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The Level of T Cells Specific to the SARS-Cov-2 Virus and Asymptomatic Infection and the Immunogenicity of a Vaccine.

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Abstract

A robust T cell response can lead to milder infections. It can also establish memory pools and can respond to certain SARS-CoV-2 variants. T cells are mainly directed toward epitopes that are part of conserved peptides. Although the effects of IL2 and IFN on long-term immunity are still unclear, it is believed that these two factors play a role in the development of TH1 responses in uninfected individuals. By analyzing the responses of the participants, we were able to determine that 9 out of the 11 individuals exhibited dual-producing IFN/IL-2+ T cells, decreasing to 8 out of 10 for the asymptomatic group. The reduction in the levels of IL2 in TH1type cells, which came from asymptomatic infection, has made it possible to predict the response of T cells to IFN in people with no previous history of infection or vaccination. After the first vaccination, the not-vaccinated participants had a high level of IL-2 response. Compared to AstraZeneca's vaccine, the Pfizer vaccine was more likely to elicit a higher L2 response. On the other hand, the IFN response of the AstraZeneca vaccine was not significantly different from that of the Pfizer vaccine.

Keywords
T- cell, SARS-Cov2, IL2, IFN, cytokine

Studies have shown that T cells can help limit the duration and severity of a disease caused by the SARS-CoV-2 virus. The presence of these cells can help prevent the spread of the infection. In non-human primates, the transfer of T cells can help prevent the spread of the virus. In humans, the induction of IFN-secreting T cells can lead to mild disease. CD8+ T cells that target the N105-113 receptor were also known to improve disease outcomes (Bitoun et al., 2022). The elicitation of certain types of T cells during an acute COVID-19 infection is linked to the specific presence of SARS-coV-2 cells. Patients' blood is filled with different types of T cells before they recover. These cells play a role as they develop an immunological response and in the maturation of memory B and plasma cells. The activation of the CD8 and CD4 T cells during acute COVID-19 cases is known to trigger convalescence and neutralization. However, prolonged and high levels of these two

cells are linked to the severity of the illness (Biswas et al., 2022).

The presence of certain SARS-CoV-2 cells in patients during the acute phase of COVID-19 can trigger the development of T cells. This suggests that these cells play a role in the disease's resolution. The Tfhs are a subset of the CD4 T cells that are involved in the development of memory B and plasma cells. The level of antibodies at normalization and convalescence can be influenced by the activation of CXCR3+ in acute COVID-19. High levels of hyperactivated CD8 and/or CD4 T cells are known to increase the severity of the illness (Rice et al., 2021).

Early studies focused on developing T cells that can bind to the common blood mononuclear cells to prevent them from becoming infected with SARS. These were then studied using an activation-induced protein. About 70% to 100% of subjects had high levels of reactive T cells, and in vitro stimulation of PBMCs using COVID-19 peptides resulted in the establishment of CD4 and CD8+ T cells. Although numerically more sets of these cells were established, the overall number was not as high (Madelon et al., 2022).

A test conducted on a small number of unexposed individuals revealed that the SARS-CoV-2 T cells exhibited cross-reactivity against other known coronaviruses. This suggests that exposure to these strains may have triggered this phenomenon. Studies have shown that individuals who were not infected by the SARS virus but had a negative PCR background showed higher levels of T-cell responses than those infected with the disease. These findings support the idea that existing protective T-cell responses could help prevent the spread of the illness. However, the high level of cross-reactivity that was observed in the test was unexpected and could suggest that the AIM test's specificity has decreased (Sadarangani et al., 2021).

Researchers were able to study the different attributes of CD8+ T-cells by staining them with the SARS-specific tetramer. They discovered the pre-established pools of these were not very diverse. The researchers discovered that the pre-existing structures of these cells were naive. They then performed studies on the membrane of CD8 T cells to identify the conserved peptides and histocompatibility complex limits. Different ex vivo factors were observed to determine the degree to which these cells were produced during the early stages of COVID-19. Some of the dominant CD8+ T cells were those that were directed toward the N105-111 target (Niessl et al., 2021; Tarke et al., 2021).

The high number of B cells labelled as naive B cells was due to the lack of certain gene segments. These B cells can be differentiated into different types by themselves. They exhibited robust functional and anti-viral responses in patients with COVID-19. The growth of B7+CD8 T cells with high functional avidity was associated with a weaker response in patients who had recovered from a severe illness. This suggests that they play a role in controlling the disease. The large populations of these cells that responded to ancestral strains and variants of concern were also observed. The diversity of the CD8 T cell repertoire can help select the appropriate cells that can protect against viral infections (Smith et al., 2021).

