Autoimmune thyroid disease and type 1 diabetes mellitus: same pathogenesis; new perspective?

Liyan Li, Shudong Liu and Junxia Yu

Abstract: Autoimmune thyroid disease (AITD) and type 1 diabetes mellitus (T1DM) are two common autoimmune diseases that can occur concomitantly. In general, patients with diabetes have a high risk of AITD. It has been proposed that a complex genetic basis together with multiple nongenetic factors make a variable contribution to the pathogenesis of T1DM and AITD. In this paper, we summarize current knowledge in the field regarding potential pathogenic factors of T1DM and AITD, including human leukocyte antigen, autoimmune regulator, lymphoid protein tyrosine phosphatase, forkhead box protein P3, cytotoxic T lymphocyte-associated antigen, infection, vitamin D deficiency, and chemokine (C-X-C motif) ligand. These findings offer an insight into future immunotherapy for autoimmune diseases.

Keywords: autoimmune thyroid disease, autoimmunity, genetics, type 1 diabetes mellitus

Introduction
Autoimmune thyroid disease (AITD) and type 1 diabetes mellitus (T1DM) are common autoimmune diseases that frequently appear together. AITD broadly comprises organ-specific autoimmune disorders characterized by dysfunction in the monitoring of self-antigens and autoreactive immune responses involving T lymphocytes and B lymphocytes, such as Graves’ disease (GD), Hashimoto’s thyroiditis (HT), atrophic thyroiditis, and postpartum thyroiditis.1-3 The pathogenesis of AITD involves humoral and cellular autoimmune mechanisms resulting from an immune reaction against the thyroid gland. AITD is characterized by the presence of thyroid-specific antithyroid peroxidase (TPOAb), antithyroglobulin (TGAAb), and thyroid-stimulating hormone autoantibodies.4-9 Apparently GD and HT are the most common forms of AITD and may coexist simultaneously or occur in one individual at different stages, for example, GD occurs 10 years after the onset of HT as reported by Troisi et al.1,10-12 A UK cross-sectional multicenter study reported an HT prevalence of 1.65% in the female population and a GD prevalence of 2.3% in the male population.13

It is well known that T1DM is a common autoimmune disease that clusters with AITD. According to a cross-sectional study carried out in Italy, there is a high prevalence (6.9%) of child/adolescent T1DM among patients with HT, which represents a significant difference according to age when compared with adults at a prevalence of 0.4%.14 The prevalence of GD is relatively lower than that of HT in patients with T1DM.15-19 Meanwhile, a Brazilian cross-sectional study showed a prevalence of AITD based on positive TPOAb and TGAAb as 21% in children/adolescents with T1DM.19 In addition, previous clinical studies have shown that the presence of thyroid antibodies in patients with T1DM and latent autoimmune diabetes in adults (LADA) predict a high risk for thyroid disease.20 Furthermore, a higher proportion of patients with T1DM positive for pancreatic islet beta-cell antibodies, insulin antibodies, and antiglutamic acid decarboxylase antibodies (GADAbs), which are often used for the diagnosis of T1DM, have been found to be positive for TPOAb.5,21-27 Therefore, it is considered that AITD is the most prevalent T1DM-related autoimmune disease, whereas LADA is an independent risk factor for the development of AITD.5,6,8,18,28-32
Accumulating evidence suggests that T1DM and AITD occur concomitantly and have similar immunogenetic susceptibilities. In this article, we summarize current knowledge in the field regarding the pathogenic factors of T1DM and AITD in order to provide a deeper understanding for the development of future immunotherapies for these autoimmune diseases. Firstly, we provide an overview of AITD/T1DM-associated literature and give a classification of the etiopathogenic factors of AITD/T1DM. Secondly, we performed a search of these factors in titles and abstracts, along with ‘AITD’ or ‘T1DM’ in all fields in PubMed and Baidu Scholar or reference lists. Finally, we selected 253 articles to review in detail; some similar or irrelevant studies were excluded (Figure 1).

**Genetics and autoimmunity**

**Human leukocyte antigen**

Human leukocyte antigen (HLA) complexes, located on human chromosome 6p21, are divided into three classes: class I (HLA-A, HLA-B, and HLA-C), class II (HLA-DR, HLA-DQ, and HLA-DP), and class III (including complement components and 21-hydroxylase). HLA complexes play key roles in the control of immune responses to exogenous and self-antigens. HLA genes are strongly linked with thyroid autoimmunity in patients with T1DM, demonstrating that some genetic determinants within the HLA region are involved in both T1DM and AITD. The HLA DRB1*0405/DQA1*0301/DQB1*0401 haplotype confers susceptibility in patients with T1DM and GADAb-positive AITD, whereas individuals with the HLA DRB1*0803/DQB1*0601 haplotype are more susceptible to AITD but not to anti-islet autoimmunity. In addition to high-risk HLA DR-DQ haplotypes, HLA class I A and C alleles also appear to be associated with T1DM in Filipino patients. HLA-DR3, which plays a pivotal role in normal immune reactions by binding peptide antigens and presenting them to T-cell receptors, is also shown to be a common indicator of a predisposition to AITD and T1DM. These studies suggest that class II and class I HLA complexes constitute shared risk factors for T1DM and AITD.

**Autoimmune regulator**

The autoimmune regulator (AIRE) is a transcriptional factor that regulates autoimmunity and is involved in immunological tolerance and genetic susceptibility to multi-organ autoimmune diseases, such as autoimmune polyglandular syndrome type 1 (APS-1), T1DM, AITD, and Down syndrome.
APS-1 is known to be caused by AIRE gene mutations (located on chromosome 21) and is characterized by different combinations of two or more autoimmune disorders such as mucocutaneous candidiasis, hypoparathyroidism, Addison’s disease, T1DM, and/or AITD, which occur simultaneously or sequentially over time.55 The clinical manifestations of AITD are a minor component of APS-1 and mostly HT, but not GD as previously described.55 Wiebolt et al. reported that GD and HT appear to show a different clustering of additional autoimmune disorders suggesting a different pathogenetic basis.56

The AIRE promoter haplotype was found to affect AIRE transcriptional activity and negative T-cell selection, contributing to susceptibility to autoimmune diseases.50 In addition, single nucleotide polymorphisms (SNPs) in AIRE (rs74203920 and rs1800525) are reported to be associated with APS type 2 (APS-2) in patients with T1DM without AITD (where APS-2 was defined as the presence of Addison’s disease combined with T1DM, AITD, or both).57 AIRE gene variations cause several autoimmune diseases, for example, G11107A polymorphism was demonstrated to be significantly related to AITD in patients with systemic sclerosis.49,53 Furthermore, AIRE gene expression decreased in a mouse model of T1DM and in peripheral blood mononuclear cells of patients with T1DM, suggesting a role in T1DM pathogenesis.58

Abnormalities of AIRE gene expression are also observed in Down syndrome, a chromosomopathy of trisomy 21, that predisposes individuals to develop HT, T1DM, and other autoimmune diseases.59-62 Turner syndrome is another type of chromosomopathy involved with the X chromosome that is a risk factor for autoimmune diseases such as AITD and T1DM. These chromosomopathies and associated diseases suggest that the function of the two chromosomes may have an important effect on the pathogenesis of different autoimmune disorder clusterings; however, the specific etiopathogenic mechanisms associated with possible genes and factors remain to be investigated.63-65

In addition to controlling T cells,51 AIRE affects peripheral autoreactive B-cell tolerance and autoantibody production.66 B cells also play a crucial role in the development of T1DM and AITD, involving multiple associated autoantibodies to islet and thyroid antigens.9,67 Autoreactive mature naïve B cells accumulate and increase the recognition of self-antigens in the peripheral tissue of AIRE-deficient patients;66 furthermore, B-cell depletion therapy exerts an inhibitory effect on T1DM development.68

Therefore, an elucidation of AIRE functions and AIRE-associated diseases will help to understand fully the underlying pathogenic mechanisms and provide therapeutic strategies for autoimmune diseases including AITD and T1DM.

**Lymphoid protein tyrosine phosphatase**

Lymphoid protein tyrosine phosphatase (LYP), encoded by the protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene, is expressed primarily in lymphoid tissues and mainly in T cells, where it acts as a powerful suppressor of T-cell activation through T-cell receptor-mediated signaling.69,70

The regulatory molecular mechanisms of LYP may involve the extracellular regulated protein kinase (ERK) and protein kinase B (AKT) signaling pathways, which regulate the proliferation, apoptosis, and survival of T cells.71 In addition, the logistic regression analysis in a genome-wide association study demonstrated that an SNP (rs2476601) of the PTPN22 gene had an independent effect on APS type 3 variant (APS3v), including T1DM and AITD in one individual child;36 this significant association agreed with other studies.72-74 Several studies have also shown that the SNP C1858T (rs2476601), that leads to the substitution of a tryptophan at position 620 of LYP for an arginine (R620W), is linked with both T1DM and AITD.56,73-78 However, some contradictory results show that this SNP in PTPN22 is associated with AITD but not with T1DM.79 Another report indicated that an SNP (rs2476601) in PTPN22 is not associated with AITD.80 The association of SNPs in PTPN22 with T1DM also differentiates between populations of different ethnicity, such as Chinese and Japanese.81-84 These differences may be due to the role of PTPN22 only as a supplementary risk factor to AITD and T1DM, or due to different additional risk factors such as age and gender.79,85 Recent research has revealed how age has a great effect on the clinical pattern of diseases; with HT and other autoimmune diseases, clustering can occur at different life stages.10,14
Therefore, further studies are still needed to identify the contribution of PTPN22 to T1DM and AITD pathogenesis. Nevertheless, numerous studies have suggested the use of PTPN22 as a prognostic factor or even as a target for novel therapeutic strategies such as treatments with LYP inhibitors, for both T1DM and AITD. The link between PTPN22 and a spectrum of human autoimmune diseases suggests interactions between a small group of shared autoimmunity genes with HLA genotypes and other still unknown factors.

