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N-cadherin/Connexin43 Axis Is Critical to Maintain Breast Cancer Stem Cells: Implication for Cancer Dormancy in Bone Marrow

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Abstract: Clinical advancement in the field of breast cancer (BC) has given access to better diagnosis and treatment. Despite these advancements, BC relapse remains a clinical problem. The clinical and research evidence have mainly attributed BC relapse to dormant BC cells (BCCs) in bone marrow, (BM). Research from our lab and others have shown that the dormant BCCs within the BM niche are cancer stem cells (CSCs). The CSCs interact with the resident BM cells such as macrophages, fibroblasts and mesenchymal stem cells (MSCs), via cytokines, exosomes and/or connexin mediated gap junction intercellular communication (GJIC). This study focuses on GJIC. Connexin 43 (Cx43) has been demonstrated to be involved in GJIC between CSCs and BM supporting cells. Since Cx43 is also important for hematopoiesis, this particular molecule could not be a druggable target to reverse the dormant phase of BCC. We therefore seek for additional target to disrupt GJIC in order for the CSCs to become chemosensitive. This study tested the hypothesis that low level of N-cadherin, an epithelial to mesenchymal transition (EMT) protein, is required for Cx43-mediated GJIC. Knockdown of N-cadherin significantly reduced GJIC, based on dye transfer between CSCs and BM stromal cells. Furthermore, N-cadherin knockdown appeared to induce the differentiation of CSCs as demonstrated by decrease expression of stem cell-associated genes and reduced ability of serial passaging of spheroids. Evidence of direct interaction between N-cadherin and Cx43 was shown by single cell imaging with the Amnis, flow-cytometry, and immunoprecipitation. Cytokines such as TGFβ and CXCL12 regulate the expression of N-cadherin. In vivo studies using a model of BC dormancy indicated that the dormant CSCs was significant reduced in the BM following knockdown of N-cadherin or Cx43. In summary, the molecular interaction between N-cadherin and Cx43 seems to be critical in sustaining dormancy of CSCs in BM. The results have implications to reverse BC dormancy for precise targeting.

Keywords: Breast cancer, Breast cancer stem cells, Mesenchymal stem cells, N-cadherin, Connexin43, Dormancy, Gap junction intercellular communication.

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