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Losing a Grip on the Notion of β-Cell Specificity for Immune Responses in Type 1 Diabetes: Can We Handle the Truth?

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COMMENTARY

You can't handle the truth!
— Jack Nicholson, *A Few Good Men*

Research utilizing human pancreata to define a role for the immune response in the pathogenesis of what we now term type 1 diabetes (T1D) has come a long way since 1902 when Schmidt, a German pathologist, noted a small cellular peri-islet infiltrate upon microscopic evaluation of the pancreas obtained from a 10-year-old child with diabetes (1). Efforts by Shields Warren in the 1920s drew attention to the relationship between this infiltrate and the age of diabetes onset (2), while the term "insulitis" was not coined until 1940 by the famous liver pathologist Hanns von Meyenburg (3). Subsequent work led by Gepts (4), LeCompte (5), Foulis (6), and others in ensuing decades (7,8) taught us much regarding this inflammatory lesion. We gained insight into its relative infrequency in older individuals diagnosed with the disease, the association with reduction in β-cell mass, identification of "pseudo-atrophic" islets (i.e., islets devoid of insulin-containing cells), the preferential targeting of insulitis for β-cells containing insulin, upregulation of class I MHC, and many other seminal findings. Taken collectively, these efforts not only formed an "intellectual cornerstone" upon which much of the research enterprise in T1D over the last 40 years has been built but also led to the oft-cited notion that T1D results from an autoimmune destruction of the insulin-secreting pancreatic β-cells.

As a community of researchers, we built our models regarding the natural history of T1D around this notion, largely focused our efforts on biomarker discovery related to it, interpreted findings from animal models in light of it, designed therapies seeking to prevent and/or reverse the disorder with respect to it, and in many cases, began introductory sentences for the research articles we pen pertaining to T1D by stating some variant of this notion. So embraced, this concept has formed a pedagogical dogma for our field.

To be clear, this view is not without intellectual merit. T1D is a disorder in which β-cells are lost, and certainly, unequivocal evidence for an autoimmune component abounds (9). However, there is another element resident to the pathogenesis of T1D that, for reasons perplexing to this author, has largely gone unnoticed: The role of the exocrine pancreas in this disorder. Indeed, while the history of islet inflammation and β-cell destruction has clearly seen due recognition, the body of literature describing abnormalities related to the exocrine pancreas largely has been overlooked and, without question, underappreciated.

Studies—some decades old—have noted a variety of unusual physiologic and pathologic features associated with the pancreas in T1D (Fig. 1). These include a propensity for exocrine insufficiency, exocrine atrophy, and other tissue-related abnormalities including fibrosis (10–12). The pancreas in T1D also is the target of a series of immunological aberrations, including autoantibodies targeting exocrine constituents, deposition of the complement degradation product C4d, and neutrophil infiltration of the pancreatic parenchyma (13–15). Beyond these, a variety of techniques and tissue sources (e.g., autopsy, organ donors) have led investigations to suggest pancreatic weights and volumes are reduced by 20–50% in T1D patients when compared with control subjects of similar age (16).

This brings us to the importance of the study by Rodriguez-Calvo et al. (17) in this issue of *Diabetes*. In this new work, the authors performed a careful analysis of pancreatic specimens obtained from the Network

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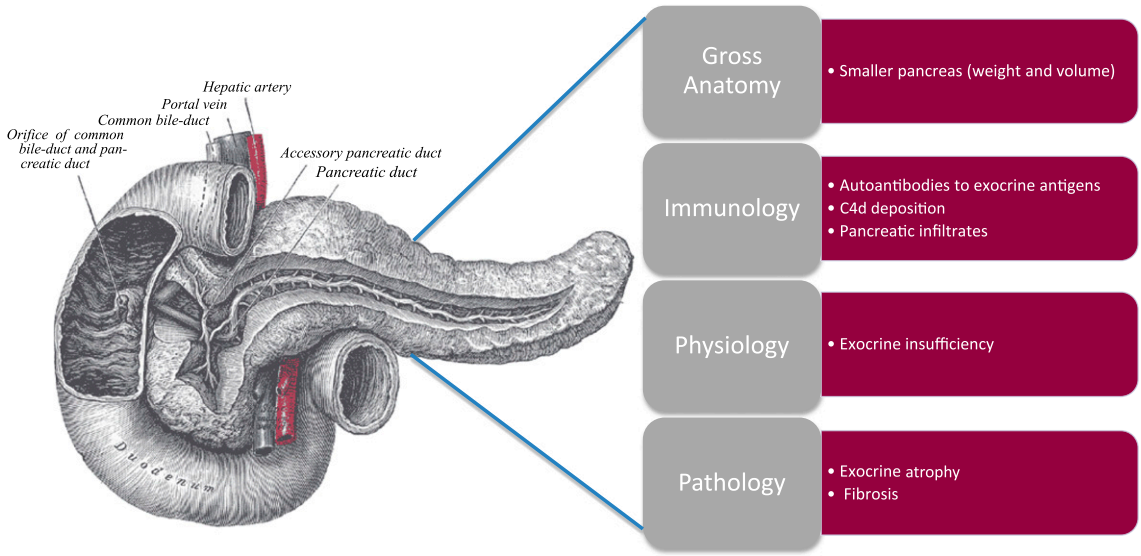

