Akiko Iwasaki, PhD

Understanding Immune System Blunders in Response to the Coronavirus

Jenny Blair writer **Peter Baker** photographer

A bewildering puzzle of COVID-19 is why the virus affects people so differently. Though older men seem to fare worst in the face of infection with SARS-CoV-2, younger people may unpredictably falter, too. Moreover, many people develop long-term symptoms. We don't yet understand why.

But for Akiko Iwasaki, PhD, the Waldemar Von Zedtwitz Professor of Immunobiology and Molecular, Cellular and Developmental Biology, pieces of the puzzle are emerging. Genetics, gender, and even botched timing on the part of the immune response all appear important. What she learns could help us better predict who is likely to sail through a bout with COVID and who may need targeted lifesaving care.

There's a lot of variation in how the human immune system mounts a defense against coronavirus. For a group of people hospitalized with either moderate or severe COVID-19, Dr. Iwasaki's team recently mapped out those differences in a study that appeared in *Nature*.

Among patients with moderate disease who recovered, proteins involved in tissue healing and repair were relatively abundant. By contrast, among those with worse disease, the cytokines were more mixed, showing up in combinations that are unusual for viral infection. More people died in that group.

Based on these immune signatures, the researchers were able to distinguish the patients' disease trajectories. Further data from a larger study, Dr. Iwasaki said, could help doctors predict a patient's course of disease and formulate tailored therapies.

One of the immune system's early defenses is a group of proteins called type I interferons. Produced by immune cells in response to viruses, interferons are key to the body's initial, rapid defense against coronavirus. But some people make too much of it, others not enough, and still others neutralize it with autoantibodies—and that makes a difference.

"In the early phase of the infection, if you can generate robust interferon, you will control the virus because interferon will trigger all these antiviral genes," Dr. Iwasaki explained. That is likely how people with asymptomatic or mild disease keep it under control, she added.

On the other hand, if the immune system doesn't create interferon soon enough, the virus can replicate undisturbed. Later, caught off guard by uncontrolled viral replication, the immune system may respond by manufacturing large quantities of interferon.

But by that point, it might be too much of a good thing. Massive amounts of interferon can drive inflammation, which in turn recruits white blood cells to the lung and make disease worse, Dr. Iwasaki described. Patients with more severe COVID-19 have been observed to have higher levels of interferon. "What I'm hypothesizing now is that the timing of the interferon really matters," Dr. Iwasaki said.

Another group of people with severe COVID-19 do not mount an interferon defense at all, Dr. Iwasaki and co-author Eric Meffre, PhD, Associate Professor of Immunobiology and of Medicine (Immunology), and a Yale Cancer Center member, explained in a recent commentary in *Nature*.

For example, a recent study of 659 people with life-threatening COVID-19 found that 23 had mutations in genes known to be important in severe viral infection. These mutations left the individuals unable to either produce or to respond to interferon. By contrast, in 534 people with milder cases, only one had such a mutation.

Another study found autoantibodies against interferon in some people with severe COVID, most of them older men. That finding may help explain men's overall heightened vulnerability to the disease.

Dr. Iwasaki also uncovered another such gender-based difference in work she published in Nature with viral epidemiologist Saad Omer, MBBS, MPH, PhD, of the Yale School of Medicine and of Public Health. Men who developed weak, defective T-cell immune responses suffered worse disease.

Autoimmunity could also help explain why so many people experience prolonged illness after a bout with COVID-19. Long after their viral tests turn negative, these people, nicknamed "long-haulers," can experience months of fatigue, shortness of breath, muscle aches, brain fog, and other symptoms. "We're trying to find out if there's any immunological mechanism that can explain long-haulers," she said. "I raised three different hypotheses, none of which are mutually exclusive."

One hypothesis is that these patients' immune systems have turned on them, resulting in long-term autoimmunity. Another possibility is that remnants of virus, such as bits of protein or genetic material, remain to stimulate the immune system. That could result in chronic inflammatory symptoms. A third scenario is that the virus in long-haulers never goes away. Instead, it may hide somewhere in the body, far from the nasal swabs that can detect it, and continue to cause infection.

Studies like these can't take place without blood and tissue samples. Dr. Iwasaki's lab contributed to the effort of the Yale COVID-19 Biorepository, which holds samples from hundreds of COVID-19 patients, including those with cancer. The biorepository, named IMPACT for Implementing Medical and Public health Action against Coronavirus (Connecticut, CT), was launched this spring by Albert Ko, MD, Yale School of Public Health's Chair of Epidemiology. Roy S. Herbst, MD, PhD, Chief of Medical Oncology at Yale Cancer Center and Smilow Cancer Hospital and a member of the IMPACT team, is leading the sample collection from cancer patients with COVID-19.

"This is the only way we could do our research," Dr. Iwasaki said of the biorepository. Thanks to these patient samples, Dr. Iwasaki, Dr. Herbst, and others are also able to study how cancer status affects COVID-19.

Understanding cancer patients' experiences with COVID-19 may help us better understand the immune system, Dr. Iwasaki explained. Some types of cancer appear to make people more susceptible to severe COVID-19, while many cancer therapies interact with specific steps in the immune response—an effect that may alter the course of COVID-19.

Cancer immunotherapy has also illuminated the way cytokines can provoke damaging inflammation, Dr. Iwasaki said. For example, the cutting-edge cancer treatment chimeric antigen receptor (CAR) T-cells can lead the immune system to release too many cytokines. A drug called tocilizumab, which blocks a cytokine called IL-6, was tested for COVID-19 patients.

Though it didn't turn out to be effective, Dr. Iwasaki said, that research was important. "These types of inflammatory responses that occur in cancer therapy have really shed light on how we might treat an inflammatory viral disease," Dr. Iwasaki said.

Testing potentially helpful treatments for COVID-19, like tocilizumab, can take a long time. But Dr. Iwasaki's lab has developed a versatile mouse model that allows for much quicker trials. Normally, mice are not susceptible to SARS-CoV-2 because they lack the ACE2 receptor that the virus uses as its doorway into cells. Mice can be bred to have this receptor, but that takes months. Instead, Benjamin Goldman-Israelow, MD, PhD, an infectious disease fellow in Dr. Iwasaki's laboratory, devised a way to introduce the receptor into mice of any genetic background by delivering it into the body with a virus called AAV.

"We're using this mouse model to rapidly get at these questions that people have about the importance of T cells and B cells and antibodies," she said. "Whatever it is, we can do it very quickly."

That speed is crucial. As the pandemic continues to rage around the world, clinical trials of therapies and vaccines have had to skip some steps, as Dr. Iwasaki and her co-authors recently explained in the *Journal of Experimental Medicine*. To better understand not only how the virus and immune system behave, but also to study treatments and potential vaccines, they wrote, "good mouse models are urgently needed. This model provides a vital platform for testing prophylactic and therapeutic strategies to combat COVID-19."