New developments for prevention of type 1 diabetes: a paradigm shift?

The discovery of insulin nearly 100 years ago heralded a treatment that prevented the death sentence that came with a diagnosis of juvenile diabetes (now known as type 1 diabetes). Research developments in insulin delivery and action have improved outcomes for many patients with type 1 diabetes. However, there has been a strong belief in medicine that type 1 diabetes is not preventable, and that type 2 diabetes is not reversible. Owing to the development of prevention strategies for both types of diabetes, and clear evidence that lifestyle change can lead to remission of type 2 diabetes, it is time this belief system was updated.

Type 1 diabetes is an autoimmune disease, yet there has been little progress in developing therapies targeting the immune system to prevent it, probably as a result of serious side effects of the general immunosuppressant, ciclosporin, in trials in the 1980s (Greenbaum et al, 2017; Jacobsen et al, 2018) and the fact that insulin is a relatively safe and effective treatment. However, the incredible heterogeneity in clinical phenotypes of people with type 1 diabetes is clearly related to the range of immunological processes that influence disease pathogenesis. The improving knowledge of immunology and autoimmune disease provides multiple novel, selective intervention options that could prevent or delay the development of type 1 diabetes (Jacobsen et al, 2018; Orabona et al, 2018; Smith and Peakman, 2018). Indeed, phase I clinical trial data showed a good safety profile for selective immunotherapies, and indicated a delay in progression of beta cell decline in patients with type 1 diabetes (Alhadj Ali et al, 2017).

Similarly, although the strong link between lifestyle and development of type 2 diabetes has been clear for decades, patients and many physicians were unconvinced that lifestyle modification alone could reverse the diagnosis. Several studies have demonstrated sustainable remission with lifestyle improvement (McCombie et al, 2017). The emphasis on intensive lifestyle intervention at diagnosis should be the cornerstone of management of type 2 diabetes yielding significant benefits in terms of both morbidity and health-care costs.

Type 1 diabetes is a heterogeneous disease

Hyperglycaemia associated with progressive reduction in serum levels of C-peptide, presence of autoantibodies and young onset are the major considerations for diagnosis of type 1 diabetes. Yet type 1 diabetes is an astonishingly heterogeneous disease which continues to increase in prevalence. Age at presentation, autoantibody profile, rate of beta cell decline, comorbidities and response to therapy vary widely, and can even lead to misclassification as type 2 diabetes and inappropriate management.

Meanwhile, advances in insulin formulation have allowed improvements in diabetes control and a reduction in complications, although insulin therapy will never match the rapid, measured glucose-dependent delivery of insulin from the native beta cell.

Developing selective immunosuppression to prevent beta cell loss or decline has been resisted, despite general immunosuppression being a necessity for patients who undergo islet transplantation. Clearer understanding of the complexity of the immune system defects that lead to beta cell destruction makes the development of personalized preventative immunotherapy more possible than ever before. There is real optimism that high risk groups can be identified before the need for insulin replacement, and that individualized therapies for prevention of type 1 diabetes are achievable within a generation.

Improved biomarkers for non-symptomatic type 1 diabetes

Type 1 diabetes is thought to progress through three major stages. The first involves initiation of an autoimmune response but with no symptoms and no appreciable beta cell loss, the second with some beta cell decline and mild hyperglycaemia but no requirement for insulin, and the third being type 1 diabetes diagnosis and the need for exogenous insulin.

The ability to identify non-symptomatic disease provides an opportunity to establish high risk populations before the need for daily insulin injections and the damage caused by hyperglycaemia. This prodromal stage is defined by the presence of one or more autoantibodies (these also provide information on the molecular pathology of the autoimmune disease), and by specific cytokines and blood biomarkers, including microRNA species, epigenetic changes and immune checkpoints. There are also confirmed genetic risk factors for autoimmunity and type 1 diabetes. It is therefore possible (if currently rather expensive) to identify individuals at the prodromal phase of type 1 diabetes development (useful for clinical study recruitment as well as risk stratification to evaluate management).

