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How Type 1 Diabetes Develops and May Be Prevented

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Abstract

Type 1 diabetes is an autoimmune disease characterized by T-cell-mediated destruction of pancreatic beta cells. We aim to provide answers regarding how type 1 diabetes develops and how it can be prevented. The earliest marker of disease development is the presence of beta-cell autoantibodies, which serve as valuable diagnostic tools but are not themselves directly pathogenic. At a later phase, T cells drive beta-cell destruction. Toll-like receptor 5 (TLR5), which is induced by flagellin from gram-negative bacteria, is an important modulator of this process, and reduced TLR5 expression is correlated with increased T-cell activity. TLR5 seems to play different roles in the two phases of type 1 diabetes pathogenesis. In addition, sulfatide provides local protection at the beta-cell level against T-cell attack. Preventive strategies include the modulation of TLR5 activity, the enhancement of sulfatide, the reduction of metabolic stress, and anti-CD3 antibody treatment. By following these strategies, the development of type 1 diabetes may be less likely.

Keywords: Beta-cell antibodies; Insulitis; Sulfatide; TLR5; Type 1 Diabetes.

Introduction

Type 1 diabetes is an autoimmune disease affecting millions of people worldwide. Autoimmune diseases have various mechanisms and different clinical presentations, but they share the common features of immune-mediated damage to self-tissues and T cell involvement in all cases [1]. Certainly, if autoimmunity is initiated by a nontoxic virus, the acquired immune system is involved [2]. In this article, we describe the development of type 1 diabetes. A main recognition is that the pathogenesis is different in the initial phase, with autoantibody production, than in the later decisive phase, with malign insulitis and overt type 1 diabetes.

Insulin is a highly immunogenic compound, as it is a peptide secreted directly into the blood without any barriers. This is in opposition to the pituitary gland, which also produces peptide hormones but is situated behind the blood–brain barrier. Other hormones secreted directly into the blood are typically small molecules, e.g., steroids, which are less immunogenic. We describe here, with respect to beta cells, that T-cell protection properties, such as sulfatide and Toll-like receptor 5 (TLR5), which are active locally at the cells to counterbalance the immunogenic effect of insulin, are essential.

Stage 1 of Development of Type 1 Diabetes

The first sign of developing type 1 diabetes is the presence of beta-cell autoantibodies (Table 1). These antibodies include IAA, GAD, IA-2, and ZNT8 antibodies [3]. If only one antibody is detectable, the type 1 diabetes risk is 15%, but if two, three, or even four antibodies are detected, the risk is substantially increased up to 100% [4].

Following a virus attack, the immune system generates not only virus-specific

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antibodies but typically also additional antibodies that may target other antigens in the physical or structural neighborhood [5,6]. In the pancreatic islets of Langerhans, the virus is often an enterovirus, which have been most investigated [7], although it might not be restricted to this [8]. Multiple studies have been made on virus etiology. These include especially Coxsackie virus B3 and B4. These viruses are most frequently seen during late summer which coincides in the northern hemisphere with a peak incidence of type 1 diabetes in the autumn months [9]. However, virus has been difficult to detect in full scale in patients. On the other hand, anti-viral drugs have been used in a trial with some effect after 1 year, but this was not present after 2 and 3 years [10].

The mentioned antibodies against beta cells have high value as diagnostic tools but have no importance for the pathogenesis of type 1 diabetes, besides one potential exception. Anti-sulfatide antibodies (ASAs) are present in healthy controls, but in pre-type 1 diabetes patients, the level of ASA is increased, but then returns to control values after diagnosis [11]. These ASAs may have a pathogenic effect by masking sulfatide at the beta-cell surface, since sulfatide is an important sphingolipid in type 1 diabetes, as will be discussed later. Other masking of sulfatide can be made by virus since sulfatide is a virus receptor [12].

Table 1: Stages of important events in the development of type 1 diabetes.

	Normal phase	Stage 1: development of beta-cell antibodies	Stage 2-3: malignant insulitis
Glucose level	Normal	Normal/ dysregulated [13]	Increased [13]
Insulin production	Normal	Sufficient [14]	Damaged [15]
TLR5 expression	Normal	Normal [16]	Low [16]
Sulfatide exposure	Normal	Reduced [17]	Low [17]
Adaptive immune involvement	No involvement	Humoral involvement [18]	T cell involvement [15]

Stage 2 And 3 of Development of Type 1 Diabetes

As mentioned, classical beta-cell autoantibodies are not pathogenic and do not themselves cause the T-cell-driven autoimmune process leading to type 1 diabetes. However, the presence of beta-cell antibodies means that some T lymphocytes have been primed against certain beta-cell antigens. When T cells are activated again, the route toward beta-cell damage is shorter. This finding fits well with the fact that many studies (nPOD, DiViD) find only traces of virus left in the islets at diagnosis [19,20], as this initial trigger may have occurred months or years before the actual onset of type 1 diabetes [4].

