Scientists discover a master key to microbes' pathogenic lifestyles

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A team of scientists from the University of Wisconsin-Madison School of Medicine and Public Health reports the discovery of a master molecular sensor embedded in the spores of the fungi that triggers a transformation from that of a benign lifestyle in the soil to a deadly pathogen.

For some microbes, the transformation from a benign lifestyle in the soil to that of a potentially deadly human pathogen is just a breath away.

Inhaled into the lungs of a mammal, spores from a class of six related soil molds found around the world encounter a new, warmer environment. And as soon as they do, they rapidly shift gears and assume the guise of pathogenic yeast, causing such serious and sometimes deadly afflictions as blastomycosis and histoplasmosis.

But how these usually bucolic fungi undergo such a transformation to become serious pathogens has always been a puzzle. Now, however, a team of scientists from the University of Wisconsin-Madison School of Medicine and Public Health reports the discovery of a master molecular sensor embedded in the spores of the fungi that triggers the transformation. The finding is reported in the April 28 edition of the journal Science.

The discovery could lead to new treatments and possibly vaccines for the diseases caused by these Jekyll and Hyde microbes, says Bruce Klein, a UW-Madison professor of pediatrics, internal medicine and medical microbiology and immunology, and the senior author of the new study.

"These microbes have to undergo an extreme makeover to survive in a host," says Klein, an authority on fungal diseases. "The million-dollar question is was what controls this change?"

Klein and colleagues Julie C. Nemecek and Marcel Wuthrich identified a molecular sensor that is conserved in these six related dimorphic fungi found worldwide. The sensor, says Klein, is like an antenna situated in the membrane of the fungi's spores. It senses temperature, and when a spore finds itself at a comfortable 37 degrees Celsius, the body temperature of a human or other animal, it kick starts a genetic program that transforms the fungi into pathogenic yeasts.

"This is a global regulator that sends signals down a molecular chain of command and governs a series of vital genetic programs," Klein explains. "It leads to changes in the organism's metabolism, cell shape, cell wall composition, and changes in virulence gene expressions."

These changes, according to Klein, are really a survival program for the microbe, conferring resistance to the host's immune responses.

The diseases caused by the fungi can be especially serious for immune compromised individuals, and some human populations seem to be more at risk for acquiring the infections. For example, U.S. soldiers who train in the American Southwest tend to be susceptible to coccidiomycosis because the organism that causes it is endemic to the region. One in three of those who train there acquire the disease, considered to be the second most common fungal infection in the United States. Of those infected, 25 percent contract pneumonia.

Histoplasmosis, a disease caused by the fungus Histoplasma capsulatum, infects as much as 80 percent of the population where the organism is endemic, including much of the eastern and central United States. It is also widespread in South America and Africa. In most instances, the infection prompts only mild symptoms. Untreated, however, it can be fatal. What's more, the microbe can lay dormant in an infected host for years.

"All of these organisms exhibit this property of latency," says Klein. "They can remain dormant until immune defenses are lowered. It's a significant medical problem in endemic regions."

The discovery of the switch that governs dimorphism and virulence in this prevalent class of fungi provides a target for new therapeutic agents and might even help underpin a vaccine able to thwart infection entirely, according to Klein.

"This could lead to therapeutics, better treatment for this class of diseases," Klein explains. "And with this finding, vaccines might now be possible. That's a strategy with promise."

The discovery of a master switch in related but diverse and geographically widespread class of fungi is an indication that it was acquired from a common ancestor deep in evolutionary history. The feature is a common mechanism used by the different organisms to adapt to a new environment: the lungs of animals.

"It is a story of how organisms are challenged in a new environment," says Klein. "They have to make themselves over so they can survive."

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Source: University of Wisconsin, by Terry Devitt