Genomics and Genetics 2022, 15(1): 16–33

Immunogenetics of Type 1 Diabetes in Asian Populations

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ABSTRACT

Type 1 diabetes (T1D) is an autoimmune disease caused by a combination of immunogenetic and environmental factors contributing to the development of auto-antibodies against islet cells and pancreatic β-cells. It has been known for several decades that the human leukocyte antigen genes have a major role associated with the disease; however, the available data were mostly obtained from the studies in Caucasian populations. With the advancement of genomic and genetic technologies, more studies have been conducted to explore the role of genetic factors associated with the development of T1D in Asian populations. This review summarizes the current immunogenetic studies and data of T1D in Asian populations to gain more understanding of its molecular pathogenesis. The estimated prevalence of T1D in southeast Asia was around 11%. In general, more than 50 genetic risk regions contribute to the pathogenesis of T1D. Similar to Caucasians, the strongest genetic risk factor of T1D in the Asian populations in the gene encoding the classical HLA on chromosome 6p21.31, accounting for 40-50%, in which DR and DQ loci show the strongest association. Other non-HLA genetic loci also contribute to the risk of T1D including both immune and non-immune related genes, which are *PTPN22*, *INS*, *CTLA4*, *IL2RA/CD25*, and others. Polymorphisms of these genes are associated with T1D in both the Asian and Caucasian populations. More studies on genetic variations, gene-environment interaction, and involvement of immunogenetic loci are required for a more in-depth understanding of the genetic basis and molecular mechanism of the pathogenesis of T1D in Asian populations, which may lead to the precise predictive model, development of genetic screening, risk assessment, and intervention strategies applicable and tailored to the genetic background of individuals.

Keywords: type 1 diabetes; genetics of type 1 diabetes, immunogenetics; pathogenesis; asian populations

INTRODUCTION

Type 1 diabetes (T1D) is a serious chronic endocrine disease in children and adolescents caused by autoimmunity mechanisms in which the self-immune system attacks pancreatic β-cells that produce insulin (Sloboda *et al.*, 2013). T1D is caused by a combination of genetic and environmental factors. This disease has a strong genetic component as evidenced by the concordance rate of approximately 50% in monozygotic twins (Singal and Blajchman, 1973). About 20% of T1D aggregate in families and its incidence is significantly increased in first-degree relatives of the patient with T1D (Kaprio *et al.*, 1992). Over 80% of T1D patients belong to families with no prior history of the disease and the genetic susceptibility of a person developing T1D is determined by both human leukocyte antigen (Forbes *et al.*, 2011) and non-HLA genes. Genetic analysis has revealed evidence of a strong linkage between T1D and the HLA complex. Other factors that influence the development of T1D are environmental ones, including some viral and microbial infections as well as dietary and psychosocial elements (Knip *et al.*, 2005). The incidence of onset of diabetes in childhood and adolescents is increasing worldwide at an overall annual rate of around 3% (Group, 2006). It can be estimated that at least 128,900 individuals under the age of 20 years have some forms of diabetes. In a study in Southeast Asia patients between the ages of 12 and 40 years, who were newly diagnosed with diabetes, classical T1D accounted for 10% of the new cases (Ramachandran *et al.*, 2014). The frequency of diabetes under 15 years was positively associated with latitude (r=0.88, p=0.001), but no such relationship was

Received 18 May 2020, Revised 9 June 2020, Accepted 25 February 2022

observed in the age ranges 15-29 years or 30 years (Weng *et al.*, 2018). Today, there are an estimated 1,110,100 active cases with T1D globally. However, the incidence rate of the disease varies among ethnicities. Based on the 9th International Diabetes Federation Atlas Data, the prevalence of diabetes in Southeast Asia and the middle east countries are 11.3% and 12.2%, respectively. T1D has an incidence rate of fewer than 5 cases/year/100,000 individuals in most countries in Asia (Patterson *et al.*, 2019, Saeedi *et al.*, 2019). In Thailand, the incidence of T1D in children aged 0-15 years increased from 0.2 per 100,000 per year in 1984-1985 to 1.65 per 100,000 per year in 1991-1995 (Tuchinda *et al.*, 2002). The Thailand Diabetes Registry Project reported the data from a cross-sectional, multi-center, hospital-based diabetes registry from the diabetes clinics of 11 tertiary centers that 250 out of the 9,419 (2.66%) diabetic patients were diagnosed before the age of 18 years, 78% had T1D, 18.4% had T2D and 3.6% had other types of diabetes (Likitmaskul *et al.*, 2006). A possible explanation for this low incidence rate can be attributed to the data collection methods, which might have not been as thorough as those in the Western countries. The frequency distribution of susceptible T1D genes, including HLA alleles in Asian populations, might also contribute to the T1D incidence. About 40% of the patients who had T1D could not be recognized until they develop diabetic ketoacidosis (White, 2000). At present and in general, the role of immunogenetics of T1D is well established but the molecular mechanisms remain unclear.

Type 1 diabetes and autoimmune disease

It is well known that T1D is an autoimmune disease. In addition, the patients with T1D also have an increased risk of the development of other autoimmune diseases such as autoimmune thyroid disease, celiac disease, pernicious anemia, idiopathic Addison's disease, systemic lupus erythematosus (SLE), rheumatoid arthritis, etc. The disease that commonly coexists with T1D is autoimmune thyroiditis, which is as high as 85%. At T1D onset, 20% of the patients also have anti-thyroid auto-antibodies, especially in young women in their second decade of life (Kawasaki, 2014).

Childhood-onset of T1D is frequent. However, autoimmune diabetes also occurs in adults, which is associated with the same HLA genes as that of childhood-onset T1D and is characterized by serum islet auto-antibodies, most notably anti-glutamic acid decarboxylase (Harrison *et al.*, 2020) auto-antibodies. Latent autoimmune diabetes in adults (LADA) is described as a form of adult-onset autoimmune diabetes that, at least initially, does not require insulin treatment. While immunogenetics and clinical characteristics of LADA have extensively been studied in Caucasians, the relationship between LADA and the other two major forms of diabetes, T1D and T2D, remains controversial. For example, LADA could be distinct from T1D and T2D but still contains certain features of each, or be part of a spectrum of autoimmune diabetes (Buzzetti *et al.*, 2020).

