Allowing Water to "Go with the Flow"

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Aquaporins are channel proteins found in cell membranes that carry out the vital function of transporting and filtering water within cells in almost all living organisms. Aquaporins, which were discovered only a quarter of a century ago, play a major role in diseases such as diabetes insipidus due to the regulation of water intake and release from vital organs. Thirteen different aquaporins are expressed in humans; however, aquaporins are found in all living organisms, ranging from animals to plants to bacteria. Aquaporin monomers consist of six long segments of helices and two short segments of helices which encompass a narrow transmembrane channel through which water travels through in single file. Just one human AQP1 molecule has a permeation rate of three billion molecules per second, the direction of which changes depending on the prevailing osmotic gradient.

Aquaporins must be highly selective in order to perform their specific functions which is achieved with the functions of two vital regions that facilitate the selection of water molecules and the exclusion of all other substances: an ar/R filter and an NPA motif. The positively charged ar/R filter allows the aquaporin to bind to water molecules and to weaken the hydrogen bonds to allow it to readily interact with the filter. Meanwhile, the NPA motif involves the local electrical fields of the atoms and amino acids along the water channel walls, which cause water molecules passing through the channel to rotate and orient themselves towards the atom's positive charge. Because of the positive charge at the center of the channel, protons and cations are prevented from passing, thereby regulating the balance of protons inside and outside of the cell membrane.

Aquaporin function is vital to major organs of the body, especially the kidneys. The kidneys filter 120 to 150 quarts of blood per day into one to two quarts of urine. There are at least seven different aquaporins that facilitate this process, but AQP2 is key in the reabsorption of water in response to antidiuretic hormone (ADH). When an insufficient amount of fluid is present in the blood, the hypothalamus in the brain signals the release of ADH from the posterior pituitary gland. Once in the bloodstream, ADH attaches to a receptor in the plasma membrane that signals the aquaporin to be moved to the apical membrane of the collecting duct cell to begin channeling water into the cell. ADH is important for concentrating urine by signaling water reabsorption to occur by moving water into the bloodstream in response to the osmotic gradient.

One disease associated with problems with the aquaporins is known as *diabetes insipidus* which results in an organism's inability to concentrate urine and is characterized by frequent urination

and excessive thirst. Two types of *diabetes insipidus* are neurogenic, in which the brain is unable to produce ADH, and nephrogenic, in which problems in the kidney inhibit normal functioning of the aquaporins. Although most cases of nephrogenic diabetes are caused by problems associated with the ADH receptor, four main types of aquaporin mutations can contribute to nephrogenic diabetes insipidus as well. One type of mutation affects the channel of the aquaporin, preventing the pore from functioning correctly. The mutations in the channel affect the functioning of the NPA region and the selectivity filter which causes the pore to narrow which may render the pore ineffective. The second main mutation affects the structure of the aquaporin which results in its inability to leave the endoplasmic reticulum of the cell. Aquaporin residues responsible for binding are affected by these mutations, which means the aquaporin cannot be trafficked; therefore, it remains in the E.R. to be destroyed by proteases that recognize the mutations. The third main mutation affects glycosylation, causing the aquaporin to be retained in the golgi apparatus or inside the vesicles within the cell. These mutations inhibit the aquaporin from being trafficked to the apical membrane. The final, most dominant mutation causes the aquaporin to be misrouted to areas in the cell rather than to the apical membrane.

Primary Citations:

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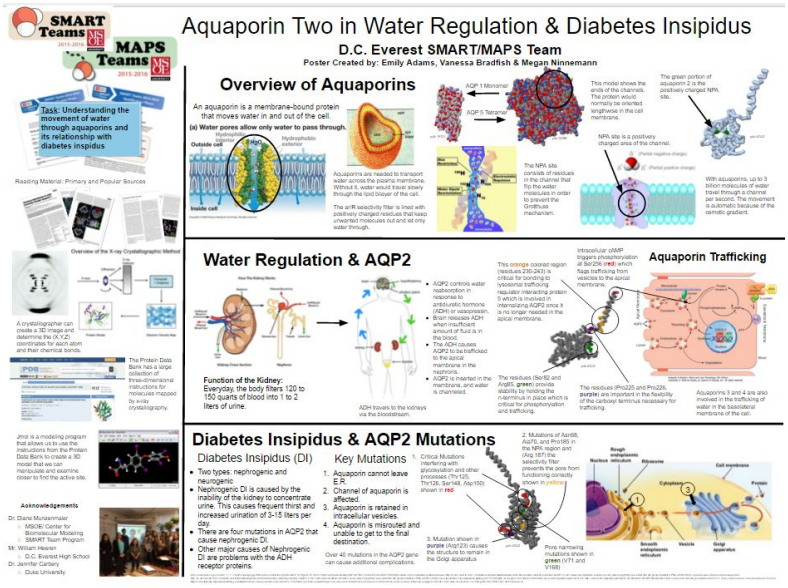

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