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Epigenetics of breast cancer and possible culprits in inducing metastasis in estrogen receptor alpha-positive breast cancer

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IndiaEstrogen receptor (ER) expression is the main indicator of potential responses to endocrine therapy (ET), and approximately 70% of human breast cancers (BCs) are hormone-dependent and ER-positive. Breast cancer that has spread to other organs is called metastatic cancer; it tends to be harder to treat and to have poorer outcomes. More effort is needed to explore drug targets that specifically aim at metastatic breast cancer. The findings of our laboratory showed estrogen-related receptor beta (ERRβ) to be a prognostic marker for breast cancer. Mechanistic analyses indicate that ERα directly targets ERRβ through estrogen response element and ERRβ also mediates cell cycle regulation through p18, p21cip and cyclin D1 in breast cancer cells. One of the histone modifier EZH2 is significantly associated with increased breast cancer progression. We identified a strong association between nicotine and EZH2 particularly in the progression of breast cancer in smokers through a novel axis involving nicotinic acetylcholine receptor and well-known transcription factor Myc. In addition, NEDD8 is an emerging molecule in the field of translational protein modification and regulation. A well-known substrate of NEDD8 is TP53 tumor suppressor protein. TP53 plays a critical role in inducing cell cycle arrest and apoptosis. Its loss or inactivation is a sine qua non of cancer. Consequently, therapies directed at restoring p53 function particularly its ability to induce apoptosis is a major focus of different cancer therapy including breast cancer and brain tumor. We are investigating the impact of NEDDylation on the activity of p53 and its activated form TP53-8D20D. Although NEDDylation of TP53 stabilizes it, its effect on p53 transcriptional activity is not well understood and obscure. In conclusion, chromatin modifiers such as NEDD8 and EZH2 are potential culprits that play a crucial role in breast cancer progression and metastasis.

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