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Timothy E. Van Meter

Nathan Rockwell

Asadullah Khan

Jocelyn Terry
College of William and Mary

Sarah Goggin
College of William and Mary

See next page for additional authors

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Abstracts

EG-17. SUV420-MEDIATED HETEROCHROMATIN CHANGES IN PEDIATRIC BRAIN CANCERS

Timothy E. Van Meter[1,2], Jocelyn Terry[2], Nathan Rockwell[1], Sarah Goggin[2], Priya Nethala[2], and Asadullah Khan[1]; [1]VCU School of Medicine, Richmond, VA, USAM; [2]College of William and Mary, Williamsburg, VA, USA

Silencing mechanisms play a role in genomic stability by maintaining condensed, non-active regions of the genome. SUV420 enzymes contain a SET domain conferring methyltransferase activity toward histones. The Histone H4 lysine 20 trimethylation (H4K20me3) mark maintained by SUV420H2 is associated with heterochromatin formation and gene silencing, whereas the dimethylated mark (H4K20me2) is associated with DNA repair. In studies of epigenetic factors in large patient cohorts with ependymoma, it was found that SUV420H2 expression was lost or diminished in patients with reciprocal increases in prognostic markers such as hTERT. To better understand the normal function of Suv4-20H1/H2 enzyme in neural progenitors, and pathological changes in cancers, a variety of differentiation paradigms were used. The NT2D1 neurally restricted cell line, and BGO1V and H9 human embryonic stem cells (ESCs), and differentiated progeny, were used alongside tumors to better understand enzyme targets and functional outcomes (e.g.,lineage, differentiation, regional chromatin modifications). Lineage stages were verified with stage-specific markers by immunofluorescence and qPCR. Suv4-20 H1 and H2 were present in ESCs and neural progenitors and decreased thereafter. RNAi knockdown of SUV420 enzymes led to decreased H4K20 methylation in cancer cells. DNA methylation microarrays and ChIP-PCR suggest 1) that SUV420 is not regulated by DNA methylation in ependymomas; 2) that active chromatin marks such as H3K4 dimethylation are enriched near the transcriptional start site in the SUV420H2 gene, and 3) that hTERT is hyper-methylated at specific CpG islands and histones in a tumor sub-group-specific manner. This data supports the hypothesis that Suv4-20H2 is highly active in progenitor cells and functionally lost in some brain cancers. These studies begin to elucidate coincident mechanisms of gene silencing active in neural progenitors that may be altered in a subset of pediatric brain cancers.