Inflammation and type one diabetes

David Bending¹, Paola Zaccone² and Anne Cooke²

¹Rheumatology Unit, University College London Institute of Child Health, London WC1N 1EH, UK
²Department of Pathology, University of Cambridge, Cambridge CB2 1QP, UK

Correspondence to: D. Bending, Rheumatology Unit, University College London Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK; E-mail: d.bending@ucl.ac.uk

Received 8 December 2011, accepted 28 February 2012

Abstract

Type one diabetes (T1D) is a complex T cell-mediated autoimmune disease, the defining feature of which is the destruction of the insulin-secreting beta- (β)-cell. Both genetic and environmental factors combine to precipitate disease, and the outcome of the pathological process is dependent on multiple inter-related factors. In this review, the mechanisms behind the initiation and propagation of the autoimmune response are analysed, and the contribution of differing T-helper (Th) subsets—in particular Th1- and Th17-related cytokines—to the disease process are discussed. An argument is then synthesized that proposes that the β-cell’s response to stress and inflammation is the critical determinant in predicting disease outcome and that, immunologically, a delicate balance exists between regulation and inflammation at the site of islet infiltration. Strategies for disease intervention, therefore, will not only require the induction of T-cell tolerance by tipping the balance towards regulation but will also need to contain approaches that result in the scavenging of inflammatory mediators, in order to facilitate repair. Ultimately, given that clinical diabetes presents late in the autoimmune process, strategies for β-cell regeneration must now be addressed. There is thus a requirement for an increased, collaborative effort between stem cell biologists and immunologists in order to tailor an optimal therapeutic strategy for the treatment of this debilitating disease.

Keywords: beta-cell, cytokines, immunoregulation, regeneration, T -cells

Introduction

Type one diabetes (T1D) is an autoimmune disease in which the pancreatic insulin-producing beta- (β)-cells are selectively destroyed by the immune system. While it is still unclear what the initiating factor/s for T1D are [a viral aetiology has been postulated (1), but this remains controversial], it is clear from animal models of the autoimmune disease that multiple immune cell types coordinate to bring about β-cell destruction. The critical outcome of this attack is the reaction of the β-cell to the inflammatory environment, which in itself may be dictated by underlying genetic factors influencing β-cell function—and, as will be discussed later, by a delicate balance between effector and regulatory T-cells (Treg).

As with most other autoimmune diseases, T1D is under complex genetic control, with many genetic loci—termed Idd—linked to T1D susceptibility. Additionally, given that the concordance rate for diabetes development in monozygotic twins is not 100% (2), the environment is thought to provide a modifier to disease risk, and evidence from animal models of T1D, such as the non-obese diabetic (NOD) mouse, has suggested that infectious agents can be important modulators of disease course (3–5). T1D, therefore, exemplifies the paradigm of a complex disease.

The disease is characterized by the progressive infiltration of islets in the pancreas by cells of the immune system—with central roles for CD4⁺ and CD8⁺ T-cells, as well as macrophages. This infiltration can result in insulinitis and the impairment of insulin production. In some individuals, this infiltration may be held in check—or regulated—without the manifestation of overt disease; in others, it can progress into a destructive immune response where β-cells are selectively killed off, and a variety of mechanisms have been proposed to contribute to β-cell death (Fig. 1). Due to the progressive nature of the infiltration, the collective function of β-cells, therefore, gradually declines. This, in theory, should present a therapeutic window in which to treat patients before overt diabetes occurs; however, by the time that the majority of patients present with clinical symptoms, insulin dependency has already been reached.

In T1D, given that there are as yet no reliable biomarkers for disease, there is an extra hurdle to overcome; the replacement of the lost β-cell mass. While the understanding of factors that contribute to disease progression will help to construct treatments to prevent any further immune destruction, a definitive cure for T1D can only be realistically
achieved if strategies to replace the β-cell mass are also engineered. This review, therefore, will seek to summarize the mechanisms behind the initiation and propagation of inflammation in T1D and will place a central focus on the β-cell’s reaction to inflammation and its environment. The review will explore the potential for therapeutic intervention—i.e., how to tip the balance back in favour of the patient—as well as discuss the need to study mechanisms for β-cell regeneration in order to provide an optimal therapeutic solution for this disease.