In normal situations, various genetic loci confer the balance between susceptibility to autoimmunity and influence self-tolerance. Once environmental factors are changed or some acquired conditions occur, for example, infection and inflammation may disrupt self-tolerance and promote the influx of self-reactive lymphocytes resulting in tissue injury. Autoimmune diseases may be systemic or organ-specific based on the distribution of autoantigens and various effector mechanisms in different autoimmune diseases. Autoimmune diseases tend to be chronic and progressive due to self-antigens that trigger these persistent reactions and various amplification systems that prolong the response. Recent studies focused on the role of T cells, the main regulators of immune responses, in contributing to autoimmunity, which is activated by peptide antigen-presented by major histocompatibility complex (MHC) molecules on antigen-presenting cells (APCs), and on the endeavor to identify the role of T-cells in the pathogenesis of T1D. The hypothesis that interaction between activated T-cells by various agents (i.e. viral infection) and beta-cells leads to beta-cell destruction was established; however; further studies should be conducted (Burrack *et al.*, 2017, Pugliese, 2017). Furthermore, genetic polymorphisms are associated with several autoimmune diseases and their main mechanisms are immune regulation and self-tolerance. Some genetic variants were also found to be associated with multiple diseases from the meta-analysis of genome-wide association studies (GWAS) (Inshaw *et al.*, 2018).

Prevalence of type 1 diabetes in Asian populations

Annually, the overall estimated global incidence of onset of diabetes in children is around 3%; however, T1D in Asian populations is less frequent (0.4-1.1 cases/year/100,000 individuals) (Park, 2006). The finding of lower incidence rates of T1D in Asian countries is partly based on limited epidemiological data collection, which is unlike that in Western countries where it was systematically recorded.

Genetic heterogeneity and environmental interaction of T1D in Asian populations may also be important factors that have an influence on the incidence and prevalence as well as clinical characteristics and pathophysiology (Patterson *et al.*, 2014). T1D among Asian patients has unique clinical characteristics than that of the patients in other regions. For example, T1D patients in some Asian populations have older ages and higher body mass index (BMI) than their European counterparts, which means that they may co-exist with obesity (Ramachandran *et al.*, 2014). Pacific Islanders with T1D were more obese with a mean BMI of 26 kg/m^2, compared to the Asian and Asian–Pacific Islander youth with the mean BMI of 20 kg/m^2 for ($P < 0.0001$) (Liu *et al.*, 2009). Additionally, insulin resistance and high body fat percentages are found in a considerable majority of Indian T1D patients (Mazumder *et al.*, 2009). In the Chinese population, T1D is more prevalent in obese and overweight patients than that in the normal BMI group (Tang *et al.*, 2019). However, a cross-sectional study in East Asian Americans showed no difference in BMIs between the T1D patients and the control group (Hsu *et al.*, 2011). The incidence and clinical characteristics of the T1D patients in Asia may also be associated with genetic susceptibility, especially in class II HLA. The HLA alleles DR and DQ are highly associated with T1D development. Although the study in the populations of Sardinians and Scandinavians showed the highest incidence of T1D in the world with a high frequency of *DRB1*0301* observed in both populations, Asians have a low frequency of *DRB1*0301*. In Asian populations, the susceptible DQ8 subtypes (*DQA1*0301-DQB1*0302*) are usually combined with protective DR4 subtypes (*DRB1*0403, *0406*) (Park, 2006). Thus, the low incidence of T1D in Asian populations may be attributed to the counterbalance between protective and susceptible alleles or DR-DQ linkage disequilibrium (LD).

Pathogenesis of type 1 diabetes

One of the important goals of T1D studies is to understand its pathogenesis. The current hypothesis is that β-cell autoimmunity is the result of genetic predisposition (HLA class II molecules including DR4, DQ8, and DQ2 are most frequent in T1D) and breakage of self-tolerance triggered by environmental factors. In other words, each person has a balance of genetic susceptibility and self-tolerance to T1D, but this balance is disrupted by some environmental factors. Adaptive immune responses including humoral (auto-antibodies) and cellular (autoreactive CD4$^+$ T cells and CD8$^+$ T cells) immune responses play key roles in the destruction of β-cells. In addition, the indirect response mechanism of the innate immune system may also be involved. The innate immune response functions as the first line of defense in protecting the body from pathogens by mainly stimulating inflammatory responses. However, a weak or strong inflammatory response may increase the risk of developing T1D. The insulin β chain peptide and other components of β-cell granules, including glutamic acid decarboxylase-65 (GAD-65), protein phosphatase-like, IA-2, and transmembrane Zn transporter (ZnT8), have been identified as autoantigens (Atkinson, 2012, Bingley, 2010). These autoantigens from damaged beta cells are taken by antigen-presenting cells (APCs); they are processed and presented by MHC I and II molecules on APCs to activate autoreactive T cells, which escape central tolerance mechanisms, in the pancreatic lymph nodes (PLNs). Autoreactive CD4$^+$ and CD8$^+$ T cells capable of recognizing these autoantigens exit PLNs to reach pancreatic islets and attack the β-cells. Autoreactive CD4$^+$ T cells can also stimulate B cells to produce auto-antibodies against β-cells. Moreover, autoreactive CD4$^+$ T cells can assist CD8$^+$ T cells to stimulate cytolytic activity to attack β-cells via the secretion of cytokines. Inflammatory cytokines from these pathways can also activate macrophages and innate responses to further damage β-cells as part of a positive feedback loop (Burrack *et al.*, 2017). The spread of the epitope causes the progression of T1D from initial activation to a chronic state. Often, a higher number of islets autoantigens react with T cells and auto-antibodies. In addition, the degree of β-cell destruction determines the severity of symptoms in each patient. T1D is a relapsing-remitting disease due to the nonlinear decline of β-cell mass over time. By the onset of hyperglycemia, 50% of β-cell destruction may have already taken place; however, generally, T1D will not show any signs until 80% of β-cells have been destroyed (Knip and Siljander, 2008). There is a strong evidence showing that the prevention of progression of pre-diabetes to diabetes is linked to genetic susceptibility and environmental triggers (Atkinson, 2012). The autoimmunity mechanism destroying pancreatic β-cells leads to the deficiency of insulin, which is the main secretory product, and the consequent de-compensation of glucose homeostasis (Li *et al.*, 2014). The relationship between immunogenetics and pancreatic β-cell destruction by auto-antibodies is shown in Figure 1.