The CD8 T cells targeted to the SARS-coV-2 receptor are known to have an immunodominant phenotype. But, they have numerically subdominant characteristics compared to the other targeted T cells. This suggests that the emergence of these new T cells was caused by a biased TCR. Some of the genes that are commonly seen in the A2S269-CD8+T cells are part of the TRBV family. To determine the molecular basis of this biased recognition, the researchers analyzed the ternary structures of the two components. They discovered that the pathway to A/S269's recognition was triggered by the combination of the conserved amino acids and the germline-

encoded residue (Niessl et al., 2021).

Although the exact details of the T cell epitopes of the SARS-CoV-2 antigen are known, they are not widely known. This is due to the limitations of the current generation of reagents used in developing new multimers. Some of the regions may have overlapping features. For instance, the S870-878 is the most common target of T cell receptors in COVID-19. This disease is caused by the presence of certain restrictions on the human leukocyte antigen. Other targets, such as the S167-180, can also be identified through reverse epitope discovery. Reverse epitope discovery is a process that involves mapping the receptor's location and isolating its identity (Jung & Shin, 2021).

There is now enough proof supporting the notion that the presence of T cells can limit the severity and recovery rate of patients infected with the SARS coronavirus. These findings should be especially relevant to those who are immunosuppressed. Although the characteristics of T cells were similar between patients with different types of solid tumors, the number of these cells in the haematological malignancies was higher (Ishii et al., 2022). These patients also exhibited a similar level of activation compared to those who survived but had fatal disease outcomes. The goal of this study was to analyze the increasing Tcell responses in individuals with no history of previous infection and to determine if these were an indication of an asymptomatic SARS CoV2 infection

Methodology

Sample collection

Between February and July 2022, 112 healthy donors participated from a public hospital in Cairo, Egypt. They were recruited from either a COVID-19 Screening Service or from members of the public who attended the hospital. None of them had any known immunosuppressive medication use. Blood samples were collected before and after the first dose and three to six weeks following the second dose. Participants were given either AstraZeneca's AdOx1 nCoV19 vaccine or Pfizer's BNT162b2 mRNA vaccine.

63% of the study population were vaccinated with the AstraZeneca vaccine while 33% were Pfizer's vaccinated. only 5% of the study sample was not vaccinated. much of the study sample were females with 52% of the participants. It was noted that the age average of the study population was 49 years.

Table1. characters of the study participant

	Mean	St deviation	Percentage
Age	49	1.08	
Gender			
Male	54	1.38	48%
Female	58	0.87	52%
Type of vaccine			
AstraZeneca	70	1.12	63%
Pfizer's	37	1.03	33%
not vacinated	5	0.86	4%
previouse SAR2 infection			
yes	95	0.983	85%
no	17	0.93	15%

Stimulation analysis

Each participant's blood was collected from a 6 or 10-ml sodium heparin vacuum tube. They were then processed in the laboratory after 12 h. A fraction of the whole blood sample was then aliquoted to be placed into microfuge tubes, which contained 30 l of the S/NP/M/combined peptide pool, 20 g of phytohaemagglutinin, or none. The samples were then incubated at 37 degrees Celsius for around 20 to 24 h. They were then centrifuged for 2 minutes at a rate of 3,000 g. The plasma samples were then stored at -20 degrees Celsius for up to a month before the start of the cytokine detection tests.

Cytokine Detection

The IFN concentration was measured using the BioLegend IFN ELISA MAX kit. It was performed according to the instructions provided

by the manufacturer, and it was quantified using the analysis prism. Microplates with a stop solution of 2N H2SO4 were read at 450nm. The values of the lower limit of the detection procedure were as low as 7 81 pg/ml. The IL2 levels were measured using a BioPlex Pro human cytokine set. The mean intensity of the beads was then determined using a BioRad 200. The concentration of the cytokines was then calculated using the control curves provided in the kit. Values below the detection limit of 6 28 pg/ml were recorded(Grifoni et al., 2020).

Antibodies detection

A direct ELISA was then developed using a 96-well plate, which was modified to include a recombinant RBD protein. The wells were then blocked with 3% nonfat dried milk powder, which was then washed in PBS. The patient's sera were then added to wells that were coated with the RBD protein. They were then washed three times with PBS. The wells were then incubated with a secondary antibody, which was an HRP. Plates were then developed using a combination of Ophenylenediamine Dihydrochloride and Sigma-Aldrich's SIGMAFASTTM. The optical density of the plates was then measured at 492 nm. The results of this procedure have been described in previous reports. The antibody concentration was measured using a BioPlex Pro human SARSCoV/S1 /S2 /N IgG panel, which was performed according to the instructions of the manufacturer. The fluorescent intensity was then measured using a BioPlex-200(He et al., 2021).