**Forkhead box protein P3**

Forkhead box protein P3 (FOXP3) is a master transcriptional regulator of the differentiation and specification of regulatory T cell (Treg)-mediated immunological monitoring and dominance tolerance. Treg malfunctions are associated with imbalanced immune homeostasis and various autoimmune diseases. FOXP3 polymorphisms and variants are significantly linked with AITD. A decrease in the number of FOXP3(+) Tregs and an increase in Th17 lymphocytes (a subtype of T cells, characterized by the excretion of interleukin-17) in patients with AITD suggest an important role for FOXP3 and a number of complex interactions in conferring genetic susceptibility to the pathogenic process of the disease.

Many contradictory results regarding the association between FOXP3 polymorphisms and T1DM have been reported. An early study by Brusko et al. indicated that the number of FOXP3(+) Tregs does not contribute to the pathogenesis of T1DM. However, studies performed in murine models of T1DM show that the function of FOXP3(+) Tregs is reduced and is involved in later events of diabetogenesis in non-obese diabetic (NOD) mice. Moreover, immunotherapy with complete Freund’s adjuvant upregulated FOXP3(+) Tregs and improved hyperglycemia, through an immunoregulatory mechanism in new-onset NOD mice. The hyperglycemia of NOD mice with recent-onset diabetes was also well controlled by a single injection of FOXP3 transduction. Similar therapeutic effects were found in NOD transgenic mice with transient expression of transforming growth factor β in the islets, which induced a significant increase in FOXP3-expressing Treg cells. These findings suggested that an immunosuppressive drug modulating FOXP3 would be a promising treatment for AITD and T1DM.

**Cytotoxic T lymphocyte-associated antigen**

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), a transmembrane protein on the surface of Tregs, has been found to play critical roles in inhibiting immune activation and regulating immune response. Moreover, the blockade of CTLA-4 has shown promising efficacy in the treatment of many carcinomas through enhancing Treg proliferation. CTLA-4 and its gene polymorphisms are reported to be important genetic determinants of the risk of T1DM and/or AITD.

A family-based study in patients with T1DM and AITD has shown a strong association between the CTLA-4 gene and T1DM plus HT, based on microsatellite marker analysis. The association of CTLA-4 SNP A/G49 (rs231775) and CT60 (rs3087243) with T1DM plus AITD (APS3v) was significant. However, it was not significant with T1DM alone, suggesting that CLTA4 is a joint susceptibility gene for T1DM plus AITD. No association of the CTLA-4 gene with T1DM only has been found in other reports. Therefore, meta-analyses support the findings that CTLA-4 polymorphism is a risk factor for T1DM susceptibility.

CTLA-4 A/G49 and CT60 polymorphisms are also reported to increase susceptibility to HT and GD (AITD) in different populations. CTLA-4 is thought to play different roles in T1DM and AITD, despite accumulating evidence that suggests a vital role for CTLA-4 in the pathogenesis of these two concomitant diseases. Enhanced expression of CTLA-4 promotes Treg function and decreases the Th17 cytokine-induced inflammatory condition. Furthermore, treatments targeting CTLA-4 (like abatacept or CTLA4-Ig) have exhibited obvious clinical side effects, whereas a complex genetic interplay between CTLA-4 and individual HLA loci has resulted in the appearance of different phenotypes.

**Environmental factors and autoimmunity**

The pathophysiology of autoimmune diseases often involves complex interactions between the immunogenetic background and environmental factors.
factors, such as infection, vitamin status, and inflammation, that trigger a pathological response.

**Infectious factors**

Accumulating evidence has suggested that infectious agents are important initiators of autoimmune diseases through molecular mimicry, polyclonal T-cell activation, and HLA class II antigen induction. Infectious agents, such as bacteria and viruses, activate aberrant immune reactions while interacting with various cytokines or other mediators in individuals with specific genetic backgrounds. In established animal models, this has been shown to lead to T1DM and other autoimmune diseases, either with a rapid or late onset; this association is supported by the Diabetes Autoimmunity Study in the Young (DAISY). A significant association between infectious agents and T1DM has been reported in several animal studies and human epidemiological studies, suggesting a diabetogenic role for damaged pancreatic islet beta-cell functions.

Table 1. Susceptible genes in common between T1DM and AITD.

| Gene and polymorphism      | Function                                      | Reference                                                                 | Therapy target |
|----------------------------|-----------------------------------------------|---------------------------------------------------------------------------|----------------|
| HLA class I and            | Control of immune responses                   | Moriguchi et al. (2011); Huber et al. (2008); Tomer et al. (2015); Kahles et al. (2015); Li et al. (2017); Chung et al. (1996); Bugawan et al. (2002); Golden et al. (2005); Kong et al. (2007); Kong et al. (2003); Dultz et al. (2009); Krischer et al. (2015) | –              |
| AIRE                       | Involvement in immunological tolerance by distinguishing self-antigens | Ferrera et al. (2007); Lovewell et al. (2015); Nagamine et al. (1997); Bruserud et al. (2016); Gavanescu et al. (2008); Wielt et al. (2011); Resende et al. (2015); Yu et al. (2006); Skogberg et al. (2014); Guaraldi et al. (2017); Aversa et al. (2016); De Luca et al. (2010); De Sanctis and Kathar (2019); Aversa et al. (2015); Wegiel et al. (2019); Sng et al. (2019); Wong and Ken (2005); Hu et al. (2007) | –              |
| LYP                        | Suppression of T cell-mediated signaling      | Tomer et al. (2015); Dultz et al. (2009); Rhe and Veillette (2012); Betterle et al. (2014); Criswell et al. (2005); Houcken et al. (2018); Bottini et al. (2004); Velaga et al. (2004); Bulut et al. (2014); Smyth et al. (2004); Lee et al. (2011); Alkhateeb et al. (2013); Liu et al. (2015); Ikegami et al. (2006); El Fotoh et al. (2019); Giza et al. (2013); Wasniewska et al. (2012); Prezioso et al. (2017); Burn et al. (2011); Blissett et al. (2017); Bottini et al. (2008) | LYP inhibitors |
| FOX3                       | Regulation of the differentiation and specification of regulatory T cells | Ban et al. (2007); Inoue et al. (2010); Villano et al. (2009); Li et al. (2015); Boskowski et al. (2013); Nakano et al. (2007); Korn et al. (2009); Li et al. (2016); Bjornvold et al. (2006); Rubio-Cabezas et al. (2009); Zavattari et al. (2004); Nakanishi and Shima (2007); Brusko et al. (2007); Tritt et al. (2008); Brode et al. (2006); Tian et al. (2009); Jaeckel et al. (2005); Peng et al. (2004); Wu et al. (2012); Zheng et al. (2009); Johnson et al. (2013) | Complete Freund’s adjuvant |
| CTLA-4                     | Inhibition of immune activation and immune response | Golden et al. (2005); Villano et al. (2009); Chen et al. (2013); Pastuszak-Lewandoska et al. (2012); Douroudis et al. (2009); Bednarczuk et al. (2003); Hou et al. (2015); Vaidya et al. (1999); Kavvoura et al. (2007); Lee et al. (2000); Ikemura et al. (2006); Mochizuki et al. (2003); Howson et al. (2007); Tang et al. (2012); Takara et al. (2000); Mayans et al. (2007); Balic et al. (2009); Ban et al. (2001); Celmeli et al. (2013); Chen and Li (2019); Wang et al. (2017); Kavvoura et al. (2005); Liu et al. (2013); Dong et al. (2014); Fathima et al. (2019); Bicke et al. (2009); Einarsdottir et al. (2003); Ban and Tomer (2003); Aversa et al. (2019); Orban et al. (2011); Orban et al. (2014) | Abatacept |

AIRE, autoimmune regulator; AITD, thyroid autoimmune disease; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; FOXP3, forkhead box protein P3; HLA, human leukocyte antigen; LYP, lymphoid protein tyrosine phosphatase; T1DM, type 1 diabetes mellitus.
Many coexisting autoimmune diseases show similar pathogenetic mechanisms, nevertheless, it is not clear whether enterovirus-mediated immune responses cause cross-reactivity with the thyroid through molecular mimicry. Recent studies have reported that commensal microbes contribute to the pathogenesis and development of T1DM via the toll-like receptor signaling pathway, which is also involved in the pathogenesis of AITD, suggesting the existence of several common elements in the pathogenesis of these diseases.160–163 Moreover, infection by *Helicobacter pylori* is known to be significantly associated with T1DM and AITD in humans, indicating that this infection may be an environmental trigger for the development of these two autoimmune diseases.164,165 Similar findings regarding this association have been reported in patients with LADA. It is thought that the CagA protein expressed by *H. pylori* might be a vital factor in the immune response.166 Further research is required to investigate the association between infectious factors and T1DM/AITD, considering the complicated pathogenic mechanisms underlying autoimmune diseases.

