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Review

Environmental Risk Factors and Type 1 Diabetes: Past, Present, and Future

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ABSTRACT

Type 1 diabetes is an autoimmune condition that results from the destruction of the insulin-producing beta cells of the pancreas. The excess morbidity and mortality resulting from its complications, coupled with its increasing incidence, emphasize the importance of better understanding the causes of this condition. Over the past several decades, a substantive amount of work has been done and, although many advances have occurred in identifying disease-susceptibility genes, there has been a lag in understanding the environmental triggers. Several putative environmental risk factors have been proposed, including infections, dietary factors, air pollution, vaccines, location of residence, family environment and stress. However, most of these factors have been inconclusive, thus supporting the need for further study into the causes of type 1 diabetes.

RÉSUMÉ

Le diabète de type 1 est une maladie auto-immune qui résulte de la destruction des cellules bêta du pancréas produisant l'insuline. La surmorbidité et la surmortalité qui découlent de ses complications, en association avec son incidence croissante, soulignent l'importance d'une meilleure compréhension des causes de cette maladie. Au cours des dernières décennies, un nombre considérable de travaux ont été réalisés et, quoique de nombreuses percées dans l'identification des gènes de prédisposition à la maladie sont survenues, il y a eu un décalage dans la compréhension des déclencheurs environnementaux. Plusieurs facteurs environnementaux présumés à risque ont été proposés, dont les infections, les facteurs alimentaires, la pollution de l'air, les vaccins, le lieu de résidence, l'environnement familial et le stress. Toutefois, comme la plupart de ces facteurs n'ont pas été concluants, il est donc nécessaire de réaliser d'autres études sur les causes du diabète de type 1.

Introduction

Type 1 diabetes is caused by inflammation and selective autoimmune destruction of the beta cells of the pancreas, resulting in insulin deficiency (1). Type 1 diabetes has a strong genetic component, and over the past several decades multiple loci have been identified (2). Human leukocyte antigen (HLA) class II molecules, DQ and DR, within the MHC locus are implicated in up to 95% of cases of type 1 diabetes, particularly the expression DQ2, DQ8, DR3 or DR4 (1–2). Other genes include the insulin gene on chromosome 11, contributing to about 10% of the genetic susceptibility, and regulators of T-cell activation (1). Only 30% to 40% of identical twins both develop the disease, so genetic predisposition is not the sole contributor to disease development, lending support to other factors in the pathogenesis of type 1 diabetes (1).

In the 1980s, Eisenbarth proposed a model for the development of type 1 diabetes that is still pertinent today (3). At baseline, everyone is born with a degree of susceptibility to developing type 1 diabetes; this susceptibility is high for some and low for others. For example, approximately one-fifth of Caucasians have a genetic susceptibility to type 1 diabetes (4). The next step requires exposure to some environmental factors that trigger the development of autoimmunity and subsequent destruction of beta cells, leading to insulin deficiency (Figure 1). There is no cure, but exogenous insulin is available for survival and to minimize the serious

