Peripheral Blood Monocyte Gene Expression Profile and Pancreatic Monocyte Infiltration in Patients with Type 1 Diabetes

Xiaoyu An[1], Katharine Irvine[1], Andrew Cotterill[2], Mark Harris[2], and Ranjeny Thomas[1]
[1]University of Queensland Diamantina Institute (UQDI), Princess Alexandra Hospital, Brisbane, Australia;
[2]Department of Pediatric Endocrinology, Mater Children's Hospital

Purpose: Heterogeneity in type 1 diabetes progression is poorly understood, and there is an urgent need for biomarkers stratifying disease control and outcome. We and others have observed abnormalities in peripheral blood (PB) monocytes and monocyte-derived dendritic cell (DC) activation in patients with type 1 diabetes. The aim of our nPOD investigation is to characterise pancreatic leukocytes, in particular monocytes and DC, in healthy and diabetic subjects.

Methods: We profiled PB monocyte gene expression in 6 healthy subjects and 16 children with type 1 diabetes diagnosed ~3 months previously, and analyzed clinical features from diagnosis to 1 year. Monocytes, macrophages, and subset-specific markers were stained in pancreas from 2 patients with no history of diabetes, 2 with a history of islet autoantibodies (AB+), 2 with a history of type 2, and 3 with a history of type 1 diabetes, using the nPOD tissue database.

Summary of Results: PB monocyte expression profiles clustered into two distinct subgroups, representing mild and severe deviation from healthy controls, along the same continuum. Patients with strongly divergent monocyte gene expression had significantly higher insulin dose-adjusted HbA1c levels during the first year, compared to patients with mild deviation. The PB diabetes-associated expression signature identified multiple perturbations in pathways controlling cellular metabolism and survival, including endoplasmic reticulum (ER) and oxidative stress (e.g. induction of HIF1A, DDIT3, DDIT4 and GRP78) and reduction in the CD16+ monocyte subset marker CX3CR1. In the pancreas of patients with type 1 diabetes, CD14+ monocytes were observed around the endothelium of blood vessels, closely associated with HLA-DR+ cells, CD123+ plasmacytoid DC, and varying numbers of CD3+ T cells. CD14+ monocytes and CX3CR1+, CD16+ or CX3CR1+CD16+ cells were observed frequently, and were much more numerous than CD68+ macrophages. Expression of CD16 and CX3CR1 varied between donors with T1D.

Conclusions: A PB monocyte gene expression signature correlates with glycaemic control in the first year after T1D diagnosis. These findings implicate monocyte phenotype as a candidate biomarker for disease progression after onset, and systemic stresses as contributors to innate immune function in type 1 diabetes. CX3CR1+ cells may be recruited to the pancreas in patients with T1D. Ongoing studies will correlate the level of pancreatic recruitment with PB monocyte phenotype, and markers of ER and oxidative stress in pancreatic islets of individuals with and without diabetes.