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PhD Dissertation Defense

Entitled

DEVELOPMENTAL PROGRAMMING OF NORMAL VERSUS METABOLICALLY ALTERED PANCREAS IN RAT: EFFECT OF GESTATIONAL DIABETES

by

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Date & Venue

12:00 PM

Thursday, 4th April, 2024

Location: Yannah Theater, Second Floor, Block C (2C010), Male Side, CMHS

Abstract

Diabetes Mellitus (DM) is a chronic condition characterised by pancreatic β-cell dysfunction and consistent elevated blood glucose levels (hyperglycaemia), either due to the inability of the body to produce any or adequate amounts of insulin or the inability of the body to effectively utilise the produced insulin (i.e., insulin resistance). DM can be classified into 3 main types: Type 1 DM (T1DM), Type 2 DM (T2DM), and Gestational Diabetes Mellitus (GDM). GDM is defined as "hyperglycaemia that is first diagnosed during pregnancy with glucose levels below those considered diagnostic of overt diabetes outside of pregnancy". The mature pancreas is a bifunctional organ composed mostly of exocrine tissue organised in acini, and a ductal scaffold. The endocrine tissue, embedded within the exocrine tissue, constitutes about 5% of the pancreas. It consists of cells that produce and secrete several peptide hormones into the bloodstream that mediate the pancreas's regulation of glucose homeostasis. These cells, which all cluster together in the islets of Langerhans, are: α- cells (produce glucagon, Gcg), β-cells (produce insulin, Ins), δ-cells (produce somatostatin), PP- cells (also known as γ cells, produce pancreatic polypeptide), and ε-cells (produce ghrelin). Malfunctions in endocrine cells can lead to diseases, for example, malfunctioning in β-cells can lead to DM.

Certain genes, such as Pdx1, Nkx6.1, Nkx2.2, Pax6, and Arx are essential for normal development of the pancreas and glucose metabolism. GDM offspring have higher risk of developing DM and metabolic diseases in later stages of life. We speculate that this increased risk begun as early as embryogenesis. We propose that the hyperglycaemic state during pregnancy alters the expression of genes involved in pancreas development and differentiation. We also speculate that GDM affects the expression of these genes in such a way interfering with the function of those genes in the pathways governing early pancreas organogenesis and development, specially α- and β-cells differentiation and maintenance and foetal pancreatic metabolism, ultimately leading to altered glucose metabolism in the offspring. These changes may be contributing to the increased foetus's risk of developing metabolic diseases later in life.

Thus, we quantified the expression of the pancreatic islet hormones, insulin and glucagon, through different developmental stages (Embryonic day (E) 13.5, E14.5, E16.5, E18.5 and 1-day old), and investigated some of the key transcription factors involved in pancreatic differentiation and maturation (Pax6, Arx, Nkx2.2, Nkx6.1, Pdx1) through two developmental stages (E18.5, and 1-day old) using immunofluorescence in embryos/pups of control and GDM rats. Then we analysed RNA from these embryos/pups through E18.5, and 1-day old to identify Differentially Expressed Genes (DEGs) and associated pathways. Finally, we verified some of the DEGs using RT-qPCR.

E18.5 GDM embryos exhibited reduced β-cell and increased α-cell number percentages compared to control embryos. They also exhibited reduced expression of insulin and glucagon among other genes. 1-day old GDM pups exhibited macrosomia, glucose intolerance in 60 minutes Intraperitoneal Glucose Tolerance Test (IPGTT) although they were not diabetic and reduced β-cell and increased α-cell area percentages compared to control pups. They also exhibited reduction in the percentage of $Pdx1^{+}$ Ins^{+}, $Nkx6.1^{+}$ Ins^{+}, $Nkx2.2^{+}$ Ins^{+}/Gcg^{+}, and $Pax6^{+}$ $Ins+/Gcg^{+}$ cells compared to control pups. The DEGs in GDM offspring were associated with insulin secretion (GO:0030073), establishment of protein localisation to extracellular region (GO:0035592), regulation of peptide transport (GO:0090087), response to glucose (GO:0009749), protein maturation (GO:0051604) and protein processing (GO:0016485), and insulin metabolic process (GO:1901142) pathways. All in all, the findings of this research contribute to our understanding of the effect of GDM on foetal pancreas development and offspring predisposition to DM in later stages of life.

Keywords: Diabetes Mellitus, Gestational Diabetes Mellitus, Pancreas, Arx, Nkx6.1, Nkx2.2, Pax6, Pdx1, Insulin, Glucagon, α-cells, β-cells, Islets of Langerhans.