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The Changing Landscape of Type 1 Diabetes: Recent Developments and Future Frontiers

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Abstract

Type 1 diabetes (T1D) research has made great strides over the past decade with advances in understanding the pathogenesis, natural history, candidate environmental exposures, exposure triggering time, disease prediction and diagnosis. Major monitoring efforts have provided baseline historical measures, leading to better epidemiological studies incorporating longitudinal biosamples (i.e., biobanks), which have allowed for new technologies ('omics') to further expose the etiological agents responsible for the initiation, progression, and eventual clinical onset of T1D. These new frontiers have brought forth high-dimensionality data which have furthered the evidence of the heterogeneous nature of T1D pathogenesis and allowed for a more mechanistic approach in understanding the etiology of T1D. This review will expand on the most recent advances in the quest for T1D determinants, drawing upon novel research tools that epidemiology, genetics, microbiology and immunology have provided, linking them to the major hypotheses associated with T1D etiology, and discussing the future frontiers.

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Compliance with Ethics Guidelines

Conflict of Interest

Kendra Vehik declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent

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Keywords

Type 1 diabetes; Epidemiology; Gene-Environment interaction; Treg; Microbiome; Gut immunity; Metagenome; Metabolome

Introduction: The Changing Epidemiology of T1D

Globally, 78,000 children develop type 1 diabetes (T1D) each year [1]. The U.S. predictions estimate an 144% increase in the prevalence in T1D for youth (<20 years) (current prevalence of 2.13/1,000 projected to increase to 5.20/1,000) by 2050 [2] if the annual incidence of T1D continues at a linear rise of 2.3% per year [3]. The burden of T1D in the US (<20 years) and Europe (<15 years) is expected to reach ~400,000 people in 2020 [4, 2].

T1D is thought to be an immune-associated destruction of the pancreatic β cells. Although the cause(s) remains elusive, great strides in understanding the natural history of T1D have been made in the last 50 years thanks to regional and worldwide registries located in Europe (EURODIAB [5], DiaMond [6]) and the U.S. (SEARCH for Diabetes in Youth Study [2]). T1D is known as a complex disease not reliant on a sole cause, but varied in pathogeny and etiology. Temporal trends have shown that the risk increases from birth, peaks at 10–14 years, declines after puberty and stabilizes in early adulthood [7] before slowly declining throughout adulthood. The past decades have shown an increasing incidence in the very young in both Europe [6] and the U.S. [3] (Figure 1) with an apparent leveling off beginning in 2000 in the youngest ages (0–4 years) in Sweden, one of the countries with the highest T1D incidence [8].

An improving hygienic environment was first proposed by H. Kolb and R. Elliot [9] as the responsible factor for the escalating worldwide trend in T1D incidence. As an adaptation from the Hygiene Hypothesis [10], this theory suggested that a lack of exposure to microbes early in life was leading to a dysfunctional immune response to pathogens later in life. The hypothesis was later expanded by E. Gale to include a possible protective effect from early exposure to microorganisms [11]. An alternative explanation, the Accelerator Hypothesis [12], speculated that increasing body size was driving the increase in T1D incidence. This hypothesis was expanded to include other environmental factors as accelerators of the disease process through the overloading (by increasing demand for insulin production possibly leading to immune damage and apoptosis) of the pancreatic β cells [13]. Questioning the overall rise in T1D incidence, given that the increase was predominantly affecting the very young, the Spring Harvest Hypothesis [14, 15] was proposed suggesting that contemporary children were burdened with a more rapid progression from a pre-clinical state to clinical disease rather than an absolute increase in T1D risk [14]. And, as a catch-all hypothesis (Unifying Hypothesis), J. Ludvigsson [16] hypothesized that no sole cause existed, but rather different or several mechanisms are at play. Inevitably, in the search for viable mechanisms, current research is embracing a multidisciplinary approach by examining genetic predisposition in combination with focusing on how the early life environment impacts T1D risk.

These far-reaching hypotheses have been driving epidemiologic research for over 20 years. To date, the majority of studies have identified risk factors utilizing a so-called ‘black box’ approach relating baseline biomarkers to development of autoimmunity and/or T1D. Recent advances in ‘omics’ research have highlighted numerous gaps in current approaches and provided the opportunity to begin opening the ‘black box’.

