Heat-resistant enzymes could produce more cost-effective drugs

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A new study published in *Proceedings of the National Academy of Sciences* could change the way scientists look at one of the most essential enzymes in medicine in hopes of designing better and more cost-effective drugs in the future.

Enzymes are molecules that speed up chemical reactions inside cells. The human body is home to thousands of enzymes that perform vital functions such as the digestion of fat and the breakdown of sugar into glucose.

The paper, co-authored by UT Biochemistry and Cellular and Molecular Biology Associate Professor Nitin Jain and student Sara Lemmonds, who has since graduated, looks closely at Cytochrome P450, an enzyme that occurs naturally in the body and other environments. This enzyme is critical in metabolizing over 90 percent of all pharmaceutical drugs.

When a drug is administered, it is usually not used up entirely by the body, and the residual excess can become toxic. "It is P450's job to bind with the leftover drug in the liver to ensure that it is safely excreted," explained Lemmonds.

Scientists know that P450 has another remarkable feature: it can remain stable under very high heat. The same enzyme has been found in bacteria in hot springs and volcanic deposits and has been observed to function normally despite extreme temperatures.

The UT researchers are honing in on the enzyme's heat tolerance.

"The chemical reactions produced by human P450 enzymes are more efficient when they occur at increasing temperatures," said Jain.

Up until now, scientists believed that P450's tolerance to heat had its origin in its rigid structure. However, Jain and Lemmonds's study suggests that these proteins may be quite flexible.

"By better understanding the relationship between flexibility and high temperature, scientists can engineer improved P450 enzymes targeted at biotechnology applications and designing better drugs for humans, producing them en masse and making them more cost effective," Jain said.

For the study, researchers collected thermophilic bacteria—those that thrive at temperatures between 106 and 262 degrees Farenheit—from hot springs and isolated the P450 enzyme.

They subjected the isolated enzymes to spectroscopy and neutron scattering, two techniques based in magnetism, to help illuminate the link between flexibility and thermal stability.

"There could be other enzymes that are as flexible at higher temperatures than P450, or that can become as flexible through simple mutations. If so, knowledge gained from future studies on them could then be used to target specific processes in the body, treat disease, or make new chemical products," said Lemmonds.

More information: Zhuo Liu et al, Entropic contribution to enhanced thermal stability in the thermostable P450 CYP119, *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1807473115

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