**Vitamin D and the vitamin D receptor pathway**

1,25-dihydroxyvitamin D3 (1,25(OH)2D3 or VD3), which is generated by hydroxylation of the precursor 25-dihydroxyvitamin D3 (25(OH)D3) in the kidney, is the main active form of vitamin D (VD). VD3 is involved in the regulation of both innate and adaptive immune systems. VD deficiency seems to be a high risk factor for autoimmune diseases such as T1DM and AITD.167–175

A large Norwegian case-control study of 35,940 pregnant women with a 15-year follow up showed that the lower the maternal serum levels of 25(OH)D3, the higher the risk of T1DM in the offspring.176,177 Accumulating evidence from clinical studies has shown that 25(OH)D3 levels are insufficient or deficient in patients with AITD with high TPOAb and TGAb levels, and that treatment via VD supplementation has a beneficial effect on TGAb levels. These findings suggest that VD is associated with the pathogenesis and development of AITD.178–188 A VD deficiency has been proposed to increase the immune response through activating the production of autoimmune thyroid antibodies in T helper-2 cells (Th-2) and B cells.189,190

Most studies have universally demonstrated that decreased VD levels are associated with T1DM through their impact on insulin sensitivity and pancreatic islet beta-cell function, indicating that VD is involved in the progression and pathogenesis of T1DM.191–195 Furthermore, earlier VD supplementation increases serum 25(OH)D3 levels, improves insulin secretion and glucose control, and decreases the risk of T1DM development in children and pregnant women.192,194,196–198 Moreover, a study on the effect of a high-dose VD3 treatment in nondiabetic children with positive islet autoantibodies is ongoing and results will be declared on completion (DiAPREV-IT2; https://clinicaltrials.gov/ct2/show/NCT01122446).199

Nevertheless, the DAISY study demonstrated no significant association between VD or 25(OH)D3 intake levels in childhood and islet autoimmunity risk or T1DM.200 These results are in agreement with a Swedish study,201 and the recently published Environmental Determinants of Diabetes in the Young (TEDDY) study.202 However, it may be difficult to control the factors that have led to different results, such as diet and additional environmental determinants.203–206

VD binds the vitamin D receptor (VDR) for signal transduction and interacts with other factors, such as the vitamin D-binding protein, retinoid X receptor, and peroxisome proliferator-activated receptor (PPAR).170,171,207,208 Previous studies have shown that the Th-2 cell response plays an important role in the pathogenesis of T1DM and AITD,209–212 whereas VD supplementation reverses the inappropriate activation of T cells and improves immune homeostasis, suggesting a therapeutic value for VD in concurrent autoimmune diseases.145,189,211 VDR is critical for the correct biological function of VD in several processes such as the modulation of calcium homeostasis and bone growth.213 Evidence demonstrates that gene polymorphisms in VDR are associated with susceptibility, not only to T1DM, but also to AITD in different populations.174,214–218

In addition, the 25-hydroxyvitamin D3-1α-hydroxylase (CYP27B1), also named 1α-hydroxylase, a mitochondrial P450 enzyme, catalyzes the conversion of 25(OH)D3 into 1,25(OH)2D3 as expected, it is an important regulator of VD activation.219–221 CYP27B1 polymorphisms have been shown to confer susceptibility to AITD or T1DM and are also
thought to be associated with decreased CYP27B1 expression and VD3 levels.\textsuperscript{222–227}

Consequently, there is some clinical evidence to suggest that VD status may be associated with T1DM or AITD; however, the underlying mechanisms of the VD/VDR-associated pathway involved in T1DM and AITD pathogenesis remain unclear. They may be linked to the multiple biological activities of VD in the body.

\textit{Chemokine [C-X-C motif] ligands}

The chemokine (C-X-C motif) ligand (CXCL) CXCL10 is a proinflammatory cytokine secreted by multiple cell types, such as T-lymphocyte neutrophils and monocytes. CXCL10 belongs to the ELR(-) CXC subfamily of chemokines and has several functions, such as regulating T-cell chemotaxis and the inflammatory response through the binding chemokine CXC receptor 3 (CXCR3), a G protein-coupled receptor.\textsuperscript{228–232} CXCL10, CXCL9, and CXCL11 also bind CXCR3 and have been implicated in the pathogenesis of many organ-specific autoimmune diseases involved in Th helper-1 cells (Th-1), including T1DM and AITD.\textsuperscript{233–238} Serum CXCL9 levels were significantly higher in patients with hyperthyroid GD than those of controls and patients with euthyroid or hypothyroid GD. However, there was a reduction in CXCL9 levels under the treatment of methimazole (an antithyroid drug), which suggests that CXCL9 plays a pathological role in GD.\textsuperscript{239} Previous evidence demonstrated that CXCL9 expression was significantly increased in GD thyrocytes induced by interferon-\gamma (IFN\gamma) and tumor necrosis factor-\alpha (TNF-\alpha), which suggests that CXCL9 expression was low in normal thyrocytes and primary GD, and that the increased effect could be inhibited by PPAR-\alpha agonist (fenofibrate) treatment.\textsuperscript{240} Recent studies have demonstrated that CXCL9 and CXCR3 levels are upregulated in patients with diabetic nephropathy, accompanied by activation of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway; the downregulation of CXCL9 suppresses apoptosis and inflammation related to JAK/STAT pathway activation.\textsuperscript{241} Moreover, CXCL11 has also been shown to be highly expressed in AITD and T1DM.\textsuperscript{239,242,243}

Relevant studies have shown that levels of CXCL13 and its receptor CXCR5 are increased in inflamed islets of NOD mice due to CXCL13-dependent effects on the structural organization of B lymphocytes. Furthermore, upregulated CXCL13 activates the ERK, STAT3, AKT, and chemokine inflammatory signaling pathways, causing neuroinflammation in mice with diabetic neuropathy.\textsuperscript{244,245} The expression of CXCR5/ CXCL13 is notably high in the thyroid and it is associated with the TPOAb levels of patients with AITD, suggesting that CXCL13/CXCR5 play a role in AITD pathogenesis.\textsuperscript{246}

A previous study has shown that the secretion of the chemokine CXCL8 is induced in thyrocytes by TNF-\alpha and inhibited by IFN\gamma, which is different from the induction of CXCL10 by IFN\gamma and not TNF-\alpha.\textsuperscript{247} Moreover, TNF-\alpha-induced CXCL8 secretion may be inhibited by IFNs in human thyrocytes, suggesting different roles for CXCL10 and CXCL8 in thyroid disease.\textsuperscript{248} Recent studies have demonstrated that CXCL10 may be involved in the initial phase of GD, while CXCL8 may be involved in a later chronic phase of GD.\textsuperscript{249} In addition, CXCL8 was found to be increased in streptozocin-induced diabetic mice, whereas the inhibition of CXCL8 had a therapeutic effect in improving renal histopathology in diabetic nephropathy.\textsuperscript{250,251} CXCL8/CXCL1-mediated leukocyte endothelial adhesion may make an important contribution to diabetic microvascular complications.\textsuperscript{252}

In short, multiple CXCLs and their receptors are involved in the progression and pathogenesis of AITD and T1DM \textit{via} several mechanisms. New strategies for treating these two autoimmune diseases may include regulation of the activity of CXCLs and their receptors.

\textbf{Conclusion}

AITD and T1DM are two common autoimmune diseases that can occur concomitantly. Recent findings have determined that HLA, AIRE, PTPN22, FOXP3, CTLA-4, infection, VD deficiency, and CXCLs confer susceptibility to the development and prognosis of AITD and T1DM, to various degrees (Figure 2). Despite accumulated data, a complete understanding of the mechanisms underlying the etiology and pathogenesis of T1DM and AITD is lacking. More studies are needed to further investigate and explore novel therapeutic targets, for example LYP, VD, and CXCLs, in the treatment of...
various autoimmune diseases, including T1DM and AITD.186,233,235,250,253

Author contributions
Liyan Li: conceptualization; investigation; writing original draft.
Shudong Liu: formal analysis; investigation; methodology; writing original draft.
Junxia Yu: conceptualization; formal analysis; methodology; writing–review and editing.

Conflict of interest statement
The author(s) declare that there is no conflict of interest.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD
Junxia Yu https://orcid.org/0000-0003-3312-1215

References
1. Ruggeri RM, Giuffrida G and Campenni A. Autoimmune endocrine diseases. Minerva Endocrinol 2018; 43: 305–322.
2. Hadj-Kacem H, Rebuffat S, Mnif-Feki M, et al. Autoimmune thyroid diseases: genetic susceptibility of thyroid-specific genes and thyroid autoantigens contributions. Int J Immunogenet 2009; 36: 85–96.
3. Tomer Y and Huber A. The etiology of autoimmune thyroid disease: a story of genes and environment. J Autoimmun 2009; 32: 231–239.
4. Weetman AP and McGregor AM. Autoimmune thyroid disease: further developments in our understanding. Endocr Rev 1994; 15: 788–830.
5. Moriguchi M, Nosu S, Kawabata Y, et al. Clinical and genetic characteristics of patients with autoimmune thyroid disease with anti-islet autoimmunity. Metabolism 2011; 60: 761–766.
6. Park YS, Kim TW, Kim WB, et al. Increased prevalence of autoimmune thyroid disease in patients with type 1 diabetes. Korean J Intern Med 2000; 15: 202–210.
7. Kordonouri O, Klinghammer A, Lang EB, et al. Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. Diabetes Care 2002; 25: 1346–1350.
8. Hughes JW, Bao YK, Salam M, et al. Late-onset T1DM and older age predict risk of additional autoimmune disease. Diabetes Care 2019; 42: 32–38.
9. Rydzewska M, Jaromin M, Pasierowska IE, et al. Role of the T and B lymphocytes in pathogenesis of autoimmune thyroid diseases. Thyroid Res 2018; 11: 2.
10. Crisafulli G, Gallizzi R, Aversa T, et al. Thyroid function test evolution in children with Hashimoto’s thyroiditis is closely conditioned by the biochemical picture at diagnosis. Ital J Pediatr 2018; 44: 22.
11. Troisi A, Novati P, Sali L, et al. Graves’ thyrotoxicosis following Hashimoto’s thyroiditis. Res Rep Endocr Disord 2013; 3: 13–15.
12. Wasniewska M, Corrias A, Arrigo T, et al. Frequency of Hashimoto’s thyroiditis antecedents in the history of children and adolescents with graves’ disease. Horm Res Paediatr 2010; 73: 473–476.
13. Boelaert K, Newby PR, Simmonds MJ, et al. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. Am J Med 2010; 123: 183.e181–189.
14. Ruggeri RM, Trimarchi F, Giuffrida G, et al. Autoimmune comorbidities in Hashimoto’s thyroiditis: different patterns of association in
adulthood and childhood/adolescence. Eur J Endocrinol 2017; 176: 133–141.

15. Mantovani RM, Mantovani LM and Dias VM. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus: prevalence and risk factors. J Pediatr Endocrinol Metab 2007; 20: 669–675.

16. Lombardo F, Messina MF, Salzano G, et al. Prevalence, presentation and clinical evolution of Graves' disease in children and adolescents with type 1 diabetes mellitus. Horm Res Pediatr 2011; 76: 221–225.

