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T cells could be critical in Covid-19 battle

More studies show that T cells may play a role in protecting individuals from severe disease

Antonio Bertoletti and Alessandra Nardin

Mr Faris Kairi, a senior research officer at ImmunoScape, working on a mass cytometry machine to process human samples for the firm's Covid-19 project. As more studies into the T cell response to Sars-CoV-2 have emerged, scientists have begun to recognise the importance of T cells in the fight against Covid-19. PHOTO: IMMUNOSCAPE

In the midst of the Covid-19 pandemic, questions usually asked by immunologists studying human immune response to viruses are now on everyone's lips. People wonder if they will get very sick should they be infected, or how long protection from a vaccine will last.

To get some answers, immunologists have had to reckon with the complexity of the immune response to viruses.

On the one hand, viruses induce production of antibodies – Y-shaped proteins that bind to the surface of the virus and thus hinder virus entry into cells. If the right antibodies are present in sufficient amounts before an individual is exposed to a virus – because they are generated by vaccination, for instance – they may be able to prevent viral infection altogether.

On the other hand, viral infection also results in the activation and expansion of immune cells called T cells. T cells come in many different forms, but they have two main functions: to recognise and kill infected cells where the virus is replicating, and to boost antibody production.

They exert their functions by recognising fragments of virus proteins that are chopped up inside infected cells and then "presented" on the cell surface – the infected cell is thus signalling to the T cells: "Hi there, I have a virus inside, please come destroy me."

T cells may not be able to completely prevent virus infection from happening, but they can rapidly stub out viral expansion in the body and therefore prevent disease. Importantly, they maintain the "memory" of a pathogen for decades and will be rapidly recruited upon new infection.

When the global efforts to contain Sars-CoV-2 – the virus which causes Covid-19 – started some months ago, the greatest emphasis was placed on designing vaccines able to induce an antibody response against the virus, especially against spike proteins on its surface.

The importance of T cells for antiviral immunity is not a new concept. It has been fundamental in the scientific community for over 50 years, but was initially largely ignored in discussions related to Covid-19 immunity and vaccine development – T cells are harder to study and some classical vaccines, such as the seasonal influenza vaccine, mostly rely on antibody generation.

Antibodies are certainly important in containing infection, but questions remain on how long-lived they may be after vaccination.

As more studies into the T cell response to Sars-CoV-2 have emerged, scientists have begun to recognise the importance of T cells in the fight against Covid-19.

We now know that T cells are indeed induced by Sars-CoV-2 infection. They are present in 100 per cent of the Covid-19 individuals that we and others have tested in our laboratories.

Using different methods, our laboratories have cumulatively screened close to 250 individuals who recovered from Covid-19. All have Sars-CoV-2-specific T cells.

Many of these people, although previously infected, had not developed any symptoms. Some of these asymptomatic individuals have a very low level of antibodies, yet they have T cells for the virus – a finding that suggests that the T cells might be very important for protection.

We have found that apart from the virus' spike protein, T cells target other structural proteins as well as proteins necessary for the virus' replication. This has potential repercussions on how a vaccine aimed at inducing a broad T cell response should be designed.

Based on how they look and behave when we analyse them, we have evidence that these T cells should be able to do their job – to kill infected cells and secrete factors with antiviral activity, and boost immune response.

Is the T cell response against Sars-CoV-2 long-lived? This question can be directly answered only in time.

To assess persistence or waning of the response, recovered individuals will need following up for months and years to come.

But there are grounds for confidence. Indeed, 23 individuals who had Sars in 2003 were recently all still found to have T cells that recognise Sars-CoV-1, which causes Sars, even 17 years after infection.

This suggests that coronaviruses do indeed induce long-lasting T cell immunity.

What is even more interesting is that many of these T cells generated by Sars-CoV-1 infection were also able to recognise Sars-CoV-2 – a phenomenon immunologists call "cross-reactivity".

This brings us to a new set of findings with potentially very important implications: many individuals who have never been infected also have T cells that can target Sars-CoV-2.

To be precise, we have seen Sars-CoV-2-specific T cells in more than 50 per cent of uninfected healthy individuals in Singapore. Some of these results were published last month in the journal Nature. To date, more than a 100 people have been tested.

This observation has recently been confirmed by studies in the United States, and is therefore likely to have global significance.

These T cells, like the "cross-reactive" T cells found in recovered Sars patients, are likely to have been generated by exposure to other coronaviruses – probably the commonly circulating coronaviruses that cause colds – which share similarities with Sars-CoV-2 in their protein structure. It may also be possible that coronaviruses identified so far only in other animal species, such as bats, induce Sars-CoV-2 T cells in humans, but this will need to be confirmed.

Thus, a certain level of pre-existing immunity against Sars-CoV-2 appears to be present in the general population. It could perhaps explain why some populations and countries have very little incidence of severe disease over total infected cases.

Is this pre-existing immunity useful against Covid-19? Does it afford protection from disease? Does it dampen symptoms? Are individuals with cross-reactive T cell immunity more likely to be asymptomatic? Is the extent of this pre-existing immunity affecting disease severity or mortality rates in populations where these rates are very low, such as Singapore?

An affirmative answer to these questions is not unreasonable but, for now, completely speculative.

Tackling this will require screening unexposed individuals for the presence or absence of pre-existing T cells against Sars-CoV-2, and then following up with these individuals to record the severity of their disease if they get exposed to the virus.

Such a study is not easy to conduct as it requires recruitment and long-term following up of large numbers of uninfected individuals, the majority of whom are not likely to get infected.

But there is reason to be hopeful.

More and more studies are showing that a healthy T cell response generated during natural infection with Sars-CoV-2 is likely to persist for years, and that T cells may play a role in protecting individuals from severe disease.

As efforts to develop effective and safe vaccines progress worldwide, we have also seen a renewed interest in understanding the extent to which current vaccines are able to generate T cell – and not only antibody – responses, and we are working alongside vaccine companies to help guide vaccine development.

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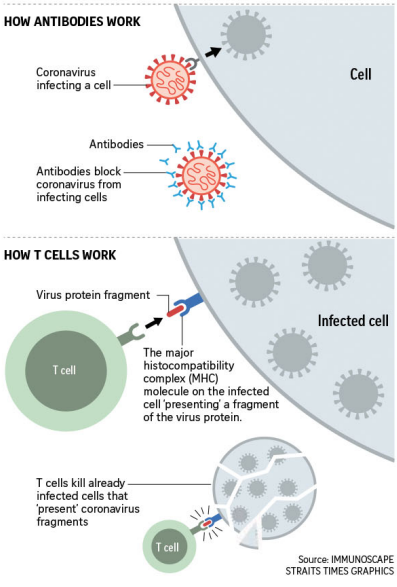
How antibodies and T cells work against coronaviruses



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About the writers

Dr Antonio Bertoletti is an expert in infectious diseases who has made pivotal contributions to the understanding of T cell response to the hepatitis B virus. His research career has spanned The Scripps Research Institute in the United States, the University of Parma in Italy, University College of London, and the Agency for Science, Technology and Research (A*Star). He is currently professor and principal investigator for the Emerging Infectious Diseases programme at Duke-NUS Medical School, and co-founder of LionTCR, a biotechnology company focused on the developing T cell therapy against viral infections and viral-related cancers.

Dr Alessandra Nardin has more than 25 years of international experience in immunotherapy and vaccine development in academic and biotech environments in the US (University of Virginia), France (IDM Pharma) and Singapore (A*Star). Dr Nardin is co-founder and chief operating officer of ImmunoScape, a Singapore and US-based start-up specialising in deep profiling of immune cells.