Review of SARS-CoV-2 Virus and Variants

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Basic Biology

SARS-CoV-2 is an RNA virus. DNA and RNA are very similar. In a human cell, DNA exists inside the nucleus. The DNA involves a language of 4 letters, or nucleic acids, which serve as a recipe for creating proteins. Proteins that become parts of cells or parts of bodies, such as skin or cell walls, are called structural proteins. But just as having ingredients is not sufficient to bring a cake into existence, there must be a way to mix the ingredients. Non-structural proteins organize the activities that use structural proteins as building blocks for larger structures such as cell walls and tissues.

Because the machinery (ribosomes) that creates proteins is outside the nucleus but DNA is inside, RNA molecules carry the recipe from the DNA to the ribosomes. RNA has a slightly different language than DNA; it shares three of the letters/nucleic acids but substitutes one of the nucleic acids.

Viruses typically have a a smaller number of letters or nucleic acids. While the human genome consists of over three billion nucleic acids a viral genome can be as small as 1,000 nucleic acids. Whereas animal and plant cells must have a recipe that solves everything, from getting energy (e.g., grabbing energy from the sun or through eating) to all the machinery needed to build themselves, viruses hijack the machinery of their hosts. The covid-19 virus has a protein on its cell wall that can bind with the surface of some human cells and then insert its RNA into the human cell. The RNA then uses the human ribosomes to create copies of itself, eventually bursting the cell and sending more viruses out to infect more cells. A single human cell might create hundreds of thousands of viruses.

SARS-CoV-2 Genome and Structure

SARS-CoV-2 has almost 30,000 letters in its genome. These letters code for only 29 proteins (the human genome has 20,000-25,000 proteins as a point of comparison). Four of the SARS-CoV-2 proteins are structural, including the spike protein that binds to human cells. The ability of SARS-CoV-2 to bind to and enter so many different types of human cells, found in variety of organs and tissues, makes the virus particularly problematic. There are also non-structural proteins that are involved in the activities needed to make the viruses work, including hijacking the machinery of the host cell to replicate as well as assemble new viral cells. Additionally, there are some proteins that inhibit the immune systems of humans.

What is a Variant?

When viruses hijack human cells to create copies of themselves, they occasionally make mistakes or point mutations; one of the 30,000 letters gets copied wrong. Changing the recipe can change the shape of the proteins that are built. The shape of a protein is critical to how it works, so a mutation can change the impact of a virus on humans. Because the changes are random, most changes will be bad for a virus; just as if a kid opens a computer and starts randomly changing things. But occasionally a mutation will cause a virus to be more infectious, or more deadly. For example, a mutation can change the shape of the spike protein such that it is more effective at binding to human cells. When a mutation causes a functional change to the virus and that change works well enough that it persists in humans, it becomes a variant. If the functional differences are large enough, the variant is called a new strain.

While the chance of any single mutation producing a variant is extremely small SARS-CoV-2 effectively has lots of lottery tickets. Each infected person is generating millions of viruses, each of which is a potential variant. With huge numbers of people, and also animals, being infected worldwide, there are enormous opportunities for variants to arise, no matter how unlikely. Over 40,000 mutations of SARS-CoV-2 have already been detected.

In addition to point mutations, new variants of SARS-CoV-2 can emerge through a process called recombination. Recombination can bring together different parts of variants, much like a book that is made by combining the first half of one book with the second half of another book. Like point mutations, recombination events are rare, but they can generate problematic versions of a virus, for example, by combining a protein that increases transmission rates with another protein that increases lethality.

How Do Variants Affect Vaccines and Acquired Immunity

Our immune systems work by destroying invading cells. To be effective, our immune system must have a sufficient number of cells capable of identifying and destroying the invading cells or foreign substances (e.g., other proteins or chemicals), a challenge made more difficult due to the large number of novel invaders and foreign material to which we are being constantly exposed. A disease that makes us sick will typically trigger production of cells that target that disease and are capable of quickly responding, which we call acquired immunity. A vaccine expedites acquiring immunity, either by inducing an immune response with a weakened version of the disease or by inducing an immune response to a part of a virus. The mRNA vaccines produced by Pfizer and Moderna utilize the latter approach. They create pseudo-cells involving lipids encapsulating RNA molecules capable of getting into human cells and triggering production of the spike proteins. However, because they only contain the recipes for the spike proteins, and not the rest of the SARS-CoV-2 proteins, they don't trigger production of the virus. However, when our cells make the spike proteins, they induce our immune system to produce cells that recognize the spike proteins, which leads to acquired immunity to covid-19. We can lose immunity if our body stops making the cells that recognize the virus, or if a variant emerges that is sufficiently different in shape that our defense system no longer recognizes it.