17. Ardestani SK, Keshtehi AH, Khalili N, et al. Thyroid disorders in children and adolescents with type 1 diabetes mellitus in Isfahan, Iran. Iran J Pediatr 2011; 21: 502–508.

18. Ghawil M, Tonutti E, Abusrewil S, et al. Autoimmune thyroid disease in Libyan children and young adults with type 1 diabetes mellitus. Eur J Pediatr 2011; 170: 983–987.

19. Riquetto ADC, de Noronha RM, Matsuo EM, et al. Thyroid function and autoimmunity in children and adolescents with type 1 diabetes mellitus. Diabetes Res Clin Pract 2015; 110: e9–e11.

20. Jin P, Huang G, Lin J, et al. High titre of antiglutamic acid decarboxylase autoantibody is a strong predictor of the development of thyroid autoimmunity in patients with type 1 diabetes and latent autoimmune diabetes in adults. Clin Endocrinol 2011; 74: 587–592.

21. Gul K, Ustun I, Aydin Y, et al. Autoimmune thyroid disease in patients with anti-GAD positive type 1 diabetes mellitus. Cent Eur J Med 2009; 4: 415–422.

22. Jonsdottir B, Andersson C, Carlsson A, et al. Thyroid autoimmunity in relation to islet autoantibodies and HLA-DQ genotype in newly diagnosed type 1 diabetes in children and adolescents. Diabetologia 2013; 56: 1735–1742.

23. Kakleas K, Paschali E, Kefalas N, et al. Factors for thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. Ups J Med Sci 2009; 114: 214–220.

24. Lindberg B, Carlsson A, Ericsson UB, et al. Prevalence of beta-cell and thyroid autoantibody positivity in schoolchildren during three-year follow-up. Autoimmunity 1999; 31: 175–185.

25. Jonsdottir B, Larsson C, Lundgren M, et al. Childhood thyroid autoimmunity and relation to islet autoantibodies in children at risk for type 1 diabetes in the diabetes prediction in skane (DiPiS) study. Autoimmunity 2018; 51: 228–237.

26. Triolo TM, Armstrong TK, McFann K, et al. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. Diabetes Care 2011; 34: 1211–1213.

27. Jonsdottir B, Larsson C, Carlsson A, et al. Thyroid and islet autoantibodies predict autoimmune thyroid disease at type 1 diabetes diagnosis. J Clin Endocrinol Metab 2017; 102: 1277–1285.

28. Denzer C, Karges B, Nake A, et al. Subclinical hypothyroidism and dyslipidemia in children and adolescents with type 1 diabetes mellitus. Eur J Endocrinol 2013; 168: 601–608.

29. Kinova S, Payer J, Kalafutova I, et al. [Autoimmune thyroid disease in patients with type 1 diabetes mellitus.] Bratislavské Lekarske Listy 1998; 99: 23–25.

30. Lu MC, Chang SC, Huang KY, et al. Higher risk of thyroid disorders in young patients with type 1 diabetes: a 12-year nationwide, population-based, retrospective cohort study. PLoS One 2016; 11: e0152168.

31. Nederstigt C, Uitbeijerse BS, Janssen LGM, et al. Associated auto-immune disease in type 1 diabetes patients: a systematic review and meta-analysis. Eur J Endocrinol 2019; 180: 135–144.

32. Karavanaki K, Kakleas K, Paschali E, et al. Screening for associated autoimmunity in children and adolescents with type 1 diabetes mellitus (T1DM). Horm Res 2009; 71: 201–206.

33. Chikuba N, Akazawa S, Yamaguchi Y, et al. Type 1 (insulin-dependent) diabetes mellitus with coexisting autoimmune thyroid disease in Japan. Intern Med 1992; 31: 1076–1080.

34. Maahs DM, West NA, Lawrence JM, et al. Epidemiology of type 1 diabetes. Endocrinol Metab Clin North Am 2010; 39: 481–497.

35. Huber A, Menconi F, Corathers S, et al. Joint genetic susceptibility to type 1 diabetes and autoimmune thyroiditis: from epidemiology to mechanisms. Endocrine Rev 2008; 29: 697–725.

36. Tomer Y, Dolan LM, Kahaly G, et al. Genome wide identification of new genes and pathways in patients with both autoimmune thyroiditis and type 1 diabetes. J Autoimmun 2015; 60: 32–39.

37. Bodis G, Toth V and Schwarting A. Role of human leukocyte antigens (HLA) in autoimmune diseases. Rheumatol Ther 2018; 5: 5–20.
38. Caillat-Zucman S. New insights into the understanding of MHC associations with immune-mediated disorders. *HLA* 2017; 89: 3–13.

39. Kahles H, Fain PR, Baker P, *et al.* Genetics of autoimmune thyroiditis in type 1 diabetes reveals a novel association with DPB1*0201: data from the type 1 diabetes genetics consortium. *Diabetes Care* 2015; 38(Suppl. 2): S21–S28.

40. Li CW, Osman R, Menconi F, *et al.* Flexible peptide recognition by HLA-DR triggers specific autoimmune T-cell responses in autoimmune thyroiditis and diabetes. *J Autoimmun* 2017; 76: 1–9.

41. Chuang LM, Wu HP, Chang CC, *et al.* HLA DRB1/DQA1/DQB1 haplotype determines thyroid autoimmunity in patients with insulin-dependent diabetes mellitus. *Clin Endocrinol* 1996; 45: 631–636.

42. Bugawan TL, Klitz W, Alejandrino M, *et al.* The association of specific HLA class I and II alleles with type 1 diabetes among Filipinos. *Tissue Antigens* 2002; 59: 452–469.

43. Golden B, Levin L, Ban Y, *et al.* Genetic analysis of families with autoimmune diabetes and thyroiditis: evidence for common and unique genes. *J Clin Endocrinol Metab* 2005; 90: 4904–4911.

44. Kong YC, Flynn JC, Banga JP, *et al.* Application of HLA class II transgenic mice to study autoimmune regulation. *Thyroid* 2007; 17: 995–1003.

45. Kong YC, Flynn JC, Wan Q, *et al.* HLA and H2 class II transgenic mouse models to study susceptibility and protection in autoimmune thyroid disease. *Autoimmunity* 2003; 36: 397–404.

46. Dultz G, Matheis N, Dittmar M, *et al.* The protein tyrosine phosphatase non-receptor type 22 C1858T polymorphism is a joint susceptibility locus for immunthyroiditis and autoimmune diabetes. *Thyroid* 2009; 19: 143–148.

47. Krischer JP, Lynch KF, Schatz DA, *et al.* The 6 year incidence of diabetes-associated autoantibodies in genetically at-risk children: the TEDDY study. *Diabetologia* 2015; 58: 980–987.

48. Anderson MS, Venanzi ES, Klein L, *et al.* Projection of an immunological self shadow within the thymus by the aire protein. *Science* 2002; 298: 1395–1401.

49. Ferrera F, Rizzi M, Sprecacener E, *et al.* AIRE gene polymorphisms in systemic sclerosis associated with autoimmune thyroiditis. *Clin Immunol* 2007; 122: 13–17.

50. Lovewell TR, McDonagh AJ, Messenger AG, *et al.* The AIRE -230Y polymorphism affects AIRE transcriptional activity: potential influence on AIRE function in the thymus. *PLoS One* 2015; 10: e0127476.

51. Liston A, Lesage S, Wilson J, *et al.* Aire regulates negative selection of organ-specific T cells. *Nat Immunol* 2003; 4: 350–354.

52. Nagamine K, Peterson P, Scott HS, *et al.* Positional cloning of the APECED gene. *Nat Gen* 1997; 17: 393–398.

53. Bruserud O, Ofedal BE, Wolf AB, *et al.* AIRE-mutations and autoimmune disease. *Curr Opin Immunol* 2016; 43: 8–15.

54. Gavanescu I, Benoist C and Mathis D. B cells are required for Aire-deficient mice to develop multi-organ autoinflammation: a therapeutic approach for APECED patients. *Proc Natl Acad Sci U S A* 2008; 105: 13009–13014.

55. Betterle C, Greggio NA and Volpato M. Clinical review 93: autoimmune polyglandular syndrome type 1. *J Clin Endocrinol Metab* 1998; 83: 1049–1055.

56. Wiebolt J, Achterbergh R, den Boer A, *et al.* Clustering of additional autoimmunity behaves differently in Hashimoto's patients compared with Graves' patients. *Eur J Endocrinol* 2011; 164: 789–794.

57. Resende E, Gomicronmez GN, Nascimento M, *et al.* Precocious presentation of autoimmune polyglandular syndrome type 2 associated with an AIRE mutation. *Hormones* 2015; 14: 312–316.

58. Yu C, Liu Y, Li Y, *et al.* Expression of AIRE gene in NOD mouse tissues and PBMC of T1DM patients. *Zhongguo Mian Yi Xue Za Zhi* 2006; 22: 299–301.

59. Skogberg G, Lundberg V, Lindgren S, *et al.* Altered expression of autoimmune regulator in infant down syndrome thymus, a possible contributor to an autoimmune phenotype. *J Immunol* 2014; 193: 2187–2195.

60. Guarraldi F, Rossetto Giaccherino R, Lanfranco F, *et al.* Endocrine autoimmunity in Down’s syndrome. *Front Horm Res* 2017; 48: 133–146.

61. Aversa T, Valenzise M, Corrias A, *et al.* In children with autoimmune thyroid diseases the association with Down syndrome can modify
the clustering of extra-thyroidal autoimmune disorders. *J Pediatr Endocrinol Metab* 2016; 29: 1041–1046.

62. De Luca F, Corrias A, Salerno M, et al. Peculiarities of Graves’ disease in children and adolescents with Down’s syndrome. *Eur J Endocrinol* 2010; 162: 591–595.

63. De Sanctis V and Khater D. Autoimmune diseases in Turner syndrome: an overview. *Acta Biomed* 2019; 90: 341–344.

64. Aversa T, Lombardo F, Valenzise M, et al. Peculiarities of autoimmune thyroid diseases in children with Turner or Down syndrome: an overview. *Ital J Pediatr* 2015; 41: 39.

