Where genes meet environment—integrating the role of gut luminal contents, immunity and pancreas in type 1 diabetes

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The rise in new cases of type 1 diabetes (T1D) in genetically susceptible individuals over the past half century has been attributed to numerous environmental "triggers" or promoters such as enteroviruses, diet, and most recently, gut bacteria. No single cause has been identified in humans, likely because there are several pathways by which one can develop T1D. There is renewed attention to the role of the gut and its immune system in T1D pathogenesis based largely on recent animal studies demonstrating that altering the gut microbiota affects diabetes incidence. Although T1D patients display dysbiosis in the gut microbiome, it is unclear whether this is cause or effect. The heart of this question involves several moving parts including numerous risk genes, diet, viruses, gut microbiota, timing, and loss of immune tolerance to β-cells. Most clinical trials have addressed only one aspect of this puzzle using some form of immune suppression, without much success. The key location where our genes meet and deal with the environment is the gastrointestinal tract. The influence of all of its major contents, including microbes, diet, and immune system, must be understood as part of the integrative biology of T1D before we can develop durable means of preventing, treating, or curing this disease. In the present review, we expand our previous gut-centric model based on recent developments in the field. (Translational Research 2017;179:183–198)

Abbreviations: BBdp = BioBreeding Diabetes-prone (rat); CAMP = cathelicidin antimicrobial peptide; CD14 = cluster of differentiation 14; CD163 = cluster of differentiation 163; CRAMP = cathelicidin-related antimicrobial peptide; CCL2 = C-C Motif Chemokine Ligand 2; CCL5 = C-C Motif Chemokine Ligand 5; CCL3 = C-C Motif Chemokine Ligand 3; cMLN = colonic mesenteric lymph nodes; CTLA4 = Cytotoxic T-lymphocyte associated antigen 4; CXCL9 = Chemokine (C-X-C motif) ligand 9; CXCL10 = Chemokine (C-X-C motif) ligand 10; CXCL11 = Chemokine (C-X-C motif) ligand 11; DIPP = Diabetes Prediction and Prevention Trial; dsRNA = double-stranded ribonucleic acid; EGFR = epidermal growth factor receptor; GAD = glutamic acid decarboxylase; GM-CSF = granulocyte-macrophage colony-stimulating factor; GWAS = genome-wide association studies; HC = hydrolyzed casein; HLA = human leukocyte antigen; HO-1 = heme oxygenase-1; IEL = intra epithelial lymphocyte; IL2RA = interleukin-2 receptor alpha chain; IL-6 = interleukin-6; IL-8 = interleukin-8; IL-10 = interleukin-10; LPS = lipopolysaccharides; MHC = major histocompatibility complex; MLN = mesenteric lymph nodes; NOD = non-obese diabetic (mouse); PBMC = peripheral blood mononuclear cells; PLN = pancreatic lymph nodes; PTPN22 = protein tyrosine phosphatase, non-receptor type 22; RNA = ribonucleic acid; rRNA = ribosomal ribonucleic acid; sMLN = small intestinal mesenteric lymph nodes; SNP = single nucleotide polymorphism; T1D = Type 1 diabetes; TEDDY = The Environmental Determinants of

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Submitted for publication July 18, 2016; revision submitted August 30, 2016; accepted for publication September 1, 2016.

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1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2016.09.001

Diabetes in the Young Study; TLR4 = Toll Like Receptor 4; TRIGR = Trial to Reduce IDDM in the Genetically at Risk