Diabetes initiation

Studies into the mechanisms behind disease progression have tended to focus on identifying the important cell types involved in T1D. Evidence from animal models has demonstrated an absolute requirement for both CD4+ and CD8+ T-cells in the development of T1D in spontaneous models of the disease (6–8); however, T1D fails to develop in the absence of macrophages (9), which are critical mediators of inflammation due to their ability to secrete cytokines, such as IL-1β and tumour necrosis factor (TNF)α (discussed later), and produce reactive oxygen species (ROS). Other cell types, such as B cells, NK cells and NKT cells, may play part roles in the process, and the cross-talk between all the cell populations will likely determine whether diabetes develops or is ultimately regulated (10).

Antigen release, presentation and T-cell priming

It is thought that failures in both central and peripheral tolerance mechanisms contribute to the emergence of autoreactive T-cells in the periphery of NOD mice (11). Some recent insight has been gleaned in to how peripheral tolerance mechanisms may be sub-optimal in diabetics. In the thymus, Autoimmune Regulator expression has been shown to play a crucial role in central tolerance by governing expression of peripheral tissue antigens (PTAs). In the periphery, the transcription factor Deformed epidermal autoregulatory factor 1 (DEAF1) has been shown to control PTA expression in secondary lymphoid tissue, and differential isoform expression of DEAF1 in the pancreatic draining lymph nodes (PLN) of both NOD mice and human T1D patients has been linked to diabetes susceptibility (12). A possible interpretation of this is that a reduction in the expression of PTAs in the PLN would increase the likelihood that autoreactive T-cells present in the lymph nodes would escape deletion.

In keeping with the idea that autoreactive T-cells are present in the PLN, it has been demonstrated that their presence is required for the development of T1D in NOD mice (13). As to what causes the release of self-antigen and its presentation in a form that triggers the autoimmune response, this is not entirely clear, but studies in the BDC2.5 NOD mouse [a TCR transgenic mouse, which expresses an autoreactive TCR taken from a diabetogenic T-cell clone BDC2.5 (14)] have suggested that the BDC2.5 antigen [thought to be a peptide sequence found in Chromogranin A (15), see also (16)] is not present in the PLN at day 10 (17), suggesting that events—one possibility being physiological β-cell death (18)—occur after this stage that somehow result in the release of self-antigen for uptake and presentation by dendritic cells (DC).

What is clear, however, is that DC antigen presentation is a key initiating event in the development of disease (19)—following DC presentation, these cells migrate to draining lymph nodes and prime autoreactive CD4+ T-cells. The nature of the environment in which the antigens are presented will then influence the nature of the adaptive T-cell response. Here, the genetic make-up of the individual will also have a marked effect—the HLA-DQ2 and HLA-DQ8 alleles are the greatest risk factors for T1D development in humans (20); furthermore, the importance of MHC alleles is similarly demonstrated in NOD mice, where T1D development requires the expression of the I-Ag7 class II molecule (21).

Early disease intervention

The context of the interaction between DC and T-cell will dictate whether a regulated or inflammatory response ensues and, as stated, the HLA status of the individual will be an important factor. This would be the ideal time to intervene in the process, but these early immunological events do not trigger the manifestation of any obvious clinical symptoms, making early intervention impractical without the identification of early biomarkers of disease activity.