Several recent reviews have covered the epidemiology of T1D [7, 17] with some specifically focusing on new finding in areas such as genetics, infant diet, nutritional biomarkers and gut immunity [18, 19]. This review will expand on the most recent epidemiology, genetics, microbiology and immunology data, it will explain how they relate to the major hypotheses about T1D etiology and it will discuss future research frontiers.

Learning from the Past

For over 30 years, those with T1D have been characterized in terms of genetic risk factors, diabetes-associated autoantibodies, family history and clinical markers (at and following diagnosis). In the last 15 years, capitalizing on knowledge of genetically high-risk T1D newborns and presence of diabetes-related autoantibodies, the established hallmarks of disease (insulin autoantibody (IAA) [20], insulinoma-associated protein 2 autoantibody (IA-2A) [21], glutamic acid decarboxylase antibody (GADA) [22], and zinc transporter 8 autoantibody (ZnT8A) [23]), and advances in epidemiological research have led to several prospective, longitudinal studies. The earlier longitudinal studies had limited environmental data and were designed to find risk or protective factors, rather than understanding mechanisms. New research is now focusing on potential mechanisms using tools such as genomics, the microbiome, the transcriptome, the metabolome and the immune system, applied within current longitudinal studies (i.e., The Environmental Determinants of Diabetes in the Young (TEDDY)). Such approaches have started to identify high risk groups and to provide knowledge about optimal handling of high-throughput ‘omics’ data.

Recent findings of these longitudinal studies now highlight the importance of a more mechanistic epidemiological approach to understanding the etiology and pathogenesis of T1D as opposed to the risk factor driven ‘black box’ approach. Prospective follow-up of genetically high risk newborns in the German BABYDIAB-BABYDIET Study Group showed that the incidence of diabetes-associated autoantibodies, in contrast to T1D incidence, has an early peak between 9 months and 2 years of age. Those who seroconverted at <2 years were most likely to develop multiple autoantibodies (IAA most often presenting first) and progress to T1D [24, 25]; thus, pointing to the *in utero* and early post natal period as a likely window to search for the candidate environmental triggers. As researchers close in on the time interval of the precipitating (triggering) event(s), the focus has shifted to identifying even earlier biomarkers that can bring more clarity to the most likely causes of T1D typically via many of the ‘omics’ approaches that are later described.

Cross-sectional screening with prospective follow-up studies have suggested varying degrees of progression from autoimmunity to T1D using clinical markers, such as HbA1c, to identify those individuals most likely to progress to T1D. Preliminary findings from the DPT-1 and Type 1 Diabetes TrialNet studies showed that a 0.5% point increase and/or ~10% relative change from baseline HbA1c measure significantly accelerated time to T1D in high-risk T1D populations, where other markers of risk (i.e., diabetes-associated autoantibodies, genetic risk, and family history) were known [26].

Since 2009 early life environmental exposures, such as, early life diet [27, 28], vitamin D levels [29–31], mode of delivery [32, 33] and enteroviral infection [34, 35] have been receiving increasing attention. Connecting knowledge across disciplines may identify the underlying mechanism(s) linking the gene-environment relationship between early life microbiome development and epigenetic factors that likely affect our innate and adaptive immune system leading to immunological disturbances, metabolic dysregulation and overt T1D.

New Genetic Frontiers

More recently, genetic research is becoming less about screening populations and more about finding mechanistic markers or homogeneous genetic risk groups. The Wellcome Trust Case-Control Consortium (WTCCC), Type 1 Diabetes Genetics Consortium (T1DGC) findings [36, 37] and subsequent replication and meta-analyses [38, 39] have provided an increased understanding of genetic factors predisposing to T1D beyond the well-established HLA associations [40, 41]. While the whole-genome approaches have been able to highlight genetic variants associated with T1D beyond HLA, another area of investigation is dissecting the well-established HLA-DR and -DQ associations with disease, where subtle effects in the HLA region may modify the risk of the known haplotypes [42, 43]. Erlich *et al.* [44] recently identified an allele at the *HLA-DRB3* locus which modifies the risk within DR3 homozygotes. DR3/3 carriers of the *HLA-DRB3**02:02 allele were at significantly higher risk of developing T1D than the DR3/3 subjects who were homozygous for the *HLA-DRB3**01:01. Difficulties experienced in this field include the strength of the DR3/4 association with disease and accounting for the strong linkage disequilibrium (LD) in the HLA region. New findings, such as the *HLA-DRB3* association, will begin to reveal those truly at higher risk by identifying more homogeneous risk groups within the HLA high risk profiles.

