Perspective article

The Beta Cell in Type 1 Diabetes Pathogenesis: a Victim of Circumstances or an Instigator of Tragic Events?

Roberto Mallone[1,2], Clémentine Halliez[1,2], Jinxiu Rui[3], Kevan C. Herold[3]

[1]Université de Paris, Institut Cochin, CNRS, INSERM, 75014 Paris, France.

[2]Assistance Publique Hôpitaux de Paris, Service de Diabétologie et Immunologie Clinique, Cochin Hospital, 75014 Paris, France.

[3]Departments of Immunobiology and Internal Medicine, Yale University, New Haven, CT 06520, USA.

Corresponding author: Roberto Mallone, MD PhD - INSERM U1016 Cochin Institute, G.H. Cochin-Port-Royal, Bâtiment Cassini - 123, boulevard de Port-Royal – F-75014 Paris, France.

Phone: +33-1-76.53.55.83 E-mail: roberto.mallone@inserm.fr.

Word count: 3,789 **Figures**: 2 **References**: 70

Key words: antigens, apoptosis, autoimmunity, beta cells, senescence, T cells, type 1 diabetes.

Abstract

Recent reports have revived interest in the active role that beta cells may play in type 1 diabetes pathogenesis at different stages of disease. Some studies suggested an initiating role and proposed that type 1 diabetes may be primarily a disease of beta cells, and only secondarily a disease of autoimmunity. This scenario is possible, and invites the search for environmental triggers damaging beta cells. Another major contribution of beta cells may be to amplify autoimmune vulnerability, and to eventually drive it into an intrinsic, self-detrimental state that turns the T-cell-mediated homicide into a beta-cell suicide. On the other hand, protective mechanisms are also mounted by beta cells and may provide novel therapeutic targets to combine immunomodulatory and beta-cell protective agents. This integrated view of autoimmunity as a disease of T-cell/beta-cell cross-talk will ultimately advance our understanding of type 1 diabetes pathogenesis and improve our chances to prevent or reverse disease progression.

Introduction

Beta-cell failure in type 1 diabetes creeps forward at a pace that is defined by a dynamic relationship between immune cells and beta-cell intrinsic responses (1, 2). This relationship is affected by host factors such as genetics, age, and poorly defined environmental triggers. In some individuals, autoimmunity is initiated but does not progress further, notably in the presence of a single autoantibody (aAb) (3). This may reflect an aborted immune process or responses of beta cells, or other cells, that prevent progression to the next stage of autoimmune amplification and beta-cell destruction (4). However, in others, particularly young individuals, beta-cell destruction is more rapid once autoimmunity (stage 1) or hyperglycemia (stage 3) appears (5, 6), with little evidence of remission phases.

The precise molecular and cellular mechanisms that account for beta-cell death remain unclear. Direct cytotoxic lysis by $CD8^+$ T cells reactive to beta-cell antigens such as preproinsulin is postulated. However, immune infiltrates in the pancreas are sparse at the time of diagnosis. While the late timing of these histological studies, i.e. years after autoimmune initiation and even after beta-cell destruction and clinical onset, may account for these findings (2), other mechanisms capable of mediating beta-cell killing at a distance have been suggested. Inflammatory molecules are produced by several cell types, including beta cells themselves (7), and may cause dysfunction or killing. Findings of shrinkage of the exocrine pancreas before type 1 diabetes diagnosis suggest that inflammation of the whole organ may occur and that beta cells are perhaps killed by soluble mediators produced by cells that are not present in the islets. Indeed, a recent trial of anti-TNF-α antibody showed how neutralizing this cytokine may arrest progression in new-onset type 1

diabetic patients (8). However, the way in which these acute inflammatory mediators affect the chronic progression remains undefined.

As part of this immune/beta-cell dynamics, a number of investigators have described how beta cells may respond to the autoimmune attack in ways that may promote their demise or protect them (9). The question of whether beta cells die by homicide vs. suicide was originally proposed by G.F. Bottazzo (10), but newer studies call for revisiting this question. Clearly, both T cells and beta cells are active disease players, but is one the initiator and the other the victim or do both accelerate beta-cell death? We here review this dynamic interplay in the light of recent studies.

"Absolving" T cells

The increasing evidence that T cells, together with other immune players, are not the sole culprits in type 1 diabetes pathogenesis has been recently reviewed (2). Briefly, arguments for their non-exclusive involvement include the following. First, experimental autoimmune diabetes cannot be induced in animal models by immunization with islet extracts or beta-cell antigens alone (2), as is the case for other autoimmune diseases such as experimental autoimmune encephalomyelitis (a model of multiple sclerosis). Second, human T cells adoptively transferred into immunodeficient mice can cause insulitis but are not diabetogenic in the absence of strong priming conditions, e.g. streptozotocin treatment to induce some beta-cell death and self-antigen release (11, 12). Third, histopathological, age-related endotypes (13, 14) mirroring clinical endotypes defined by age and aAb targets (5, 6) indicate that a number of other factors may determine rates of progression. Finally, a universal state of 'benign' autoimmunity is found in the circulation of all individuals, as

witnessed by the presence of islet-reactive (and largely naïve) $CD8^+$ T cells (15-17) and islet-reactive $CD4^+$ T cells (18, 19). T cells with the same antigen specificities are enriched in the pancreas of type 1 diabetic donors (15, 16), pointing to local factors that may affect the phenotypes of T cells and attract them into the target organ. Although two case reports of type 1 diabetes transfer upon grafting of bone marrow from a diabetic donor (20) and grafting of islets into a diabetic recipient (21) argue for a central role of T cells, an alternative explanation contemplating the contribution of beta cells is possible, as explained below.

"Incriminating" beta cells

The active role of beta cells in type 1 diabetes pathogenesis has been linked to their specialized function of insulin secretion (1) – a paradigm that may apply more generally to other endocrine cells. Namely, the high endoplasmic reticulum (ER) and oxidative stress imposed by the requirements for rapid and considerable insulin bio-synthesis, the rich islet vascularization - which exposes cells to inflammatory soluble mediators and cells, and the secretion of insulin and other antigenic granule contents directly in the bloodstream with high amplitude (22) are all features that may render beta cells more vulnerable to autoimmunity.

Importantly, new emerging data extend this picture to alterations of the exocrine pancreas (23). A reduced pancreas organ weight was reported in single-aAb^+ donors (24) and even in aAb-negative first-degree relatives (25). Other studies reported reduced serum trypsinogen and lipase levels starting at stage 1 (≥2 aAbs) type 1 diabetes (26, 27), and enriched exocrine immune infiltration (28) and HLA Class II expression in ductal cells from type 1 diabetic donors (29). Another notable

recent single-cell epigenomics study (30) documented high expression of novel type 1 diabetes risk gene variants (e.g. chymotrypsinogens, lipase and cystic fibrosis transmembrane conductance regulator) in acinar and ductal cells, which is postulated to promote subclinical pancreas inflammation favoring later immune infiltration.

