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Environmental factors in the development of Type 1 diabetes

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Abstract Environmental factors appear to play an important role in the pathogenesis of childhood-onset type 1 diabetes (T1D). The most important factors are thought to be infectious, dietary, perinatal, and psychosocial. Enteroviruses (especially Coxsackie B virus), breastfeeding, the early presence or lack of certain foods, birth weight, childhood over-nutrition, maternal islet autoimmunity, and negative stress events have been shown to be related to the prevalence of T1D. However, clear conclusions to date are limited because most studies lacked power to detect exposure/disease associations, were not prospective or long-term, did not start in infancy, had imprecise or infrequent exposure estimates, had confounding exposures, and failed to account for genetic susceptibility. In addition to the identification of specific antigenic triggers, several more general hypotheses, including the accelerator and hygiene hypotheses, are testable approaches worth pursuing.

Keywords Autoimmunity · Infectious · Dietary · Perinatal · Psychosocial · Nutrition · Gene-environment

Abbreviations

T1D	(type 1 diabetes)
HEV	(human enterovirus)
HLA	(human leukocyte antigen)
GAD	(glutamic acid decarboxylase)

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1 Introduction

Type 1 diabetes (T1D) is an autoimmune disease occurring in about 0.3% of the US population [1]. Both genetic and non-genetic factors contribute to disease risk. HLA DR-DQ (IDDM1) is by far the most important genetic loci identified so far, but human linkage studies have revealed at least 15 other genetic risk loci of lesser effect [2, 3]. Nonetheless, studies of familial clustering suggest that genetics accounts for only about half of the risk fraction [4, 5]. Even among subjects with high genetic risk at both HLA-DQ and all other known T1D risk loci (e.g., insulin promoter, PTPn22, CTLA4) the majority still do not develop T1D. Further, the concordance of T1D among monozygotic twins is less than 40% overall [6, 7]. Not withstanding small roles for (a) unlucky stochastic events in the immune system, or (b) post-conceptional genetic factors such as imprinting [8, 9], many lines of evidence suggest that environmental factors play a significant role in disease penetrance. First, T1D incidence is increasing annually by an average of 3 to 5% in most countries around the world [10–13]. While this may be attributable in part to a shift in presentation to younger ages [14–16], an increase at all ages is observed. The rate of increase is too rapid to be attributable to changes in the population gene pool. Second, different regions of the world vary up to 500-fold in T1D prevalence in a way not attributable simply to genetic background. For example, there is a close to six-fold gradient in the incidence of type 1 diabetes between Russian Karelia and neighboring Finland, although the predisposing HLA-DQ genotypes are equally frequent in the two populations [17]. Third, there are many reports of local or regional "epidemics" of T1D in geographic pattern best explained by environmental exposure [18–23]. Taken together, these findings are consistent with a model of genetic susceptibility influenced by non-genetic factors of roughly equal magnitude.

The identification of the environment risk factors contributing to the etiology of T1D is important because avoiding them could be a simple and effective preventive measure. This approach may be among the least toxic of all proposed T1D prevention methods, a key consideration given the vulnerability of the target population and the relative tolerability of insulin. Ultimately, environmental triggers of T1D are likely to prove multiple and heterogeneous, and not all will be identified or avoidable. Nevertheless, a substantial decrease in disease incidence seems possible. Although the final confirmation of the role in T1D of any identified environmental factor must be via a prevention study, the initial step is identification of such factors.

Identification of environmental factors contributing to T1D has been difficult, likely due to the heterogeneous and evanescent nature of environmental exposures and the challenge of measuring them in young children where the early pathogenesis often occurs. Most studies have lacked power to detect exposure/disease associations, were not prospective or long-term, did not start in infancy, did not sample frequently, had imprecise exposure estimates, did not use state of the art sample analysis techniques such as nutrient biomarkers, and failed to account for genetic susceptibility. Over the past 30 years, we have seen no shortage of candidates for the title of *the* environmental trigger in T1D. Specific infectious agents, dietary factors, perinatal factors, socioeconomic factors, and psychosocial factors have each been considered as the most important exposure for T1D. Today, however, no single factor has been identified that is clearly responsible for triggering of (or protection from) autoimmune beta-cell destruction. So far, available data are partially conflicting (reviewed in [24, 25]). Many plausible hypotheses, including the hygiene hypothesis, fertile field hypothesis, and the accelerator or overload hypothesis, have been proposed. This review will focus on the identification of environment factors and processes which trigger or protect from human T1D. We will attempt to limit inclusion of animal data to situations where it is directly relevant to the human disease.

