Specific Extracellular Matrix Components Accumulate in Islets and Lymphoid Tissues of Type 1 Diabetic Patients

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Purpose: The process of β cell destruction in T1D relies on migration of inflammatory cells from the blood stream into pancreatic islets via interaction with the extracellular matrix (ECM). We examined the role of ECM molecules in creating a permissive environment for autoimmune attack, focusing on hyaluronan (HA), an ECM glycosaminoglycan. Our study aims to 1) determine the changes that occur in the amount and distribution of HA in the ECM of T1D pancreatic islets and lymphoid tissues, and 2) examine the HA-dependent binding capacity of T cells to the ECM and whether it is altered in T1D.

Methods: Pancreas and lymphoid tissue sections from T1D patients and age-matched controls were provided by nPOD. HA presence and localization were examined by affinity histochemistry and HA accumulation determined semi-quantitatively. T cells, freshly isolated from T1D subjects and controls, were cultured on ECM enriched in HA to determine their HA-binding capacity and examined for the expression of the HA receptor CD44v6.

Summary of Results: In both T1D and control pancreatic tissues, HA was present in islets, associated with the islet capillaries. The relative and total intra-islet HA positive area varied among samples. Two of 12 T1D tissues contained islets with insulitis. Intra-islet HA staining was markedly elevated in these tissues which contained inflammatory cells that were embedded in this HA-enriched ECM. Evaluation of HA involvement in the islets of two different animal models of T1D, the NOD mouse and BB rat, revealed a similar distribution of HA associated with inflammatory cell infiltrates in the islets. To examine whether similar ECM changes occurred in T and B cell germinal centers (GC), HA staining was performed in pancreatic lymph nodes and spleens from T1D and control donors. Results indicated that HA was present in the T cell areas of lymph nodes and spleens in the controls. However, this staining was markedly intensified in the T cell compartments and in the enlarged GC of B cell follicles in the T1D tissues. 58% of follicles in the T1D spleen accumulated HA, occuping more than 50% of the GC area, while only 14% of follicles in the non-diabetic spleen were HA positive. Similarly, in contrast to control lymph nodes in which only 16% of follicles showed weak HA staining, 96% of T1D follicles presented moderate to strong HA staining covering more than 80% of their area. These results indicate that major ECM changes also occur in tissues other than islets in T1D. In an *in vitro* assay, CD4 T cells adhered to an HA-enriched ECM in a hyaluronidase-sensitive manner. HA binding and clearance are mediated by CD44, particularly, the CD44v6 isoform. Upon activation, CD4 T cells isolated from T1D subjects expressed less CD44v6 relative to healthy controls, suggesting that HA may accumulate in follicles of T1D patients due to impaired CD44v6-mediated HA turnover and these differences may influence the interaction of T cells with HA-enriched matrices.

Conclusions: Our preliminary data indicate that HA accumulates in islets and lymphoid tissues of T1D patients. HA occurs in close physical association with infiltrating leukocytes in insulitis and amasses in T cell areas and enlarged GC in lymphoid follicles, both in human and rodent T1D tissues, indicating the participation of HA in the inflammatory processes in T1D. Work is in progress to further clarify the role HA may play in these processes.