T-cell differentiation and islet infiltration

CD4+ T-cells can differentiate into several different effector subsets, the best characterized being T1, T2 and T17 cells. Some useful tools, which have been used to understand how differing T-cell populations may be involved in T1D, are the adoptive T-cell transfer models of T1D. While useful in showing the potential for a subset to mediate disease, it is important to appreciate the caveats in these systems (see below). As these systems serve as a simplification of the disease model, they are therefore reductionist, and the cellular requirements can differ markedly from spontaneous models—in some models, T1D can be transferred in the absence of CD8+ T-cells [which differs from the NOD spontaneous model (8)]. They also often employ lymphopenic recipients (SCID or RAG−/−), which have been shown to reveal...
phenotype plasticity, which may be non-physiological (22), in T\(_h\) populations (23, 24). Nonetheless, some mechanistic insight into the behaviour of T\(_h\) subsets in T1D has been achieved using these models. The following section, therefore, reviews the evidence for the roles of T\(_h1\), T\(_h2\) and T\(_h17\) cells in the immunopathogenesis of T1D.

**The uses and limitations of T-cell transfer models of T1D**

Early studies into the ability of T\(_h1\) and T\(_h2\) clones to transfer disease to recipient mice demonstrated that T\(_h1\) but not T\(_h2\) cells were capable of inducing overt diabetes (25, 26); interestingly, however, the T\(_h2\) clones were still capable of inducing peri-islet inflammation—but clearly, only T\(_h1\) cells could evoke a destructive inflammatory infiltrate.

More recently, since the discovery of T\(_h17\) cells, it has been shown that populations arising from both T\(_h1\) and T\(_h17\) cells can mediate the transfer of T1D into lymphopenic recipients, but for the latter, this is due to the conversion to a T\(_h1\)-like phenotype (23, 24). Investigating the roles of the T\(_h17\) subset to transfer T1D into lymphopenic recipients, Martin-Orozco et al. (23) demonstrated that T\(_h17\) cells promote pancreatic inflammation but not overt diabetes; incidentally, however, T\(_h1\) cells or activated BDC2.5 T-cells (27) have been shown to be able to transfer diabetes into adult lymphopenic NOD mice. Despite this discrepancy in the behaviour of T\(_h17\) cells between different environments, there is some mechanistic insight into the types of inflammation that may result in diabetes. Work performed in the Cooke group has suggested that IFN\(\gamma\) derived from effector T-cells [in this case T\(_h17\) cells that had converted to T\(_h1\)-like cells (24)] acted to up-regulate inducible nitrogen oxides synthase (iNOS) expression in the pancreas and also enhanced MHC Class II expression on pancreas-infiltrating CD11b\(^+\) cells (e.g. macrophages) (24).

The majority of TCR transgenic systems, therefore, have shown that diabetes can be ‘caused’ by T\(_h1\)-like effector cells, but this is unlikely to be the sole mechanism in lymphopenic individuals, where the situation is more complicated due to the presence of many other cell types, including Treg.

**The roles of T-cell-derived cytokines in diabetes progression**

Data from the aforementioned transfer models have indicated that IFN\(\gamma\) is likely to be an important T-cell-derived cytokine in the pathogenesis of T1D; however, analysis of the role of T\(_h1\) cell cytokines in spontaneous models of T1D has produced less than clear-cut results. For example, evidence for the importance of IFN\(\gamma\) in T1D has often produced conflicting results, in part due to strategies used to disrupt the IFN\(\gamma\) response.

It is known that IFN\(\gamma\) can drive pathology at many points in the diabetic process (28). Several lines of evidence support this view: disease is ameliorated by the blockade of IFN\(\gamma\) using a soluble non-immunogenic form of the IFN\(\gamma\) receptor (29), disease is absent in STAT4-deficient mice (30), and diabetes is accelerated by exogenous IL-12 (a known promoter of T\(_h1\)/IFN\(\gamma\) responses) administration (31). Additionally, the T\(_h1\) mas-

ter transcription factor, T-bet, is indispensable for the development of T1D as its absence results in diabetes resistance (32). Despite this large body of evidence, there are still conflicting reports in the literature, however, which suggest that IFNyR-signalling is dispensable for the development of T1D in NOD mice (33) and, additionally, that disruption of the IFN\(\gamma\) gene delays but does not prevent the onset of diabetes in NOD mice (34).