2 Environment factors

2.1 Infectious agents including viruses

Infection might trigger islet autoimmunity via several distinct mechanisms, many of which have been studied in animal models. Some models mimic massive acute beta cell viral infection (EMC-D virus) or chronic low-grade beta cell infection followed by islet autoimmunity (RIP-LCMV). While massive acute beta cell death is inconsistent with the long autoantibody-positive prodrome most commonly observed in human T1D, an acute or chronic low-grade beta cell infection with subsequent bystander activation of immunity to islet self antigens is not inconsistent with this pattern. This is reminiscent of the repeated low-dose streptozocin diabetes rodent model which clearly has an autoimmune finale [26, 27]. In fact, some studies have identified virus within human islets, or cultured virus from isolated human islets obtained from individuals with diabetes [28], although it has been difficult to obtain evidence that this is typical or common. It should be noted that since both islets and exocrine pancreas drain to the same lymph nodes, viral triggering against islet antigens could occur in the setting of viral infection within exocrine and not endocrine pancreatic tissue [29]. A different mechanism is molecular mimicry, where antigen(s) from the infectious agent share epitopes with an islet antigen. A widely known candidate is the sequence shared between a portion of GAD65 and the Coxsackie B virus P2-C protein [30]. Firm evidence in favor of this mechanism has been elusive. Another possible mechanism involves activation of innate immunity such as that seen with the Kilham rat virus model in the BB rat, or the enhancement seen with poly I:C administration in certain rodent models [31]. Innate nonspecific immune mechanisms facilitate specific adaptive immune responses during most immune responses, and may also be relevant to islet autoimmunity. Notwithstanding this notion, the most obvious approach to dissecting mechanisms connecting infection and islet autoimmunity begins with identifying the relevant specific infections. This is where the most study has occurred.

The relationship between viral infections and the pathogenesis of T1D has long been a subject of intense interest and review [32–38]. An early observation was the association of congenital rubella infection with a very high rate of subsequent T1D [39]. Subsequently, other human viruses were reported to be associated with human T1D, including but not limited to Coxsackie B virus [40, 41], mumps [42], echovirus [43, 44], cytomegalovirus [45–47], Epstein-Barr virus (EBV) [48, 49], retrovirus [50], rotavirus [51] and parvovirus B19 [52, 53].

Human enteroviruses (HEV), especially Coxsackie B4 but also echovirus, are the most studied among this long list and serve as an example of the challenges of this type of study. Despite decades of study, the evidence linking HEV infections and T1D remains inconclusive. HEV infections are particularly interesting as T1D triggers since they infect tissues in contact with the gut-associated lymphoid system [54–56] and the pancreas. Studies in isolated adult human islets revealed that several different Coxsackie virus strains can infect human beta-cells [47]. Depending on the specific strain, infection may have no apparent immediate adverse effects, may result in functional impairment, or may result in death, usually by pyknosis. Studies from autopsy

