Scientists show protein-making machinery can switch gears with a small structural change process

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For the past several years, Min Guo, an assistant professor at The Scripps Research Institute, has focused on the intricate actions of an ancient family of catalytic enzymes that play a key role in translation, the process of producing proteins.

These complex enzymes are a group of fundamental molecules that make building blocks for protein production. Present in every cell, these enzymes—known as aminoacyl-transfer RNA synthetases (tRNA synthetases)—select the proper amino acid and assign them to transfer RNAs to make a protein in the ribosome. As an essential step of determining the genetic code, tRNA synthetases have been around for billions of years.

However, this essential part of the protein-making machine did not stop evolving. Now, in a new study published online ahead of print on November 15, 2012, by the journal *Molecular Cell*, Guo, Ehud Razin of The Institute for Medical Research Israel-Canada, and a large team of international scientists have shown that this enzyme can actually also work in another fundamental process in humans. In this case, the enzyme activates a process that creates a copy of RNA from DNA—transcription, which is the first step leading to gene expression. All this takes is a single chemical alteration (phosphorylation) at a specific site on the enzyme, which then triggers a cascade of structure changes, freeing the enzyme from translation to another role regulating

transcription.

"If you think about the structural changes that occur in the synthetase we looked at in the study, it's very much like the movie Transformers," Guo said. "It's a machine that changes structure and turns into another machine that can accomplish a completely different task—like from a car to a giant robot. This is the first time anyone has been able to show how you can change the function of this enzyme from a mechanistic perspective, to know exactly how that works."

This newly discovered ability has large implications for our understanding of immune response, including allergies, and cancer, Guo said. He notes the unusual transformation of tRNA synthetases was initially discovered in mast cells, which are the body's first line of defense against pathogens such as bacteria and viruses. To recognize pathogens and other signs of infection, mast cells are dispersed throughout most tissues, but are crucially located at the body's interfaces with the environment, such as the skin and mucosae. Activation of mast cells is a key step in initiating allergies, in which activated mast cells secrete preformed mediators, such as histamine, and synthesize new mediators that augment the allergic response. It turns out that mast cells mobilize the tRNA synthetases to participate in transcriptional regulation and carry along this entire signal cascade, within minutes.

"This shows how a housekeeping machine can be re-shaped for a regulatory response," Guo said, "something that is only now starting to get noticed."

Recent research has also shown that the transformed synthetase in the new study also increases metastasis in breast cancer cells.

"By designing a way to prevent this synthetase transformation, you could potentially limit metastasis," Guo said. "But you have to know the

mechanism before you can design something to alter it. This new study gives us a basic framework that shows how this transformation works."

The first authors of the study, "Structural Switch of Lysyl-tRNA Synthetase between Translation and Transcription," are Yifat Ofir-Birin of The Institute for Medical Research Israel-Canada and Pengfei Fang of TSRI. In addition to Guo, Razin, Ofir-Birin, and Fang, other authors include Steven P. Bennett, Jing Wang, Ryan Shapiro, Jorge Pozo, Paul Schimmel and Xiang-Lei Yang of TSRI (Sharpiro and Schimmel are also affilitated with the Skaggs Institute for Chemical Biology at TSRI); Inbal Rachmin, Jing Song, and Arie Dagan of The Institute for Medical Research Israel-Canada; Hui-Min Zhang and Alan G. Marshall of Florida State University; Sunghoon Kim of Seoul National University; and Hovav Nechushtan of the Hadassah Medical Center, Israel.

"This study required team work, as it spanned the boundaries of different biological fields, including cell biology, structural biology, immunity and cancer," Guo said. "This and future work is made possible by the close collaborations among scientists around the world."

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