The pathogenic role of beta cells could theoretically be called into question at three sequential stages (**Fig. 1**):

1) Self-initiated homicide: are beta cells the original drivers of T-cell autoimmunity?

2) Self-amplified homicide: do beta cells enhance T-cell-mediated killing?

3) Self-finalized suicide: do beta cells under attack eventually die by suicide?

1) Self-initiated homicide

Studies by Larger and Boitard, nearly 30 years ago, showed that beta cells are needed to initiate autoimmune diabetes in NOD mice (31). These results support a primary role of beta cells in developing an autoimmune repertoire endowed with beta-cell specificity, since splenocytes from beta-cell-deficient mice could not transfer diabetes, but the mice were otherwise immune competent and developed other autoimmune manifestations, i.e. sialitis. This observation pointed to an early critical time window in which T cells are primed by beta-cell antigens and trigger diabetes. Of further note, this priming occurs primarily in pancreatic lymph nodes and is an early event, as pancreatic lymphadenectomy at 3 weeks, but not at 10 weeks of age, led to near-complete diabetes protection in NOD mice (32). Pancreatic lymph nodes may also harbor stem-like $CD8^+$ T cells that can proliferate and generate effector T cells that invade islets (33).

Several lines of experimental evidence suggest that beta-cell aberrancies, which may include increased antigen exposure and neo-antigen expression, may be the first drivers of islet autoimmunity. Islet autoimmunity does not develop if beta cells are not visible to the immune system due to reduced antigen expression, i.e. if immune ignorance is maintained. An emblematic example is provided by NOD mice carrying an insulin B16 mutation that abolishes the immunogenicity of the initiating epitope Ins B9-23, which are completely protected from diabetes (34). Serreze et al found that initiation of autoimmune diabetes in NOD mice is dependent on MHC Class I (35). β2-microglobulin $(\beta 2m)^{-/-}$ mice, which are MHC Class I-deficient, did not develop insulitis or diabetes, whereas splenocytes from diabetic NOD donors transferred diabetes into both wild-type and $\beta 2m^{-/-}$ NOD/*scid* recipients. In contrast, splenocytes from young prediabetic NOD donors transferred diabetes only to wild-type NOD/*scid* recipients, while $\beta 2m^{-/-}$ NOD/*scid* recipients required prior grafting with wild-type islets to become diabetic. The authors concluded that islet expression of MHC Class I (i.e. beta-cell visibility) was needed to prime T cells, which could then mediate beta-cell destruction independent of MHC Class I (35). Other adoptive T-cell transfer models suggest that, in addition to antigen presentation, beta-cell alterations such as those imprinted in the NOD background or induced by streptozotocin, are needed to enable antigen-driven T-cell priming and beta-cell killing (2). On the same lines, T-cell receptor transgenic models in which T cells recognize a foreign antigen transgenically expressed in beta cells show that provision of costimulatory or inflammatory signals is required to activate these T cells (36). These mouse studies may provide an interpretation for some observations in patients. A case report of identical twin-to-twin transplantation of a non-diabetic pancreas into a type 1 diabetic recipient led to rapid autoimmune relapse (21); and conversely, bone marrow transplantation from a type 1

diabetic sibling into a HLA-identical non-diabetic recipient triggered type 1 diabetes (20). In both cases, the previous priming of the autoimmune T-cell repertoire prior to transplantation may have bypassed the need for a beta-cell trigger.

Recent elegant studies have revived interest in this hypothesis of self-initiated homicide by showing that the induction of an early and transient beta-cell dedifferentiation protects NOD mice from diabetes. A first model of NOD mice with high beta-cell proliferation rates and decreased antigen expression (37) was obtained either with a liver-specific insulin receptor genetic knock out (LIRKO) or by pharmacological treatment with an insulin receptor antagonist from 4 to 6 weeks of age. In a second model (38), a conditional knock-out of the inositol-requiring enzyme (IRE)1α, which activates the unfolded protein response (UPR) in beta cells, was induced by tamoxifen treatment during the neonatal period (1 to 5 days of life), resulting in a similar dedifferentiated beta-cell phenotype. Both NOD models are protected from diabetes.

Can all these extreme murine models that "blind" the immune system from beta cells be taken as evidence for an active role of beta cells at initiating autoimmunity? Other arguments from human genetic studies need to be considered. First, the contribution of type 1 diabetes-associated gene variants expressed in beta cells to genetic susceptibility is marginal when compared to HLA Class II polymorphisms (2) – a feature that type 1 diabetes shares with several other autoimmune diseases. Second, the major influence of HLA Class II haplotypes is on the antigen specificity and rate of aAb seroconversion (i.e., autoimmune initiation) rather than on the rate of actual beta-cell destruction (i.e., clinical progression) (2, 39, 40), suggesting a driving effect on pathology. This may further suggest that beta-cell-related non-HLA gene variants may act as modulators of this

later clinical progression rather than drivers. Third, monogenic forms of neonatal diabetes causing beta-cell defects, including mutations (e.g. in *INS* and *EIF2AK3* genes) that induce severe ER stress, show little evidence of islet autoimmunity, even in the context of high-risk HLA Class II haplotypes, with only 5.4% found positive for islet aAbs, mostly (92%) for a single aAb (41). This is observed in spite of a dysregulated expression of genes (and proteins) associated with monogenic forms of diabetes resulting from ER stress in the pancreas of type 1 diabetic and aAb^+ donors (42), suggesting a role of primary beta-cell alterations as disease contributors rather than drivers.

However, an alternative explanation could be that the beta-cell contribution to type 1 diabetes pathogenesis may simply be less genetically imprinted and more environmentally driven than the immune contribution. This hypothesis may invite the search for environmental triggers that may compromise beta-cell health rather than immune tolerance *per se*, e.g. islet-tropic viral infections and/or xenotoxic agents.

Altogether, this literature suggests that beta-cell stress/dysfunction may play a role at initiating islet autoimmunity, and then significantly contribute to its amplification, as discussed in the next section.

2) Self-amplified homicide

A key observation suggesting the role of beta-cell-driven initiation and amplification mechanisms is the heterogeneity of insulitis across islets, which do not appear to be attacked and destroyed at

the same time (43). There are multiple mechanisms by which beta cells amplify the autoimmune attack (**Fig. 2**). The inflammatory environment of insulitis, particularly interferons, stimulate several active responses in beta cells that go beyond the passive effect of inducing ER stress, dysfunction and apoptosis. First, inflammation drives beta cells themselves to release chemokines (e.g. CCL5, CXCL2, CXCL9, CXCL10) and cytokines (e.g. IL-1β, IL-6) (7), which further attract immune cells to the pancreas and contribute to their activation in situ.

