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Review

Type 1 Diabetes and Type 1 Interferonopathies: Localization of a Type 1 Common Thread of Virus Infection in the Pancreas

Virginie S.E. Jean-Baptiste [a], Chang-Qing Xia [b], Michael J. Clare-Salzler [c], Marc S. Horwitz [a,*]

[a] Department of Microbiology and Immunology, Infection, Inflammation, and Immunity (I3) Research Group, Life Sciences Institute, University of British Columbia, Vancouver, British Columbia V6T 1Z3, Canada
[b] Department of Pathology, Immunology and Laboratory Medicine, University of Florida College of Medicine, Gainesville, Florida 32610, USA
[c] Department of Endocrinology, Diabetes and Metabolism, University of Florida College of Medicine, Gainesville, Florida, USA

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ABSTRACT

Type 1 diabetes (T1D) has been associated with both genetic and environmental factors. Increasing incidence of T1D worldwide is prompting researchers to adopt different approaches to explain the biology of T1D, beyond the presence and activity of autoreactive lymphocytes. In this review, we propose inflammatory pathways as triggers for T1D. Within the scope of those inflammatory pathways and in understanding the pathogenesis of disease, we suggest that viruses, in particular Coxsackieviruses, act by causing a type 1 interferonopathy within the pancreas and the microenvironment of the islet. As such, this connection and common thread represents an exciting platform for the development of new diagnostic, treatment and/or prevention options.

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1. Introduction

Type 1 Diabetes (T1D) is a disease characterized by the discriminatory destruction of pancreatic beta cells (Gillespie, 2006). T1D is a process that requires both autoimmunity and autoinflammation where the pancreas is infiltrated by immune cells such as macrophages, dendritic cells and natural killer cells secreting pro-inflammatory cytokines, and autoreactive B and T cells specific for islet antigens such as insulin, glutamic acid decarboxylase (GAD)-65, and islet antigen(IA)-2 (Li et al., 2014; Arvan et al., 2012). Although no single etiology is known for T1D, epidemiological and genome-wide association studies have linked T1D with both genetic factors i.e. polymorphisms in human leukocyte antigen (HLA) haplotypes, and environmental factors such as viral infections (Christoffersson et al., 2016; Richardson and Horwitz, 2014). While T1D is canonically considered a T-cell mediated disease (Berry

* Corresponding author.
E-mail address: mhorwitz@mail.ubc.ca (M.S. Horwitz).

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and Waldner, 2013; Kelly et al., 2003), research has demonstrated that the mere presence of autoreactive T cells is not the initiating factor but rather a determinant of disease progression (Laitinen et al., 2014; Serreze et al., 2000). Additionally, the presence of autoantibodies can be detected years before clinical disease, and not all islet autoantibody-positive individuals develop T1D (Reynier et al., 2010; Kulmala et al., 1998). Thus, we propose the inflammatory pathway as a focus for understanding early triggering events in T1D, and viral infections in acceleration of an established autoimmune/inflammatory process. Here, we review T1D inflammation as it relates to the interferon (IFN) signature, and establish a link with Type 1 interferonopathies (type 1 IFN-opathies) and viruses, specifically Coxsackieviruses. Type 1 IFN-opathies constitute a group of human diseases associated with overproduction of the pro-inflammatory type I IFNs, and are widely thought to be controlled by genetics (Crow and Manel, 2015; Lee-Kirsch et al., 2015). These diseases, often systemic and clinically symptomatic, are associated with destructive inflammation as well as development of autoimmune phenomena. We propose that persistent or chronic Coxsackievirus infections in pancreatic islet cells simulate a local type 1 IFN-opathy in the islet microenvironment that is clinically silent before diabetes onset. As several of the candidate susceptibility genes are involved in IFN responses and because virus infections would amplify genetic tendencies for a heightened IFN response, we propose that the underlying molecular mechanisms associated with type 1 IFN-opathies can serve as a foundation or reference point for the evaluation of inflammatory processes of T1D.

With the increasing incidence of T1D worldwide (Tuomilehto, 2013; Patterson et al., 2009), deciphering the inflammatory pathways represents a direct and relevant approach for the development of new targeted therapeutics to prevent, interrupt, or overturn progression of disease.

2. The Interferon Signature

IFNs are a group of pro-inflammatory cytokines. To date, three types of IFNs have been identified: type I (which includes IFNα, IFNβ, IFNε, IFNκ and IFNώ), type II (IFNγ), and the recently discovered type III (IFNλ) (Donnelly and Kotenko, 2010; Sheppard et al., 2003).

