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Review

Type 1 diabetes: Through the lens of human genome and metagenome interplay

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ABSTRACT

Diabetes is a genetic- and epigenetic-related disease from which a large population worldwide suffers. Some genetic factors along with various mutations related to the immune system for disease mechanism(s) have contrastively been determined. However, sometimes mechanisms have not been fully managed for the clarification of the initiation and/or progression of diseases to help patients. In the recent years, due to familiarity with the role of gut microbiota in the health, it has been found that the changes of the microbial balance in the industrialized societies can cause a battery of modern diseases, for which we have no specific definition of how they emerge. This work aims to explore the relationship between the human gut microbiota and the immune system along with their possible role in avoiding/emerging of type 1 diabetes (T1D) accompanied with the relation between genome and metagenome and their imbalance in causing T1D. Moreover, it provides novel view on how to balance the intestinal microbiota by lifestyle to hinder the mechanisms leading to T1D.

1. Introduction

Type 1 diabetes is a complex disorder whose cause is an intricate interplay of various factors. When viewed through the lenses of immunologic, T1D is mediated through (a) the activation of autoreactive lymphocytes, (b) the production of autoantibodies, and (c) the inevitable destruction of T-cell-mediated pancreatic β-cells in genetically predisposed individuals [1]. Because of the severity of T1D and its complications, it should be noted that the observed increase of the disease over the past several decades is of great concern, which is unfortunately at a rate far beyond the rate of the population growth. Rapid changes in the environment, modern lifestyle, and nutrition are contributors to such increase [2].

Although there are large genetic components associated with T1D, reports on mutations associated with the disease have been controversial in different populations [3,4]. In addition, it should be highlighted that the genetic susceptibility in the early life requires a decade or more time course to autoimmunity become apparent and symptomatic. Moreover, intriguingly, in monozygotic twins, the concordance rate of T1D is only 50%, which makes genetic involvement in the disease disputable and uncertain. Such inconsistencies imply that additional components, aside from the genetic counterpart(s), may somehow play a key role in triggering the pathogenesis of the disease, which has influenced the T1D investigations in the recent decades [5].

As demonstrated in Fig. 1, various environmental factors have been proposed to trigger the autoimmunity within islet, including birth delivery mode (natural or cesarean section), infant feeding (breastfeeding or cow's milk), birth weight [6], viral infections, molecular mimicry between certain viral/bacterial and β-cell antigens, certain dietary components (gliadin, cereal), increased pharmaceutical use (especially antibiotics), improved sanitation, and decreased childhood infections [7–11]. These factors probably contribute to the disease development either through triggering the early autoimmune responses or modifying this disastrous process at different times throughout the disease [12]. Further, it should be articulated that all the environmental stress-related causes can influence the bacterial population of the gut (microbiota).

Of note, the human body hosts a huge number of bacterial species as the second genome (the so-called bacterial combined genomes or metagenome) that encompasses 150-fold more genes than that of the human perse [13] and plays key roles in terms of the health and diseases. The crosstalk between the human and microbiota along with

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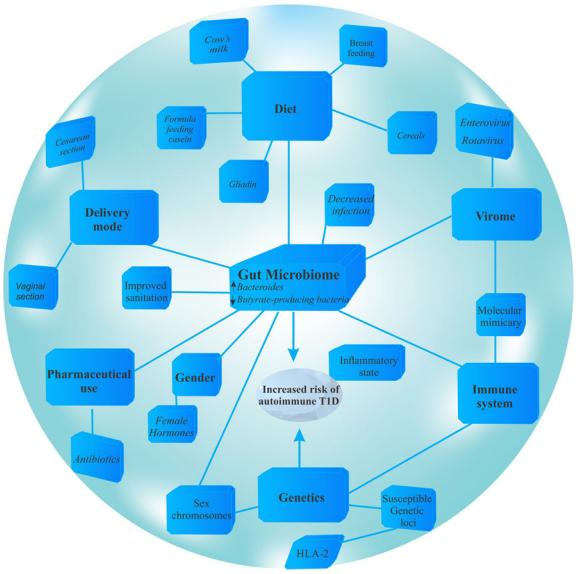

Fig. 1. The complex network between the genetics, and gut microbiota in the development of T1D. Both genetic and environmental factors can affect the development of the gut microbiota including mode of delivery, diet, pharmaceutical use, and virome. On the other hand, microbiota as human second genome (metagenome), in crosstalk with genome can modify their epigenetic, metabolome, and physiologic state and cause T1D disease. Environmental stress-related factors (as the italicized words show) can alter the gut bacterial population. In turn, aberrant intestinal microbiota can alter immune responsiveness and contribute to T1D development.

their metabolome (the complete set of metabolites produced by the gut inhabitant microorganisms) maintain human health in a way that the slightest imbalance may make one susceptible to a variety of metabolic and modern diseases such as T1D.