pancreata detected some virus-positive islet cells in newborn infants who died of fulminant Coxsackie virus infection and T1D, but not in control pancreata. Unlike in mouse models, no infected cells were seen in human exocrine tissue [57, 58]. The most well known study involved isolation of Coxsackie virus from the pancreatic islets of a child who died at T1D onset, followed by in vitro culture in rodent islets and the demonstration that the virus could then cause T1D in a rodent model [28]. These acute, fulminant infections do not reflect the commonly observed natural history of human T1D, but also do not rule out the possibility that HEV infections may play a more subtle role in initiating islet autoimmunity. Acute HEV infections have in fact been associated with seroconversion to islet autoantibody positivity [51, 59, 60] with plausible timing [61]. In the Finnish DIPP study, enterovirus RNA was detected by serum RT-PCR in 57% of the case subjects during the 6-months preceding the first appearance of autoantibodies compared with 31% of the matched control children in the same age-group [62]. In contrast to the pre-diabetic children, those with newly diagnosed disease were negative for HEV RNA [63]. Four years later in the same study, combined serum and stool analyses in 878 Finnish DIPP children revealed a significantly higher frequency of HEV infections in children at the time of islet autoantibody appearance compared with age-matched children without signs of islet autoimmunity [64]. A similar increase in HEV infections (83% vs. 29%) was observed in Finnish children who subsequently developed islet autoantibodies versus those that did not in the TRIGR study [65]. Nevertheless, prospective case-control studies of children at high risk of developing T1D (DAISY) using conditional logistic regression gave no evidence that the frequency of HEV infection was associated with beta-cell autoimmunity. Multiple infections were not observed prior to conversion in either cases or controls, based on analyses of serum, saliva and rectal swabs [66]. Similarly, another careful prospective study (BABY-DIAB) observed no association between Coxsackie virus infections in pregnancy or early childhood and subsequent islet autoantibody development [67]. These studies are typical of the conflicting results on the relationship between HEV and islet autoimmunity in dozens of studies. These studies use varying approaches, such as different virus detection methods and different populations, which complicate their interpretation and render the controversy difficult to resolve.

A somewhat different situation is the effect of HEV infection on already established beta cell autoimmunity in autoantibody-positive normoglycemic individuals. While very late infections that simply increase insulin resistance and precipitate T1D in those with barely adequate residual islet function are not especially interesting, the natural history of human T1D has a long autoantibody positive interval with significant beta cell mass still remaining. Many authors thus agree that, once autoimmunity has been triggered and islet autoantibodies appear, the progressive decrease in beta cell function and progression to clinical disease may be accelerated by subsequent exposure events [68, 69]. This is analogous to passing the "checkpoint" from peri-insulitis to destructive insulitis in the NOD mouse model [70]. This would clearly best be investigated by studying non-diabetic subjects with islet autoantibodies, but these cohorts are difficult to identify. Studies at onset of T1D are less ideal but more common, and some showed strong association of HEV RNA with newly diagnosed T1D in Australia [72] and Sweden [73], although others were negative [63]. Many of these studies had poor matching, for example, for HLA genotype [71]. Further, examination of 31 autopsy pancreata at onset of T1D with well-preserved RNA failed to detect any pancreatic Coxsackie virus infections [74]. Overall, these mixed results leave unclear the role of HEV as an accelerant, just as the previous studies left unclear the role of HEV as initiators. Further study of the role of HEV in T1D is urgently needed [75]. Large groups of young children at risk for T1D must be followed prospectively with collection of appropriate samples at frequent intervals. State-of-the-art techniques must be used for sensitive and specific detection of both microbial nucleic acids (to demonstrate current acute or persistent infection] and antibodies (to document past infection). Finally, studies must be sufficiently powered to detect effects of modest magnitude expected for a single exposure type.

Congenital rubella virus infection is also associated with the occurrence of diabetes [76–80]. In one study, more than 12% of children with congenital rubella virus infection acquired T1D [81]. Fortunately, the incidence of congenital rubella in young children has fallen dramatically due to effective vaccination programs, and cannot explain the broad observed increase in T1D incidence. It nonetheless serves as an excellent example of how intrauterine events can affect islet autoimmunity later in life.

No specific bacterial agent has been linked with onset of T1D or with diabetes-associated autoimmunity. However, bacterial influences in the gut are notoriously difficult to measure. Bacterial superantigens have been suggested as a possible non-specific immune stimuli playing a role in stimulating prediabetic autoimmunity [82]. The list of candidate source bacteria includes *Mycobacterium tuberculosis*, *Mycoplasma* species, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, and *Yersinia enterocolitica* [83]. Rather than considering specific triggers, these bacterial exposures might also be considered in terms of modulating effects via overall infectious/inflammatory signals to the immune system. Such effects are discussed below in the section on hypotheses of non-specific T1D triggering.

