Researchers find gene that regulates mold's resistance to drugs

November 7 2008

Montana State University scientists concerned about lethal mold infections have found a gene that regulates the mold's resistance to drugs.

The gene, called srbA, allows molds to thrive during infections even when inflammation reduces its oxygen supply, said Robert Cramer, senior author of a paper published in the Nov. 7 issue of *PLoS Pathogens*. When the gene is removed, the mold becomes much more vulnerable to lack of oxygen and can no longer grow to cause disease.

The gene is found in humans and molds, but the researchers studied it in a common mold called Aspergillus fumigatus, said Cramer, assistant professor of fungal pathogenesis in MSU's Department of Veterinary Molecular Biology. A. fumigatus can invade the lungs and cause dangerous diseases, including Invasive Pulmonary Aspergillosis. Patients with a compromised immune system, especially organ transplant patients, are particularly at risk.

"The incidence of potentially lethal infections caused by normally benign molds has increased tremendously over the last two decades," the researchers wrote.

The scientists discovered the value of srbA after creating a mutant version of the fungus without the gene, Cramer said. Tests showed that the loss of srbA affected 87 genes in the fungus. Without the gene, the mutant could no longer grow when oxygen was limited, which occurs

during mold infections. The mutant mold without srbA could no longer cause disease. It was also highly susceptible to antifungal drugs, more vulnerable than the original, complete mold.

Further study showed that srbA plays a critical role in the making of ergosterol, the fungal-form of cholesterol, Cramer said. The gene in humans is associated with the making of cholesterol. Ergosterol and cholesterol are necessary components of cell membranes.

"The reason we're interested is because ergosterol is a target for most of the antifungal drugs that are available," Cramer said. "These drugs target the synthesis of ergosterol. ... If you get rid of ergosterol, you kill the mold."

Sven Willger, a postdoctoral researcher in Cramer's lab and first author of the *PLoS Pathogens* paper, said the absence of srbA changed the way the mold cells grew. Instead of growing from the tip, they branched off from several other locations. The confusion became apparent under a transmission electron microscope.

The researchers said in their paper that they demonstrated for the first time that it is significant that invasive molds adapt to reduced oxygen levels during infection.

Source: Montana State University