Type 1 diabetes is a complex and varied autoimmune disease

Immune tolerance is the act of distinguishing 'self' from 'invader' and laying down a cellular memory to protect healthy cells from destruction. It involves presentation of self-antigens by antigen-presenting cells to highly specialized regulatory T cells to generate appropriate signals to prevent self-attack (see additional *Figure 2* online). Autoimmune disease results from a defect in the development or maintenance of tolerance. A pathogenic T-cell response on the insulin-producing beta cells ultimately generates type 1 diabetes and the need for exogenous insulin.

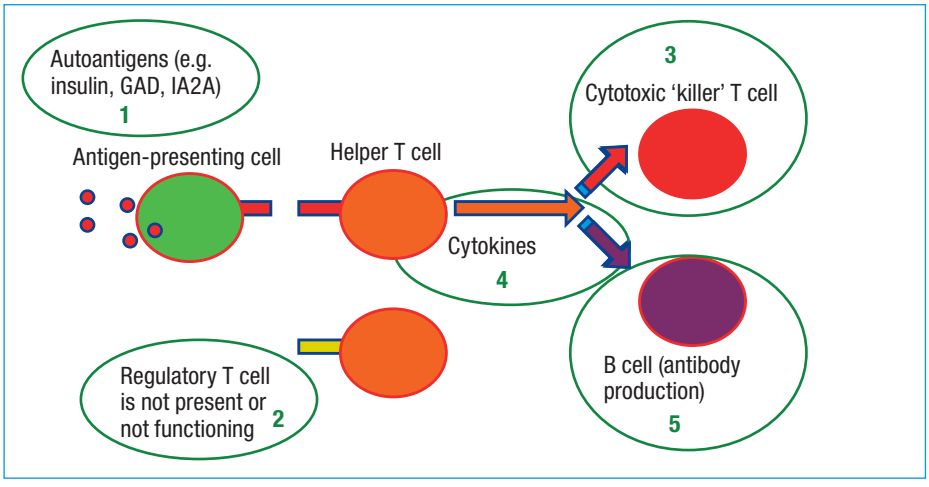
There are several points in the tolerance pathway where this response can go wrong, including misprocessing of beta cell peptides (self-antigens), loss of action of specific regulatory T cell populations, and

Dr Christopher J Schofield, Consultant Diabetologist, Diabetes Centre, Ninewells Hospital and Medical School, Dundee

Professor Calum Sutherland, Professor of Molecular and Cellular Diabetes, Department of Cellular Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY

Correspondence to: Professor C Sutherland (c.d.sutherland@dundee.ac.uk)

Figure 1. Points in the immune tolerance pathway that are being investigated in autoimmune diseases and have the potential to be harnessed to prevent beta cell damage in type 1 diabetes. 1. Generate tolerance by presenting more self antigens (e.g. oral insulin, antigenic peptides). 2. Treatment with agents to enhance regulatory T cell action (e.g. antiCD3 such as teplizumab which also reduces cytotoxic T cells), or infusion with the patient's own regulatory T cells activated artificially outside the body. 3. Agents that block cytotoxic T cell function (e.g. abatacept, CTLA4-Ig used in arthritic conditions, and mycophenolate, used in transplant protection). 4. Agents that modify cytokine actions, includes anti-IL6R (e.g. tocilizumab), anti-IL-1R (e.g. canakinumab) designed to reduce inflammation and also reduce activation of cytotoxic T cells. Some success in arthritic conditions. Ustekinumab blocks IL12 and IL23, which enhances regulatory T cell action while reducing the inflammatory activation of cytotoxic T cells used in psoriasis. 5. Block B cell function (e.g. rituximab, antibody to the B cell protein CD20 which triggers B cell death and is used in many autoimmune diseases, and mycophenolate which inhibits both T and B cell proliferation, reducing purine synthesis selectively in B and T cells). GAD = glutamic acid decarboxylase; IA2A = protein tyrosine phosphatase-like antigen.



