Neanderthal-derived protein may reduce the severity of COVID-19

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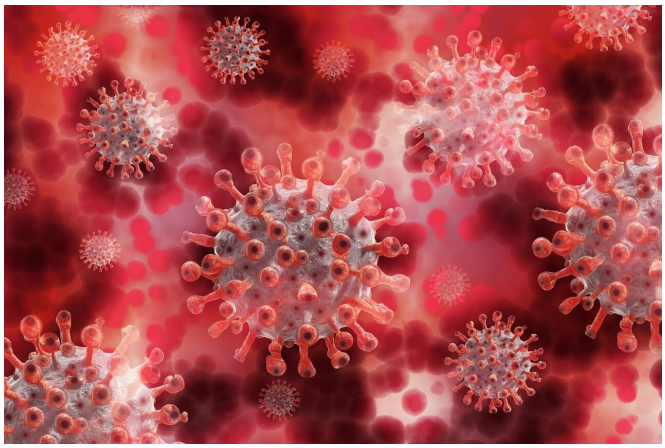

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Researchers at the Lady Davis Institute (LDI) at the Jewish General Hospital have discovered that increased levels of the protein OAS1 are associated with reduced mortality and less severe disease requiring ventilation among patients with COVID-19. Using drugs that boost OAS1 levels could be explored to try to improve these outcomes. The findings are published today in *Nature Medicine*.

"Our analysis shows evidence that OAS1 has a protective effect against COVID-19 susceptibility and severity," explains Dr. Brent Richards, a senior investigator at the LDI's Centre for Clinical Epidemiology and Professor of Medicine, Human Genetics, Epidemiology and Biostatistics at McGill University. "This is a very exciting development in the race to identify potential therapies to treat patients because there are already therapies in pre-clinical development that boost OAS1 and could be explored for their effect against SARS-CoV-2 infection."

Understandably, a great deal of effort is being invested in vaccine development. However, with hundreds of millions of people already infected around the world, it is important not to neglect the search for disease-specific therapies since few such therapies have been identified. Moreover, given the prevalence of vaccine hesitancy in the community and uncertainty as to how long any vaccine will prove to be protective, COVID-19 is most probably going to be a global issue for years to come. Thus, the need for therapeutic treatments will continue.

Researchers in Dr. Richards' lab explored proteins detectable in peripheral blood as a potential target. The challenge lay in determining which proteins play a causal role in disease progression, since their levels may also be influenced by COVID-19 itself or other confounding factors. Recent advances in proteomic technology—that is, the capacity to isolate and measure hundreds of circulating proteins at once—combined with genetic analyses through Mendelian randomization (MR) makes possible the delicate work of untangling which proteins affected COVID-19 adverse outcomes, rather than vice versa.

From genetic determinants of 931 circulating proteins, Dr. Sirui Zhou, a post-doctoral fellow at the LDI and first author on the paper, found that increase in OAS1 levels was associated with reduced COVID-19 death or ventilation, hospitalization, and susceptibility in up to 14,134 COVID-19 cases and 1.2 million controls. The results were consistent in multiple sensitivity analyses. They proceeded to measure OAS1 levels in 504 patients with different COVID-19 outcomes from the Biobanque Québec COVID-19, and found that increased OAS1 levels in post-infection patients were associated with protection against very severe COVID-19, hospitalization, and susceptibility.

"The protective effect was particularly large," points out Dr. Zhou, "such that we observed a 50% decrease in the odds of very severe COVID-19 per

standard deviation increase in OAS1 circulating levels. Interestingly, for non-African peoples, this protective effect is likely inherited from a Neanderthal derived form of OAS1 called p46."

This form of OAS1 likely emerged in people of European ancestry through interbreeding with Neanderthals tens of thousands of years ago. Evolutionary pressure slowly increased the prevalence of this form of OAS1, such that it is now detectable in more than thirty-percent of people of European descent. It is likely that the form of the protein has served as protection against earlier pandemics.

Because drug development, even in the accelerated environment of pandemic research, takes time it is particularly exciting that molecules which can increase OAS1 activity are currently in pre-clinical development for eventual deployment in clinical trials.

"Our recommendation is that those medications that trigger increased OAS1 levels be further studied for their effect on COVID-19 outcomes so that we may better treat infected patients," said Dr. Richards.

More information: Sirui Zhou et al. A Neanderthal OAS1 isoform protects individuals of European ancestry against COVID-19 susceptibility and severity, *Nature Medicine* (2021). DOI: 10.1038/s41591-021-01281-1

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