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**Perspective article**

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

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## **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<sup>+</sup> 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- $\alpha$  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 insulinitis 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<sup>+</sup> T cells (15-17) and islet-reactive CD4<sup>+</sup> 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<sup>+</sup> donors (24) and even in aAb-negative first-degree relatives (25). Other studies reported reduced serum trypsinogen and lipase levels starting at stage 1 ( $\geq 2$  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<sup>+</sup> 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).  $\beta 2$ -microglobulin ( $\beta 2m^{-/-}$ ) mice, which are MHC Class I-deficient, did not develop insulinitis 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)1 $\alpha$ , 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<sup>+</sup> 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 insulinitis 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 insulinitis, 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-1 $\beta$ , 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<sup>+</sup> 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-insulinitis to destructive insulinitis. 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- $\beta$  superfamily member that was found downregulated in beta cells from type 1 diabetic individuals and upon in-vitro exposure to IL-1 $\beta$  and IFN- $\gamma$  (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-1 $\beta$ , 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 antioxidant 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 insulinitis (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 insulinitis and T-cell diabetogenicity, *Tet2*<sup>-/-</sup> NOD mice were protected from diabetes, even after grafting *Tet2*<sup>+/+</sup> 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- $\gamma$  and IFN- $\alpha$  (61). Beta cells also secrete anti-microbial peptides (e.g., CRAMP), a process triggered by in-vitro exposure to IL-1 $\beta$  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<sup>+</sup> 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.

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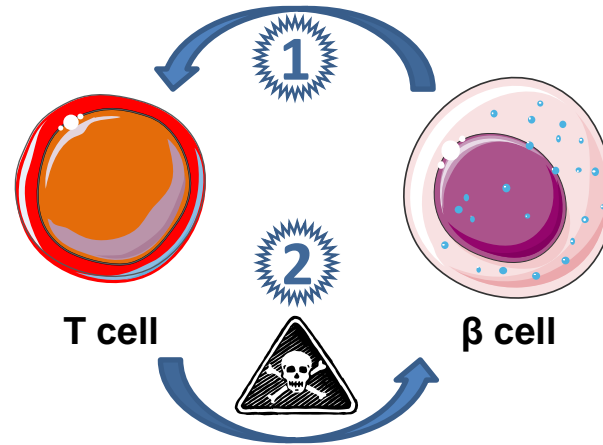


## Figure legends

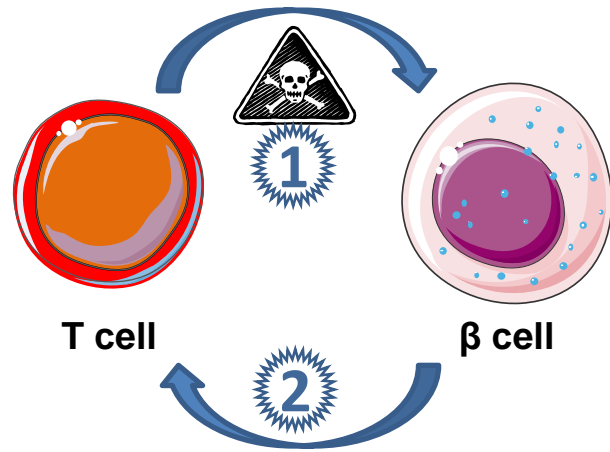
**Figure 1. Pathogenic role of beta cells in type 1 diabetes.** The three possible stages of initiation, amplification and finalization of the pathogenic cascade where beta cells can come into play are depicted.

**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*?

