Iron triggers dangerous infection in lung transplant recipients

By Nicoletta Lanese

Researchers at the School of Medicine have identified elevated tissue iron as a risk factor for life-threatening fungal infections in lung transplant recipients.

The study, reported Feb. 21 in *Science Translational Medicine,* investigated why lung transplant patients are more vulnerable to this fungus, *Aspergillus fumigatus*. "People rarely think about how a change in the patient's body tissues might make it better ground for invasion," said Mark Nicolls, MD, professor of pulmonary and critical care medicine and senior author of the study. Informed by this research, Nicolls has proposed a potential new approach for curbing these infections.

Aspergillus fumigatus is an extremely common mold, prevalent in even the most pristine hospital settings. "It's everywhere — we inhale thousands of these spores per day," said Joe Hsu, MD, assistant professor of medicine and lead author of the study. One-third of lung transplant recipients develop *Aspergillus*-related diseases, including severe asthma and often-fatal lower respiratory infections. The leading cause of death among these patients is transplant rejection, which the mold accelerates dramatically.

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Aspergillus fumigatus is a common mold, prevalent even in pristine hospital settings.

There are many risk factors for *Aspergillus* infection that are difficult to address in lung transplant recipients. Transplant patients are given medications that leave them less able to ward off infections, but without these drugs, their immune systems would attack their new lungs. During recovery, patients have no ability to cough up invading pathogens, making them especially vulnerable to the omnipresent spores. This is because the lung transplant procedure disrupts signals from the vagus nerve, which controls the cough reflex. Patients are usually put on antifungal medications in an attempt to prevent infection, but these pathogens are becoming more drug-resistant over time.

'Like fertilizer for Aspergillus'

All lung transplants carry these known risks, but not all lung transplants result in *Aspergillus* infections. Something causes the organism to behave differently in cases of infection, Hsu said. The study identified iron as a critical factor. "Iron is like fertilizer for the *Aspergillus*," Nicolls said.

Hsu was interested in finding the *Aspergillus* trigger switch — the factor that prompts it to invade tissue. He studied the pathogen in mouse models by transplanting windpipes from one mouse to another. Observing the rejection process, he found that the transplanted tissue bled and accrued high levels of iron. Hsu biopsied human transplant patients and found the same distribution of iron, with higher levels in the transplanted tissue than the host. Thinking he may have found the trigger, Hsu introduced *Aspergillus* into the mice, comparing how it acted with and without access to iron.

He found that elevated iron prompted *Aspergillus* to invade. In experimental conditions that provided the pathogen more iron, it invaded the transplant. The more iron, the deeper the invasion progressed into the tissue. The results indicate increased iron is a major determinant of *Aspergillus* invasion. Differences in iron levels between transplant patients seem to explain why some become infected while others don't. "You could have lots of *Aspergillus* in the airway, which is fine because its everywhere, but it wouldn't penetrate the tissue unless there was iron beneath it," Nicolls said.

A potential treatment

The study suggests infection can be prevented by starving the *Aspergillus* organism of iron. Without iron to fuel it, the mold doesn't invade. The depth of invasion decreased in mice injected with an iron-reducing chemical. The result suggests a novel treatment route. Rather than targeting *Aspergillus* itself, doctors could modify tissue iron levels to change the organism's behavior, Hsu said. His next step is to study this treatment approach in humans, he said. High iron is characteristic of other pulmonary diseases, and Hsu predicts this methodology may be applicable across the field of pulmonary care.

Nicolls is an inventor on a new patent describing how lung transplant blood vessels may benefit from a low-iron environment, a property that could also include preventing mold invasion. He developed the technology with a number of collaborators, including Geoffrey Gurtner, MD, professor of surgery at Stanford, and Jayakumar Rajadas, PhD, director of Stanford's Biomaterials and Advanced Drug Delivery Lab, who is also a co-author of the study. The patent is a chemical solution that captures excess iron so the pathogen cannot use it. Nanoparticles act as a vehicle to transport the chemicals into the body.

STEVE FISCH

Mark Nicolls is the senior author of a study showing that elevated iron levels in the tissue can make lung transplant patients vulnerable to infection from the *Aspergillus fumigatus* fungus.

"The capacity to deliver these compounds directly to the lungs is novel," Hsu said. "For the first time, we have a new way to treat these infections aside from antibiotics that try to wipe out the organism itself." The solution can be applied like a paint during surgery, inhaled into the lungs or injected intravenously.

