

Researchers give mutants another chance

February 11 2009

Researchers at Fox Chase Cancer Center have demonstrated that it might be possible to treat genetic diseases, including some forms of cancer, by "rescuing" the misshapen, useless proteins produced by some mutant genes.

In the current issue of the *Journal of Biological Chemistry*, available online now, researchers detail how they were able to restore the function of a mutant human gene in a yeast model of disease by manipulating the available amounts of a so-called chaperone protein, named Hsp70, which helps amino acid chains fold into their proper protein form.

"In some cases, despite a mutation, it is possible to coax a misfolded protein back into a functional conformation," says the paper's lead author Warren Kruger, Ph.D., senior faculty member at Fox Chase. "In essence, we're using Hsp70 to call a biochemical mulligan, a do-over."

"Hsp70 pulls a misfolded amino acid chain apart like a twisted rubber band and allows it to snap back into place, which we found can restore a significant percentage of proteins to working shape," Kruger says. "If this can be done in humans, it could represent a way of reducing the severity - or perhaps correcting - certain hereditary diseases, even some familial cancers."

Kruger and his colleagues are currently studying how to adapt these findings to human disease. While the study was done in a yeast model for human disease, humans possess at least nine members of the Hsp70 family of chaperones. Evidence suggests that it might be feasible to

modify the chaperone environment in order to give Hsp70 better opportunities to rescue broken proteins. "The more chances we give Hsp70 proteins to try to 'fix' the output of mutant genes, the more chances are that they will succeed," Kruger says.

Very often, genetic mutations occur when errors in the DNA code substitute one amino acid for another. It is this sort of mutation that is at the center of a disease called cystathionine β -synthase (CBS) deficiency, an inherited metabolic disorder that the Kruger laboratory uses as a genetic model.

Through experiments performed by Laishram Singh, a post-doctoral fellow in the lab, Kruger learned that exposure to alcohol restored the function of a mutant human CBS protein expressed in genetically engineered yeast cells. This exposure activates heat shock proteins, like Hsp70, which help the cell respond to the shock, or damage, from stress. The sudden excess of Hsp70, in turn, had the side effect of rescuing mutated proteins in addition to those damaged by alcohol.

According to Kruger, Hsp70 works in equilibrium with another heat shock protein, Hsp26, as a sort of biochemical damage control system. While Hsp70 acts like a chaperone to restore the function of such proteins, Hsp26 targets the misfolded proteins to the proteasome, the "garbage disposal" of the cell. The two proteins, it seems, function in opposition, competing to clean up damaged proteins within cells.

The relationship between these two proteins may provide an opportunity for intervention, Kruger reasons. When Kruger and his colleagues removed the gene encoding Hsp26 from yeast, they saw a nine-fold increase in the amount of properly functioning human CBS protein. "If we can target Hsp26 and take it out of circulation, we might be able to give Hsp70 more room to operate," Kruger says.

Source: Fox Chase Cancer Center

Citation: Researchers give mutants another chance (2009, February 11) retrieved 26 April 2024 from <https://phys.org/news/2009-02-mutants-chance.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.