Brief Progress Report on T Cell Responses in COVID-19

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Outline of SARS-CoV2 Pandemic

At the end of December 2019, a local epidemic of pneumonia of unidentified cause was identified in Wuhan (Hubei, China), and was rapidly revealed to be caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Being extremely infectious, this novel coronavirus disease, also known as Corona Virus Disease 2019 (COVID-19), has spread fast all over the world and paralyzed the global economy [1]. Coronaviruses are a distinct group of viruses infecting several distinct animals, and they can cause mild to severe respiratory infections in humans. During 2002 and 2012, respectively, two highly pathogenic coronaviruses with zoonotic origin, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV), emerged in humans and caused fatal respiratory disease. Likewise, to patients with SARS and MERS, SARS-CoV2 infected patients exhibited symptoms of viral pneumonia, including fever, cough, chest discomfort, and in severe cases dyspnea and bilateral lung infiltration [2,3]. As of 1 November 2020, almost 45.7 million people have been infected with infectious SARS-CoV2 globally, approximately 195 countries have been affected and more than 1.1 million deaths, according to the COVID-19 Map of the Johns Hopkins Coronavirus Resource **https://coronavirus.jhu.edu/map.html.**

Immune responses in viral infection

The immune system is the safest and best defense since it supports the body's natural ability to defend against pathogens (eg, viruses, bacteria, fungi, etc.) and compete against infections. As long as the immune system is operating naturally, infections with SARS-CoV2 unnoticed and resolved by their immune system. There are three arms of immunity first, innate immunity (rapid response), second, adaptive immunity (slow response), and passive immunity which may be natural, received from the maternal side, and artificial immunity received from the vaccine [4]. As we know the immune response against viral infection is the key to the disease development toward the severity against it, especially T cells are central players in the immune response to viral infection. An improved understanding of human T cell-mediated immunity in COVID-19 is important for optimizing therapeutic and vaccine strategies.

When the SARS-CoV-2 virus, which causes COVID-19, initially infects the epithelial cells found in the airways, it replicates inside the cells, using the host machinery, which ultimately causes the host cell death, releasing molecules called damage-associated molecular patterns [5]. These pattern recognition receptors (PRRs) recognize attacking SARS-CoV2. Viruses provoke numerous key host immune responses such as increasing the secretion of inflammatory factors, induction, and maturation of dendritic cells (DCs) and expanding the synthesis of type I interferons (IFNs), which are important in restricting viral spreading [6]. The immune system i.e. the innate and acquired immune response is activated by SARS-CoV-2 infection. The helper CD4+ T cells stimulate antibody-producing B cells to produce anti-virus antibodies like anti-SARS-CoV2 IgG and IgM. Numerous types of T cells are associated with viral immune responses, CD4+ T helper (Th) cells cooperate with cytotoxic CD8+ T cells, which drive kill virus-infected cells by the cytotoxic response. The CD8+ T cells directly recognize viral peptides presented at the surfaces of infected cells via MHC-I, causing apoptosis and avoiding the further spreading of viruses.

To date what do we know about T cell responses in COVID-19

Several studies evaluating the clinical features of SARS-CoV2 infected patients and have reported an incubation time of 4 - 7 days before the onset of symptoms, and a further 7 - 10 days before development to the severity of COVID-19 disease [1]. As we know, several primary virus infections normally take 7 - 10 days to prime and develop the adaptive T cell immune responses to control the virus, and this correlates with the typical time it takes for patients with COVID-19 either to recover or to develop severe illness [7]. This raises the possibility that a poor initial T cell response contributes to persistence and severity of SARS-CoV-2, whereas early strong T cell responses may be protective. In severe SARS-CoV-2 infection, lymphopenia (reduction in lymphocyte numbers), which settles when patients recover from severity. Some of the studies show the correlation between disease intensity and lymphopenia, in children, the mortality rate is very low and no observation of lymphopenia in another side the older peoples infected with SARS-CoV2 the mortality rate is higher and shown lymphopenia, which indicate the lymphocyte played an important role in the severity of diseases, but still no clear mechanism of

lymphopenia in COVID-19 known so far [8]. Few SARS-CoV2 infected patients, lymphopenia has been reported which mostly the CD4+ T cells, CD8+ T cells, B cells, and natural killer cells, while other studies suggest that SARS-CoV-2 infection has a superior influence on CD8+ T cells [9-13]. Acute viral infections in humans stimulate the activation and proliferation of T cells, including both CD4+ T cells and CD8+ T cells, therefore SARS-CoV-2 infection may not be exceptional in this view. Though, hypoactivation or hyperactivation of T cells, or distorting for an ineffective differentiation state or delayed or faulty anti-viral type I interferon responses could potentially distort T cell responses.

The CD4+ T cell response in COVID-19: There are few studies shows the functional impairment and increased expression of activation, and/or exhaustion markers and reduced IFNγ production by CD4+ T cells in patients with COVID-19 [12,14,15]. As we know several studies observed lymphopenia in COVID-19, which affects CD4+ T cells, although a few studies suggest that the impact is a smaller amount than CD8+ T cells [13,16]. Few studies also show the virus-specific CD4 T cell memory in addition to CD8 [17-19]. There are several questions unanswered like, how these CD4+ T cells respond to SARS-CoV-2 and impact on its functionality, disease outcome.

The CD8+ T cell response in COVID-19: As we understand CD8 T cells play an important role in viral infection, several investigators analyze the role of CD8 T cells in SARS-Cov2 infection. There are studies reported alterations in the activation and/or differentiation status of CD8+ T cells in severe disease reviewed in [20]. Robust T cell responses to the SARS-CoV2 occur in most people with Covid-19. Numerous studies have reported that a few individuals who have not been exposed to SARS-CoV-2 have preexisting 20 to 50% reactivity to SARS-CoV-2 sequences discussed in, this reactivity might be due to preexisting memory responses against human "common cold" coronaviruses [21]. These T cell memory responses might protect a few people newly infected with SARS-CoV-2 by remembering previous infection close homology other human coronaviruses. This might clarify why some patients seem to protect the virus and less prone to becoming severely ill with COVID-19.

Researchers have discovered that T-cell antigen receptors (TCR), on CD4+ or CD8+ T cells recognize the conformational structure of the antigen-binding-grove together with the associated antigen peptides presented by MHC-Class I or II. Therefore, different HLA haplotypes are associated with distinct disease susceptibilities. The repertoire of the HLA molecules composing a haplotype determines the survival during evolution. Accordingly, it seems advantageous to have HLA molecules with increased binding specificities to the SARS-CoV-2 virus peptides on the cell surface of antigen-presenting cells. The dynamics and cross-reactivity of the SARS-CoV-2 specific T cell response studies are much needed, therefore the importance of epitope/TCR discovery in SARS-CoV2 is a vital element to understand the T cell immunity and future consideration in vaccine strategy and immunotherapy.

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