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56693 THE TYPE 3 DEIODINASE IS HIGHLY EXPRESSED IN BREAST CANCER

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Introduction: Thyroid hormone (TH) status regulates the balance between proliferation and differentiation in normal and tumoral cells. An altered TH status can contribute to the development of tumors. Intracellular T3 bioavailability is controlled in a tissue-specific manner, depending primarily on its activation by type 2 deiodinase (D2) and inactivation by type 3 deiodinase (D3). D3, a known fetal protein, is mainly responsible for TH inactivation. D3 is reactivated in several human neoplasias, and it has been associated with tumor behavior. Breast cancer is the most common cancer in women worldwide. D3 status in breast cancer is unknown and could contribute to tumor progression. **Objectives:** To evaluate D3 expression in breast cancer and its correlation with tumor subtype and TNM staging. **Methods:** D3 expression in breast cancer samples was analyzed by immunohistochemistry (IHQ) using anti-D3 antibodies. Samples were classified into four subtypes: luminal A, luminal B, triple negative and HER2. D3 expression was quantified by H-score. For further studies, estrogen receptor positive (ER+) (MCF-7) and ER- (MDA-MB-231) cell lines were used. Cell proliferation was analyzed by cumulative population doubling. Cell cycle distribution and apoptosis were assessed by flow cytometry after staining MCF-7 and MDA-MB-231 cells with propidium iodide (PI) and Annexin V/PI, respectively. Protein levels of D3 after treatment with T3 and with/without specific siRNA was evaluated by Western Blotting using anti-D3 antibody and was quantified using image densitometry. **Results:** D3 expression was observed in all breast cancer subtypes analyzed, as well as in ER+ (MCF-7) and ER- (MDA-MB-231) cell lines. Interestingly, MDA-MB-231 cell proliferation was reduced by 35% ($p = 0.004$) after 48 hours of transient D3 silencing (D3 siRNA) whereas MCF-7 proliferation was not significantly affected by D3 transient inhibition in the presence or absence of T3 (100 nM). To further explore the effects of D3 knockout in breast cancer cells, we intend to use CRISPR/Cas9 technology to selectively modulate enzyme expression and intracellular T3 levels in different breast cancer cell lines. **Conclusion:** Our results demonstrate that D3 is highly expressed in breast cancer, and the inhibition of D3 activity is associated with reduced proliferation in an estrogen negative cell line.

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