus binds to the ACE2 receptor, it prevents ACE2 from performing its normal function to regulate ANG II signaling.
- As such ACE2 action is inhibited, removing the protective mechanism from ANG II signaling through increased availability of ANG II to injure tissues, especially in the lungs & heart

## GENES IMPLICATED IN SEVERE COVID-19 INFECTIONS IN HUMANS

Approximately 15% of cases are severe & some of them are accompanied by a dysregulated immune system & cytokin storm.

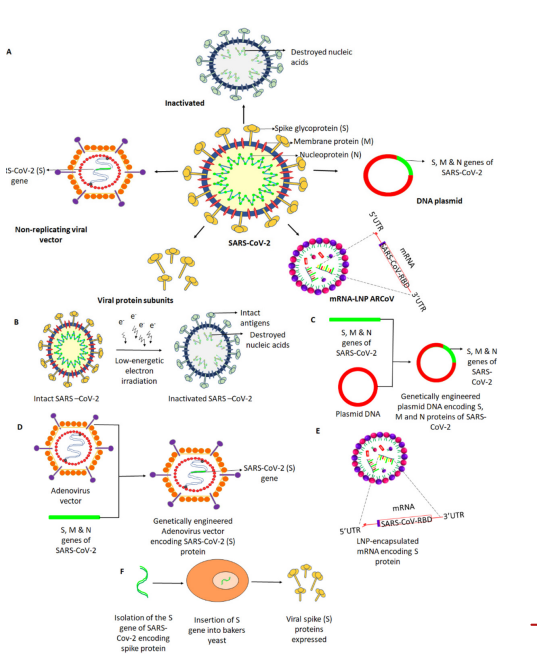
There is increasing evidence that severe cases of COVID-19 might be attributed to human genetic variants in genes related to immune deficiency & inflammasome activation

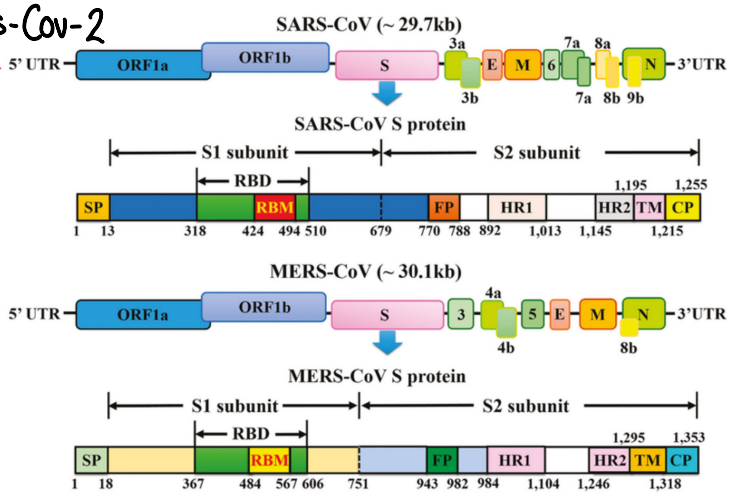
40 genes were found to be associated w/ viral susceptibility & 21 of them were associated w/ severe SARSCoV disease & Severe COVID-19

| Clinical Manifestation | Gene Associated |
|---|---|
| Susceptibility to SARS-CoV infection | CD14, HLA-B, FCGR2A, CCL2, CCL5, MxA, ABO, MBL, OAS-1, ICAM3, DC-SIGN |
| Susceptibility to SARS-CoV2 infection | ALOXE3, TMEM181, BRF2, ERAP2, LC6A20, LZTFL1, CCR9, FYCO1, CXCR6, XCR1 |

## APPROACHES FOR VACCINE DEVELOPMENT AGAINST SARS-CoV-2

- The elucidation of the genome organization & functional domains of S protein for SARS-CoV, achieved through the work of scientists & geneticists all over the globe, has facilitated a deep understanding of the mode of action of this virus which has lead to the development of a myriad of vaccine & drug candidates in an effort to mitigate the spread of this virus, as well as to assist in the diagnosis & managment of infected patients




Potential vaccines under development involve 5 leading platforms (inactivated viruses, protein subunit, DNA, RNA & non-replicating vector)

Intact SARS-CoV-2 is neutralized by treatment w/ radiation to cease its ability to infect & replicate while preserving induction of an immune response

A plasmid DNA is genetically engineered w/ S, M, & N genes of SARS-CoV-2 encoding the respective proteins that may facilatate an immune response

A replication-defective Adenovirus (Ad) vector is genetically engineered to express SARS-Cov-2 spike (S) protein

An mRNA (replication-defective) that encodes the S protein of SARV-CoV-2 is encapsulated in a lipid nanoparticle (LNP), which

when injected induces the body cells to produce the spike protein & direct the immune response

Spike protein-encoding (S) gene of SARV-CoV-2 was isolated & genetically engineered into a baker's yeast, producing the spike protein antigens when grown. The produced S antigens can be collected & purified