Recent study offers new insight into deadly fungal invasion of the lungs

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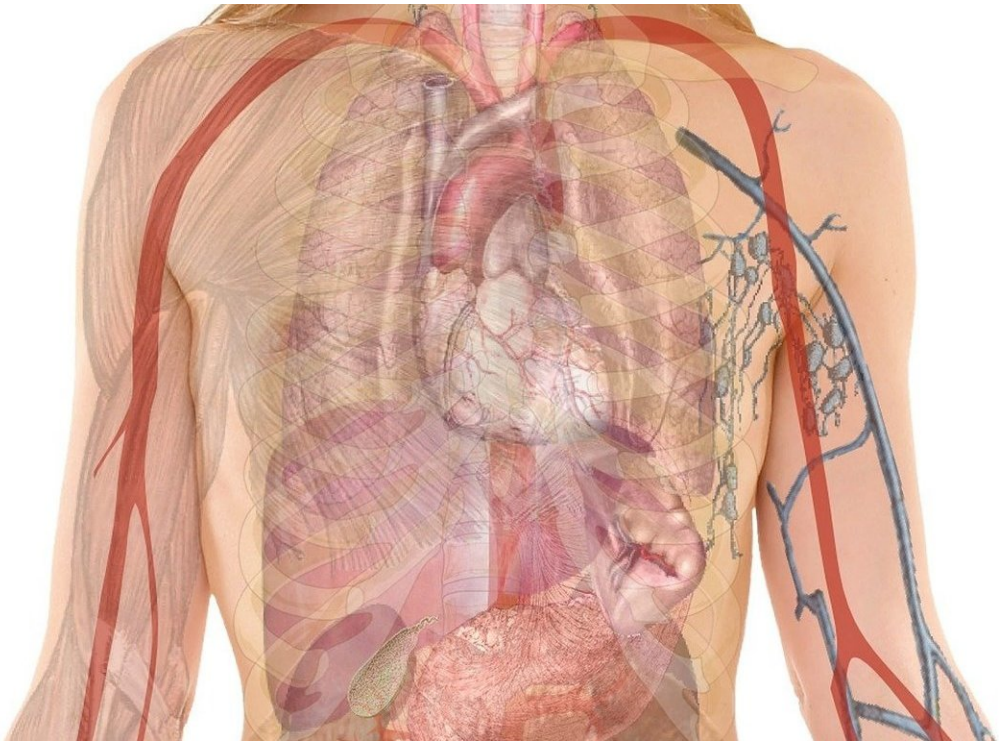

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Fungi such as Aspergillus are so common in our surroundings that we breathe in hundreds to thousands of spores every day. In healthy people, fungi typically pose no threat, but they can cause deadly infections in those with compromised immune systems. However, it is increasingly recognized that viral infections such as influenza or SARS-CoV-2 can

increase the risk of invasive Aspergillus infections even in healthy people.

The World Health Organization (WHO) has stated that invasive fungal infections are an increasing threat to human health and has reiterated that more research is needed. Until now little was known about how the Aspergillus fungus was able to take root, and what could be done to get rid of it. Researchers at the University of Calgary working with researchers at McGill University have provided new insight on why the immune system fails.

"We discovered that influenza and COVID-19 destroy a previously unknown natural immunity that we need to resist invasive fungal infections," says Nicole Sarden, a Ph.D. candidate at the University of Calgary and first author on the study.

The findings published in *Science Translational Medicine* show that two types of white blood cell (neutrophils and a unique type of B cells) normally work together to fight fungal infection. However, viruses like SARS-CoV-2 and influenza impede the special B cells from doing their job.

Working with mice and human blood and tissue samples, the researchers were able to see that following a viral infection, neutrophils sensed a fungal infection and were gathering nearby, but weren't acting to destroy the invader as expected. The scientists delved further and learned that viral molecules were rendering these B cells apathetic, preventing them from cooperating with neutrophils as they normally would, and thus protecting the fungi from destruction. Understanding this process led to the next discovery.

"We also found that current therapies exist that could be repurposed in a realistic and meaningful way to replace the natural antibodies not being

produced by the virally-damaged B cells and re-establish the neutrophils ability to fight these infections," says Sarden.

"This research was sparked by a young man I cared for in the ICU on life support who died of influenza-associated aspergillosis, where every therapy we tried failed," says Dr. Bryan Yipp, MD, clinician researcher at the Cumming School of Medicine and senior author on the study. "Our findings are very timely given the high numbers of patients affected by multiple respiratory viruses including influenza."

Sarden and Yipp believe these findings will lay the groundwork for new diagnostic tests, based on natural antibody levels to predict who is at the highest risk for invasive fungal infections, and that currently available antibody replacement strategies could be tested to treat Aspergillus infections in future clinical trials.

"These discoveries provide a new understanding of how we can best support the body to fight off deadly fungal infections," says Yipp.

More information: Nicole Sarden et al, A B1a–natural IgG–neutrophil axis is impaired in viral- and steroid-associated aspergillosis, *Science Translational Medicine* (2022). DOI: 10.1126/scitranslmed.abq6682

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