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Invited Review-pharmacology across disciplines

Antibiotics, gut microbiota, environment in early life and type 1 diabetes

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ABSTRACT

The gut microbiota interact with innate immune cells and play an important role in shaping the immune system. Many factors may influence the composition of the microbiota such as mode of birth, diet, infections and medication including antibiotics. In diseases with a multifactorial etiology, like type 1 diabetes, manipulation and alterations of the microbiota in animal models have been shown to influence the incidence and onset of disease. The microbiota are an important part of the internal environment and understanding how these bacteria interact with the innate immune cells to generate immune tolerance may open up opportunities for development of new therapeutic strategies. In this review, we discuss recent findings in relation to the microbiota, particularly in the context of type 1 diabetes.

Contents

1. Gut microbiota and type 1 diabetes

Type 1 diabetes (T1D) is a T cell-mediated autoimmune metabolic disease which is commonly seen in children and young adults [1] although it can also present in older adults. The insulin-producing beta cells of the pancreatic islets are damaged and destroyed by activated autoreactive T cells resulting in disordered blood glucose regulation [2]. This destruction is the result of a complex interaction between genetic susceptibility genes and environmental factors [3,4]. Genetic screening has shown that certain major histocompatibility complex (MHC) class II genes, also called human leukocyte antigen (HLA) genes, *DQA1*0301* (DQ2), *DQB1*0302* (DQ8), *DRB1*DR301* (DR3) and a number of DR4 alleles are associated with susceptibility to T1D in patients [5,6]. However, only a small portion of individuals carrying those alleles will develop T1D [7]. Yet, a sharp rise of T1D incidence has been seen in recent years [8] in a time frame that is not sufficient for genetic change, indicating that environmental factors may play a crucial role in diabetes development [9]. Prenatal influence, viral infections, dietary factors in the young as well as "hygiene" can all affect the disease onset [10]. More recently, several studies have shown commensal microbiota to be connected with the development of this autoimmune disease [11]. Although triggering factors for T1D have not yet been clearly identified, the gut microbiota are believed to play an important role in the development of the disease [12,13].

The gut microbiota are associated with the development of several diseases including obesity and type 2 diabetes [14], liver disorders [15], intestinal inflammatory syndromes [16], allergic diseases [17], disorders in the central nervous system [18], and

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especially, autoimmune diseases [19–22]. We, and others, have recently reported that alteration of gut microbiota by pharmacological means can protect from or accelerate T1D development in non-obese diabetic (NOD) mice [23–27], a well established animal model for T1D research [28].

We were among the first to demonstrate that the gut microbiota shape the NOD mouse innate immune system [11]. MyD88 is a central adaptor in most innate immune Toll-like receptor signaling pathways and MyD88-deficient NOD mice do not develop autoimmune diabetes in a clean, but not sterile, housing environment; however, germ-free MyD88-deficient mice develop full-blown diabetes [11]. This indicates that commensal bacteria, especially gut bacteria play a very important role in triggering the autoimmune disease. When a defined microbial mixture was introduced orally into the germ-free MyD88-deficient mice, diabetes development in these mice was attenuated [11]. Similar results were later observed in different mouse models of human diseases including Celiac Disease [29], obesity/type 2 diabetes [30], and autoimmune uveitis [31].

There are 10-fold more microorganisms residing in the gut than the total number of human cells [32], and they protect the host from infection by various pathogens [33]. The main roles of gut bacteria are to aid in nutrition derived from the diet and to generate energy. A healthy microbiota composition helps to keep the gut epithelia intact and reduce permeability [34,35]. Furthermore, the interaction between gut epithelia and the bacteria promotes the development of a normal immune system [36,37]. Several reports have demonstrated that colonization by some specific bacteria in the gut can protect mice from developing type 1 diabetes; these bacteria include SFB (Segmented Filamentous Bacteria) [38], *Lactobacillus johnsonii* N6.2 [39], as well as some Streptococcal species [40], and glycoprotein extracts from *Klebsiella pneumoniae* [41].

