REVIEW ARTICLE

Innate inflammation in type 1 diabetes

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Type 1 diabetes mellitus (T1D) is an autoimmune disease often diagnosed in childhood that results in pancreatic β-cell destruction and life-long insulin dependence. T1D susceptibility involves a complex interplay between genetic and environmental factors and has historically been attributed to adaptive immunity, although there is now increasing evidence for a role of innate inflammation. Here, we review studies that define a heightened age-dependent innate inflammatory state in T1D families that is paralleled with high fidelity by the T1D-susceptible biobreeding rat. Innate inflammation may be driven by changes in interactions between the host and environment, such as through an altered microbiome, intestinal hyperpermeability, or viral exposures. Special focus is put on the temporal measurement of plasma-induced transcriptional signatures of recent-onset T1D patients and their siblings as well as in the biobreeding rat as it defines the natural history of innate inflammation. These sensitive and comprehensive analyses have also revealed that those who successfully managed T1D risk develop an age-dependent immunoregulatory state, providing a possible mechanism for the juvenile nature of T1D. Therapeutic targeting of innate inflammation has been proven effective in preventing and delaying T1D in rat models. Clinical trials of agents that suppress innate inflammation have had more modest success, but efficacy is improved by the addition of combinatorial approaches that target other aspects of T1D pathogenesis. An understanding of innate inflammation and mechanisms by which this susceptibility is both potentiated and mitigated offers important insight into T1D progression and avenues for therapeutic intervention. (Translational Research 2015;■:1–14)

Abbreviations: AAs = autoantibodies; AAT = alpha-1 antitrypsin; BB = biobreeding rat strain; BBDP = biobreeding diabetes prone; BBDR = biobreeding diabetes resistant; ELISA = enzyme-linked immunosorbent assay; GI = gastrointestinal; HLA = human leukocyte antigen; HRS = high-risk sibling (healthy, autoantibody negative, and possess DR3 and/or DR4 haplotype); IFN-α = interferon gamma; IL-1 = interleukin 1; IL-10 = interleukin 10; IL-1RN = interleukin 1 receptor antagonist; KRV = Kilham's rat virus; LRS = low-risk sibling (healthy, autoantibody negative, lacking either DR3 or DR4 haplotype); MHC = major histocompatibility complex; PBMC = peripheral blood mononuclear cell; Poly I:C = polyinosinic-polycytidylic acid; PRR = pattern recognition receptor; PTPN22 = protein tyrosine phosphatase nonreceptor type 22; RO T1D = recent-onset type 1 diabetes; T1D = type 1 diabetes mellitus; TGF-β = transforming growth factor β; TLR = toll-like receptor; Tregs = regulatory T lymphocytes; uHC = unrelated healthy control (no family history of type 1 diabetes)

Q2

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Q1

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INTRODUCTION

Type 1 diabetes mellitus (T1D) is an autoimmune disease in which the insulin-producing pancreatic β-cells are targeted and destroyed by infiltrating immunocytes, resulting in lifelong dependence on exogenous insulin. T1D is one of the most common chronic diseases of childhood with peak ages of onset at 5–7 years and again peripubertally.[1] Although residual β-cells have been detected in patients with even long-standing T1D, evidence supports that individuals present clinically after a significant loss of β-cell mass and function,[2,3] at which point glucose homeostasis can no longer be maintained. As such, hyperglycemia develops with classic symptoms of polyuria, polydipsia, and weight loss. Globally, the incidence of T1D has been increasing for more than the past several decades, with the number of new cases rising by approximately 3% per year in children and teens.[4]

T1D is a complex disease involving an interaction of multiple genetic loci and environmental factors, perhaps best reflected by the study of T1D in monozygotic twins who exhibit <100% concordance rates despite long-term follow-up.[5] The largest genetic contribution to T1D risk is conveyed by the human leukocyte antigen (HLA) locus, with >90% of patients possessing *DR3* and/or *DR4* HLA-DRB1 class II alleles compared with a carrier frequency of approximately 40% in Caucasians.[5,6] These high-risk alleles appear to be evolutionarily selected for their ability to present a broad range of microbial peptides to T cells, but are associated with many autoimmune diseases,[7] likely because of their propensity to also present self-peptides to T cells.[8] In addition to the HLA locus, genome-wide association studies have identified >40 additional loci that contribute lesser degrees of risk. Within these mapped regions reside disease-promoting genetic variants; many of the most highly characterized candidate genes encode protein products related to immune function (eg, *PTPN22*, *CTLA4*, *IFIH1*, *IL2RA*, and *SH2B3*).[9] The environmental triggers of T1D remain unknown, but the process of autoimmunity, once initiated, occurs for more than months to years.[10,11] During this time of declining β-cell function and mass, disease-specific but nonpathogenic autoantibodies (AAs) against β-cell autoantigens appear in various titers and combinations. These serve as a marker of β-cell autoimmune responses and risk of disease progression and are present in >90% of newly diagnosed T1D patients.[12] Notably, the risk of progressing to T1D increases with the number of detectable AAs, such that the presence of 2 or more AA indicates a >80% likelihood of developing T1D within 15 years.[13] However, there is considerable variability in the rate of progression from seroconversion (development of AA) to clinical T1D onset, ranging from weeks to decades.[14] The factors that govern this variability are not understood.

Historically, studies of T1D pathogenesis have focused on adaptive immunity; however, increasing attention is now being directed toward the role of innate immunity (reviewed in Zipris[15]). Studies by our group and others support the hypothesis that T1D pathogenesis involves increased innate immune activity coupled with failures in central and peripheral tolerance mechanisms that allow expansion of autoreactive T cells.[16,17] Several observations are driving an increased focus on innate immune processes in T1D pathogenesis: (1) monotherapies that have aggressively targeted and suppressed adaptive immunity have failed to induce sustained disruption in the underlying disease process,[18-20] whereas recent preclinical studies using combination therapies targeting both innate and adaptive immunities suggest greater efficacy.[21,22] (2) The increase in T1D incidence that has occurred in recent decades is too rapid to be because of solely genetic shifts; this is supported in part by the observation that those with "low risk" HLA genotypes now have the highest rate of increased T1D incidence.[23,24] These epidemiologic changes suggest the presence of environmental changes that potentiate autoimmunity, perhaps through dysregulated innate immune processes.

A full understanding of the mechanisms underlying age-dependent diabetes susceptibility remains unclear. This review will focus on recent studies that have identified a heightened innate inflammatory state associated with diabetes susceptibility in T1D families and T1D rat models; proposed mechanisms for how this baseline innate inflammation progresses to T1D, such as through viral triggering and defective immunoregulation; and how therapeutically targeting innate inflammatory processes may reduce disease incidence.

INNATE IMMUNITY AND INFLAMMATION IN T1D

The innate immune system plays a vital role as the first line of defense against microbial infection. Leukocytes of the innate immune system, which consist of natural killer cells, granulocytes (mast cells, eosinophils, basophils, and neutrophils), macrophages, and dendritic cells, function within the immune system by recognizing common microbial ligands and initiating generalized inflammatory responses against the microbe or infected cells (reviewed in Medzhitov[25]). Innate pattern recognition receptors (PRRs), including toll-like receptors (TLRs), RIG-I–like helicases (immunoreceptors for viral RNA), and nucleotide-binding oligomerization domain–like receptors, are largely responsible for this