2.2 Dietary factors

Dietary factors could initiate T1D pathogenesis and/or accelerate or inhibit its progression. The mechanisms are not known, but could involve specific food antigens or non-antigenic aspects of diet (e.g., overall calories, dietary toxins, protective factors in breast milk, etc.). Specific exposures and mechanisms may differ at different times of life (e.g., intrauterine, newborn, toddler, older child). Importantly, many factors occur in combinations and are difficult to analyze in isolation. Examples of this are (a) increased cow's milk exposure and decreased breastfeeding; (b) increased cow's milk exposure and increased caloric intake; and (c) increased breastfeeding and lower Vitamin D intake. Such confounders have often received inadequate attention. Further, although many correlations have been observed between environmental exposures and population-based T1D prevalence, few studies test these findings rigorously using case-control or cohort studies. Those that do, tend to measure only single exposures over a limited time period, often using data collection methods subject to recall bias, and seldom using biomarkers of actual nutritional exposures. For all these reasons, or due to small effect size, results on dietary factor effects often conflict. Nonetheless, for a few major dietary factors, more than one study has been done, and some measure of effect on T1D can be learned.

Among dietary factors found to decrease development of islet autoimmunity are greater intake of breast milk, nicotinamide, zinc, and vitamins C, D, and E, while factors increasing islet autoimmunity are the early introduction of cereals, potatoes/carrots, fruit/berries, cow's milk, N-nitroso compounds, and increased calories causing increased linear growth and weight. These have been reviewed [102, 103]. Thus far, only breastfeeding, cow's milk, and vitamin D have been studied in both case-control and cohort settings, while early cereal introduction has been studied in a cohort setting.

Most of the surveys on breastfeeding and weaning diets have been retrospective. Prospective studies have been initiated, but their results have been inconsistent. Many case-control studies suggested that short breastfeeding and/or early cow's milk introduction increases T1D risk [104–107] including recent data from a large study of randomly selected children from Southeast Sweden [108, 109]. The mechanism of cow's milk effect was postulated as related to development of human antibodies to bovine insulin [112]. One study found that increased amounts of cow's milk ingestion, but not age at introduction, was associated with T1D risk [110], while another found increased cow's milk intake to be protective against T1D [111]. However, three prospective studies in at-risk neonates did not demonstrate increased risk for developing islet autoantibodies in children who received cow's milk (rather than breast milk) early in life [113–117]. These include DAISY (HLA risk or a T1D relative, 34 children with autoantibodies), the German BABYDIAB study (at risk by T1D relative, 133 with autoantibodies and 22 with T1D before age 5), and Australian BABYDIAB (at risk by T1D relative, 62 with autoantibodies). These studies each showed no association of breastfeeding or age at introduction of cow's milk feeding with emergence of any islet autoantibodies. However, these prospective studies have so far been underpowered for the detection of risk ratios less than 1.5, which is the modest risk level for cow's milk identified by a prominent meta-analysis [118]. In the Finnish DIPP Study (HLA risk, 65 children with autoantibodies before age 4) early introduction of cow's milk and short duration of exclusive breastfeeding were associated with development of IA-2ab and for presence of all four autoantibodies [119], a finding not confirmed in their later analysis with a 5-fold higher number of endpoints and more accurate dietary data collection [120]. Taken together, and despite some inconsistency, the data suggest that early introduction of a cow's milk diet confers a small increase in risk of T1D. However, given the small effect, identifying a mechanism is especially difficult. Confounders such as shorter duration of breastfeeding [121] and increased caloric content of cow's milk diets versus breastfeeding diets (accelerator hypothesis, see below), could be responsible for the effect, rather than ingestion of a cow's milk protein. Ongoing studies including one large international prevention study (TRIGR) may provide clearer information in the future.