In a recent study [16], we elucidated what might initiate T-cell-driven beta-cell destruction and thereby the autoimmune process. Toll-like receptor 5 (TLR5) is an important molecule (Table 2) in deciding whether innate immune cells, granulocytes, and macrophages, on the one hand, should be favored in a certain immune reaction or, on the other hand, T lymphocytes should be preferred [21,22]. TLR5 expression is stimulated by flagellin, a structural protein that composes the filaments of flagella in gram-negative bacteria [23]. Hence, in microbe-rich ("dirty") surroundings, TLR5 is largely expressed but less so in very clean environments. This is found in mice in germ-free surroundings [24] but might also apply to humans in Scandinavia, especially Finland, where environmental hygiene standards are higher than those in Russian Karelia, which has a much lower incidence of type 1 diabetes [25]. Interestingly, we found that the mRNA levels of TLR5 in islets are one-third lower at the time of diagnosis of type 1 diabetes than during the phase of antibody positivity [16]. Additionally, TLR5 increases again after diagnosis [16]. Furthermore, we found an inverse correlation between T cells in the islets, which were less common in patients with higher TLR5 [16].

In contrast to cellular immunity, humoral immunity is dependent on high or normal levels of TLR5 [26]. For type 1 diabetes, TLR5 expression in the initial disease phase of beta-cell antibody development differs from TLR5 expression in the phases of malignant insulitis and clinical type 1 diabetes [13]. Hence, there are two different pathogenic mechanisms involved in the initial and final phases of type 1 diabetes development. This may well be the reason why antibody-positive persons do not necessarily develop type 1 diabetes, and why type 1 diabetes patients, in about 10% of the cases, are diagnosed without any beta-cell antibodies [27]. In Africa type 1 diabetes is commonly seen without presence of beta-cell antibodies [28]. The etiology of this special diabetes might be (toxic) virus, agent that herd sphingolipid production such as fungi toxins (see below), Helicobacter bacteria, or other changes as described here.

High beta-cell activity can make beta cells vulnerable [29] since it might create defective ribosomal products (DRiPs), which are molecules encoded by an alternative open reading frame that is highly immunogenic [30]. Additionally, hybrid insulin peptides (HIPs), which are autoantigens that stimulate T cells, can also be generated under high beta-cell activity [31]. Interestingly, when beta cells are incubated with elevated levels of glucose, which induces high beta cell activity, the only TLR that increases is TLR5, which might

function to protect against damage by T cells [32]. In contrast, NOD mice maintained in germ-free facilities (with no TLR5 stimulation) have the highest diabetes incidence, especially among male animals [33].

Another interesting aspect is the extent to which exogenous factors can influence TLR5 expression. As previously described, bacteria may invade the ductus pancreaticus via the papilla Vateri, which is also known to occur in the ductus choledochus. In fact, bacteria, including *Staphylococcus aureus* [34], which has previously been shown to inhibit the presence of TLR5 [35], can be present in the ductus pancreaticus in humans. Interestingly, fusidic acid, an antibiotic that targets *Staphylococcus,* has been found to reduce the incidence of diabetes in biobreeding (BB) rats [36], possibly due to diminished inhibition of TLR5. Another relevant bacteria present in the pancreatic environment is *Helicobacter pylori*, which has been associated with a 1.77-fold increase in type 1 diabetes in humans [37]. *H. pylori* can also inhibit TLR5 by masking its expression [38] and thereby may contribute to the development of type 1 diabetes. Therefore, at least two bacterial species commonly found near the pancreas are capable of downregulating TLR5 expression, potentially enhancing T-cell activity, in contrast to many other bacteria that increase TLR5 expression, as mentioned.

