Development of new computational workflow for the identification of hAQP5 modulators

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Aquaporins (AQPs) are membrane channels which facilitate the flow of water and other small molecules, such as glycerol, across biological membranes. They play a crucial role in cell homeostasis and volume regulation, being widely distributed in all organisms. In mammals, there are three subsets of AQPs, divided according to their permeability profiles and sequence homology. Due to its biological importance, deregulation of AQPs activity and/or expression can induce changes in the cell homeostasis, causing health problems and diseases, such as carcinogenesis (1-3). The relationship between AQPs and cancer has been thoroughly studied and, as a result, it was concluded that AQPs are overexpressed in a wide variety of tumors, especially AQP1, AQP3 and AQP5 isoforms. Moreover, the discovery of efficient and selective modulators of human AQPs (hAQPs) has been considered as a potential strategy for cancer treatment/therapy. However, the inhibitors reported thus far exhibit high toxicity and poor selectivity, making them inappropriate to proceed for drug development. (4). Therefore, the main goal of this work, was to develop and apply a new computational workflow to identify hAQP5 modulators from a Sigma-Aldrich database of compounds. This approach combined the use of Molecular Dynamics, Molecular Docking, and MM-PBSA methodologies, allowed for the identification of compounds with high affinity for hAQP5 (5). The five most promising hits were experimentally tested for their inhibitory effect on hAQP5 in an optimized yeast cell model expressing this isoform, by permeability assays using the fluorescence stopped-flow technology. Here, we present and discuss our results highlighting the limitations of our approach and propose the future methodological perspective that will be pursued to find better and specific hAQP5 inhibitors.

Keywords: hAQP-5; AQP modulators; structure-based drug discovery; water permeability; stopped-flow spectroscopy

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