Researchers find active transporters are universally leaky

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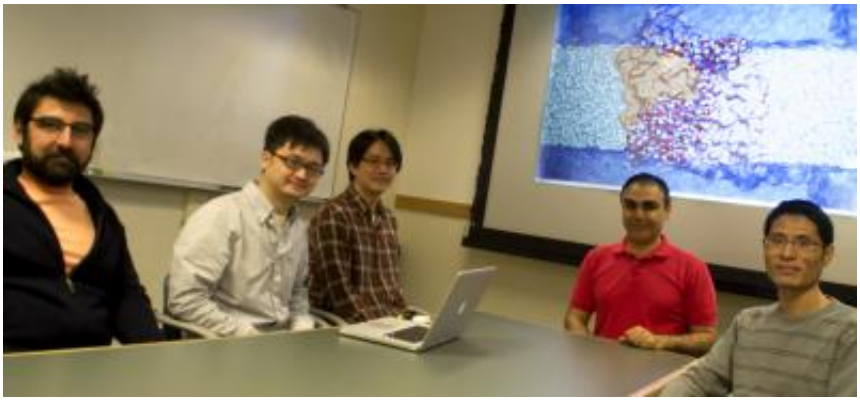

The lab group of Illinois professor of biochemistry Emad Tajkhorshid (pictured left to right: Giray Enkavi, Jing Li, Po-Chao Wen, Emad Tajkhorshid, and Zhijian Huang) found that as active transporters in cell membranes undergo conformational changes to allow their main substrates to pass through through, small molecules like water slip through as well. Credit: Chelsey B. Coombs

Professor of Biochemistry Emad Tajkhorshid and colleagues have discovered that membrane transporters help not just sugars and other specific substrates cross from one side of a cellular membrane to the other—water also comes along for the ride.

There are two main ways that molecules can cross a membrane. In passive transport, molecules are able to pass through a membrane protein called a channel (which provides a wide open pathway) to get from the high concentration side to low concentration side of the membrane. This

requires no energy as the molecule flows easily down its concentration gradient. In active transport, molecules are pumped by a membrane protein called an active transporter to get from the low concentration side to the high concentration side. This process requires energy, because the molecule must be pumped across the membrane against its natural concentration gradient.

In order to do their job, active transporters use the alternative access mechanism. At first, only one side of the transporter protein is open, allowing only substrate molecules on that side of the membrane to bind to the transporter. Then, a change in the transporter's shape occurs so that first the open side closes, and then the other side of the transporter protein opens, successfully moving the substrate molecule to its destination.

The surprise is that this perfect coordination works only for the main substrate of active transporters, while small molecules such as water seem to be able to sneak through while the protein is undergoing its shape change. The research conducted by the Tajkhorshid group suggests that this is likely a universal behavior for all active membrane transporters and a result of the very large structural changes they undergo.

Researchers study membrane proteins using a tool called molecular dynamics. "All the molecules in biology have to move to do their job. While you can see a lot of nice pictures of proteins showing their structure, but that's just a frozen state," Tajkhorshid said. "In order to describe the function of a biomolecule, you have to see its motion, and molecular dynamics is a nice way to do this. The method essentially solves the Newtonian equations of motion for all the atoms in the molecule we like to study."

The computer simulations involved in molecular dynamics determine the

motion of the transporters using algorithms that define how the atoms of a transporter interact with each other, how they interact with solvent, and how they interact with other molecules in the system. These rules are used to calculate the total force acting on every atom at each step of the transporter's motion.

However, challenges arise when doing these computer simulations because of the sheer number of atoms and the small time steps these simulations require.

"Atoms vibrate of a period of 10 femtoseconds [one quadrillionth of a second], so if you want to have ten snapshots nicely showing how it moves, you have to take a picture every one femtosecond to describe the natural motion of the system. Because we have to take such short time steps, calculating even a few microseconds of protein motion becomes computationally very expensive. Thanks to the power provided by the national supercomputing centers we have been able to accomplish such calculations." Tajkhorshid said.

Once these molecular dynamics simulations were up and running, members of Tajkhorshid's lab noticed something that they never expected to see: the transporters were leaking, allowing small amounts of water to pass through along with the substrate.

"Initially, I was surprised, because many people, including myself, assumed that these were perfect machines going back and forth between inward facing and outward facing states," Tajkhorshid said. "For almost two years, my students told me that there was some water passing through, and I just told them to repeat their simulations using more carefully designed setups, and that something was probably wrong with their simulations!"

With a little digging, the researchers found that some other labs had

experimentally shown that some transporters did, in fact, have this leaky quality.

"What we did in this work was to propose that it's not just one particular family that has this leakiness, but all of the transporters that we have been studying in the lab. We found that in all cases, every time the protein starts to undergo those large structural changes, leaks form," Tajkhorshid said.

Tajkhorshid likens this mechanism to a scenario familiar to most pet owners.

"When you open the door for someone to come in, the door has to completely open, but that provides access to small things like a dog or a cat to get out of the house. Because transporters move so much when allowing a substrate in, these leaks form, allowing water molecules in," Tajkhorshid said.

Although Tajkhorshid doesn't believe transporter leakiness plays a physiological role in the cell, this discovery adds some interesting new knowledge to the field about transporters.

"Transporters are extremely important proteins, and we would love to understand their function and how they move. If we understand that better, then we might be able to design better, more specific drugs for transporters," Tajkhorshid said.

More information: The paper, "Transient formation of water-conducting states in membrane transporters," is available online.

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