Understanding heterochromatin dysfunction in cancer

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Chromatin alterations are fundamental to the molecular and histopathological classification of cancer, and are key drivers of oncogenesis. Therapeutic targeting of these alterations has therefore become a rapidly growing area for drug development and clinical trials. Chromatin exhibits considerable specialization beyond ‘open’ euchromatin or ‘closed’ heterochromatin. For instance, the pericentromere and inner centromere make up the centromere, which has critical roles in mitosis and safeguarding genome content during cell division. Although both centromeric compartments are categorized as constitutive heterochromatin, they differ extensively with respect to histone variants, histone post-translational modifications, non-coding RNAs, and associated proteins. Notably, pericentromeric heterochromatin is defined by repressive marks involving trimethylation of histone H3-lysine 9 (H3K9me3) and histone H4-lysine 20 (H4K20me3). Loss of the latter has emerged as a consistent feature of cancer cells, yet the underlying basis remains undefined. The goal of our research has been to characterize the dynamics of these epigenetic marks and their associated protein machinery as a function of malignant progression in a breast cancer model. Using a series of mouse and human breast cancer cell lines, patient samples, and in vivo tumor models, we have found that H4K20me3 levels are consistently attenuated. Moreover, analysis of quantitative proteomic data indicates this occurs together with global changes in protein composition of the pericentromere. In this context, the lysine methyltransferases SUV39H1/2 (H3K9me3) and SUV420H1/2 (H4K20me3), together with the chromobox protein CBX5 (aka HP1α), have critical roles in the stability and propagation of pericentromeric heterochromatin. To investigate the basis of these roles, we have evaluated the localization and mobility of these proteins with a combination of fluorescence recovery after photobleaching (FRAP) and time lapse microscopy. This has revealed fundamental differences in the dynamics of the SUV39H1/2, SUV420H1/2 and CBX5 proteins that provide novel insight to the maintenance of pericentromeric heterochromatin. Together, these data provide an important framework for understanding heterochromatin dysfunction in cancer.


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**Specialty and Present Interest:**
Chromatin, epigenetics, nuclear structure & function, protein dynamics