Crystal-Clear Water Transport

It is now well-established that the water channel aquaporin-1 (AQP1) corresponds to the ultrasmall pores located in endothelial cells lining the peritoneal capillaries. These transcellular pores greatly facilitate the transport of water during peritoneal dialysis with hypertonic glucose as the osmotic agent—that is, crystalloid osmosis. The functional importance of AQP1 in peritoneal dialysis has been evidenced by studies in knock-out mice: deletion of the water channel is reflected by a 50% decline in ultrafiltration and the disappearance of sodium sieving (1).

Aquaporin-1 is characterized by a high permeation rate (3 billion water molecules per second) and a strict selectivity for water (no permeability for protons or other ions). Previously, available crystal structures revealed that each AQP1 molecule acts as a water channel, with six membrane-spanning α-helices surrounding an hourglass-shaped central pore. Two symmetrical loops that insert into the lipid bilayer from opposite sides of the membrane form a seventh, pseudo-transmembrane α-helix. These two conserved segments each contain an asparagine–proline–alanine (NPA) motif near the center of the pore and a selectivity filter (arginine and histidine residues) on the narrowest extracellular side of the channel. Together, those two elements orient water molecules and facilitate their transport through the pore, while blocking the transport of protons (2).

In a recent tour de force, Kosinska Eriksson *et al.* (3) detailed water flow inside the pore by reporting the radiographic structure of the yeast aquaporin-1 (Aqy1) at an unprecedented resolution of 0.88 Å (less than 1×10^{-10} m). Because they achieved such a high resolution, those authors were able to demonstrate the hydrogen bonding between the key residues along the critical NPA and selectivity filter domains and the water molecules. Their data showed that the flow of water molecules through the pore in a pairwise fashion involves the asparagine residues of the NPA regions and also substantiates the role of the histidine and arginine residues in the selectivity filter. Dynamic simulations capturing water movement in the pore evidenced a correlated, pair-wise movement of water molecules within the selectivity filter, which contains four stable water positions. Because those positions are very close, the two water molecules are separated by an empty position—in other words, 1,3

or 2,4 occupancy. That mechanism, which resembles the mechanism operating in potassium channels (4), represents the optimal configuration for facilitated water transport (3).

The take-home message: High-resolution radiography of structure coupled with simulations of molecular dynamics has resolved the complex mechanism supporting the selectivity and the high permeation rate of the AQP1 water channel. Those two functions are essential for achieving ultrafiltration with glucose-based dialysates during peritoneal dialysis. The availability of an exquisite structure of AQP1 will be useful in view of current efforts to discover new ways to regulate water transport (5).

Olivier Devuyst
Deputy Editor

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