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Could a simple model of COVID-19 infections be the key to designing better virus-based therapies?

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Since the emergence of COVID-19, the spotlight on viruses has become negative.

However, viruses are not only our enemies, due to their ability to deliver DNA and RNA into cells, viruses can also be repurposed as therapeutics. This ability is already used to treat genetic diseases and cancer (2, 4). However, an important factor that is often overlooked when developing virus-based therapies is the fact that each patient's immune system might respond differently to the treatment which can determine its effectiveness (3). Recently, the Ke Lab at Los Alamos National Laboratory developed a simplistic model of the immune response to SARS-CoV-2 infection that can explain why some individuals have severe symptoms while others quickly resolve the infection (1). The simplicity of this model suggests that one day it could not only help understand viral infections but help improve virus-based therapies.

Current designs for virus-based therapeutics mainly focused on the delivery system itself. Much like if you were designing a system to deliver medicine to houses, you might first want to optimize the delivery vehicle to be used for delivering the medicine and identify routes for the delivery. Now imagine that this system was developed just around the delivery of the medication itself without consideration of what might happen when the medicine is delivered. If you deliver this medicine to a house that is, much like a cell, unaware of why the medicine is coming, the recipient may dispose of the said medication.

Since the injection of DNA or RNA from a virus into a cell is typically associated with a disease, it is reasonable to assume that the cell has processes at hand that interfere with virus-based treatments. The model from the Ke lab might help therapy-designers to predict and mitigate these processes just as the model is able to explain why some people get severe COVID-19 and others do not.

The focus of the model is the immune response generated by the molecular footprint left by the viral disease. This footprint results from the viral infection itself but is also generated by cells being damaged by the immune system. Both contribute to sustaining an active immune response in patients. The model simplifies many of the processes that generate and remove this footprint in order to reduce complexity. Their approach to making the model simple can be compared to trying to plan out how long it takes to drive from San Francisco to Los Angeles. There are many factors that contribute to how quickly one can drive—traffic and headwind—but one could probably reduce it down to the average speed.

Once they developed the framework of their model, they simulated the model 1 million times while assigning variables randomly to a range of different values and demonstrated that there were two possible outcomes that the simulations followed. In the driving example, this would be akin to simulate the journey with different values for driving speed. One state represented a hyperinflammatory state, while the other represented a resolved inflammatory state, both of which exhibited consistency when compared with known clinical outcomes.

Further analysis revealed that the most important predictor of which state was achieved was how quickly the molecular footprint of the disease was cleared. This implies that targeting the processes that clear the molecular footprint may be effective strategies for future treatments, such as drugs that activate macrophages which are immune cells that eat sick, dying cells and debris. The model also allowed the authors to examine how current treatments and their time of administration influenced which of the two states was reached. In doing so they were able to show that while anti-inflammatory drugs are effective at both early and late-stage infection in individuals with a hyperinflammatory response, antivirals need to be administered early on to be useful.

Although not stated by the authors, the simplicity of the model suggests that it could be extended to assess not only disease-related viral infections but also purposeful viral infections such as when delivering DNA or RNA in therapies, because the immune system processes induced are the same. Scientists could then reveal limitations to virus-based therapies and routes for mitigating these limitations in order to make viral therapies as effective as possible for every patient.

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