Before the discovery of insulin in 1921, patients who developed type 1 diabetes (T1D) died not long after diagnosis. It is the most severe form of diabetes diagnosed mainly in children and young adults whose immune system destroys the islet β-cells. Nearly a century later, the treatment remains daily injections of insulin that do not restore normoglycemia, leading to complications that shorten life span.[1] The development of T1D is complex and occurs as a result of a combination of genetically determined chronic inflammatory processes[2] strongly linked to agents commonly encountered in the environment, many of which enter the body via the gut.[3] The vast majority of individuals who possess T1D risk genes do not develop T1D and ~85%–90% of cases do not have a first-degree relative with the disease.[3-5] There is no cure and recent clinical trials of immune suppression and antigen- and cell-based therapies have failed or shown only temporary benefit.[4] It is important to remember that no matter what treatment is attempted, even if it is temporarily successful, the original environmental conditions are still present and unless these are also modified or circumvented, the likelihood of relapse is high. To increase the chances of success in preventing or treating T1D, we must better understand and deal with the environmental factors that influence the development of this disease.

The nexus of interaction between self and nonself is the gastrointestinal tract where we are exposed to commensal and pathogenic microbes and dietary compounds[6] that the gut immune system must distinguish as either harmless (tolerance or anergy inducing) or harmful (immunogenic/inflammatory). It has been clear for some time that the environment is the major determinant of who will develop T1D and when this will occur.[3,7,8] From early reports of a strong influence of diet on T1D, it was evident a priori and later demonstrated that gut immunity must play a central role in pathogenesis.[8-10] Recently, the involvement of gut immunity has been re-emphasized as a result of studies linking the gut microbiome and T1D. Therefore, it is important to consider the gut immune system and the endocrine pancreas as part of an interconnected network strongly influenced by the contents of the gut lumen which include the microbiota (commensal bacteria, opportunistic pathogens, fungi, archaea, protozoa, and viruses) and dietary constituents. We have proposed an integrated model of T1D in which an ineffectively regulated gut immune system reacts inappropriately, adopting a pro-inflammatory state in response to common gut lumen antigens, resulting in a β-cell specific autoimmune attack.[3,8] In this review, we update our gut-centric view of T1D (Fig 1) and highlight recent findings that address these concepts as the field begins to expand (Box 1) from the immunogenetics era to include a detailed mechanistic analysis of the many environmental constituents that comprise what has been termed "The Exposome."[15,16]

THE PANCREAS PLAYS AN ACTIVE ROLE IN T1D

The pancreas is a complex organ that is not easily accessible for study. It was assumed for some time that the pancreas and islet β-cells played a passive role and were "normal" in those who developed T1D with the major fault being a dysregulated immune system. This concept led to the immunogenetics era with a strong emphasis on the major immune risk genes. Several genome-wide association studies (GWAS) confirmed the importance of selected major histocompatibility complex (MHC) class II region genes, insulin, cytotoxic T-lymphocyte associated antigen 4 (CTLA4), protein tyrosine phosphatase, non-receptor type 22 (PTPN22), interleukin-2 receptor alpha chain (IL2RA), and revealed numerous additional risk genes (>50 gene loci), most with odds ratios of <1.2.[5,17,18] Newer data demonstrate that human β-cells express as many as 50%–80% of the mostly immune candidate genes from GWAS analyses.[19] This unexpected finding raises the question of how these genes influence susceptible target β-cells and their interaction with the dysregulated immune system. Many of the risk loci are in the noncoding regions of the genome, suggesting potential involvement in the regulation of β-cells by noncoding ribonucleic acids (RNA).[17] Bergholdt et al[19] recently used a holistic approach to identify candidate genes by integrating GWAS, human islet gene expression, and protein-protein interaction data to reveal 3 cytokine-regulated networks and several T1D-related single nucleotide polymorphisms (SNP). Eizirik et al have also been at the forefront in studies of β-cell candidate gene and pathway discovery. They recently identified >15,000 genes within the human islet transcriptome using RNA seq and report that >60% of T1D candidate genes are present in the islet and 35% undergo alternative splicing. Exposing human islets to T1D-related pro-inflammatory cytokines or dsRNA revealed modification of some 3000 genes including several key chemokines (CCL2, CCL5, CCL3, CXCL9, CXCL10, CXCL11), cytokines (IL-6,