Journal of Autoimmunity 71 (2016) 10–18

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review article

Immune recognition and response to the intestinal microbiome in type 1 diabetes

Alexandra Paun [a, 1], Christopher Yau [a, b, 1], Jayne S. Danska [a, b, c, *]

[a] Program in Genetics and Genome Biology, Hospital for Sick Children, Toronto, ON, Canada
[b] Department of Immunology, University of Toronto, Toronto, ON, Canada
[c] Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada

ARTICLE INFO

Article history:
Received 28 January 2016
Received in revised form
3 February 2016
Accepted 4 February 2016
Available online 20 February 2016

Keywords:
Autoimmune diabetes
Gut microbiome

ABSTRACT

Type 1 diabetes (T1D) is an autoimmune disease resulting from T cell-mediated destruction of the insulin-secreting pancreatic beta cells. During the past 50 years T1D incidence has increased dramatically in many countries accompanied by an earlier age of onset especially in persons with lower genetic risk. These observations have prompted investigations of dynamic environmental factors that may contributor to risk for anti-pancreatic immunity. The gut and pancreas are anatomically and biochemically linked through the enteroinsular axis, a system in which gut-derived immune and metabolic signals have the potential to evoke effects in the pancreas. The gut microbiome (i.e. the 100 trillion symbiotic microorganisms which inhabit the mammalian gastrointestinal tract) influences numerous aspects of host metabolism, development and immunity. Here we examine recent evidence linking gut microbiome composition and function to pancreatic autoimmunity. Studies in children with genetic risk factors for T1D and analyses of the microbiome in rodent models have begun to associations between an altered microbiome composition potentially favoring a pro-inflammatory intestinal metabolic milieu and T1D. We discuss how environmental factors during critical developmental windows – gestation, birth, weaning and puberty may contribute to T1D risk. For example mode of delivery (vaginal or C-section) and exposure to antibiotics (pre- or post-natally) are two factors that modulate the maternal and/or offspring microbiome and can impact T1D development. Taken together, these emerging data underscore the requirement for longitudinal studies and mechanistic investigations in human subjects and rodent models to identify the basis for microbiome modulation of T1D and to identify biomarkers and therapeutics to improve the delayed onset and prevention of the disease.

Contents

* Corresponding author. Peter Gilgan Research Tower, 686 Bay St., Toronto, ON M5G0A4, Canada.
E-mail address: jayne.danska@sickkids.ca (J.S. Danska).
[1] Authors contributed equally to this work.

http://dx.doi.org/10.1016/j.jaut.2016.02.004
0896-8411/

1. Epidemiology of T1D: evidence for genetic and environmental factors

Type 1 diabetes (T1D) is an autoimmune disease characterized by a T-cell driven attack on the insulin-secreting pancreatic beta cells. Haplotypes at the human leukocyte antigen loci are strongly associated with heritable risk of developing T1D and more than a decade of genome wide association studies have identified an additional 40 common polymorphisms associated disease susceptibility [1]. In addition to the strong evidence for heritable factors, multiple lines of evidence identify the influence of poorly defined environmental and epigenetic factors disease risk. Disease concordance in monozygotic twins has been assessed at less than 50% [2]. Over the last 50 years, multiple immune-mediated diseases have seen a dramatic rise in frequency in childhood. They include T1D, inflammatory bowel diseases and asthma. T1D incidence has increased at a rate of 3–4% per year, and the age at onset has declined over the past 50 years [3]. An increasing frequency of patients harbor lower-risk *HLA* class II haplotypes compared to those diagnosed 50 years ago. These trends suggest that environmental factors, particularly affecting younger children at lower genetic risk, account for the increased incidence [4,5]. In a recent report from The Environmental Determinants of Diabetes in the Young (TEDDY) study, the development of the first islet autoantibody was evident during the first nine months of life, suggesting that prenatal or early post-natal exposures may trigger early autoimmune progression [6]. Thus the recent increase in T1D frequency likely reflect dynamic changes in our environment, including diet, physical activity, hygiene, and use of antibiotics in agriculture and medicine. These factors impact on our exposures to pathogenic microbes as well as the composition of microbial communities that inhabit mucosal tissues where they regulate host immunity and metabolism. The intestinal ecosystem of bacteria, fungi and viruses, (collectively the “microbiome”) is emerging as a critical interface between a dynamic external environmental and host immune homeostasis.

