UAEU جامعة الإمارات العربية المتحدة United Arab Emirates University

The College of Graduate Studies and the College of Medicine and Health Science Cordially Invite You to a

Ph.D. Dissertation Defense

Entitled

The role of nutrient sensitive protein O-GlcNAcylation in developmental cortical neurogenesis

by

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Date & Venue

4:00 – 5:00 PM

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Abstract:

The nutrient responsive *O*-GlcNAcylation is a dynamic, posttranslational protein modification present on many nucleocytoplasmic and mitochondrial proteins. Previous research has indicated that hyperglycaemia increases the levels of total *O*-GlcNAcylation within cells. Transcription factors and histones are among hundreds of proteins that have been reported to be *O*-GlcNAcylated and have importance in cell fate determination during cell growth, proliferation, and differentiation. However, the role of protein *O*-GlcNAcylation in epigenome control in response to nutritional perturbations is poorly understood.

Hyperglycaemia induced protein *O*-GlcNAcylation have been linked to several pathologies, including obesity, diabetes, cancer, cardiovascular and neurodegenerative diseases. Given that maternal hyperglycaemia during pregnancy is linked to adverse neurodevelopmental outcomes in the offspring, it is interesting to identify the impact of elevated protein *O*-GlcNAcylation on embryonic neurogenesis. Herein, we investigate and confirm the implications of protein *O*-GlcNAcylation by pharmacological induction of *O*-GlcNAc during embryonic neurogenesis by directed differentiation of human embryonic stem cells (hESCs) into cortical neurons, which precisely mimics early events of human embryonic corticogenesis. The presence of total *O*-GlcNAc levels during neural differentiation was determined by immunocytochemistry and western blotting techniques. Investigation of several regulatory transcription factor genes and histones needed for stem cell fate during neurogenesis was carried out through different molecular biology techniques including, western blotting, qPCR, and immunocytochemistry. The impact of elevated *O*-GlcNAc on transcriptional/epigenetic mechanisms was investigated through high-throughput RNA sequencing and ChIP-qPCR. We found that increased *O*-GlcNAcylation is associated with decreased neural progenitor proliferation, premature cortical neurogenesis, reduced AKT signalling, induced apoptosis and defective expression of several genes essential for neural differentiation. This also led to increased expression of key neurogenic transcription factor (TF) genes. Further investigation has shown that de-repression of neurogenic TFs is associated with increased H3K4me3 and decreased H3K27me3 (promoter bi-valency) levels at the promoter of these genes. Increased *O*-GlcNAc levels also increased Pol IISer5 phosphorylation whereas, levels of H2BS112*O*-GlcNAc and H2BK120Ub1 were inconsistently affected at different gene promoters. We also studied the effect of elevated *O*-GlcNAc levels on embryonic neurogenesis in a rat model of maternal hyperglycaemia. We observed similar epigenetic defects including changes in promoter bivalency and induced Pol IISer5p, H2BS112*O*-GlcNAc and H2BK120Ub1 in the developing embryo brain cortex due to hyperglycaemia. Our findings show *O*-GlcNAc regulated chromatin sensitivity based on maternal nutritional status on neurodevelopment and suggest that metabolic dysregulations can affect stem cell fate decisions via *O*-GlcNAc mediated epigenetic gene regulating mechanisms during development. These results may have implications in neurodevelopmental disorders associated with metabolically compromised pregnancies.

Keywords: hESCs, Neurodevelopment, O-GlcNAcylation, Pluripotency, Differentiation, Transcription factors, Epigenetic, Histone.