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EPIGENETIC REPROGRAMMING OF EPITHELIAL TO MESENCHYMAL TRANSITION IN BREAST CANCER USING THE CRISPR DCAS9 PLATFORM

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Dysregulated epigenetic regulation is an important step in breast cancer progression, allowing silencing of tumour suppressors and/or reversion of developmental programs. The epithelial to mesenchymal transition (EMT) is one such disrupted program whereby epithelial cells reduce their cell-cell adhesion and polarity and adopt a more mesenchymal phenotype, with increased cell motility facilitating metastatic dissemination, and stem cell-like characteristics supporting therapeutic resistance. The clinical relevance of EMT is highlighted by its enrichment in aggressive triple negative breast cancers, particularly the basal-like and claudin-low subtypes. While EMT signatures contain hundreds of genes, their expression is controlled by core of effector transcription factors (TFs) including the pro-mesenchymal TWIST1/2, SNAI1/2 and ZEB1/2 which bind E-box sites and recruit epigenetic modifier complexes to silence genes such as pro-epithelial *CDH1* (E-cadherin). Pro-epithelial miRNA, such as the miR-200 family, helps establish switch-like behaviours that allow fate acquisition, and importantly, this provides plasticity along the EMT axis, allowing the reverse mesenchymal to epithelial transition (MET) process. Together with their ability to simultaneously target multiple EMT-associated transcripts, miRNAs are thus emerging as critical regulators of EMT. In many mesenchymal breast cancers pro-epithelial miRNAs are silenced through DNA and histone modifications while pro-mesenchymal TFs are upregulated, providing an opportunity to restore control over the regulatory networks controlling EMT. Using the CRISPR/dCas9 effector system, repression of these key TFs will drive MET and establish a therapeutic window in breast cancers associated with a poor prognosis. This ability to epigenetically manipulate and reprogram breast cancer cells will help to elucidate cancer pathogenesis and provide novel genome-based opportunities for therapeutic intervention of chemo-resistant malignancies.

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