The team's work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Other Stanford-affiliated co-authors of the study are Karl Clemons, PhD, senior lecturer in medicine; Mohammed Inayathullah, PhD, basic life research scientist; Raymond Sobel, MD, professor of pathology; Hasan Nazik, MD, visiting research scholar; Venkata Pothineni, PhD, basic life science research associate; Shravani Pasupneti, MD, postdoctoral scholar; and David Stevens, MD, professor of medicine.

Researchers at the Veterans Affairs Palo Alto Health Care System, Medical University Innsbruck and University of Maryland School of Medicine also contributed to the study.

The work was supported by the National Heart, Lung and Blood Institute; the Austrian Science Foundation; and the Parker B. Francis Family Foundation.

Stanford's Department of Medicine also supported the work. ISM

Five-year neuroscience awards named in honor of Ben Barres

By Ruthann Richter

The Chan Zuckerberg Initiative, a Palo Alto-based philanthropic organization, has launched a major research effort to inject fresh energy, ideas and talent into understanding the basic biology of neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis, the organization announced Feb. 20.

The research will be funded through two programs, including one that will support early career investigators willing to pursue bold, innovative ideas. These five-year awards, known as the CZI Ben Barres Early Career Acceleration Awards, are named in honor of Ben Barres, PhD, a distinguished Stanford neuroscientist who died in December at the age of 63.

CZI will also fund a series of collaborative science awards — three-year grants for small, interdisciplinary groups of scientists, clinicians and engineers working together on innovative high-risk, high-impact projects in basic science.

'A spiritual guide'

Both grant programs are part of CZI's new Neurodegeneration Challenge Network, which aims to fill in the gaps in the still-limited understanding of the basic cellular and molecular mechanisms behind these devastating illnesses.

Cori Bargmann, PhD, president of Chan Zuckerberg Science, said the group chose to name the young investigator awards in Barres' honor because he was "a spiritual guide" for the work. An advocate for basic science and for the mentorship of young researchers, Barres had been an adviser to CZI since its inception in 2015 and had a hand in helping craft the awards program, Bargmann said.

"Ben was a truly exceptional scientist and human being. He exemplified the values of the Chan Zuckerberg Initiative, especially our work in neurodegenerative disease. His commitment to collaboration between basic science and medicine, his creative work in neurodegeneration, and his advocacy for women, underrepresented groups and young scientists inspire us all," Bargmann said.

Barres made significant discoveries about the role of glial cells, the underrecognized cells that comprise the majority of brain cells, and in doing so revolutionized the field of neuroscience. A professor of neurobiology, of developmental biology and of neurology, he was widely praised for the passion he brought to his work.

Barres was particularly known for his dedication to his trainees and was a champion for basic science, helping establish the Master of Science in Medicine program at Stanford to teach PhD students about human biology and disease and thus prepare them to turn new discoveries into clinically useful treatments.

Ben Barres

"Ben was a selfless and steadfast champion of young researchers. As his colleague and friend, I am moved that these awards will commemorate him and continue his legacy of celebrating and supporting early-career scientists," said neuroscientist Marc Tessier-Lavigne, PhD, president of Stanford University.

'A remarkable person'

Lloyd Minor, MD, dean of the School of Medicine, said the awards "are an inspired way to honor the memory of Ben, a remarkable person and a beloved mentor who embodied the spirit of the awards in his brilliance, creativity and passion for neuroscience."

The CZI Ben Barres Early Career Acceleration Awards are open to scientists from throughout the world working in a variety of disciplines. The awards are open to MDs and PhDs who are new to the field of neurodegeneration. Awardees will receive $500,000 a year for five years, for a total of $2.5 million. The collaborative science awards will provide recipients with $350,000 a year for three years, or a total of $1.05 million.

CZI was founded by Silicon Valley couple Priscilla Chan, MD, and Mark Zuckerberg, chairman and CEO of Facebook, to advance science, education and social justice. One of CZI's first initiatives was the creation of the Chan Zuckerberg Biohub, an independent nonprofit research center supported by $600 million over a 10-year period. The center brings together physicians, scientists and engineers at Stanford, UC-San Francisco and UC-Berkeley to engage in innovative scientific exploration and invent new tools to advance discoveries.

Information about the awards is available at https://chanzuckerberg.com/science/rfa. ISM