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

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***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

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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 (TGAb), 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 TGAb 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]

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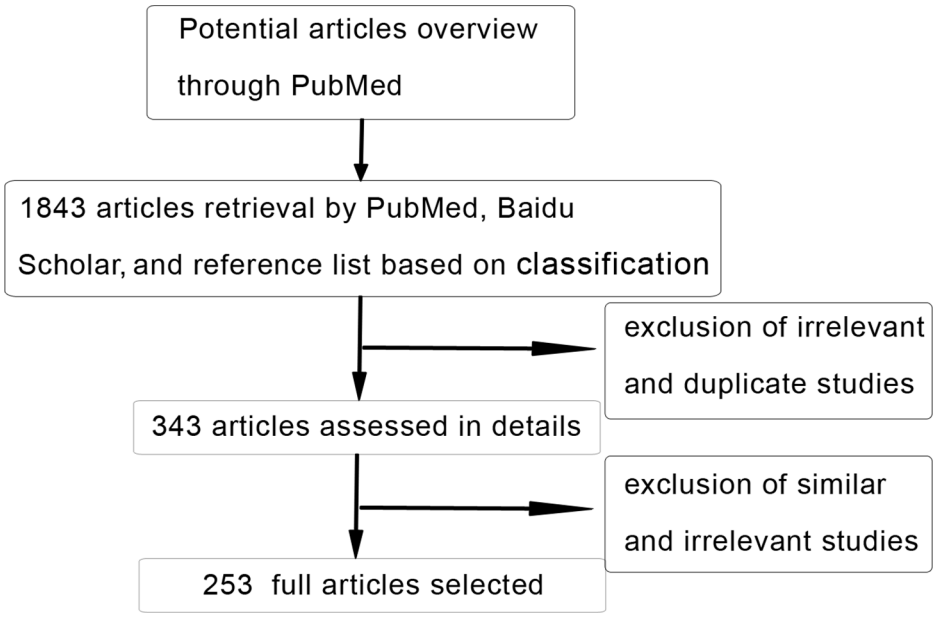

Figure 1. A flow diagram of the literature retrieval process.

Accumulating evidence suggests that T1DM and AITD occur concomitantly and have similar immunogenetic susceptibilities.[5,6,8,33–36] 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-DP, HLA-DQ, and HLA-DR), 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.[37,38] 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.[35,36,39,40] 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.[5,41] 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.[42] 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.[43–47] 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.[48–54]

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.[46,73–78] 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.[86] 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.[70,86–88] 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.[41,74,89]

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.[90–93] FOXP3 polymorphisms and variants are significantly linked with AITD.[94–97] 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.[98–101]

Many contradictory results regarding the association between FOXP3 polymorphisms and T1DM have been reported.[102–105] An early study by Brusko *et al.* indicated that the number of FOXP3(+) Tregs does not contribute to the pathogenesis of T1DM.[106] 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.[107,108] Moreover, immunotherapy with complete Freund's adjuvant upregulated FOXP3(+) Tregs and improved hyperglycemia, through an immunoregulatory mechanism in new-onset NOD mice.[109] The hyperglycemia of NOD mice with recent-onset diabetes was also well controlled by a single injection of FOXP3 transduction.[110] 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.[111] These findings suggested that an immunosuppressive drug modulating FOXP3 would be a promising treatment for AITD and T1DM.[112–114]

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.[115–120] CTLA-4 and its gene polymorphisms are reported to be important genetic determinants of the risk of T1DM and/or AITD.[43,96,121–134]

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.[43] The association of CLTA-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.[96] No association of the CTLA-4 gene with T1DM only has been found in other reports.[135–137] Therefore, meta-analyses support the findings that CTLA-4 polymorphism is a risk factor for T1DM susceptibility.[121,132,138–142]

CTLA-4 A/G49 and CT60 polymorphisms are also reported to increase susceptibility to HT and GD (AITD) in different populations.[122,124,125,143,144] 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.[145] 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.[129,130,146–150](Table 1)