Statistics analysis

SPSS24 was used to perform statistical analyses of the data sets. The normality of the data set was evaluated using the Shapiro-Wilk test. Other methods were also utilized, such as the Kruskal-Wallis test and the Dunn test. The results of the analysis were then analyzed using linear regression analysis. The significance of the tests was stated numerically or by using the abbreviated notations provided by the symbols. For instance, the first number indicates that the test has a nominal significance of $p < 0.05$

Results

Tcell cytokine profile

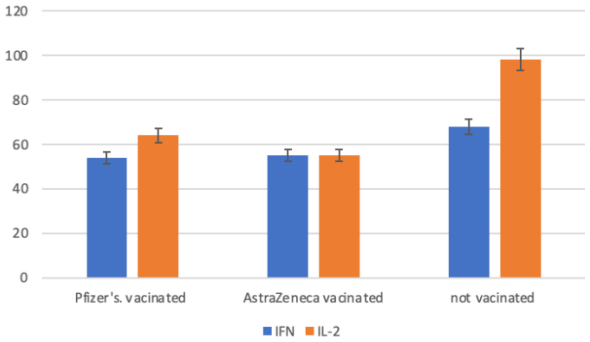

Figure 1. the cytokine response of IL2 and IFN in the study sample after the first vaccine dosage.

A previous analysis of the SARSCoV2-specific Tcell cytokine profile revealed that the TH1type IFN+ and IL2+ responses were dominant in the functional responses. then the researcher performed a whole-blood stimulation analysis to evaluate the TH1type responses' magnitude. Participants who were not vaccinated against the SARS virus were analyzed for their Tcell responses. They were individuals with a confirmed prior infection, a strong history of exposure to SARS, or no known history. After the first vaccination dosage, The not vaccinated participants showed a high IL-2 response. while Pfizer's vaccine was higher in L2 response than the AstraZeneca vaccine. On the other hand, IFN response didn't show any significant difference between the two vaccines but was the highest in the not vaccinated samples. Significant differences were observed in the Tcell responses of previously infected COVID-19-positive individuals with IL2 and IFNpositive Tcells compared to those of uninfected individuals. Even though there was a significant increase in IFN and IL-2 production in all participants regardless of their known history of exposure to SARS, there was a lack of an IL-2 response in the uninfected individuals.

Antibodies analysis

We then compared the magnitude of these responses with the evidence of antibody

serconversion. After identifying eleven participants with both positive and negative Tcell responses, we used the above criteria to define the cutoffs. In addition, the levels of anti-SARSCoV2-specific Tcells and antibodies were elevated. These findings suggest that the individuals had previously been infected with the virus before the pandemic started.

The function of the SARS-CoV2-specific T cells derived from prior asymptomatic infection was studied. We analyzed the responses of eleven healthy individuals with no history of previous infection and compared them with those of 11 convalescent individuals with a positive COVID-19 status. The levels of IFN and IL2 production were significantly decreased in the asymptomatic individuals.

When analyzing the TH1 responses by the participant's symptoms and infection status, we were able to identify dual-producing IFN-+/IL-2+ Tcells in 9 of the 11 symptomatic individuals, decreasing to 8 of 10 in the asymptomatic group. The reduction in the production of IL2 in the TH1type cells derived from prior asymptomatic infection has made IFN a more reliable read-out when assessing the responsiveness of T cells in people with no history of vaccination or infection.

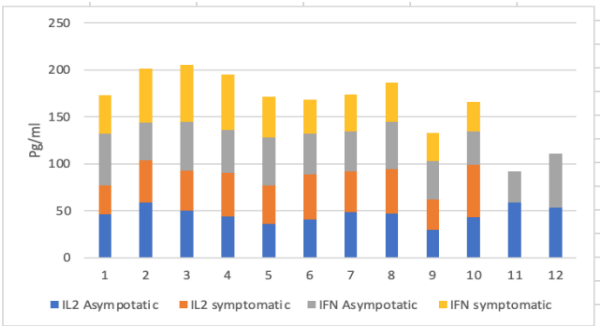

Figure 2. Asymptomatic and symptomatic participant's profile.

Discussion

The ability to accurately detect the response of Tcells to SARS-CoV2 is The study shows that the various constituents of immunity against COVID-19 can be important in order to stop future outbreaks. Tcells can provide a more accurate evaluation of the protection against the virus when combined with other COVID-19 measures. The approval of a Tcell diagnostic test for the treatment of patients infected with SARS-Cov2 shows the growing acceptance of the technology.The study revealed that measuring plasma TH1 type effectsor cytokines using a peptide derived from the SARS-CoV2-virus can accurately identify the virus' cellular response. The findings support previous studies that indicated that the IFN, as well as IL2, are the primary factors which trigger the T-cell response to the virus, but their relevance to the long-term immunity of uninfected people is still unclear.