Novel genetic findings are helping piece together the mechanistic pathway(s) in one of the more promising environmental candidates for T1D prevention – vitamin D. Epidemiologic research has suggested that exposure to low levels of vitamin D in utero are associated with T1D [45, 46] and early childhood [47, 48]; however, these findings have been conflicting. Changes in vitamin D intake over the years [48] have led some to speculate about its contribution in the increasing incidence of T1D, especially in Finland [49]. The biological pathways through which vitamin D may protect against T1D are still unknown, but likely involve immunomodulation and cell protection [50]. Human studies have been limited and more restricted primarily showing associations with autoimmunity and T1D in case-control and cohort studies. Recent studies [31] have found significant T1D associations with variants in pathway genes related to vitamin metabolism, cholesterol synthesis and hydroxylation. Frederiksen *et al.* recently reported an interaction between the vitamin D receptor gene (VDR) and protein tyrosine phosphatase, non-receptor type 2 (PTPN2), as well as the association of a different VDR SNP, with progression to clinical diabetes in autoantibody positive subjects in the DAISY prospective cohort [51], suggesting a possible role for vitamin D in the progression from autoimmunity to T1D. Another area of research has focused on an essential component, vitamin D binding protein (VDBP), responsible for the transport of metabolites, preservation, absorption of dietary vitamin D, immunomodulatory functions, and a surrogate for circulating 25-hydroxyvitamin D (25(OH)D) levels [52]. Blanton *et al.* [30] recently reported that low levels of VDBP were associated with T1D. In combination, the above studies begin to indicate that vitamin D serves some role in T1D onset or pre-clinical disease progression, but much like the etiology of T1D itself, it will most likely have multiple avenues or levels (i.e., production, receptor, absorption, and interaction with other genes) at which this impact is expressed.

The genetic blueprint, while constant from conception onwards, may influence disease development at any age. Aside from *in utero* effects, the first opportunity the environment has to influence the body is the mode of delivery. It has been previously reported that Caesarean section delivery may increase the risk of T1D by 20% [53]. Bonifacio *et al.* [32] have found that not only did children delivered by C-section have an increased risk of T1D, but that there was also an interaction with the *IFIH1* variant rs2111485. Both the environmental and genetic factors in this case are linked to immune system development. C-section delivery exposes the neonate to a different set of bacteria and viruses compared with

vaginal delivery [54], while the *IFIH1* gene produces a protein, helicase C domain 1, which plays a role in sensing viral RNA and inducing the interferon response. In the last decade, C-section rates have increased by 53% in the U.S. [55] paralleling the increasing incidence in T1D while the prevalence of *IFIH1* variant, a very common variant, has not changed over time [56]. A possible link to explain the finding by Bonifacio *et al.* is the recent report from Cinek *et al.* that found that *IFIH1* variant rs1990760, a good proxy for rs21111485, was significantly associated with enterovirus RNA frequency in healthy children from the Norwegian MIDIA T1D study [34]. The complex interplay between genetic susceptibility and environmental exposures overlaying the development of the microbiome and innate response systems in early life is beginning to unravel the many potential pathways involved in T1D risk.

