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T cells: an essential but neglected component against COVID-19

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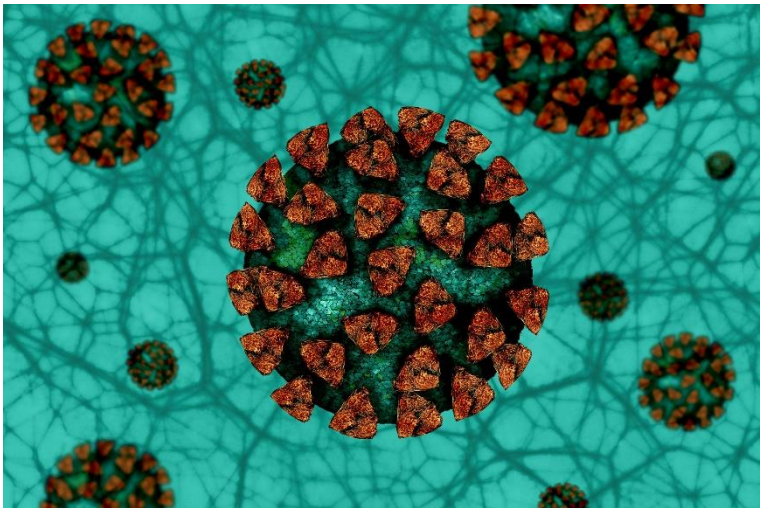
Antibodies protect our bodies against viruses. Nevertheless, one other highly specialized component of the adaptive immune system: T cells. Our recent findings characterize virus-specific T cells in COVID-19 patients and in healthy non-infected individuals.



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The current COVID-19 pandemic has brought into our daily conversations scientific topics previously only discussed among scientists in academic environments. When the media inform us about the rise or fall of new cases of SARS-CoV-2 infection in the world, questions about immunity and protection follow immediately. Antibodies often take the spotlight soon after that. Antibodies are soluble molecules produced by our immune cells that can bind directly to the virus and prevent it from entering the cell.

However, the way the immune system is protecting us from viral infection and its consequences is complicated and certainly not dependent only on the presence or absence of antibodies. Another component of the immune system that has evolved very specialized anti-viral function is T cells also called T lymphocytes.

Two subpopulations of T lymphocytes perform two essential functions in the control of viral infection: the first one, CD8+ T cells or cytotoxic T cells, can directly detect if a cell got infected by the virus. After recognition, they get activated and kill the cells directly, harboring the virus. Doing so, they suppress the virus's ability to multiply and contain the viral spread within the infected host. Instead, a second function is taken care of by the CD4+ T cells, also called T helper cells. They also sense the presence of viral antigens (pieces of proteins of the virus) in the body. Then, they expand and produce soluble factors (cytokines) that help the CD8+ T cells perform their killing function and help B cells to produce

antibodies. In other words, they deliver provisions to help the other immune cells (B cells and cytotoxic T cells) to perform their task.

We need to remember that viruses are intracellular parasites. Outside a cell, they do not "replicate" or exert any function. When they are outside a cell, they are basically in search of a new cell to colonize. Antibodies can block the infection, but they cannot do anything once a virus is inside a cell. By infecting cells in direct contact with air, respiratory viruses are very good at bypassing the defensive control of antibodies. The T cells instead recognize the cells that harbor viruses.

Now, if the T cells are so crucial in virus defense, why, during the current COVID-19 pandemic, everybody talks only about antibodies? Why has science been muted for a long time in analyzing SARS-CoV-2-specific T cells? The answer to these questions is that antibodies are easy to understand. They directly bind the virus and block infection. T cells are instead complex, and we need to write quite a long paragraph to try to describe what they do. Besides, while antibodies are relatively easy to measure and study in patients' blood, T cells are much more complicated to study. They require to be alive and in good shape to demonstrate their virus-specificity.

This is why reports about SARS-CoV-2-specific T cells in patients appeared in the scientific literature only 3-4 months after the beginning of the pandemic, and the work that we have done in our laboratory in Singapore has been one of the first to describe SARS-CoV-2-specific T cells in COVID-19 patients. In reality, our expertise is the study of immune responses to Hepatitis B virus (HBV), but since we are very familiar with the role of T cells in HBV infected patients, we felt that we need really to understand whether T cells constitute an essential part of the antiviral immune defense of COVID-19 patients. Furthermore, we thought it was crucial to understanding how long virus-specific T cells can last and form a "memory" response after the resolution of infection. Singapore provides us a peculiar advantage to properly answer this question. Seventeen years ago, Singapore was hit by SARS, and patients from that time collaborate with us to try to understand whether the new but related coronavirus can elicit a long memory T cell immunity. Finally, we also tested how frequent SARS-CoV-2 memory T cells can be detected in the general population since other coronaviruses, classically causing the common cold, might be able to induce what we call cross-reactive T cells, T cells that recognize fragments of the virus that share similar sequences with other viruses.

Our results demonstrate that T cells (both CD4 and CD8 T cells) are induced by SARS-CoV-2 infection, and they can be found in 100% of COVID-19 patients that recovered from the infection. We also show that individuals who recovered from SARS seventeen years ago still harbor SARS-specific T cells. This piece of evidence supports the idea that T cell responses against coronaviruses are long-lasting.

We also detected that more than 50% of uninfected healthy individuals have SARS-CoV-2 specific T cells, despite having never been in contact with the virus. Significantly, these T cells recognize sequences of non-structural proteins found in other humans but also animal coronaviruses.

In conclusion, our effort to study T cells gives us some concrete answers. The first is that infection with Coronaviruses can induce long-lasting virus-specific T cells. The second message is that T cells (and not only antibodies) are an essential part of immunity against SARS-CoV-2. The third message is that a level of pre-existing immunity against SARS-CoV-2 appears to exist in the general population. Whether such pre-existing T cells have a protective effect or, in contrast, can alter the course of the

disease will need to be studied carefully. But what is clear is that our work, among the work of others, has put back T cells into the focus they deserve in the battle against this virus.