Self-regulating molecular 'transformers' control intracellular protein delivery

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Scientists from the California Institute of Technology (Caltech) have uncovered the Transformer like properties of molecules responsible for carrying and depositing proteins to their correct locations within cells. The research could eventually lead to novel treatments for diseases that result from flaws in protein delivery as well as the development of new types of antibiotics.

Shu-ou Shan, an assistant professor of chemistry at Caltech, and her colleagues looked specifically at a pair of proteins that sort cellular proteins and deliver them to their destinations--a process that is essential for establishing and maintaining cellular organization. The proteins, known as the signal recognition particle (SRP) and the SRP receptor (SR), are responsible for shuttling more than a third of all cellular proteins to their targets, including the insulin protein. The SRP/SR system is present in all three kingdoms of life, from humans and other animals, to plants and fungi, to bacteria and primitive archaean organisms.

By tracking the movement of fluorescently tagged molecules, Shan and her colleagues were able to track the behavior of SRP and SR during the protein pick-up and delivery process.

They found that the binding of a protein cargo by the SRP molecule triggered the accelerated assembly of a molecular complex containing SRP, the cargo, and the SR protein. The SRP-SR complex then delivered the cargo to the cell membrane. Once there, the SRP-SR complex

spontaneously changed its shape and deposited the cargo at the membrane, like a tiny Transformer toy morphing from a semi-truck delivering goods into a forklift that unloads them. The scientists described their discovery in a recent paper in the Proceedings of the National Academy of Sciences.

"The Transformer analogy is very appropriate," says Shan. "The 'truck' is able to sense that cargo has been loaded and starts the engine running without instructions from a driver. It can also sense that it has arrived at the destination and, without workers coming to unload the goods, is able to switch on another system to do that by itself." This self-sufficient system, she says, represents "a new way that biology builds switches to regulate complex cellular pathways."

Shan and colleagues also found that the presence of protein cargo delays the breakdown of a small-molecule energy carrier called guanosine triphosphate, or GTP, from which the SRP and SR harvest the energy to form a complex with each other and to undergo all their molecular transformations. "GTP hydrolysis is like a timer that allows the SRP-SR complex to exist for a specified period of time before turning it off. By delaying this timer, the SRP-SR complex persists about 10 times longer than it would without the cargo. This ensures that there is sufficient time for the cargo to be properly delivered to the membrane," Shan says.

"Understanding which steps are important for protein delivery by the SRP could allow the development of medications that prevent diseases that result from defects in the pathway," Shan says. For example, prion disease can be caused by tiny snippets of misfolded prion proteins that accumulate in the cytoplasm of cells when the SRP pathway does not work properly. The accumulation of cytoplasmic prions leads to the degeneration of neurons, and the eventual death of the affected organism."

The research could also lead to the development of novel artificial delivery systems that can shuttle particular proteins to specific locations, and may spur the design of new types of antibiotics that target the SRP protein in bacteria. Blocking the bacterial SRP will indeed kill bacteria, Shan says, but because humans have SRP proteins, it "will also likely affect the operation of cells in your body. Detailed mechanistic studies are required to figure out the difference between the mammalian and the bacteria SRP pathway, and find places to intervene where the bacterial SRP is uniquely susceptible."

More information: "Multiple conformational switches in a GTPase complex control co-translational protein targeting," *PNAS*.

Source: California Institute of Technology