Susan G. Komen

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Epigenetic coding of EMT regulators as diagnostic targets for breast cancer

Investigator(s): Yun Zhang, Ph.D; Robert Weinberg, Ph.D. (Mentor)

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Public Abstract:

Despite extensive research on breast cancer in the past few decades, breast cancer patients and oncologists are still facing two major problems: First, although there are over 230,000 women diagnosed in this country annually with breast cancer, only about 39,000 die from it. The difference between these numbers indicates the fact that many women are diagnosed with a form of breast cancer that would not progress to a life-threatening state even if left untreated. However, lack of information about the molecular network that governs the transition from a benign status of breast cancer cells to an aggressive one significantly limits the development of diagnostic methods to distinguish such patients. Second, for breast cancer patients with metastasis or recurrence, there are limited therapeutic options, largely due to the resistance of such diseases to currently available antitumor therapies. Accumulating studies conducted in various laboratories have confirmed the existence of cancer stem cells (CSCs) in breast cancer. CSCs are referred to as a subpopulation of neoplastic cells within a tumor that exhibit elevated abilities to seed new tumors and increased resistance to various types of chemotherapy. These abilities of CSCs naturally link it with tumor recurrence and metastasis - two problems accounting for more than 90% of breast cancer patient deaths. In a recent study performed in our lab, others found that non-CSC population within basal breast cancer cell lines, but not those within luminal cell lines, were responsive to certain microenvironmental stimuli, notably TGF-ß of stromal origin, to undergo an epithelial-mesenchymal transition (EMT) and generate CSCs de novo, raising the intriguing possibility that the aggressiveness of breast cancer is determined not by its existing content of CSCs but by its

responsiveness to contextual signals of generating new CSCs. The differing abilities of non-CSC-to-CSC conversion between luminal vs. basal cells are correlated with different histone modifications within the promoter region of ZEB1 gene, a master transcription factor regulating the EMT program. Therefore, the differing clinical behaviors of luminal vs. basal breast cancer cells can be explained, at least in part, by the differences in the configuration of the ZEB1 promoter in the respective non-CSCs. Based on these results, I plan to further our understanding on the epigenetic control of the non-CSC-to-CSC conversion in this proposal by identifying additional epigenetically regulated genes that control this process and characterizing the molecular mechanisms of these epigenetic modulations by the tumor microenvironment, which may eventually lead to the development of effective therapies that prevent non-CSC-to-CSC conversions. Importantly, I will also examine the potential of using epigenetic coding of the already-documented ZEB1 gene in diagnosing breast cancer patients with higher likelihood to progress into an aggressive stage.