Salvaging SNAREs
Scientists catch a protein-recycling machine in the act.

Cells are huge proponents of recycling. They reuse everything from tiny electrons to massive molecular complexes. Despite this penchant for salvage, scientists have never been able to see one form of cellular recycling in action—until now. A group led by HHMI Investigator Axel Brunger recently captured a protein in the act of pulling apart a spent cluster of membrane fusion molecules.

“Membrane fusion is a process akin to the merging of soap bubbles into larger ones,” says Brunger, a structural biologist at Stanford University. “But that’s where the analogy ends, since biological membranes do not merge all that easily.” To facilitate the process, cells use membrane-bound SNARE proteins. During fusion, SNAREs located on opposing membranes zip together into a stable complex, linking the membranes. When the two membranes have become one, a protein called NSF recycles the SNARE components.

A cell’s NSF complex uses SNAP proteins (orange) to grasp and unwind membrane-embedded SNARE proteins (red and blue helices).

IN BRIEF

As preventing the formation of new blood vessels, protecting cells in the retina and brain from damage, and stopping cancer cells from growing. Despite considerable effort by scientists in academia and industry, the identity of the receptors had, until recently, remained a mystery. This long-standing puzzle was so intractable that it took HHMI Early Career Scientist Hui Sun and his team at the University of California, Los Angeles, seven years to solve. “We were initially intrigued by this problem because of PEDF’s broad medical value in treating major diseases,” says Sun. “But the hunt for the receptor turned out to be an extremely challenging adventure.” His team methodically searched for PEDF’s binding partner by looking at various native tissues and cells, as well as in databases of molecules with unknown functions. Finally, they found two proteins that fit the bill—PLXDC1 and PLXDC2.

As Sun’s team reported December 23, 2014, in eLife, these two proteins confer cell-surface binding to PEDF, transduce PEDF signals into distinct types of cells that respond to PEDF, and function in a cell type-specific manner. Because of the critical role of these cell-surface receptors in PEDF signaling, they have high potential as therapeutic targets for cancer and other diseases.

UNIVERSAL PROTEIN SYNTHESIS

The process of gene expression is, at its core, universal. But different organisms use different methods to carry out the “DNA makes RNA and RNA makes protein” recipe. For example, the signals used to recruit ribosomes and start protein synthesis in bacteria are not the same signals used by eukaryotes. Yet much of the structure and function of the ribosome, the molecular machine that translates RNA into proteins, is conserved in both types of organisms. This made HHMI Early Career Scientist Jeffrey Kieft at the University of Colorado Denver wonder if a universal start signal existed that could be recognized by both eukaryotic and prokaryotic ribosomes.

A structured region of an RNA molecule dubbed an internal ribosome entry site (IRES), which is used by some viruses to initiate translation in eukaryotes, fit the bill. Taking a close look at the molecule, Kieft’s team discovered that it could also initiate protein synthesis in prokaryotes. This particular IRES, it turns out, binds both bacterial and eukaryotic ribosomes in a similar structure-dependent manner, but the bacterial interaction appears transient and weaker.

The findings, published March 5, 2015, in Nature, suggest there might be other naturally occurring structured RNAs that can initiate bacterial protein synthesis. One of Kieft’s next steps will be to determine if other such structures do indeed exist, and, if so, what they mean in terms of evolution and gene regulation.