Electron microscopy reveals how vitamin A enters the cell

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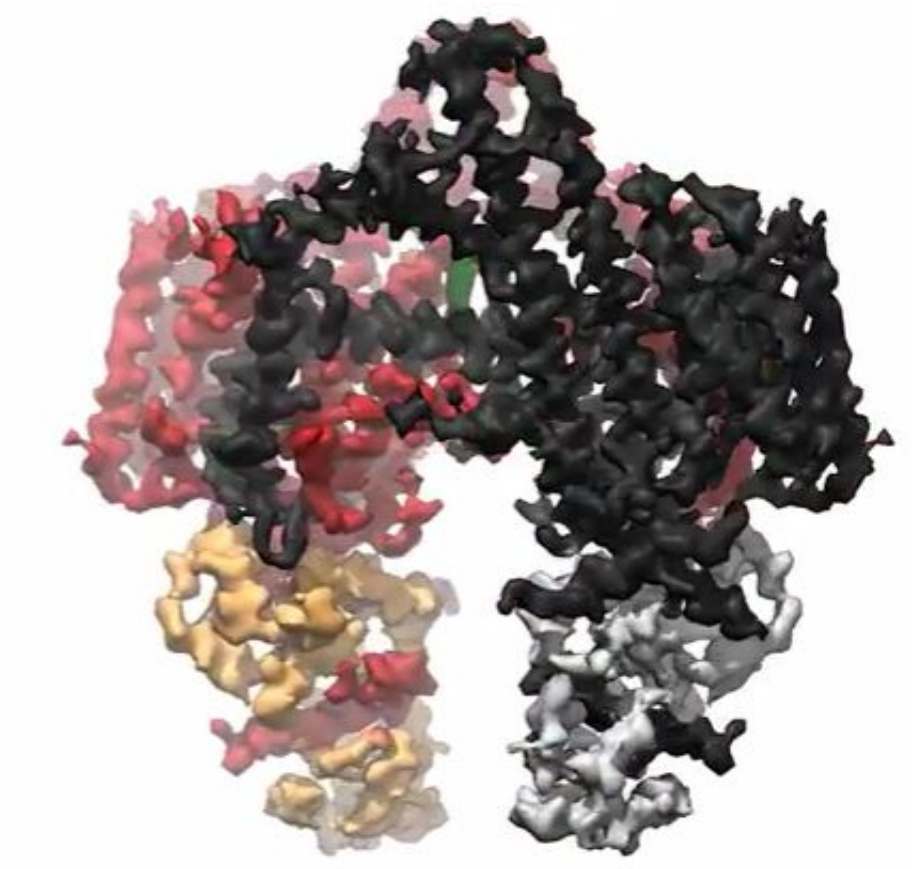

Using a new, lightning-fast camera paired with an electron microscope, Columbia University Medical Center (CUMC) scientists have captured images of one of the smallest proteins in our cells to be "seen" with a

microscope.

The protein—called STRA6—sits in the membrane of our cells and is responsible for transporting vitamin A into the cell interior. Vitamin A is essential to all mammals and is particularly important for making light receptors in our eyes, and to ensuring normal fetal development.

Images of the protein, which revealed several unusual features, were published in the August 26th issue of the journal *Science*, by structural biologist Filippo Mancia, PhD, assistant professor of physiology and cellular biophysics at CUMC. Dr. Mancia led a team of scientists, including Wayne Hendrickson, Larry Shapiro, Joachim Frank and Bill Blaner at CUMC, Loredana Quadro at Rutgers University, Chiara Manzini at George Washington University, and David Weber at the University of Maryland School of Medicine.

Until the new study, the way STRA6 transports vitamin A into the cell had been a mystery. Most transporters interact directly with the substances they move. But STRA6 only interacts with Vitamin A via an intermediary protein that carries the greasy vitamin A in the bloodstream. Revealing the structure of STRA6 may not only give the researchers insight into Vitamin A transport, but may also provide clues about how other related transporters work.

A new type of camera technology was key to obtaining the images of STRA6. When paired with an electron microscope, the camera allows biologists to see tiny, previously unseen structural details of the inner machinery of our cells.

"We can now get near-atomic resolution because the new camera is much faster and allows us to take a movie of the molecules," says Oliver Clarke, PhD, an associate research scientist in the Hendrickson lab at CUMC. "Even under the electron microscope, the molecules are moving

around by a tiny amount, but when you take a picture of something that is moving, the image is blurry. With the new camera technology, we can align the frames of the movie to generate a sharper image."

Imaging the molecule also depended on painstaking biochemical procedures, developed by Yunting Chen, PhD, an associate research scientist in the Mancia lab, to generate large quantities of the protein and separate it from the cell's other components. "It's a very delicate protein, and we had to mimic its environment to keep it from getting out of shape," she says. Those efforts took about two years to perfect.

The researchers used approximately 70,000 individual pictures of STRA6 to generate a 3-dimensional map of the protein, which was used to construct an atomic model accurate to the smallest detail. The images and model revealed that STRA6 is "a bit of a freak," says Dr. Clarke. Even more surprising was the fact that STRA6 does not work alone, but is instead tightly associated with another protein, calmodulin, which plays a key role in calcium signaling.

Although Vitamin A moves through STRA6 to enter the cell, there is no channel in STRA6 like most transporters. Instead, vitamin A enters the top of STRA6, but then appears poised to exit through a side window that opens directly into the cell membrane, not the cell interior.

Though this needs to be verified, the mechanism may be a way to protect cells from absorbing too much vitamin A. "Vitamin A is actually somewhat toxic," says Dr. Mancia. "Trapping vitamin A inside the membrane may keep control of the amount that gets into the cell."

The new model of STRA6 advances the understanding of a critical cellular function and may help researchers understand how other, still mysterious, cellular components work.

More information: "Structure of the STRA6 receptor for retinol uptake," *Science*, science.sciencemag.org/cgi/doi … 1126/science.aad8266

Provided by Columbia University Medical Center

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