The second major outcome of islet inflammation is HLA Class I upregulation, which results in the exposure of a larger and more diversified repertoire of antigenic peptides (16), thus increasing the visibility and vulnerability of beta cells to infiltrating T cells. Not surprisingly, peptides derived from proteins of secretory granules (e.g. insulin, chromogranin A, secretogranin-5, urocortin-3, proconvertase-2) are highly represented across different human and murine MHC restrictions (16, 17) and are targeted by diabetogenic CD8+ T cells, which induce disease when transferred into NOD/*scid* mice (17). This pathogenic role may rely on features that granule proteins share with (pro)insulin (44). All these antigens are synthesized as pro-protein precursors, which are subsequently enzymatically cleaved, mostly by proconvertases, to generate their bio-active products. Hence, the impaired proinsulin processing by proconvertases described in beta cells from type 1 diabetic patients (44, 45) may extend to all these proteins, possibly diverting their degradation towards the MHC Class I presentation pathway. In addition, all of these proteins are released in the bloodstream with insulin exocytosis, both in intact form and as antigenic degradation products (22). They can thus be taken up by extra-pancreatic antigen-presenting cells and prime T cells at distance upon uptake by extra-pancreatic antigen-presenting cells (1).

The MHC-peptide repertoire displayed by beta cells further includes neo-antigens, i.e. peptide sequences that are not templated in the genome and may therefore be regarded as non-self and trigger autoimmunity, since they have not participated in the physiological mechanisms of immune tolerance. These neo-antigens are produced through different mechanisms: alternative mRNA splicing (16, 17), out-of-frame protein translation due to defective ribosomal scanning under high insulin demand (46), post-translational modifications (47) and transpeptidation (16, 48), i.e. the fusion of non-contiguous peptide fragments from the same protein or from two distinct partners.

Other amplification mechanisms may be related to beta-cell sensitivity to stress-induced senescence. A recent study (49) documented the accumulation of senescent beta cells in NOD mice during a critical early time window that marks the transition from peri-insulitis to destructive insulitis. Although these senescent beta cells increase the expression of pro-survival factors such as Bcl2, they also have a key role in amplifying the autoimmune response because they produce a specific secretome (the so called SASP – senescence-associated secretory phenotype) enriched in factors (e.g. IGFBP3, serpin E1) that propagate this senescent phenotype to neighboring beta cells; and in cytokines/chemokines (e.g. IL-6, CXCL10), that as noted above, attract and activate immune cells in the pancreas. Senescence markers (CDKN1A, serpin E1, IL-6) were also observed in the pancreas of type 1 diabetic patients (49). Importantly, when senescence was inhibited by an anti-Bcl2 small molecule that drives apoptosis specifically in these cells, diabetes was prevented, thus documenting the pathogenic role of the senescent phenotype. This observation identifies a novel therapeutic target involving a rather counter-intuitive strategy of inducing apoptosis of selected beta-cell subsets. This also suggests that the physiologic process of clearing senescent beta cells, or hypersecreting mutants (adenomas) (50), is misdirected in autoimmunity. It will be

important to clarify whether the relationship between beta-cell dysfunction, senescence and apoptosis is sequential, mutually exclusive and/or naturally reversible.

Besides inciting autoimmunity via all these immunogenic signals, beta cells may further amplify these mechanisms by ceasing to secrete protective anti-apoptotic factors. A notable example is growth/differentiation factor (GDF)15, a transforming growth factor-β superfamily member that was found downregulated in beta cells from type 1 diabetic individuals and upon in-vitro exposure to IL-1β and IFN-γ (7). Although its mechanisms of action remain unclear, GDF15 protects NOD mice from diabetes (7), presumably through anti-inflammatory effects, and exerts additional effects in the hindbrain (reducing food intake and promoting weight loss) and in peripheral tissues (hepatocytes, myocytes and adipocytes), by increasing insulin sensitivity.

3) Self-finalized suicide *vs* protection

Further compensatory mechanisms mounted by beta cells may be self-detrimental ("suicidal") in the long term, acting through intrinsic mechanisms that do not require the participation of other cells (**Fig. 2**).

Some cytokines (e.g. IL-1β, IL-6) that are secreted by beta cells themselves (7) can be pro-apoptotic in an autocrine/paracrine loop. Their secretion may be particularly important during the extended period of time – as long as 5 years – when insulin secretion may be impaired but clinically silent. The ability to compensate for metabolic demands becomes critical during this time for beta-cell survival. As metabolic demands increase, reactive oxygen species are needed for glucose-

induced insulin secretion (51) and mass expansion (52). However, the low expression of antioxidant enzymes such as catalase and superoxide dismutase exposes beta cells to cell-intrinsic oxidative damage, particularly in the ER (53). Even beta-cell identity may be affected by this oxidative stress, since exposure to hydrogen peroxide can induce loss of nuclear localization of MafA, a transcription factor associated with mature beta cells that may enhance the beta-cell anti-oxidant defenses, protecting them against deterioration during hyperglycemia (54-56). Increased metabolic demands also upregulate the UPR, which is constitutively active in beta cells due to their basal ER stress from high protein (mostly insulin) biosynthesis rates. This increased UPR can drive apoptosis when reaching a critical threshold (1). Indeed, UPR upregulation was observed in beta cells from two type 1 diabetes mouse models and from patients (57), as identified by the expression of activating transcription factor-6 (ATF6) and spliced X-box binding protein-1 (sXBP1). The deleterious effect of what is initially a compensatory response is suggested by the observation that surviving beta cells display lower ATF6 and sXBP1 expression, and that relieving UPR with tauroursodeoxycholic acid (TUDCA) protects mice from diabetes (57).

We recently showed that Tet2 is increased in beta cells from NOD mice and in human insulitis (58). Its deleterious beta-cell-intrinsic outcomes were documented in several ways. In beta cells that survive autoimmune attack, Tet2 expression was reduced. Despite unchanged insulitis and T-cell diabetogenicity, *Tet2*$^{-/-}$ NOD mice were protected from diabetes, even after grafting *Tet2*$^{+/+}$ bone marrow or transferring diabetogenic splenocytes. Tet2 affects the epigenetic control of signaling molecules such as STAT1, NFκB and IRF2. While its loss was associated with CXCL10 downregulation by beta cells, there was also reduced expression of the CXCR3 homing receptor on beta-cell-reactive T cells in pancreatic lymph nodes.

