AMPATHCHAT no. 78

COVID-19 T-CELL RESPONSES

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KEY MESSAGES

- Cellular (T-cell) immune responses may be more durable than humoral (antibody) responses following infection with SARS-CoV-2 or COVID-19 vaccination.
- SARS-CoV-2 variants of concern are less likely to evade cross-protective T-cell responses than neutralising antibodies.
- T-cell responses, and in particular $CD8^+$ T-cells, have been shown to play a critical role in viral clearance.
- Cross-reactive T-cell responses have been documented in SARS-CoV-2 naïve or seronegative persons as a result of prior exposure to other human common cold coronaviruses, which could potentially provide some degree of cross-protection against severe COVID-19 disease.
- Ampath Laboratories offers T-cell proliferation tests either against SARS-CoV-2 spike protein only, or against both SARS-CoV-2 nucleocapsid (N) and spike (S) proteins.

Since the emergence of SARS-CoV-2 (the virus that causes COVID-19) in December 2019, a key area of research has been to understand the host's immune response to the virus. Studies into adaptive immune responses are particularly important to develop vaccines and therapeutic agents, as the adaptive arm of the immune system is usually associated with long-term protective responses. While a large component of research into the adaptive responses has focused on the humoral (antibody) component of the immune response, and particularly neutralising antibody responses, it is also crucial to understand the role of the cellular immune response to COVID-19 infection, vaccination and SARS CoV-2 variants of concern.

T-CELL RESPONSES FOLLOWING INFECTION WITH SARS-COV-2

Several studies have demonstrated that antibody levels may wane as early as 6–8 months after natural infection with SARS-CoV-2. Antibodies were also shown to wane during investigations following the outbreak of the original SARS coronavirus, yet memory T-cell responses were still detectable more than 10 years following infection. Such responses are important to consider given the limited time frame to study the duration of recall responses following SARS-CoV-2 infection. Activation of SARS-CoV-2 specific T-cell responses (including memory T-cell responses) has been demonstrated in recent studies to various proteins of SARS-CoV-2, including the spike and the nucleocapsid protein, in persons following infection. T-cell responses, and in particular $CD8^+$ T-cells, have been shown to play a critical role in viral clearance. SARS-CoV-2 reactive T-cells have also been described in between 35 and 60% of SARS-CoV-2 naïve or seronegative persons, which may be ascribed to cross-reactive T-cell recognition following prior exposure to other human coronaviruses associated with common cold symptoms. Although the extent of protection provided by cross-reactive T-cell responses against COVID-19 is still unclear, recent findings demonstrated more cross-protective T-cells in healthcare workers who repeatedly tested negative for SARS-CoV-2 and remained seronegative, compared with persons who were infected with SARS-CoV-2.

Average levels of detectable antibody response following COVID-19 infection have been shown to be lower in persons who have asymptomatic or mild disease, in comparison with people with severe COVID-19 infection. Not only does this phenomenon suggest that a robust antibody response in itself is insufficient to avoid severe illness, but it has prompted further assessment of the protective non-humoral immune responses that allow efficient recovery from infection in mild disease. Recent findings demonstrated significantly higher T lymphocyte induction in mild COVID-19 disease compared to those with severe COVID-19 and also that the largest proportion of SARS-CoV-2 specific T-cells in patients with mild disease recognised peptides from the nucleocapsid and spike proteins.

T-CELL RESPONSES FOLLOWING COVID-19 VACCINATION

The majority of vaccines induce protective immune responses through the induction of specific neutralising antibodies. The major target for neutralising antibodies is the receptor-binding domain of the spike protein. The spike protein is considered highly immunogenic and has been selected as the main target in most COVID-19 vaccine candidates. Cellular immune responses are less well studied following vaccination against COVID-19 than humoral (antibody) responses, but a growing body of evidence suggests that T-cell responses are important to consider.

