Diabetes in 3D
- β-cell mass assessments in disease models & evaluation of SPECT based imaging

Saba Parween

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie/medicine doktorsexamen framläggs till offentligt försvar i Hörsal B Unod T9, Norrlands Universitets sjukhus, torsdagen den 15:e december 2016, kl. 09:00.
Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Prof. Eckhard Lammert,
Institute of Metabolic Physiology, Heinrich-Heine-University of Düsseldorf, Düsseldorf, Germany.

Author
Saba Parween

Title
Diabetes in 3D
- β-cell mass assessments in disease models & evaluation of SPECT based imaging

Abstract

Diabetes is a rapidly growing disease with 415 million affected adults worldwide. The pancreatic endocrine cells, most importantly the insulin producing β-cells, play an important role in regulating blood glucose homeostasis. Type 1 diabetes (T1D) is characterized by the inability of the pancreas to secrete sufficient amounts of insulin due to autoimmune destruction of insulin producing β-cells. Type 2 diabetes (T2D) on the other hand is characterized by defects in insulin secretion and insulin sensitivity. Alterations in the β-cell mass (BCM) and/or function play a major role in the development and progression of the disease. Understanding BCM dynamics in disease models is therefore a key aspect for better interpretation of research results. In this thesis, we have used optical projection tomography (OPT) as a tool to evaluate a non-invasive imaging modality for β-cell scoring and to study disease dynamics in frequently used animal models for T1D and T2D.

The possibility to monitor BCM in vivo would radically improve our competence in studying the pathogenesis of diabetes and in therapeutic interventions. Single photon emission computed tomography (SPECT) is a widely used technique that has become a promising approach to monitor changes in BCM in vivo. A key issue for using this approach is to evaluate the β-cell specificity and read out of the utilized radiotracers. This is most commonly performed by conventional stereological approaches, which rely on the extrapolation of 2D data. We developed a protocol for SPECT-OPT multimodal imaging that enables rapid and accurate cross evaluation of SPECT based assessments of BCM. While histological determination of islet spatial distribution was challenging, SPECT and OPT revealed similar distribution patterns of the radiotracer 111In-exendin-3 and insulin positive β-cell volumes respectively between different pancreatic lobes, both visually and quantitatively. We propose SPECT-OPT multimodal imaging as an accurate and better approach for validating the performance of β-cell radiotracers.

The leptin deficient ob/ob mouse is a widely used model for studies of metabolic disturbances leading to T2D, including obesity and insulin resistance. By OPT imaging we created the first 3D-spatial and quantitative account of BCM distribution in this model. We observed a previously unreported degree of cystic lesions in hypertrophic islets, that were occupied by red blood cells (RBCs) and/or fibrin mesh. We propose that these lesions are formed by a mechanism involving the extravasation of RBCs/plasma due to increased blood flow and islet vessel instability. Further, our data indicate that the primary lobular compartments of the ob/ob pancreas have different potentials for expanding their β-cell population. Unawareness of these characteristics of β-cell expansion in ob/ob mice presented in this study may significantly influence ex vivo and in vivo assessments of this model in studies of β-cell adaptation and function. The tomographic data, on which this study was based, will be made publically available as a resource to the research community for the planning and interpretation of research involving this model.

There are limited studies on early metabolic and functional changes of BCM in the settings of T1D. In order to assess initial metabolic alterations in BCM before the onset of diabetes, we characterized congenic diabetes prone Bio-breeding (BB) DR.lyp/lyp rats, a widely used model for T1D diabetes. We observed lower acute insulin response, reduced islet blood flow and a significant reduction in the BCM of small and medium sized islets at a very early stage (40 days), i.e. before insulitis and development of diabetes. Underlying changes in islet function may be a previously unrecognized factor of importance in the development of T1D.

Keywords
Optical projection tomography, Diabetes, β-cell mass, disease etiology, 3D imaging, radiotracers, Single photon emission computed tomography.