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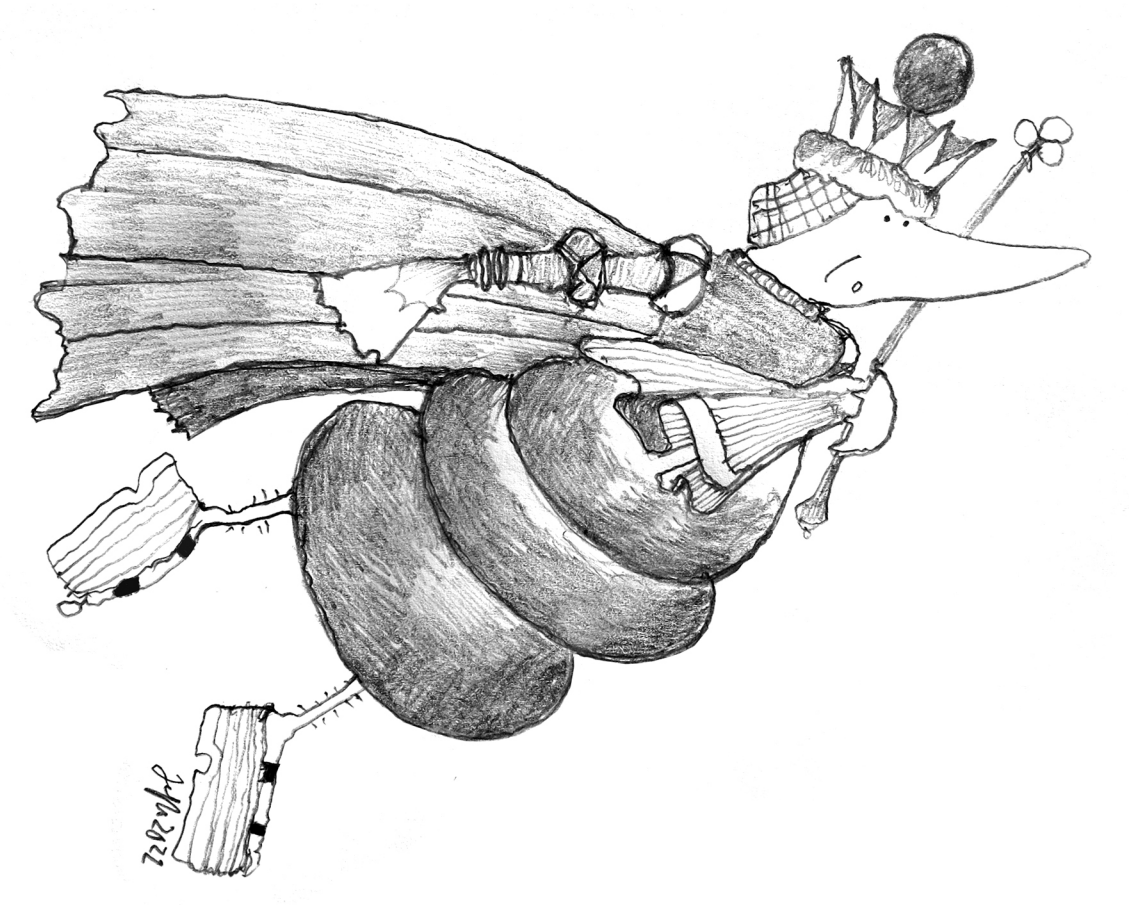
STICKY WICKET

Corona XLVIII – Red Queens and mutant genes

Mole



Original artwork by Pete Jeffs - www.peterjeffsart.com

Hi there! I'm sitting outside on an unseasonably glorious winter day that feels much more like spring than winter. And while I am not complaining (it really is *very* nice), I do worry that this is yet another portent of global climate change. It is a bit like the moment in Stephen King's Thinner (I didn't read it, but I saw the movie) when the formerly obese target of the curse drops enough weight to "look wonderful," before slowly becoming emaciated. It isn't a good movie, and I can't recommend it, unless you want to see Michael Constantine 'chewing the scenery,' which is theater talk for outrageously overacting. But like many things by Stephen King, it's hard to get it out of your head. I did love Michael Constantine in My Big Fat Greek Wedding, where he played Gus Portokalos, the father of the bride – actually, Michael Constantine's original name was Gus as well. Okay, I didn't know that last bit until I looked him up. But we aren't here to talk about any of this. ("Really, Mole?" Yes, really. But you knew that because you are very smart.)

