URLs

EVOLUTION

A helping hand

Heat shock protein 90 (HSP90) is a well-known molecular chaperone, but is also a therapeutic target in cancer. Recent studies of the evolution of drug resistance in pathogenic fungi show that HSP90 might also influence the evolution of new traits by potentiating the phenotypic effects of genetic variation.

As a chaperone for many signal transducers, HSP90 buffers the effects of genetic variation by enabling the cell to tolerate mutations. Although HSP90 is highly inducible following environmental stress, the demand that occurs due to 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 another role in the emergence of new traits — by allowing a mutation to have immediate effects, rather than buffering against it, HSP90 might potentiate the appearance of new phenotypes.

Cowen and 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 showed that the development of resistance depended on high-level expression of HSP90. Moreover, HSP90 was required to maintain resistance.

The HSP90-dependent effect was specific to rapid selection, which favours mutations that prevent the accumulation of toxic metabolites, rather than gradual selection, which involves upregulation of a multidrug transporter. However, enhanced resistance in all 11 previously identified *S. cerevisiae* drug-resistant deletion strains was HSP90-dependent, showing that HSP90 can influence resistance that is caused by a range of genetic lesions.

How does HSP90 achieve this? One possibility is that a common regulator mediates HSP90-dependent effects on different mutations. An obvious candidate was calcineurin, one of the targets of HSP90, which regulates the cell's response to certain antifungal agents. Satisfyingly, inhibition of calcineurin strongly reduces fluconazole resistance in all HSP90-dependent resistant strains.

This suggests an attractive therapeutic strategy against fungal infection as similar results were seen with several fungal pathogens, including *Candida albicans* isolates that were collected from an HIV-infected individual. With continued exposure to fluconazole, the fungi evolved towards HSP90-independent resistance, prompting speculation that HSP90 initially allows the phenotype, but that environmental stress drives the cell towards stablizing 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 resistance.

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References and links

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)
FURTHER READING Rutherford, S. L. Between genotype and phenotype: protein chaperones and evolvability. *Nature Rev. Genet.* **4**, 263–274 (2003)