“Unraveling the Breast Cancer Metastasis Epigenome”

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Abstract: The development of metastasis is the primary contributor to death from breast cancer. An understanding of the genomic basis of metastasis is crucial for the development of new diagnostic and therapeutic modalities. Epigenetic aberrations are critical for the metastatic process but these alterations are poorly defined on a genome-wide scale. The central hypothesis of this application is that important epigenetic alterations underlie the development of breast cancer metastasis. Through a systematic approach employing global, large-scale analysis of primary tumors with diverse metastatic ability, analysis of isogenic human breast cancer cells with varying metastatic potential, and validation of putative epigenetic marks prognostic of metastasis, we propose to elucidate the epigenomic landscapes underlying breast cancer metastasis. Our specific aims are the following. First, we will systematically profile DNA methylation and histone modifications using primary breast tumor samples with varying metastatic activity and isogenic cells from an *in vivo* selection model of metastasis (Aim1). These studies will utilize microarray and next-generation sequencing technologies. Second, we will optimize and validate an epigenomic signature for distant failure (Aim2). Third, we will directly study how the metastatic phenotype is altered by top candidate epigenetic targets using multiple mouse models of metastasis (Aim 3). These studies would constitute the first detailed characterization of the metastasis epigenome. The characterization of the metastasis epigenome will not only be of tremendous clinical diagnostic value but will lay the foundation for future mechanistic studies focused on the generation of novel therapeutic agents for the treatment of metastases.