Comparative analysis of weighted amino acid networks of the sodium-dependent phosphate transporter NaPi2b

Vlasenkova R.A.[1], Kozlova A.S.[2], Akberova N.I.[1], Kiyamova R.G.[1], Bogdanov M.V.[2]

[1]"Biomarker" Research Laboratory, Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan, 420008, Russia
[2]McGovern Medical School, The University of Texas Health Science Center, Houston, USA
E-mail: r.mukhamadeeva@yandex.ru

The active roles of individual amino acids within the protein are determined by various factors, including nearby amino acids, secondary structure, and post-translational modifications. Comparison of Weighted Amino Acid Networks (WAANs) of proteins with different molecular characteristics allows us to explore topological information and capture the global connectivity in proteins.

Sodium-dependent phosphate transporter NaPi2b is a membrane protein that belongs to the SLC34 family, it is a marker of ovarian and other cancers [1]. We assume that the MX35 epitope that located in the large extracellular domain (ECD) and is recognized by the MX35 antibody in tumor cells has tumor-specific conformation due to the presense of disulfide bonds within ECD [2].

The aim of this work was to develop robust algorithm for comparative analysis of WAANs based on amino acid residue characteristics of NaPi2b with the absence and the presence of potential disulfide bonds within ECD.

The NaPi2b structure was predicted and thermodynamically stabilized by Molecular Dynamics. Two potential disulfide bonds (aa 303-328, aa 328-350) were introduced into ECD by Controlled Molecular Dynamics. WAANs were constructed, the weights were determined by several parameters of amino acid residues. Clustering of the WAANs was performed using proximity propagation of adjacency matrices, and the similarity score was calculated for each cluster. The overall similarity score was calculated as the median of the cluster scores.

This algorithm that takes into account the amino acid residue interactions and weights, as well as the topology of the WAANs was utilized to compare the WAANs of NaPi2b with and without disulfide bonds. The similarity scores of WAANs were as follows: no bond vs 303-328 − 0.85, no bond vs 328-350 − 0.83, 303-328 vs 328-350 − 0.87. The scores of WAANs showed the difference not only in the ECD where two potential disulfide bonds (aa 303-328, aa 328-350) were introduced but in several other extra- and transmembrane domains of NaPi2b.

This paper has been supported by the Kazan Federal University Strategic Academic Leadership Program (PRIORITY-2030).

1. Kiyamova R.G., Vlasenkova R.A., Bulatova L.F. Sodium-dependent phosphate transporter NaPi2b as a candidate for targeted therapy: features of structure, function, and expression. Advances in Molecular Oncology. 2024;11(2):74-84.
2. Bulatova L, Savenkova D, Nurgalieva A, et al. Toward a Topology-Based Therapeutic Design of Membrane Proteins: Validation of NaPi2b Topology in Live Ovarian Cancer Cells. Front Mol Biosci. 2022;9:895911.