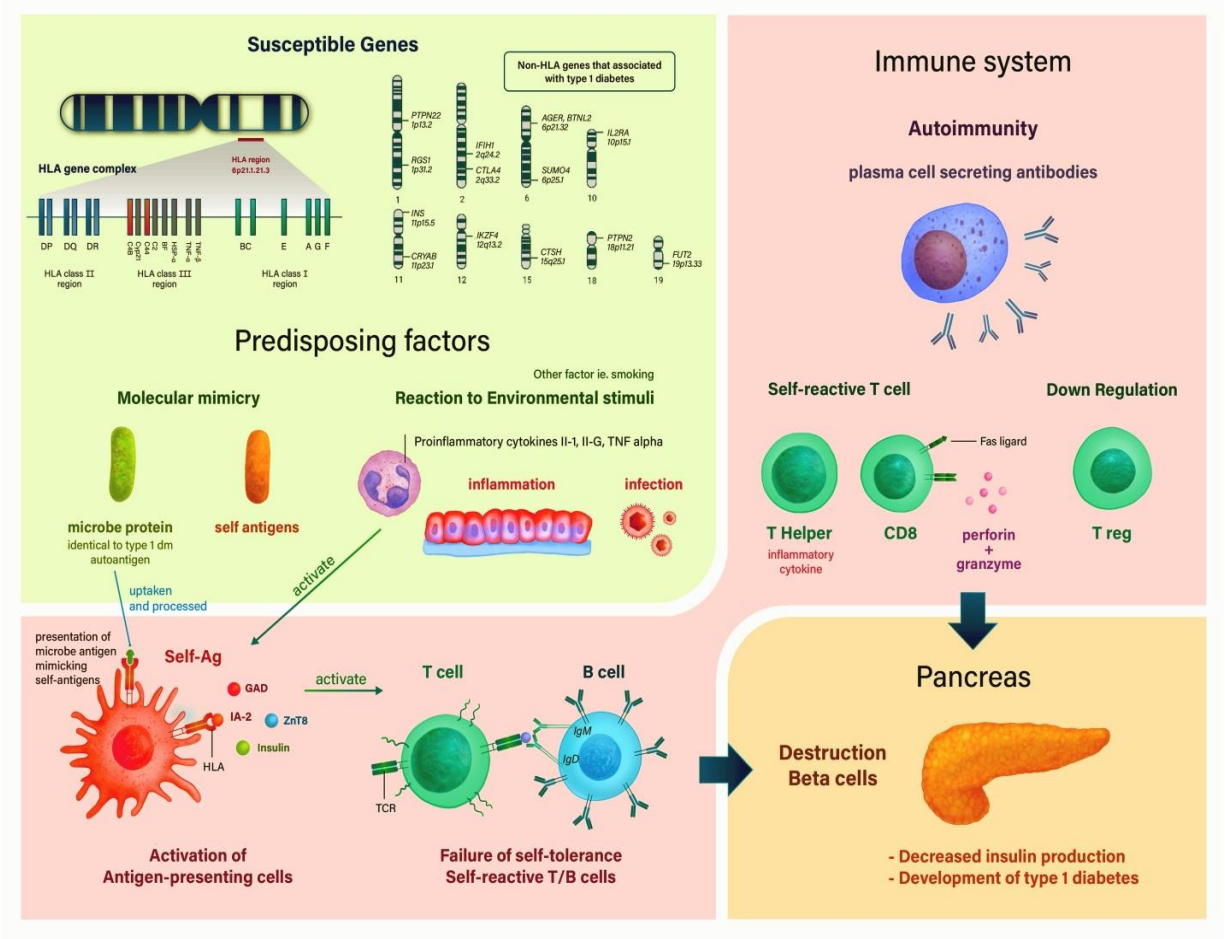

Figure 1 Immunological pathogenesis of type 1 diabetes (T1D) is the result of the interaction of genetic susceptibility gene, including HLA and non-HLA gene, and environmental assaults e.g. viral infection, tissue inflammation, etc. Microbe proteins can be processed and presented on HLA of antigen-presenting cells mimicking self-antigen (molecular mimicry) while other environmental assaults cause inflammation and activation of antigen-presenting cells presenting self-antigen. Known self-antigens targets include GAD, IA-2, ZnT8, and insulin. Consequently, failure of tolerance occurs with the activation of self-reactive T and B lymphocytes and down-regulation of regulatory T lymphocytes. $CD4^+$ T cells activate B cells to produce auto-antibodies targeting beta cells and assist $CD8^+$ T cells cytotoxicity activities against beta cells through cytokine production. $CD8^+$ T cells induce beta-cell apoptosis through the perforin-granzyme pathway and Fas-Fas ligand interaction. Inflammatory chemokines and cytokines from the process can also attract neutrophil and innate immune responses to further damage beta cells. These immunological processes lead to the destruction of beta cells in the pancreas, which results in insulin depletion and the development of T1D.

Genetic factors in T1D

Several putative risk factors of T1D have recently been discovered, including genetic factors of T1D susceptibility, immune system responses, and environmental factors (Pociot and Lernmark, 2016, Rewers and Ludvigsson, 2016). Although most genetic risk variants of T1D remain unknown, the association between the immune genes and T1D is linked to the genes encoding MHC or human leukocyte antigen (Forbes *et al.*) region (Forbes *et al.*, 2011). HLA is the most relevant and crucial inherited risk factor, leading to 40-50% of all T1D cases (Xie *et al.*, 2014). Genetic variants of Classes I and II HLA genes are understood for several different autoimmune diseases such as rheumatoid arthritis (RA), celiac disease (CD), systemic lupus erythematosus (SLE), multiple sclerosis (MS), and T1D. The strongest genetic risk factors in T1D are located on the HLA Class II. Additionally, multiple genes outside the HLA regions also play roles in the development of T1D.

HLA and T1D risk

The HLA system is determined by a cluster of loci on the short arm of chromosome 6 (6p21.3) . HLA proteins consist of cell-surface molecules that combine and display small peptide antigens (Bjorkman and Parham, 1990). The HLA complex is further classified into two classes (Class I and Class II) and three subtypes within each class (Choo, 2007). The Class I HLA region has three subtypes known as A, B, and C, and contains a polypeptide chain that forms a heterodimer with β-2 microglobulin (Bjorkman and Parham, 1990). The Class II HLA region also has three regions known as DR, DQ, and DP, and includes a heterodimer (α and β polypeptides) (Bjorkman *et al.*, 1987). While all HLA Class II alleles are linked to T1D susceptibility, the strongest association is DQ and DR loci (Steck and Rewers, 2011).

