Light-based 'remote control' for proteins inside cells developed

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Scientists at Stanford University have developed an intracellular remote control: a simple way to activate and track proteins, the busiest of cellular machines, using beams of light.

The new method, described in a paper to be published Nov. 9 in *Science*, will let researchers shine light on a specific cell region to quickly activate a protein in that area, producing an unusually fine-grained view of the location and timing of protein activity. In addition, the method may eventually enable physicians to direct the movement and activity of stem cells used to treat injury or illness in light-accessible body parts, such as the eye or skin. Stanford has filed a patent application for the work.

The method involves splicing two pieces of a specific fluorescent protein to other proteins of interest. The resulting hybrids—called fluorescent, light-inducible proteins, or FLIPs—have two interesting features: Not only are they turned on by light, but they also glow less brightly when activated, a change that provides an easy way to sense protein activity.

"It's sort of like having a garage door opener that also tells you if the garage door is open or closed," said Michael Lin, MD, PhD, an assistant professor of pediatrics and of bioengineering and the senior author of the paper. "I'm always driving out of my house, closing the garage door, and then wondering after I drive away if it's shut, so I have to drive back and check." If garage doors were like FLIPs, Lin would be spared his return trip, since these proteins not only turn on at the flip of a light

switch, but also tell an observer that they're working. "One molecule can tell you where it is and what it's doing," said Lin.

The trick to the new method is that it uses pieces of a Velcro-like fluorescent protein called Dropna. In the dark, Dropna units adhere to each other and fluoresce. Under cyan-colored light, the units detach and begin to dim. Lin's team spliced a Dropna unit to each end of the proteins they wanted to study to make the FLIPs. In the dark, the Dropna units stuck together and physically blocked the active sites of the proteins under study. When cyan-colored light was shone on the proteins, the Dropna units fell apart, exposing the protein's active site so it could work. Under cyan light, the Dropna units also glowed less brightly, signaling that the FLIP was switched on.

It's easiest to build FLIPs from proteins that fold with both their head and tail ends near the active site, though the research team is now figuring out how to attach Dropna units to other parts of a protein, not just an end. With that modification, Lin anticipates that FLIPs could be created from most proteins that scientists want to investigate.

"For science geeks, this is very interesting in that it converges two exciting fields: biological sensing, which has been dominated by fluorescent proteins, and optogenetics, the use of light to investigate biology," Lin said.

In the past, scientists who specialized in biological sensing have tagged bits of the cellular machinery with fluorescent proteins to see where certain processes occurred in the cell. Separately, optogenetics experts—using methods that originated at Stanford—have figured out how to switch on specific neuron circuits with light. Lin's method combines advantageous features of both techniques, and is the first instance of optogenetics-type techniques being applied to individual proteins.

Outside the research lab, the method could be used to give directions to stem cells injected for therapeutic purposes. For instance, if the stem cells were engineered to contain FLIPs that control cell motility, a beam of light could then direct implanted stem cells to a particular location. Similarly, FLIPs and appropriately timed light beams could be used to control what a stem cell does when it reaches its destination.

"If you think about how we might want to use stem cells to regenerate tissues, we may need control over where cells go, when they proliferate and when they die," Lin said. At present, this application seems most likely for tissues at the body's surface, such as the eye and skin, because physicians would need to be able to deliver light to the treatment site.

More information: "Optical Control of Protein Activity by Fluorescent Protein Domains," by X.X. Zhou, *Science*, 2012.

Provided by Stanford University Medical Center

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