The "IFN signature" refers to expression of genes that are known to be regulated by IFNs. Overall, the repertoire of responses induced by IFNs covers a wide range of activities. These activities can go from: priming an antiviral state in local cells, to secretion of cytokines and chemokines that recruit and arm effector cells of the adaptive immune system to regulation of neuronal connectivity, but also T cell dysfunction and establishment of chronic inflammation (Filiano et al., 2016; Odendall and Kagan, 2015; Teijaro et al., 2013; Hultcrantz et al., 2007; Curtsinger et al., 2005). Some recognized type I IFN-stimulated gene products include: IFIT1 (interferon-induced protein with tetratripeptide repeats 1), OAS1/2 (2′-5′-oligoadenylate synthetase 1/2), MX1 (myxovirus resistance protein 1/MxA), ISG15 (interferon stimulated protein 15), and CCL5 (chemokine C-C motif ligand 5). Other gene products stimulated by both type I and II IFNs include: STAT1/2 (signal transducer and activator of transcription 1/2), and CXCL9 (chemokine C-X-C motif ligand 9) (Carrero et al., 2014; Zhang et al., 2014; Carrero et al., 2013; Li et al., 2008). Expression of the aforementioned genes is suggestive of either an ongoing viral infection that elicited production of IFNs or an inherent defect in controlling IFN production.

In the literature, "IFN signature" and "type I IFN signature" have been used interchangeably, suggesting that the signature depends mainly on type I IFNs. It is noteworthy that the contribution of type II and III IFNs should not be discounted. Specifically, type III IFN-inducible genes have not been investigated as extensively as for type I/II IFNs, but appear to induce a signature almost identical to type I IFN (Domsgen et al., 2016; Egli et al., 2014; Donnelly and Kotenko, 2010). Type I, II and III IFNs are reported to use the JAK/STAT signalling pathway, and a recent study revealed that type I and III IFNs use redundant pathways for the induction of an antiviral response against influenza A virus (Crotta et al., 2013; Liu et al., 2012a; Ank et al., 2008). Still, plasmacytoid dendritic cells and epithelial cells appear to be the primary responders to type III IFNs, thus the affects of type III IFNs may be confined whereas those of type I IFNs would apply to almost all tissues (Odendall and Kagan, 2015; Ank et al., 2008; Sommereyns et al., 2008). Nonetheless, recent investigations with Coxsackievirus B3-infected human pancreatic islets *in vitro* have revealed expression of type I and III IFNs with an associated IFN signature (Domsgen et al., 2016). Therefore, this area warrants further investigations to decipher the involvement of type III IFNs in T1D.

Systemic Lupus Erythematosus (SLE) can be considered the prototypic platform for the study of inflammatory profiles associated with an IFN signature. SLE is an autoimmune disease hallmarked by overexpression of type I IFNs, specifically IFNα. Studies using a variety of methods such as microarrays, quantitative polymerase-chain reaction, and laser-capture isolation of kidney cells were instrumental in solidifying the idea of an IFN signature in SLE. These studies demonstrated the IFN signature both in the peripheral blood and the kidney of SLE patients but not control patients. (Peterson et al., 2004; Han et al., 2003; Baechler et al., 2003). Taken together, these clinical studies demonstrate an underlying inflammatory process not only systemically but also at the level of end-organ autoimmunity. Importantly, these studies in SLE also support the concept of inflammation as a crucial component for understanding the pathogenesis of additional autoimmune disorders such as T1D, beyond the presence of autoreactive lymphocytes.

3. Experimental Evidence for an Interferon Signature in T1D

IFNα is known to stimulate expression of class I major histocompatibility complex (MHC-I) molecules at the surface of exposed cells. Hyper-expression of MHC-I molecules on islets along with detection of IFNα in pancreases of T1D patients compared to non-diabetic patients was an early suggestion that IFNs may be pathogenic (Huang et al., 1995; Foulis et al., 1987b). This hypothesis was also supported by earlier experiments in mice and rats indicating the potential nefarious role of type I IFNs in mammals (Gresser et al., 1980). Since then, many teams have led investigations into the role of IFNs in the pathogenesis of T1D using both human samples and mouse models such as the non-obese diabetic (NOD) mouse. Consequently, T1D has been related to the IFN signature discussed above, further supporting a role for inflammation as an initial triggering event during T1D. However, it is noteworthy that human data for an interferon signature is limited and this is likely due to the limited expression in the microenvironment of the islet.

Comparisons of gene expression profiles in pancreatic lymph node $CD4^+$ T cells of NOD mice (which spontaneously develop diabetes ~12 weeks of age) and NOD/BDC2.5 T cell receptor transgenic mice (where more than 90% of T cell receptors are islet-antigen reactive and the mice develop diabetes ~3 weeks of age) identified the up-regulation of IFN-stimulated genes in the mice. mRNA expression for IFN-stimulated genes included IFIT1, IFIT3, ISG15, and OAS1. Moreover, the up-regulated IFN-stimulated genes positively correlated with age of the mice where levels were higher in 6 week-old mice compared to 2 week-old mice (Li et al., 2008). Similarly, Planas et al. reported a data set of whole genome transcription profiles of human T1D pancreases and purified islets, which revealed an overall overexpression of both innate immunity and IFN-responsive genes (Planas et al., 2010). Even though the study by Planas and colleagues only included a small population (4 T1D patient pancreases and 7 non-T1D pancreases), the findings represented a valuable platform for organ-specific transcriptomic analysis in T1D and established a significant ground for additional large-scale investigations of locally relevant inflammation.

A study, by Diana et al., analyzing initiation of diabetes in the NOD mice and the non-autoimmune prone C57Bl/6 and BALB/c mice observed IFNα and IFNα-stimulated gene products in NOD mice only (Diana et al., 2013). Additionally, the study established plasmacytoid

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