Studies have shown that the adaptive immune responses of patients with mild and moderate COVID19 cases were lower than those of severe cases(Lozano-Ojalvo et al., 2021; Woldemeskel et al., 2022). This suggests that the lower viral loads may have led to the lower production of IFN and IL2. A longitudinal study conducted on asymptomatic patients with SARS-CoV2 revealed that the IFN and IL2 responses were significantly different from those of the symptomatic individuals within three months. The differences in the post-viral sampling periods were also apparent(Mateus et al., 2021).

The study showed that even though the number of Tcells did not increase, the cellular and functional responses of these cells remained in almost all the individuals infected with SARS-CoV2 . This suggests that they could still maintain their immunity. The study revealed that the immune responses of patients with SARS-CoV2 infections could potentially protect them from the emerging mutant viruses. More studies are needed to analyze the role of T-cells in this response (Ahmed et al., 2020; Ameratunga et al., 2021).

BNT162b2 vaccine is known to stimulate robust CD4 T cell responses in peripheral blood and lymph nodes. Twenty-one days following the first dose, these cells were detected. They exhibited a particular type of memory phenotype, and they

were able to maintain this for over 200 days. The T-cell populations that were T-specific to the Tetramer antigen were also detected at 30 days after the second dose.The first dose of the vaccine significantly increased the number of Tfh cells in the lymph nodes, and these cells were observed for around 170 days. The development of these cells was linked to the emergence of antibodies. Different CD8 and CD4 T cells were also developed in the vaccinated individuals. The kinetics of CD4 and CD8 T cells are different due to the different peptide-HLA combinations used. Following the vaccination, the CD4 T cells were mainly composed of central memory T cells and effector memory cells. The trajectory of these cells within the vaccine was studied through the UMAP approach (Heitmann et al., 2022; Sette & Crotty, 2021).

Studies suggest that the development of T cells is slower than the emergence of IgG antibodies in the first few months following the SARS-CoV2-infected individuals' infections(Sahin et al., 2020; Sauer & Harris, 2020). The memory pools of these T cells can last for up to 8 months in convalescent patients. The majority of these were directed toward the ORF3a membrane, and other peptides. The CD8+ and CD4+ T cells that were specifically designed for the SARS-coV-2 virus decreased after the disease onset. In contrast, those that were made for the vaccine developed a resilient cTfh. The persistence of CD8 T cells in convalescent patients who were infected with COVID-19 was stable. The dominant CD8 T cells from the N105 and B7N105 groups exhibited stable magnitudes 270 days after the disease's onset, while the T cells from the Tetramer-specific lineage exhibited a stem cell memory phenotype. Despite the decrease in the number of T cells, their phenotypes remained stable in patients who were convalescent (Kalimuddin et al., 2021).

Following the mRNA vaccination, T cells known as CD4+ and CD8+ were produced. The contraction of the latter was observed in peripheral blood. This suggests that viral infections can trigger a similar response in humans and animals. In convalescent patients infected with SARS-coV-2 who were still alive, memory pools of CD4T cells were also established. The number of circulating circulating circulating cTfh cells significantly decreased six months after the mRNA vaccine was given. Tfh responses in the nodes were also stable. The stability of the spike-specific Th1 cells was also observed over a period of three to six months. Research has shown that the generation of specific T cells for the SARS-2 virus from the BNT162b2 vaccine can trigger immunological memory pools (Castillo et al., 2021).

Conclusion

A strong T cell response can help with mild infections and establish memory pools. It can also respond to certain types of infections, such as SARS-CoV-2, by targeting conserved peptides. Although the exact mechanism by which IFN and IL2 affect long-term immunity is still unknown, it's widely believed that these factors contribute to the development of TH1. Through a comprehensive analysis of the participants' responses, we were able to identify 9 out of the 11 individuals who had dual-producing IFN and IL-2+ T cells, while the number of those who had no previous history of vaccination or infection decreased to 8 out of 10 for those who were asymptomatic. The reduction in levels of IL2 in the TH1type cells, which was caused by an asymptomatic infection, allowed us to predict the response of these T cells to IFN in individuals with no previous history of vaccination or infection. Participants who were not vaccinated experienced a high level of IIL-2 response after the first vaccination. The Pfizer vaccine was more prone to eliciting an L2 response than AstraZeneca's vaccine.

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Conflicts of Interest

The authors declare no conflict of interest.

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