

Researchers find protein-building enzymes have metamorphosed and evolved new functions

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Scientists at The Scripps Research Institute (TSRI) and Hong Kong University of Science and Technology (HKUST) and their collaborators have found that ancient enzymes, known for their fundamental role in translating genetic information into proteins, evolved myriad other functions in humans. The surprising discovery highlights an intriguing oddity of protein evolution as well as a potentially valuable new class of therapeutic proteins and therapeutic targets.

"These new protein variants represent a previously unrecognized layer of biology—the ramifications of this discovery are now unfolding," said team leader Paul Schimmel, Ernest and Jean Hahn Professor of Molecular Biology and Chemistry at TSRI (California and Florida) who also holds an appointment at HKUST Jockey Club Institute for Advanced Study (IAS).

Mingjie Zhang, IAS Senior Fellow and Kerry Holdings Professor of Science, Division of Life Science at HKUST, added, "This breakthrough finding not only uncovers a vast area of new biology, but also provides opportunities to develop protein-based drugs for various human diseases associated with malfunctions of these newly discovered proteins. The successful collaboration among scientists from HKUST, TSRI and two biotech companies from the U.S. and Hong Kong also serves as a wonderful example of the close connections between basic research and biotechnology development."

The findings appear in the July 18, 2014 issue of *Science*.

Greater Complexity

The discovery concerns aminoacyl tRNA synthetases (AARSs), a group of 20 enzymes whose most basic function is to connect the nucleotide codes contained in genes to their corresponding protein building-blocks, namely, the 20 amino acids. Because AARSs are essential for the translation of genetic information into working proteins, they are found in all life forms on the planet.

Scientists have been finding evidence in recent years that AARS enzymes exist in greater complexity in more evolutionarily advanced organisms. In essence, these enzymes have acquired new segments or "domains." Curiously, these domains have no apparent relevance to protein translation. While largely absent in lower forms of life, these domains are added in a progressive and accretive way in evolution, in the long ascent over billions of years to humans.

To investigate further, Schimmel collaborated with colleagues at TSRI in California and Florida, HKUST (including at the IAS), the San Diego biotech company aTyr Pharma (which Schimmel co-founded), Stanford and the Hong Kong biotech company Pangu Biopharma (an aTyr subsidiary).

Using advanced, sensitive techniques, the team identified nearly 250 previously unknown gene-transcript variants of AARS in different human cell types. These variants, known as splice variants, are alternative assemblies of the discrete sequences of information (exons) contained in AARS genes. Genes frequently contain multiple exons that can be spliced together in alternative ways—thus in principle enabling a single active gene to encode multiple proteins with different functions. But the new findings suggest that evolution has been unusually prolific at

creating AARS splice variants.

Potential New Class of Drug Targets

The team's further investigations revealed that the new AARS variants often are produced only in specific cell types such as brain or immune cells and/or appear only during certain stages of development.

Remarkably, most of the new splice variants lack entirely the standard "catalytic domain" that supports protein translation—confirming that they are not directly involved in that fundamental process. Initial screening of the biological activities of these variants hinted at a diversity of other functions. One variant selected for analysis turned out to be a powerful driver for the proliferation of muscle fiber cells in a laboratory dish.

Schimmel and his collaborators will now turn to more comprehensive studies of the new AARS variants and their specific functions. "We believe that these proteins have relevance to multiple human diseases," he said. "They thus represent a very important class of new protein therapeutics analogous to widely used injectable protein therapeutics such as growth hormone, insulin, erythropoietin (EPO) (which regulates red blood cell production) and granulocyte colony-stimulating factor (G-CSF) (which stimulates the bone marrow)."

More information: "Human tRNA synthetase catalytic nulls with diverse functions," by W.-S. Lo et al. www.sciencemag.org/lookup/doi/.../1126/science.1252943

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