The effects of HLA Class I alleles towards T1D progression are weaker than those of HLA Class II alleles. Also, Class I HLA molecules are involved in the activation of cytotoxic $CD8^+$ T-cells that respond to antigenic peptides. Furthermore, a protective effect of the *HLA-A*03* allele was noticed in T1D children without the DR3/DR4 combination. Conversely, *HLA-B*39* had a significant effect on T1D patients with the DR3/DR4 genotype (Lipponen *et al.*, 2010). HLA Class I loci (A, B, and C) on 1,753 multiplex pedigrees demonstrated that the most notable T1D–associated alleles were *HLA-B*5701* and *HLA-B*3906*. The reported findings also described the predisposing alleles (e.g., *HLA-A*2402, A*0201, B*1801*, and *C*0501*) and protective alleles (e.g., *HLA-A*1101, A*3201, A*6601, B*0702, B*4403, B*3502, C*1601*, and *C*0401*) (Noble *et al.*, 2010). The HLA alleles also notably contribute to the age of onset in multiple populations. These HLA alleles include *A*24:02, B*39:06, B*44:03, B*18:01*, and *DRB1-DQB1* (Valdes *et al.*, 2012). Interestingly, DQA1*03-DQB1*02 is associated with earlier onset than other genotypes like in DQ2/DQ8 positive individuals but early-onset was demonstrated only in male subjects carrying DR3 and/or DQB1*02 on another chromosome, unlike DQ2/DQ8. The investigators concluded that it is due to the interaction of X-linked genetic factors and (DR3-) DQB1*02 haplotypes (Van Autreve *et al.*, 2004). The *HLA-B*39* alleles contribute to the risk of developing T1D as revealed by an examination of the HLA Class II haplotypes: *HLA-DRB1*04:04-DQB1*03:02* and *HLA-DRB1*08-DQB1*04* (Mikk *et al.*, 2014). The *HLA-B*3906* was present in the Finnish population and found on the *(DR8)-DQB1*04* haplotype (Mikk *et al.*, 2017). The risk factors for the co-occurrence of T1D were observed with *HLA-C*07* contributing to the presence of C1 ligand rather than that with *B*08* due to no KIR ligand, which could have an impact on the innate immunity systems of T1D susceptibility (Schweiger *et al.*, 2015). Recently, the results of studies on the high-risk HLA Class I molecules revealed that *HLA-B*3906* is restricted to autoreactive $CD8^+$ T cells in T1D (Yeo *et al.*, 2020). This is also supported by the presence of β-cell reactive $CD8^+$ T cells, which are restricted by disease-associated HLA Class I molecules that present the autoreactive antigen (Sidney *et al.*, 2016). The associations of HLA and T1D in Asian populations are shown in Table 1, which will be discussed in the later section.

Genes outside the HLA region (Non-HLA loci)

Multiple genes outside the HLA region associated with T1D are shown in Table 2. The *insulin* (*INS* I/I) genotype is linked to higher susceptibility to T1D while the interaction of *INS* I/I and *CTLA4* G/G genotypes in older children with T1D is not different from that of the normal group (Felner *et al.*, 2005). The *INS* risk genotype (−23HphI; rs689) was notably associated with susceptibility to T1D in Finnish patients. In contrast, the autoimmune regulator (*AIRE*) gene does not seem to affect T1D susceptibility (Turunen *et al.*, 2006). Subsequently, *PTPN22* (C1858T) polymorphism was seen in T1D in the North Indian population (Kumar *et al.*, 2014). Genotyping of the *BTNL2* rs2076530 (S360G) presented remarkable links to T1D in the patients in Southwest Netherlands (Orozco *et al.*, 2005). The interferon (IFN) induced with helicase C domain 1 (*IFIH1*) gene produces MDA5 protein and inflammatory cytokines that can support autoimmune destruction of β-cells as mediated by T-cells. Rare variants of *IFIH1* [rs35744605 (E627X) and rs35667974 (I923V)] decreased the risk of T1D in the Russian population (Chistiakov *et al.*, 2010). In investigations of the Finnish and Hungarian populations, there was a strong association of *IFIH1* (Ala946Thr) with T1D (Jermendy *et al.*, 2010, Lempainen *et al.*, 2015). Aminkeng *et al.* localized the association of *IL-2RA/CD25* with T1D to single nucleotide polymorphisms (rs41295061) amongst the Belgian population (Aminkeng *et al.*, 2010). The *PTPN2* gene located on the LD block is expressed in several cell types, including β-cells. The frequency of the *PTPN2* variant (rs2542151), the G allele, is

related to an increased risk of T1D (Espino-Paisan *et al.*, 2011). A meta-analysis showed that *SUMO4* (rs237025; M55V) is linked to T1D susceptibility in both Asians and Europeans (Song *et al.*, 2012). Auto-antibodies were also found to be associated with non-HLA genes from analysis of T1D genotype in subjects from the environmental determinants of diabetes in the young (Krischer *et al.*, 2017) study. Regions near *SH2B3*, *PTPNSS*, and *PPIL2* were shown to be associated with the risk of developing persistent islet auto-antibodies. Development of insulin auto-antibody (IAA) was found to be associated with *INS* and *TTC34/PRDM16*, while glutamic acid decarboxylase antibody (Harrison *et al.*, 2020) was found to be associated with *RBFOX1* (Sharma *et al.*, 2018). Furthermore, both *INS* (rs689) and *IKZF4* (rs1701704) polymorphisms were investigated in T1D patients with IAA positive detection (Lempainen *et al.*, 2013). The associations with the *RGS1* (rs2816316) and *CCR3-CCR5* (rs11711054) regions were also considered and relationships between *FUT2* and *CD69* SNPs in children with multiple autoimmune diseases were discovered (Parkkola *et al.*, 2017). Thus far, a study of auto-antibodies development patterns and analyses of the risk genotypes in children below the age of 10 years by the Finnish Pediatric Diabetes Register (FPDR) showed that *INS* was associated with IAA development as the first auto-antibodies, whereas *IKZF4-ERBB3* was associated with developing GADA as first auto-antibodies (Ilonen *et al.*, 2018).

Non-HLA genes may also have roles in the development of T1D in Asian populations. Studies have identified an association between more than ten polymorphisms and T1D, including polymorphisms of *CTLA-4*, *PTPN22*, *NEUROD1*, cytokine polymorphism, and vitamin D receptor polymorphism. Further details would be discussed in the next topic (Allam *et al.*, 2018, Jaya *et al.*, 2018, Kavvoura and Ioannidis, 2005, Taniyama *et al.*, 2010, Wang *et al.*, 2014),