What I do want to talk about is the Red Queen hypothesis. If you are just joining us, we've been talking about Omicron and how quickly it spreads. We also talked about how it evades two of the three monoclonal antibodies being used to treat COVID-19, and why this isn't a portent of doom for the vaccinated among us. (If you aren't up on your immunology, it might be good to read the last Corona File before jumping headfirst into this one. Besides, you'll learn all about a cool superhero.) All set? Okay, let's go!

The Red Queen hypothesis is an evolutionary scenario originally described by Leigh Van Valen in an attempt to explain the observation that extinction rates in a taxon (a group of similar organisms, such as a species or genus) do not correlate with the age of the taxon but rather remain constant for millions of years (but are different for other taxa). This, he reasoned, is because the environment in which a taxon evolves decays at a steady rate, effectively impacting the fitness of the adapted organism. His insight was that this decay reflects the adaptation of other taxa in the environment and corresponding adaptations in the original taxon, resulting in a zero-sum game. It is called the Red Queen hypothesis because in the book Through the Looking-Glass, the Red Queen tells Alice that "it takes all the running you can do, to stay in the same place." (Actually, she said "it takes all the running *you* can do," but taken out of context it nicely sums up this useful evolutionary hypothesis.)

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One of the very best applications of the Red Queen hypothesis I have read was provided by my great friend Professor Hedgehog, who wanted to explain an interesting paradox about the adaptive immune system. The adaptive immune system is composed of the T cells, B cells and antibodies that produce responses to infections in such a way that subsequent responses to infection with the same organism (but not a different one) are amplified – a phenomenon called 'immune memory.' People who lack any component of the adaptive immune response are at extreme risk of infection.

But the vast majority of multicellular organisms on the planet do not have an adaptive immune system – it is present only in the subphylum Vertebrata – and while defects in the adaptive immune response among vertebrates lead to catastrophic disease, these other plants and animals seem to do just fine. They do have immune defenses, but these are so-called 'innate immune responses' that do not display the property of specific immune memory, and we have them as well. And yet, while these innate responses work to control infections in other organisms, they do not seem to be up to the task in us. Why?

Professor Hedgehog reasoned that the emergence of the adaptive immune system in the vertebrates triggered a Red Queen scenario in the organisms that infect us. In order to survive to reproduce, those organisms that required vertebrate hosts had to evade this immune response, and thus variants that did so were selected. If these variants caused disease that impacted the fitness of the host, then this would select for immune processes that acted to restrict those infections, and the zero-sum game was afoot. As a result, we can be infected by organisms that, without our adaptive immune responses, can kill us.

Our friend Red Fox (you've met her many times) has brilliantly elaborated on the alternative to this zero-sum game evoked by the Red Queen. Rather than go into the 'kill or be killed' conflict, organisms can co-evolve to promote cooperative defense strategies that allow us to co-exist with microbes. The first time I understood her concepts, it blew my mind (and continues to do so), but we'll save the consequences of these ideas for another time.

The Red Queen hypothesis is at the core of all the current discussions on immune evasion by the virus that is causing this Terrible Pandemic, and especially the Omicron variant. But to see the flaws in the argument that the virus is mutating to evade our immunity, we have to detour into a couple of other well-known viral infections that actually *do* evade immunity by mutation. We'll start with the flu.

