Heat shock protein drives yeast evolution

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Whitehead Institute researchers have determined that heat shock protein 90 (Hsp90) can create heritable traits in brewer's yeast (*Saccharomyces cerevisiae*) by affecting a large portion of the yeast genome. The finding has led to the conclusion that Hsp90 has played a key role in genome evolution.

"This has been viewed as a very exciting, even revolutionary way of looking at how it is organisms could rapidly evolve new traits," says Whitehead Member Susan Lindquist. "We've come about as close to proving such a broad evolutionary process as it's likely that we can at this present date."

The results are reported in the December 24, 2010 issue of the journal *Science*.

Proteins perform numerous functions in cells, including promoting chemical reactions, translating DNA, and maintaining the cell's structure. To perform its job, a protein must fold from a long chain of amino acids into a precise form. Moreover, many vital proteins adopt unstable conformations. If the protein loses its normal shape due to, for example, excessive heat, toxins or other stressors, it can no longer perform its job and may even become toxic to the cell. To provide tolerance against such stresses , cells employ a repertoire of heat-shock proteins (Hsps) that guide other proteins into their proper shape. This ancient class of proteins is present in virtually all organisms, ranging from bacteria to humans.

One of these proteins, Hsp90, is particularly abundant, comprising 1-2% of all proteins in a cell. Yet, under normal conditions, a cell uses only about 10% of its Hsp90, leaving a large reservoir of its function available should conditions suddenly turn more stressful.

Over the past several years, Lindquist has built the case that this Hsp reservoir is responsible for substantial evolutionary changes in relatively short periods of time. Her lab has shown that the pathogenic Candida albicans and Aspergillus fungi rely on Hsp90 to evolve drug-resistance. Cancer cells often exploit the Hsps' function to support carcinogenic proteins. Earlier research has also shown that selective breeding can enrich variation responsible for these phenotypes, allowing an Hsp90-reliant trait to be inherited even in the absence of stress.

The Hsp90 buffer appears to function in two ways with mutant proteins: either to mask or reveal the phenotypic consequences of mutations. In the first case, Hsp90 braces mutant proteins into "normal" shapes, thereby hiding the mutant proteins' traits. As conditions become increasingly stressful, the Hsp90 buffer must act on more and more proteins. At a certain point, the Hsp90 buffer becomes overwhelmed, and the mutant proteins' traits are exhibited.

In the second scenario, proteins that are not functional on their own are shaped into working forms. These mutant proteins cannot perform their jobs without the aid of Hsp90, so when the Hsp90 buffer is overwhelmed, the cells lose the mutant proteins' traits.

In both of these scenarios, consumption of the Hsp90 reservoir by environmental stress allows numerous traits to be exhibited or lost immediately and simultaneously. If the new phenotype is beneficial for this stressful environment, the organism will survive. Because the new phenotypes are based on genetic variation they can be passed on to the next generation and evolution progresses. If the traits are detrimental, the

organism will not survive and its traits will die with it.

This method of suddenly unveiling a new phenotype consisting of multiple traits could also explain the evolution of interdependent traits that are detrimental on their own. Such a seeming leap forward in evolution has puzzled biologists since Darwin.

Although earlier evidence indicated that Hsp90 activity could affect evolution, a Lindquist postdoctoral researcher, Daniel Jarosz, wanted to understand mechanistically Hsp90's effects on one species and provide solid evidence for Hsp90's impact on evolution.

In the Science paper, first author Jarosz analyzed the effects of Hsp90 on 102 genetically diverse strains of brewer's yeast by placing them under various stressful conditions and inhibiting Hsp90. All of the strains had substantial growth changes in specific conditions.

Jarosz then learned more about the Hsp90-affected traits by crossing two strains and looking at the progeny. He determined that about half of the traits affected by Hsp90 were positive and half were negative. Also, reducing Hsp90 in several of the crossed strains' progeny revealed multiple interdependent traits.

To see how much Hsp90 affects the phenotypes of yeast strains, Jarosz looked at the genetic sequences of 48 strains and compared the genotypes to the phenotypes that he saw in those strains. When Hsp90 functioned normally, the genotype and phenotype weakly resembled each other. But when the Hsp90 reservoir was depleted, the correlation between genotype and phenotype became much stronger.

"We've only looked at a few cases, but in all of them, there was a clear link between Hsp90 activity and phenotype," says Jarosz. "What we show here is that Hsp90's effects are very broad, and it operates on about

20% of all genetic variation in this organism."

For Lindquist, the way Hsp90 is able to affect phenotypes may explain a longstanding mystery of evolution: how an organism could change multiple, interdependent traits in response to environmental changes.

"Taking what had been theory and very isolated incidents that had tremendous potential, we can help explain how organisms can rapidly acquire new traits," says Lindquist, who is also a Howard Hughes Medical Institute investigator and professor of biology at MIT. "We can show that the stress of environmental change and selective pressures can actually influence how evolutionary processes occur. And now we have a much more solid framework to hang that on."

Lindquist says she would like to learn more about the fixation process, which makes an Hsp90-reliant trait heritable, even in the absence of stress. By looking at genome sequences, her lab will try to determine whether Hsp90 affects the mechanisms of genome stability or if it perhaps influences the way that organisms accumulate new genetic variation.

More information: "Hsp90 and environmental stress transform the adaptive value of natural genetic variation" *Science*, December 24, 2010.

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