How can microbes in the gut influence autoimmune responses in the pancreas? Increased gut permeability and microbial translocation into the systemic circulation has been identified in several diseases. One cause of immune activation in patients with chronic HIV infection is microbial translocation, likely from the gut, evidenced by elevated levels of LPS, soluble CD14 [7] and bacterial rDNA [8] observed in sera. Alterations in intestinal permeability and structure have been reported in human subjects either preceding T1D onset or concomitant with the disease [9,10] [11]. There is also some evidence for increased gut permeability in the non-obese diabetic (NOD) mouse model [12,13]. Whether gut barrier compromise contributes to autoimmune pancreatic infiltration, or results from a disrupted microbial community secondary to T1D, is unclear. Alternatively, the anatomical connection and reciprocal signaling by nutrients, hormones and neural signals of the entero–insular axis [14] may enable systemic immune sensing of host–microbial interactions even in the presence of an intact gut epithelial barrier. The key knowledge gaps are a lack of evidence for specific role(s) of intestinal microbes in the T1D development, and how the immune system responds to changes in gut microbiome composition that may accompany progression to T1D. Recent advances in analysis of the composition and function of the gut microbiome in rodent models and human subjects are enabling us to begin to address these questions.

2. Mucosal ecosystems

The 10^{14} bacterial cells found in the human gastrointestinal tract outnumber host cells 10:1 [15,16]. In humans bacteria are present on the skin, digestive, respiratory and genitourinary mucosa, but the gastrointestinal tract comprises by far the highest density of microbes, 10^{12} per gram of luminal contents, roughly 1.5 kg of bacteria, with a coding capacity of over 3 million genes [17]. The importance of gut microbes to host nutrition such as processing of indigestible carbohydrate and in vitamin synthesis has been known for decades [18]. However, the difficulty of culturing these largely anaerobic, often fastidious microbes using classical anexic microbiology methods has limited our appreciation of their roles in host biology. Recent advances in culture-independent, high-throughput sequencing [19] methods and analytical techniques have enabled an appreciation of the gut microbiome as a bona fide “organ”, an integral regulator to human physiology. Two global initiatives, the Human Microbiome Project and MetaHIT, have employed 16S rRNA gene HTS and, more recently, whole genome sequencing (metagenomic analysis) of human microbiomes. These collaborative projects have contributed critical microbial reference genomes for analysis of complex microbiota and have advanced our understanding of the composition of microbial communities at various mucosal sites, during human development, and in human disease [20,21]. Many groups are now studying the interactions between the gut microbiome and the development of host immunity as well as its roles in autoimmune, inflammatory and neoplastic diseases [22–24]. While microbiome complexity and inter-individual variation [25] currently limit unambiguous association of specific bacterial taxa with a given disease state, the consensus is that a diverse microbiota benefits the host, whereas decreased diversity and certain changes in composition (i.e. dysbiosis) are associated with autoimmune and inflammatory conditions [26–28]. Since specific biomarkers of islet autoimmunity, anti-islet autoantibodies are increasingly observed in infants and young children, an understanding of microbiome development in early life will be essential to designing experiments to test the role of this factor in T1D risk and progression.

3. Microbiome regulation of mucosal adaptive immunity

Gut mucosal surfaces are exposed to food antigens, commensal and pathogenic microbes and the immune system must maintain tolerance to food antigens and commensals while reacting to potentially invasive species [29]. Gut associated lymphoid tissues (GALT) are central to the constant crosstalk between food,-derived antigens, microorganisms and host immune cells. The GALT is the largest immunological organ in mammals, consisting of a network of secondary lymphoid organs (Peyer's patches and mesenteric lymph nodes (mLN)), tertiary lymphoid structures (cryptopatches and isolated lymphoid follicles) and immune cells dispersed in the lamina propria [30] and intraepithelial spaces [31]. Exposure to commensal microbiota is essential to the normal development and