**Changing perspectives on the progression of type 1 diabetes**

**Noel G Morgan & Sarah J Richardson**

Institute of Biomedical & Clinical Science, University of Exeter Medical School.

Correspondence:

Prof Noel Morgan; Director, Institute of Biomedical & Clinical Science, University of Exeter Medical School, or Dr Sarah Richardson; Lecturer in Biomedical Sciences, University of Exeter Medical School

University of Exeter Medical School

Level 4; RILD Building,

Barrack Rad, Exeter EX2 5DW.

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Type 1 diabetes remains an enigmatic disease from both a scientific and a clinical viewpoint. The symptoms are widely understood to present when the insulin-secreting beta cells in the islets of Langerhans are destroyed via a process of autoimmunity1,2. For this reason, the immediate therapeutic approach at diagnosis is to supplement the endogenous insulin deficiency with an exogenous supply. This has been the *status quo* over many years and, for the majority of patients, it provides an appropriate means to stabilise their condition and allows for effective glucose control over the longer term. However, this is not universally true and despite the best efforts to maintain glucose homeostasis, the disease is still associated with significant morbidity and mortality. Therefore, important questions remain about whether alternative therapeutic approaches which prevent rather than treat the condition might be developed in future.

At present, identifying those individuals who are progressing to type 1 diabetes among the background population is a difficult task because presentation of the disease occurs sporadically and is usually unheralded. It develops most frequently in subjects with a specific genetic predisposition and considerable efforts have been invested to identify the genes involved3. However, this information has not stimulated widespread attempts to screen for such individuals. There are various reasons for this, not least the fact that many members of the general population have the “high risk” genetic profile yet do not develop the disease. Allied to this is a still more basic problem which, in our view, defines the nub of the issue most starkly; namely that we still have only a rudimentary understanding of the processes that cause the disease in the pancreas.

**Background**

It may come as a surprise to learn that, since the beginning of the 20th century, the underlying pancreatic pathology of type 1 diabetes has been studied in detail in only about 200 individuals with recent-onset disease, worldwide4-6. Hence, our collective understanding of the progression of the illness at the cellular level derives from a very limited evidence base. As such, this has militated against attempts to develop preventive rather than therapeutic options for type 1 diabetes. Thankfully, this situation is changing and immunotherapeutic trials are already underway in the UK to explore whether disease progression can be halted or slowed to allow the preservation of residual beta cell function in newly diagnosed patients7,8. These trials are important and their outcomes will be awaited with bated breath. However, it remains true that the success of such initiatives depends on the validity of assumptions made about the underlying causes of the disease and the suspicion persists that many of these are still concealed within a black box.

One reason is that the endocrine tissue within the pancreas is not amenable to interrogation or analysis in living individuals (although efforts are underway to try to solve this problem). Thus, it is a sad fact that the majority of cases which become available for study represent tragic instances in which a patient (usually a child) dies at, or soon after, disease diagnosis9,10. Methods to biopsy the pancreas in living subjects have been developed but are subject to significant constraints. In some cases, needle biopsies 11,12 have been taken but the amount of tissue which then becomes available for study is very limited and may not be representative of the pathology across the wider pancreas. More recently, a laparoscopic procedure has been employed in a Norwegian study and, while this has yielded larger quantities of tissue and important new information, only six patients had been recruited when the trial was discontinued because of unexpected complications associated with the procedure13. Thus, the availability of relevant tissue for study remains a limiting factor.

Despite these impediments, progress has been made in understanding the causes of type 1 diabetes and this is partly because of the establishment of new collections of samples (notably via the network of pancreatic organ donor (nPOD) initiative in the USA14; although this still contains very few cases of recent-onset disease) and partly by the advent of improved methods to study the extant collections10. Together these have yielded new insights and also provided some surprises.

**The state of the art**

One of the most important conclusions is that the underlying processes which lead to beta cell death in patients with type 1 diabetes do not occur uniformly across the pancreas. Rather, the disease develops in a lobular manner such that some regions of the gland are affected very profoundly while others, often nearby, appear entirely normal6. The reasons for this remain completely mysterious. A second surprise relates to the process by which the beta cells are destroyed. This involves the influx of specific cells of the immune system which migrate to the islets and then target the beta cells for destruction. It had been assumed that this process (“insulitis”) proceeds in a broadly similar manner in most patients and that the disease is manifest at a point when the majority (70-90% for typical “textbook” figures) of the beta cells have been destroyed. However, new evidence suggests that these conclusions are over-simplified and that the underlying processes vary between patients15. As such, this has important implications for the understanding of the disease and how it might be prevented.

