Researchers identify how steroids benefit severe COVID-19 patients

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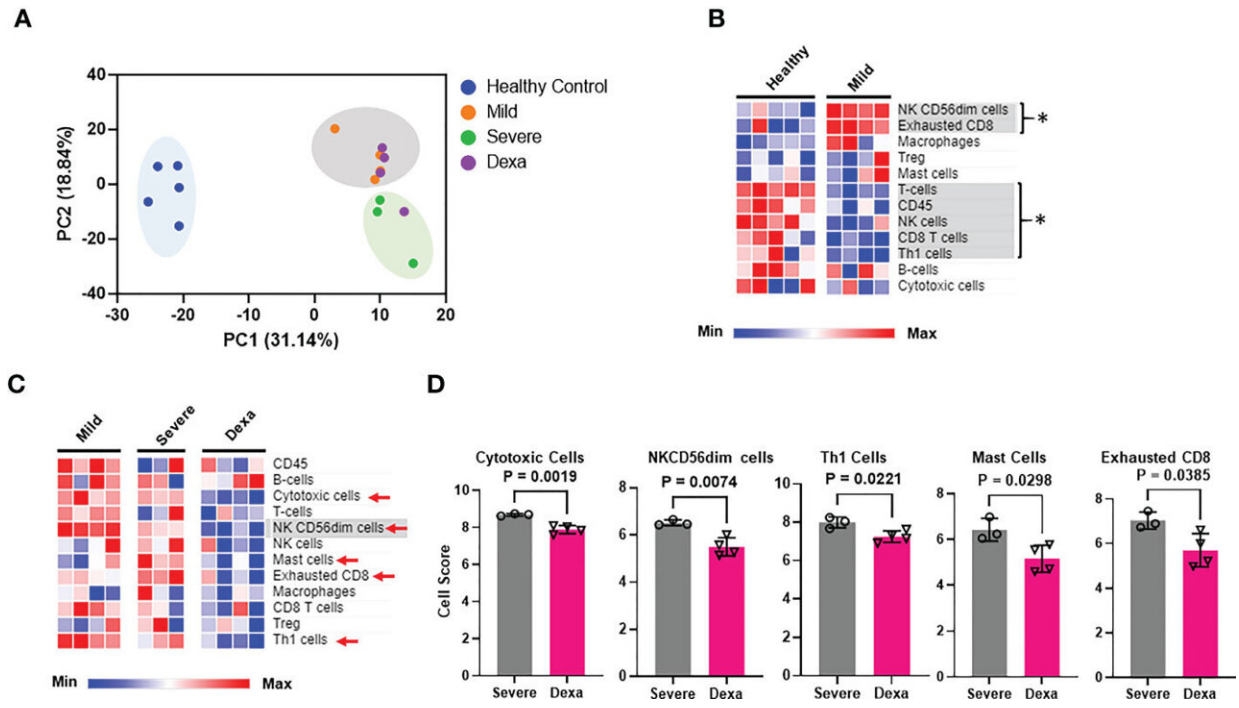

Immune cell profiling of PBMCs from healthy controls, mild and severe COVID-19 patients and severe COVID-19 patients treated with dexamethasone. **(A)** Principal components analysis (PCA) of NanoString transcriptomic data. **(B)** Heatmap depicting immune cell abundance in PBMCs from healthy donors (n=5) and mild COVID-19 patients (n=4). Significantly altered cell types are highlighted in gray and represented by *. **(C)** Heatmap depicting abundance of immune cell types in PBMCs from patients with mild (n=4), severe COVID-19 (Severe, n=3), and severe COVID-19 + dexamethasone (Dexa, n=4). Significantly altered cell types between mild and severe are highlighted in gray, and those altered between severe +/- dexamethasone are marked by red arrows. **(D)** Cell types significantly altered by dexamethasone treatment in severe

COVID-19 patients. Bars represent means ± SD. In **(A, D)**, each symbol represents an individual patient or healthy donor. Dexa = dexamethasone. Significance was determined by unpaired t-test and by Mann-Whitney rank sum test where samples failed normality. The abundance of the different immune cell types (at the RNA level) in the various patient cohorts was calculated as $\log_2$ cell type scores. The cell scores for a specific cell type can only be compared between two groups (such as mild vs. severe COVID-19) but do not support claims that a cell type is more abundant than another cell type within the same group. Credit: *Frontiers in Immunology* (2023). DOI: 10.3389/fimmu.2023.1143350

In the early months of the COVID-19 pandemic, doctors tried a variety of medications to determine what was helpful to prevent the deaths caused by a virus which humans had no natural immunity against.

At the same time, researchers tried to decipher the nature of the complex immune responses to the SARS-CoV-2 virus and develop effective drugs and vaccines. It was reported that using dexamethasone, a common steroid, prevented deaths in patients who had severe COVID-19 and were on ventilators in the intensive care unit, but it was not known why it helped.

In the summer of 2020, a team of University of Cincinnati researchers led by Ameet Chimote, Ph.D., from the laboratory of Laura Conforti, began studying the mechanisms of how dexamethasone works to treat COVID-19. They recently published their findings in the journal *Frontiers in Immunology*.