The concept of early introduction of food proteins causing immunopathology has been widely considered not only in the context of cow's milk proteins, but also many other foodstuffs. The gut has the largest collection of immune tissue in the body, increasing its relevance in regulating tolerance [103, 122–125]. The neonatal gut is known to be quite permeable to proteins, but with increasing age, the permeability of the intestine to immunogenic proteins decreases, and both non-specific and specific immune defense mechanisms of the gut mature [125]. As the permeability of the intestine to immunogenic larger proteins decreases, the initial immune responses to these proteins weaken. Therefore, dietary antigens associated with T1D are more likely to affect the immune system in early infancy than later in childhood, and their study must start early in life. Early introduction of potatoes/carrots and fruits/berries associated independently with beta cell autoimmunity in the DIPP study [120]. In two recent studies from DAISY [114] and German BABY-DIAB [116], it was suggested that risk to develop islet autoimmunity is markedly increased in children with early exposure to

cereal proteins, and particularly gluten. The number of exposed children was small, but the effect was significant in both studies. A German interventional trial (BABY-DIET study) has been initiated to test whether delaying dietary gluten influences the development of islet autoimmunity in newborns at genetically elevated T1D risk [126].

Chronic gut inflammation is known to cause increased gut permeability, leading to the speculation that chronic gut diseases such as celiac disease might increase T1D triggering by this mechanism. However, while many T1D subjects subsequently get celiac disease, not very many celiac disease subjects subsequently get T1D, especially when taking into account HLA risk [127]. Nonetheless, since subclinical celiac disease generally goes undetected, defining the relationship between celiac disease and T1D will require further study using, for example, celiac-specific autoantibody testing.

Other nutritional factors may modulate the T1D process as well. Recently, much attention has been paid to the role of vitamin D in protection against T1D, and this has been reviewed [128–130]. Vitamin D may act by modulating immune cell function [131, 132]. Case-control studies from both Norway (545 cases, 1668 controls) and the EURODIAB-2 study (820 cases, 2335 controls) suggested that early vitamin D supplementation decreased T1D risk [133, 134]. Adjustment for possible confounders, such as low birth weight, short duration of breast-feeding and advanced maternal age in logistic regression analysis, did not nullify this protective effect. Cod liver oil supplementation during pregnancy was also associated with a reduced T1D risk [135] although it was unclear if this was due to its vitamin D or omega-3 fatty acid content and remains to be confirmed in a prospective study. A study conducted in Rome found no significant correlation between vitamin D and risk for type 1 diabetes [104] perhaps because the region studied was in a sunny Mediterranean climate. Ultraviolet irradiation of the skin is a major source of this vitamin, and skin synthesis of vitamin D can provide up to 10,000 IU upon whole body exposure [136], an effect expected to be population-wide. The first prospective study of Vitamin D protection from T1D included 12,055 pregnant women living in the far north of Finland [137]. Vitamin D supplementation was determined from medical records, usually at multiple time points. Most children were given regular or occasional Vitamin D supplements as recommended to prevent rickets. The relative risk of developing T1D was 0.12 and 0.16 in those given regular and occasional Vitamin D supplements, respectively, as compared to children not given supplements. The protective effect was also dose-related (>2,000 IU/day, RR 0.14; exactly 2,000 IU/day, RR 0.22; both compared to supplementation with <2,000 IU/day). These highly significant and very convincing results suggest that infant supplementation with Vitamin D, at least in northern locations and in high doses, protects against T1D.

According to a nested case-control observation, vitamin E may protect from T1D [138]. Exposure to the mycotoxin bafilomycin A1 has been recently suggested as another candidate environmental cause of T1D [139] but this agent seems to cause islet atrophy, rather than autoimmune activation, in rodent models. Although not formally dietary agents, air pollution and passive smoking [140] have also been associated with increased risk of T1D.

Another important dietary factor in children is the overall caloric intake, which is the most important determinant of both child growth and weight gain. Despite difficulties in exact quantification, reports indicate that children who develop diabetes tend to have been overfed in terms of total calories and all categories of nutrients before onset of disease, when taking body size into account. A high intake of mono- and di-saccharides seemed particularly associated with risk [141, 142]. This will be discussed as the accelerator hypothesis below.

