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Researchers find new method of fixing broken proteins to treat genetic diseases

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Researchers at Fox Chase Cancer Center have demonstrated how it could be possible to treat genetic diseases by enhancing the natural ability of cells to restore their own mutant proteins. In particular, they found that drugs called proteosome inhibitors could provide one way of manipulating cells into producing more of a so-called chaperone protein, named Hsp70, which helps amino acid chains fold into their proper protein form.

Their latest findings, presented in the journal PLoS Genetics, expand their previous research from yeast models of disease to human cell cultures and animal models. According to the researchers, if this approach works in humans, it could be a way to turn certain debilitating - or even fatal - genetic diseases into more treatable, chronic conditions.

"Hsp70 pulls misfolded mutant proteins apart like a twisted rubber bands and allows them to snap back into place, eventually a significant percentage of these proteins will snap back into something approaching a functional shape," says the study's leader, Warren Kruger, Ph.D., professor in Fox Chase's Cancer Biology program. "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."

Genetic diseases are often caused by a specific type of genetic alteration called a missense mutation that makes cells add an incorrect amino acid into the protein chain. Since the shape of a protein depends on the specific arrangement of amino acids, even a single error amid a gene's

very long stretch of DNA can cause the gene's protein product to become misshapen. Kruger and his colleagues studied ways to reverse the functional effects of missense mutationsfor three genetic diseases: two severe inherited metabolic disorders (CBS deficiency and MTHFR deficiency) and one inherited cancer syndrome (Li-Fraumeini).

In each case, the Fox Chase researchers found that it was possible to restore the function of the mutant proteins by tricking the cell into increasing levels of Hsp70. "We have shown that the more opportunities we give Hsp70 proteins to try to 'fix' mutants, the more likely it is that they will succeed," Kruger says.

While this approach has yet to be applied to clinical medicine, there are several drugs that are known to induce Hsp70 in humans. Kruger found that treating yeast and mammalian cells with a drug called bortezomib elevated the amount of available Hsp70 and rescued mutant proteins. Bortezomib is a member of a class of drugs called proteasome inhibitors, which decreases the effectiveness of enzymes that cells use to dispose of non-functioning proteins. Bortezemib (known under the brand name Velcade) is currently used to treat patients with multiple myeloma.

"We found that bortezomib can stabilize and restore mutants by tripling the amount of available Hsp70," Kruger says. "While we do not yet know the entiremechanism, we do know that bortezomib doesn't rescue mutants in cells that lack the gene for Hsp70."

Kruger and his colleagues are currently studying how to best adapt these findings to human disease.

"Of course, the big question we need to answer is one of safety - what are the long term effects of sustained Hsp70 elevation?" Kruger says. "The answer may be very disease-specific, one of how many mutant proteins must be restored to reduce the severity of a given genetic

disease."

Provided by Fox Chase Cancer Center