Why Are C-Section Deliveries Linked to Childhood Type 1 Diabetes?

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The incidence of type 1 diabetes (T1D) is increasing worldwide at an annual rate of 3.9% (1). Early life factors have been shown to be associated with increased T1D risk and perhaps involved in the development of the immune system (2). Cesarean section (C-section) deliveries have increased by 50% since the 1990s (3) and have paralleled the increasing trend in the incidence of T1D (4). A recent meta-analysis of 20 studies worldwide reported that C-sections, independent of maternal age, birth weight, and breastfeeding, contributed a 20% increase in the risk of T1D (4).

Altered gut microbiota, bacterial exposures during pregnancy, perinatal stress, and the hygiene hypothesis have all been proposed as possible explanations for the observed associations (4). A potential mechanism that has received recent attention suggests that the types of bacteria found on the newborn's skin may influence the development of their immune systems and their future health (5). Studies have shown that vaginal delivery exposes the baby to microbes that resemble the mother's vaginal bacteria (e.g., *Lactobacillus*, *Prevotella*, and *Sneathia*); in contrast, C-section exposes the baby to microbes that resemble those found on the skin (e.g., *Staphylococcus*, *Corynebacterium*, and *Propionibacterium*) (5). Children born by C-section lack the benefit of protective vaginal bacteria, which may make them more susceptible to viruses, allergies, and asthma later in life (6). Such findings are contributing to the development of novel etiological hypotheses for T1D development by suggesting that the initial microbiota to which a neonate is exposed, and which may be related to the type of delivery, is important in the development of child's immune system and in modulating its response to external agents later in life.

Yet, not all high-risk children delivered via C-section develop T1D (4). In a Norwegian case-control study, a *PTPN22* (protein tyrosine phosphatase, nonreceptor type 22) polymorphism has been shown to increase T1D risk if the child was delivered vaginally (7), underscoring the importance of exploring potential interactions between perinatal exposures and susceptibility genes in the pathogenesis of T1D. Genome-wide association studies have identified the *IFIH1* gene to be associated with T1D (8). *IFIH1* is a helicase enzyme that produces type 1 interferon in response to viral infections, such as enteroviruses. It has been proposed that *IFIH1* is activated by exposure to a virus to produce type 1 interferons, which leads to an upregulation of major histocompatibility complex class 1 on β-cells, thus increasing autoreactive $CD8^+$ cytotoxic T lymphocyte recognition of β-cells (9). Liu et al. (10) analyzed 13 single nucleotide polymorphisms (SNPs) in the 450kb *IFIH1* genomic region and identified four variants to be significantly associated with T1D in two large U.S. Caucasian cohorts (rs3747517, rs1990760, rs2111485, and rs13422767). Their analysis revealed that the major allele (G) carriers were at higher risk of T1D with the highest risk conferred to those with the homozygous genotype (GG), even after adjustment for sex, diagnosis age, and *HLA-DQB1* genotypes. Additionally, they found that *IFIH1* expressivity was significantly higher for the major allele homozygous genotypes. Carriers of the *IFIH1* major allele polymorphism have a higher *IFIH1* expression, which possibly controls the immune response to environmental exposures and increases the risk for T1D (10).

Bonifacio et al. (11) proposed an interesting and novel explanation for the observed association between C-section delivery and increased T1D risk that this group and others had previously reported (Fig. 1). First, C-section delivery, a surrogate marker for early life microbiota, specifically influences progression from a preclinical disease state (autoimmunity) to T1D. Second, this progression is further enhanced in the presence of genes that modulate the immune response to environmental agents, such as the *IFIH1* polymorphism. As a result, the highest risk of progression is seen in children exposed to both environmental and genetic factors associated with immune response modulation. Such findings, if replicated in other populations, offer novel avenues for prevention of T1D through interventions affecting host's immune response to environmental agents and likely targeted at children who have already developed autoimmunity.

The BABYDIAB study provides a mature cohort of children identified at birth and prospectively followed for the development of T1D. Several limitations inherent to this cohort exist and include the fact that this is not a population-based cohort but one enriched with individuals at high genetic and familial risk for autoimmunity and T1D. The high genetic risk apparently has no effect on the findings reported here, given that both this and a previous study reported no association between *HLA* and *IFIH1*; however, the high prevalence of maternal T1D, which has been shown to protect against development of autoimmunity (12), may obscure some associations. Another important challenge is the small number of children with T1D, which likely led to some of the findings being of marginal statistical significance. Moreover, although the researchers reported similar gene associations with T1D for *CD25* (i.e., α-chain of the interleukin-2 receptor) and *IFIH1* (10,13), they were unable to report an association for *PTPN22* (7). Furthermore, the *IFIH1* SNP chosen for the analysis has been shown to have no effect on any known

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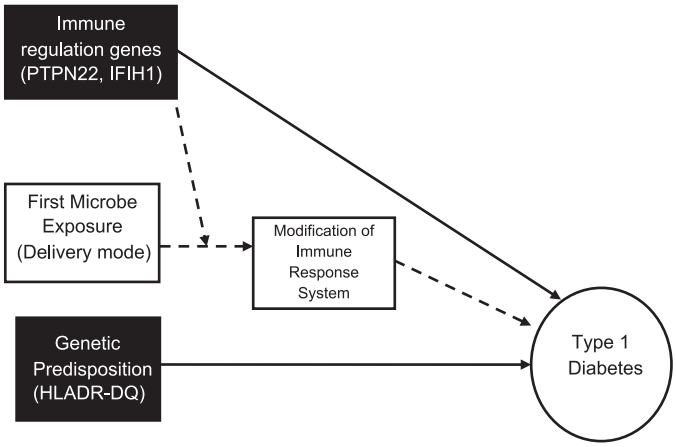

FIG. 1. Hypothesized gene-environment interaction in the pathogenesis of T1D. Dotted arrows, pathway under investigation.

transcriptional factor binding sites, or contributing to the regulation of *IFIH1* expression. Nevertheless, it was shown to be in strong linkage disequilibrium (r^2 = 0.85) with a known nonsynonymous *IFIH1* SNP rs1990760; thus, even though the analyzed SNP is intergenic and not nonsynonymous, it is likely a good surrogate SNP for rs1990760 (10).

The most important contribution of this study to the current knowledge of T1D determinants is that it furthers our understanding of the complex interplay between genetic susceptibility, early life environmental exposures, and the innate immune response contributing to the pathogenesis of T1D. Although these new findings and proposed potential mechanisms are novel and exciting, further exploration and replication in larger cohorts of children without familial T1D are needed. The Environmental Determinants of Diabetes in the Young (TEDDY) study provides an excellent opportunity, based on a large international cohort of predominantly general population (although high-risk) children, to replicate these associations and further elucidate the proposed mechanisms and their contribution to the development of both autoimmunity and T1D.

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