The flu, of course, is influenza, a virus that infects many vertebrates and is marvelously adapted to its hosts. Our immune systems predominantly recognize and respond to two proteins produced by the virus, the hemagglutinin (H) and the neuraminidase (N). Each year, migrating birds carry the latest flu variant around the world, causing that year's epidemic. And most years, there is a different H and a different N in that year's virus. This happens, as my friend Professor Wallaby showed a long time ago, because if a host is simultaneously infected by two influenza viruses, these recombine to sort into different Hs and Ns in the emerging virus (thus combinatorically increasing the distributions of mutations in the genes encoding these proteins). We have banks of Hs and Ns ready to be combined into a pre-approved vaccine and do our best to match these to the virus that is emerging for next year. The match is often not perfect, which is why flu vaccines have different efficacy year to year. But it is a pretty good effort that greatly reduces the morbidity and mortality that flu epidemics can bring. (When I say *we* do it, I do not mean that *I* do this. I'm talking about 'we scientists.' Me, I wouldn't know a flu virus if it went up my nose. But then, I always get vaccinated against flu each year.)

Coronaviruses do not recombine the way flu does, which is lucky for us. Of course, like replicating things, coronaviruses mutate, and mutations that improve the fitness of the virus are selected. So, can our adaptive immune responses (such as those induced by vaccination) select for variants that evade those responses? To answer that question, we can look at another virus that does do this: HIV.

The 'killer' T cell response to HIV is important in limiting the infection. These T cells tend to predominantly recognize specific peptide bits of certain HIV proteins, presented on the surface of infected cells attached to our own MHC molecules (to be clear, each T cell recognizes only one peptide on one of our several MHC molecules, but the population of T cells recognizes only relatively few of all possible HIV peptide–MHC complexes). A mutation in one of these peptides that prevents it from binding to our MHC molecule therefore reduces the killer T cell response to the virus. Alternatively, a mutation in the protein can arrange things so that this peptide is not produced by our intracellular machinery that degrades proteins into peptide bits, also reducing our T cell response. So why isn't this going on with Omicron (and it isn't)?

Here's the thing: HIV is a chronic disease that co-evolves with the immune response in the infected individual; mutant viruses that evade some of the T cell response replicate, new immunity emerges, and new virus mutations emerge and reproduce. It is a Red Queen scenario that happens in the individual. But, and this is an important 'but,' the emergent virus is very unlikely to better evade immune responses in another individual than could the original virus. This is because the several genes encoding our MHC molecules are the most *polymorphic* genes we have; that is, it is very unlikely that you and I share all, or even some of them unless we are closely related (and I assure you, we are not – count yourself lucky). Each of our different MHC proteins bind and 'present' different peptides generated by the degradation of the viral proteins. A mutation that affects the binding of a peptide to one of your MHC proteins is very unlikely to have any effect on peptide binding to any of my MHC molecules. Indeed, this is almost certainly why our MHC molecules have evolved to be so polymorphic.

SARS-CoV-2 is not a chronic virus (even in 'long-haul' COVID, we do not see evidence of a Red Queen scenario), so mutations that arise that might affect binding of one of the peptides in the virus (or the vaccine) to one of the MHC molecules in our population will not have a strong selective advantage. It is true that some MHC alleles are relatively common, but even so, we would need a heavily infected, rather homogeneous human group to give any mutant such a selective edge.

And, in fact, we already have evidence that supports my claims. It turns out that the T follicular helper cells induced by the vaccine tend to favor one particular peptide, but only if the individual carries one of the most common MHC alleles (again, though, most of us will have T cells that recognize a different peptide, since we have different MHC molecules). And while the Omicron variant has 17 mutations in the spike protein, none of these are in (or even near) this peptide. Our T cells are not in a Red Queen scenario with Omicron.

Last time, I mentioned a video I was sent in which a popular 'wellness guru' mocked us for not realizing that COVID will simply mutate to evade any vaccine we produce. It would therefore take us "all the running [we] can do, to stay in the same place." I also mentioned that this was dangerous nonsense, and now you know why. If someone brings up this concern to you, you can tell them. Go ask Alice.