Protective mechanisms are also mounted by beta cells (**Fig. 2**). During progression of autoimmunity in NOD mice, we described degranulation, loss of *Ins1*/*Ins2* gene expression and acquisition of a more undifferentiated phenotype, with expression of other islet hormones (e.g. *Gcg*, *Sst*) and stem cell markers (*Sox9, L-Myc, Oct-4*) in residual beta cells (59). In addition to insulin, there was reduced expression of other diabetes autoantigens (GAD, ZnT8, IA-2). In line with these results, Damond et al. compared beta cells from new-onset and long-standing type 1 diabetic patients to non-diabetic individuals by image cytometry pseudo-timing using nPOD specimens (60). Beta-cell destruction was preceded by downregulation of identity markers (INS, PIN, IAPP, PTPRN) with (pseudo)time, without changes in beta-cell transcription factors PDX1 and NKX6-1. Loss of lineage-specific markers may thus be an early event, before further disease progression driven by beta-cell death. In our study (59), dedifferentiated beta cells also expressed immunoregulatory ligands (PD-L1, Qa-2) and resisted immune killing by islet infiltrates or cytokines, unlike their mature counterparts. PD-L1 is induced on human and murine beta cells by IFN-γ and IFN-α (61). Beta cells also secrete anti-microbial peptides (e.g., CRAMP), a process triggered by in-vitro exposure to IL-1β or LPS (62) that is impaired in NOD mice (63). Besides inducing tolerogenic antigen-presenting cells and Tregs (63), these peptides reduce beta-cell apoptosis and production of inflammatory prostaglandin E2 (62). These mechanisms, while protective against killing in specific experimental settings, clearly fail to arrest the autoimmune response in most clinical settings.

Altogether, the available literature suggests that, following autoimmune insult, beta cells may also contribute in a direct way to their own killing. This concept of self-detrimental vs protective beta-

cell responses has clinical relevance. Successful immunotherapies (e.g. teplizumab, anti-thymocyte globulin, alefacept, rituximab) share a mechanism of modulation/deletion of inflammatory cells. While treatment is often followed by C-peptide stabilization, a decline subsequently occurs in many patients (64), suggesting either that the conditions that led to clinical onset have recurred or that beta-cell-intrinsic mechanisms may drive this decline. As an example, even continuous administration of CTLA-4-Ig at type 1 diabetes onset did not avoid a decline in beta-cell function after an initial improvement (65). This suggests that maintaining beta-cell-intrinsic protective mechanisms together with immunomodulation may limit this later decline.

Therapeutic strategies under development to boost beta-cell protective mechanisms

The concepts of beta-cell responsiveness to autoimmune attack also suggest ways in which autoimmunity might be arrested with a combination of agents that target immune and beta cells. Evidence (33, 66) for stem-like features of islet-reactive $CD8^+$ T cells that can proliferate and are the source of short-lived effector cells that migrate to the pancreas highlights the challenge in purging the repertoire of effector T cells sufficiently to prevent disease (33). Intriguingly, results from teplizumab trials (67) suggest that immunotherapies may be most effective when beta-cell stress is occurring, i.e. at the stage 2 of rapid C-peptide decline, consistent with preclinical data in NOD mice. Although the beta-cell changes occurring during this period of rapid progression may expose new and more antigen targets, the T cells that recognize them may represent the more differentiated ones that are amenable to treatment.

Modulating the beta-cell and antigen targets of autoimmune T cells may thus be needed in addition to immunotherapies. Clinical studies are ongoing with agents that are postulated to limit beta-cell stress responses, such as verapamil (NCT04545151), a calcium channel blocker that inhibits

TXNIP, a mediator of oxidative stress (68), and TUDCA (NCT02218619), a chemical chaperone that mitigates ER stress (57). In a previous study of the tyrosine kinase inhibitor imatinib as a single agent, a significant effect on C-peptide responses was not sustained (69), but ongoing studies are evaluating effects on markers of beta-cell stress. Other studies with agents such as JAK1/2 inhibitors, that can block critical signaling pathways in beta cells as well as blunting T-cell activation, are under development. Finally, in a randomized 4-arm placebo-controlled trial, anti-IL-21 antibodies and the GLP-1 receptor agonist liraglutide significantly reduced C-peptide decline at 54 weeks in patients with recently diagnosed type 1 diabetes compared to placebo (70). The finding that this decline was lower than with either agent alone suggests that immune and beta-cell combination therapies may be synergistic in achieving clinical outcomes.

Conclusions and perspectives

These studies highlight the dynamic relationships between immune effector cells and their beta-cell targets. The findings have shown how both parties contribute to killing, but also suggest that therapies that are directed only at one arm may be insufficient to completely arrest the ongoing process. Much work has been done to characterize the autoimmune repertoire, including the targets and features of T and B cells that can mediate disease. Attention to the attributes of beta cells that can instill protection from or participation in autoimmunity are now needed.

Acknowledgements. We apologize with colleagues whose publications could not be referenced due to space constraints. Figures 1 and 2 were created with elements from Servier Medical Art (smart.servier.com).

Funding. Work performed in the Laboratory of R.M. is supported by The Leona M. and Harry B. Helmsley Charitable Trust (Helmsley #1901-03689), the *Agence Nationale de la Recherche* (ANR-19-CE15-0014-01) and the *Fondation pour la Recherche Medicale* (EQU20193007831); and by the Innovative Medicines Initiative 2 Joint Undertaking under grant agreements 115797 and 945268 (INNODIA and INNODIA HARVEST), which receive support from the EU Horizon 2020 program, the European Federation of Pharmaceutical Industries and Associations, JDRF, and The Leona M. & Harry B. Helmsley Charitable Trust. C.H. was funded by an *Année Recherche* fellowship of the Paris Saclay University. Work performed in the Laboratory of K.C.H. is supported by NIH grant DK057846, DK101122, DK104205, DK045735, JDRF grant SRA2014-142-S-B, a Pilot Award from the Yale Diabetes Research Center P30DK116577 and a gift from the Howalt family.

Duality of Interest. K.C.H. is co-inventor on a patent application for use of teplizumab. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. R.M. and K.C.H. wrote manuscript. C.H. and J.R. contributed to discussion, reviewed/edited manuscript. R.M. is the guarantor of this work.

.