Immunogenetics of T1D in Asian populations

In the Asian populations, HLA Class II genes including DR and DQ are commonly associated with T1D (Table 1). A previous study demonstrated the prevalence of *HLA-DPB1*1301* in the Northeastern Thais and Thai-Khmers volunteer groups (Chandanayingyong *et al.*, 1994). However, *HLA-DPB1*1301* polymorphism has not been reported in Thai patients with T1D. In a study of Japanese and Korean patients with T1D, the result showed that *HLA-DRB1*0405-DQB1*0401* and *DRB1*0901-DQB1*0303* contribute to the genetic predisposition to T1D (Kawabata *et al.*, 2002). The association of islet cell antigen 2 (IA-2) humoral autoreactivity with HLA-DR3/4 was observed in Korean T1D patients (Park *et al.*, 2004). Moreover, a study in Korean children also reported that HLA-DRB1*14, DRB1*15, DQB1*05, and DQB1*06 are protective genes (Jung *et al.*, 2004). In Singaporean-Chinese, the HLA-DR haplotype (*DRB1*0401, *0404*, and **0405, DRB1*0301*, *DRB*030l/*0901*, and *DRB1*0301/*04*) and *HLA-B* (HLA B58) (Chan *et al.*, 1995) was associated with T1D. However, in Filipino T1D patients, only the HLA-DR haplotype *DRB1*0405* (Bugawan *et al.*, 2002) played a role in disease onset. A strong association of *DQA1*0301/ DQA1*05011* haplotype with T1D in Hong Kongese was also noticed (Chang *et al.*, 1998). In a cross-sectional study, the diabetic auto-antibodies [islet cell auto-antigen 512 (ICA-512) and GAD65] were examined together with the HLA-DR/DQ genotype. The results showed a strong association between *HLA-DQB1*0201/0302* and *DRB1*03/04* with T1D in Saudi children (Manan *et al.*, 2010). In this study, the protective allele against T1D was *HLA-DPB1*0401*, and the subjects at high risk of T1D had a DR/DQ haplotype (Al-Hussein *et al.*, 2003). In Iranian T1D patients, the *DRB1*1301–DQB1*0603* is the most protective haplotype (Kiani *et al.*, 2015). In Thai children with T1D, the alleles *DQB1*0201/02* and *DQB1*0302* were commonly observed (Thammarakcharoen *et al.*, 2017). Recently, the *HLA-DRB1*03* haplotype was found to have positive association with T1D in North Indians and there was a negative association with *DRB1*07*, **11*, **13*, and **15*. At the HLA Class I locus, *HLA-A*02, A*26, B*08*, and *B*50* were significantly enlarged in T1D patients when compared with the control group (Kumar *et al.*, 2019). Finally, the *DRB1*08:03-DQB1*06:01* haplotype was found to protect against T1D in Taiwan (Tung *et al.*, 2018). Furthermore, genes in the HLA region also encode for tumor necrosis factor-alpha (TNF-α) and genotyping of rs1800629 resulted in higher expression of *TNF-α* gene in T1D in North Indians (Das *et al.*, 2006).

Table 1 HLA loci polymorphisms associated with type 1 diabetes in Asian populations.

Asian populations	Populations	HLA loci	Haplotypes and alleles	Sample size
East Asian	Hong Kongese	HLA-DQ	*DQA1*0301/ DQA1*05011*	76 unrelated Chinese patients and 250 controls (Chang *et al.*, 1998)
	Japanese and Korean	HLA-DR, DQ	*DRB1*0405-DQB1*0401* *DRB1*0901-DQB1*0303*	132 Japanese T1D patients and 157 control subjects, 67 Korean patients and 109 control subjects (Kawabata *et al.*, 2002)
Southeast Asia	Singaporean	HLA-DR	*DRB1*0401, *0404, *0405* *DRB1*0301, DRB*030l/*0901* *DRB 1*0301/*04*	64 unrelated patients with IDDM and 80 controls (Chan *et al.*, 1995)
		HLA-B	*B58*	
	Filipino	HLA-DR	*DRB1*0405*	90 T1D patients and 94 Filipino normal subjects (Bugawan *et al.*, 2002)
	Thai	HLA-DQ	*DQB1*0201/02* and *DQB1*0302*	46 T1D patients and 124 Healthy controls (Thammarakcharoen *et al.*, 2017)
South Asia	North Indian	HLA-DR	*DRB1*0301*	38 unrelated children with T1D and 308 healthy unrelated subjects (Kanga *et al.*, 2004)
		TNF-α	rs1800629	130 T1D patients with early-onset and 133 normal healthy volunteers in North India (Das *et al.*, 2006)
		HLA-A, HLA-B	*A*02, A*26* *B*08, B*50*	259 T1D patients and 706 controls from North India (Kumar *et al.*, 2019)
Middle East	Jewish (Ethiopian in Israel)	HLA-DR, DQ	*DRB1*0301 DQA1*05* *DQB1*02* *DRB1*0404* *DQA1*03DQB1*0302* *DRB1*0405 DQA1*03* *DQB1*0302*	33 T1D patients and 119 unrelated controls (Zung *et al.*, 2004)
	Saudi Arabia	HLA-DR, DQ	*DQB1*0201/0302* *DRB1*03/04*	103 Saudi T1D patients and 180 healthy controls (Manan *et al.*, 2010)
		HLA-DP	*DPB1*0401*	86 Saudi IDDM patients and control subjects (Al-Hussein *et al.*, 2003)
	Iranian	HLA-DR, DQ	*DRB1*04:01,03:01* *DQB1*03:02, 02:01,* *DRB1*03:01/04:01, 03:01/13:03* *DQB1*02:01/03:02* *DRB1*04:01 DQB1*03:02* *DRB1*03:01-DQB1*02:01* *DRB1*07:01-DQB1*03:03* *DRB1*13:01–DQB1*06:03*	105 Iranian T1D and 100 unrelated Iranian controls (Kiani *et al.*, 2015)

Table 2 Genes associated with the risk of type 1 diabetes that are located outside the HLA regions.

