Medical & healthcare, Drug discovery

# Single cell analysis of human infection responses

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Researchmap https://researchmap.jp/jbwing?lang=en

## Abstract

The production of antibodies is a tightly regulated process involving complex cellular interactions. During acute COVID-19, we have discovered a sex-dependent disruption in the balance between cells that inhibit antibody production (T-follicular regulatory cells) and a network of cells that stimulate antibody production (T-peripheral helper, atypical B-cells and plasmablasts). Using single-cell proteomics by mass cytometry, we observed that male patients experience a significantly greater loss of circulating follicular regulatory T cells (cTfr), which typically control antibody responses. This disruption is accompanied by the emergence of a male sex-associated cellular network that strongly correlates with neutralizing antibody concentrations. The identification of this sex-specific immune signature provides new insights into the differential disease progression observed between male and female patients.

## Background & Results

The antibody response to COVID-19 is a key part of our defense against infection. Sex-specific differences in infection outcomes have been well documented, with male sex being a recognized risk factor for severe disease. However, our understanding of these processes has remained incomplete due to the complex interaction of rare cell types that are difficult to resolve using common techniques. While the conventional pathway of antibody production driven by T-follicular helper cells is inhibited during COVID-19, neutralizing antibodies are still produced, though their quality and specificity may vary. Our research reveals that antibody concentrations in severe COVID-19 patients' serum are closely associated with a network of extrafollicular T and B cells. Notably, T-follicular regulatory cells—critical for suppressing antibody production—show the most dramatic reduction in male patients, suggesting a fundamental difference in immune regulation between sexes. This dysregulation appears to be particularly pronounced in severe cases, potentially explaining the higher rate of severe outcomes in male patients.

## Significance of the research and Future perspective

A better understanding of the cellular interactions controlling antibody production in COVID-19 may enable the development of new treatments to control the disease. The discovery that male patients exhibit strong but dysregulated antibody production, characterized by reduced T-follicular regulatory cells and enhanced extrafollicular responses, suggests that sex-specific treatment approaches may be necessary. These findings clarify the complex network of cells responsible for antibody production in COVID-19 patients and highlight the importance of considering sex-based differences in therapeutic strategies. This insight into sex-specific immune responses could lead to more personalized and effective treatments for COVID-19 patients, potentially improving outcomes for both male and female patients through targeted immunomodulation. Furthermore, these findings may have broader implications for understanding sex-based differences in immune responses to other viral infections and autoimmune conditions, potentially opening new avenues for sex-specific therapeutic interventions in a wider range of diseases.

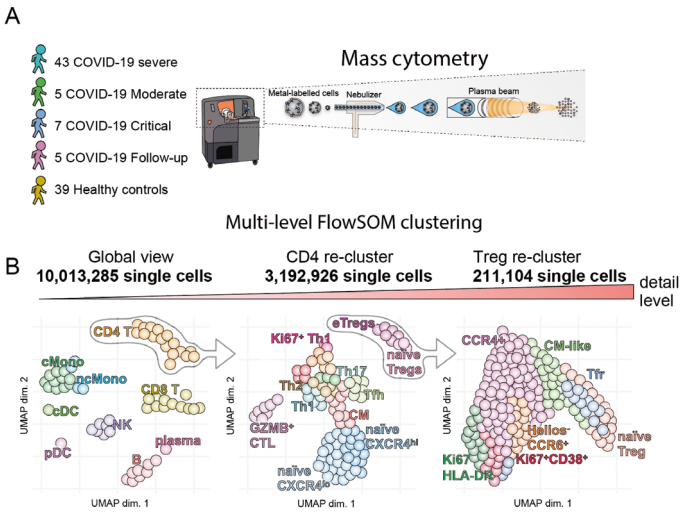


Figure 1. Study design A) Large cohorts of COVID-19 patients analysed by single cell proteomics (Mass Cytometry/CyTOF) B) In depth multistep analysis of human immune cells T-cells

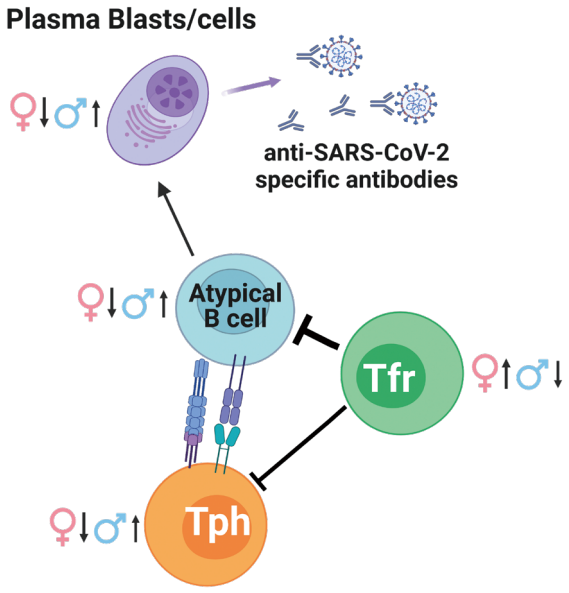


Figure 2. Gender differences in antibody production regulation mechanisms during the acute phase of COVID-19 infection
Tfr: Follicular regulatory T cell
Tph: Peripheral helper T cell
Atypical B cell: Atypical B cell
Plasma blast: Plasma cell

Patent

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URL https://www.cider.osaka-u.ac.jp/en/researchers/James.html

Keyword T-follicular regulatory cells (Tfr) , T-follicular helper cells (Tph), atypical B-cells, plasma cells