Heterogeneity of Pancreas Pathology and Disease Mechanisms

Expression and Regulation of Chemokines in Human Islets and Type I Diabetes

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Purpose: More than half of the 46 known human chemokines have been associated with and/or implicated in the pathogenesis of type 1 diabetes (T1D), yet their actual expression patterns in the islet environment of T1D patients remain at present poorly defined. This study was designed to identify relevant chemokine proteins expressed *in situ* in the pancreata of individuals with T1D to provide a foundation for the informed selection of potentially suitable targets within the chemokine/receptor family.

Methods: Here, we have employed an integrated and unbiased approach using a human islet culture system, murine models of virus-induced and spontaneous T1D, and the histopathological examination of pancreata from healthy and diabetic organ donors. Principal experimental methods included microarray analyses, qRT-PCR and immunohistochemical analyses using a set of in part newly validated reagents.

Summary of Results: CCL5, CCL8, CCL22, CXCL9, CXCL10 and CX3CL1 were the major chemokines transcribed (in an iNOS- but not NF-κB-dependent fashion) and translated in response to inflammatory stimuli. CXCL10 was identified as a dominant chemokine expressed at the protein level in the islet environment of both experimental animals and T1D patients, while CCL5, CCL8, CXCL9 and CX3CL1 were expressed at lower levels in murine and human T1D. Unexpectedly, these chemokines, and in particular CXCL10, were also expressed in the acinar tissue of the exocrine pancreas.

Conclusions: The utility of our integrated screening approach was validated by identification of CXCL10 as a particularly prominent chemokine expressed in the pancreata of T1D patients, and further provides evidence for the potential importance of CCL5, CCL8, CXCL9 and CX3CL1 in the pathogenesis of human T1D. Importantly, expression of these chemokines in both islets and acinar tissues emphasizes an underappreciated involvement of the exocrine pancreas in the natural course of T1D that will require consideration for further T1D pathogenesis and immune intervention studies.