Environmental factors and autoimmunity

The pathophysiology of autoimmune diseases often involves complex interactions between the immunogenetic background and environmental

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

Gene and polymorphism	Function	Reference	Therapy target
HLA class I and class II	Control of immune responses	Moriguchi *et al.* (2011);[5] Huber *et al.* (2008);[35] Tomer *et al.* (2015);[36] Kahles *et al.* (2015); [39] Li *et al.* (2017);[40] Chuang *et al.* (1996);[41] Bugawan *et al.* (2002);[42] Golden *et al.* (2005);[43] Kong *et al.* (2007);[44] Kong *et al.* (2003);[45] Dultz *et al.* (2009);[49] Krischer *et al.* (2015)[47]	–
AIRE	Involvement in immunological tolerance by distinguishing self-antigens	Ferrera *et al.* (2007);[49] Lovewell *et al.* (2015);[50] Nagamine *et al.* (1997);[52] Bruserud *et al.* (2016);[53] Gavanescu *et al.* (2008);[54] Wiebolt *et al.* (2011);[56] Resende *et al.* (2015);[57] Yu *et al.* (2006);[58] Skogberg *et al.* (2014);[59] Guaraldi *et al.* (2017);[60] Aversa *et al.* (2016);[61] De Luca *et al.* (2010);[62] De Sanctis and Khater (2019);[63] Aversa *et al.* (2015);[64] Wegiel *et al.* (2019);[65] Sng *et al.* (2019);[66] Wong and Wen (2005);[67] Hu *et al.* (2007)[68]	–
LYP	Suppression of T cell-mediated signaling	Tomer *et al.* (2015);[36] Dultz *et al.* (2009);[49] Rhee and Veillette (2012);[70] Betterle *et al.* (2014);[72] Criswell *et al.* (2005);[73] Houcken *et al.* (2018);[74] Bottini *et al.* (2004);[75] Velaga *et al.* (2004);[76] Bulut *et al.* (2014);[77] Smyth *et al.* (2004);[78] Lee *et al.* (2011);[79] Alkhateeb *et al.* (2013);[80] Liu *et al.* (2015);[81] Ikegami *et al.* (2006);[82] El Fotoh *et al.* (2019);[83] Giza *et al.* (2013);[84] Wasniewska *et al.* (2012);[85] Prezioso *et al.* (2017);[86] Burn *et al.* (2011);[87] Blasetti *et al.* (2017);[88] Bottini *et al.* (2006)[89]	LYP inhibitors
FOXP3	Regulation of the differentiation and specification of regulatory T cells	Ban *et al.* (2007);[94] Inoue *et al.* (2010);[95] Villano *et al.* (2009);[96] Li *et al.* (2015);[97] Bossowski *et al.* (2013);[98] Nakano *et al.* (2007);[99] Korn *et al.* (2009);[100] Li *et al.* (2016);[101] Bjornvold *et al.* (2006);[102] Rubio-Cabezas *et al.* (2009);[103] Zavattari *et al.* (2004);[104] Nakanishi and Shima (2007);[105] Brusko *et al.* (2007);[106] Tritt *et al.* (2008);[107] Brode *et al.* (2006);[108] Tian *et al.* (2009);[109] Jaeckel *et al.* (2005);[110] Peng *et al.* (2004);[111] Wu *et al.* (2012);[112] Zheng *et al.* (2009);[113] Johnson *et al.* (2013)[114]	Complete Freund's adjuvant
CTLA-4	Inhibition of immune activation and immune response	Golden *et al.* (2005);[43] Villano *et al.* (2009);[96] Chen *et al.* (2013);[121] Pastuszak-Lewandoska *et al.* (2012);[122] Douroudis *et al.* (2009);[123] Bednarczuk *et al.* (2003);[124] Hou *et al.* (2015);[125] Vaidya *et al.* (1999);[126] Kavvoura *et al.* (2007);[127] Lee *et al.* (2000);[128] Ikegami *et al.* (2006);[129] Mochizuki *et al.* (2003);[130] Howson *et al.* (2007);[131] Tang *et al.* (2012);[132] Takara *et al.* (2000);[133] Mayans *et al.* (2007);[134] Balic *et al.* (2009);[135] Ban *et al.* (2001);[136] Celmeli *et al.* (2013);[137] Chen and Li (2019);[138] Wang *et al.* (2017);[139] Kavvoura *et al.* (2005);[140] Liu *et al.* (2013);[141] Dong *et al.* (2014);[142] Fathima *et al.* (2019);[143] Bicek *et al.* (2009);[144] Einarsdottir *et al.* (2003);[146] Ban and Tomer (2003);[147] Aversa *et al.*[148] (2019); Orban *et al.* (2011);[149] Orban *et al.* (2014)[150]	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.

