



Commentary

Diabetes, the TYK2 Gene and the Interferon Response: In Search for Environmental Causes

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Type 1 diabetes mellitus (T1DM) is a complex, heterogeneous disease mediated by the interaction of genetic and non-genetic factors. Variants of the HLA-DQA1, HLA-DQB1, HLA-DRB1 genes, which play a critical role in immune responses, account for approximately 40% of the genetic predisposition to the disease. Over 60 additional non-HLA genes are also associated with T1DM (Pociot and Lernmark, 2016), many with defined roles in innate and adaptive immunity (PTPN22, IFIH1, STAT4, CTLA4, etc.), inflammatory responses (IL10, IL21, IL12, IL27, TNFAIP3, PRKCO, etc.), and apoptosis (BAD, PRKCO, ERBB3, etc.). Evidence from migrant populations and twin studies also invoke a major causative role for non-genetic factors, most strikingly in adult-onset diabetes. Viral infections (especially by members of the *Picornaviridae* family) contribute to those non-genetic causes of T1DM (Genoni et al., 2017).

This Commentary discusses the characteristics of autoimmune T1DM that illustrate the heterogeneity of the disease. In this issue of EBioMedicine, Mine and co-authors (Mine et al., 2017) report that many Japanese patients present with T1DM in adult life and show evidence of both an autoimmune and an autoinflammatory disease. Strikingly, they detected a diabetes subtype (35% of their cohort) with neither of these features, yet enriched for a variant of the TYK2 gene encoding tyrosine kinase 2, a member of the Janus family kinases that mediates signalling for type-I interferons (IFN) and type-III IFN (also called IFN lambda; IFNL). The finding is consistent with the possible role for viral infections in select forms of diabetes. It follows that in adult-onset T1DM Japanese patients, as in other racial groups, different immune response pathways could cause insulin-requiring adult-onset diabetes (Leslie et al., 2016).

Recent studies in non-Japanese populations illustrated the early onset of distinct autoimmune responses: one cohort being associated with HLA DQ8 and both insulin and IA2 autoantibodies, the other with HLA DQ2 and glutamic acid decarboxylase autoantibodies (GADA). However, GADA continue to appear in serum of at-risk subjects into adulthood, implying non-genetic events initiate autoimmune diabetes even after childhood.

Autoimmune diabetes in adults is as prevalent as childhood-onset T1DM, but the clinical phenotype ranges from insulin-dependent to non-insulin dependent. This latter phenotype resembles type 2 diabetes and has been called latent autoimmune diabetes of adults (LADA), or, in the Japanese, slowly progressive insulin dependent diabetes (SPIDDM). Intriguingly, in adult-onset autoimmune diabetes, irrespective of its mode of presentation, the protective HLA DQB1*0602 genotype is as prevalent as in controls, while it is rare in childhood-onset T1DM. In other words, the HLA-mediated dominant protection typical of childhood-onset T1DM is lost in adult-onset autoimmune diabetes. The likely role of antigen-specific T regulatory cells for this HLA-mediated dominant protection provides clear inference that an aggressive adaptive immune response is less vital in adult-onset disease (Ooi et al., 2017).

The study of Japanese adult-onset diabetes cases (Mine et al., 2017) implicates some role for viruses, supported by the increased frequency of mild respiratory infections before diagnosis. Furthermore, given that respiratory viral infections and variants of the IFIH1 gene (interferon induced with helicase C domain 1) predispose to childhood-onset T1DM (Gorman et al., 2017), it follows that viral infections may contribute to T1DM across a wide age-range.

In line with a key role for viruses, the Japanese investigators had previously shown that partial loss-of-function of TYK2 was responsible for making mice susceptible to virus-induced diabetes, perhaps due to inadequate IFN responses. Shortly thereafter, they also associated TYK2 promoter variants with human diabetes. It is possible, therefore, that the TYK2 variant enriched in the subgroup of insulin-dependent Japanese patients could increase susceptibility to infection and, consequently, to diabetes (Mine et al., 2017; Kreins et al., 2015).

TYK2-dependent IFNL isoforms and their receptor are specifically expressed in epithelial cells, including pancreatic islet cells (Lind et al., 2013). Stimulation of cultured human islets by exogenous IFNL activates the JAK1 and TYK2 kinases which drive the expression of interferon-inducible genes. In coxsackievirus B3-infected islets it has been shown that IFNL up-regulates anti-viral defences and restrains both virus replication and cytopathic effects (Lind et al., 2013).

Taken together, the new findings imply that individuals carrying TYK2 variants may be a target of slowly-acting pancreotropic viruses due to their dampened IFN response (Genoni et al., 2017; Mine et al., 2017). The results could also be of therapeutic value, as inhibitors of JAK kinases (including TYK2) are potentially valuable in autoimmune

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disease (Roskoski, 2016), in which we would aim for protection from autoimmunity without inducing immunodeficiency.

In virus-induced diabetes, however, treatment should primarily aim at blocking the virus that may be replicating into endocrine cells. At present, IFNL is being tested for chronic B and C hepatitis. Promising results have been obtained by administering pegylated IFNL that generates a robust innate and adaptive immunity and also co-operates in virus clearance (Phillips et al., 2017).

Thus, TYK2 deficiency, if confirmed as relevant to some cases of insulin-dependent diabetes, might reflect a treatable single-gene inborn error of immunity that predisposes to diabetes (Kreins et al., 2015). Identification of such genetically susceptible subjects and the development of appropriate antiviral vaccines could reduce the risk of virus-induced diabetes.

Conflicts of interest

Authors declare no conflicts of interest to be reported.

Authors' contributions

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