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Mild or severe COVID-19? An antibody story

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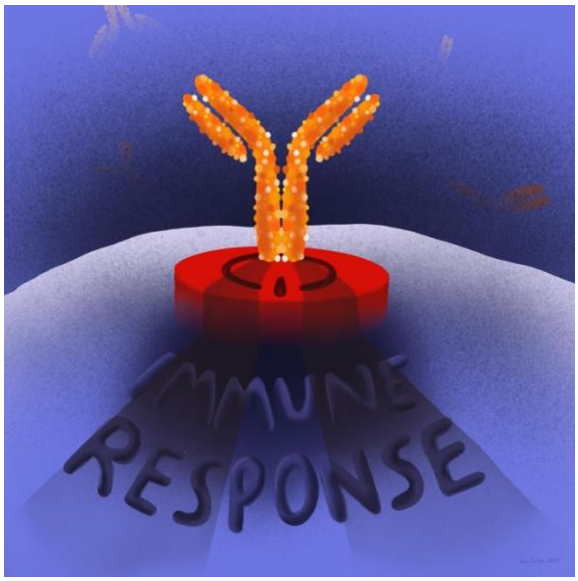
ABSTRACT

The effects of COVID-19 in humans are highly variable, with symptoms ranging from none to those severe enough to require intubation and intensive care. Our study identified that immune cells responding to the viral infection (seen in patients with mild-moderate symptoms) are systemically absent in severe patients, and their blood contain auto antibodies that prevent the production of these cells.



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At this point, we're no strangers to COVID-19, the disease caused by the viral agent SARS-CoV-2. Why some people got very sick with COVID-19, even die, while others had an only mild illness, barely even noticing they are sick, was an enigma even as the pandemic was raging across the world. Understanding what differentiates a mild course of the disease from a severe one would put us one step closer to a treatment for the worst-hit Covid-19 patients. Since the immune system is the body's defense against pathogens, we were drawn to the idea that the immune system could be crucial to this difference.

The immune system is a complex ballet with many performers. Various types of T and B Lymphocytes, Monocytes, Neutrophils, and more communicate flawlessly using messenger proteins, cytokines to produce a coordinated attack against a subcellular threat to the body. In the specific event of a viral infection, cells produce a class of cytokines, interferons, that actively prevent the viral replication. They also warn cells in the vicinity to raise their defenses and recruit immune cells to the site of infection to fight the infection. We chose to study the differences in blood immune composition between mild and severe patients as the Circulatory System transports immune cells from all over the body to the site of infection. The circulating immune

state is a good proxy for the harder-to-collect lung tissue.

Thanks to an unprecedented collaboration between more than 170 scientists and frontline healthcare workers at UCSF (https://www.comet-study.org/) we collected blood from patients with COVID-like symptoms within hours of admission. We then studied all collected samples through a technique called single-cell-RNA sequencing (scRNA-seq). This cutting-edge technology allows us to measure the relative expression of each human gene (for reference, there are around 30,000) in every single cell in the blood sample. This technology allows us to precisely identify different immune cell types and states as RNA expression guides the physical role of a cell.

We used supercomputers to study the scRNA-Seq results from our patients, grouping immune cells together into major landmark cell types -- neutrophils, platelets, monocytes, T cells, natural killer cells, B cells, plasma cells, and eosinophils -- based on similarities in their gene expression (RNA content). Each cell type could be further broken down into specialized subtypes. A deeper dive into the neutrophils, one of the first responders to infection, identified seven unique subtypes. While most of these states were similar in frequency between patients with severe and mild symptoms, one subtype was constantly low in patients with severe disease. The major difference we noticed between this subtype and others was a strong expression of Interferon Stimulated Genes (ISGs), genes expressed by cells in response to interferons (or a viral infection). Other landmark immune populations similarly showed a subtype strongly expressing ISGs that was consistently decreased or absent in severe patients.

This significant finding led us to ask, Why? Why does every immune cell type in the blood of severe patients appear unable to mount an adequately coordinated response to interferons? The reason was not a lack of cytokines -- we tested for that and found no differences in interferon production between severe and mild. Interestingly, the answer was an antibody-mediated dampening effect. Antibodies are Y-shaped molecules produced by the immune system to recognize and target pathogen-specific molecules. The upper portion of the 'Y' recognizes specific pathogen-related molecules (e.g., The covid-19 vaccine helps generate recognition to the spike protein of SARS-CoV-2). The lower portion of the "Y" (termed Fc or constant fragment) engages other cell surface proteins non-specifically to turn overall immune responses up or down.

We cultured blood from healthy donors in tubes containing interferon-α and serum (blood lacking its cellular content) from severe or mild patients. We found that "autoantibodies" (self-targeting antibodies) present only in severe patients blocked the induction of ISG in immune cells by engaging a specific Fc receptor named CD32b. We further found this mechanism could be reverted using a synthetic antibody directed at CD32b that prevents Fc-mediated autoantibody binding, effectively rescuing the expression of ISGs in the blood immune cells.

Overall, this study demonstrates how SARS-COV-2 can hijack an immune regulatory mechanism to favor its replication, manifesting in a severe pathology. While our results would need to be confirmed in a trial setting, it opens the possibility to therapeutically target CD32b and restore proper anti-viral immune response in patients with severe COIVD-19. Incidentally, such therapies, called Immune checkpoint blockade, have already revolutionized cancer treatment, acknowledged by the 2018 Nobel Prize in Physiology.