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Significance of the tyrosine kinase 2 gene in both type 1 and type 2 diabetes

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The prevalence of diabetes is increasing globally. The International Diabetes Federation reported that the number of diabetes cases reached 425 million in 2017, and this is predicted to total 693 million globally by 2045. Most increases in the diabetic patients were type 2 (T2D), supposed to be due to the changes in lifestyle including overeating, obesity, low exercise, and aging. On the other hand, the number of type 1 diabetes (T1D) mainly caused by the autoimmunity against pancreatic β-cells is increasing at 3% every year. The rate of increase of T1D due to autoimmunity cannot explain the increasing level of T1D. Environmental factors including toxins and viruses are also considered to be responsible for the increasing prevalence of T1D.[1 2]

Although there is no diabetes virus, so many viruses have been known to cause T1D.[1 2] Viruses contribute to diabetes development in several ways: direct β-cell destruction, triggering β-cell-specific autoimmunity, bystander damage via local inflammation, and the induction of dedifferentiation.[1 2] Among many candidate diabetogenic viruses, coxsackie B viruses belonging to picornavirus have been extensively studied as the most important diabetes causal virus. Picornavirus infection is known to be controlled by the innate immunity that is involved in the protection against acute type viral infections, mainly dependent on interferon (IFN).[2]

Pattern recognition receptors, such as toll-like receptors, retinoic acid-inducible gene I receptor and IFN-induced with helicase

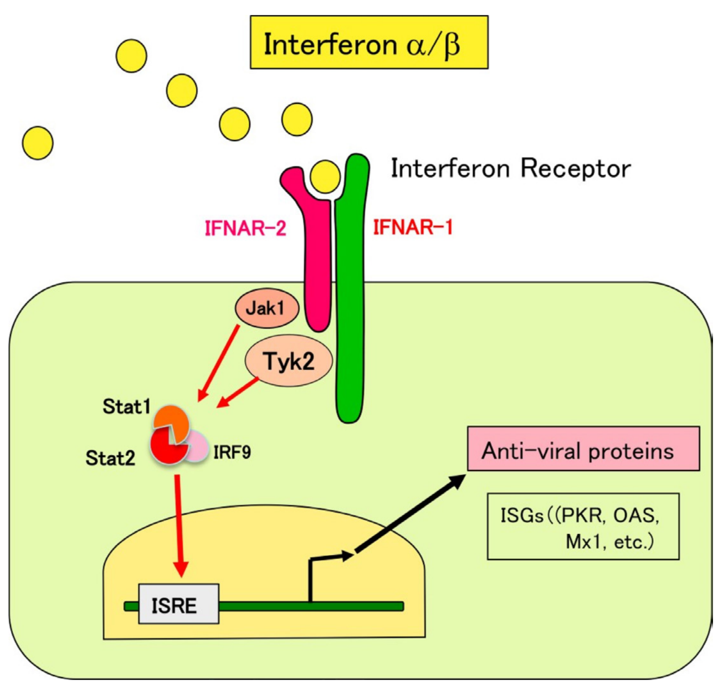

Figure 1 IFN α/β stimulated signaling pathway to provide antiviral response. IFN, Interferon; IFNAR, IFN α/β receptor; IRF, IFN releasing factor; ISGs, IFN-stimulated genes; ISRE, IFN-stimulated response element; Jak1, Janus kinase 1; Mx1, IFN-induced GTP-binding protein Mx1; OAS, 2',5'-oligoadenylate synthetase; PKR, RNA-dependent protein kinase; Stat, Signal transducers and activator of transcription; Tyk2, Tyrosine kinase 2.

C domain 1 receptor, on the surface and/or as intracellular molecules of cells to recognize the virus and increase the production of IFN.[2] IFN binds to the IFN receptors (IFNR1, IFNR2) and activates the downstream signaling including the Janus kinase/Signal transducers and activator of transcription (Jak/Stat) pathway, leading to the production of antiviral IFN-stimulated genes such as RNA-dependent protein kinase, 2',5'-oligoadenylate synthetase, IFN-induced GTP-binding protein Mx1, etc.[2] (Figure 1)

The tyrosine kinase 2 (*TYK2*) gene, which encodes a signal-transducing molecule associated with the IFN α/β receptor and mediates the activation of *Jak* and *Stats*, plays a major role in resistance to viruses, bacteria, and parasites[2] (Figure 1). Diabetogenic encephalomyocarditis virus strain D (EMC-D) in rodents has been well studied as a model of virus-induced diabetes. It was found that a naturally occurring mutation of the *Tyk2* gene in susceptible strains of SJL mice reduces *Tyk2* gene expression in islets.[3] Owing to this natural mutation of the *Tyk2* gene, EMC-D virus infection causes severe islet-cell damage, associated with an impaired IFN-stimulated intracellular antiviral response resulting in the development of diabetes in SJL mice.[3] Interestingly, recent findings suggested a critical role for TYK2 in pancreatic β-cell development[4] and antiviral defense against coxsackievirus.[5] In addition, TYK2 suppression was reported to have an inhibitory role in autoimmune TID model mice,[6 7] suggesting that *Tyk2* gene has a bidirectional role dependent on the pathogenesis of diabetes at least in mice.

Most importantly, we have identified polymorphisms of the promoter region and exon 1 of the human *TYK2* gene, which show complete linkage disequilibrium.[8] The associated haplotype has been named *TYK2* promoter variant (*TYK2PV*) (NCBI (National Center for Biotechnology Information) ClinVar ID: 440728) and it is closely associated with the risk of T1D.[8] Specifically, *TYK2PV* is associated with a significant risk of T1D (OR 2.4), especially in patients with a flu-like syndrome at the onset of disease (OR 3.6), independent of anti-glutamic acid decarboxylase antibody status.[8 9] Surprisingly, we also identified *TYK2PV* as a risk factor for T2D (OR 2.1).[8 10] Interestingly, patients with T1D had elevated IgE (median, 56.7 U/mL; p<0.0001) compared with patients with T2D (22.5 U/mL) and controls (43.3 U/mL).[9] There was no direct correlation between *TYK2PV* and IgE levels, while patients with T1D with anti-GAD Ab negative and non-elevated IgE significantly carried the *TYK2PV* (p=0.032).[9]

Moreover, we found that *TYK2PV*-positive patients with T2D were not obese and showed a low level of insulin secretion.[10] Taking these findings together, *TYK2PV* is associated with T2D as well as T1D, possibly because it induces islet damage. Thus, impaired insulin secretion in T2D can be associated with *TYK2PV*, and this might represent a novel type of T2D.[8–10]

Those studies taken together, the *TYK2* gene is associated with both type 1 and type 2 diabetes, emphasizing the significance of vaccine development for the prevention of not only T1D but also T2D, caused by viral infection.

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