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Long Non-Coding RNAs Mediated Regulation of Diabetes in Humanized Mouse

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Abstract : Long noncoding RNA (lncRNA) mediated post-transcriptional gene regulation, and their epigenetic landscapes have been shown to be involved in many human diseases. However, their regulation in diabetes through governing islet's β-cell function and survival needs to be elucidated. Due to the technical and ethical constraints, it is difficult to study their role in β-cell function and survival in human under in vivo condition. In this study, humanized mice have been developed through transplanting human pancreatic islet under the kidney capsule of NOD.SCID mice and induced β-cell death leading to diabetes condition to study lncRNA mediated regulation. For this, human islets from 3 donors (3000 IEQ, purity > 80%) were transplanted under the kidney capsule of STZ induced diabetic NOD.scid mice. After at least 2 weeks of normoglycecemia, lymphocytes from diabetic NOD mice were adoptively transferred and islet grafts were collected once blood glucose reached > 200 mg/dl. RNA from human donor islets, islet grafts from humanized mice with either adoptive lymphocyte transfer (ALT) or PBS control (CTL) were ribodepleted; barcoded fragment libraries were constructed and sequenced on the Ion Proton sequencer. lncRNA expression in isolated human islets, islet grafts from humanized mice with and without induced β-cell death and their regulation in human islets function in vitro under glucose challenge, cytokine mediated inflammation and induced apoptotic condition were investigated. Out of 3155 detected lncRNAs, 299 that highly expressed in islets were found to be significantly downregulated and 224 upregulated in ALT compared to CTL. Most of these are found to be collocated within 5 kb upstream and 1 kb downstream of 788 up- and 624 down-regulated mRNAs. Genomic Regions Enrichment of Annotations Analysis revealed deregulated and collocated genes are related to pancreas endocrine development; insulin synthesis, processing, and secretion; pancreatitis and diabetes. Many of them, that found to be located within enhancer domains for islet specific gene activity, are associated to the deregulation of known islet/βcell specific transcription factors and genes that are important for β-cell differentiation, identity, and function. RNA sequencing analysis revealed aberrant lncRNA expression which is associated to the deregulated mRNAs in β-cell function as well as in molecular pathways related to diabetes. A distinct set of candidate lncRNA isoforms were identified as highly enriched and specific to human islets, which are deregulated in human islets from donors with different BMIs and with type 2 diabetes. These RNAs show an interesting regulation in cultured human islets under glucose stimulation and with induced β-cell death by cytokines. Aberrant expression of these lncRNAs was detected in the exosomes from the media of islets cultured with cytokines. Results of this study suggest that the islet specific lncRNAs are deregulated in human islet with β-cell death, hence important in diabetes. These lncRNAs might be important for human β-cell function and survival thus could be used as biomarkers and novel therapeutic targets for diabetes.

Keywords : β-cell, humanized mouse, pancreatic islet, LncRNAs
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