2.3 Perinatal factors and postnatal growth

Extra-genetic influences on individual health begin in utero. When studied, association of in utero maternal infections with later diabetes are not impressive [67, 143–147], with the well-known exception of congenital rubella infection. Although congenital rubella infection leads to rate of diabetes of up to 20%, its effective prevention did not decrease the incidence of T1D. Interestingly, rubella infection or immunization after birth does not seem to be especially risky for T1D [148]. Other perinatal factors associated with increased T1D risk (other than T1D in the mother) include older maternal age at birth [149–151], excessive maternal weight gain, amniocentesis (usually to determine fetal maturity in high risk pregnancies), pre-eclampsia [149, 152], cesarean section delivery, complicated delivery (breech, forceps, vacuum extraction) and jaundice associated with maternal-fetal blood group incompatibility [153–155]. Relative risks are significant but low, in the 1.5–3-fold range. Probably due to the low relative risk, one study found no increased risk with pre-ecclampsia [156] and another no significant association of T1D with Cesarean section delivery [155]. It is unclear whether an "immunologic" stress (for example a rubella infection or a maternal immune reaction against "foreign" fetal antigen) is necessary, or whether general stress (for example amniocentesis, complicated delivery) is the causative factor [149, 157]. Protective factors appear to include being a firstborn child, having a low birth weight, or having a short birth length [158–162]. However, increased maternal age was

associated with a longer duration of breast feeding. [121]. Also, birth order relates to family size [163]. These points remind us that confounders must be considered at all times.

The possibility that transplacental transfer of maternal islet autoantibodies confers an increased risk for type 1 diabetes has been suggested [164] questioned [145, 165–167] and discussed in recent reviews [168–170]. Even in infants whose mother has diabetes-related autoantibodies, these placentally-transferred autoantibodies almost always fade in infancy, followed by an autoantibody negative period prior to development of autoantibodies usually after age 15 months in young children who subsequently develop T1D [171]. In fact, when type 1 diabetes parents delivered a child who is GAD65 or IA-2 autoantibody positive at birth, there was actually a lower risk of having multiple islet autoantibodies at 5–8 years of age, compared to offspring who were islet autoantibody negative at birth [172]. This protection in offspring with islet autoantibodies at birth was associated with HLA types other than the high risk DRB1*03/DRB1*04 genotype. While not well understood, this observation could explain why, despite matching for genetic risk, offspring of a diabetic father have a higher risk than offspring of a diabetic mother [173]. Data from both DAISY and BABY-DIAB indicated that presence of cord blood islet autoantibodies was not predictive of subsequent development of islet autoimmunity in children of diabetes-susceptible HLA genotypes [166, 172].

Large scale studies as EURODIAB Substudy 2, Norwegian diabetes study group, UK regional study, and the Sweden DISS group, have used birth registry data to show that high birth weight is associated with a modest but significant increase in the risk of childhood-onset T1D [155, 160, 174, 175]. While other, smaller studies have not found a significant association [176, 177] or have found low birth weight may increase T1D risk [178–180], it is possible that the small studies lacked the power to detect the small effect, or that the effect differs in different populations. A further confounder is that diabetes-associated HLA genotypes have been shown to affect birth weight in the general population [181]. If the intrauterine rate of increase in body weight and length is associated with the risk of diabetes in childhood, the question arises, whether the rate of postnatal growth has a similar effect. This will be discussed in detail below regarding the accelerator hypothesis.

The overall findings seem to imply that a stressful pregnancy and high birth weight moderately predispose to later T1D, but that beta cell-specific autoimmunity in the predisposed infant has a distinct beginning years after birth. Importantly, with the exception of early rubella vaccination, most factors which contribute to in utero effects are not easily modified.

2.4 Psychosocial environment

Psychological mechanisms are directly linked to hormonal and nervous signals that can change insulin sensitivity and affect immune system regulation. Increased psychological stress has been hypothesized to be an environment factor associated with an increased risk of T1D. Psychological stress can be direct to the child or indirect via the family since psychosocial stress in the family induces stress in the child [182].