Figure 1—Features of the exocrine pancreas noted to be aberrant in T1D. Pancreas illustration from *Gray's Anatomy*, 20th edition (ca. 1902), courtesy of open reproduction policy (Bartleby.com).

for Pancreatic Organ Donors with Diabetes (nPOD) program (18). The availability of these high-quality (i.e., transplant grade) tissues, obtained from whole-pancreas recoveries, allowed the conduct of an impressive series of investigations that historically would have been difficult to achieve, especially with a large number of study subjects. Previous efforts by this group (19) had already identified CD8 T cells—including those directed against known β-cell autoantigens—as a major constituent of the insulitis lesion in T1D. This finding is consistent with, and builds on, the aforementioned body of literature supporting the relative specificity (including antigenic) of the infiltrate for pancreatic islet β-cells. However, the new work introduces a profound twist to this landscape because it highlights marked CD8 T-cell infiltration of exocrine pancreas in T1D. Interestingly, the enhanced exocrine presence of CD8 T cells was neither specifically associated with insulitis nor limited to people with diabetes of short duration. The latter finding suggests that the T1D pancreas may harbor an extended, and perhaps a lifetime, disposition to this aberration. The enhanced pancreatic infiltration was not limited to CD8 cells. Elevations of both CD4 T cells and $CD11c^+$ cells were similarly observed in the tissue samples that were studied. Finally, consistent with an emerging body of information suggesting the potential for shared pathogenic features between T1D and type 2 diabetes, the authors suggested that the exocrine tissue of the latter group also may be prone to elevations in pancreatic infiltration. Taken together, these studies provide quite novel and potentially very exciting information regarding a means by which inflammation of the pancreas may influence the pathogenesis of T1D.

At first glance, some might call into question the potential validity of these findings with concerns that they reflect experimental artifact due to the source of donor tissues (i.e., brain-dead organ donors). This potential concern follows from a report (20) suggesting an increased frequency of $CD45^+$ cells in pancreatic parenchyma as a function of time in the intensive care unit (ICU) prior to organ procurement, with the most pronounced effects occurring at or after 6 days of life support. Notably, the new report directly addressed this issue and saw no relationship between ICU time and exocrine infiltration. It should be noted that very few nPOD cases exceed 6 days of ICU time (data not shown), perhaps reflecting differences in end-of-life practices in Europe (20) versus those in the U.S. (18). However, as noted by Rodriguez-Calvo et al. (17), this consideration is associated with both a limitation and an avenue for future direction in that expanded studies of this important question should be performed to clarify the issue. Beyond this, much more in the way of "relevance" (for lack of a better word) to the disease is required before the overall importance of this finding of pancreatic CD8 infiltration to the disorder's pathogenesis, including the aforementioned pancreatic features, can be established. Examples could include impact on the propensity to develop insulitis, effects on both exocrine and endocrine function, and the degree of antigen specificity for infiltrating cells.

In sum, despite repeated discussion of autoimmune responses directed against pancreatic islets in T1D, a growing body of old and new literature suggests that the immune contributions to this disorder may not be quite so β-cell specific. Given that as a community, the role for the exocrine pancreas has historically been ignored and resigned to a β-cell–centric focus, we must

ask ourselves whether these observations support a truth that we can't handle.

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Duality of Interest. M.A.A. serves as the executive director of the nPOD program, which provided the tissues that were investigated in the commented-on article. nPOD is a peer-reviewed, but open-access, tissue bank open to investigation, including requests for tissues, to any qualified investigator.

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