65. Wegiel M, Antosz A, Gieburowska J, et al. Autoimmunity predisposition in girls with turner syndrome. *Front Endocrinol* 2019; 10: 511.

66. Sng J, Ayoglu B, Chen JW, et al. AIRE expression controls the peripheral selection of autoreactive B cells. *Sci Immunol* 2019; 4: eaav6778.

67. Wong FS and Wen L. B cells in autoimmune diabetes. *Rev Diabet Stud* 2005; 2: 121–135.

68. Hu CY, Rodriguez-Pinto D, Du W, et al. Treatment with CD20-specific antibody prevents and reverses autoimmune diabetes in mice. *J Clin Invest* 2007; 117: 3857–3867.

69. Brownlie RJ, Zamoyska R and Salmond RJ. Regulation of autoimmune and anti-tumour T cell responses by PTPN22. *Immunology* 2018; 154: 377–382.

70. Rhee I and Veillette A. Protein tyrosine phosphatases in lymphocyte activation and autoimmunity. *Nat Immunol* 2012; 13: 439–447.

71. Baghbani E, Baradaran B, Pak F, et al. Suppression of protein tyrosine phosphatase PTPN22 gene induces apoptosis in T-cell leukemia cell line (Jurkat) through the AKT and ERK pathways. *Biomed Pharmacother* 2017; 86: 41–47.

72. Betterle C, Garelli S, Coco G, et al. A rare combination of type 3 autoimmune polyendocrine syndrome (APS-3) or multiple autoimmune syndrome (MAS-3). *Auto Immun Highlights* 2014; 5: 27–31.

73. Criswell LA, Pfeiffer KA, Lum RF, et al. Analysis of families in the multiple autoimmune disease genetics consortium (MADGC) collection: the PTPN22 620W allele associates with multiple autoimmune phenotypes. *Am J Hum Genet* 2005; 76: 561–571.

74. Houcken J, Degenhart C, Bender K, et al. PTPN22 and CTLA-4 polymorphisms are associated with polyglandular autoimmunity. *J Clin Endocrinol Metab* 2018; 103: 1977–1984.

75. Bottini N, Musumeci L, Alonso A, et al. A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. *Nat Gen* 2004; 36: 337–338.

76. Velaga MR, Wilson V, Jennings CE, et al. The codon 620 tryptophan allele of the lymphoid tyrosine phosphatase (LYP) gene is a major determinant of Graves’ disease. *J Clin Endocrinol Metab* 2004; 89: 5862–5865.

77. Bulut F, Erol D, Elyas H, et al. Protein tyrosine phosphatase non-receptor 22 gene C1858T polymorphism in patients with coexistent type 2 diabetes and Hashimoto’s thyroiditis. *Balkan Med J* 2014; 31: 37–42.

78. Smyth D, Cooper JD, Collins JE, et al. Replication of an association between the lymphoid tyrosine phosphatase locus (LYP/PTPN22) with type 1 diabetes, and evidence for its role as a general autoimmunity locus. *Diabetes* 2004; 53: 3020–3023.

79. Lee HS, Kang J, Yang S, et al. Susceptibility influence of a PTPN22 haplotype with thyroid autoimmunity in Koreans. *Diabetes Metab Res Rev* 2011; 27: 878–882.

80. Alkhateeb A, Marzouka NA and Tashtoush R. Variants in PTPN22 and SMOC2 genes and the risk of thyroid disease in the Jordanian Arab population. *Endocrine* 2013; 44: 702–709.

81. Liu HW, Xu RY, Sun RP, et al. Association of PTPN22 gene polymorphism with type 1 diabetes mellitus in Chinese children and adolescents. *Genet Mol Res* 2011; 10: 2007–2014.

82. Ikegami H, Fujisawa T, Kawabata Y, et al. Genetics of type 1 diabetes: similarities and differences between Asian and Caucasian populations. *Ann N Y Acad Sci* 2006; 1079: 51–59.

83. El Fotoh W, El Razek Midan DA and El Shalakany AH. Role of C1858T polymorphism of lymphoid tyrosine phosphatase in Egyptian children and adolescents with type 1 diabetes. *Curr Diabetes Rev* 2019; 16: 73–79.

84. Giza S, Goulas A, Gbandi E, et al. The role of PTPN22 C1858T gene polymorphism in diabetes mellitus type 1: first evaluation in Greek children and adolescents. *Biomed Res Int* 2013; 2013: 721604.

85. Wasniewska M, Corrias A, Salerno M, et al. Thyroid function patterns at Hashimoto’s thyroiditis presentation in childhood and...
adolescence are mainly conditioned by patients’ age. *Horn Res Paediatr* 2012; 78: 232–236.

86. Preziosi G, Comenga L, Di Giulio C, et al. C1858T polymorphism of protein tyrosine phosphatase non-receptor Type 22 (PTPN22): an eligible target for prevention of type 1 diabetes? *Expert Rev Clin Immunol* 2017; 13: 189–196.

87. Burn GL, Svensson L, Sanchez-Blanco C, et al. Why is PTPN22 a good candidate susceptibility gene for autoimmune disease? *FEBS Lett* 2011; 585: 3689–3698.

88. Blasetti A, Di Giulio C, Tumini S, et al. Role of the C1858T polymorphism of protein tyrosine phosphatase non-receptor type 22 (PTPN22) in children and adolescents with type 1 diabetes. *Pharmacogenomics J* 2017; 17: 186–191.

89. Bottini N, Vang T, Cucca F, et al. Role of PTPN22 in type 1 diabetes and other autoimmune diseases. *Semin Immunol* 2006; 18: 207–213.

90. Fontenot JD and Rudensky AY. A well adapted regulatory contrivance: regulatory T cell development and the forkhead family transcription factor Foxp3. *Nat Immunol* 2005; 6: 331–337.

91. Hori S, Nomura T and Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. *Science* 2003; 299: 1057–1061.

92. Feurer M, Hill JA, Mathis D, et al. Foxp3+ regulatory T cells: differentiation, specification, subphenotypes. *Nat Immunol* 2009; 10: 689–695.

93. Bennett CL, Christie J, Ramsdell F, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nat Gen* 2001; 27: 20–21.

94. Ban Y, Tozaki T, Tobe T, et al. The regulatory T cell gene FOXP3 and genetic susceptibility to thyroid autoimmunity: an association analysis in Caucasian and Japanese cohorts. *J Autoimmun* 2007; 28: 201–207.

95. Inoue N, Watanabe M, Morita M, et al. Association of functional polymorphisms related to the transcriptional level of FOXP3 with prognosis of autoimmune thyroid diseases. *Clin Exp Immunol* 2010; 162: 402–406.

96. Villano MJ, Huber AK, Greenberg DA, et al. Autoimmune thyroiditis and diabetes: dissecting the joint genetic susceptibility in a large cohort of multiplex families. *J Clin Endocrinol Metab* 2009; 94: 1458–1466.

97. Li CW, Concepcion E and Tomer Y. Dissecting the role of the FOXP3 gene in the joint genetic susceptibility to autoimmune thyroiditis and diabetes: a genetic and functional analysis. *Gene* 2015; 556: 142–148.

98. Bossowski A, Moniuszko M, Dabrowska M, et al. Lower proportions of CD4+CD25(high) and CD4+FoxP3, but not CD4+CD25+CD127(low) FoxP3+ T cell levels in children with autoimmune thyroid diseases. *Autoimmunity* 2013; 46: 222–230.

99. Nakano A, Watanabe M, Iida T, et al. Apoptosis-induced decrease of intrathyroidal CD4(+)CD25(+) regulatory T cells in autoimmune thyroid diseases. *Thyroid* 2007; 17: 25–31.

100. Korn T, Bettelli E, Oukka M, et al. IL-17 and Th17 cells. *Annu Rev Immunol* 2009; 27: 485–517.

101. Li C, Yuan J, Zhu YF, et al. Imbalance of Th17/Treg in different subtypes of autoimmune thyroid diseases. *Cell Physiol Biochem* 2016; 40: 245–252.

102. Bjornvold M, Amundsen SS, Stene LC, et al. FOXP3 polymorphisms in type 1 diabetes and coeliac disease. *J Autoimmun* 2006; 27: 140–144.

103. Rubio-Cabezas O, Minton JA, Caswell R, et al. Clinical heterogeneity in patients with FOXP3 mutations presenting with permanent neonatal diabetes. *Diabetes Care* 2009; 32: 111–116.

104. Zavattari P, Deidda E, Pitzalis M, et al. No association between variation of the FOXP3 gene and common type 1 diabetes in the Sardinian population. *Diabetes* 2004; 53: 1911–1914.

105. Nakanishi K and Shima Y. No contribution of a GT microsatellite polymorphism in the promoter region of the FOXP3 gene and common type 1 diabetes in the Japanese population. *Clin Chim Acta* 2007; 384: 171–173.

106. Brusko T, Wasserfall C, McGrail K, et al. No alterations in the frequency of FOXP3+ regulatory T-cells in type 1 diabetes. *Diabetes* 2007; 56: 604–612.

107. Tritt M, Sgouroudis E, d’Hennezel E, et al. Functional waning of naturally occurring CD4+ regulatory T-cells contributes to the onset of autoimmune diabetes. *Diabetes* 2008; 57: 113–123.

108. Brode S, Raine T, Zaccone P, et al. Cyclophosphamide-induced type-1 diabetes in the NOD mouse is associated with a reduction
of CD4+CD25+Foxp3+ regulatory T cells. J Immunol 2006; 177: 6603–6612.

109. Tian B, Hao J, Zhang Y, et al. Upregulating CD4+CD25+FOXP3+ regulatory T cells in pancreatic lymph nodes in diabetic NOD mice by adjuvant immunotherapy. Transplantation 2009; 87: 198–206.

110. Jaeckel E, von Boehmer H and Manns MP. Antigen-specific FoxP3-transduced T-cells can control established type 1 diabetes. Diabetes 2005; 54: 306–310.

