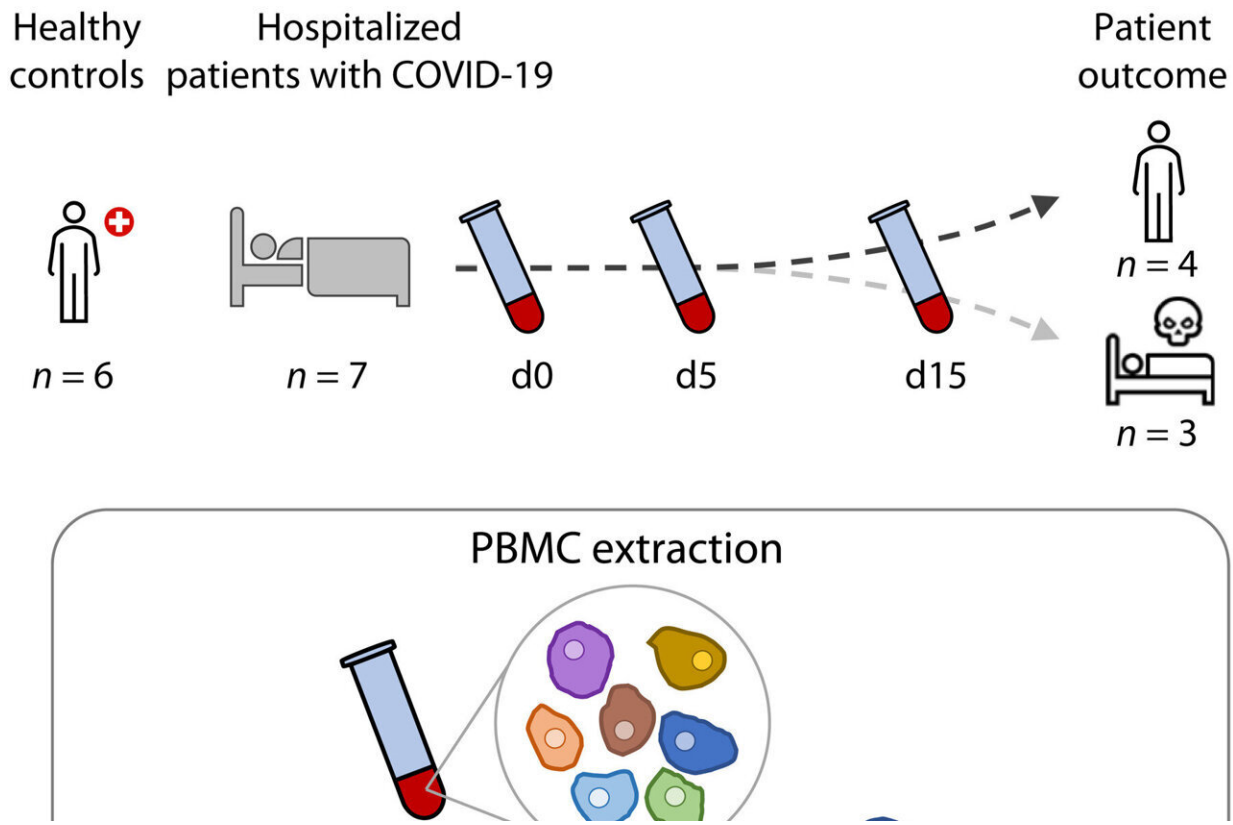
Three drugs that could reduce mortality in severely ill COVID-19 patients

June 9 2022



Study design summary. Blood samples were collected from healthy controls and from severely ill patients with COVID-19 at the time of hospitalization (d0) and at follow-ups (days 5 and 15) during their stay in the critical care unit. PBMCs were isolated from the blood and captured for single-cell RNA sequencing (scRNA-seq). CD14+ monocytes were also enriched from PBMCs for epigenetic analyses: chromatin accessibility by assay for transposase-accessible chromatin sequencing (ATAC-seq) and DNA methylation by whole-genome bisulfite sequencing (WGBS). Credit: *Science Advances* (2022). DOI:

10.1126/sciadv.abm2510

Despite the availability of highly efficacious vaccines, SARS-CoV-2 still causes serious medical complications. The lack of an effective drug treatment for hospitalized patients with severe COVID-19 has contributed to the more than six million deaths worldwide since the beginning of the pandemic, including more than 50,000 deaths in May 2022 alone. To address this therapeutic gap, a team of researchers from the Research Institute of the McGill University Health Center (RI-MUHC), the Canadian Center for Computational Genomics (C3G), and the McGill Genome Center studied host biological responses of patients hospitalized with severe COVID-19, looking for differences between patients who recovered and those who succumbed to the disease.

