New way to fight drug-resistant fungal infections discovered

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(PhysOrg.com) -- The secret to fighting often lethal drug resistant fungal infections is to knock out the bug's molecular chaperone, according to U of T researchers.

An international team led by Professor Leah Cowen of the University of Toronto's Department of Molecular Genetics has discovered that the fungal pathogen Candida albicans (known as C. albicans) is able to resist drug treatment because of an associated protein - or molecular chaperone -- called heat shock protein 90, or Hsp90.

In research published today in the journal PLoS Pathogens, the researchers found that compromising Hsp90 function renders the fungal-fighting drugs known as echinocandins more effective at killing C. albicans laboratory strains and clinical isolates. Enhancing the ability of existing drugs to battle often drug-resistant fungal infections greatly enhances the ability to treat the most vulnerable patients.

"Our results suggest that interfering with Hsp90 function provides a powerful and much-needed strategy to render existing antifungal drugs more effective in the treatment of life-threatening fungal infections," said Cowen, who collaborated with colleagues from Duke University on the project.

By impairing the function of C. albicans Hsp90 - through the use of either using potent drugs or genetic techniques -- Cowen's team discovered that this rendered the fungus much more sensitive to killing

by the echinocandins. This strategy to cripple the fungus worked even against isolates that evolved resistance to echinocandins in human patients. The strategy was shown to be effective in both test tube experiments and mouse models. Cowen's research suggests that treating patients with combination therapy, including a drug that inhibits Hsp90 along with an echinocandin, could have major benefits for individuals with life-threatening fungal disease.

Candida albicans can cause a wide range of disease from superficial infections such as yeast infections to life-threatening infections in the bloodstream. They can be especially lethal for people with compromised immune systems, such as those with AIDS or people undergoing treatment for cancer or organ transplantation, and they are the fourth leading cause of hospital acquired infectious diseases. C. albicans is the most frequently encountered Candida species in the clinic and is the fourth most common cause of hospital acquired infectious disease with mortality rates approaching 50 per cent.

Cowen, Canada Research Chair in Microbial Genomics and Infectious Disease, has spent many years focusing on Hsp90's role in enabling the evolution of fungal drug resistance and developing strategies to harness Hsp90 as a tool to block the emergence of drug resistance and render resistant pathogens more responsive to treatment. Last March, in a paper published in the journal *Current Biology*, she reported that Hsp90 acted as a kind of thermostat for C. albicans; shutting down the protein's temperature-sensitivity can shut down the spread of infection.

Provided by University of Toronto (news : web)