Unusual folding of NaPi2b transporter extramembrane domain 4 during malignant transformation

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Abstract

Background

Searching for specific targets in cancer diagnosis and treatment is one of the most important problems in clinical oncology. We put forward a new concept of the emergence of tumor-specific epitopes of integral membrane proteins by changing their topology under mutations, glycosylation and tumor conditions including low pH and hypoxia on the model of Na-dependent phosphate-cotransporter NaPi2b. NaPi2b (SLC34A2, NaPi-IIb, NPT2b) belongs to the SLC34A2 transporters family and is involved in maintaining phosphate homeostasis in the human body. NaPi2b express in a number of normal and malignant tissues, including ovarian, breast and triple-negative breast cancer. It is an integral membrane protein with a large extramembrane domain 4 (EMD4, 234-362 aa), 8 transmembrane domains, N - and C - ends located in the cytoplasm.

Methods

We have cloned the epitope for antibodies MX35 and L2 (20/3) within 311-340 aa region of NaPi2b, which recognition depends on disulfide bonds, glycosylation and is canceled by the mutation at the T330V position. Topology of the protein undergoing significant changes in hypoxia and low pH conditions.

Results

N-terminal domain of NaPi2b can be localized outside the cells during hypoxia and low pH and return to its primary topology at the inner leaflet membrane in normoxia conditions. This reorientation makes it as a potential tumor-specific domain.

Conclusions

The obtained data are of both fundamental and applied importance in the development of new targeted antitumor drugs of high specificity.

Clinical trial identification

Editorial acknowledgement

Legal entity responsible for the study

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Disclosure

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