Online links

Candida albicans
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj&cmd=Retrieve&dopt=Overview&list_uids=9526

Saccharomyces cerevisiae
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj&cmd=Retrieve&dopt=Overview&list_uids=9518

ANTIFUNGALS

A helping hand

Hsp90 is well known for its role as a molecular chaperone — a protein that assists the folding of other proteins ('clients'). Now, research published in ***Science*** reveals that Hsp90 might also influence the evolution of new traits by potentiating the phenotypic effect of genetic variation. Studies of the evolution of drug resistance in several strains of pathogenic fungi demonstrate an essential role for Hsp90 and its client protein calcineurin, and implicate Hsp90 as a novel antifungal target.

As a chaperone for many signal transducers, Hsp90 is able to 'buffer' the effects of genetic variation by enabling the cell to tolerate mutations. Although Hsp90 is highly inducible following environmental stress, the demands of stress-induced protein misfolding can outpace its induction, enabling previously silent mutations to act combinatorially and generate new phenotypes. It now seems that Hsp90 has yet another role in the emergence of new traits: by allowing a mutation to have immediate effects rather than buffering against it, HSP90 might actually potentiate the appearance of new phenotypes.

Leah Cowen and Susan Lindquist examined the role of Hsp90 in the evolution of resistance to antifungal drugs. Using rapid selection of three strains of ***Saccharomyces cerevisiae*** with varying levels of Hsp90, they demonstrated that the development of resistance depended on high-level expression of Hsp90. Moreover, Hsp90 was required to maintain resistance rather than just to cope with the initial selection stress.

The Hsp90-dependent effect was specific to mutants generated by rapid selection, which favours mutations that prevent the accumulation of toxic metabolites, rather than gradual selection which involves upregulation of a multidrug transporter. However, in 11 previously identified ***S. cerevisiae*** drug-resistant deletion strains, all were found to be Hsp90-dependent, showing that Hsp90 can influence the resistance caused by a variety of different genetic lesions.

But how does Hsp90 achieve this? One possibility is that a common regulator exists to mediate Hsp90-dependent effects on different mutations. An obvious candidate was calcineurin, an Hsp90 client known to regulate the cell's response to azoles. Accordingly, inhibition of calcineurin strongly reduced fluconazole resistance in all Hsp90-dependent resistant strains.

These findings reveal an attractive therapeutic strategy against fungal infection, as similar results were seen with several fungal pathogens. It is particularly significant that Hsp90 was crucial for the evolution of antifungal resistance in clinical isolates of ***Candida albicans*** collected from an HIV-infected individual. With continued exposure to fluconazole, the clinical isolates evolved towards Hsp90-independent resistance, prompting speculation that Hsp90 initially allows the phenotype to be expressed but that environmental stress drives the cell towards stabilizing the resistant phenotype. Inhibiting Hsp90 early in infection could therefore render resistant fungal pathogens sensitive to conventional treatment or could prevent the initial development of antifungal-drug resistance. Moreover, Hsp90 inhibitors are already being evaluated in clinical trials for cancer, and seem to be well tolerated at levels that achieve significant inhibition.

Joanna Owens, Associate Editor,
Nature Reviews Drug Discovery

References

ORIGINAL RESEARCH PAPER Cowen, L. & Lindquist, S. Hsp90 potentiates the rapid evolution of new traits: drug resistance in diverse fungi. *Science* **309**, 2185–2189 (2005)