There are several possible interpretations of these data. To start with, redundancy may account for the absence of phenotype in knockout or genetic disruption experiments; additionally, gene(s) closely linked to (such as to the IFN\(\gamma\) receptor) may result in the mistaken interpretation of knock-out data if insufficient backcrossing or targeting is performed (35). Ideally, the actions of IFN\(\gamma\) should be disrupted in situ, for example, by neutralization with specific antibodies or the use of soluble receptors. Having said that, it should also be appreciated that there are inherent caveats with dose, timing and delivery of treatments, which arise when in situ disruption of a molecule is attempted—although doses of antibody may be sufficient to clear IFN\(\gamma\) from the serum, local concentrations (for example around the islets in the pancreas) may in fact still be high, and therefore, it becomes difficult to ensure that there has been completely effective neutralization. Taking the evidence together, the more moderate conclusion may be that there is a likely, but not essential, role for IFN\(\gamma\) in disease progression.

In a similar fashion, analysis of T\(_h17\)-type cytokines in the pathogenesis of T1D has shown that IL-17A can be damaging (36, 37) or—paradoxically—protective (38, 39). In the two papers to date where attempts have been made to disrupt IL-17A in the non-manipulated spontaneous form of diabetes, these have yielded conflicting results: one group has demonstrated that IL-17A neutralization is protective (37), and a second group, using RNA interference to downregulate IL-17A, have found this cytokine to have no significant effect on the incidence of T1D in NOD—but, importantly, IL-17A interference did inhibit the induction of experimental autoimmune encephalomyelitis in transgenic NOD mice (40), thus demonstrating that the knock down could evoke real physiological effects.

Given that the body of literature assessing the role of IL-17A in this form of T1D is currently small, such findings will need to be repeated by other groups before a consensus can be reached; similarly, in terms of IL-17A in human pathogenesis of T1D, there appears to be gathering evidence for the increased presence of T\(_h17\) cells in the peripheral blood of patients (41, 42). Furthermore, there is also increasing evidence that IL-17 may be toxic to islets in vitro (43), particularly in the presence of pro-inflammatory cytokines, such as IL-1\(\beta\), IFN\(\gamma\) and TNF\(\alpha\) (44). The cellular source, however, of IL-17A may be non-T-cell derived as data have suggested that NK-like populations may play a previously under-appreciated role in T1D pathogenesis and that IL-17A may arise from not T\(_h17\) cells but so called iNKT17 cells (45).

**Targeting T-cell cytokines**

Given the lack of absolute requirement for IFN\(\gamma\) or IL-17A in T1D development, it is uncertain what clinical benefit could...
be achieved by the targeting of these proteins—and if such a strategy were employed, the optimal window for intervention has not been intensely studied; however, in the last few years, a Th17-related cytokine, IL-21, has been shown to be critical for T1D development in NOD mice (46). This places IL-21 in a small category of proteins that have been shown to be absolutely required for disease—although how IL-21 may mediate these effects and which cells contribute to its production are currently under investigation. Interestingly, however, IL-21 appears to be a later-acting cytokine since early neutralization does not have an effect on diabetes outcome (47) but is effective at a late preclinical stage in NOD mice. This would suggest that IL-21 could be a potential target that may warrant future investigation in humans (48).

**Tipping the balance towards destructive inflammation**

During T1D, there is a progressive reduction in the insulin-producing capability of pancreatic β-cells, which results from a reduction in both β-cell number and function. In spontaneous animal models, such as the NOD mouse, up to 90% of female mice become diabetic by 30 weeks of age. In all mice, the infiltrates contain a high proportion of Foxp3+ Treg, which indicates that there are active attempts to regulate the inflammation. The identification of factors that tip the balance and allow the effector cells to win out or become refractory to regulation is thus crucial to understand.

Since the discovery of Treg, there has been a strong focus on characterizing this population of cells. This has generated questions such as are Treg numbers sub-optimal/sub-functional/defective in regulating the inflammation? More recently, however, there is a growing consensus that Treg themselves may not be defective, and it is in fact the effector cells that are not susceptible to regulation (49) (Fig. 2). If this is indeed true, then this has profound effects on strategies for therapeutic intervention.

