

Features of the expression of WNT, Hedgehog and NOTCH signaling pathways in HER-2 overexpressed and triple negative subtypes of breast cancer with high and low content of stem tumor cells.



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Background & Objectives

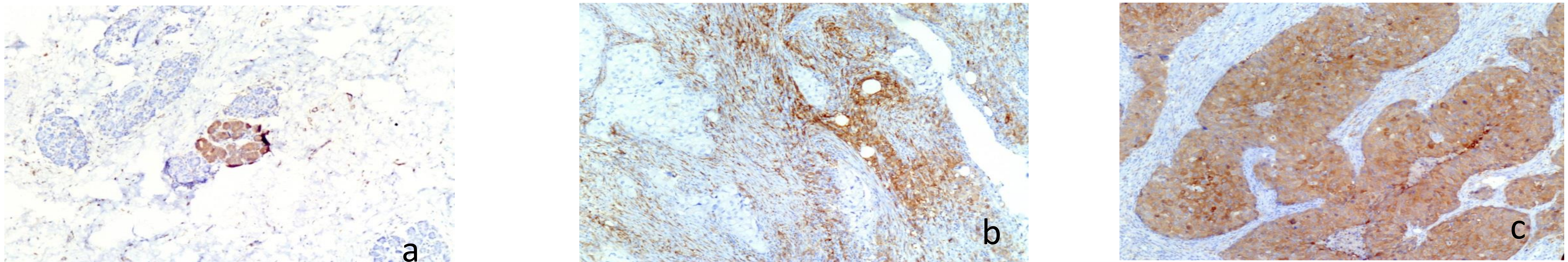
There are three main cascades - WNT, Hedgehog and NOTCH, occur in cancer stem cells during the embryogenesis. However, the conducted studies indicate the existence of other signaling mechanisms of regulation - NF- κ B and PI3K signaling pathways. In our work, we investigated the expression of NF- κ B, PI3K, PTEN molecules, as well as WNT, Hedgehog, NOTCH in cells of triple negative and HER-2 overexpressed breast cancer with high and low content of cancer stem cells (positive and negative ALDH1A1 expression). There are two immunohistochemical subtypes of breast cancer with high content of cancer stem cells – triple negative and HER-2 overexpressed. Cancer cells of these subtypes have high level of proliferation and do not have receptors for estrogen and progesterone, and that's why it is necessary to find additional targets for chemotherapy.

Methods

We studied material of 110 cases of invasive breast cancer. To determine the stem cells in the tumor population, the presence of ALDH1A1 protein in cancer cells was investigated. In all cases, expression of estrogen, progesterone receptors, as well as expression of HER-2 and Ki-67 protein, was studied by immunohistochemistry to determine a subtype of breast cancer. The expression of the signaling pathways molecules PI3K, NF- κ B, PTEN, WNT, Notch, Hedgehog was also determined.

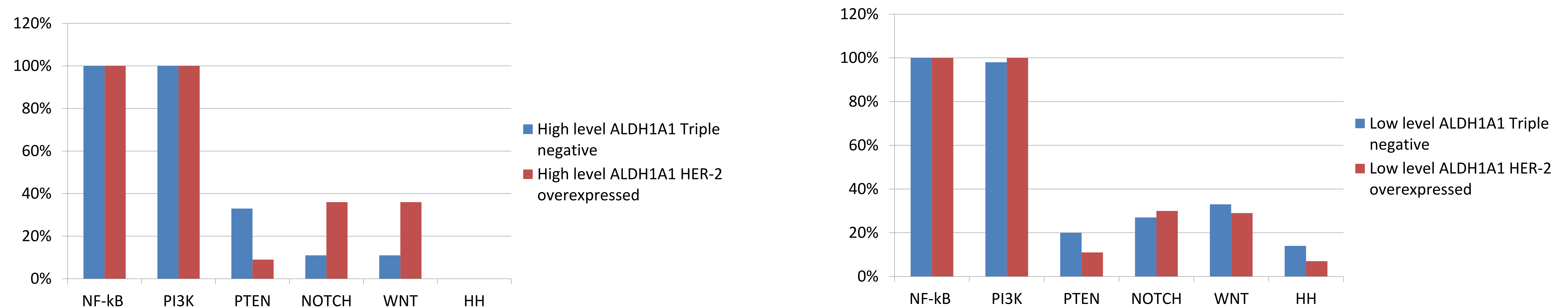
Results

All cases were investigated for ALDH1A1 expression and were divided into two groups - with low (expression of ALDH1A1 was estimated as 0, 1+) and high (expression of ALDH1A1 was estimated as 2+, 3+) content of cancer stem cells. (pic.1)



Picture 1. ALDH1A1 expression in breast cancer

a (1+) amount of positive cells $\leq 10\%$, b (2+) amount of positive cells more than 50% and less than 10%, c-3+) amount of positive cells more than 50%



Picture 2. The features of distribution signaling pathways in groups with high and low level ALDH1A1 expression.

It was found, that cancer cells of all cases of Triple negative and HER-2 overexpressed subtypes expressed NF- κ B, PI3K signaling pathways molecules. Activation of Notch and WNT signaling pathways was more common for cells of HER-2 overexpressed subtype than Triple-negative subtype ($p < 0.05$) in the group with high level of ALDH1A1, while in the group with low level of ALDH1A1, expression of NOTCH and WNT in cancer cells of both subtypes was not significantly different ($p > 0.05$). We did not find any activity of Hedgehog (HH) signaling pathway in the group with high level of ALDH1A1, while in the group of low level of ALDH1A1, expression of HH signaling was positive in some cases, and besides, it was higher in cancer cells of Triple negative subtype than HER-2 overexpressed subtype ($p < 0.05$). (pic.2)

Conclusion

Expression WNT, Hedgehog and NOTCH signaling pathways in HER-2 overexpressed and triple negative subtypes is different in HER-2 overexpressed and triple negative subtypes and depends of ALDH1A1 positive cells presence.