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

PhD Dissertation Defense

Entitled

CHARACTERIZATION OF THE LONG NON-CODING RNA, POSITIVE REGULATOR OF INSULIN (PROINS) IN HUMAN PANCREATIC ß-CELL

by

Shereena Saeed Ahmed Lootah

Faculty Advisor

Dr. Starling Emerald Bright David, Department of Anatomy
College of Medicine and Health Sciences

Date & Venue

16:00 PM
Monday, September 19, 2022
Online, MS Teams meeting
Click here to join the meeting

Abstract

It is well established that the genome is pervasively transcribed. Only 2% of those transcripts are translated into proteins, and the remaining 98% are non-translated, generating the non-coding RNAs (ncRNAs) species. A close observation of these transcripts directed the scientific community to their increasing potential functional roles in the cells. Indeed, the literature exponentially unveils this notion, with many ncRNAs showing substantial and variable biological functions. The field is in its infancy; however, efforts are accelerating to discover and define this ocean of new species.

Long non-coding RNAs (lncRNAs) are sub-species of ncRNAs with an arbitrary size of more than 200 nucleotides with fewer coding abilities. They are expressed in a controlled manner in different tissue types and developmental phases. They show very low sequence conservation among other species. The functional significance of lncRNAs is exponentially identified in many organisms, including humans. This thesis tried to characterize an intriguing lncRNA, which we termed the Positive Regulator Of Insulin (PROINS), based on its functional role in human pancreatic ß-cells. PROINS is located upstream of the master regulator of ß-cells, pancreatic and duodenal homeobox1 (*PDX1*) on chromosome 13 in humans. Hence, studying its possible regulatory roles in these metabolically relevant cells is important for our understanding of metabolism. The main objective of this work is to characterize PROINS in human pancreatic ß-cells, with a focus on its possible regulatory effects on insulin production. After verifying the existence of the lncRNA PROINS in human pancreatic ß-cells, we studied its expression in various human tissues and assessed its subcellular localization. We analyzed its expression in response to glucose stimulation in human □-cell model 1.1B4, followed by a gain of function and loss of function studies of PROINS, and observed the consequence of this perturbation on mainly insulins expression.

Interestingly, we have identified that PROINS upregulates INS expression in these cells. However, we did not find any correlation between this regulatory function and the vital transcription factor of ß-cell, *PDX1*as we anticipated. Instead, we did show a possible interaction of PROINS with the Maf Avian musculoaponeurotic fibrosarcoma oncogene homolog A (MAFA). MAFA is another well-recognized transcription factor in ß-cell, which plays an essential role in glucose-stimulated insulin secretion. This study sheds light on a novel regulatory layer of the insulin gene. Perturbation of insulin expression in ß-cells is an important underlying cause of type 2 diabetes (T2D) and type 1 diabetes (T1D). Thus, further understanding of insulin production's intricate regulatory mechanisms would open opportunities for novel therapies for both types of diabetes.

Keywords: lncRNAs, PROINS, T2D, pancreatic ß-cells, insulin, MAFA, PDX1 and PLUTO.