References

1. Mallone R, Eizirik DL: Presumption of innocence for beta cells: why are they vulnerable autoimmune targets in type 1 diabetes? Diabetologia 2020;63:1999-2006
2. Carré A, Richardson SJ, Larger E, Mallone R: Presumption of guilt for T cells in type 1 diabetes: lead culprits or partners in crime depending on age of onset? Diabetologia 2021;64:15-25
3. Insel RA, Dunne JL, Atkinson MA, Chiang JL, Dabelea D, Gottlieb PA, Greenbaum CJ, Herold KC, Krischer JP, Lernmark A, Ratner RE, Rewers MJ, Schatz DA, Skyler JS, Sosenko JM, Ziegler AG: Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care 2015;38:1964-1974
4. Faucher P, Beuvon F, Fignani D, Sebastiani G, Afonso G, Zhou Z, Dousset B, Boitard C, Dotta F, Mallone R, Larger E: Immunoregulated insulitis and slow-progressing type 1 diabetes after duodenopancreatectomy. Diabetologia 2021;64:2731-2740
5. Frohnert BI, Ide L, Dong F, Baron AE, Steck AK, Norris JM, Rewers MJ: Late-onset islet autoimmunity in childhood: the Diabetes Autoimmunity Study in the Young (DAISY). Diabetologia 2017;60:998-1006
6. Hao W, Gitelman S, DiMeglio LA, Boulware D, Greenbaum CJ, Type 1 Diabetes TrialNet Study G: Fall in C-Peptide During First 4 Years From Diagnosis of Type 1 Diabetes: Variable Relation to Age, HbA1c, and Insulin Dose. Diabetes Care 2016;39:1664-1670
7. Nakayasu ES, Syed F, Tersey SA, Gritsenko MA, Mitchell HD, Chan CY, Dirice E, Turatsinze JV, Cui Y, Kulkarni RN, Eizirik DL, Qian WJ, Webb-Robertson BM, Evans-Molina C, Mirmira RG, Metz TO: Comprehensive Proteomics Analysis of Stressed Human Islets Identifies GDF15 as a Target for Type 1 Diabetes Intervention. Cell Metab 2020;31:363-374 e366
8. Quattrin T, Haller MJ, Steck AK, Felner EI, Li Y, Xia Y, Leu JH, Zoka R, Hedrick JA, Rigby MR, Vercruysse F, Investigators TGS: Golimumab and Beta-Cell Function in Youth with New-Onset Type 1 Diabetes. N Engl J Med 2020;383:2007-2017
9. Atkinson MA, Bluestone JA, Eisenbarth GS, Hebrok M, Herold KC, Accili D, Pietropaolo M, Arvan PR, Von Herrath M, Markel DS, Rhodes CJ: How does type 1 diabetes develop?: the notion of homicide or beta-cell suicide revisited. Diabetes 2011;60:1370-1379
10. Bottazzo GF: Lawrence lecture. Death of a beta cell: homicide or suicide? Diabet Med 1986;3:119-130
11. Tan S, Li Y, Xia J, Jin CH, Hu Z, Duinkerken G, Li Y, Khosravi Maharlooei M, Chavez E, Nauman G, Danzl N, Nakayama M, Roep BO, Sykes M, Yang YG: Type 1 diabetes induction in humanized mice. Proc Natl Acad Sci USA 2017;
12. Viehmann Milam AA, Maher SE, Gibson JA, Lebastchi J, Wen L, Ruddle NH, Herold KC, Bothwell ALM: A Humanized Mouse Model of Autoimmune Insulitis. Diabetes 2014;63:1712-1724
13. Leete P, Mallone R, Richardson SJ, Sosenko JM, Redondo MJ, Evans-Molina C: The Effect of Age on the Progression and Severity of Type 1 Diabetes: Potential Effects on Disease Mechanisms. Curr Diab Rep 2018;18:115
14. Leete P, Oram RA, McDonald TJ, Shields BM, Ziller C, team Ts, Hattersley AT, Richardson SJ, Morgan NG: Studies of insulin and proinsulin in pancreas and serum support the existence of aetiopathological endotypes of type 1 diabetes associated with age at diagnosis. Diabetologia 2020;
15. Culina S, Lalanne AI, Afonso G, Cerosaletti K, Pinto S, Sebastiani G, Kuranda K, Nigi L, Eugster A, Osterbye T, Maugein A, McLaren JE, Ladell K, Larger E, Beressi JP, Lissina A, Appay V, Davidson HW, Buus S, Price DA, Kuhn M, Bonifacio E, Battaglia M, Caillat-Zucman S, Dotta F, Scharfmann R, Kyewski B, Mallone R, ImMaDiab Study G: Islet-reactive CD8+ T cell

frequencies in the pancreas, but not in blood, distinguish type 1 diabetic patients from healthy donors. Sci Immunol 2018;3:eaao4013
16. Gonzalez-Duque S, Azoury ME, Colli ML, Afonso G, Turatsinze JV, Nigi L, Lalanne AI, Sebastiani G, Carre A, Pinto S, Culina S, Corcos N, Bugliani M, Marchetti P, Armanet M, Diedisheim M, Kyewski B, Steinmetz LM, Buus S, You S, Dubois-Laforgue D, Larger E, Beressi JP, Bruno G, Dotta F, Scharfmann R, Eizirik DL, Verdier Y, Vinh J, Mallone R: Conventional and Neo-antigenic Peptides Presented by beta Cells Are Targeted by Circulating Naive CD8+ T Cells in Type 1 Diabetic and Healthy Donors. Cell Metab 2018;28:946-960 e946
17. Azoury ME, Tarayrah M, Afonso G, Pais A, Colli ML, Maillard C, Lavaud C, Alexandre-Heymann L, Gonzalez-Duque S, Verdier Y, Vinh J, Pinto S, Buus S, Dubois-Laforgue D, Larger E, Beressi JP, Bruno G, Eizirik DL, You S, Mallone R: Peptides Derived From Insulin Granule Proteins are Targeted by CD8+ T Cells Across MHC Class I Restrictions in Humans and NOD Mice. Diabetes 2020;69:2678-2690
18. Viglietta V, Kent SC, Orban T, Hafler DA: GAD65-reactive T cells are activated in patients with autoimmune type 1a diabetes. J Clin Invest 2002;109:895-903
19. Danke NA, Koelle DM, Yee C, Beheray S, Kwok WW: Autoreactive T cells in healthy individuals. J Immunol 2004;172:5967-5972
20. Lampeter EF, Homberg M, Quabeck K, Schaefer UW, Wernet P, Bertrams J, Grosse-Wilde H, Gries FA, Kolb H: Transfer of insulin-dependent diabetes between HLA-identical siblings by bone marrow transplantation. Lancet 1993;341:1243-1244
21. Sutherland DE, Sibley R, Xu XZ, Michael A, Srikanta AM, Taub F, Najarian J, Goetz FC: Twin-to-twin pancreas transplantation: reversal and reenactment of the pathogenesis of type I diabetes. Trans Assoc Am Physicians 1984;97:80-87
22. Wan X, Zinselmeyer BH, Zakharov PN, Vomund AN, Taniguchi R, Santambrogio L, Anderson MS, Lichti CF, Unanue ER: Pancreatic islets communicate with lymphoid tissues via exocytosis of insulin peptides. Nature 2018;560:107-111
23. Alexandre-Heymann L, Mallone R, Boitard C, Scharfmann R, Larger E: Structure and function of the exocrine pancreas in patients with type 1 diabetes. Rev Endocr Metab Disord 2019;20:129-149
24. Campbell-Thompson M, Wasserfall C, Montgomery EL, Atkinson MA, Kaddis JS: Pancreas organ weight in individuals with disease-associated autoantibodies at risk for type 1 diabetes. JAMA 2012;308:2337-2339
25. Campbell-Thompson ML, Filipp SL, Grajo JR, Nambam B, Beegle R, Middlebrooks EH, Gurka MJ, Atkinson MA, Schatz DA, Haller MJ: Relative Pancreas Volume Is Reduced in First-Degree Relatives of Patients With Type 1 Diabetes. Diabetes Care 2019;42:281-287
26. Li X, Campbell-Thompson M, Wasserfall CH, McGrail K, Posgai A, Schultz AR, Brusko TM, Shuster J, Liang F, Muir A, Schatz D, Haller MJ, Atkinson MA: Serum Trypsinogen Levels in Type 1 Diabetes. Diabetes Care 2017;40:577-582
27. Ross JJ, Wasserfall CH, Bacher R, Perry DJ, McGrail K, Posgai AL, Dong X, Muir A, Li X, Campbell-Thompson M, Brusko TM, Schatz DA, Haller MJ, Atkinson MA: Exocrine Pancreatic Enzymes Are a Serological Biomarker for Type 1 Diabetes Staging and Pancreas Size. Diabetes 2021;70:944-954
28. Rodriguez-Calvo T, Ekwall O, Amirian N, Zapardiel-Gonzalo J, von Herrath MG: Increased immune cell infiltration of the exocrine pancreas: a possible contribution to the pathogenesis of type 1 diabetes. Diabetes 2014;63:3880-3890