Metabolome and T1D

We have entered the realm of ‘omics’ research with the hope of untangling the possible pathways involved in the pathogenesis of T1D. New systems, such as metabolomics, can help characterize the varying phenotypes, essentially by profiling metabolically the chemical fingerprints (i.e., end-product metabolites) of those individuals that develop T1D. The metabolome is a collection of small molecules, such as metabolic intermediates or hormones, within a given biological sample (usually plasma or serum) typically identified by mass spectrometry and then analyzed by bioinformatics to reveal a broad profile of small molecules and potential differences in various cellular or metabolic signal pathways [57]. Serum metabolic profiles of T1D children and the NOD mouse have revealed dysregulation in both lipid and amino acid metabolism which appears to occur prior to islet autoimmunity [58, 59]. Finland has lead the way in T1D human metabolomics research where serum metabolite profiles were compared between 50 children from the Type 1 Diabetes Prediction and Prevention study (DIPP) who progressed to T1D and 67 nonprogressors who remained healthy and autoantibody negative [58]. Development of T1D was preceded by reduced levels of succinic acid and phosphatidylcholine at birth and reduced levels of triglycerides and antioxidant ether phospholipids during follow up. Increased levels of proinflammatory lysoPCs were observed months before seroconversion to autoantibody positivity. Of note, prior to appearance (0–18 months) of insulin autoantibodies (IAA), there was a significant reduction of ketoleucine indicating impaired branched chain amino acid catabolism. The above altered metabolic profiles were partially stabilized after seroconversion. A follow-up study was performed employing a reverse translational model examining NOD mice for metabolic disturbances preceding cell autoimmunity as identified in children [59]. Their findings demonstrated that female NOD but not male mice exhibit the same lipidomic pattern as prediabetic children. These metabolic changes corresponded with enhanced glucose-stimulated insulin secretion, upregulation of insulinotropic amino acids in islets, and diminished gut microbial diversity of the *Clostridium leptum* group. In a small cohort of children who developed autoantibodies <2 years of age compared to those who seroconverted >8 years, the BABYDIAB study identified metabolic profiles distinct by age and autoimmunity where children developing autoimmunity early in life had 2-fold lower concentrations of methionine [60]. Taken together, these studies and others [61] have clearly indicated that metabolic disturbances are reflected in the serum preceding the first autoimmune response; thus, providing hints to the environmental triggers, such as diet or infectious agents, possibly affecting the microbiome and, subsequently, the immune system, as well as, potentially opening an earlier therapeutic window for potential immunosuppressive clinical intervention and prevention of T1D.

Microbiome

The link between our genetic blueprint, *in utero* exposures and the development of our microbiome in early life sets our baseline health state. Increased gut permeability, intestinal inflammation and deregulated oral tolerance have all been observed in children with T1D. However, the factors leading to these conditions are not fully understood. Notably, an altered mucosal immune response may be a major contributor to the failure of T-cells to develop cell tolerance, and thus could underlie T1D autoimmunity. Failure to develop cell tolerance may be potentiated by specific intestinal microorganisms transiting across a leaky intestinal epithelial barrier, triggering an inappropriate immune response leading to autoimmunity. As seen in animal models, increased intestinal permeability has also been observed in humans [62–64]. The described increase in intestinal permeability often precedes the onset of clinical symptoms, suggesting a direct correlation between gut leakiness and T1D [65]. However, whether this association is cause or effect of T1D is yet to be determined.

In contrast to animal models, the role of intestinal microbiota is less clear in human T1D development. Giongo *et al.* made progress towards defining the autoimmune microbiome for T1D in a recent study [66]. Although using a limited human cohort, results from this study suggested an association between changes in the microbiota and the development of autoantibodies. Additionally, the level of bacterial diversity diminished over time in patients who developed autoimmunity relative to that of age and genotype-matched non-autoimmune individuals [66]. In terms of the relationship between cell autoimmunity and the microbiome, a recent study demonstrated that the intestinal microbiota significantly differed between children with at least two diabetes-associated autoantibodies with age/gender/early feeding history/HLA-matched autoantibody-negative children. There was a low abundance of lactate- and butyrate-producing species associated with presence of autoantibodies. In addition, a lack of *Bifidobacterium* species, *Bifidobacterium adolescentis* and *Bifidobacterium pseudocatenulatum*, and an increased abundance of the *Bacteroides* genus were identified in children with cell autoimmunity. These findings begin to demonstrate that specific populations within the intestinal microbiome can potentially impact T1D autoimmune progression and certainly warrant further studies into the microbial populations identified and associated with cell autoimmunity [67].

Dietary components have garnered much attention over the years and have been implicated as a potential trigger of autoimmunity and/or T1D. The TRIGR Finnish pilot recently reported that after up to 10 years of age early nutritional intervention with hydrolyzed formula in infancy significantly reduced the appearance of diabetes-associated autoantibodies but not T1D [68]; and, although, the mechanism(s) is unknown, Knip *et al.* suggest that lack of exposure to intact bovine insulin, gut immunity, gut microbiota and/or induction of Treg maturation may be possible routes [68]. A similar study in the BB-rat model observed a 50% reduction in the development of T1D when BB-rats were weaned to a hydrolyzed casein diet instead of a whole-protein diet. The reduction in the development of T1D in this experiment correlated with a decrease in intestinal permeability and an increase in intercellular tight junction-related proteins [69]; further supporting the involvement of the microbiome through improved intestinal barrier function as an intermediary in the prevention of autoimmunity and T1D.