Aside from the balance of inflammation versus regulation, factors that affect the apoptotic threshold in β-cells are highly likely to affect the overall outcome of disease progression. The Bcl-2 family of proteins is a known regulator of apoptosis. A recent study has tried to underpin the signaling pathways involved in the induction and/or control of the mitochondrial pathway of apoptosis in β-cells (50). The authors demonstrated that stimulation of islets with IFNγ and TNFα up-regulated pro-apoptotic proteins, such as Bim and PUMA in β-cells (Fig. 3). Furthermore, Bim expression was shown to be transcriptionally regulated by STAT1 signalling, thus leading to the notion that ‘a highly regulated and context-dependent modulation of specific Bcl-2 members’ controls this apoptotic pathway in β-cells during inflammation (50).

Thus, collectively, it appears likely that multiple mechanisms, which may differ between individuals, come into play to bring about diabetes. In terms of T1 β-cells, their apparent plasticity—in particular for Th17 cells (51, 52)—may complicate the interpretation of the roles of T1 β subsets, particularly when most analysis is performed on ‘snap shots in time’ scenarios. The existence of methods to generate viable NOD embryonic stem (ES) cells (53, 54) should now lead to the generation of reporter mice, which will no doubt help to track and analyse the roles of differing populations of cells. A recent example is the use by Feuerer et al. (55) of a Foxp3-conditional knockout mouse, where conditional ablation of the Treg transcription factor, Foxp3, resulted in the rapid onset of diabetes, with a notable role for NK cell-derived IFNγ in orchestrating the autoimmune attack.

**Tipping the balance towards regulation**

An interesting avenue, which has provided insight into how regulation may be enhanced, is through the study of how infectious agents—or their antigens—may alter this delicate balance. Studies from mouse models have identified many organisms that can inhibit T1D, ranging from bacterial species, such as *Salmonella typhirium* (56), to parasitic species, such as *Schistosoma mansoni* (5). The timing and mechanisms of diabetes prevention differ, suggesting that T1D pathogenesis can be disrupted in many different ways. Antigens from organisms, such as *Schistosoma mansoni*

---

**Fig. 2.** Do T effectors become refractory to regulation? Tregs can suppress T effector responses via both cell contact (possibly by CTLA-4) and soluble mediators (anti-inflammatory cytokines like TGFβ and IL-10). It has been reported that Tregs in the inflamed sites are functional, but it is the T effectors that become—through an unknown mechanism—refractory to effective regulation. It is forseen that, in the case of T1D, the effectors win out, tipping the balance towards inflammation and β-cell destruction.

**Fig. 3.** The reaction of the β-cell to stress and apoptotic signals is crucial in determining the outcome of the disease process. Inflammation can trigger stress in the β-cell. Its response may be to activate stress pathways, which may affect the ability of the cell to perform its function in regulating blood glucose. The result may be a further rise in blood glucose, amplifying the stressful effects on the cell. In addition, cytokine signalling can induce the expression of pro-apoptotic markers, such as Bim and PUMA. Diabetes susceptibility genes, such as the recently associated *PTPN2* gene, may modulate the threshold of apoptosis. Increases in cytokines and/or ROS can set in motion a downward spiral leading to eventual β-cell death.
Egg Antigen (SEA), have been shown to also confer protection from T1D, leading to the possibility that therapeutics (biomodulators) could be derived from the fractionation of antigens from organisms that have been shown to have diabetes-preventing properties. For instance, treatment with SEA results in an increased proportion of Treg in the pancreas (57). Thus, these biomodulators act to tip the balance back towards regulation.

Another approach, which has aimed to readdress the balance, is the use of non-depleting antibodies to CD4 or CD3 epitopes. These have been shown to be effective in preventing T1D in animal models (58, 59) and it has been proposed that anti-CD3 therapy promotes tolerance by selectively depleting pathogenic cells, while sparing Treg (60). Anti-CD3 therapy has been trialed in humans but the results have so far been somewhat disappointing, and authors have cited the importance of treating individuals as soon as possible after diagnosis in order to boost the chances of seeing a clinical effect (61).

