MedicalXpress

Simple fungus reveals clue to immune system protection

April 21 2011

A discovery by Johns Hopkins scientists about how a single-celled fungus survives in low-oxygen settings may someday help humans whose immune systems are compromised by organ transplants or AIDS.

A report on the discovery in a yeast called Schizosaccharomyces pombe appears April 22 in *Molecular Cell*.

Previous work by the Hopkins team showed that Schizosaccharomyces pombe, a model organism that's often used to study individual genes, contains a protein named Sre1 that allows the organism to adapt to conditions in which oxygen is very low or missing altogether.

To find out what regulates Sre1, the researchers turned to their collection of 2,626 individual strains of fission yeast, each of which is modified to lack a different gene from the organism's genome. First, they subjected each of the mutant strains to low-oxygen conditions and identified 28 genes whose absence stopped the yeast from growing. Four of the mutants regained their ability to grow in low oxygen when the scientists added back Sre1.

"Unless something removes it, Sre1 stays attached to the cell membrane and therefore is unable to travel to the nucleus to do its job," says Peter J. Espenshade, Ph.D., an associate professor of physiology and member of the Center for Metabolism and Obesity Research at the Johns Hopkins University School of Medicine. "Only when cut and released from the membrane can SRE1 go to work."

To find that cutting mechanism, the researchers examined the four mutant yeast strains, looking for evidence of the molecular machinery that allows the short, active "business part" of Sre1 to make its way to the nucleus of the cell to turn on genes. Cells that can't cut Sre1 to activate it look and fare just like those that are completely missing it, Espenshade says.

The team identified four genes called defective for Sre cleavage (dsc 1-4) and showed that they are responsible for making the protein components of the cutting mechanism — a so-called Dsc E3 ligase complex that resides in a compartment of the cell called the Golgi.

Sre1 is required for virulence in disease-causing fungi such as Aspergillus fumigatus, which ravage people whose immune systems have been weakened by cancer or infections. The dsc 1-4 genes, according to Espenshade, are conserved in Aspergillus as well as a number of other fungi that cause a range of diseases.

"Our studies suggest that dsc proteins are an attractive target for the development of new drugs to combat fungal infections in immune compromised people," Espenshade says.

More information: www.cell.com/molecular-cell/

Provided by Johns Hopkins Medical Institutions