Aquaporin2

Trafficking, Mutations, and Diabetes Insipidus

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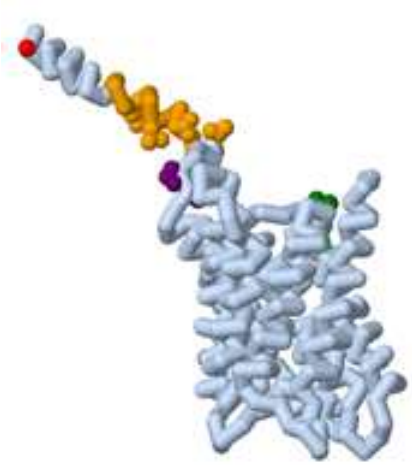
Vahedi-Faridi, A., Lodowski, D., Engel, A., Transcontinental EM Initiative for Membrane Protein Structure**.** The Structure of Aquaporin (unpublished work but information deposited for pdb file 4OJ2)

PDB Files: 4OJ2, 4NEF (Models below are from 4OJ2, Web page images shows elements of from both files)

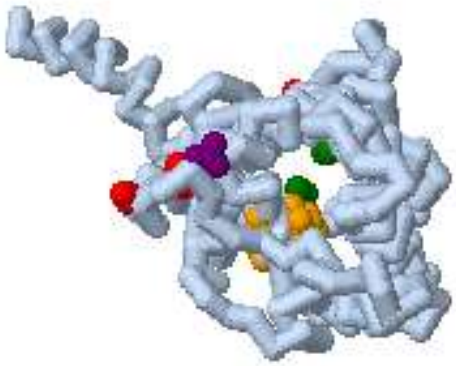
Located in the collecting duct cells of nephrons, Aquaporin 2 (AQP2) protein is an intramembrane water channel essential in regulating water levels in the body. Found in intercellular vesicles within the collecting ducts, AQP2 is trafficked to the apical membrane by a series of chemical events initiated by ADH (antidiuretic hormone). After the channels are inserted in the membrane of collecting duct cells, water is able to be reclaimed from the urine to the blood in response to the osmotic gradient. Once water levels are restored, ADH is no longer released from the brain which causes aquaporin 2 to be removed from the apical membrane. As such, this protein plays an important role in everyday water regulation and is critical in the disease, diabetes insipidus, described below.



Important Trafficking Residues

An essential part of the trafficking of the aquaporin 2 from the intracellular vesicles to the apical membrane is the phosphorylation of serine 256 (red). Protein kinase A phosphorylates serine 256 which initiates transport of the aquaporin along the microtubule to the apical membrane for exocytosis. The flexibility of the carboxyl tail needed for the availability of serine 256 is aided by residues proline 225 and 226 (purple). Additionally, glutamic acid 3 (not pictured), arginine 85, and serine 82 (green) are important in the trafficking of aquaporin 2 because they stabilize the N terminus. Once water levels are restored, aquaporins are removed from the apical membrane. The lysosomal degradation of aquaporin 2 is assisted by the attachment of the aquaporin to LIP5. LIP5 binds to the aquaporin at leucine 230, 234, 237, and 240 (orange).

Discoveries have revealed that over 40 potential aquaporin 2 mutations exist, some of which lead to complications such as nephrogenic diabetes insipidus (NDI). This disorder causes increased urination and thirst due to the inability of the body to reclaim water within the collecting ducts of the nephrons. These mutations cause various dysfunctions of the aquaporins which can be seen in the diagram above. For instance, channeling mutations of asparagine 68, alanine 70, and proline 185 have been found to impact the NPA region and the selectivity filter regions (yellow). Mutations of valine 71 and 168 result in the narrowing of the pore which contributes to reduced water trafficking. Other mutations have different effects on aquaporins. A mutation at asparagine 123 (purple) prevents glycosylation of the aquaporin, leading to aquaporin retention in the Golgi apparatus of the cell. Another mutation involves residues threonine 125 and 126 and aspartic acid 150 (red) which causes the hydrophobic regions of the protein to be exposed, leading to the hydrolyzation of the aquaporin. Ultimately, the aquaporin is unable to leave the endoplasmic reticulum.



Residue Locations of Some Key Mutations

Bibliography:

National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD): The Library; 2016 March 14. AQP2- Aquaporin 2 – Genetics Home Reference; [Reviewed 2010 April; Published 2016 March14 2013 Sep 19]. Available from: https://ghr.nlm.nih.gov/gene/AQP2