Regarding antibiotic treatment, it has recently been shown in a meta-analysis that administration to young individuals increases the risk of developing type 1 diabetes [39]. We have also found that antibiotic treatment using a combination of ampicillin, vancomycin, and neomycin decreases TLR5 expression in the pancreas of female BALB/c mice. Furthermore, in relation to the development of type 1 diabetes, it is of interest that flagellin can stimulate NLR family CARD domain-containing protein 4 (NLRC4), which may subsequently inhibit TLR5 and thereby activate T lymphocytes [40]. NLRC4 seems to be connected to type 1 diabetes through polymorphisms and the actual lowering in TLR5 expression may be due to this factor [41].

Among other agents that depress T cells is the sphingolipid sulfatide [17,42,43] (Table 2). Importantly at diagnosis, human type 1 diabetes islets represent only 23% of the normal sulfatide level [17]. Sulfatide is a highly interesting molecule composed of two fat chains, the amino acid L-serine, and a galactose group to which a sulfate is connected. If D-serine is present, e.g., after serine racemase activity [44], the amount of sulfatide is reduced due to its inhibitory effects on sulfatide production [45]. As recently outlined also by another research group, sulfatide is important for the function of beta cells [46]. In beta cells, sulfatide has several properties: it folds the insulin molecule; it preserves the insulin crystals at pH 5.5; at pH 7.4, it mediates hexa- and monomerization of the insulin molecules; it facilitates actual insulin secretion; and it is present at the surface of beta cells [47–49]. Also, sulfatide inhibits the potassium channel and after insulin release, and thereby sulfatide secretion, relaxes the individual beta-cell [50]. Verapamil influences the calcium channels and hence creates lower beta-cell activity and is thus a candidate for human medication [51]. The physiological properties are due to C16 sulfatide [50], whereas C24 sulfatide has immunological qualities [52], similarly to alpha-galactosylceramide, it diminishes the incidence of diabetes in NOD mice [52,53]. This finding fits well with the findings of Holm *et al*., who reported that long-chain sulfatide inhibits T cells [17]. As indicated by its name, C24 sulfatide is a long-chain fatty acid that requires special transporter proteins to be absorbed into beta cells. In a recent study, we found that long-chain fatty acid transporter proteins are reduced at the time of type 1 diabetes diagnosis [54].

Another aspect of sulfatide is important and should be mentioned. Sulfatide promotes class II NKT cells which are inhibitory for development for type 1 diabetes [55]. Class II NKT cells are anti-inflammatory and are important for reducing diabetes incidence in NOD mice, but this system is less pronounced in humans [56].

Sulfatide also enhances regulatory T cells (Tregs) and low amount of Tregs has been found in patients with newly diagnosed type 1 diabetes [57,58]. Interestingly, Treg cells are reduced by galectin-3 [59] which is a molecule produced by macrophages, typically after a virus infection. These include, in mice, EMC virus [60] and, in humans, Coxsackie B3 virus [61]. Highly interestingly, both of these viruses have been connected to diabetes development [2,7]. Galectin-3 has been found to be upregulated in human serum of beta cell autoantibody-positive persons and type 1 diabetes patients [59], and in IL-1beta-exposed human and rat islets [62].

Beta-cell function progressively declines after the humoral phase, marked by antibody generation, leading to the clinical diagnosis of type 1 diabetes. This might be due to beta-cell stress-induced changes in ceramide-sphingomyelin levels caused by the activation of sphingomyelinase 2 (SMase2) [46], and the influence of cytokines may strengthen this process [46,63]. This may diminish the production of beta-galactosyl ceramide, which is the precursor of sulfatide [17]. Furthermore, for the initiating enzyme building sphingolipids, palmitoyl serine transferase, several polymorphisms exist against blood glucose parameters and type 1 diabetes [64]. Also, various fungi toxins can downregulate one of the building enzymes [65,66]; such one, Fumonisin B1, can be present in bread if grains have been less well stored [67]. This phenomenon is likely important both immunologically and functionally for beta cells.

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Table 2: Factors associated with decreased sulfatide and TLR5 expression in type 1 diabetes pathogenesis.

Decreased expression of:
Sulfatide
- Anti-sulfatide antibodies after virus infection [11]
- Beta-cell stress [68]
- Mycotoxins [66]
- Racemase and D-serine [44]
TLR5
- Staphylococcus aureus [35]
- Helicobacter pylori [38]
- Excessively clean environment and change hereof [25]
- Altered gut microbiome, possible connection to antibiotics [39]
- NLRC4 [40]

In the last trimester of pregnancy, the incidence of diabetes is 3.8 times higher than that outside pregnancy [69]. During this period, there is considerable pressure on insulin production, which might play a role in this process. In spite of the ongoing diabetes process during the actual pregnancy, only 1 out of 55 of the fetuses of newly diagnosed type 1 diabetes mothers developed diabetes, and none of the healthy children displayed beta-cell autoantibodies [70]. This corresponds well with the fact that TLR5 is expressed in the human placenta [71,72], which is also biologically reasonable since the T cells of the mother must not reject the fetus, which partly presents foreign antigens.

