Cellular network transforms fungus when temperatures rise

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(Phys.org) —When the infectious fungus *Histoplasma capsulatum* feels the temperature start to rise, it undergoes a transformation. As it shifts its shape from long filaments to oval cells, the pathogen switches on genes that equip it to infect its host. New research from Howard Hughes Medical Institute scientists has revealed the cellular network that activates these temperature-sensitive changes.

H. capsulatum is endemic to the Ohio and Mississippi River Valleys of the United States. It lives in the soil, but can become airborne and infect humans or other mammals when it enters the lungs. Not everyone who is infected with H. capsulatum develops symptoms, but the fungus can cause serious respiratory or systemic disease in immunocompromised people or healthy hosts who inhale a large inoculum. Up to 25,000 people develop life-threatening infections each year.

"This fungus is well known clinically, but molecularly it is poorly understood," says HHMI early career scientist Anita Sil, who led the new research. H. capsulatum belongs to a family of understudied fungi that make a similar transformation in shape and virulence in response to temperature changes. These thermally dimorphic fungi are all capable of causing significant disease in healthy people. "Very little is known about how these pathogens respond to their hosts and manipulate the immune system," says Sil, who is at the University of California, San Francisco. She and her colleagues published their findings about how H. capsulatum converts to its infectious form in the July 2013 issue of the journal *PLOS Biology*.

In the soil, H. capsulatum forms long filamentous chains of cells, which Sil says likely help the fungus expand through its environment to access limited resources. This form is less suitable for living inside host cells, so there the fungus dramatically changes, adopting a spherical shape known as its yeast form. That change is triggered by the increased temperature of the new environment. It accompanies a similarly dramatic change in gene activity inside the fungal cells, which switch on a host of virulence genes that enable them to cause disease.

In 2008, Sil and her colleagues identified three regulatory proteins that are required for H. capsulatum's switch to the yeast phase: Ryp1, Ryp2, and Ryp3. The first of these belongs to a family of proteins known to control developmental switches in other fungi by altering gene expression. Ryp2 and Ryp3 also have family members in other fungi, but their molecular functions are unknown. H. capsulatum that is genetically engineered to lack Ryp1, Ryp2, or Ryp3 remains in its filamentous form, regardless of temperature.

Sil and her colleagues wanted a better understanding of how these proteins induce temperature-sensitive changes. To find out, they began by undertaking a comprehensive survey of exactly which genes the Ryp proteins switch on or off when the temperature changes. By comparing the activity of all of the organism's genes at different temperatures, in normal H. capsulatum and in mutants lacking each of the three Ryp proteins, the researchers identified more than 750 genes whose activity was specific to either the yeast or the filamentous form of the fungus. The list included genes that influenced cell shape, structure, and metabolism, as well as virulence genes.

In cells lacking any of the three Ryp proteins, gene activity patterns were essentially the same at room temperature as they were at body temperature. So it was clear that the proteins were essential regulators of the transformation in shape and virulence. But Sil and her colleagues did

not know whether they were acting directly on the relevant genes, or whether other players might be mediating their effects.

So their next step was to examine the proteins' physical interactions with the DNA. Those experiments revealed that each of the Ryp proteins physically interacts with regulatory regions near known virulence genes. "We were able to identify these genes as direct targets." Sil explains. By examining associated proteins, the researchers also discovered of a fourth protein that is required for H. capsulatum to grow in its yeast form, which they called Ryp4.

At temperatures associated with life inside a host, the four Ryp proteins work together to both enhance the activity of yeast-phase genes and prevent the inappropriate activity of genes specific to the filament phase, Sil explains. Now, she wants to understand how the fungus senses the temperature increase that signals that it is inside a host, rather than in the soil. Her lab is investigating whether the regulators they have already identified might function differently depending on temperature, or whether other players might be involved.

Sil acknowledges that H. capsulatum is challenging to study. In its filamentous form, the fungus is slow-growing and hazardous enough that it must be handled in level-3 biosafety facilities. It's difficult to work with for other reasons, too, including a tough cell wall that protects its contents. Simply accumulating enough fungal cells to carry out the necessary experiments took a heroic effort on the part of postdoctoral researcher Sinem Beyhan and research associate Matias Gutierrez, she says. Likewise, because so little is known about the H. capsulatum, the data analysis was a "tour de force" for Beyhan, Gutierrez, and bioinformaticist Mark Voorhies.

Nonetheless, there's a lot to learn about the clinically significant pathogen, and Sil suspects much of what researchers learn about H.

capsulatum may also be relevant to other thermally dimorphic fungi. "Our hope is that by opening up some of these molecular approaches, we can get more labs interested in how these organisms cause disease," she says.

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