Viral enteric infections have also been proposed as triggers of T1D by either molecular mimicry as observed in rotavirus infections where T-cells specific for epitopes of rotavirus VP7 protein cross-react with the antigenic epitope of islet autoantigens [70], or by directly infecting cells as in the case of enteroviruses as shown both *in vitro* and *in vivo*. Direct infection of cells by enteroviruses could result in islet destruction leading to T1D [71].

Alternatively, enteric viral infections may be simply causing a disruption in the intestinal epithelium leading to increased permeability and robust immune activation [72]. Exploring the complex associations between the intestinal microbiota and the development of T1D will provide important information about the etiology of the disease, potentially enabling new interventions and even preventatives of disease onset.

T-Cells and T1D Immunology - Oh T-Cell Where Art Thou?

To further complicate our understanding of the natural history of T1D, a recent review by Skog *et al.* [73] challenges the notion that T1D is a T-cell mediated autoimmune process by suggesting it is an innate inflammatory disease precipitated by chronic pancreatic bacterial infections via the intestines further implicating the microbiome as a potential suspect in T1D etiology. Our current understanding is that T1D is described and characterized as a T-cell mediated autoimmune disease that is initiated by processing of self-peptides by antigen presenting cells (macrophages or dendritic cells) to autoreactive CD4⁺ T-cells in the pancreatic lymph nodes; thereby, initiating a pro-inflammatory detrimental cascade resulting in the generation of autoantibody producing B-cells and activated cytotoxic CD8⁺ T-cells [74–76]. Autoreactive B-cells can generate a series of autoantibodies to various cell autoantigens such as GAD, IA-2, insulin, and ZnT8. Pancreatic infiltrating CD8⁺ T-cells can then target and induce destruction of pancreatic cells resulting in a terminal dependency of exogenous insulin injections. This widely held belief has been strongly supported by rodent models such as the NOD mouse or BB-rats which have a similar but more acute phenotype of T1D [77], yet minimal clinical data has been derived to extensively evaluate this mechanism occurring *in vivo* during longitudinal progression of T1D. Surprisingly, the “smoking gun” has typically not been found until recently in terms of identification of autoreactive cell specific CD8⁺ T-cells within the pancreas of T1D patients. Islet insulinitis is composed of CD4⁺ lymphocytes, B-lymphocytes, macrophages, natural killer (NK) cells, but predominantly composed of CD8⁺ T-cells [78]. Despite the widely held belief that T1D is T-cell autoimmune-mediated, there is a paucity of evidence directly demonstrating this process from clinical T1D patient samples. A comprehensive meta-analysis evaluating reported insulinitis from literature published between 1902–2010 in human T1D found evidence of this immunological process being described in only 150 cases over the past century [79]. Further evidence evaluating autoantibody-positive organ donors without T1D identified insulinitis in only 10% of islets or less [80]. Taking into consideration the limited available sources of pancreatic tissue from people with T1D, there has been a significant gap in the literature identifying the presence of autoantigen-specific CD8⁺ T-cells at the level of the pancreatic islets until very recently. Direct evidence of this has now been shown by Coppieters *et al.* that identified isletautoreactive CD8⁺ T-cells in insulinitic lesions from recent onset and long-term T1D patients [81]. Frozen pancreatic sections were obtained from 45 cadaveric T1D donors with disease durations ranging from 1 week to >50 years obtained from the Network for Pancreatic Organ donors with Diabetes (nPOD) and analyzed for insulin-sufficient B-cells, CD8⁺ insulinitic lesions, and HLA class I hyperexpression. CD8⁺ T-cell autoreactivities were detected in a subset of patients up to 8 years following T1D clinical onset. Interestingly, insulin producing cells were identified in patients without detectable C-peptide despite having T1D for 56 years.