Regarding immunological tolerance, there is a biological compromise during pregnancy. On the one hand, the prenatal beta cells should not be too mature and produce too much insulin, as this would lead to an overly large baby that is difficult to deliver [73]. On the other hand, more mature beta cells provide stronger immunological self-protection. Mothers with type 1 diabetes tend toward the latter, since these mothers display higher blood glucose values that stimulates the fetal beta cells to produce more insulin and to be more mature. This results in larger babies who often must be delivered by cesarean section or born preterm, but who have a lower risk of developing type 1 diabetes compared with children of fathers with type 1 diabetes [74]. Correspondingly, in a study using BB rats we stimulated neonatal beta-cell maturation and observed reduced diabetes incidence, likely due to improved self-tolerance [75].

In contrast to other autoimmune diseases, it is impossible to immunize mice in the periphery to induce type 1 diabetes by injecting beta cell homogenate with Freund's adjuvants, etc., which will not create autoimmunity [76], most likely because of the local protection by TLR5 and sulfatide, as mentioned above. Furthermore, even in nondiabetic humans given repeatedly old-fashion insulin preparations (mean 59 injections) for psychiatric reasons to create insulin shock, no development of type 1 diabetes was observed [77]. In a later investigation, only two out of 27 examined former insulin-treated individuals displayed insulin antibodies. This is in accordance with the anticipation that these otherwise healthy nondiabetic persons have normal sulfatide levels and, in agreement with this, have no tendency to produce beta-cell-associated antibodies, such as those against insulin [77].

Type 1 diabetes is closely related to celiac disease, as they have the same tissue type preference [78,79]. We and others have shown that the gluten component gliadin, especially its 33-mer peptide, stimulates T cells [80,81]. In an animal study, this peptide has been shown to be present in islets and to activate tissue transglutaminase (tTG), which is a key component in celiac disease [80]. On the other hand, given a gluten-free diet, this peptide is of course not present in the islets, resulting in less T-cell stimulation. Interestingly, bakers who are chronically exposed to inhaled gliadin, which has been shown to be present in their nasal passages, develop regulatory T cells in the pancreatic lymph node and display a reduced incidence of type 1 diabetes [82].

The increased male incidence of type 1 diabetes is not always observed in low-incidence regions, where females may have a higher frequency – similar to patterns seen in other autoimmune diseases [83]. The male predominance is a rule in countries with high economic development and a modern (Western) lifestyle, likely due to more pronounced beta-cell stress.

Small beta-cell clusters may be part of non-fully developed islet, and it might be imagined to be a sign of modest islet volume. Such one must have more active beta cells and may then theoretically have a higher risk of diabetes development and especially destruction of the small clusters [84]. Actually, regarding anticipated small beta-cell volume in BB rats, the heaviest individuals with the lowest insulin production have double as high risk for developing early diabetes [85].

Prevention and Early Treatment

Owing to the abovementioned considerations, we suggest the following prevention strategies, which are shown in Table 3: 1) Before beta-cell damage, the TLR5 level should be increased by treatment with flagellin or flagellin compounds combined with pneumococcus [1]. Additionally, the environment should not be excessively clean, and exposure to nonpathological active bacteria should be encouraged. 2) Sulfatide can be enhanced by treatment with serine [86]. 3) A gluten-free diet is established in diabetic animal models. Additionally, nasal gliadin treatment could be instituted [87]. 4) The number of HIP and DRiP molecules should be decreased by avoiding beta-cell stress [31,88]. This can be