111. Peng Y, Laouar Y, Li MO, et al. TGF-beta regulates in vivo expansion of Foxp3-expressing CD4+CD25+ regulatory T cells responsible for protection against diabetes. Proc Natl Acad Sci U S A 2004; 101: 4572–4577.

112. Wu T, Zhang L, Xu K, et al. Immunosuppressive drugs on inducing Ag-specific CD4(+)CD25(+)Foxp3(+) Treg cells during immune response in vivo. Transpl Immunol 2012; 27: 30–38.

113. Zheng Q, Xu Y, Liu Y, et al. Induction of Foxp3 demethylation increases regulatory CD4+CD25+ T cells and prevents the occurrence of diabetes in mice. J Mol Med 2009; 87: 1191–1205.

114. Johnson MC, Garland AL, Nicolson SC, et al. Beta-cell-specific IL-2 therapy increases islet Foxp3+Treg and suppresses type 1 diabetes in NOD mice. Diabetes 2013; 62: 3775–3784.

115. McCoy KD and Le Gros G. The role of CTLA-4 in the regulation of T cell immune responses. Immunol Cell Biol 1999; 77: 1–10.

116. Wolchok JD and Saenger Y. The mechanism of anti-CTLA-4 activity and the negative regulation of T-cell activation. Oncologist 2008; 13(Suppl. 4): 2–9.

117. Lan KH, Liu YC, Shih YS, et al. A DNA vaccine against cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) prevents tumor growth. Biochem Biophys Res Commun 2013; 440: 222–228.

118. Fernandez-Garcia EM, Vera-Badillo FE, Perez-Valderrama B, et al. Immunotherapy in prostate cancer: review of the current evidence. Clin Transl Oncol 2015; 17: 339–357.

119. Ueda H, Howson JM, Esposito L, et al. Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. Nature 2003; 423: 506–511.

120. Kavanagh B, O’Brien S, Lee D, et al. CTLA4 blockade expands FoxP3+ regulatory and activated effector CD4+ T cells in a dose-dependent fashion. Blood 2008; 112: 1175–1183.

121. Chen Z, Fei M, Fu D, et al. Association between cytotoxic T lymphocyte antigen-4 polymorphism and type 1 diabetes: a meta-analysis. Gene 2013; 516: 263–270.

122. Pastuszak-Lewandoska D, Sewerynek E, Domanska D, et al. CTLA-4 gene polymorphisms and their influence on predisposition to autoimmune thyroid diseases (Graves’ disease and Hashimoto’s thyroiditis). Arch Med Sci 2012; 8: 415–421.

123. Douroudis K, Prans E, Kisand K, et al. Cytotoxic T-lymphocyte antigen 4 gene polymorphisms are associated with latent autoimmune diabetes in adults. Clin Chim Acta 2009; 403: 226–228.

124. Rednarczuk T, Hiromatsu Y, Fukutani T, et al. Association of cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) gene polymorphism and non-genetic factors with Graves’ ophthalmopathy in European and Japanese populations. Eur J Endocrinol 2003; 148: 13–18.

125. Hou HF, Jin X, Sun T, et al. Cytotoxic T lymphocyte-associated antigen 4 gene polymorphisms and autoimmune thyroid diseases: an updated systematic review and cumulative meta-analysis. Int J Endocrinol 2015; 2015: 747816.

126. Vaidya B, Imrie H, Perros P, et al. Cytotoxic T lymphocyte antigen-4 (CTLA-4) gene polymorphism confers susceptibility to thyroid associated orbitopathy. Lancet 1999; 354: 743–744.

127. Kavoura FK, Akamizu T, Awata T, et al. Cytotoxic T-lymphocyte associated antigen 4 gene polymorphisms and autoimmune thyroid disease: a meta-analysis. J Clin Endocrinol Metab 2007; 92: 3162–3170.

128. Lee YJ, Huang FY, Lo FS, et al. Association of CTLA4 gene A-G polymorphism with type 1 diabetes in Chinese children. Clin Endocrinol 2000; 52: 153–157.

129. Ikegami H, Awata T, Kawasaki E, et al. The association of CTLA4 polymorphism with type 1 diabetes is concentrated in patients complicated with autoimmune thyroid disease: a multicenter collaborative study in Japan. J Clin Endocrinol Metab 2006; 91: 1087–1092.

130. Mochizuki M, Amemiya S, Kobayashi K, et al. Association of the CTLA-4 gene 49
A/G polymorphism with type 1 diabetes and autoimmune thyroid disease in Japanese children. *Diabetes Care* 2003; 26: 843–847.

131. Howson JM, Dunger DB, Nutland S, et al. A type 1 diabetes subgroup with a female bias is characterised by failure in tolerance to thyroid peroxidase at an early age and a strong association with the cytotoxic T-lymphocyte-associated antigen-4 gene. *Diabetologia* 2007; 50: 741–746.

132. Tang ST, Tang HQ, Zhang Q, et al. Association of cytotoxic T-lymphocyte associated antigen 4 gene polymorphism with type 1 diabetes mellitus: a meta-analysis. *Gene* 2012; 508: 165–187.

133. Takara M, Komiya I, Kinjo Y, et al. Association of CTLA-4 gene A/G polymorphism in Japanese type 1 diabetic patients with younger age of onset and autoimmune thyroid disease. *Diabetes Care* 2000; 23: 975–978.

134. Mayans S, Lackovic K, Nyholm C, et al. CT60 genotype does not affect CTLA-4 isoform expression despite association to T1D andAITD in northern Sweden. *BMC Med Genet* 2007; 8: 3.

135. Balic I, Angel B, Codner E, et al. Association of CTLA-4 polymorphisms and clinical-immunologic characteristics at onset of type 1 diabetes mellitus in children. *Human Immunol* 2009; 70: 116–120.

136. Ban Y, Taniyama M, Tozaki T, et al. No association of type 1 diabetes with a microsatellite marker for CTLA-4 in a Japanese population. *Autoimmunity* 2001; 34: 39–43.

137. Celmeli F, Turkkahraman D, Ozel D, et al. CTLA-4 (+49A/G) polymorphism and type-1 diabetes in Turkish children. *J Clin Res Pediatr Endocrinol* 2013; 5: 40–43.

138. Chen M and Li S. Associations between cytotoxic T-lymphocyte-associated antigen 4 gene polymorphisms and diabetes mellitus: a meta-analysis of 76 case-control studies. *Biosci Rep* 2019; 39: BSR20190309.

139. Wang B, Du W, Jia Y, et al. Cytotoxic T-lymphocyte-associated protein 4 +49A/G polymorphisms contribute to the risk of type 1 diabetes in children: an updated systematic review and meta-analysis with trial sequential analysis. *Oncotarget* 2017; 8: 10553–10564.

140. Kavvoura FK and Ioannidis JP. CTLA-4 gene polymorphisms and susceptibility to type 1 diabetes mellitus: a HuGE Review and meta-analysis. *Am J Epidemiol* 2005; 162: 3–16.

141. Liu J, Zhang HX, Feng GY, et al. Significantly association of diabetes mellitus with CTLA-4 gene polymorphisms based on a meta-analysis of epidemiological evidence in Asians and non-Asians. *Genet Mol Res* 2013; 12: 3919–3930.

142. Dong F, Yang G, Pan HW, et al. The association of PTPN22 rs2476601 polymorphism and CTLA-4 rs231775 polymorphism with LADA risks: a systematic review and meta-analysis. *Acta Diabetol* 2014; 51: 691–703.

143. Fathima N, Narne P and Ishaq M. Association and gene-gene interaction analyses for polymorphic variants in CTLA-4 and FOXP3 genes: role in susceptibility to autoimmune thyroid disease. *Endocrine* 2019; 64: 591–604.

144. Bicek A, Zaletek K, Gaberscek S, et al. 49A/G and CT60 polymorphisms of the cytotoxic T-lymphocyte-associated antigen 4 gene associated with autoimmune thyroid disease. *Human Immunol* 2009; 70: 820–824.

145. Jeffery LE, Qureshi OS, Gardner D, et al. Vitamin D antagonises the suppressive effect of inflammatory cytokines on CTLA-4 expression and regulatory function. *PLoS One* 2015; 10: e0131539.

146. Einarsdottir E, Soderstrom I, Lofgren-Burstrom A, et al. The CTLA4 region as a general autoimmunity factor: an extended pedigree provides evidence for synergy with the HLA locus in the etiology of type 1 diabetes mellitus, Hashimoto’s thyroiditis and Graves’ disease. *Eur J Human Genet* 2003; 11: 81–84.

147. Ban Y and Tomer Y. The contribution of immune regulatory and thyroid specific genes to the etiology of Graves’ and Hashimoto’s diseases. *Autoimmunity* 2003; 36: 367–379.

148. Aversa T, Corica D, Zirilli G, et al. Phenotypic expression of autoimmunity in children with autoimmune thyroid disorders. *Front Endocrinol* 2019; 10: 476.

149. Orban T, Bundy B, Becker DJ, et al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; 378: 412–419.

150. Orban T, Bundy B, Becker DJ, et al. Costimulation modulation with abatacept in patients with recent-onset type 1 diabetes: follow-up 1 year after cessation of treatment. *Diabetes Care* 2014; 37: 1069–1075.

151. Tömer Y and Davies TF. Infections and autoimmune endocrine disease. *Bailliere’s Clin Endocrinol Metab* 1995; 9: 47–70.
152. Bach JF. Infections and autoimmune diseases. *J Autoimmun* 2005; 25(Suppl.): 74–80.

153. Oldstone MB and von Herrath M. Virus-induced autoimmune disease: transgenic approach to mimic insulin-dependent diabetes mellitus and other autoimmune diseases. *APMIS* 1996; 104: 689–697.

154. Snell-Bergeon JK, Smith J, Dong F, et al. Early childhood infections and the risk of islet autoimmunity: the diabetes autoimmunity study in the young (DAISY). *Diabetes Care* 2012; 35: 2553–2558.

