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Histone isoforms and variants: Differential incorporation in chromatin regulates the dynamic behavior of cancer epigenome

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Epigenetic mechanisms help to coordinate changes in gene expression that accompany the transition from undifferentiated embryonic cells to terminally differentiated tissue to ensure cellular homeostasis. Over the past few years, there has been a growing appreciation for histone variants and their isoforms in altering nucleosome, chromatin properties and thereby influencing transcriptional regulation. A broad array of environmental factors such as diet, stress, toxicants or even the emotions influence epigenetic landscape to alter cell physiology and disease susceptibility. Recently, we have performed a detailed study investigating the association between histone isoforms/variants abundance and histone modification enrichments on a global genome-wide level correlating with aberrant gene expression in cancer. The data suggest an increase in expression of histone isoforms/variants, H2A.1 and H3.2 in hepatocellular carcinoma, and also in various human cancer cell lines compared to normal counterpart having H2A.2 and H3.3. Further, biophysical and biochemical experiments along with in silico molecular simulation studies have shown that H2A.1 containing nucleosomes are more stable and are associated with the increase in cellular proliferation. The differential incorporation of H3 variants is directly correlated with levels of variants specific histone chaperones. Interestingly, there exists a hierarchy amongst the nucleosomes in context of their stability, with the H2A.1/H3.2 variant being the most stable and H2A.2/H3.3 the least stable. Also, the cancer epigenome has condensed chromatin organization with the decrease in euchromatic and increase of heterochromatic histone modification 'marks'. These alterations are directly associated with nucleosome reorganization, decrease in the rate of global transcription and aberrant expression profile of various genes including tumor suppressors in cancer cells compared to normal counterparts. Together, study suggests for the first-time co-operative interplay between histone modifiers, variants, chaperones and their transcriptional regulation which results in the stable maintenance of the highly dynamic histone 'marks' required for maintaining the deregulated epigenetic landscape of cancer epigenome.

Biography

Sanjay Gupta received his PhD degree in Biochemistry and Molecular Biology at Banaras Hindu University, Varanasi in 1995 and performed Postdoctoral work with Professor M S Kanungo at Institute of Life Sciences, Bhubaneswar and Banaras Hindu University, Varanasi. He joined Cancer Research Institute, Tata Memorial Center, Mumbai in 1999. Presently, his group 'Epigenetics and Chromatin Biology laboratory' at ACTREC is involved in understanding how histone modifications and variants are associated with cancer, development and DNA repair. Further, there is an ongoing evaluation of molecules to find out new inhibitors of histone modifying enzymes for their potential role in cancer therapeutics.

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