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Researchers describe new way to identify, evolve novel enzymes

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The intricate interplay of proteins and other chemicals that underlies most biological activities requires the participation of enzymes, specialized molecules that accelerate chemical reactions between molecules. The creation of totally new enzymes can help improve the synthesis of chemicals and pharmaceuticals, devise new tools for molecular biology research, and develop new therapies.

In the August 16 issue of Nature, two Massachusetts General Hospital (MGH) researchers describe a way of creating novel enzymes that, for the first time, does not require prior understanding of exactly how the enzymes work.

“To date, the only source of enzymes has been biology,” says Jack Szostak, PhD, of the MGH Department of Molecular Biology, the report’s senior author. “Great efforts are going into modifying and improving these natural enzymes, and our work demonstrates the potential of evolving completely new enzymes in the laboratory.”

Szostak and his co-author Burckhard Seelig, PhD, used a technique called mRNA display –previously developed in Szostak’s lab – that allows the identification and amplification of proteins that fit particular criteria. In order to create an enzyme that would stimulate or catalyze the joining of two segments of RNA in a way that does not occur naturally, they began by generating a library of 4 trillion small proteins with slight variations in their sequences. Each protein was then brought together with the RNA segments to be joined, called substrates.

If a particular protein induced the RNA substrates to join, resulting in a significantly larger molecule, that signified the protein was an active enzyme. The investigators could select out the larger RNA strands, generate more of the enzymes, and repeat the experiment. The induction of random mutations to produce different forms of the enzymes and reducing the time allowed for the splicing reaction enabled the development of more efficient versions by means of guided evolution.

Szostak notes that the final version of the enzyme they created is quite small and still not very stable, but it is a starting point to discovering additional strategies that may help improve its activity. The same mRNA-display technique can also identify enzymes that break down or otherwise modify their substrate molecules.

“We hope our work on optimizing this enzyme will demonstrate that we can evolve catalysts with activity as good as that of naturally occurring enzymes,” Szostak explains. “We’d also like to determine the 3D structure of our new enzyme to understand how it binds to its relatively larger substrates and catalyzes the joining of the two RNA strands.” The Alex Rich Distinguished Investigator in Molecular Biology at MGH, Szostak also is a professor of Genetics at Harvard Medical School, a Howard Hughes Medical Institute investigator and a member of the MGH Center for Computational and Integrative Biology. This study was supported by a grant from the NASA Astrobiology Institute, and Seelig’s was supported in part by the Emmy Noether-Programm of the Deutsche Forschungsgemeinschaft.

Source: Massachusetts General Hospital