Negative life events during the first 2 years of life, such as divorce [183], serious family illness or loss of a close relative [184], high parenting stress, foreign origin of the mother, and low paternal education level [185, 186], severe accident or hospitalization or death of a close friend, conflict with a teacher, death of a pet, failure in competition, quarrel between parents, punishment, physical attack, living in a country at war, near drowning, and learning disabilities were all independent risk factors for T1D [187]. Maternal experiences of serious life events such as divorce and neonatal intensive care should especially be noted [183, 186]. Interestingly, cold climate, which might be considered as a chronic stressor, has also been found to associate with T1D risk [188]. Unfortunately, retrospective studies reporting an association between stressful life events and TID [184, 189–191] have often been methodologically flawed due to recall bias. Prospective studies, perhaps with the inclusion of biomarkers of stress such as salivary cortisol, may be better suited to study the effects of exposures of this type.

3 Selected hypotheses on non-specific triggers

Non-specific factors, especially as applied to infectious and dietary exposures, may have substantial merit when considering environmental influences in T1D penetrance. These have generally been discussed in the form of "hypotheses."

For infectious exposures, the hygiene hypothesis proposes that lack of normal background infections predisposes the immune system to autoimmunity, including T1D [85]. Infections, especially in early childhood, may in fact prevent or delay disease [86]. In some studies, the frequency of childhood infections correlated inversely with the incidence of T1D [87–91]. As one example, the EURODIAB Substudy 2 Study showed Pre-school day-care attendance and a proxy measure for total infectious disease exposure in early childhood was found to be inversely associated with diabetes [92]. This is reminiscent of the effect of infections and inflammation (e.g., non-SPF conditions) to decrease disease in rodent models of T1D [93–97]. In general, infectious exposures including viruses and bacteria stimulate

innate immunity via toll-like receptors, and such stimulation of circulating immune cells may be important in the development of regulatory T-cells (Tregs) that hold autoimmunity in check [192, 193]. Some have even suggested a unique partnership between plasmacytoid dendritic cells and Tregs [194]. Lower levels of background infection in the population could lead to lesser transfer of maternal immunoglobulins via placenta or breastmilk. Common pinworm infections, whose frequency has decreased rapidly in recent decades, might be protective against autoimmunity by promoting immune deviation towards Th2 responses [98]. Despite these interesting proposed mechanisms, the hygiene hypothesis in T1D is not entirely consistent with a similar theory postulating that asthma and atopy are associated with improved hygiene [99]. Moreover, the simplicity of the hygiene hypothesis has been criticized recently [100, 101].

The other side of the coin for infectious disease is the fertile field hypothesis, which proposes that non-specific inflammation (e.g., multiple unrelated infections) may accelerate islet autoimmunity, especially if the latter is already established [37, 84]. It has been shown that repeated infections using different viruses can lead to activation of memory T-cells of unrelated specificity [195, 196]. This is similar to the known effect of Interferon-alpha therapy to precipitate clinical autoimmune disease. Since many individuals with autoantibodies to multiple distinct islet autoantigens do not progress to clinical disease, factors that sustain or accelerate islet autoimmunity are important. In any case, non-specific infectious exposures are difficult to measure in their totality, and the combination of prospective design and biomarkers of infectious inflammation plus microarrays including a large number of specific pathogens, may be needed to address the hygiene and fertile field hypotheses. A steady pattern of changing exposure in parallel with the incidence trend would provide convincing support. Finally, suitable genetically susceptible prediabetic (autoantibody-positive) cohorts would be required.

