

Epigenetic Regulation of Chromatin Dynamics and Gene Expression: Implications in Differentiation, Disease and Therapeutics

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The dynamic nature of the eukaryotic genome, which is organized into a nucleoprotein structure called chromatin is regulated by epigenetic modifications of DNA and associated proteins, which in turn control the underlying gene function. Chromatin organization is also closely linked to the function of chromatin associated nonhistone proteins. Our laboratory has discovered that the highly abundant human transcriptional coactivator PC4, is a chromatin organizer, and helps in maintenance of epigenetic state of the genome and thereby the global regulation of gene expression and cell cycle. Our recent observations suggest that PC4 is an important factor in breast cancer progression. From the angle of development, we have found that PC4 is absolutely critical for life, as its absence leads to embryonic lethality in mouse. The conditional PC4 brain knockout mice show specific defects in spatial memory, while their viability, fertility and motricity are normal. Gene expression analysis of the dorsal hippocampus of the knockout mice, which was performed to explain these specific defects, revealed dysregulated expression of several neural function-associated genes. This could be a unique role for a chromatin-associated protein in memory extinction.

However, the altered function of any epigenetic modification also causally affects the physiological homeostasis in different pathophysiological conditions such as cancer, neurodegenerative disorders, diabetes, asthma, COPD etc. Among the different epigenetic enzymes we focus on three important classes: lysine acetyltransferases, arginine methyltransferases and Aurora Kinases in the context of cancer and neurodegenerative diseases. Our laboratory has discovered several small molecule modulators of these enzymes, which may serve as lead scaffolds to design new generation therapeutics. By using a novel histone acetyltransferase activator molecule, we find that p300/CBP mediated acetylation of histones is an important inducing factor for robust neurogenesis; which presumably contributes to long-term spatial memory. Besides, as potential therapeutic agents, these molecules may also be highly useful to elucidate the epigenetic regulation of differentiation pathways; as we have elucidated the role of histone H3R17 asymmetric dimethylation in astroglial differentiation by employing a specific inhibitor of PRMT4/CARM1. Furthermore, by employing our newly discovered Aurora Kinase inhibitor, Felodipine (an antihypertensive drug) we found how surface enhanced Raman spectroscopy, could be used as a novel drug discovery tool.