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"Epigenetic Reprogramming of Breast Cancer Cells into Dormant Cancer Stem Cells"

By

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Monday, March 6th, 2023
9:00 A.M.
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ABSTRACT

Metastasis of breast cancer cells (BCCs) to the bone marrow (BM) correlates with poor prognosis. In BM, BCCs can remain undetected as dormant cells for decades. Since dormant BCCs have cancer stem cell (CSC) properties, they can initiate tertiary metastasis during cancer resurgence. Additionally, BC progenitors can dedifferentiate into CSCs. This process can occur through interactions with BM niche cells and by cell-autonomous methods. In order to understand the process of BC dormancy, this thesis used previously deposited and new RNA-seq analyses to identify molecules potentially involved in dormancy and CSC regulation. *In silico* analyses predicted that BCCs dictate the release of the histone 3, lysine 4 (H3K4) methyltransferases, KMT2B and KMT2D, and DNA methyltransferase (DNMT1) from BM mesenchymal stem cells (MSCs) to transition into dormancy. Therefore, this thesis tested the hypothesis that cell-autonomous regulation of CSCs is mediated by KMT2B, KMT2D, and DNMT1. *In vitro* interrogation of the role of H3K4 and DNA methylation in BCCs with pharmacological inhibitors revealed a significant decrease in CSCs and a concomitant increase of BCC progenitors, indicating a role for these epigenetic factors in maintaining CSCs. These findings were confirmed in BCCs with knockdown for KMT2B, KMT2D, and DNMT1. Moreover, the knockdown BCCs were significantly sensitive to chemotherapy *in vitro* and *in vivo*, indicating that these factors are potential therapeutic targets for BC. An examination of BCC-mediated changes in MSCs showed that MSCs can retain multipotency, but they transitioned into CXCL12-Abundant reticular (CAR) cells. This transition allows the MSCs to interact with the dedifferentiated BCCs for protection in the BM. Furthermore, we showed that MSC-derived exosomes blunt the differentiation of KMT2B, KMT2D, and DNMT1 knockdown BCCs, suggesting that other molecules can promote BC dormancy. These findings support the key role of the BM microenvironment in BC dormancy and further indicate the consideration of BM niche cells during treatment. Overall, this thesis provides crucial insights into the epigenetic regulatory mechanisms underlying BC dormancy and shows how BCCs leverage BM microenvironmental cells to evade treatment.