29. Fasolino M, Schwartz GW, Patil AR, Mongia A, Golson ML, Wang YJ, Morgan A, Liu C, Schug J, Liu J, Wu M, Traum D, Kondo A, May CL, Goldman N, Wang W, Feldman M, Moore JH, Japp AS, Betts MR; HPAP Consortium, Faryabi RB, Naji A, Kaestner KH, Vahedi G: Single-cell multi-omics analysis of human pancreatic islets reveals novel cellular states in type 1 diabetes. Nat Metab 2022; 4:284-299
30. Chiou J, Geusz RJ, Okino ML, Han JY, Miller M, Melton R, Beebe E, Benaglio P, Huang S, Korgaonkar K, Heller S, Kleger A, Preissl S, Gorkin DU, Sander M, Gaulton KJ: Interpreting type 1 diabetes risk with genetics and single-cell epigenomics. Nature 2021;594:398-402
31. Larger E, Becourt C, Bach JF, Boitard C: Pancreatic islet beta cells drive T cell-immune responses in the nonobese diabetic mouse model. J Exp Med 1995;181:1635-1642
32. Gagnerault MC, Luan JJ, Lotton C, Lepault F: Pancreatic lymph nodes are required for priming of beta cell reactive T cells in NOD mice. J Exp Med 2002;196:369-377
33. Gearty SV, Dundar F, Zumbo P, Espinosa-Carrasco G, Shakiba M, Sanchez-Rivera FJ, Socci ND, Trivedi P, Lowe SW, Lauer P, Mohibullah N, Viale A, DiLorenzo TP, Betel D, Schietinger A: An autoimmune stem-like CD8 T cell population drives type 1 diabetes. Nature 2022;602:156-161
34. Nakayama M, Abiru N, Moriyama H, Babaya N, Liu E, Miao D, Yu L, Wegmann DR, Hutton JC, Elliott JF, Eisenbarth GS: Prime role for an insulin epitope in the development of type 1 diabetes in NOD mice. Nature 2005;435:220-223
35. Serreze DV, Chapman HD, Varnum DS, Gerling I, Leiter EH, Shultz LD: Initiation of autoimmune diabetes in NOD/Lt mice is MHC class I-dependent. J Immunol 1997;158:3978-3986
36. Brezar V, Carel JC, Boitard C, Mallone R: Beyond the hormone: insulin as an autoimmune target in type 1 diabetes. Endocr Rev 2011;32:623-669
37. Dirice E, Kahraman S, De Jesus DF, El Ouaamari A, Basile G, Baker RL, Yigit B, Piehowski PD, Kim MJ, Dwyer AJ, Ng RWS, Schuster C, Vethe H, Martinov T, Ishikawa Y, Teo AKK, Smith RD, Hu J, Haskins K, Serwold T, Qian WJ, Fife BT, Kissler S, Kulkarni RN: Increased beta-cell proliferation before immune cell invasion prevents progression of type 1 diabetes. Nature metabolism 2019;1:509-518
38. Lee H, Lee YS, Harenda Q, Pietrzak S, Oktay HZ, Schreiber S, Liao Y, Sonthalia S, Ciecko AE, Chen YG, Keles S, Sridharan R, Engin F: Beta Cell Dedifferentiation Induced by IRE1alpha Deletion Prevents Type 1 Diabetes. Cell Metab 2020;31:822-836 e825
39. Valdes AM, Erlich HA, Carlson J, Varney M, Moonsamy PV, Noble JA: Use of class I and class II HLA loci for predicting age at onset of type 1 diabetes in multiple populations. Diabetologia 2012;55:2394-2401
40. Dufort MJ, Greenbaum CJ, Speake C, Linsley PS: Cell type-specific immune phenotypes predict loss of insulin secretion in new-onset type 1 diabetes. JCI insight 2019;4
41. Wyatt RC, Hagopian WA, Roep BO, Patel KA, Resnick B, Dobbs R, Hudson M, Consortium E-TD, De Franco E, Ellard S, Flanagan SE, Hattersley AT, Oram RA, Johnson MB: Congenital beta-cell defects are not associated with markers of islet autoimmunity, even in the context of high genetic risk for type 1 diabetes. Diabetologia 2022;in press
42. Hiller H, Beachy DE, Lebowitz JJ, Engler S, Mason JR, Miller DR, Kusmarteva I, Jacobsen LM, Posgai AL, Khoshbouei H, Oram RA, Schatz DA, Hattersley AT, Bodenmiller B, Atkinson MA, Nick HS, Wasserfall CH: Monogenic Diabetes and Integrated Stress Response Genes Display Altered Gene Expression in Type 1 Diabetes. Diabetes 2021;70:1885-1897