The process of insulitis involves several different types of immune cell and the key effectors mediating the ultimate demise of the beta cells are a subtype of T-cells known as cytotoxic “CD8+” T-cells16. These are attracted to the islets by mechanisms that are still being debated but, on arrival, they are primed to kill the beta cells. This is analogous to the role played by CD8+ cells in fighting infections elsewhere in the body except that, in the pancreas, the attack is directed against “self-antigens” in a process of autoimmunity. The most recent evidence has confirmed that, while CD8+ T-cells probably play a similar overall role in all patients, the rate at which they kill beta cells and the extent to which they are attracted to the islets, is variable. This is because a second cell type, CD20+ B-cells, also contributes to the inflammatory process (a more unexpected conclusion). By examining the insulitic profiles of islets across a range of individuals who had died very soon after the diagnosis of type 1 diabetes, it became clear that the patients fall into two categories15. Some have a profile of insulitis in which the T-cells are accompanied by significant numbers of B-cells during the islet attack while, in others, B-cells are present in much reduced numbers in the islets (though they may still be present in the pancreatic parenchyma). The significance of this only became clear when the patients were stratified according to their age at diagnosis of type 1 diabetes. Rather than finding a random distribution of the two insulitic profiles among the patients, it was discovered that children who were diagnosed at or below 6 years of age displayed one phenotype, while those diagnosed in their teenage years (or beyond) displayed the other15. In particular, those in whom the insulitic profile was characterised by the presence of significant numbers of both T- and B-cells (“CD20Hi”) developed the disease early in life while those with the alternative profile (T-cells but few B-cells; “CD20Lo”) were older at diagnosis.

In studying this unexpected phenomenon more closely, it was discovered that a second feature also differentiates the two forms of the disease. In patients with a CD20Hi profile of insulitis, few residual beta cells could be found in the pancreas at disease diagnosis; which is consistent with the accepted wisdom that the clinical symptoms arise once most beta cells are destroyed. However, this dogma was challenged by analysis of the residual beta cells in patients with a CD20Lo insulitic profile (i.e. those diagnosed as teenagers or older). In many such patients, significant numbers of beta cells could still be found at the time of disease diagnosis. This suggests that the destructive process is less efficient in this group than in younger children and that the clinical symptoms arise in the older patients before beta cell destruction is complete15. Thus, in those who were older at diagnosis, beta cell dysfunction might also contribute significantly to the clinical onset of disease. In support of this, it was recently shown that islets isolated from patients who had been newly diagnosed with type 1 diabetes beyond their teenage years contain residual beta cells17. Importantly, however, these islets were largely unresponsive to glucose. Strikingly, when they were cultured *ex vivo* for a few days, their insulin secretory response to glucose improved; thereby confirming that the beta cells had not been completely destroyed but, rather, they had become refractory to glucose stimulation17. Extending this idea, others have found by using a newly-developed high sensitivity assay for endogenous C-peptide, that some patients who have had type 1 diabetes for many years, still display a meal-induced rise in insulin secretion, implying the sustained persistence of some beta cells18,19. Moreover, examination of the pancreases of patients who died as long as 50 years after diagnosis of type 1 diabetes, has also revealed the presence of islets containing immunoreactive insulin20. Thus, the oft-treasured notion that patients with type 1 diabetes inevitably lose their entire complement of beta cells early during disease progression, appears incorrect.

**Implications for the future**

Clearly, these various new insights have important implications for the design of approaches to therapy in the future. Firstly, it remains critical that a still more detailed understanding of the underlying immune cell mediated attack on beta cells is gained since a “one size fits all” approach to therapy is unlikely to be successful. Secondly, it will be necessary to learn more about the role of B-cells as catalysts of the autoimmune attack since this is still not widely appreciated. Of course, it is well understood that islet autoantibodies are found commonly in the blood of patients with type 1 diabetes and that such antibodies are secreted by activated B-cells. However, the B-cells that reside in inflamed islets do not appear to be secreting antibodies and must have a different function. If, as seems likely, they can orchestrate the T-cell mediated attack, then interventions designed to impede this action could be therapeutically effective. The newly published results should inform this debate since they suggest that such interventions are likely to be most effective in younger patients. In support of this, it is noteworthy that, in earlier trials of the efficacy of the anti-B-cell reagent, Rituximab, in patients with new-onset type 1 diabetes, the most promising outcomes were seen in younger patients21,22. Finally, if those who develop type 1 diabetes beyond their earliest years of life, retain a significant beta cell reserve at diagnosis; then therapeutic approaches which aim to enhance the functionality of these cells should also be considered alongside attempts to attenuate the autoimmunity.

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**Author Contributions**

N.G.M. and S.J.R wrote and critically reviewed the manuscript.

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