Gene	Chromosome	Protein	T1D risk-associated polymorphisms	Gene functions
PTPN22	1p13.2	Protein tyrosine phosphatase nonreceptor type 22	rs2476601 (R620W) (Kumar *et al.*, 2014) rs2488457 (Jaya *et al.*, 2018) rs1310182 (Taniyama *et al.*, 2010)	An important inhibitor of the activation and proliferation of T lymphocytes.
RGS1	1q31.2	Regulator of G-protein signaling 1	rs2816316 (Parkkola *et al.*, 2017)	Inhibits signal transduction by increasing the GTPase activity of G protein alpha subunits thereby driving them into their inactive GDP-bound form
IFIH1	2q24.2	Interferon (IFN) induced with helicase C domain 1	rs35744605 (E627X); rs35667974 (I923V) (Chistiakov *et al.*, 2010)	Regulation of the MDA5 protein, which plays a crucial role in innate immunity.
			rs1990760 (A946T) (Jermendy *et al.*, 2010)	
CTLA4	2q33.2	Cytotoxic T lymphocyte-associated protein 4	rs231775 (A49G) (Klitz *et al.*, 2002, Kumar *et al.*, 2015)	Negative regulation through *CTLA4* in autoreactive T cells
BTNL2	6p21.32	Butyrophilin-like 2	rs2076530 (S360G) (Orozco *et al.*, 2005)	Negative regulator of T-cell proliferation and Regulation immune response
AGER	6p21.32	Advanced glycosylation end-product specific receptor	rs2070600 (G82S) rs17493811 (Forbes *et al.*, 2011)	An important role in regulating the production/expression of TNF-α and oxidative stress
SUMO4	6q25.1	Small ubiquitin like modifier 4	rs237025 (M55V) (Song *et al.*, 2012)	*SUMO4* conjugates with IκBα and negatively regulates NF-κβ.
IL2RA	10p15.1	Interleukin-2 receptor α gene region	rs41295061 (Aminkeng *et al.*, 2010)	A shared autoimmune susceptibility locus
INS	11p15.5	Proinsulin (Insulin)	rs689 (Turunen *et al.*, 2006)	Inhibitor for insulin-producing
CRYAB	11q23.1	Alpha B-crystallin	rs2234702 (Sun *et al.*, 2012)	Important roles in different biological events including apoptosis, inflammation, and autoimmunity
IKZF4	12q13.2	Zinc finger protein Eos	rs1701704 (Lempainen *et al.*, 2013)	Essential for the inhibitory function of regulatory T-cells (Treg)
CTSH	15q25.1	Cathepsin H	rs3825932 (Koskinen *et al.*, 2020)	A role in the β-cell function
PTPN2	18p11.21	Protein tyrosine phosphatase non-receptor type 2	rs2542151 (Espino-Paisan *et al.*, 2011)	The sensitivity of β-cells for apoptosis induction. Regulation of T cell activation.
FUT2	19q13.33	Galactoside 2-alpha-L-fucosyltransferase 2	rs601338 (Koskinen *et al.*, 2020)	Responsible for the synthesis of the H antigen

Moreover, non-HLA genes are also associated with T1D in the Asian populations as demonstrated in the following studies. In a meta-analysis, a polymorphism in the *NEUROD1* gene, p.Ala45Thr, did not significantly increase the risk of T1D. Instead, the threonine allele raised the susceptibility of developing T1D in Asian populations, although it had no significant association in European populations (Kavvoura and Ioannidis, 2005). Jaya *et al.* found that the non-HLA gene *PTPN22* c.-1123G>C (rs2488457) SNP in T1D patients in South Sumatra did not have a significant association with *CTLA-4* c.+49A/G polymorphism (Jaya *et al.*, 2018) (Table 2). In contrast, *CTLA-4* exon 1 p.A49G variation was found to be associated with T1D in Filipino and North Indian patients (Klitz *et al.*, 2002, Kumar *et al.*, 2015). Originally, *PTPN22* p.R620W polymorphism was also reported in T1D patients (Kahles *et al.*, 2015). A rare variant of *PTPN22* (rs1310182) was also observed in T1D in the Japanese population (Taniyama *et al.*, 2010). The study in Korea also found the association between T1D and the variable number of tandem repeats of the insulin gene (Chung *et al.*, 2010).

Additionally, cytokine polymorphisms may be related to risk factors of T1D (Eerligh *et al.*, 2004). Cytokine gene polymorphisms (*IFN-γ +874T* allele, *TNF-α −308A* allele, *IL-1β −511T* allele, and *IL-4 −590T* allele) were reported as risk factors for T1D in Saudi Arabian population (Allam *et al.*, 2018). According to the results of a meta-analysis, vitamin D receptor (*VDR*) gene polymorphisms (*Fok*I and *Bsm*I) are also associated with an increased risk of T1D. *Bsm*I polymorphism was shown to relate to increased risk of T1D development in East Asian populations, while *Fok*l was shown to relate to increased risk of T1D development in West Asian populations (Wang *et al.*, 2014).

Latent autoimmune diabetes in adults (LADA) is genetically related to both T1D and T2D but the strongest genetic risk locus is shared with T1D (Buzzetti *et al.*, 2020). In Chinese, the HLA-DR9/DR9 genotype is a high-risk of LADA (Luo *et al.*, 2016). These findings imply that the LADA risk imparted by HLA-DRB1-DQA1-DQB1 loci varies considerably from T1D risk (Luo *et al.*, 2016). The distribution of HLA class II alleles in Israeli patients did not differ significantly between individuals with rapidly developing T1D and those with LADA (Hirsch *et al.*, 2007). Even in the patients with low-titer GAD auto-antibodies (Harrison *et al.*, 2020), HLA diabetes–susceptible haplotypes were more common in the LADA Chinese study (Zhou *et al.*, 2013). Therefore, future in-depth studies of HLA risk haplotype differences between T1D and LADA are necessary to understand their immunopathogeneses.

Biomarkers of β-cell auto-antibodies

In patients with T1D, auto-antibodies are produced by the immune system to attack different islet cells or insulin-producing β-cells. Each type of auto-antibody has its specific antigen target. Around 70-80% of the newly diagnosed T1D patients have at least two of these auto-antibodies, namely, type 1A DM (Bingley, 2010). Prediction of type 1A DM is associated with autoimmunity and related HLA-encoded genetic susceptibility (Liu and Eisenbarth, 2002). At present, five different auto-antibodies typically identified at the first presentation of T1D are strongly associated with the onset of disease (Taplin and Barker, 2008), for example, islet cell auto-antibodies (Liu *et al.*, 2009) targeting islet cells (including alpha, beta, delta, PP, and epsilon cells). The NIH-Funded Diabetes Prevention Trial–Type 1 (DPT-1) reported that when auto-antibodies are present in combination, the risk of developing T1D increases (Winter and Schatz, 2011). In contrast, 0.5% of the general population and about 3-4% of relatives of the patients with T1D may have some positive islet auto-antibodies. At the time of diagnosis, insulin auto-antibodies (IAA) are detected in at least 50% of all cases. IAA is also usually the first auto-antibody detected in young children with positive diagnoses but it is less common after adolescence. The use of IAA to measure within 1 week after the start of therapeutic injected insulin or exogenous insulin therapy should be cautioned because insulin antibodies against exogenous insulin will be indistinguishable from IAA. Moreover, glutamic acid decarboxylase auto-antibodies target a form of glutamic acid decarboxylase, an enzyme that synthesizes γ-aminobutylic acid (GABA), which is the inhibitory neurotransmitter in the brain, may also be detected in the T1D patients. GADA exists in two isoforms: GADA-65 and GADA-67. Only GADA-65 is expressed in β cells and the auto-antibodies respond to this isoform. In T1D patients, the detection rate of GAD-67 antibodies is lower than that of GAD-65 (Lühder *et al.*, 1994). Auto-antibodies for GAD-65 can be observed months to years before the onset of diabetes. GADA is also found in 70% of all T1D patients and it is especially common in individuals diagnosed after adolescence. However, these auto-antibodies are also observed in other autoimmune diseases such as myasthenia gravis. In Thai patients with T1D, CD69-expressing T cells were observed in

