INHIBITORS OF AQUAPORINS AS NOVEL ANTI-CANCER DRUGS

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Abstract: Aquaporins are channel proteins that allow rapid transport of water and small molecules across the membrane. Thirteen mammalian AQPs (AQP0-AQP12) have been described and are expressed in a variety of human tissues. AQPs have recently been implicated in various diseases such as cancer, cataract, brain edema, gallstone disease and nephrogenic diabetes insipidus, as well as in the development of obesity and polycystic kidney disease. Recently, expression of AQP1 was found to be involved in tumorigenesis. AQPs share several conserved amino acid sequences, including two asparagine-proline-alanine (NPA) motifs, with overall amino acid identities of 30-60% after sequence alignment. Peptides like Vasopressin; small molecules like tetraethylammonium, acetazolamide; and metal ions all interact with AQPs. Addition of monovalent sodium ions increases the water influx whereas the addition of bivalent cations like mercury and cadmium block the transport. In the case of tetraalkylammonium compounds only TEA and to some extent its propyl analogue inhibit water transport. Other tetraalkylammonium analogues methyl, butyl, pentyl, hexyl do not inhibit water transport. It is also reported that fertilizers like DDT and surfactants like non-octylglycosides could interact with AQP. Such differential binding indicates the specificity and affinity of AQP-ligand interaction. We hypothesize that metal ions and small molecules in water recognize specific motifs in the loop structure thereby controlling the 3D structure, pore constriction and hence modulating water permeability. A combination of sequence analysis and molecular modeling were used to test the hypothesis. We have constructed a comprehensive Protein-Metal Ion Site-frequency (ProMIS) dataset by mining RCSB-Protein Data Bank (http://www.rcsb.org/pdb) and Protein ligand interaction using occluded surfaces analysis post structural modeling. Based on a scoring matrix constructed from ProMIS, we evaluated the likelihood of common mono/bivalent metal ions interaction with the AQP loops. Loop E sequences of most of the mammalian AQPs showed higher ProMIS scores for the bivalent metal ions Hg²⁺ and Cd²⁺ in comparison to the loops A or C suggesting a site for biomolecular control of water transport. Tetraalkylammonium compounds specifically interacted with charged residues in the C and E loop. Our observations provide valuable insight into membrane protein recognition, ionic control of water transport and structural basis for anti-cancer drug discovery.

Keywords: Aquaporins, anti-cancer drugs, drug discovery, inhibitors, water transport.

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