Within the realm of dietary and nutritional influences, the "accelerator hypothesis" [197] has generated a large amount of support. More recently, it has been extended as beta-cell stress or overload hypothesis [198]. The accelerator hypothesis suggests that the increased incidence of T1D may be caused by an accelerated progression rather than by an increase in the absolute lifetime risk [197]. The accelerator hypothesis proposes that increased insulin resistance associated with the epidemic of childhood overweight and obesity creates greater insulin secretory demand on the islets, leading to acceleration of beta cell destruction and T1D. It predicts that among those who develop T1D, heavier children will do so at a younger age [14, 197, 199] in some ways similar to how obesity accelerates the development of type 2 diabetes. Indeed, wherever in the world there has been an increase in type 2 diabetes, there has been a parallel increase in childhood T1D [10, 200, 201]. It is also plausible that overweight children with active islet autoimmunity who might have otherwise reestablished tolerance, instead dip below the minimum required beta cell mass and develop clinical T1D due to their body's greater insulin needs. This would represent not just a shift to a younger incidence age but also a greater cumulative T1D incidence [202–206]. Both of these phenomena have been recently noted worldwide [10]. Given the evidence that susceptibility to autoimmune destruction increases with beta cell secretory rate, and since this rate must necessarily increase with greater insulin resistance, the proposed mechanism seems plausible. Though Ginsberg reported on measurements of insulin sensitivity in patients with T1D as early as 1977 [207], the concept that insulin sensitivity has a role in the early stages of T1D development has only recently gained widespread acceptance [208, 209]. Evidence for this mechanism in humans is extensive although somewhat circumstantial. The prevalence of pediatric overweight and pediatric T1D has increased in parallel [210]. The well known peak in T1D incidence at puberty parallels the known surge in insulin resistance during this period [211–214]. Another documented physiological state of insulin resistance, pregnancy [215] is also associated with an increased risk of T1D development [216]. Relatives positive for islet autoantibodies who progressed most rapidly to T1D had a subtle disturbance of insulin-glucose homeostasis years before T1D onset, distinguished by greater insulin resistance for a given level of insulin secretion [217]. More rapid growth in height and/or weight in early childhood, presumably with greater relative insulin secretion, has been widely shown to be associated with increased T1D risk [202, 204–206, 218–221]. Recently, it has been shown that age at presentation of childhood T1D is indeed related inversely to body mass index (BMI) [178]. The Early Bird research group in Germany showed that pre- and post-T1D-onset BMI were both well above the population mean [222]. In Austria, regional distribution of childhood T1D risk appears to match regional variation in BMI [223]. However, the SEARCH study found that increasing BMI is associated with younger age at diagnosis of T1D only among U.S. children with reduced beta-cell function, suggesting that "acceleration" occurs only late during the natural evolution of T1D, when beta-cell function is already under an autoimmune attack [180]. Overall, given the great increase in size, overweight and obesity in Western populations, the accelerator hypothesis is perhaps the most interesting and important proposal so far in attempting to explain the effect of environment on the development of T1D.

4 Problems and hope

It is clear that environmental factors must play a substantial role in the development of T1D, but it is difficult to identify the clear role of any single environment factors as triggering or modulating the pathogenesis of T1D based on the current body of studies. Unfortunately, animal models may not adequately reflect the human situation [224, 225]. Even different human studies of the same exposure agent yield different answers, perhaps due to different sources of exposure information, different population, different sample sizes and power, etc. Many studies have been confounded by imprecise assessment of exposure, recall bias, failure to account for genetic susceptibility, failure to assess exposures at very early ages or the inability to follow a sufficient sample of children long-term with high intensity, limitations in sensitivity or specificity of methodology, failure to account for confounding factors, failure to consider groups of different exposures, and lack of sufficient study size to be powered to detect modest effects. None of these problems is easy to address despite the creative approaches of numerous investigators. However, a hopeful attempt towards overcoming many such issue is the recently established TEDDY study (The Environmental Determinants in Diabetes of the Young), a consortium of six international centers using a common protocol designed to identify environmental factors that contribute to the risk of T1D (http://teddy.epi.usf.edu/). The study is prospective, large, uses biomarkers where possible, begins very early in life, carefully defines genetic susceptibility in the studied cohort, and systematically screens candidate environmental and genetic factors using "cutting edge" molecular immunologic and genetic techniques. In addition to identifying factors which trigger T1D or which protect against the disease, another long-term TEDDY goal is to create a valuable resource of biological samples for investigators proposing innovative hypotheses concerning candidate environmental and genetic factors. It is hoped that identification of such factors will lead to a better understanding of disease pathogenesis and result in new, safe, effective strategies to prevent, delay or reverse type 1 diabetes.

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