

P053 Induction of cell cycle inhibitor and proapoptotic genes in human beta cells exposed to hyperglycemia

Katsuta H., Katsuta R., Duran L., Marselli L., Bonner-Weir S. and Weir G.C.

Joslin Diabetes Center, Harvard Medical School, Boston, Mass

Human islets (500 IEQ) were transplanted into the kidneys of either normoglycemic or STZ-diabetic ICR-scid mice. At 4 wk fed glucoses were 6.4-10 vs 22-31 mM. Beta cell rich tissue was dissected by laser capture microdissection, RNA amplified, and Affymetrix X3P arrays used (N= 6 vs 6). Changes were analyzed by dChip. 948 genes were upregulated in the hyperglycaemic group; 174 were down. The following cell cycle inhibitors genes were increased by hyperglycemia; Rb1, p16, p18, p21, E2F4 and E2F6. In addition, the following proapoptotic genes were up: Caspases 6 and 7, Bax, Bak, Bad, Bid and Fas. While Bcl2 and Bcl-x did not change, there was upregulation of A20, catalase, superoxide dismutase and glutathione peroxidase.

In a separate series of normoglycemic and hyperglycaemic mice with human islet transplants at 4 wk, replication was measured Ki67 and insulin immunostaining. In the hyperglycaemic grafts were 0.55% of 3521 beta cells; in the normoglycemic mice it was 0.43% in 4815 cells. These replication rates are far higher than in normal pancreas.

These data raise the question of whether inhibition of the cell cycle could prevent glucose driven replication that might otherwise be higher. In addition, there is a shift in the balance between proapoptotic and antiapoptotic genes. These findings suggest mechanisms that could contribute to loss of beta cell mass in transplantation and diabetes.