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.[151–153] 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).[153,154] A significant association between childhood enterovirus infections and T1DM has been reported in several animal studies and human epidemiological studies, suggesting a diabetogenic role for damaged pancreatic islet beta-cell functions.[154–159]

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 $1,25(OH)_2D_3$; 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.[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.

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.[228–232] CXCL10, CXCL9, and CXCL11 also bind CXCR3 and have been implicated in the pathogenesis of many organ-specific autoimmune diseases involved in T helper-1 cells (Th-1), includingT1DM and AITD.[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.[239] Previous evidence demonstrated that CXCL9 expression was significantly increased in GD thyrocytes induced by interferon-γ (IFNγ) and tumor necrosis factor-α (TNF-α), which suggests that CXCL9 expression was low in normal thyrocytes and primary GD, and that the increased effect could be inhibited by PPAR-α agonist (fenofibrate) treatment.[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.[241] Moreover, CXCL11 has also been shown to be highly expressed in AITD and T1DM.[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.[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.[246]

A previous study has shown that the secretion of the chemokine CXCL8 is induced in thyrocytes by TNF-α and inhibited by IFNγ, which is different from the induction of CXCL10 by IFNγ and not TNF-α.[247] Moreover, TNF-α-induced CXCL8 secretion may be inhibited by IFNs in human thyrocytes, suggesting different roles for CXCL10 and CXCL8 in thyroid disease.[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.[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.[250,251] CXCL8/CXCL1-mediated leukocyte endothelial adhesion may make an important contribution to diabetic microvascular complications.[252]

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

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

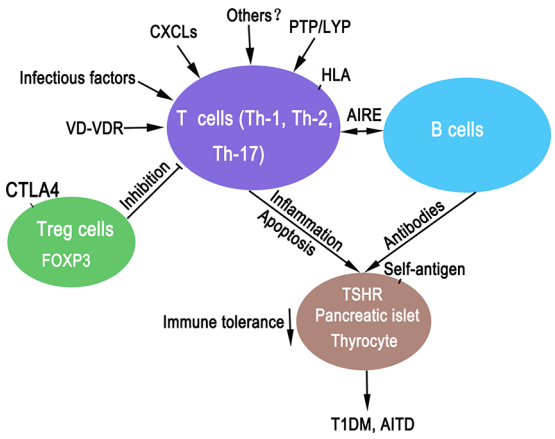

Figure 2. Proposed diagram of the pathogenic mechanisms involved in the development and progression of thyroid autoimmune disease and type 1 diabetes mellitus.
AIRE, autoimmune regulator; AITD, autoimmune thyroid disease; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; CXCLs, chemokine (C-X-C motif) ligands; FOXP3, forkhead box protein P3; HLA, human leukocyte antigen; PTP/LYP, lymphoid protein tyrosine phosphatase; Th, T helper cell; T1DM; type 1 diabetes mellitus; Treg, regulatory T cells; TSHR, thyroid-stimulating hormone receptor; VD, vitamin D; VDR, vitamin D receptor.

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

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