Detection of Enteroviral Proteins and Cellular Antiviral Responses in the Islets of Type 1 Diabetes Patients – A Comparative Analysis of Two Cohorts

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Purpose: nPOD type 1 diabetes cases with disease duration of less than 8 years were examined to establish whether islet endocrine cells display evidence of enteroviral infection. nPOD non-diabetic controls, autoantibody positive cases and patients diagnosed with type 2 diabetes were also studied, and a comparison made with a previously analysed UK cohort of diabetic patients.

Methods: Formalin-fixed paraffin embedded pancreatic sections from selected nPOD cases (6 type 1 diabetes; 7 type 2 diabetes, 10 non-diabetic controls and 3 young (<24y) autoantibody positive), were examined by immunohistochemistry for the presence of the enteroviral capsid protein vp1 (Dako antibody; 5D8/1), insulin, protein kinase R (PKR) and class I MHC. Results were compared with those of a previously analysed UK cohort, consisting of 72 cases of recent-onset type 1 diabetes and 50 non-diabetic paediatric and neonatal controls, as well as 25 adult patients with type 2 diabetes and 69 non-diabetic adults (Richardson et al, Diabetologia 52; 1143-51, 2009).

Summary of Results: Multiple intensely vp-1 positive islet cells were observed in many insulin-containing islets (ICI) of 4 of 6 (67%) nPOD type 1 diabetes cases. Of the two cases having no evidence of vp1 expression, one was devoid of ICI. Thus, vp1 was present in 4 of 5 cases with ICI (80%). Only 2/10 (20%) non-diabetic controls had vp1 positively stained islet cells and these were also only rarely detected in the islets of autoantibody positive cases. One striking difference between the type 1 diabetes cases from the nPOD and UK cohorts was a dramatic increase in the number of individual endocrine cells within any given islet which were immunopositive for enteroviral vp1 in the nPOD cases. The expression of vp1 correlated with an increase in protein kinase R expression within the islets of the nPOD cases studied - a finding that was confirmed in the UK cohort, where vp1 and PKR co-localised within individual beta-cells. These results imply that enteroviral infection occurs commonly in type 1 diabetes and that an anti-viral response is mounted in infected islet cells. Analysis of vp1 staining in the nPOD type 2 diabetes cohort (predominantly young-onset; 18-44y, with one older case; 76y) yielded unexpected results: 5 of 7 cases (all young) demonstrated multiple intensely positive vp1 cells within the islets, and hyperexpression of class I MHC antigens by islet endocrine cells was detected in the islets of 4 of these cases. These findings were not reproduced in the UK type 2 diabetes cohort (all older patients), where only occasional immunoreactive vp1 positive endocrine cells were found in 40% of cases, and MHC I hyperexpression was never seen.

Conclusions: Enteroviral vp1 expression is observed at high frequency in the ICI of type 1 diabetes cases in both the nPOD collection and in a separate (older) UK cohort. In both cohorts, enteroviral vp1 expression correlated with increased expression of the pathogen-recognition receptor, PKR and with hyperexpression of class I MHC. The number of individual islet cells that were immunopositive for vp1 was much higher in the nPOD than in the UK cohort. Among the nPOD samples, the islets of patients diagnosed with type 2 diabetes at an early age, also displayed evidence of marked vp1 expression. This was associated with hyperexpression of class I MHC, which was never seen among type 2 diabetes cases in the UK cohort, raising the possibility that some of the nPOD patients do not have typical type 2 diabetes.