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The Role of Long Non-Coding RNAs in EMT and Cancer Stem Cells

Studies have shown that the majority of the mammalian genome is transcribed even though <2% is occupied by coding regions. These transcripts are called non-coding RNAs (ncRNAs). While there has been a great deal of focus on the biological roles of a class of small ncRNAs, called miRNAs, much less is known about the vast majority of transcripts represented by lncRNAs. One theme is that many lncRNAs function through interactions with chromatin modifying complexes and control chromatin architecture. While a variety of functional roles for lncRNAs have been implicated in many processes, only a relatively few cases have been well defined. As might be expected from the roles of lncRNAs in transcriptional regulation, epigenetics, and development, there is increasing evidence of their misregulation in cancer. Breast cancer stem cells (CSCs) have been shown to be more resistant to therapy compared to non-CSCs. Claudin-low subtype breast cancer tumors are enriched for functional CSCs and have an epithelial to mesenchymal transition (EMT) signature. Additionally, it has been determined that inducing EMT in human mammary epithelial cells endows them with stem cell-like properties. Together these lines of evidence suggest important molecular links between EMT and the CSC-enriched claudin-low tumors. We hypothesize that lncRNAs play a critical role in EMT program governed in part by RNA-mediated epigenetic regulation leading to resistance to conventional therapies in breast cancer. Through comparative gene expression analyses of EMT cell line models and breast tumors, we have identified and implicated lncRNAs in the EMT process. The goal of this proposal is to determine if these lncRNAs regulate the EMT/CSD phenotype of claudin-low tumors and to determine their mechanisms. This includes understanding their subcellular localization and identifying interacting protein complexes which will begin to provide a picture of how they function. While claudin-low tumors only represent ~ 12-14% of breast cancers, their enrichment in cells with the EMT/CSC phenotype will enable elucidation of information pertinent to these cells in the subtypes with smaller CSC populations.

Completing the goals of this proposal will enhance our understanding of the molecular mechanisms that regulate cancer stem cells (CSCs). This will be critical for devising new treatments that selectively target these aggressive and therapy-resistant

cancer cells. This will enable us to ultimately translate these findings into the clinic in order to sensitize tumors to conventional therapies by targeting critical regulation of EMT/CSC-pathways by long non-coding RNA mediated epigenetic mechanisms.