Retain CHD7, an Epigenetic Regulator, in the Nucleus to Combat Breast Cancer Metastasis

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Metastasis accounts for ~90% of deaths from breast cancer (BC). This study aims to address the fundamental question of how cancer cells in the primary breast tumor become metastatic. CHD7 is an ATP-dependent nucleosome remodeling factor which acts in the nucleus to epigenetically regulate gene expression. I found that CHD7 is primarily localized in the cytoplasm of highly metastatic BC cell lines, where it is unable to function. I hypothesize that exporting CHD7 into the cytoplasm plays a critical role in the metastasis of BC cells. First, I examined the cellular localization of CHD7 in human invasive BC tumors. In normal breast duct epithelial cells, CHD7 was exclusively localized in the nucleus; whereas in epithelial cells of BC tumors, a large portion of CHD7 was localized in the cytoplasm. This result strongly supports the clinical relevance of the subcellular localization of CHD7 in metastatic BC cells. Next, through reporter analyses, I identified a nuclear export signal (NES) sequence of CHD7 in MDA-MB-231 metastatic cells. I applied CRISPR/Cas9 to mutate the NES sequence of endogenous CHD7 and showed that mutating the NES sequence led to accumulation of CHD7 in the nucleus of MDA-MB-231 cells and significantly reduced their invasiveness. Finally, I revealed that CHD7, when present in the nucleus, upregulates CDH1/E-cadherin transcription through reducing the nucleosome density of its promoter. CDH1/E-cadherin is well-known to repress BC cell invasiveness. Our data collectively suggest that retaining CHD7 in the nucleus may serve as an effective therapeutic strategy to inhibit BC metastasis.

Awards Won:

Third Award of $1,000