

Unpacking the body's interferon response to COVID-19

August 19 2021



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Interferons are potent natural antivirals, rallying other parts of the immune system to defend against viruses. Some clinical trials have tested interferons as a treatment for COVID-19, but results have been mixed, and the science has been unclear about whether interferons are helpful or harmful. New research in *Cell*, led by Ivan Zanoni, Ph.D. at Boston Children's Hospital, provides a more complete picture of interferons'

role in mild versus severe COVID-19, informing future research, and potentially, treatment.

"We think what we've found could change the view of interferons in COVID-19, and may be useful for designing more defined therapeutic interventions," says Zanoni, an immunologist at Boston Children's and co-senior author on the paper.

The general scientific view has been that severe COVID-19 results from a delayed, weakened interferon response to SARS-CoV-2. Building on [a study published last year](#), Zanoni and colleagues show a more complex picture: Interferons play differing, even opposite roles in the upper and [lower respiratory tract](#), and that different types of interferons have different effects.

"We show how the production of specific interferons determines the severity of COVID-19," says Zanoni. "Disease severity also depends on when and where they are produced."

Zanoni, with co-senior author Nicasio Mancini, MD, of San Raffaele Hospital (Milan, Italy) and first authors Benedetta Sposito and Achille Broggi, Ph.D., in the Zanoni Lab, analyzed nasopharyngeal swab samples from 170 patients in Italy with mild COVID-19 and 31 controls who tested negative for the virus. They also studied bronchoalveolar lavage samples from the lungs of 56 patients with severe COVID-19, nine patients with severe lung disease from other infections such as influenza, and 56 patients with severe lung disease of non-infectious causes.

Using RNA sequencing and protein analysis, the team was able to identify the specific types of interferon being produced in different parts of the respiratory tract and what kinds of genes turned on in response.

In the [upper respiratory tract](#) (nose, throat, mouth), they found:

- Interferon is produced only when the viral load, or amount of virus present, exceeds a certain threshold. But high viral load itself did not correlate with disease severity.
- People with mild COVID-19 produce more interferons in response to high viral loads than those with severe disease, and [younger people](#) produce more interferons than do people 70 or older. "The correlation between viral load and interferon production in the upper airways disappears in older people, and likely helps explain why older people get sicker," says Zanoni.
- People with mild vs. severe COVID-19 produced different *types* of interferon in the upper airways. Those with mild COVID-19 produced high levels of two kinds of Type 3 interferons—lambda 1 and lambda 3—which have a protective effect. "If you have lambda 1 and 3, you upregulate about 50 genes that restrict SARS-CoV-2," says Zanoni.
- In contrast, patients with more severe COVID-19 produced predominantly Type 1 interferons and the Type 3 lambda 2 interferon, which appear not to be protective. "These patients did not show stimulation of genes that protect against the virus," Zanoni notes.
- In agreement with [findings published earlier this year at Boston Children's](#), the protective interferons were made by epithelial cells in the nasopharynx.

In the lower respiratory tract (bronchi and lungs), sampled in people with severe COVID-19, the researchers found high levels of interferons as compared to patients with other forms of severe lung disease. But these were mostly Type 1 interferons and the Type 3 interferon lambda 2, which, again, are not protective.

"There was no signature of antiviral genes," says Zanoni, "but instead a signature associated with cell death (apoptosis) and decreased cell proliferation. We believe these interferons are part of the detrimental

pro-inflammatory response seen in severe COVID-19."

The study also looked at interferons in patients' blood, but found no correlation with patterns of interferon production in the lung.

Overall, the study supports the view that an early, protective interferon response in the upper respiratory tract is associated with mild COVID-19. Without such a response, SARS-CoV-2 can spread to the lungs, where a different, harmful [interferon response](#) contributes to the severe inflammation and tissue damage typical of severe COVID-19.

"Our findings reconcile a large portion of the literature on interferons, and further stress the key role played by interferon 3, compared to interferon 1, during life-threatening viral infections," the researchers write.

Treatment implications?

The study observations suggest that patients could benefit from interferons—specifically Type 3 interferons—given locally, as in a nasal spray, early in the course of SARS-CoV-2 infection. This, however, raises logistical questions: While Type 3 interferons are clinically available, they are expensive drugs with potential side effects and would need to be given by a medical professional. By the time a patient feels sick enough to see a doctor, the treatment window may have closed.

"I think vaccines are still the best way to protect people," Zanoni says.

But at the other end of the spectrum, the study supports the idea of using drugs to block harmful [interferon](#) signaling later in the lungs, he adds.

More information: Benedetta Sposito et al, The interferon landscape along the respiratory tract impacts the severity of COVID-19, *Cell*

(2021). [DOI: 10.1016/j.cell.2021.08.016](https://doi.org/10.1016/j.cell.2021.08.016)

Provided by Children's Hospital Boston

Citation: Unpacking the body's interferon response to COVID-19 (2021, August 19) retrieved 11 May 2024 from <https://medicalxpress.com/news/2021-08-body-interferon-response-covid-.html>

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