43. Campbell-Thompson M, Fu A, Kaddis JS, Wasserfall C, Schatz DA, Pugliese A, Atkinson MA: Insulitis and beta-Cell Mass in the Natural History of Type 1 Diabetes. Diabetes 2016;65:719-731
44. Carre A, Mallone R: Making Insulin and Staying Out of Autoimmune Trouble: The Beta-Cell Conundrum. Front Immunol 2021;12:639682
45. Sims EK, Chaudhry Z, Watkins R, Syed F, Blum J, Ouyang F, Perkins SM, Mirmira RG, Sosenko J, DiMeglio LA, Evans-Molina C: Elevations in the Fasting Serum Proinsulin-to-C-Peptide Ratio Precede the Onset of Type 1 Diabetes. Diabetes Care 2016;39:1519-1526
46. Kracht MJ, van Lummel M, Nikolic T, Joosten AM, Laban S, van der Slik AR, van Veelen PA, Carlotti F, de Koning EJ, Hoeben RC, Zaldumbide A, Roep BO: Autoimmunity against a defective ribosomal insulin gene product in type 1 diabetes. Nat Med 2017;23:501-507
47. Purcell AW, Sechi S, DiLorenzo TP: The Evolving Landscape of Autoantigen Discovery and Characterization in Type 1 Diabetes. Diabetes 2019;68:879-886
48. Delong T, Wiles TA, Baker RL, Bradley B, Barbour G, Reisdorph R, Armstrong M, Powell RL, Reisdorph N, Kumar N, Elso CM, DeNicola M, Bottino R, Powers AC, Harlan DM, Kent SC, Mannering SI, Haskins K: Pathogenic CD4 T cells in type 1 diabetes recognize epitopes formed by peptide fusion. Science 2016;351:711-714
49. Thompson PJ, Shah A, Ntranos V, Van Gool F, Atkinson M, Bhushan A: Targeted Elimination of Senescent Beta Cells Prevents Type 1 Diabetes. Cell Metab 2019;29:1045-1060 e1010
50. Korem Kohanim Y, Tendler A, Mayo A, Friedman N, Alon U: Endocrine Autoimmune Disease as a Fragility of Immune Surveillance against Hypersecreting Mutants. Immunity 2020;52:872-884 e875
51. Leloup C, Tourrel-Cuzin C, Magnan C, Karaca M, Castel J, Carneiro L, Colombani AL, Ktorza A, Casteilla L, Pénicaud L: Mitochondrial reactive oxygen species are obligatory signals for glucose-induced insulin secretion. Diabetes 2009;58:673-681
52. Ahmed Alfar E, Kirova D, Konantz J, Birke S, Mansfeld J, Ninov N: Distinct Levels of Reactive Oxygen Species Coordinate Metabolic Activity with Beta-cell Mass Plasticity. Sci Rep 2017;7:3994
53. Tersey SA, Nishiki Y, Templin AT, Cabrera SM, Stull ND, Colvin SC, Evans-Molina C, Rickus JL, Maier B, Mirmira RG: Islet beta-cell endoplasmic reticulum stress precedes the onset of type 1 diabetes in the nonobese diabetic mouse model. Diabetes 2012;61:818-827
54. Guo S, Dai C, Guo M, Taylor B, Harmon JS, Sander M, Robertson RP, Powers AC, Stein R: Inactivation of specific beta cell transcription factors in type 2 diabetes. J Clin Invest 2013;123:3305-3316
55. Harmon JS, Bogdani M, Parazzoli SD, Mak SS, Oseid EA, Berghmans M, Leboeuf RC, Robertson RP: beta-Cell-specific overexpression of glutathione peroxidase preserves intranuclear MafA and reverses diabetes in db/db mice. Endocrinology 2009;150:4855-4862
56. Kaneto H, Kajimoto Y, Miyagawa J, Matsuoka T, Fujitani Y, Umayahara Y, Hanafusa T, Matsuzawa Y, Yamasaki Y, Hori M: Beneficial effects of antioxidants in diabetes: possible protection of pancreatic beta-cells against glucose toxicity. Diabetes 1999;48:2398-2406
57. Engin F, Yermalovich A, Nguyen T, Hummasti S, Fu W, Eizirik DL, Mathis D, Hotamisligil GS: Restoration of the unfolded protein response in pancreatic beta cells protects mice against type 1 diabetes. Sci Transl Med 2013;5:211ra156
58. Rui J, Deng S, Perdigoto AL, Ponath G, Kursawe R, Lawlor N, Sumida T, Levine-Ritterman M, Stitzel ML, Pitt D, Lu J, Herold KC: Tet2 Controls the Responses of beta cells to Inflammation in Autoimmune Diabetes. Nat Commun 2021;12:5074

59. Rui J, Deng S, Arazi A, Perdigoto AL, Liu Z, Herold KC: Beta Cells that Resist Immunological Attack Develop during Progression of Autoimmune Diabetes in NOD Mice. Cell Metab 2017;25:727-738
60. Damond N, Engler S, Zanotelli VRT, Schapiro D, Wasserfall CH, Kusmartseva I, Nick HS, Thorel F, Herrera PL, Atkinson MA, Bodenmiller B: A Map of Human Type 1 Diabetes Progression by Imaging Mass Cytometry. Cell Metab 2019;29:755-768 e755
61. Osum KC, Burrack AL, Martinov T, Sahli NL, Mitchell JS, Tucker CG, Pauken KE, Papas K, Appakalai B, Spanier JA, Fife BT: Interferon-gamma drives programmed death-ligand 1 expression on islet beta cells to limit T cell function during autoimmune diabetes. Sci Rep 2018;8:8295
62. Sun J, Xu M, Ortsäter H, Lundeberg E, Juntti-Berggren L, Chen YQ, Haeggström JZ, Gudmundsson GH, Diana J, Agerberth B: Cathelicidins positively regulate pancreatic β-cell functions. FASEB J 2016;30:884-894
63. Sun J, Furio L, Mecheri R, van der Does AM, Lundeberg E, Saveanu L, Chen Y, van Endert P, Agerberth B, Diana J: Pancreatic beta-Cells Limit Autoimmune Diabetes via an Immunoregulatory Antimicrobial Peptide Expressed under the Influence of the Gut Microbiota. Immunity 2015;43:304-317
64. Greenbaum CJ, Schatz DA, Haller MJ, Sanda S: Through the fog: recent clinical trials to preserve beta-cell function in type 1 diabetes. Diabetes 2012;61:1323-1330
65. Orban T, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, Gottlieb PA, Greenbaum CJ, Marks JB, Monzavi R, Moran A, Raskin P, Rodriguez H, Russell WE, Schatz D, Wherrett D, Wilson DM, Krischer JP, Skyler JS: Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet 2011;378:412-419
66. Abdelsamed HA, Zebley CC, Nguyen H, Rutishauser RL, Fan Y, Ghoneim HE, Crawford JC, Alfei F, Alli S, Ribeiro SP, Castellaw AH, McGargill MA, Jin H, Boi SK, Speake C, Serti E, Turka LA, Busch ME, Stone M, Deeks SG, Sekaly RP, Zehn D, James EA, Nepom GT, Youngblood B: Beta cell-specific CD8(+) T cells maintain stem cell memory-associated epigenetic programs during type 1 diabetes. Nat Immunol 2020;21:578-587
67. Herold KC, Bundy BN, Long SA, Bluestone JA, DiMeglio LA, Dufort MJ, Gitelman SE, Gottlieb PA, Krischer JP, Linsley PS, Marks JB, Moore W, Moran A, Rodriguez H, Russell WE, Schatz D, Skyler JS, Tsalikian E, Wherrett DK, Ziegler AG, Greenbaum CJ, Type 1 Diabetes TrialNet Study G: An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. N Engl J Med 2019;381:603-613
68. Ovalle F, Grimes T, Xu G, Patel AJ, Grayson TB, Thielen LA, Li P, Shalev A: Verapamil and beta cell function in adults with recent-onset type 1 diabetes. Nat Med 2018;24:1108-1112
69. Gitelman SE, Bundy BN, Ferrannini E, Lim N, Blanchfield JL, DiMeglio LA, Felner EI, Gaglia JL, Gottlieb PA, Long SA, Mari A, Mirmira RG, Raskin P, Sanda S, Tsalikian E, Wentworth JM, Willi SM, Krischer JP, Bluestone JA, Barr M, Blanchfield JL, Bluestone JA, Buchanan J, Bundy BN, Cabbage J, Coleman P, De La Vega M, DiMeglio LA, Evans-Molina C, Felner EI, Ferrannini E, Ferrara C, Gaglia JL, Gitelman SE, Gottlieb PA, Healy F, Higgins L, Hildinger M, Jenkins M, Kayton Bryant N, Kinderman A, Koshy N, Kost B, Krischer JP, Krishfield S, Kucheruk O, Lim N, Lindsley K, Long SA, Mantravadi M, Mari A, Mesfin S, Michels A, Migre ME, Minnock P, Mirmira RG, Mohammed-Nur E, Nelson J, Nursing A, O'Donnell R, Olivos D, Parker M, Raskin P, Redl L, Reed N, Resnick B, Sanda S, Sayre P, Serti E, Sims E, Smith K, Soppe C, Stuart F, Szubowicz S, Tansey M, Terrell J, Tersey S, Torok C, Tsalikian E, Watson K, Wentworth JM,