They found that certain cellular pathways were overactivated at the time of intensive care unit (ICU) admission in the deceased patients. The researchers then identified three existing drugs targeting these pathways. Their study, published in *Science Advances*, provides the required preclinical data to support the testing of these drugs—tacrolimus, zotatifin and nintedanib—in controlled clinical studies.

"We identified overactivation of messenger RNA metabolism, RNA splicing and interferon signaling pathways in patients who would not survive," says Vinicius Fava, Ph.D., a research associate at the RI-MUHC, co-first author of the study. "The identification by different assays of these differentially activated pathways in the cells of COVID-19 survivors and deceased patients suggests that they are determinants of prognosis and makes them promising targets for pharmacological intervention at the earliest point of hospitalization of critically ill patients."

Understanding physiology of immune cells in severe COVID-19

The researchers performed a series of cellular and genomic analyses on seven patients hospitalized in the ICU of the McGill University Health Center, in Montreal, Canada, at the start of the pandemic, between March and April 2020. These patients, of whom three died and four recovered, had the same level of disease severity on the WHO ordinal scale at the time of ICU admission.

The team of researchers characterized the transcriptome (expression of messenger RNA molecule) and the epigenetic landscape (alterations in the DNA structure that affect the ability of cells to regulate gene expression) of the patients' immune cells at different timepoints: at their admission, at day 5 and at day 15 post admission, to monitor disease evolution. They compared the data between the deceased patients, those who survived and six healthy individuals.

Specifically, the team used single-cell RNA sequencing to understand the cellular composition and the physiological state of Peripheral Blood Mononuclear Cells (PBMCs) following hospitalization. PBMCs are critical components of the immune system that mediate the response to pathogens entering the human body. The analyses focused on three major PBMC cell populations: B cells, myeloid cells and T cells. The team found significant differences in proportions of T cells and myeloid cells between patients who exhibited critical versus moderate symptoms. Critically ill patients at day 5 and day 15 showed a significant reduction of T cells ($P = 0.006$) and a significant increase of myeloid cells ($P = 0.04$), suggesting that COVID-19 severity has an impact on PBMC proportions.

"Our results show a strong correlation of PBMC composition with

disease progression. Critically ill patients with poor prognosis showed a significant reduction of T cells and a significant increase of monocytes, consistent with previously reported findings in patients suffering from severe COVID-19," write the authors of the study.

In contrast, at the time of hospital admission, the researchers detected significant changes in the expression of genes in key molecular pathways that are associated with epigenetic changes in monocytes, a type of white blood cells that transform into macrophages, which are cells capable of traveling to an area where an infection is present to kill the pathogen and control proliferation.

"This study confirms the pivotal role of monocytes in COVID-19 severity and disease prognosis, as well as the involvement of interferon pathways in the development of COVID-19," says David Langlais, Ph.D., Assistant Professor in McGill's School of Biomedical Sciences based at the McGill Genome Center and co-senior author of the study. "It also suggests that variations in transcriptional activity, and the accompanying epigenomics changes, mostly occurred at an early stage of COVID-19 disease, dictating how the disease will evolve in terms of severity and final outcome."

Repurposing the right drug for the right target

The researchers used various approaches to identify drugs that could suppress the cellular pathways overactivated in monocytes of patients who succumbed to COVID-19.

The initial approach resulted in more than 1,500 candidate drugs, which were narrowed down to 53 candidate drugs/compounds previously used to treat cancers and/or inflammatory conditions. Using drug-protein and protein-protein interaction databases, the team was finally able to identify three promising candidate drugs (tacrolimus, zotatifin, and

nintedanib) that act on the targeted pathways.

"Our work demonstrates the power of combining transcriptomic and epigenomic analyses to identify biological factors that influence the evolution of COVID-19 hospitalization and the survival of patients with severe disease," says Erwin Schurr, Ph.D., a scientist in the Infectious Diseases and Immunity in Global Health Program at the RI-MUHC and Professor at McGill's Department of Medicine, and co-senior author. "We are looking forward to clinical trials that hopefully will confirm the efficacy of the three drugs to reduce mortality of severely ill COVID-19 patients."

More information: Vinicius M. Fava et al, A systems biology approach identifies candidate drugs to reduce mortality in severely ill patients with COVID-19, *Science Advances* (2022). DOI: 10.1126/sciadv.abm2510

Provided by McGill University

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