Seminar Announcement

PHYSIOLOGY
National University of Singapore

Title **Chromatin Modifications in Neural Differentiation and Memory: Implications of Lysine Acetylation and Arginine Methylation**

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Date Monday, 02 September 2013

Time 12.00 nn – 1.00 pm

Venue MD9 (Level 1, Workshop room)

Abstract
Eukaryotic genome is organized into a highly dynamic and ordered nucleoprotein structure, chromatin, which, along with DNA, is made of histones, non-histone proteins and non-coding RNA. Dynamic opening and closure of the chromatin fibre along with histone assembly and disassembly fine tune the spatio-temporal regulation of gene expression in most of the physiological phenomena including maintenance of pluripotency and differentiation. Covalent modification of histones, namely acetylation and arginine methylation have been shown to be important determinants in development and different lineage commitment. We have found that histone H3R17 methylation mediated by PRMT4/CARM1 is critical for astroglial lineage commitment in human embryonic stem cells as well as in zebrafish model. This effect may be regulated at various levels including the direc inhibition of H3R17 methylation or indirectly by dysregulated miRNAs downstream. On the other hand, 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. In brief, a small molecule activator of the histone acetyltransferases CBP/p300 (TTK21), when conjugated to glucose based carbon nanosphere (CSP), can cross the blood brain barrier without inducing any toxicity and reach different parts of the brai CSP-TTK21 significantly induces histone acetylation in the hippocampus and frontal cortex following an intraperitoneal injection in mice. Remarkably, CSP-TTK21 treatment promoted the formation of long and highly branched doublecortin positive neurons in the subgranular zone of the dentate gyru and reduced BrdU incorporation, suggesting that CBP/p300 activation favors maturation and differentiation of adult neuronal progenitors. Furthermore, CSP-TTK21 treatment was tested on spatial memory formation and we show that CBP/p300 activation during training did not improve retention of a recent memory, but significantly extended memory vividness to 16 days post-acquisition. This report is the first evidence of CBP/p300-mediated histone acetylation in the brain by an activator molecule, with functional implications on brain functions. Presumably, the direct stimulation of acetyltransferase function could be important in terms of therapeutic options for neurodegenerative diseases. These results will be discussed in the context of new small molecule based approaches to elucidate the role of epigenetic modifications in differentiation and stem cell research. These results also indicate at application of such molecules as therapeutic options in diseases.

Convener: A/Prof Reshma Taneja

All Are Welcome