33% of the patients after activation with glutamic acid decarboxylase (Harrison *et al.*) (Boonyasrisawat *et al.*, 2002). The higher level of GAD might be due to positive lymphoproliferative in Thai patients (Banchuin *et al.*, 2002). Furthermore, insulinoma-associated-protein-2 auto-antibodies (IA-2A) particularly targeting a protein found in insulin-releasing cells were positive in about 60% at diagnosis of the T1D patients (Yu *et al.*, 2012). In addition, zinc-transporter 8 auto-antibodies (ZnT8A), which target zinc transporters in β-cells, were also observed in the patients with T1D. ZnT8A was found in up to 80% of the T1D patients at diagnosis (Wenzlau *et al.*, 2007) but only 26% of those who were tested positive for other auto-antibodies later developed T1D (Wenzlau and Hutton, 2013). The measurement of ZnT8 antibodies may be useful in monitoring islet destruction when following up on therapeutic intervention outcomes (Wenzlau *et al.*, 2007). Moreover, ZnT8A may also be related to other autoimmune diseases such as thyroid disease (Tantawy, 2008). Genetic factors may also influence the production of islet cell auto-antibodies (Liu *et al.*, 2009, Pihoker *et al.*, 2005). The Diabetes Prevention Trial 1 stated that ICA was observed at a higher frequency in siblings of the T1D patients than those of offspring or parents of the patients (Mrena *et al.*, 2006). In these cases, HLA haplotypes were associated with each ICA. For example, GADA is more frequent in the patients with HLA DR3-DQ2 than IAA, while IA-2A is more frequent in the patients with HLA DR4-DQ8 (Pihoker *et al.*, 2005).

Environmental factors

The question of how individuals develop auto-antibodies against self-islet antigens needs to be considered. Other important factors that contribute to the onset of T1D are the environmental factors, which may trigger islet autoimmunity and progression of T1D. Many environmental factors have been investigated in previous studies, including infection history, dietary habits, vaccine history, personal hygiene, presence of intestinal microbiota, vitamin D levels, presence of toxins and other substances, maternal DNA, and birth history (Esposito *et al.*, 2019). However, some factors increase the risk of developing T1D while others have protective effects. For example, many studies have reported the association between previous viral infections and the development of their potential risk of T1D (Forrest *et al.*, 1971, Honeyman *et al.*, 2000, Hyöty *et al.*, 1988, Hyöty and Taylor, 2002, Kaufman *et al.*, 1992, Menser *et al.*, 1978, Snell-Bergeon *et al.*, 2012). Several viruses have been discussed more often than bacterial infections since there have been suggested to trigger the T1D onset in a seasonal pattern of winter and then summer (Karvonen *et al.*, 1998). Furthermore, children who had recurrent viral respiratory tract infections during infancy were at higher risk of developing T1D in the future (Beyerlein *et al.*, 2016). Of all the viruses, enteroviruses are discussed most in detail as they are strongly correlated with T1D development (Coppieters *et al.*, 2012). The worst of all the enteroviruses triggering islet damage were coxsackieviruses, particularly strains and serotypes A2, A4, A16, B1, and B4 (Laitinen *et al.*, 2014). For example, the incidence of insulin-dependent diabetes mellitus (Chiasson *et al.*, 2002b) increased after the coxsackievirus B5 epidemic was reported in Jefferson County, Alabama (Wagenknecht *et al.*, 1991). The underlying mechanism of how such phenomena occur remains unclear although it is hypothesized in some studies to be molecular mimicry. The enteroviral P2-C protein sequence and glutamic acid decarboxylase (Harrison *et al.*) expressed in islet cells are similar, leading to cross-reaction of antibodies against the target virus (Kaufman *et al.*, 1992). Another study showed that during pregnancy fetuses may develop islet autoimmunity after chronic enterovirus infection (Viskari *et al.*, 2012). In a MIDIA study (Norwegian acronym for "Environmental Triggers of Type 1 Diabetes") conducted in Norway, enterovirus RNA was found in 10.5% of all diagnosed T1D children (Cinek *et al.*, 2014). Moreover, other viruses that are also potentially associated with T1D are the herpes virus, Epstein-Barr virus (EBV), cytomegalovirus (CMV), parechoviruses, rotaviruses, influenza viruses, rubella, and mumps virus (Principi *et al.*, 2017). Other risk factors for T1D were revealed in a study of intestinal microbiota dysbiosis, which influence lipid and glucose metabolism, immunity, and systemic inflammation outside of the intestine that can cause autoimmune diseases. Recent studies have also started to investigate the role of intestinal microbiota in modulating islet immunity (Esposito *et al.*, 2019). A study by Vatanen *et al.* compared children who had T1D and a control group who did not. It was found that the control group had higher levels of *Streptococcus thermophiles* and *Lactococcus lactis* species while children with T1D had higher levels of *Bifidobacterium pseudocatenulatum*, *Roseburia hominis*, and *Alistipes shahii* (Vatanen *et al.*, 2018). Moreover, rapid weight gain and infant growth that can lead to high blood glucose and insulin resistance, which may cause β-cell stress. Besides rapid growth, being overweight, puberty,

low physical activity, trauma, previous infection history, and glucose overload may cause β-cell stress and that might play an important role in the initiation of T1D (Lamb *et al.*, 2008). Other environmental factors such as dietary habits, type of solid food consumed, vaccine history, personal hygiene, vitamin D intake, presence of toxins and presence of certain chemicals did not have a significant influence on T1D onset (Rewers and Ludvigsson, 2016).

Gene-environment interactions

Environmental factors can trigger autoimmunity in genetically susceptible individuals leading to the destruction of pancreatic beta cells. Thus far, known environmental triggers are viral infection, ethnicity, dietary, toxin, perinatal, stress, microbiome variation, and combination of several environmental factors but data on interactions between those factors and genetic predisposition are not clearly understood.

The most studied interaction is between ethnic groups and genetic variations. Multiple susceptible genes for T1D (*HLA*, *INS*, *CTLA4*, *PTPN22*, and *IL2RA/CD25*) are associated with T1D in Caucasian (Western) and Asian (Eastern) populations (Ikegami *et al.*, 2008). The roles of the *HLA* and *INS* genes in contributing to the incidence of T1D have been thoroughly investigated in both Caucasian and Asian populations. The *PTPN22* gene is also associated with T1D in Japanese (Taniyama *et al.*, 2010) and *ERBB3* and *CLEC16A* were both significantly associated with T1D in Japanese, especially in autoimmune thyroid disease patients (Awata *et al.*, 2009).

