Researchers uncover molecular pathway through which common yeast becomes fungal pathogen

March 16 2012

Scientists at the University of Toronto have found a molecular mechanism that plays a key role in the transition of *Candida albicans* yeast into disease-causing fungus—one of the leading causes of hospital-acquired infection. The finding highlights the importance of heat in fungal growth, and provides a new target for drug therapies to counter *Candida albicans* infection.

Candida albicans is a normally harmless yeast that is present in all humans. It becomes infectious in various genetic and environmental conditions, with temperature as a key determinant. It can produce infections that are mild—persistent vaginal or gut infections, for example—or severe, such as systemic, potentially fatal bloodstream infections in patients with AIDS or those who have undergone chemotherapy (or even a simple round of antibiotics).

The molecular workings of *Candida albicans* were mapped for the first time in 2009 by Professor Leah Cowen of the University of Toronto's Department of Molecular Genetics, whose lab showed that growth of the fungus is tied to the function of a "molecular chaperone" called heat-shock protein 90 (Hsp90). In a study that will appear in the March 20 edition of the journal *Current Biology,* Prof. Cowen and her colleagues detail a mechanism that controls response to elevated temperature through a protein named Hms1 in conjunction with a cyclin (another type of protein) and its partner protein called a cyclin-dependent kinase.

"This circuitry fundamentally influences how *Candida albicans* senses temperature, which is crucial for Candida's ability to cause disease," said Prof. Cowen, who holds the Canada Research Chair in Microbial Genomics and Infectious Disease—a prestigious five-year award for which she was renewed this week.

"We were looking for a transcription factor at the end of a pathway we previously showed was key to the change in shape of the fungus that accompanies elevated temperature or compromise of Hsp90 function, and instead we found an entirely new pathway, with components that haven't been characterized in Candida, so it was very surprising," said Prof. Cowen.

The researchers also showed that deletion of Hms1 inhibits *Candida albicans* infection, pointing toward a possible clinical therapy. "We observed those weaker disease phenotypes in an insect model system, but the results suggest it may also work in more complicated systems," said Prof. Cowen.

The source of pesky vaginal and gut infections, *Candida albicans* is a burgeoning problem on implanted medical devices—it's fatal in roughly one-third of device-associated infections—and is the fourth-leading cause of hospital-acquired infection. The number of acquired fungal bloodstream infections has increased by more than 200% over the last twenty years, owing in part to growing numbers of AIDS and cancer survivors whose treatments have compromised their immune function.

On finding that the Hms1 pathway affects the growth and development of Candida albicans, and knowing of other key regulators through which Hsp90 operates and suspecting many more exist, Prof. Cowen and her lab examined other pathways and proteins that interact with Hsp90 in another study.

In collaboration with Professor Gary Bader at U of T's Donnelly Centre for Cellular and Biomolecular Research, Prof. Cowen's group mapped a much larger portion of the chaperone network with which Hsp90 interacts through a "chemical genomics" approach that had never been applied to Candida albicans. "If we want to have a more global understanding of what Hsp90 is doing during the transition of this fungus between distinct morphological states with different disease causing properties, we need to take global approaches to determine what its interacting with," said Prof. Cowen.

Their results, published online today in the journal PLoS Genetics, showed 226 genetic interactors with Hsp90 in various conditions, such as different temperatures and during exposure to anti-fungal drugs. Of those interactions, 224 were previously unknown. "That's a lot," said Prof. Cowen. "We now have a myriad of new targets through which Hsp90 could be regulating morphogenesis and drug resistance in Candida."

As well, the researchers drew several predictive rules from their study that govern the Hsp90 chaperone network. Some interactors were only important in a small subset of stress conditions, and these are likely to function "downstream" of Hsp90 regulating specialized cellular processes. Other interactors were important in many stress conditions, and so are likely to work "upstream" of Hsp90 regulating its function.

"Hsp90 stabilizes many proteins, but previously nobody could predict what made an Hsp90 client. That we can make such predictions from the chaperone network is pretty cool and unanticipated, so we're further ahead than we expected," said Prof. Cowen.

Provided by University of Toronto

Citation: Researchers uncover molecular pathway through which common yeast becomes fungal pathogen (2012, March 16) retrieved 26 April 2024 from https://phys.org/news/2012-03-uncover-molecular-pathway-common-yeast.html

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