Revelation of Altered Expression of B7-H4: Decrease in Type 1 Diabetes and Increase in Insulinoma

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Purpose: B7-H4 is a novel negative T-cell co-signaling molecule. Our study results indicate that B7-H4 shows weaker expression levels in the pancreatic islet β cells from both human autoantibody-positive cadaver donors (IAPD) and type 1 diabetes (T1D) patients, compared with those from normal controls. Moreover, our research shows that B7-H4 is co-expressed with insulin in the islet β cells, and that its expression is concomitantly reduced with insulin in the pancreas of T1D patients. In contrast, increased B7-H4 protein expression has recently been found in a variety of human cancer cells, including lung, ovarian, breast, pancreas, brain, stomach, uterine, and kidney. We study here the expression of B7-H4 and insulin in the 'normal'-appearing islets and β cell adenomas of pancreatic samples from patients with insulinoma in comparison with those of islets from patients with T1D and from normal controls.

Methods: Ten archival insulinoma pathology samples were studied by bright-field immunohistochemistry (IHC) for the B7 family of molecules (B7-H1, -H2, -H3, -H4) as well as for insulin. Ten samples each from normal and T1D pancreas sections were included for comparison. Multi-fluorescence IHC was used to study marker expression level [mean fluorescence intensity (MFI) of positive cells and co-localization of markers (expressed as Pearson's correlation coefficient r)]. B7-H4 mRNA transcripts and protein were determined by qRT-PCR and Western blot assay, respectively.

Summary of Results: All insulinoma samples show moderate B7-H4 and strong insulin expression by bright-field IHC in the β cells from both the islets and adenomas. Co-expression of B7-H4 and insulin in the islet and adenoma β cells is reduced, respectively, at 0.66 ± 0.03 (N=19, $p<0.0001$) and 0.51 ± 0.03 (N=19, $p<0.0001$), compared to the normal control islets at 0.83 ± 0.01 (N=78), and T1D islets at 0.45 ± 0.03 (N=43, $p<0.0001$). Levels of B7-H4 and insulin expression are higher in islet and adenoma β cells than those of normal controls: B7-H4 cellular MFI in the insulinoma islet and adenoma β cells are, respectively, 55.77 ± 2.64 (N=19, $p<0.0001$) and 53.02 ± 3.83 (N=19, $p<0.0001$), compared to that of normal controls at 30.77 ± 1.11 (N=78); while insulin MFI in the insulinoma islet and adenoma β cells are, respectively, 88.35 ± 4.16 (N=19, $p<0.0001$) and 82.8 ± 3.88 (N=19, $p<0.0001$), compared to that of normal controls at 55.74±0.99 (N=78).

Conclusions: This study has shown that β-cell B7-H4 expression is deceased in T1D and increased in insulinoma patients. This suggests that B7-H4 may be involved in the pathogenesis and development of these diseases, possibly through breakage of immune tolerance to β cells in T1D or—in contrast—through facilitating malignant cell evasion from immunosurveillance in insulinoma.