There are 4 potential strategies for vaccines to keep up with emerging variants. First, by reducing infections globally we will reduce how quickly variants emerge. The faster we get the global population vaccinated and/or the more effective our interventions are (e.g., social distancing, mask wearing), the more likely current vaccinations are likely to protect us. Second, vaccines can target parts of the virus that are less likely to change. This is still an emerging area of active research, but further research may lead to development of vaccines that are effective broadly across all coronaviruses, or more narrowly, effective across all variants within SARS-CoV-2. Third, boosters or new vaccines are being developed that target variants. While existing vaccine technology allows rapid development of new vaccines, there will always be the chance that new variants will emerge faster than we can develop and distribute boosters. Fourth, it could be that boosting existing vaccines will provide sufficient protection to variants. While there is evidence that vaccines are less effective with variants, they do still seem to work. Using boosters to keep our immune systems primed for a SARS-CoV-2 infection, even if they are not designed to target specific variants, may provide substantial protection from emerging variants.

What is Happening with SARS-CoV-2 Variants?

1. The UK variant is doubling in the US population approximately every 10 days. At this rate it is likely to become the dominant strain in the US by March.

2. Given that the UK variant has been documented in Colorado (almost 100 documented cases by the end of February) and mountain communities have tourists that introduce new strains, it is likely to be in Gunnison County.
3. Estimates are that the transmission rate of the UK variant is 30-40% higher than the original strain. There is some evidence that this higher transmission rate is because the variant causes people to be infectious longer.
https://dash.harvard.edu/bitstream/handle/1/37366884/B117Trajectories_10Feb2021.pdf?sequence=1&isAllowed=y
4. There is some evidence that the mortality of the UK variant is 35% higher, though there is still a great deal to be learned.
https://www.medrxiv.org/content/10.1101/2021.02.01.21250959v1
5. The combination of increased transmission and increased mortality suggests the potential for another surge of mortality/hospital cases.
6. Despite the presence of emergence of the UK variant, however, infection and mortality rates have been declining across the US, indicating factors other than the emergence of new variants are more important for infection and mortality rates.
7. There is some evidence that the UK variant, and some of the other emerging variants, are partially escaping the protection otherwise afforded by current vaccinations and prior acquired immunity.
https://www.cnn.com/2021/02/02/health/variant-mutation-e484k/index.html
8. The technology to adapt the vaccinations to the new variants is well developed, though the challenge is generating a vaccine that protects individuals against all possible variants, and the supply chain logistics to produce and distribute updated vaccines. If one new variant were to become dominant, it would be easy to adapt the vaccinations to that variant. However, if the variants continue to change, it could be difficult to distribute updated vaccines quickly enough to keep up.
9. There is a second strain of concern, L452R (also referred to as CAL20C), that has also been identified in Colorado, with 30+ cases detected in CO. Less is known about whether it increases transmission or causes more health problems. It is still being evaluated.

Implications of Variants for Public Health

1. The initial evidence is that the variants are not completely escaping the vaccines.
2. Until we know more, maintaining preventative measures (e.g., masks, social distancing, ventilation, etc.) will be important, including for individuals who are vaccinated.
3. It is unclear how the balance between high transmission/mortality from the new strains will balance out with the increased vaccination rates. Increasing vaccination rates will reduce transmission rates and substantially reduce loads on hospitals, especially given the high vaccination rates among vulnerable individuals. How the emergence of the variants affects that is currently unknown.
4. One likely scenario is that the variants generate high transmission rates in the younger age groups community while we see reduced hospitalizations. We based this prediction on:
a. Younger age groups have been associated with outbreaks both locally and nationally.
b. Because of more immediate and negative health impacts on older population, younger age groups are less cautious.
c. Vaccination programs are focusing on at-risk groups which should bring down hospitalizations.
5. Over the long-term, the fewer opportunities the virus has to evolve through fewer infected individuals because of effective uptake of public health measures and rapid administration of vaccinations to the large majority of the population, the less likely it will be that variants emerge that escape the vaccines or naturally acquired immunity.

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10. A nice popular article review on reinfections and acquired immunity. https://www.theatlantic.com/science/archive/2021/02/coronavirus-reinfection/618128/