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RESEARCH NEWS

Claudins get a closer look

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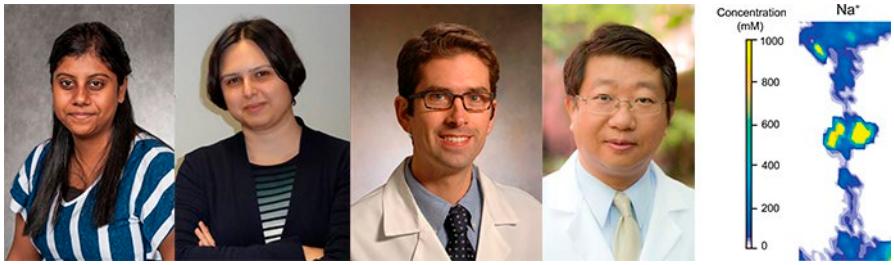
***JGP* study examines claudin-15 ion selectivity and permeation.**

Epithelia form a barrier to regulate the exchange of materials between a tissue and its environment. To do this, the cells that make up an epithelial sheet seal with their neighbors using tight junctions. Tight junctions restrict the flow of materials through the space between epithelial cells, but they are not simple plugs; tight junctions incorporate channels, formed by proteins called claudins, to allow the passage of ions and water through the space between cells. Different claudins selectively allow passage of different ions or molecules, and claudin-2 is known to be gated so the channels can open and close (1). However, how claudins accomplish selectivity and gating is currently unknown. In this issue of the *Journal of General Physiology*, Samanta et al. explore the structure of claudin-15 channels and explain how this claudin's selectivity filter works (2).

"My colleague, Dr. Le Shen, and I have been studying claudins for more than 10 years because there are several conditions, particularly in the intestines, where tight junctions are altered," says Dr. Chris Weber, from the University of Chicago. Each epithelial surface in the body is distinguished by a different complement of claudins; the gut epithelium expresses claudin-2 and claudin-15.

"Claudin-2 and claudin-15 are selective for positively charged molecules, and without claudin-15, the GI tract cannot absorb glucose, because sodium passing through those channels is critical for driving glucose absorption," elaborates Shen, also from the University of Chicago.

The recent publication of a claudin-15 crystal structure (3) enabled researchers to construct a model (4) for how claudins might form channels. The model suggests that two cells partner to form claudin channels: one cell contributes two claudin molecules, whose extracellular portions join together to form one half of a barrel-shaped pore, and the neighboring cell mirrors this arrangement to contribute the other half. Subsequently, computer simulations confirmed some features of this model (5), but the structural basis for claudin-15's cation selectivity, and the pathway used by ions to transit the channel, remained unclear. Weber and Shen collaborated with Dr. Fatemeh Khalili-Araghi at the University of Illinois at Chicago to study claudin-15 more closely. Priyanka Samanta, a graduate student in Khalili-Araghi's laboratory, spearheaded the simulation efforts.



Left to right: Priyanka Samanta, Fatemeh Khalili-Araghi, Christopher Weber, Le Shen, and colleagues (not pictured) studied claudin-15 structure and ion permeation (see simulation at right). Photos courtesy of the authors.

"We used all-atom molecular dynamics simulations of this protein at large scale to build a model that could actually capture the ion permeation and selectivity features of claudin-15," says Khalili-Araghi. "These are relatively large simulations because these channels are formed by the assembly of many monomers and we are including everything—lipid, water, and protein—in all-atom detail."

The simulations, performed over two years on the Blue Waters supercomputer at the University of Illinois' National Center for Supercomputing Applications at Urbana-Champaign and at UIC's High Performance Computing Cluster, revealed how positively charged ions are shepherded through the channel via interactions with certain negatively charged amino acids lining the channel's mouth and pore. They also demonstrated that a particular amino acid, the aspartate at position 55 (D55), forms the channel's ion selectivity filter. Four D55 residues (one contributed by each claudin-15 monomer) jut into the center of the channel's pore to govern ion flow.

Simulations predicted that altering D55 and certain other amino acids to positively charged or neutral ones would alter the channel's selectivity. The authors inserted these mutations individually into claudin-15, expressed the mutant proteins in kidney epithelial cells, and examined whether the channel behaved similarly to the simulations. It did.

The simulations run by Samanta et al. also provide insight into aspects of channel function that would be difficult to measure experimentally, such as how water passes through the channel. The authors next plan to leverage their detailed model to study complex problems such as gating, and the selectivity of other claudins.

1. Weber, C.R., et al. 2015. *eLife.* 4:e09906.
2. Samanta, P., et al. 2018. *J. Gen. Physiol.* https://doi.org/10.1085/jgp.201711868
3. Suzuki, H., et al. 2014. *Science.* 344:304–307.
4. Suzuki, H., et al. 2015. *J. Mol. Biol.* 427:291–297.
5. Alberini, G., et al. 2017. *PLoS One.* 12:e0184190.

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