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accomplished by reducing the intake of refined carbohydrates (sugars, candy, and lemonade) and by engaging in a reasonable amount of exercise [89]. 5) Anti-CD3 T-cell antibodies have been approved and shown to inhibit type 1 diabetes development [90]. 6) The intestinal microbiota should include (i) short-chain fatty acid-producing bacteria [91], as these products, such as butyrate, are beneficial against autoimmune diseases, including type 1 diabetes [92]. (ii). *Akkermansia muciniphila* has been shown to reduce the incidence of diabetes in NOD mice [93]. (iii). Some *Bacteroides fragilis* can produce alpha-galactosyl ceramide [94], which has been shown to be beneficial against diabetes in NOD mice [52]. 7) Atopic diseases, including eczema, are less common in patients with type 1 diabetes [95]. By creating eczema artificially in NOD mice, the incidence of diabetes is reduced, and the mechanism seems to be related to an increased number of NKT cells [96]. Points 1, 3, 4, 5 and 7 have been proven or shown to be likely in human studies, whereas points 2, 3, 6, and 7 have so far only been supported by findings from animal studies. Finally, various pharmaceutical compounds that inhibit the acquired immune system, e.g. vitamin D [97] can be considered.

The reason why 90% of new type 1 diabetes cases do not have first degree relatives with the disease [98] might well be due to the difficult coincidence of events: reduced sulfatide, loss of TLR5, beta-cell stress, unlucky intestinal flora, etc.

Future Perspectives

The protection by TLR5 and sulfatide should be further substantiated both in animal and human studies; furthermore, falsification according to Popper should be attempted.

Due to the increasing preventive possibilities, screening for beta-cell autoantibodies in school-aged children should be performed two to three times while they are growing up to monitor the onset of autoimmune activity. The procedure is minimally invasive, requiring only 6 mL of blood from a fingertip, which can be tested by well-established high-throughput screening technologies. The primary problems are logistical and associated costs.

Conclusion

In conclusion, we describe how type 1 diabetes develops (Table 1 and 2). Importantly, the pathogenic mechanisms are different in the early antibody phase than in the later malignant insulitis phase in patients with clinical diabetes. We are aware that due to age and other factors the detailed manifests for type 1 diabetes may vary. However, as stated here the reduction of the two molecules TLR5 and sulfatide that inhibit T lymphocytes are decisive for the type 1 diabetes process, and prevention should include such a reduction not to happen. Thus, we hope that understanding the development of type 1 diabetes has now been outlined and that preventive treatments are within reach.

Table 3: Contributors to type 1 diabetes (T1D) development and suggested preventive treatments.

Diminished amount of T cells	Development of T1D	Examples	Treatment	Based on animal or human studies
TLR-5 [16]	Very clean [99], Germ-free surroundings [24]	Finland [25]	"Dirty" surroundings [25].	Human.
Sulfatide [52]	Fungi toxins [66]	High Racemase activity [44]	L-serine [86].	Animal.
Gluten-free [80], Nasal gluten [82]	Oral gluten intake [81]	Less incidence of diabetes among bakers exposed to nasal gliadin [82]	Gluten-free diet [81], Nasal gliadin [87].	Animal. Human.
Beta-cell activity [29]	Stress of beta cells [29], Refined carbohydrates, Sweet lemonades [29]	Increased antigen expression [100], DRiPs [30], HIPs [31]	Relax of beta cells, Better diet, Exercise [89], Verapamil [51].	Human.
Thymus dependent immune system [2]	Certain tissue types [78]	Less T1D in other tissue types [78]	Anti-CD3 antibodies [90].	Human.
Intestinal bacteria [91]	Lack of short-chain fatty acid producing bacteria [92]	Butyrate [91]	*Akkermansia muciniphila [93], Bacteroides fragilis [94].*	Animal.
Atopic diseases: Asthma, Eczema [95]	Reduced NKT cell activity [56]	Atopic dermatitis [95]	Creation of an eczema spot [96].	Animal.

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Abbreviations

ASA: Anti-Sulfatide Antibody

BB: BioBreeding

DiViD: Diabetes Virus Detection

DRiP: Defective Ribosomal Product

HIP: Hybrid Insulin Peptide

NLRC4: NLR family CARD domain-containing protein 4

nPOD: network for Pancreatic Organ Donors with Diabetes

SMase2: Sphingomyelinase 2

T1D: Type 1 Diabetes

TLR5: Toll-Like Receptor 5

Tregs: Regulatory T cells

tTG: Tissue Transglutaminase

Author Contributions

The idea of the manuscript in the first draft, is conceptualized and written by Karsten Buschard, with input from Rikke Thea and Camilla Hartmann Friis Hansen. All authors confirm they had full access to all data behind the manuscript and accept responsibility for publication. All authors edited and approved the final manuscript.

Conflict of Interest

The authors declare that no conflict of interest exists.

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