

**Mesenchymal stem cells regulate the epigenetic landscape of breast cancer cells to facilitate dormancy in bone marrow**

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Breast cancer cells (BCCs) can remain undetected for decades in the bone marrow (BM), leading to poor prognosis. BCCs survive in the BM by adopting dormancy and exhibiting cancer stem cell (CSC) properties. In a larger percentage of cancer relapse, dormant BCCs/CSCs in the BM have been reported to be the source of tumor initiation for tertiary metastasis. Intercellular communication between BCCs and microenvironment cells such as mesenchymal stem cells (MSCs) within the BM niche was shown to facilitate BC dormancy. **However, the mechanisms by which BCCs utilize MSCs within the BM to transition into dormancy and acquire a CSC phenotype remain poorly understood.** The ability of BCCs to adopt dormancy can be partly explained by epigenetic alterations activating stem cell-associated genes. We identified exosomes released from MSCs in response to communication with BCCs within the BM niche. These exosomes contain an mRNA cargo encoding five specific epigenetic regulators, TET3, DNMT1, KMT2B, and KMT2D. Based on the potential for these epigenetic factors to promote the transition of BCCs into dormancy, we tested the following **hypothesis: BCCs instruct MSCs to transcribe these epigenetic regulators to be released by exosomes, resulting in BCCs acquiring dormancy and CSC phenotype.** Upon entry into BCCs, exosomes released their epigenetic factors-encoding mRNA cargo, resulting in epigenetic reprogramming. Interestingly, inhibition of global DNA methylation in BCCs resulted in an increase of the most primitive cellular subset, referred to as CSCs, possibly due to de-repression of stem cell genes. Inhibition of histone H3 methylation at lysine 4 (H3K4me) promotes enrichment of progenitor BCCs, which are susceptible to treatment. We are investigating the role of these epigenetic regulators in MSCs and BCCs to determine their targeting genes related to BC dormancy. Overall, these studies will provide crucial insights into the epigenetic regulatory mechanisms underlying BC dormancy.