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"Interrogating N-cadherin in Breast Cancer Dormancy: The Cancer Stem Cell Hurdle"

by
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Tuesday, April 7th, 2020
9:00 A.M.
MSB: B619

ABSTRACT

Breast cancer (BC) remains a clinical issue despite advancement in treatment and early diagnosis. A major issue is the ability of BC cells (BCCs) to adapt dormancy within the bone marrow (BM) niche. The most dormant BCCs have been identified as cancer stem cells (**CSCs**) and are primarily responsible for cancer recurrence, decades after remission. The dormant CSCs are chemoresistant and can evade immune detection. The CSCs can adapt dormancy decades before clinical detection underscoring the need to understand how these cells survive within the BM stromal compartment. The CSCs can remain in cycling quiescence by establishing gap junctional intercellular communication (GJIC) via connexin 43 (**Cx43**) with the major supportive BM cells (stromal cells and mesenchymal stem cells, **MSCs**) where they exchange miRNA. Since Cx43 is important to hematopoietic regulation, it is not a suitable target since this could cause untoward effects on the hematopoietic system. Thus, to identify areas of drug target, it is important first to understand how Cx43 is regulated and what other molecules are involved. This thesis focused on N-cadherin (CDH2) since it is required in other model systems for membrane expression of Cx43. I, therefore, tested the **hypothesis that CDH2 regulates Cx43 expression in CSCs to permit BC dormancy.** Indeed, loss and gain of function studies indicated that CDH2 can regulate Cx43-mediated GJIC, and this required intercellular interaction between these two molecules, in cell lines and primary BCCs in BM biopsies. RNA-seq indicated that CDH2 knockdown predisposes the CSCs to chemosensitivity with loss of stemness. Further analyses of the 5´ regulatory regions of *CDH2* indicated that specific miRNAs facilitated CDH2-mediated BC dormancy. Together, this thesis indicated that pathways involved CDH2 could reverse and prevent BCCs from adapting dormancy and allow the otherwise chemosensitive BCCs to be targeted by available drugs.