Shifting focus

Conforti's laboratory researches factors that decrease immune cell functions in cancers and has identified that alterations in molecules on

the surface of immune cells called ion channels contribute to this decrease in function.

While at home during the pandemic lockdown and unable to physically be in the laboratory and continue their cancer research, the team shifted its focus to COVID-19.

"In those uncertain days, COVID-19 was on everyone's minds. We all wanted to do our best to help move forward and do our small part in contributing to the scientific research that was happening all over the world to understand this disease," said Laura Conforti, Ph.D., corresponding author on the study and a professor in the Division of Nephrology in the Department of Internal Medicine.

"So we decided, why don't we take our expertise on how ion channels affect immune cell functions in cancer and apply our knowledge to understanding the immune response to COVID-19?"

Cytokine storms

In patients with severe COVID-19, the virus attacks the lungs, triggering a response from the body's immune cells aimed at eliminating the virus from the body.

"The immune cells congregate in the lungs and secrete proteins called cytokines that try to kill the virus, which in turn also attract other immune cells to strengthen the attack," said Chimote, lead author on the study and a research scientist in Conforti's lab.

"What happens during severe COVID-19 infections is that, as a response to high levels of the virus, a whole bunch of immune cells are recruited that secrete a lot of cytokines to kill the virus, but while doing so, they trigger a very bad inflammatory response in the lung, which damages the

lung tissue," he added.

The damaged lung tissue causes the lungs to begin filling up with fluid and the patients start having trouble breathing, which often leads to patients needing supplemental oxygen or to be placed on a ventilator. This process of lung damage caused by an abundance of immune cells and inflammation in the lungs is called a "cytokine storm," and it remains the main cause for deaths in patients that have severe COVID-19.

A paper published in the *New England Journal of Medicine* in July 2020 identified that the steroid drug dexamethasone prevented deaths caused by cytokine storms in severe COVID-19 patients.

"Dexamethasone has since then become a standard of care for any person with severe COVID-19 who is on a ventilator in the ICU," Chimote said. "Steroids are known to inhibit your immune system, but what are the mechanisms? And why was dexamethasone lifesaving in severely ill COVID-19 patients experiencing cytokine storms? Nobody knew."

Working together to make a difference

Conforti, Chimote and their colleagues set out to describe why dexamethasone prevents cytokine storms, especially by studying its effect on ion channels and ion channel-mediated immune cell function (that includes cytokine production), the focus of their research.

"The only thing that worked at that time to prevent deaths in severe COVID-19 was dexamethasone. At that time there was no COVID-19 vaccination, at that time no single drug or antibody treatments were shown to be beneficial," he said. "So we wanted to see what are the pathways by which dexamethasone was inhibiting cytokine storm and

proving to be a lifesaver."

The team obtained samples through the UC-based Cincinnati COVID-19 Repository, which collected blood and plasma specimens of COVID-19 patients at the height of the pandemic and was led by Kristin Hudock, MD, and Margaret Powers-Fletcher, Ph.D.

"Along with banking the COVID-19 patient samples, they had compiled a large database of the clinical features of these individuals, so we knew what medications they were receiving, how sick they were, their demographics, their clinical outcomes, including how many days they were in the ICU and what oxygen or ventilatory support they had," Chimote said.

Using samples from patients with mild COVID-19, severe COVID-19 and severely ill patients who had been treated with dexamethasone, the team measured around 700 different genes through RNA analysis.

"We identified what kind of immune cells and what kind of immune cell function-related pathways were altered by the disease severity," Chimote said. "We further conducted data analysis to determine what disruptions were happening within the immune system of mild and severe patients. We also wanted to evaluate the alterations in the immune cells from the severely ill patients after they were administered dexamethasone in the ICU."

The research found that dexamethasone specifically inhibited many inflammatory pathways and several critically important genes contributing to the cytokine storm, inflammatory signaling and antiviral responses in immune cells. This could prevent the immune cells from attacking and destroying the patient's lungs, thus avoiding deaths due to cytokine storm.

"All of the genes that trigger cytokine storm in severe COVID-19 were inhibited by dexamethasone," Chimote said. "We also saw that dexamethasone inhibited the expression and function of ion channels that regulate immune responses, especially cytokine production."

Moving forward, Chimote said the COVID-19 virus is continuing to mutate quickly, highlighting the need to identify a specific target or drug to make treatments more effective.

"Just giving monoclonal antibody infusions is not going to help long term because the viral mutations are happening, and newer and newer strains are coming," he said. "But if we try to understand the mechanism by which the inflammation or the severity of the disease is produced, then maybe we can identify something that can be consistently targeted."

"Our findings that dexamethasone may act by inhibiting the ion channels also raises an exciting prospect that drugs that inhibit the function of these ion channels (that are currently in clinical trials in autoimmune diseases) can be used as a treatment modality in severe COVID-19," added Conforti, "and this could also be of benefit in other pathologies where cytokine storm occurs such as microbial infections and autoimmunity."

Ongoing research is also needed to understand the immune system mechanisms that lead to systemic problems like long COVID-19.

More information: Ameet A. Chimote et al, Immune and ionic mechanisms mediating the effect of dexamethasone in severe COVID-19, *Frontiers in Immunology* (2023). DOI: 10.3389/fimmu.2023.1143350

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