Humoral immune response may be short-lived, while memory T-cell responses are anticipated to last longer. Vaccination with the majority of available COVID-19 vaccines has been shown to result in robust T-cell response memory and effector functions have been demonstrated against multiple viral epitopes. T-cell responses have been demonstrated in persons who remained seronegative following COVID-19 vaccination, particularly in those with underlying immune suppression, but it remains unknown how protective T-cell responses are in the absence of detectable antibodies. Vaccine efficacy studies (Phase III trials) have mostly been based on clinical efficacy, where the endpoints are clinical disease or infection. Phase I and II trials assess neutralising antibody levels following vaccination to determine immunogenicity of the vaccine candidates, often in addition to cellular responses ($CD4^+$ and $CD8^+$ T-cells). Immune correlates of protection, on the other hand, refer to the measurement of either a humoral or cellular response by means of a laboratory assay that reliably predicts protection against an infection or the clinical disease caused by it. The exact immune correlates of protection for COVID-19 remain uncertain.

T-CELL RESPONSES AGAINST SARS-COV-2 VARIANTS OF CONCERN

One of the major concerns surrounding emerging COVID-19 variants is whether these variant SARS-CoV-2 viruses are able to evade vaccine-induced immune responses. The spike protein that is used in the design of the current commercially available COVID-19 vaccines are based on the pre-existing SARS-CoV-2 (Wuhan) reference strain. Given the fact that the spike protein plays a pivotal role in viral attachment to the host target cell, this is also the area that is more prone to mutations, which may advance the binding and transmission abilities of the mutant virus. The SARS-CoV-2 variants of concern typically have spike gene mutations, which may impact on the ability of vaccine-induced antibodies to neutralise viral particles from a variant strain.

T-cell responses may offer broader cross-reactive protection against SARS-CoV-2 variants of concern. Several studies that investigated T-cell responses following natural COVID-19 infection with the pre-existing SARS-CoV-2 strain and variant lineages Alpha, Beta, Gamma, and Epsilon, as well as post-vaccination T-cell responses following administration of mRNA vaccines, found negligible differences between $CD4^+$ and $CD8^+$ T-cell responses to all four variants. Variant mutations appear not to affect T-cell epitopes, which indicates that cellular immune responses generated following either natural SARS-CoV-2 infection or vaccination likely offer longer lasting responses that are less prone to viral escape. Despite the recently emerged Omicron variant's unprecedented number of spike mutations, with demonstrable neutralising antibody escape, various studies have demonstrated preservation of $CD4^+$ and $CD8^+$ T-cell recognition in participants who had received mRNA and recombinant vector viral vaccines against the Omicron variant of concern.

LABORATORY TESTING OF T-CELL RESPONSES TO SARS-COV-2

The following COVID-19 T-cell proliferation tests are available at Ampath:

Test name	Mnemonic	Sample type	Notes
SARS-CoV-2 T-cells (N and S proteins)	COVIDTPR	Blood – 5x citrate tubes	Specimens to be collected on Sundays to Thursdays
SARS-CoV-2 spike T-cells	COVIDTSPR	Blood – 5x citrate tubes	Specimens to be collected on Sundays to Thursdays

Results are expressed as a Stimulation Index (SI), which is a ratio comparing the patient's T-cell response with and without SARS-CoV-2 proteins. The SARS-CoV-2 N and S protein T-cell assay offers more comprehensive assessment in persons who had prior natural infection with and/or exposure to SARS-CoV-2, while assessment of only the spike T-cells could be considered to assess vaccine-induced cellular immune responses. Cross-reactive T-cells due to previous infection with common cold coronaviruses can also occur. T-cell proliferation results should ideally be interpreted in conjunction with antibody results. For more information on this in-house assay, please refer to the following publication:

Van Rooyen, C., Brauer, M., Swanepoel, P., Van den Berg, S., Van der Merwe, C., Van der Merwe, M., Green, R. and Becker, P. 2022. Comparison of T-cell immune responses to SARS-CoV-2 spike (S) and nucleocapsid (N) protein using an in-house flow-cytometric assay in laboratory employees with and without previously confirmed COVID-19 in South Africa: nationwide cross-sectional study. *Journal of Clinical Pathology*.

Note: Test performance will be affected by the use of oral cortisone or immunosuppressive medication. Where feasible or safe to discontinue said treatment for the purpose of performing a T-cell test, the patient will need to wait 14 days from the last dose before having their blood sample taken.

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REFERENCES ARE AVAILABLE ON REQUEST.