In addition to the pro-inflammatory cell attack observed in T1D, there is also a concordant dysfunction in the maintenance of peripheral tolerance via loss of regulatory T-cell (Treg, CD4⁺CD25⁺) control in autoimmune T-cell responses [82]. Analysis of islet inflammation in T1D revealed the absence of Treg in inflamed pancreatic islets of recent onset T1D patients [83]. In addition to an absence of Treg in T1D pancreatic islets, studies have indicated Treg dysfunction by evaluating this cell population in the pancreatic-draining lymph nodes of T1D patients and demonstrating an overall Th17-proinflammatory cellular

profile [84, 85]. Other studies have also shown dysfunctional Tregs capable of producing IFN- γ in T1D patients [86]. The emerging immunological profile of T1D strongly suggests the existence of the wrong T-cell (CD8+) in the wrong place (pancreatic islet) or the absence of the right T-cell (Treg) in the right place leaving us with an overall conundrum of, “Oh T-cell Where Art Thou.” Nonetheless, the therapeutic potential of Tregs in the treatment of T1D is tremendous due to their pleiotropic immunosuppressive nature and overall plasticity [87].

Conclusion

As the current dogmas are challenged, new sciences are opening doorways and the collaborative marrying of biological disciplines through concentrated efforts on mechanistic studies may allow for better phenotypic profiling, novel biomarker discovery for earlier intervention and improved therapies to prevent or reverse T1D. At present, this will most likely be accomplished through large longitudinal prospective cohorts with serial samples measured over short, regular intervals collected in parallel with reported environmental exposure and clinical data. The international multi-center TEDDY study [88] will be essential in confirming findings from earlier studies, which were often beset by conflicting results due to small sample size. However, the heterogeneous nature of the disease has made it very difficult to elucidate the factors and mechanisms responsible for disease onset. Novel approaches incorporating pathways analyses into observational study designs and connecting epidemiology with basic biological research will expand our understanding of biological processes and disease mechanisms.

Innovative technologies will help fill in the blanks in current etiological hypotheses by providing a platform to move from a one-dimensional analytical approach to one that can accommodate high-dimensionality data. New frontiers in T1D research point to a systems epidemiology approach [89] such as a linked prospective and nested case-control studies or registries with integrated biobank data to begin unraveling the mechanisms involved in T1D.

The plateau effect in the incidence of T1D predicted by E. Gale in 2002 is beginning to unfold (i.e., Sweden) and is possible that other countries with high T1D incidence will follow. Registries have been instrumental in furthering our research efforts and monitoring trends. Research continues to focus on the environment as the key trigger tying all the hypotheses together and proposing multiple phenotypes and mechanisms. The numerous hypotheses about the etiology of T1D may become more attractive and easier to test as new technologies (-omics) become available and high-dimensional data analytical approaches are developed.

In 1986, G. Eisenbarth modeled the natural history of T1D by describing the stages of T1D development [90]. Although the original model has been modified and refined many times, it has remained the basis of what we believe is true. New science is starting to identify the gaps and weaknesses in our current knowledge or areas that are incompletely understood. The interplay between our biological systems, especially the symbiotic relationship between our microbiota and our immune system, may provide a clearer biological explanation (Figure 2) for the pathways involved in the development of T1D. However, a long journey still lies ahead as the tedium of testing mechanisms *in vivo* is a major challenge along with the translational approaches necessary for the development of safe and effective preventive treatments for T1D.

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Figure 1. Increasing trend in the incidence of T1D in the very young in Europe (1990–1999) [6] and the U.S. (1978–2004) [3]. Percent increasing incidence of T1D (95% confidence intervals) by age group in years (*red bars: Europe; blue bars: U.S.*).

Figure 2.

Stages of T1D development (modified (blue text) from the original figure (black text) published by George Eisenbarth [88] in the NEJM). Numerous factors as listed above can impact the microbiome, which include genetics, diet, environment, and infection. Synergistically or individually this can alter the gut microbiome with the residing microbiota impacting intestinal functionality, permeability, and overall tolerance. Taken together, immunological intolerance driven by the residential microbiota can tip the scales of pancreatic cell autoimmunity and potentially initiate T1D onset and progression. (Modified from: Eisenbarth GS. Type I diabetes mellitus. A chronic autoimmune disease. The New England Journal of Medicine. 1986;314(21):1360-8) [90].