

A fused protein named CiDRE renders alveolar macrophages susceptible to SARS-CoV-2 invasion

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Individuals with the T allele at rs13050728 in the IFNAR2/IL10RB locus, which is strongly associated with COVID-19 severity, have high expression of the "hybrid" receptor CiDRE. In addition, in human alveolar macrophages with the T/T genotype, CiDRE enhances IL-10 signaling and attenuates type I IFN signaling as a decoy receptor, promoting severe COVID-19. Credit: Department of Immunology, TMDU

Despite intensive research since the pandemic began, much remains unknown about COVID-19, particularly why it can be so severe in some cases and relatively mild in others. Now, researchers from Japan have identified a genetic quirk that could make some patients more likely to experience severer forms of COVID-19.

In a study published in *Immunity*, researchers from Tokyo Medical and Dental University (TMDU) have revealed that expression of a fusion transcript by a specific immune cell subtype makes patients more likely to experience severe COVID-19 symptoms.

Cytokine storm is an intense immune reaction that can occur during COVID-19 infection, with serious consequences for the patient. This immune reaction occurs when severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the angiotensin-I-converting enzyme 2 (ACE2) receptor, which is expressed by a variety of cell types, although it remains unclear which cells are responsible for <u>cytokine</u> <u>storm</u>.

"Alveolar macrophages, which are <u>immune cells</u> that reside in the lungs, have been considered not to be susceptible to infection by SARS-CoV-2 because of their low ACE2 expression," says lead author of the study



Yuichi Mitsui. "However, recent studies have suggested that these cells may indeed be invaded by SARS-CoV-2 and participate in promoting cytokine storm."

To determine whether <u>alveolar</u> macrophages do in fact play a role in severe COVID-19, the researchers analyzed <u>gene expression</u> in hamsters infected with SARS-CoV-2 compared with uninfected hamsters. They then looked at data from <u>human patients</u> to see what their observations in hamsters meant clinically.

"The results were very clear," explains Takashi Satoh, senior author. "The anti-inflammatory factor interleukin-10 (IL-10) was highly upregulated in the infected animals. Importantly, IL-10 induced normal <u>alveolar macrophages</u> to express ACE2, making them susceptible to invasion by SARS-CoV-2."

Analysis of patients' samples showed that the genetic polymorphism of IFNAR2 gene, which is located near IL10RB, a subunit of the IL-10 receptor gene that amplifies IL-10 signals, was significantly associated with COVID-19 severity.

The researchers found that in individuals with the genetic risk of COVID-19 severity, a readthrough transcript that essentially fuses the two genes together produces a fused protein that they named "COVID-19 infectivity enhancing dual receptor" (CiDRE). Alveolar macrophages expressing CiDRE exhibited high levels of the gene encoding ACE2 and substantial SARS-CoV-2 invasion in the presence of IL-10.

This study showed that high IL-10 and CiDRE expression are potential risk factors for severe COVID-19. It seems likely that treatment with IL-10R and CiDRE inhibitors could help prevent cytokine storm in patients with COVID-19. Additionally, this first report of a genotype-



based functional readthrough transcript in immune cells suggests that other readthrough transcripts may play a functional role in immune cells.

More information: Yuichi Mitsui et al, Expression of the readthrough transcript CiDRE in alveolar macrophages boosts SARS-CoV-2 susceptibility and promotes COVID-19 severity, *Immunity* (2023). DOI: 10.1016/j.immuni.2023.06.013

Provided by Tokyo Medical and Dental University

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