While anti-CD3/CD4 therapy seeks to alter the balance of effectors to Tregs in the favour of the latter, another approach is to simply boost Treg numbers by using Treg transfer therapies. This works on the premise that Treg can be isolated from a patient’s peripheral blood, expanded ex vivo, before transfer back into the patient. This is a highly active area of research, still in its early days; however, recent notions of apparent Treg instability (62) have highlighted the importance of understanding T-cell differentiation and factors influencing plasticity in order to ensure that any Treg generated ex vivo remain stable and effective when transferred back into patients. The issue, though, that the defect may be with the effector cells’ susceptibility to regulation may mean that such therapies do not yield as much success as may be currently hoped for (Fig. 2).

Inflammation and the β-cell

One of the critical determinants of whether diabetes ultimately ensues is the reaction of the β-cell to the inflammatory environment in which it finds itself. In 1986, Dr Gian Franco Bottazzo (63) tried to conceptualize the demise of the β-cell, where he considered the extent to which the biology of the β-cell versus its autoimmune attack contributed to its own downfall. Atkinson et al. (64) have more recently explored this issue in an insightful review where the authors concluded that T1D appears to resemble ‘a case of (immune) self-assisted homicide’ (64).

In the following section, β-cell extrinsic factors that may lead to its ultimate demise will be explored.

Cytokines and ROS

The three cytokines that have been reported to be the most likely to impact on the β-cell are IFNγ [sources of which may not just be T-cell derived (55)] but also the innate inflammatory cytokines TNFα and IL-1β. In fact, it is thought that these cytokines are most potent when acting in synergy—as observed when IFNγ and IL-1β are incubated with mouse islets, this combination results in the upregulation of iNOS, with subsequent production of NO (65). Although reactive oxygen intermediates have been proposed to play a role in β-cell destruction, a recent paper that demonstrated killing by these pro-inflammatory cytokines in the presence of IL-17A excluded involvement of NO (44). This would strongly suggest that multiple mechanisms exist, which can contribute to β-cell death. Excessive cytokine signalling in the β-cell may also contribute to, or potentiate, on going endoplasmic reticulum (ER) stress (66, 67). Additionally, a newly identified candidate gene for T1D, PTPN2, has been shown to modulate IFNγ-induced β-cell apoptosis (68), suggesting that the biology of the β-cell can directly affect its response to the inflammatory environment (Fig. 3).

Cytokines may also act indirectly to activate (e.g. TNFα may activate islet residing macrophages to produce IL-1β) or recruit cells to the sites of inflammation. Therefore, the control and regulation of local cytokine production are likely to be critical factors in determining the outcome of the autoimmune process.

The disruptive effects of autoimmune-mediated islet attack may lead to defects in the control of blood glucose levels, and it has been shown that mild hyperglycemia triggers stress in the β-cell (69), and thus, a vicious cycle may start to set in where initial cytokine stress may lead to metabolic stresses and a further loss in β-cell function.

Targeting innate cytokines

Given the importance of cytokines in driving β-cell pathology, targets such as IL-1β and TNFα would appear attractive as possible other factors to target while additionally using a tolerogenic agent, such as anti-CD3. A pilot study examining the effects of an anti-TNFα therapy has demonstrated that in a 3-month window, it appears to preserve c-peptide function (a good clinical indicator of insulin production capability) and maintain metabolic control (70). IL-1β targeting has, interestingly, proven effective in treating type two diabetest and larger trials are underway to establish the efficacy of targeting the IL-1β pathway in T1D (71). In vivo studies using soluble IL-1R in combination with a non-depleting anti-CD4 had previously suggested that this combination could lead to improved NOD β-cell survival from autoimmune attack (72), and recent studies have confirmed that combination therapies targeting T-cells and IL-1 are able to modify T1D in NOD mice (73).

