NUS National University of Singapore | Department of Anatomy
Yong Loo Lin School of Medicine

NUHS National University Health System

PhD Oral Defense

EFFECTS OF MATERNAL FACTORS ON DNA METHYLATION PATTERN IN HUMAN NEURAL PROGENITOR CELLS

Several maternal factors such as diet, hyperglycemia and infection, has been shown to influence the normal course of fetal brain development. This study aimed at understanding the effects of maternal factors i.e., High glucose (HG) and Zika virus (ZIKV) infection on DNA methylation patterns in human neural progenitor cells (hNPCs). In the first part of the study, HG exposure of hNPCs was found to alter the DNA methylation pattern of genes involved in several signalling pathways including axon guidance (SLIT1-ROBO2 signalling pathway), and Hippo signalling pathways that regulate brain development. SLIT1 and its effector genes ROBO2, SRGAP1 and CDC42 were found to be downregulated in hNPCs exposed to HG in vitro, as well as in the developing forebrain of embryos from mouse model of diabetic pregnancy. In addition, further validation revealed a downregulation in the expression of Hippo signalling pathway effectors, YAP and TAZ proteins in hNPCs exposed to HG. Recent reports suggest a possible cross-talk between SLIT1-ROBO2 and Hippo signalling via CDC42, a SLIT1 effector and a mediator of actin dynamics. Consistent with this, SLIT1 knockdown downregulated the expression of its effectors (ROBO2, SRGAP1, CDC42) and TAZ in hNPCs, suggesting that HG perturbs the cross-talk between SLIT1-ROBO2 and Hippo signalling. The second part of the study was aimed to understand if ZIKV alters the DNA methylome of human neural progenitor cells (hNPCs). ZIKV infection altered the DNA methylation of several genes such as WWTR1 (TAZ) and RASSF1 of Hippo signalling pathway which regulates organ size during brain development, and decreased the expression of several centrosomal-related microcephaly genes, and genes involved in stemness and differentiation in human neural progenitor cells. Thus, ZIKV downregulated the Hippo signalling pathway genes which perturb the stemness and differentiation process in hNPCs. Taken together, this study demonstrated the possible molecular and epigenetic mechanisms by which maternal factors (HG/ZIKV) contribute to neurological disorders.

Thursday
28 November 2019
10.00 am – 11.00 am
Seminar Room, MD10
Level 2, Anatomy Museum

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