**Historical and new insights into pathogenesis of type 1 diabetes (2)**

**F. S. Wong* and T.I Tree†**

* Division of Infection and Immunity, Cardiff University School of Medicine, Cardiff, UK,

† Programme of Infection and Immunity, Department of Immunobiology, Faculty of Life Sciences and Medicine, King's College London, Borough Wing, Guy's Hospital, London, UK

Correspondence: F. S. Wong, Division of Infection and Immunity, Cardiff University School of Medicine, Cardiff, CF14 4XN, UK.
E-mail: wongfs@cardiff.ac.uk

## Summary

In this second and final part of the collection of articles for the Immunology of Diabetes Society review series on insights into pathogenesis of type 1 diabetes, we present two articles. The first of these covers a debate that took place in the Immunology of Diabetes Society meeting in London 2018, in which five investigators presented a case for specific immune cells/targets to be the "Achilles Heel of type 1 diabetes". The second article presents further insights into the generation of post-translationally modified peptides. It focuses on mechanisms and processes that lead to new potentially autoantigenic targets for $CD8^+$ T cells, and complements the review of new hybrid peptide targets for $CD4^+$ T cells in the first part of our series.

Nearly 50 years ago, we first began to appreciate that Type 1 diabetes had an immune basis and, from many lines of evidence, hypotheses were generated that the immune system plays a central role in the pathogenesis of type 1 diabetes. It is very clear that there is not a simple relationship between an immune attack on an innocent bystander organ in the development of type 1 diabetes. There are a complex set of interactions that lead to damage and destruction of the pancreatic islet insulin-producing beta cells, leading to insulin deficiency. This multi-faceted disease has several important components, summarised by Peters and colleagues earlier in this review series (1), and there is increasingly strong support for a model that suggests that the beta cells may themselves play a role (2). Nevertheless, the immune system attack is clearly a very important component. Here, in the first of these new articles, in a debate format, we highlight in more detail an interesting way to consider the immune components - neutrophils, B cells, $CD8^+$ T cells, regulatory $CD4^+$ T cells, as well as enteroviruses and their effects on pancreatic beta cells. These components of the disease process are presented in this review as not only playing a very important role in the pathogenesis of type 1 diabetes, but as potentially the "Achilles Heel" of type 1 diabetes (3) (Battaglia et al, 2021). Readers will judge for themselves whether any one of these individual components could be considered to be the "Achilles Heel" - an area of weakness or vulnerable spot, or something missed or underappreciated, and which could represent a therapeutic target.

As we increase our focus on immune therapeutics, it remains critical that we understand the various factors leading to the ultimate demise of the pancreatic beta cell, and the complexities of heterogeneity of the disease. The immune system clearly plays a central

role, (3) (Battaglia et al, 2021) and escape from central and peripheral tolerance can be demonstrated, together with processes that then attract these immune cells to the target organ (reviewed in (4)). Even though our hypotheses for the immune damage may include a component of involvement of the beta cells in their own demise, as a result of beta cell stress including viral infection (3) (Battaglia et al, 2021), nevertheless, understanding the nature of the targets of T cells is essential. CD8 T cells are central players for which there is ample evidence for their role (3) (Battaglia et al, 2021); here we include the article by Faridi and colleagues (5) (Faridi et al, 2021), which details mechanisms for generation of novel targets for $CD8^+$ T cells, although at this time, the modified peptides that have been found to be targets in type 1 diabetes have mostly been identified for CD4 $T^+$ cells (6). We need to understand the processes whereby both $CD4^+$ and $CD8^+$ T cells evade tolerance as part of the immune process and different mechanisms may be employed in the generation of novel autoantigenic targets, which may partly explain their escape from central tolerance (5, 6).

We are in an era where immunotherapeutic approaches are being hotly pursued. Whilst several biologics have been trialled in human type 1 diabetes, recently reviewed by Ke and colleagues (7), there have been few immunological interventions that have had a lasting effect when administered after diabetes onset. Most recently, anti-CD3 (Teplizumab) presents exciting promise - when administered in autoantibody-positive individuals, the onset of overt type 1 diabetes has been delayed (8). Thus, an ability to predict who will develop disease will be critical (9) and appreciating the largest context, including the multiple players in this process will be vital for development of future therapeutics.

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