Histone Deacetylase Inhibitors Reprogram Triple Negative Breast Cancer to be Less Aggressive by Targeting Cell Proliferation, Metastasis, and Cancer Stemness

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Triple negative breast cancer (TNBC) is highly aggressive and the most difficult type of breast cancer to treat due to its lack of receptors to target. Novel studies have explored the epigenetic mechanisms to i nhibit or reverse aggressive characteristics of this subtype of breast cancer. Histone deacetylases (HDA Cs) control gene expression by changing the chromatin conformation to a closed state, which leads to t ranscriptional repression of certain genes. Recent studies have suggested that specific inhibitors targeti ng HDAC may cause tumor suppressor genes to be re-expressed in cancer cells, reversing cancer progr ession. Epigenetic mechanisms may also play a role in reprogramming cancer stem cells (CSCs) in TNBC . CSCs are primarily drivers of recurrence and metastasis, and therefore associated with poorer progno ses. In this study, we have examined the effects of HDAC inhibitors on cell proliferation, metastasis, and cancer stemness in TNBC cells. Two TNBC cell lines, 4T1 and SUM-159, were treated with the HDAC inh ibitors, Vorinostat (SAHA) and Panobinostat, and their effects on cell proliferation, tumor suppressor ge nes and metastatic markers were determined by MTT assay and qPCR analysis. HDAC inhibitors on the formation of mammospheres and the stemness properties were further determined. We found that H DAC inhibitors decrease cell proliferation and downregulate cancer genes such as MYC, NFKb, and MM P9 while upregulating tumor suppressor genes such as CDKN1a. HDAC inhibitors have a modest effect on mammosphere forming efficiency and the CD24low/CD44high subpopulation. In conclusion, HDAC i nhibitors target the cell proliferation pathway and to a lesser extent cancer stemness in TNBC. Supporte d by NIH R25ES020721.