2. Modification of the gut microbiota

Although controversial, germ-free mice [11,42–44] may have accelerated T1D. Conversely, there has been speculation that gut bacteria may trigger T1D development in genetically susceptible humans [45] and mouse models of T1D [46]. One possible means by which this could occur could be transfer of metabolites or cell components of the bacteria through a “leaky” gut wall and uptake by antigen presenting cells, processing and presentation of the antigen to activate T cells [47]. Tight junctions represent the major barrier within the paracellular pathway between intestinal epithelial cells. Alterations in intestinal permeability allow access of bacterial toxin [45], infectious agents and dietary antigens from the lumen to mucosal immune elements [48,49]. Another possible mechanism is some bacterial product(s) share the molecular homology with islet autoantigen(s) and the islet beta cells are attacked by the immune cells that are reactive to the bactierial antigens [46].

Autoantibodies have been observed in T1D patients as young as several months old [50,51]. Animal model studies have also shown that alteration of gut microbiota early in life, and gut permeability are important in shaping the host immune system [25,52,53], especially at the prenatal or neonatal stages.

Efforts have been made to investigate which bacteria in the gut may be beneficial or harmful in the development of T1D [45,46,54–57]. Researchers have studied altered gut microbiota in experimental mice after treating with a combination of 4 antibiotics, including Ampicillin, Metronidazole, Neomycin and Vancomycin [58]. Although there are studies using germ-free (GF) mice to test whether one or more species of bacteria introduced into the mice has an impact on diabetes development [42,59], which species are probiotic and which are detrimental have not been conclusively determined, as most of the bacteria in the gut are non-culturable.

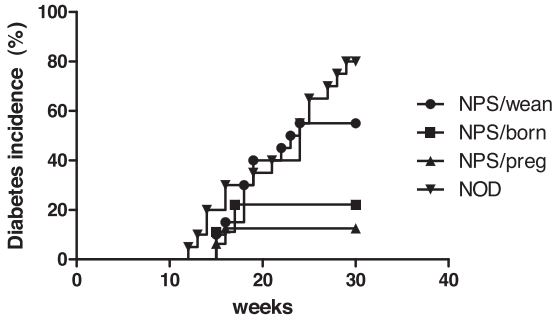

Fig. 1. Maternal antibiotic treatment protects offspring from diabetes development in NOD mice. Antibiotic treatment (3 week) starting at different times of life led to a different phenotype of T1D development. NPS (Neomycin/Polymyxin B/Streptomycin); NPS/preg (NOD offspring from mothers treated with NPS during pregnancy); NPS/born (NOD treated with NPS from birth to weaning); NPS/wean (NOD treated with NPS immediately after weaning). The change in diabetes incidence was dependent on the time of antibiotic treatment.

Other studies have been conducted using vancomycin, a specific gram-positive bacterial inhibitor, to modify the gut bacteria. Antibiotic intervention during the prenatal period revealed an acceleration of diabetes onset [27,60], whereas NOD mice receiving vancomycin from birth onwards gave the opposite result [52]. Recently, Brown and colleagues showed that using Neomycin and Vancomycin to treat NOD mouse pups from the neonatal period for their lifetime [61] accelerated diabetes development. These studies indicated that the time at which antibiotic treatment is commenced is crucial and that treating the mothers may be a way of having an effect while avoiding direct administration of the antibiotics to the pups. Many of these studies used an approach giving long-term antibiotic treatment, although long-term antibiotic treatment rarely occurs in humans. Thus, the advantage of studying short-term treatment makes the studies in animals closer to humans [25,27]. In addition, human studies have shown that approximately 30% of pregnant women in the USA have had a short-course of antibiotic medication during their pregnancy [62] and the number could be higher in other countries. It should be noted that long-term antibiotic treatment could cause resistant bacteria to propagate in the gut [63].

3. Protective bacteria that arise from pharmacological alteration of gut microbiota in early life

The colonization of gut microbiota is strongly influenced by microbial exposure at birth [64]. When antibiotic treatment is used to study the effect of gut microbiota on disease, it is clear that the timing of administration, duration of treatment, as well as the type of antibiotic used must be taken into account. We have published a study showing that Neomycin/Polymyxin B/Streptomycin- treated NOD mice were protected from T1D development [25]. This protection was more significant when mice were treated at the prenatal stage (Fig. 1, adapted from Ref. [25])

It is clear that the earlier the NOD mice received the antibiotics, the better the protection from diabetes development. In our study, NOD mice treated with NPS at different time points early in life delayed and overall reduced T1D onset. When pregnant mothers were treated with antibiotics, the offspring were most protected from diabetes, while mice receiving antibiotics from birth or weaning were also protected from disease development although this was not statistically significant. Here, not only did the NPS treatment generate a gut bacterial composition that was protective but it was also clear that the timing of treatment was very important in