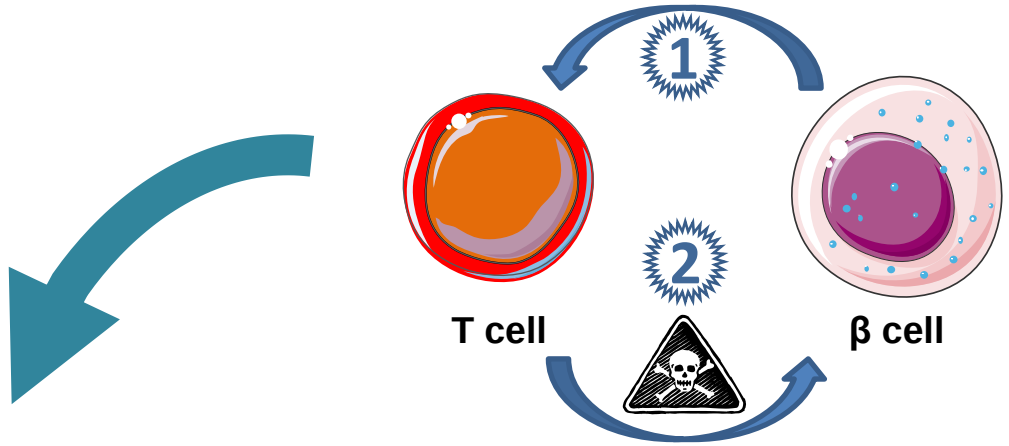
Wesch R, Willi S, Woerner S: Imatinib therapy for patients with recent-onset type 1 diabetes: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol 2021;9:502-514
70. von Herrath M, Bain SC, Bode B, Clausen JO, Coppieters K, Gaysina L, Gumprecht J, Hansen TK, Mathieu C, Morales C, Mosenzon O, Segel S, Tsoukas G, Pieber TR, Anti ILlSGi, contributors: Anti-interleukin-21 antibody and liraglutide for the preservation of beta-cell function in adults with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol 2021;9:212-224

Figure legends

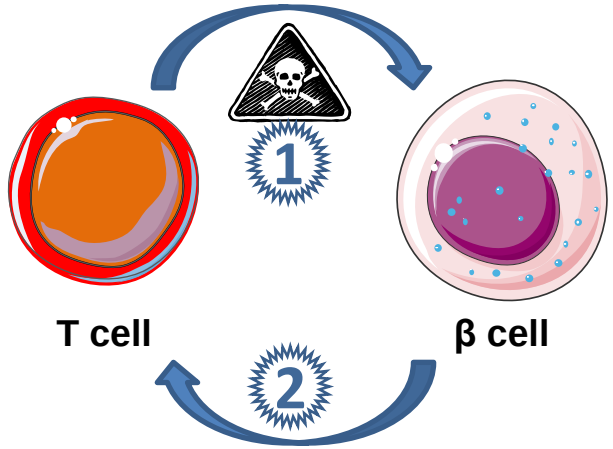
Figure 1. Pathogenic role of beta cells in type 1 diabetes. The three possible stages of initiation, amplification and finalization of the pathogenic cascade where beta cells can come into play are depicted.

Figure 2. Beta-cell mechanisms of self-amplified homicide/suicide (red) vs. protection (blue). See text for details.

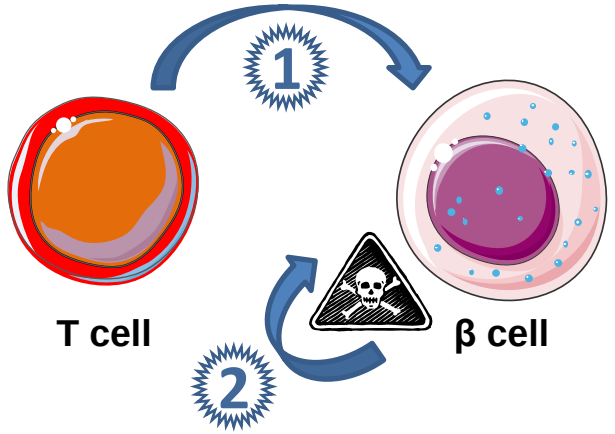
1) *Self-initiated* homicide?
Do beta cells *initiate* the T-cell killing?



2) *Self-amplified* homicide?
Do beta cells *enhance* the T-cell killing?



3) *Self-finalized suicide*?
Do beta cells *finalize* the killing *themselves*?



Blood
Benign autoreactive T cells
Pathogenic autoreactive T cells
T-cell recruitment
T-cell activation
T-cell recruitment
T-cell activation
PLN
Presentation of β cell antigens to T cell by DCs
↑release of insulin granule antigens
Pro-apoptotic cytokine - chemokine secretion
• ↑ER stress/UPR
• ↑Tet2
• ↓ anti-apoptotic factors
• ↑ HLA Class I, (neo)antigen presentation
Stressed β cell
Environmental triggers mainly acting on β cells
Apoptotic β cell
Secretion of:
• Senescence factors
• Cytokines
• Chemokines
Senescent β cell
• GDF15 expression
• Anti-microbial peptide secretion
Healthy β cell
• ↓ UPR
• ↓ Tet2
• ↑ PD-L1
• Dedifferentiation
Surviving β cell