inappropriate secretion of cytokines, although the underlying cause of each remains unclear. Therefore, there are multiple intervention points with the potential to restore immune homeostasis and prevent further tissue destruction (*Figure 1*). These include:

1. Antigen-based therapies where self-antigens (e.g. pro-insulin) are delivered to the patient's endogenous populations of antigen-presenting cells to enhance tolerance (similar to vaccination)
2. Selective expansion of tolerance-inducing immune cells, such as regulatory T cells, tolerogenic dendritic cells and macrophages (both ex vivo and in vivo)
3. Targeting specific populations of regulatory cells using antibodies (blocking, stimulatory or inhibitory), cytokines and cytokine receptors to amplify or attenuate cytokine signalling.

As type 1 diabetes is heterogeneous in pathophysiology, specific patient attributes will dictate the response to each type of intervention. One therapy will not fit all, and this may explain some of the poor results from early immunotherapy trials. Clearly, there is scope and a need for 'personalized' treatments to prevent type 1 diabetes.

Could immunotherapy be used for all patients with type 1 diabetes?

Therapeutic intervention to alter disease outcome would be most useful in the prodromal (non-symptomatic) stages of type 1 diabetes, which can persist for years, where individuals could be identified by serum autoantibodies and other blood biomarkers. However, such therapies could reverse autoimmunity and maintain residual beta cell mass even at the point of clinical diagnosis of type 1 diabetes. Significant beta cell mass remains at diagnosis in most patients, explaining why ciclosporin induced remission in patients with new onset type 1 diabetes (Sobel et al, 2010). It is also worth considering immunotherapy in patients with long-standing type 1 diabetes to protect residual beta cell function. In some patients with type 1 diabetes maintenance of even a small amount of functional beta cell mass would improve glycaemic control sufficiently to reduce insulin dependence and morbidity.

Conclusions

Management of type 1 diabetes has essentially remained the same over the past 100 years. The initial focus of diabetes management was preventing early death. Once this was achieved, the focus shifted to prevention of diabetes-related complications. Prevention of type 1 diabetes would achieve both of these goals and avoid a lifetime of insulin injections. Identifying those at highest risk and the promise of personalized immunotherapy are realistic objectives, providing growing optimism that type 1 diabetes will be preventable within a generation. This, combined with strong evidence that type 2 diabetes can be prevented and reversed by lifestyle modification, should underpin the fight to eradicate most diabetes in the next 100 years. **BJHM**

KEY POINTS

- The prevention of type 1 diabetes is now an achievable goal.
- Improved understanding of the role of autoimmunity in the development of diabetes provides novel preventative opportunities.
- Targeted immunological manipulation provides safer options for the treatment of autoimmune disease.
- Improved biomarker assays should allow the identification of those at high risk of developing type 1 diabetes.
- It is vital that physicians recognize and support ongoing clinical trials in the prevention of type 1 diabetes.
- Improved understanding of the immune system provides genuine opportunities to develop new therapies to prevent beta cell loss and the need for exogenous insulin.

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Figure 2. **a.** Adaptive immunity is a process that detects potentially harmful infection threats and responds by generating a defensive cellular response to eradicate the infective agent along with infected cells. The host has to distinguish its own cells and molecules from potentially harmful invaders. **b.** During host development immune tolerance develops whereby regulatory T cells are programmed to protect the host from self attack. When this tolerance is poorly developed or fails to be maintained then autoimmune diseases can develop. **c.** In type 1 diabetes the immune system targets the host beta cells and destroys them. The general processes involved are understood but the reasons for the loss of tolerance in type 1 diabetes are only just starting to be unravelled. GAD = glutamic acid decarboxylase; IA2A = protein tyrosine phosphatase-like antigen.