β-Cell death and its consequences

Pancreatic islets not only consist of insulin-secreting β-cells but also the glucagon-producing α-cells. As in most autoimmune diseases, the immune attack on the β-cell is highly selective and specific—a fact that has been recently visualized with three-dimensional imaging (74). Such specific attack could be orchestrated by antigen-specific CD8-mediated cytotoxicity—autoreactive CD8+ T-cells have been associated with T1D pathogenesis (75) and are likely to play a role in the pathogenesis of disease (Fig. 1). Death signalling via fatty acid synthase (FAS)—fatty acid synthase ligand (FASL) is another possible pathway involved in the death of β-cells. It has been observed that FAS and FASL are present on β-cells and infiltrating T-cells (76) and that expression of
a dominant negative isoform of FAS-associated death domain (FADD) protein (which forms part of the FAS/FASL signalling pathway) can delay the onset of T1D (77).

Once the β-cells are destroyed, the patient loses the ability to make insulin and it seems that, in these patients, there is no effective regeneration of β-cells. The consequence of this is that permanent insulin therapy is often required following clinical diagnosis. Understanding the regeneration of β-cells and methods to replace the lost β-cell mass are thus an integral part in designing a complete therapy for this disease.

Combination therapy—the need for regeneration

For the reasons stated above, the best treatment approach will require the collaboration of both stem cell biologists and immunologists in designing strategies to treat T1D in patients. It is probable that therapeutic approaches combining the induction of T-cell tolerance and the scavenging of inflammatory mediators in order to facilitate repair and regeneration processes in the pancreas will prove to be an optimal strategy.

There is evidence that β-cells can be replenished by cell division (78), by neogenesis from progenitors in the pancreatic ducts (79–81), or by the transdifferentiation of pancreatic α-cells (82), or liver cells (83). However, it appears that even when autoimmunity is halted in T1D, these processes do not become effective in restoring the destroyed β-cell mass (84, 85). These studies, therefore, collectively illustrate that there is the potential for the endogenous processes of repair and regeneration to restore the β-cell mass, but it is important to try to understand why this does not occur under the tolerogenic conditions currently employed. It may be that there is some impairment in the regenerative potential in a diabetic individual, and this may be one of the predisposing genetic factors influencing diabetes onset and/or the tolerogenic approaches themselves impede the drivers for regeneration. By understanding what the key factors are that drive regeneration and repair, it may be possible to deliver a therapeutic approach that combines tolerance and repair.

The other approach to restore destroyed β-cell mass is through exogenous sources, for example, islet transplantation or through stem cells such as ES cells or induced pluripotent stem cells (iPSC cells). There is currently considerable effort being expended to differentiate exogenous stem cells into stable insulin-producing and glucose-responsive β-cells (86, 87). Although currently most protocols have not succeeded in fully realizing this aim, it is to be anticipated that stem cell and developmental biologists will eventually develop a robust protocol, which can then be coupled with tolerogenic protocols to control and prevent autoimmunity and, therefore, restore glycaemic control in a diabetic individual.

Conclusions

The reaction to, and by, the β-cell to the immune system is what dictates the overall outcome in T1D. The disease is complex and involves multiple immune cell types—of which CD4+ T-cells play a key role—that coordinate over time to bring about β-cell death. β-Cell death and dysfunction are a likely result of both direct (CTL and FAS–FASL interactions) and indirect (cytokines, ER stress, and hyperglycemia) immune and metabolic factors. Targeting these factors is likely to preserve remaining β-cell function, but ‘curative’ treatments can only be realistically achieved by attempting to replace some of the β-cell mass that has been lost during the autoimmune process.

Acknowledgements

Paola Zaccone is funded by the Medical Research Council. David Bending is funded by an Arthritis Research UK foundation fellowship (grant 19761).

References

through a mechanism involving transforming growth factor-beta. 


39 Han, G., Wang, R., Chen, G. et al. 2010. Interleukin-17-producing gammaderivative T cells protect NOD mice from type 1 diabetes through a mechanism involving transforming growth factor-beta. Immunology 129:197.


Inflammation and T1D