The following sections review the connotation between the human microbiota crosstalk and the immune system in the pathogenesis of T1D, focusing on how alterations in the composition of gut microbiota might rigorously affect the disease. Furthermore, the mechanisms by which the gut microbiota imbalances cause the development of T1D are reviewed and some novel insights on how to balance the gut microbiota by lifestyle to hinder the mechanisms leading to T1D are put forward.

2. The human genome and metagenome

T1D is the consequence of a complex process causing the interaction between genetic and environmental factors.

2.1. Genome in T1D

T1D is believed to have a robust genetic component because it has a significantly high correspondence with monozygotic twins and effectively influences families with a high sibling risk. More than twenty different chromosomal regions and more than 40 genetic loci have been shown to associate with T1D in multiple studies [14]. A long table of genetic loci associated with T1D has also been reported (available at: www.T1DBase.org), which provides some important information on (a) specific polymorphisms in the human leukocyte antigen (HLA) [15], (b) cytotoxic T lymphocyte-associated protein 4 (CTLA-4) [16], and (c) lymphocyte-specific protein tyrosine phosphatase (PTPN22) genes [17]. In spite of the presence of a large genetic component related to T1D, uncovering the causative genes is difficult since studies on diabetic patients genome screening together with gene polymorphism have reported several controversial results in different populations [4]. Therefore, there is a growing demand for some thorough investigations to resolve the genetic discrepancies in the diabetic patients. These evidence along with the statement that the risk of T1D for monozygotic twins is not 100% suggest that genetic factors, on their own, cannot account for the emergence or deterrence of the disease, but rather, the environmental factors (in particular gut microbiota) forming human metabolome should be taken into account. Taken all, consideration of these parameters (as natural or lifestyle-dependent factors) can significantly affect the initiation or prevention of the disease and even guaranteeing or threatening the health integrity.

2.2. Metagenome in T1D

Of environmental factors, the gut microbiota has gained attention in recent years [18]. Compelling evidence to date strongly highlights the impact of intestinal microbiota, mainly via their effect(s) on gut structure/functionalities and also development of the immune functions, on the pathogenesis of T1D. Accordingly, numerous lines of evidence not only suggest that gut is an important element in the progression of T1D as a factor or place for the initiation of β-cell autoimmunity, but also that the manipulation of gut microbiota offers potentials for postponing and perhaps even preventing the disease [19]. However, understanding the mechanism(s) and effect(s) of gut microbiota on the changing incidence of T1D at different time courses of life within different populations remains to be fully uncovered.

The human gastrointestinal tract (GIT) harbors a complex, symbiotic, and active population of microorganisms composed of at least 1000–5000 different species, which have co-evolved with human [20–23]. The ecosystem of gut microbiota is markedly changed by the birth delivery mode, during the first year of life, and is further affected by the breastfeeding, and the introduction and consumption of foods [19]. At the start, the microbiota is dominated by *Enterobacteriaceae* and *Staphylococci* that are oxygen-tolerant species, then compelling anaerobes take over like *Bifidobacteria*, *Clostridia*, and *Eubacteria*. After few years, the microbiota of child has a tendency to be like the composition of the adults [24,25]. It should be expressed that the human intestinal microbiota is comprised of four main phyla: *Proteobacteria, Firmicutes, Actinobacteria,* and *Bacteroidetes,* 90% of which belongs to the *Firmicutes* and *Bacteroidetes*. The composition of the adult gut microbiota displays some commonalities and some differences, that is to say, approximately 50% of bacterial species is carried by 50% of the population while the rest of it seems to differ among individuals, rendering the total microbiota composition – perhaps, unique for every individual.

Microbiota and its collective genomes encode more unique genes with respect to humans and provide the host with genetic and metabolic attributes and a wide range of enzymes as well as metabolites [26]. Consequently, it provides human with novel functions and strongly influences health, development, nutrition, immunity, homeostasis, and diseases [27–30]. The gut microbiota is an important factor in the regulation of several metabolic pathways. Ample evidence is indicative of the fact that the cross-talk between the host and gut bacteria is achieved via specific metabolites such as short-chain fatty acids (SCFAs) and molecular patterns of microbial membranes such as lipopolysaccharides (LPS), which activate the host cell toll-like (TLRs) and G-protein-coupled receptors (GPCRs).

Microbiota is in constant interaction with the host metabolism benefiting his/her health via different mechanisms. It influences energy metabolism by breaking down indigestible food, facilitating absorption of complex carbohydrates, and regulating the fat storage and systemic lipid homeostasis of the host. Microbiota also regulates the digestion process through mediating bile acid and vitamin synthesis (in particular, vitamin K and group B vitamins), lysine and threonine metabolism, and lipid absorption. Further, it contributes to the nitrogen and micronutrient homeostasis. Most importantly, through nutrient- and metabolite-dependent mechanisms, microbiota and its byproducts are able to regulate the homeostasis, development, and function of the immune system [23,31], upon which it can directly/indirectly regulate the production of immune modulators posing anti-inflammatory effects