Early differences in islets from prediabetic NOD mice: combined microarray and proteomic analysis

Type 1 diabetes is an endocrine disease where a long preclinical phase, characterised by immune cell infiltration in the islets of Langerhans, precedes elevated blood glucose levels and disease onset. Although several studies have investigated the role of the immune system in this process of insulitis, the importance of the beta cells themselves in the initiation of type 1 diabetes is less well understood. The aim of this study was to investigate intrinsic differences present in the islets from diabetes-prone NOD mice before the onset of insulitis. The islet transcriptome and proteome of 2-3-week-old mice was investigated by microarray and 2-dimensional difference gel electrophoresis (2D-DIGE), respectively. Subsequent analyses using sophisticated pathway analysis and ranking of differentially expressed genes and proteins based on their relevance in type 1 diabetes were performed. In the preinsulitic period, alterations in general pathways related to metabolism and cell communication were already present. Additionally, our analyses pointed to an important role for post-translational modifications (PTMs), especially citrullination by PAD2 and protein misfolding due to low expression levels of protein disulphide isomerases (PDIA3, 4 and 6), as causative mechanisms that induce beta cell stress and potential auto-antigen generation. We conclude that the pancreatic islets, irrespective of immune differences, may contribute to the initiation of the autoimmune process. All microarray data are available in the ArrayExpress database (www.ebi.ac.uk/arrayexpress) under accession number E-MTAB-5264.