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Progress report

Alterations in the extracellular matrix (ECM) structural components are a key feature of islet histopathology in type 1 diabetes (T1D). ECM is the non-cellular compartment of the tissue and is essential for the maintenance of tissue integrity and function. We recently found that hyaluronan (HA), a major component of the islet ECM, extensively accumulates in human islets in diabetes, forming large deposits along the islet microvessels and in the areas of islet inflammatory cell infiltrates defined as insulitis. The modification of the HA/ECM in islet tissue and in regions of islet inflammation matters because HA is a keystone molecule in the inflammatory milieu and has been increasingly implicated in the regulation of immune responses.

This DRC supported project aimed to determine whether a modified HA/ECM forms in human islets in the early pre-symptomatic stages of T1D, and how this modified HA/ECM relates to the presence and location of islet immune cell infiltrates. To this end, we studied a large set of pancreas tissues from non-diabetic organ donors who had tested positive for one or more islet cell autoantibodies (aAbs). These tissues were identified through the Juvenile Diabetes Research Foundation network for Pancreatic Organ Donors (JDRF nPOD).

We initially examined whether the pancreas tissues from the aAb+ donors contained abnormal amounts of HA in their islets. We discovered that abundant HA deposits had formed in a large subset of these donors who were at different stages of islet autoimmunity. We found a positive correlation between the amount of islet HA staining and the number of aAbs, with prominent islet HA accumulations present in donors positive for more than one islet aAb. Further, we found that islet HA accumulation occurs independently of and precedes insulitis, which indicates that ECM modification is an early histopathologic change in islets in T1D. Importantly, we learned that the first immune cells infiltrate only those islets that have accumulated large amounts of HA. These novel observations indicate that the precursory islet HA build-up may determine the sites of subsequent immune-cell entry into islets and that insulitis initiates in islets that have accumulated a ‘critical’ mass of HA. Additional islet HA deposition was concurrent with expansion of insulitic infiltrates inside islets, which suggests that the continuous amassment of HA not only may serve as a blueprint for islet immune-cell infiltration but also may influence the advancement of insulitis. Work is in progress to determine the nature of the HA-rich pro-inflammatory islet ECM and the mechanisms by which the HA/ECM-immune cell interactions promote islet invasion by these cells.

Looking at the bigger picture, our research strives to develop a comprehensive understanding of the role of the islet ECM in the development of islet inflammation. Our DRC-supported studies identified the earliest detectable histopathologic changes in human islets and provide new insight into the pathogenetic process in T1D. This knowledge will help determine when and how the ECM could be a therapeutic target to stop or prevent T1D. We would like to express our deepest gratitude to the donors and to the staff of the DRC for supporting this project.

With great appreciation,

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