NOVEL APPROACHES TO IDENTIFYING ISLET CRITERIA THAT PREDICT CLINICAL OUTCOMES

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Primary graft non-function and later graft failure remain major obstacles to successful clinical islet transplantation and their pathogenesis is poorly understood. We propose that there will be specific gene profiles that will be predictive of islet function after transplantation.

We have profiled mRNA expression in islets isolated from 7 organ donors with normal glucose tolerance by Affymetrix microarray. Even with the small number of islet samples, many genes showed high correlation with islet insulin secretory function. Among those genes identified were several members of the apoptotic family, including caspase-9 and BCL11A, as well as a number of nuclear genes encoding mitochondrial proteins. To help establish proof of principle we have evaluated this technique further in a mouse model. In islets that suffered primary non-function after transplantation there was higher expression of hypoxia inducible factor 1a and its downstream targets VEGF, glucose-6-phospho-isomerase (G6PI), phosphoglucomutase (PGM), phospho-fructokinase (PFK) and aldolase. Conversely, better secretory function correlated with higher expression of the islet transcription factors Pax6 and Isl1.

In order to study late graft loss we propose to undertake protocol serial biopsies to understand the mechanisms within the hepatic microenvironment for the progressive loss of islet function. It is our hypothesis that changes to the hepatic microenvironment will result in hepatic steatosis (fat), hepatic insulin resistance, relative hepatic ischaemia and inflammation, and is a potential major cause of for the long term destruction of islets.