# Characterization of immune responses in patients with COVID-19

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From the beginning of the COVID-19 pandemic, it has been important to characterize immune responses that occur in patients with COVID-19. By the series of studies, we precisely characterized immune cells from patients with COVID-19 at molecular and cellular levels. In detail, we revealed for the first time that type I interfeons contribute to the cytokine storm in patients with severe COVID-19. Moreover, we reported for the first time that SARS-CoV-2-specific CD8 T cells are not exhausted, but functional in patients with COVID-19. These results have provided academic basis for the treatment of patients with COVID-19 and the vaccine development.

## 1. Background (objectives)

COVID-19, which is caused by SARS-CoV-2 infection, is the ongoing pandemic disease at the present time. When SARS-CoV-2 emerged, it was necessary to quickly identify the characteristics of human immune responses against SARS-CoV-2. Major immunological questions were as follows: "Why do some patients suffer from severe or critical COVID-19 while others experience asymptomatic or mild infection?", "Why does cytokine storm occur in patients with severe or critical COVID-19?", "Do antibody or T-cell immune responses are successfully elicited in patients with COVID-19?", and "How long do memory immune responses last after recovery from COVID-19?". Amid the COVID-19 pandemic, our research team has tried to address these questions.

## 2. Contents

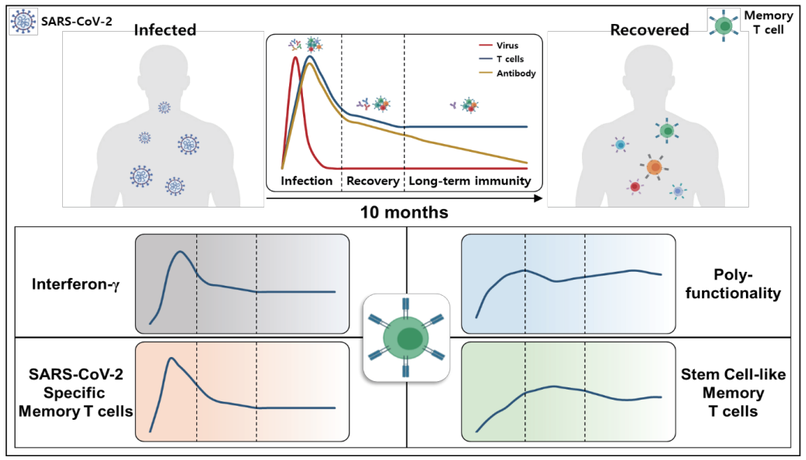
Although most SARS-CoV-2-infected individuals experience mild COVID-19, some patients suffer from severe COVID-19, which is accompanied by systemic inflammation. To identify factors driving severe progression of COVID-19, our research team analyzed gene expression profiles at the single-cell level using peripheral blood immune cells obtained
from healthy donors, patients with mild or severe COVID-19, and patients with severe influenza. As a result, we found that immune cells from patients with severe COVID-19 exhibit hyper-inflammatory signatures, particularly exaggerated type I interferon response that has been originally known as anti-viral response (Sci Immunol 5:eabd1554, 2020). This result unexpectedly indicated that the type I interferon response plays a pivotal role in exacerbating inflammation in patients with severe or critical COVID-19. According to this result, we proposed that the timing of administration and targeted subgroups need to be considered with caution when interferon protein is used for the treatment of COVID-19 patients (Nat Rev Immunol 20:585, 2020).

Next, our research team focused on the function of SARS-CoV-2-specific T cells in patients with COVID-19 using a cutting-edge technology for detection of virus-specific T cells. This was an important issue because it had been reported that T cells are dysfunctional in patients with COVID-19 in the early days of the pandemic. As a result, we found that SARS-CoV-2-specific T cells are normally functioning in patients with COVID-19 (Immunity 54:44, 2021). In addition, we also reported that SARS-CoV-2-specific T cell memory is sustained in COVID-19 convalescent individuals at least for 10 months (Nat Commun 12:4043, 2021). In particular, we demonstrated that stem cell-like memory T cells are successfully developed in COVID-19 convalescent individuals, suggesting long-term maintenance of SARS-CoV-2-specific memory T cells after recovery from COVID-19.

## 3. Expected effect

In the early days of the COVID-19 pandemic, clinical studies were conducted to use interferon protein as an antiviral agent. The result of our study led to a discussion in the medical community that interferon protein should be administered only to patients with mild symptoms in the early stages of SARS-CoV-2 infection (Nat Rev Immunol 20:585, 2020). In addition, by revealing that the T-cell immune response is normally functioning in patients with COVID-19 and the memory T-cell response is sustained at least for 10 months after recovery, we proposed T cell-oriented strategies for controlling the COVID-19 pandemic (Nat Rev Immunol 21:687, 2021). Moreover, we suggested development of novel SARS-CoV-2 vaccines that target T-cell immune responses and prevent the progression to severe COVID-19 (Nat Biotech 2021-12-13, https://doi.org/10.1038/d41587-021-00025-3).

**Figure.**
T cell immunity after recovery from COVID-19




### Research outcomes

Paper

Lee JS, Park S, Jeong HW, Ahn JY, Choi SJ, Lee H, Choi B, Nam SK, Sa M, Kwon JS, Jeong SJ, Lee HK, Park SH, Park SH, Choi JY, Kim SH, Jung I, Shin EC*. Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19. Sci Immunol 5:eabd1554, 2020 (Impact factor = 17.727)

Rha MS, Jeong HW, Ko JH, Choi SJ, Seo IH, Lee JS, Sa M, Kim AR, Joo EJ, Ahn JY, Kim JH, Song KH, Kim ES, Oh DH, Ahn MY, Choi HK, Jeon JH, Choi JP, Kim HB, Kim YK, Park SH, Choi WS, Choi JY, Peck KR, Shin EC*. PD-1-expressing SARS-CoV-2-specific CD8+ T cells are not exhausted, but functional in patients with COVID-19. Immunity 54:44-52, 2021 (Impact factor = 31.745)

Comment papers on the COVID-19 pandemic

1) Lee JS, Shin EC. The type I interferon response in COVID-19: implications for treatment. Nat Rev Immunol 20:585-586, 2020 (Impact factor = 53.106)
2) Noh JY, Jeong HW, Kim JH, Shin EC. T cell-oriented strategies for controlling the COVID-19 pandemic. Nat Rev Immunol 21:687-688, 2021 (Impact factor = 53.106)

### Research funding

Samsung Science and Technology Foundation (The origin, action, and fate of highly cytotoxic NKG2D+CD8+ T cells and their role in viral infection)