Fungal Squatters

This fungus makes itself at home in the lungs, evading immune defenses and causing disease.

The soil of the Ohio and Mississippi River Valleys is home to a fungus called *Histoplasma capsulatum*, whose long filaments extend into the environment to collect nutrients. Once airborne, however, the fungus can be inhaled by humans or other animals. Inside the lungs, it must quickly shift gears—and shape—to survive.

*Histoplasma* responds rapidly to the elevated temperature of its new home. Its slender body morphs into a spherical cell, better suited for evading mammalian immune defenses. At the same time, the fungus turns on myriad disease-causing genes. Not everyone who is infected with *Histoplasma* gets sick, but some experience lung disease or vision loss. Up to 25,000 people in the midwestern United States, where the fungus is more abundant, develop life-threatening systemic complications each year.

Anita Sil, a microbiologist and HHMI early career scientist, is fascinated by the dramatic changes that *Histoplasma*—and related organisms known as thermally dimorphic fungi—undergo when they find themselves in the warm lungs of a host. Her team can trigger the same transformation by moving the fungi from room temperature to a warm incubator in the lab. Many shape-shifting fungi can cause disease, Sil says, but little is known about how they recognize that they’ve been taken up by a host and then adapt to manipulate the host’s immune system.

Sil has been working on that puzzle for more than a decade, at the University of California, San Francisco. Her lab is specially equipped to ensure safe handling and containment of the hazardous pathogen. Along with being dangerous for healthy people, *Histoplasma* is slow growing and difficult to study. “But there is so much we don’t know,” Sil says. Finding answers about *Histoplasma* and related fungi is crucial not only because of the organisms’ unique biology, but also for human health. “It’s very hard to prevent exposure to pathogens that live in the soil,” Sil says. “Part of the solution is going to lie in better understanding their virulence mechanisms.”

In 2008, Sil and her colleagues unearthed their first clues to the pathogen’s strategy for switching to its virulent form (known as its yeast phase). They discovered three regulatory proteins—Ryp1, Ryp2, and Ryp3—that are necessary for *Histoplasma’s* change from its filamentous, soil-dwelling form to its spherical, yeast form.

By comparing those three Ryp proteins to similar proteins in other organisms, Sil and her colleagues predicted that the Ryp proteins control the fungi’s transformation by altering gene activity. They analyzed the activity of each of the fungus’s 9,000 genes and revealed more than 750 genes with activity specific to either the yeast or the filamentous form of the fungus. Genes on that list appear to influence many cellular features, including shape, structure, metabolism, and virulence.

Sil and her colleagues showed that the proteins physically interact with *Histoplasma* DNA, regulating gene activity directly. In addition, their experiments revealed a fourth protein, which they dubbed Ryp4, that is also necessary for *Histoplasma* to grow in its yeast phase.

In the July 2013 issue of the journal PLOS Biology, Sil and her colleagues reported how, at a warm temperature, the four Ryp proteins work together to enhance the activity of yeast-phase genes and to shut down genes specific to the filament phase. Now, her team is studying how the fungus senses the temperature increase that triggers its transformation. They’ve turned up a few signaling molecules...
that may carry out this function.

A next step will be determining whether the molecules and pathways they have identified in *Histoplasma* are responsible for shape and virulence changes in other thermally dimorphic fungi.

“All of these organisms are evolutionarily related, but we don’t really know whether they are using overlapping or distinct pathways,” she says. “Now that we’ve developed the tools and ways of thinking about how to find these pathways in related organisms, we’re especially interested in studying *Coccidioides.*” This fungus is endemic in the southwestern United States and causes valley fever, a disease that often resolves on its own, but can become severe. The disease is on the rise in Sil’s home state of California, as well as Arizona, Nevada, New Mexico, and Utah.

There’s another big question that provokes Sil’s curiosity: Why have these fungi evolved these remarkable capabilities? “These organisms do fine in the soil,” she says. “They don’t need a mammalian host to propagate. So how do these pathways benefit the organism in the environment?” There may be an advantage to hitching a ride in a mammalian host to a new habitat, she says, but *Histoplasma* and its relatives must wait for their host’s death before they can return to the soil. She wonders whether temperature sensing might more directly enhance survival or reproduction in the soil. Identifying *Histoplasma’s* temperature-sensing pathways are a first step toward finding out.

—Jennifer Michalowski

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