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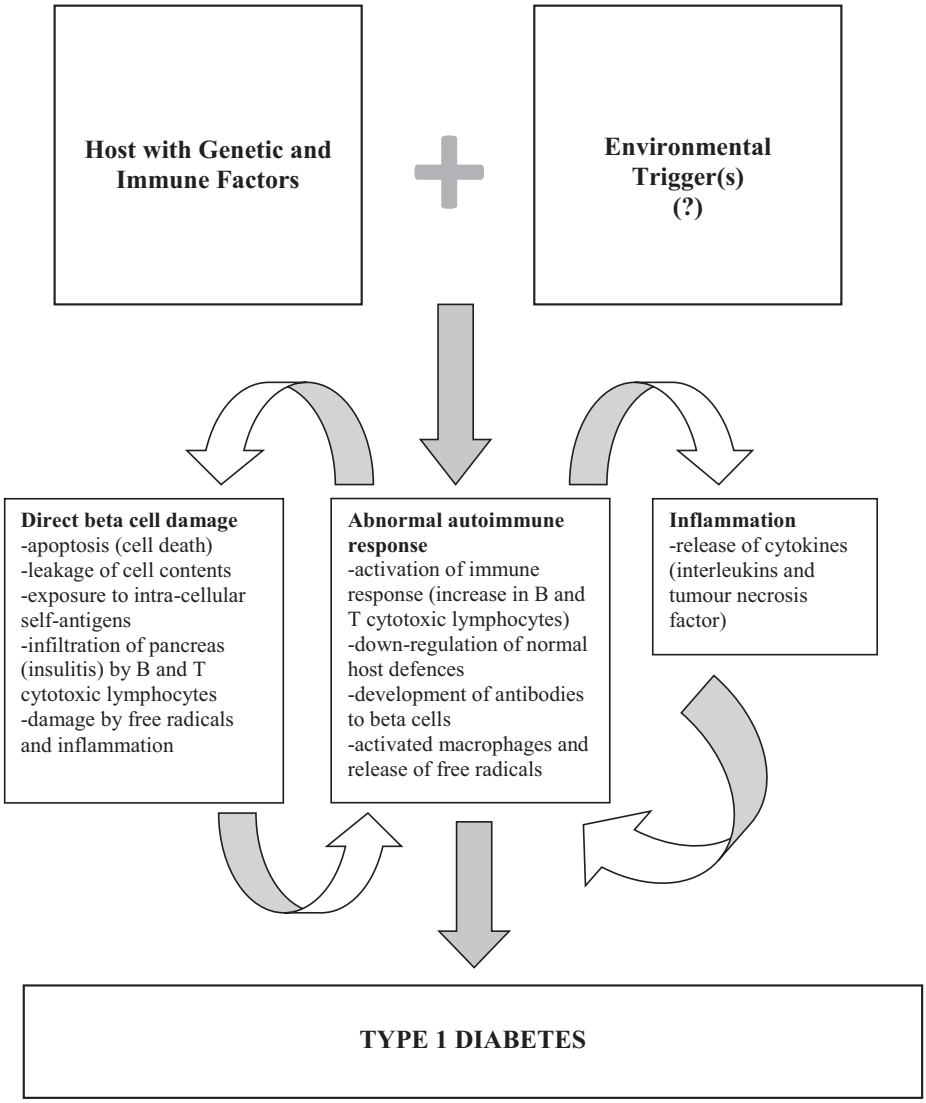

Figure 1. Environmental triggers in the pathogenesis of type 1 diabetes.

complications of diabetes, including kidney failure, adult blindness, lower-limb amputation and cardiovascular disease (1,5–7). Unlike other autoimmune conditions such as inflammatory bowel disease (IBD), type 1 diabetes has no relapse phase (8).

Although most attention to the diabetes epidemic focuses on the increase in type 2 diabetes, there is also a concerning rise in the incidence of type 1 diabetes, which is a global epidemic (8–14). Type 1 diabetes had a stable and relatively low incidence during the first half of the 20th century; however, the incidence of type 1 diabetes has been increasing worldwide by 3% to 5% per year since the 1960s, giving a doubling time of 14 to 23 years (8–15). The highest incidences of type 1 diabetes are most commonly observed in industrialized nations, including Finland, Sweden, Canada and the United Kingdom, but with improved epidemiologic surveillance, we are also appreciating high incidence rates in other areas, such as Egypt, India and Saudi Arabia (9,16–18). The highest incidence is in Finnish children, with 40 cases per 100,000 (age-adjusted) per year followed by rates in Canada and the United Kingdom, which are estimated to be between 13 and 25 per 100,000 (age-adjusted) per year (9,16).

Environmental factors are believed to be responsible for the increase in the incidence of type 1 diabetes because genetics alone could not explain the changes observed in the short time frame. The lines of evidence supporting the role of environmental risk factors include: 1) migration studies showing increased incidence in groups who have moved from areas of low incidence to those of high incidence (19–20) 2) a shift to earlier onset of disease (21); 3) increased incidence in all age groups (9) and 4) greatest increase in rate of incidence observed in previously low-incidence countries (8,10). Furthermore, the increases in incidence and prevalence rates of type 1 diabetes are most marked in the very young and in countries experiencing rapid economic growth, again suggesting a relationship with environmental factors (17). A number of environmental factors have been explored in studying the pathogenesis of type 1 diabetes. In this article, we summarize the current literature concerning the most commonly studied environmental factors and their connection with the development of type 1 diabetes.

Trigger hypothesis

Several theories have been proposed to link type 1 diabetes and environmental factors. One favoured hypothesis is the trigger hypothesis, which proposes that an environmental agent triggers the pathogenesis of type 1 diabetes. Some factors may initiate the autoimmune process, whereas other factors may drive beta-cell autoimmunity