155. Kondrashova A and Hyoty H. Role of viruses and other microbes in the pathogenesis of type 1 diabetes. *Int Rev Immunol* 2014; 33: 284–295.

156. Karaoglan M and Elski F. The coincidence of newly diagnosed type 1 diabetes mellitus with IgM antibody positivity to enteroviruses and respiratory tract viruses. *J Diabetes Res* 2018; 2018: 8475341.

157. Hober D and Sauter P. Pathogenesis of type 1 diabetes mellitus: interplay between enterovirus and host. *Nat Rev Endocrinol* 2010; 6: 279–289.

158. Varela-Calvino R and Peakman M. Enteroviruses and type 1 diabetes. *Diabetes Metab Res Rev* 2003; 19: 431–441.

159. Pearson JA, Agriantonis A, Wong FS, et al. Modulation of the immune system by the gut microbiota in the development of type 1 diabetes. *Hum Vaccin Immunother* 2018; 14: 2580–2596.

160. Kim CH. Microbiota or short-chain fatty acids: which regulates diabetes? *Cell Mol Immunol* 2018; 15: 88–91.

161. Burrows MP, Volchkov P, Kobayashi KS, et al. Microbiota regulates type 1 diabetes through Toll-like receptors. *Proc Natl Acad Sci U S A* 2015; 112: 9973–9977.

162. Peng S, Li C, Wang X, et al. Increased toll-like receptors activity and TLR ligands in patients with autoimmune thyroid diseases. *Front Immunol* 2016; 7: 578.

163. Dvornikova KA, Bystrova EY, Platonova ON, et al. Polymorphism of toll-like receptor genes and autoimmune endocrine diseases. *Autoimmun Rev* 2020; 19: 102496.

164. Zekry OA and Abd Elwahid HA. The association between Helicobacter pylori infection, type 1 diabetes mellitus, and autoimmune thyroiditis. *J Egypt Public Health Assoc* 2013; 88: 143–147.
during pregnancy in mothers whose children later developed type 1 diabetes. *Diabetes Metab Res Rev* 2016; 32: 883–890.

178. Kim D. Low vitamin D status is associated with hypothyroid Hashimoto’s thyroiditis. *Hormones* 2016; 15: 385–393.

179. Mazokopakis EE, Papadomanolaki MG, Tsekouras KC, *et al.* Is vitamin D related to pathogenesis and treatment of Hashimoto’s thyroiditis? *Heliönucl Med* 2015; 18: 222–227.

180. Mansournia N, Mansournia MA, Saedci S, *et al.* The association between serum 25OHD levels and hypothyroid Hashimoto’s thyroiditis. *J Endocrinol Invest* 2014; 37: 473–476.

181. Bozkurt NC, Karbek B, Ucan B, *et al.* The association between severity of vitamin D deficiency and Hashimoto’s thyroiditis. *Endocr Pract* 2013; 19: 479–484.

182. Ke W, Sun T, Zhang Y, *et al.* 25-Hydroxyvitamin D serum level in Hashimoto’s thyroiditis, but not Graves’ disease is relatively deficient. *Endocr J* 2017; 64: 581–587.

183. Chaudhary S, Dutta D, Kumar M, *et al.* Vitamin D supplementation reduces thyroid peroxidase antibody levels in patients with autoimmune thyroid disease: an open-labeled randomized controlled trial. *Indian J Endocrinol Metab* 2016; 20: 391–398.

184. Simsek Y, Cakir I, Yetmis M, *et al.* Effects of vitamin D treatment on thyroid autoimmunity. *J Res Med Sci* 2016; 21: 85.

185. Choi YM, Kim WG, Kim TY, *et al.* Low levels of serum vitamin D3 are associated with autoimmune thyroid disease in pre-menopausal women. *Thyroid* 2014; 24: 655–661.

186. Mirhosseini N, Brunel L, Muscogiuri G, *et al.* Physiological serum 25-hydroxyvitamin D concentrations are associated with improved thyroid function-observations from a community-based program. 2017; 58: 563–573.

187. Skaaby T, Husemoen LL, Thuesen BH, *et al.* Prospective population-based study of the association between vitamin D status and incidence of autoimmune disease. *Endocrine* 2015; 50: 231–238.

188. Giovinazzo S, Vicchio TM, Certo R, *et al.* Vitamin D receptor gene polymorphisms/haplotypes and serum 25(OH)D3 levels in Hashimoto’s thyroiditis. *Endocrine* 2017; 55: 599–606.

189. Malik A, Saleem S, Basit Ashraf MA, *et al.* 25-dihydroxyvitamin D3, a potential role player in the development of thyroid disorders in schizophrenics. *Pak J Med Sci* 2016; 32: 1370–1374.

190. Kivity S, Agmon-Levin N, Zisapel M, *et al.* Vitamin D and autoimmune thyroid diseases. *Cell Mol Immunol* 2011; 8: 243–247.

191. Bae KN, Nam HK, Rhie YJ, *et al.* Low levels of 25-hydroxyvitamin D in children and adolescents with type 1 diabetes mellitus: a single center experience. *Ann Pediatr Endocrinol Metab* 2018; 23: 21–27.

192. Savastio S, Cadario F, Genoni G, *et al.* Vitamin D deficiency and glycemic status in children and adolescents with type 1 diabetes mellitus. *PLoS One* 2016; 11: e0162554.

193. Nwosu BU and Maranda L. The effects of vitamin D supplementation on hepatic dysfunction, vitamin D status, and glycemic control in children and adolescents with vitamin D deficiency and either type 1 or type 2 diabetes mellitus. *PLoS One* 2014; 9: e99646.

194. Liu C, Wang J, Wan Y, *et al.* Serum vitamin D deficiency in children and adolescents is associated with type 1 diabetes mellitus. *Endocr Connect* 2018; 7: 1275–1279.

195. Miettinen ME, Niinistö S, Erlund I, *et al.* Serum 25-hydroxyvitamin D concentration in childhood and risk of islet autoimmunity and type 1 diabetes: the TRIGR nested case-control ancillary study. *Diabetologia* 2020; 63: 780–787.

196. Panjijar RP, Dayal D, Attri SV, *et al.* [Sustained serum 25-hydroxyvitamin D concentrations for one year with cholecalciferol supplementation improves glycaemic control and slows the decline of residual beta cell function in children with type 1 diabetes.] *Pediatr Endocrinol Diabetes Metab* 2018; 2018: 111–117.

197. Hyponnen E, Laara E, Reunanen A, *et al.* Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 2001; 358: 1500–1503.

198. Wolden-Kirk H, Rondas D, Bugliani M, *et al.* Discovery of molecular pathways mediating 1,25-dihydroxyvitamin D3 protection against cytokine-induced inflammation and damage of human and male mouse islets of Langerhans. *Endocrinology* 2014; 155: 736–747.

199. Groenbaum C, VanBuecken D and Lord S. Disease-modifying therapies in type 1 diabetes: a look into the future of diabetes practice. *Drugs* 2019; 79: 43–61.

200. Simpson M, Brady H, Yin X, *et al.* No association of vitamin D intake or 25-hydroxyvitamin D levels in childhood with...
risk of islet autoimmunity and type 1 diabetes: the diabetes autoimmunity study in the young (DAISY). Diabetologia 2011; 54: 2779–2788.

201. Granfors M, Augustin H, Ludvigsson J, et al. No association between use of multivitamin supplement containing vitamin D during pregnancy and risk of type 1 diabetes in the child. Pediatr Diabetes 2016; 17: 525–530.

202. Silvis K, Aronsson CA, Liu X, et al. Maternal dietary supplement use and development of islet autoimmunity in the offspring: TEDDY study. Pediatr Diabetes 2019; 20: 86–92.

203. Elding Larsson H, Vehik K, Haller MJ, et al. Growth and risk for islet autoimmunity and progression to type 1 diabetes in early childhood: the environmental determinants of diabetes in the young study. Diabetes 2016; 65: 1988–1995.

204. Uusitalo U, Lee HS, Andren Aronsson C, et al. Early infant diet and islet autoimmunity in the TEDDY study. Diabetes Care 2018; 41: 522–530.

205. Skyler JS. Prediction and prevention of type 1 diabetes: progress, problems, and prospects. Clin Pharmacol Ther 2007; 81: 768–771.

206. Lamb MM, Miller M, Seifert JA, et al. The effect of childhood cow’s milk intake and HLA-DR genotype on risk of islet autoimmunity and type 1 diabetes: the Diabetes Autoimmunity Study in the Young. Pediatr Diabetes 2015; 16: 31–38.

207. Wang HY, She GT, Sun LZ, et al. Correlation of serum vitamin D, adipose tissue vitamin D receptor, and peroxisome proliferator-activated receptor gamma in women with gestational diabetes mellitus. Chin Med J 2019; 132: 2612–2620.

208. Tamura M, Ishizawa M, Isojima T, et al. Functional analyses of a novel missense and other mutations of the vitamin D receptor in association with alopecia. Sci Rep 2017; 7: 5102.

209. Takiishi T, Ding L, Baeke F, et al. Dietary supplementation with high doses of regular vitamin D3 safely reduces diabetes incidence in NOD mice when given early and long term. Diabetes 2014; 63: 2026–2036.

210. Driver JP, Foreman O, Mathieu C, et al. Comparative therapeutic effects of orally administered 1,25-dihydroxyvitamin D(3) and 1alpha-hydroxyvitamin D(3) on type-1 diabetes in non-obese diabetic mice fed a normal-calcaemic diet. Clin Exp Immunol 2008; 151: 76–85.

211. Gregori S, Giarratana N, Smiroldo S, et al. A 1alpha,25-dihydroxyvitamin D(3) analog enhances regulatory T-cells and arrests autoimmune diabetes in NOD mice. Diabetes 2002; 51: 1367–1374.

212. Mallone R, Brezard V and Boitard C. T cell recognition of autoantigens in human type 1 diabetes: clinical perspectives. Clin Dev Immunol 2011; 2011: 513210.

