Size matters -- in virulent fungal spores -- and suggests ways to stop a killer

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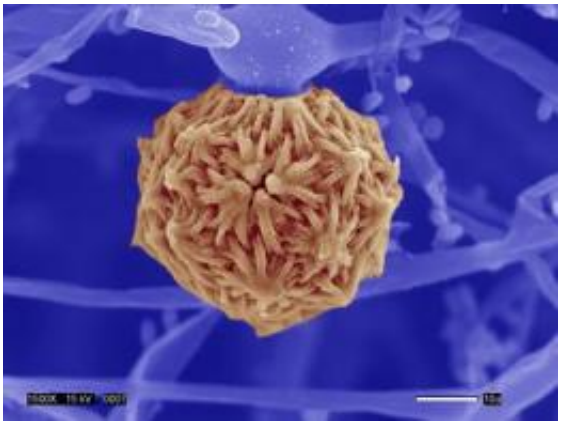


This colored photograph is of a sexual spore (also known as a zygospore) of the human pathogenic zygomycete, *Mucor circinelloides.* Credit: Valerie Knowlton, NC State University; Joseph Heitman and Soo Chan Lee, Duke University Medical Center

Scientists at Duke University Medical Center have found that larger fungal spores can be more lethal. Their findings about two different spore sizes of the fungus *Mucor circinelloides*, a pathogen that kills half or more of its victims, could help to develop new treatments and fight other types of fungal infections.

Mucor infection is in the news as an environmental fungus contracted by people who had trauma in the wake of tornadoes in Joplin, Mo. Three out of eight patients had died by June 11. This group of fungi can be

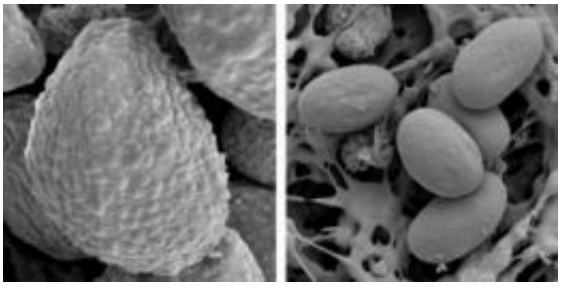
common in the environment but only particular hosts with high risks become infected. In Joplin, some people got the fungal infection through traumatic skin wounds.

The study showed a new way to categorize fungi. Scientists traditionally describe a fungus through its growth pattern: either fingerlike hyphal growth, like bread mold, or round and symmetric isotropic growth, like an expanding balloon.

Now the researchers say there is another way to categorize a fungus, by whether it produces larger or smaller spores.

"This kind of dimorphism is something new," said co-senior author Soo Chan Lee, Ph.D. The larger spores can be over than 20 microns, while the tiny spores are only 4-5 microns, the perfect size for penetrating into the recesses of the lungs. The mycologists found that the larger spores caused worse infections in laboratory animals and more readily evaded immune cells.

The work was published in *PLoS Pathogens* online on June 16.



Scanning electron microscopic images of giant spores (left) from a (-) mating type strain of the human pathogenic zygomycete *Mucor circinelloides* and smaller spores (right), from a (+) mating type strain. Images are in the same scale. Credit: Deborah Springer, Joseph Heitman and Soo Chan Lee, Duke University Medical Center

When the scientists performed an experiment that made the smaller spores grow into larger spores, "We found in that case, the smaller spore that became large acted like the larger spores," Lee said. "We believe that this spore bypassed the natural growth stage of isotropic growth and that was how it becomes more virulent."

"This means we might be able to find a way to arrest them in the smaller stage before they grow into more virulent, larger spores," he said.

Interestingly, other scientists have recently published related findings about the dual cell sizes in another virulent fungal pathogen, *Cryptococcus neoformans*, in which gigantic cells form in the lungs of infected animals and patients.

Normally immune cells called macrophages engulf and destroy dangerous fungal spores. Small spores can be contained by macrophages, but the larger spores switch too quickly to hyphal growth and thereby can destroy the macrophage. When the macrophages, a first-line defense, split open, they undergo cell death and are unable to protect an infected human or other host animal.

"This finding shows another example of adaptation through fungal cell gigantism, which lets pathogenic fungi establish infection in the hosts, particularly those that are immune compromised," said Joseph Heitman, M.D., Ph.D., co-senior author and chair of the Duke Department of Molecular Genetics and Microbiology. "We used a diabetic model of mice, which is also an immunocompromised type of animal. We found the fungal subspecies that we studied is highly virulent in mice, which correlates well with this subspecies' frequent occurrence in clinical human specimens."

Heitman said the hope is to find a way to arrest the isotropic growth stage. "Clinically, these mucor infections are reasonably common in diabetic patients, transplant patients, and lung-cancer chemotherapy patients," he said. "Having a high blood-glucose level is immunosuppressive, and predisposes diabetic patients to difficult-to-manage fungal infections."

The collaboration for this study grew from pioneering work done by co-authors Rosa M. Ruiz-Vazquez and Santiago R. Torres-Martinez who chose to work at Duke during a sabbatical from the Department of Genetics and Microbiology at the Universidad de Murcia in Murcia, Spain. There they pioneered genetic and genomic approaches to study Mucor. They began by studying the fungus' sensitivity to light, and then took up its pathogenic properties.

The next steps in this research will be to investigate the minus and plus sex determinants of the fungi, which are related to sexual reproduction and spore size, Lee said.

Provided by Duke University Medical Center