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IMAGING

Tuning transparency in human cells

Proteins that control the optical properties of cephalopod skin cells can modulate the transparency of mammalian cells.

Reversible invisibility is widespread in the worlds of science fiction and superheroes. Although the prospect of an invisible person may seem far-fetched, there are many examples in nature of largely translucent creatures and of creatures that can rapidly and reversibly change color in response to environmental cues.

For microscopists and those interested in imaging deep into animals and their tissues, the opaque nature of most tissues can be a challenge, as it limits the penetration of light. A number of tricks can be used to mitigate these issues, including tissue clearing and imaging in the 'optical window' spectral region of tissues where the absorption of molecules like water and hemoglobin is minimal. However, versatile methods for deep tissue imaging in live specimens are still needed.

Alon Gorodetsky along with his student Atrouli Chatterjee and colleagues at the University of California, Irvine wanted to know whether they could manipulate the optical properties of human cells. Says Gorodetsky, "We were inspired not only by the real-life transparency-changing abilities of the female *Doryteuthis opalescens* squid, but also by classic works of science fiction, such as H. G. Wells's *The Invisible Man*."

D. opalescens is a remarkable creature that can modulate the color and transparency of its body. Specifically, females of the species can reversibly switch a stripe on their bodies from nearly transparent to opaque white to avoid unwanted aggression. This dramatic change in coloration is due to specialized cells called tunable leucophores in the squids' skin. These cells contain protein-based structures called leucosomes, which can alter the transmission and scattering of light on the basis of their geometry. In the case of the female *D. opalescens*, the injection of acetylcholine into the surrounding tissues can tune the transparency of the leucophore-containing stripe.

Some of the proteins that form leucosomes are called reflectins. Reflectins are widely conserved across different cephalopod species and are made of what these researchers call a "peculiar composition" of amino acids. This composition is thought to underlie the proteins' diverse self-assembly properties.

Gorodetsky and his team wanted to see whether they could express reflectins and thereby generate protein-based structures that resembled leucosomes in mammalian cells. They chose human embryonic kidney cells for their ability to effectively express proteins from other organisms and the reflectin A1 isoform for its ability to form high refractive index, stimuli-responsive architectures that strongly reflect or scatter light.

"The most surprising aspect of our results was the similarity of the reflectin-based nanostructures formed in our engineered mammalian cells to the reflectin-based leucosomes found in cephalopod leucophores," Gorodetsky recalls. Electron microscopy images of the cells revealed distinct, electron-dense nanostructure arrangements throughout the cells. These structures were also functional. Although the reflectin-expressing cells were largely transparent, when they were subjected to different salt concentrations, the cells became more opaque to light, much as is observed in the female *D. opalescens* squid.

Despite their initial success, Gorodetsky notes that there is much more to learn. "Some of the next steps would include developing an improved understanding of the structure of reflectins, as well as developing methods for better controlling these proteins' self-assembly within living systems." He also notes that, in addition to making transparent cells more opaque, similar technology could be used to make them more invisible. "One of the key aspects of our technology is the ability to adaptively change the refractive index of our cells with respect to the surroundings. The scattering of light is due to differences in refractive index within its path, so, in principle, if one can locally 'match' the refractive index to eliminate such differences, the light would not be scattered as strongly, leading to enhanced transparency."

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