Several studies have shown that certain viral infections may play a role in the pathogenesis of T1D, but data regarding interaction with genetic factors are scarce. In the mice model, EMCV infection can induce diabetes depending on both the genetic background and virus strain. In another rat model, Kilham's rat virus was isolated from diabetic rats and induced diabetes in diabetes-resistant BB/Wor rats. KRV did not induce diabetes in MHC complex-concordant and discordant non-BB rats. Moreover, it did not accelerate diabetes in diabetes-prone BB/Wor rats unless the rats has been reconstituted with DR spleen cells (Guberski *et al.*, 1991). In humans, enterovirus infection is the most studied viral infection that induces diabetes; however, several studies failed to identify susceptibility genes that, in combination with enteroviral infection, contribute to disease development (Blanter *et al.*, 2019).

Dietary factors such as nutritional status and exposure to complex proteins have been implicated in the development of auto-antibodies. In an analysis of the TEDDY study, male sex, father or sibling as the diabetic proband, introduction of probiotics under 28 days of age and weight at age of 12 months were associated with IAA, while only father as the diabetic proband and weight at age 12 months were associated with GADA (Krischer *et al.*, 2017). Exposure to bovine insulin in cow's milk has been hypothesized to play a role in beta cells autoimmunity. Bovine insulin is immunogenic and cross-reactive with human insulin. In some studies, early cow's milk exposure and disease are dependent on HLA-DQ genotypes (Kostraba *et al.*, 1993, Perez-Bravo *et al.*, 1996, Virtanen *et al.*, 2000). A study in Finland shows that infants with *PTPNN22* gene polymorphism who were fed with cow's milk-based formula only before 6 months have increased risk of auto-antibodies, while *CTLA-4* did not confer an increased risk of autoimmunity irrespective of infant feeding pattern (Lempainen *et al.*, 2009).

Changes in intestinal microbiota have been shown to impact innate immune response and may predispose to autoimmune diabetes, potentially through toll-like receptors. In a study of infants from Southeast Sweden, the relationship between protective HLA haplotypes, bacterial genera Intestinibacter, and Romboutsia were established. Hence, genetic risk as a result of HLA can be explained by microbiome variation (Russell *et al.*, 2019). Microbiota study in the TEDDY cohort demonstrated a reduction in bacterial pathways producing short-chain fatty acids in children who developed islet auto-antibodies or T1D, although there was no decrease in microbiota diversity (Vatanen *et al.*, 2018).

CONCLUSIONS

T1D is a multifactorial autoimmune disease and its immunogenetic mechanisms are complicated and mainly unknown. Immune system modulation plays a key role in the prevention and protection against T1D. However, it is a combination of both genetic and environmental factors that contribute to the onset and pathogenesis of T1D. Candidate genes identified by GWAS influence not only the immune system but also pancreatic islet β-cells. More studies were conducted in Caucasian populations than in Asian populations, which have shown the heterogeneous pathogenesis of T1D in both populations. Understanding the potential pathogenic mechanisms will be helpful in the development of new treatments and/or prevention of T1D. At present, the relationship between HLA and non-HLA is used to predict the onset of T1D and to identify a person's risk factor for the disease. The overall picture is shown in Figure 2.

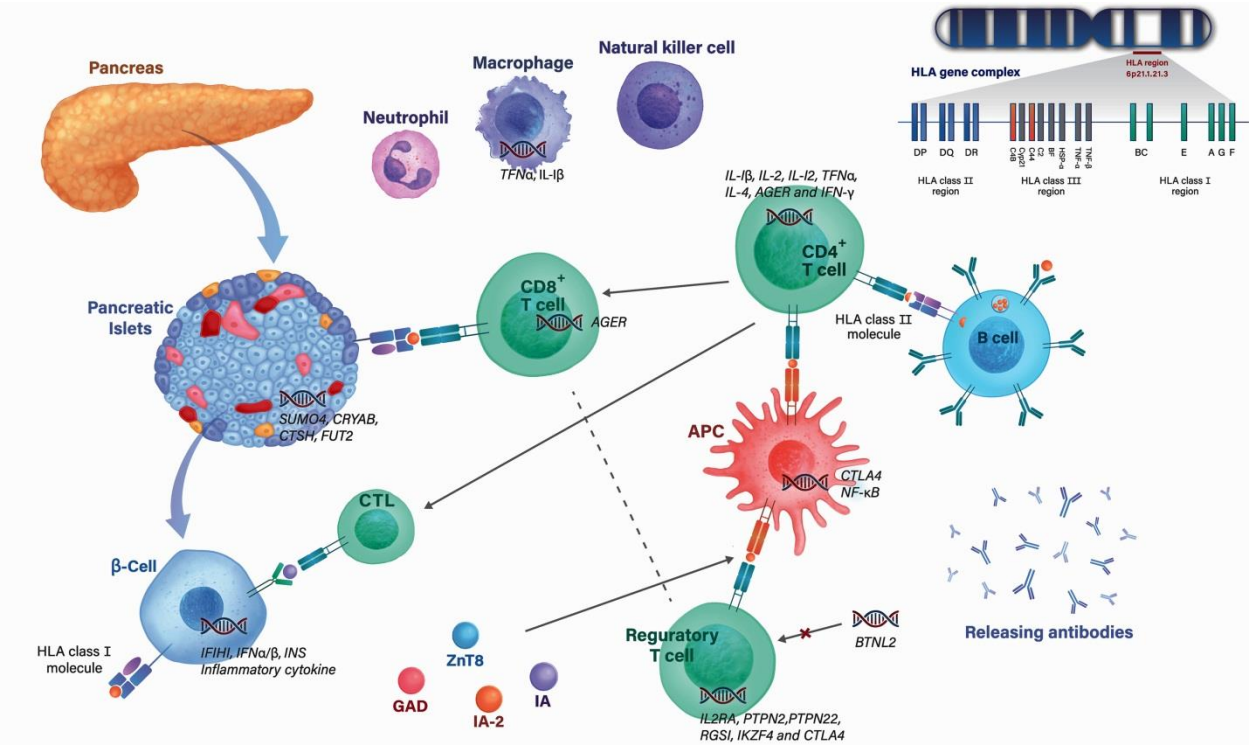

Figure 2 An overall process in T1D development including immunologic and genetic aspects of pathogenesis. Genetic predisposition and interaction with external triggers stimulate the complex immunological process. Activation of self-reactive $CD4^+$, $CD8^+$, and B lymphocytes contribute to humoral and cellular recognition of self-antigens and destruction of beta cells, responsible for insulin production.

ACKNOWLEDGMENTS

This work was supported by Siriraj Research Grant for Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University (to WT and NT).

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