213. Rochel N, Wurtz JM, Mitscherl A, et al. The crystal structure of the nuclear receptor for vitamin D bound to its natural ligand. Mol Cell 2000; 5: 173–179.

214. Kirac D, Dincer Yazan C, Gezmis H, et al. VDBP, VDR mutations and other factors related with vitamin D metabolism may be associated with type 1 diabetes mellitus. Cell Mol Biol 2018; 64: 11–16.

215. Qin WH, Wang HX, Qiu JL, et al. A meta-analysis of association of vitamin D receptor BsmI gene polymorphism with the risk of type 1 diabetes mellitus. J Recept Signal Transduct Res 2014; 34: 372–377.

216. Guleryuz B, Akin F, Ata MT, et al. Vitamin-D receptor (VDR) gene polymorphisms (TaqI, FokI) in Turkish patients with Hashimoto’s thyroiditis: relationship to the levels of vit-D and cytokines. Endocr Metab Immune Disord Drug Targets 2016; 16: 131–139.

217. Stefanic M, Papic S, Suver M, et al. Association of vitamin D receptor gene 3’-variants with Hashimoto’s thyroiditis in the Croatian population. Int J Immunogenet 2008; 35: 125–131.

218. Zarrin R, Bagheri M, Meh dizadeh A, et al. The association of FokI and ApaI polymorphisms in vitamin D receptor gene with autoimmune thyroid diseases in the northwest of Iran. Med J Islam Repub Iran 2018; 32: 4.

219. Sawada N, Sakaki T, Kitanaka S, et al. Enzymatic properties of human 25-hydroxyvitamin D3 1alpha-hydroxylase coexpression with adrenodoxin and NADPH-adrenodoxin reductase in Escherichia coli. Eur J Biochem 1999; 265: 950–956.

220. Meyer MB, Benkusky NA, Kaufmann M, et al. A kidney-specific genetic control module in mice governs endocrine regulation of the cytochrome P450 gene Cyp27b1 essential for vitamin D3 activation. J Biol Chem 2017; 292: 17541–17558.

221. van Etten E, Stoffels K, Gysemans C, et al. Regulation of vitamin D homeostasis:
implications for the immune system. *Natr Rev* 2008; 66: S125–S134.

222. Lopez ER, Zwermann O, Segni M, et al. A promoter polymorphism of the CYP27B1 gene is associated with Addison’s disease, Hashimoto’s thyroiditis, Graves’ disease and type 1 diabetes mellitus in Germans. *Eur J Endocrinol* 2004; 151: 193–197.

223. Hussein AG, Mohamed RH and Alghobashy AA. Synergism of CYP2R1 and CYP27B1 polymorphisms and susceptibility to type 1 diabetes in Egyptian children. *Cell Immunol* 2012; 279: 42–45.

224. Bailey R, Cooper JD, Zeitels L, et al. Association of the vitamin D metabolism gene CYP27B1 with type 1 diabetes. *Diabetes* 2007; 56: 2616–2621.

225. Frederiksen BN, Kroehl M, Fingerlin TE, et al. Association between vitamin D metabolism gene polymorphisms and risk of islet autoimmunity and progression to type 1 diabetes: the diabetes autoimmunity study in the young (DAISY). *J Clin Endocrinol Metab* 2013; 98: E1845–E1851.

226. Ramos-Lopez E, Bruck P, Jansen T, et al. CYP2R1-, CYP27B1- and CYP24-mRNA expression in German type 1 diabetes patients. *J Steroid Biochem Mol Biol* 2007; 103: 807–810.

227. Yang J and Xiong F. [Relevance of CYP27B1 gene promoter polymorphism to autoimmune thyroid diseases.]*Nan Fang Yi Ke Da Xue Xue Bao* 2008; 28: 606–608.

228. Belperio JA, Keane MP, Arenberg DA, et al. CXC chemokines in angiogenesis. *J Leukoc Biol* 2000; 68: 1–8.

229. Smit MJ, Verdijk P, van der Raaij-Helmer EM, et al. CXCR3-mediated chemotaxis of human T cells is regulated by a Gi- and phospholipase C-dependent pathway and not via activation of MEK/p44/p42 MAPK nor Akt/PI-3 kinase. *Blood* 2003; 102: 1959–1965.

230. Antonelli A, Ferrari SM, Corrado A, et al. Autoimmune thyroid disorders. *Autoimmun Rev* 2015; 14: 174–180.

231. Meier CA, Chicheportiche R, Dreyer M, et al. IP-10, but not RANTES, is upregulated by leptin in monocyctic cells. *Cytokine* 2003; 21: 43–47.

232. Cristillo AD, Macri MJ and Bierer BE. Differential chemokine expression profiles in human peripheral blood T lymphocytes: dependence on T-cell coreceptor and calcineurin signaling. *Blood* 2003; 101: 216–225.

233. Antonelli A, Ferrari SM, Giuggioli D, et al. Chemokine (C-X-C motif) ligand (CXCL10 in autoimmune diseases. *Autoimmun Rev* 2014; 13: 272–280.

234. Ruffilli I, Ferrari SM, Colaci M, et al. [CXCR3 and CXCL10 in autoimmune thyroiditis.] *La Clinica Terapeutica* 2014; 165: e237–e242.

235. Fallahi P, Ferrari SM, Corrado A, et al. Targeting chemokine (C-X-C motif) receptor 3 in thyroid autoimmunity. *Recent Pat Endocr Metab Immune Drug Discov* 2014; 8: 95–101.

236. Antonelli A, Ferrari SM, Frascerra S, et al. Circulating chemokine (CXC motif) ligand (CXCL)9 is increased in aggressive chronic autoimmune thyroiditis, in association with CXCL10. *Cytokine* 2011; 55: 288–293.

237. Rotondi M, Chiovato L, Romagnani S, et al. Role of chemokines in endocrine autoimmune diseases. *Endocr Rev* 2007; 28: 492–520.

238. Fallahi P, Ferrari SM, Ragusa F, et al. Th1 chemokines in autoimmune endocrine disorders. *J Clin Endocrinol Metab* 2020; 105: 1046–1060.

239. Antenelli A, Ferrari SM, Corrado A, et al. Increase of interferon-gamma inducible CXCL9 and CXCL11 serum levels in patients with active Graves’ disease and modulation by methimazole therapy. *Thyroid* 2013; 23: 1461–1469.

240. Antonelli A, Ferrari SM, Frascerra S, et al. CXCL9 and CXCL11 chemokines modulation by peroxisome proliferator-activated receptor-alpha agonists secretion in Graves’ and normal thyrocytes. *J Clin Endocrinol Metab* 2010; 95: E413–E420.

241. Yu J, Wu H, Liu ZY, et al. Advanced glycation end products induce the apoptosis of and inflammation in mouse podocytes through CXCL9-mediated JAK2/STAT3 pathway activation. *Int J Mol Med* 2017; 40: 1185–1193.

242. Aktas A, Berberoglu Z, Fidan Y, et al. Higher levels of circulating CXCL-9 and CXCL-11 in euthyroid women with autoimmune thyroiditis and recurrent spontaneous abortions. *Gynecol Endocrinol* 2014; 30: 157–160.

243. Jamali Z, Nazari M, Khoramdelazad H, et al. Expression of CC chemokines CCL2, CCL5, and CCL11 is associated with duration of disease and complications in type-1 diabetes: a study on Iranian diabetic patients. *Clin Lab* 2013; 59: 993–1001.
244. Liu S, Liu X, Xiong H, et al. CXCL13/CXCR5 signaling contributes to diabetes-induced tactile allodynia via activating pERK, pSTAT3, pAKT pathways and pro-inflammatory cytokines production in the spinal cord of male mice. *Brain Behav Immun* 2019; 80: 711–724.

245. Henry RA and Kendall PL. CXCL13 blockade disrupts B lymphocyte organization in tertiary lymphoid structures without altering B cell receptor bias or preventing diabetes in nonobese diabetic mice. *J Immunol* 2010; 185: 1460–1465.

246. Aust G, Sittig D, Becherer L, et al. The role of CXCR5 and its ligand CXCL13 in the compartmentalization of lymphocytes in thyroids affected by autoimmune thyroid diseases. *Eur J Endocrinol* 2004; 150: 225–234.

247. Rotondi M, Coperchini F, Pignatti P, et al. Interferon-gamma and tumor necrosis factor-alpha sustain secretion of specific CXC chemokines in human thyrocytes: a first step toward a differentiation between autoimmune and tumor-related inflammation? *J Clin Endocrinol Metab* 2013; 98: 308–313.

248. Rotondi M, Coperchini F, Sideri R, et al. Type I and type II interferons inhibit both basal and tumor necrosis factor-alpha-induced CXCL8 secretion in primary cultures of human thyrocytes. *J Interferon Cytokine Res* 2013; 33: 508–513.

249. Ferrari SM, Ragusa F, Paparo SR, et al. Differential modulation of CXCL8 versus CXCL10, by cytokines, PPAR-α agonists, or PPAR-α agonists, in primary cells from Graves’ disease and ophthalmopathy. *Autoimmun Rev* 2019; 18: 673–678.

250. Cui S, Zhu Y, Du J, et al. CXCL8 antagonist improves diabetic nephropathy in male mice with diabetes and attenuates high glucose-induced mesangial injury. *Endocrinology* 2017; 158: 1671–1684.

251. Higurashi M, Ohya Y, Joh K, et al. Increased urinary levels of CXCL5, CXCL8 and CXCL9 in patients with Type 2 diabetic nephropathy. *J Diabetes Complications* 2009; 23: 178–184.

252. Omatsu T, Cepinskas G, Clarson C, et al. CXCL1/CXCL8 (GROalpha/IL-8) in human diabetic ketoacidosis plasma facilitates leukocyte recruitment to cerebrovascular endothelium in vitro. *Am J Physiol Endocrinol Metab* 2014; 306: E1077–1084.

253. Li X, Liu Y, Zheng Y, et al. The effect of vitamin D supplementation on glycemic control in type 2 diabetes patients: a systematic review and meta-analysis. *Nutrients* 2018; 10: 375.