

Genetic background of type 1 diabetes mellitus: A review

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Abstract

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by the complete lack of insulin secretion due to the immune system's destruction of insulin-producing pancreatic β -cells. Approximately 50% of the risk factors for T1DM are attributed to genetic susceptibility, with the remaining causes linked to epigenetic modifications and environmental factors. The major gene region involved in T1DM is the major histocompatibility (MHC) complex, which is the first region discovered, conferring 50% of the genetic risk, followed by the insulin (INS), cytotoxic T lymphocyte-associated protein (CTLA4), protein tyrosine phosphatase, non-receptor type 22 (PTPN22), interleukin 2 receptor alpha (IL2RA) and interferon-induced with helicase C domain (IFIH1) genes. The remaining genetic susceptibility has been uncovered through genome-wide association (GWA) studies, which have identified 120 single nucleotide polymorphisms (SNPs) associated with T1DM risk to date. Additionally, non-coding RNAs (ncRNAs) also play a role, affecting the expression of the genes involved in T1DM. Epigenetics bridges the gap between genetic predisposition and environmental factors, which act as a trigger for T1DM in susceptible individuals. In this paper, the major genes involved in the risk of T1DM are reviewed.

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1. Introduction

Type 1 diabetes mellitus (T1DM) is characterized by a complete lack of insulin secretion due to immune-mediated destruction and chronic inflammation of insulin-producing pancreatic β -cells. The condition manifests clinically when 90% of the β -cells have been destroyed. The autoimmune process is characterized by the presence of autoantibodies, such as those against glutamic acid decarboxylase, islet cells, insulin, zinc transporter-8, and insulinoma-associated protein-2. One or more of these autoantibodies are found in 85–90% of individuals at the time of diagnosis. However, they can be detected months to years before the diagnosis of T1DM, indicating the pre-clinical state of islet autoimmunity. [1]. Several components of the immune system are involved in the destruction of the β -cells, which includes antigen-presenting cells (APCs), dendritic cells (DC), macrophages, B lymphocytes, natural killer (NK) cells, $CD4^+$ and $CD8^+$ cells [2].

In the general population, the risk for developing T1DM is 0.4%. Relatives of people who have T1DM are at higher risk, being from 12% to 67.7% for identical twins, and 6% to 7% for siblings [3].

Even though the risk of developing T1DM is higher among relatives, over 85% of people who develop it do not have a first degree relative with the pathology of T1DM [4].

According to the International Diabetes Federation (IDF), in the year of 2022, around 8.75 million people were living with T1DM, 1.52 million being under the age of 20. In Bosnia and Herzegovina, it is estimated that 6,224 people are living with T1DM [5]. With the prevalence of T1DM increasing by 0.34% every year, it is estimated that the prevalence of T1DM will be 17.4 million by the year of 2040 [6]. The Caucasians are considered to be in the highest risk, while the Asians are at much lower (Zayed, 2016).

The major causes of T1DM are genetic susceptibility, and 50% of risk factors are hereditary [8]. The rest is due to environmental exposure and epigenetic modifications. About 50% of the heritability is attributed to the major histocompatibility complex (MHC) region [9], discovered in the 1970s, which was the first region to be contributing to T1DM susceptibility. The next locus which was identified to be associated with T1DM was the insulin (INS) gene in 1984, followed by cytotoxic T lymphocyte-associated protein 4 (CTLA4) in 1996, protein tyrosine phosphatase, non-receptor type 22 (PTNP22) in 2004, interleukin 2 receptor alpha (IL2RA) in 2005, and interferon-induced with helicase C domain 1 (IFIH1) gene in 2006. Starting with the year of 2007, genome-wide association studies (GWAS) increased the number of loci to 60 [10]. More than 60% of the T1DM candidate genes are expressed in human pancreatic islets, and proinflammatory cytokines regulate many of them, which suggest that the genetic susceptibility to T1DM affects both the function of β -cells, and the immune system (Flyøel et al., 2014).

This paper examines the key genes associated with the risk of T1DM. It highlights the significant role of the major histocompatibility complex (MHC) and other important genes such as INS, CTLA4, PTPN22, IL2RA, and IFIH1, as well as some of the other genes discovered through GWAS, and SNPs connected to T1DM susceptibility.

2. Genetic studies – how the genes were discovered

To detect the risk loci for T1DM susceptibility, three approaches were used: linkage studies, association studies and GWAS. The loci identified using these approaches accounts for ~80% of heritability of T1DM. Linkage studies analyzed large number of sibling pairs, searching for the regions in genome that are more frequently shared among the relatives with T1DM. They provide information about which regions on the chromosome is contributing to the risk of developing T1DM. By this method, the human leukocyte antigen (HLA) contribution to T1DM risk was confirmed (Klak et al., 2020).

In contrast to linkage studies, association studies can identify alleles that have much more modest effects on disease risk, provided those alleles are relatively common. These studies use carefully chosen markers in genes of interest, which are genotyped in both affected individuals (case patients) and unaffected individuals (controls), or in some cases, patients and their parents. Initial association studies in T1DM concentrated on candidate genes. This approach led to the identification of the four well-established risk loci: HLA, INS, CTLA4, and PTPN22 (Klak et al., 2020).

GWAS revolutionized the way genes and genome are studied. GWAS let scientist to survey the whole genome and search for variants that contribute to the disease, but cannot be sufficient to cause the disease by itself. In early GWAS, genome-wide genotyping approach of nonsynonymous SNPs discovered the sixth gene associated with T1DM – IFIH1, which is not involved in the immune pathways, but in sensing viral RNA. (Klak et al., 2020b). Today, more than 120 genetic variants outside of the HLA-regions were found to be associated with the development of T1DM [14].

2.1. Major genes

2.1.1. HLA genes

In order for a T-cell receptor to recognize parts of the antigens, they need to be presented on the surface of the cells by the surface protein – major histocompatibility complex (MHC) molecule, which is encoded by the MHC locus. MHC locus contains two main classes: I and II. Class I is presented on all nucleated cells in the body,

and presents antigens from the cytosol to CD8⁺ cells, which recognize and kill the cells which are expressing those antigens. Class II, however, are only expressed on the surface of antigen-presenting cells (APCs), and presents antigens from the spaces outside the cells, for example, from bacteria or fungi. They present the antigens to CD4⁺ cells, which further activates the immune system to destruct the invaders [15].

In humans, MHC is referred as human leukocyte antigen (HLA) complex. Class I is encoded by A, B and C loci in humans, and class II is encoded by DP, DQ and DR loci. Class III have a little in common with class I and II, and is responsible for encoding molecules critical to the immune system. Class I-III genes are called classical, and in addition to these, there are non-classical genes that have more specialized functions, and are expressed in specific type of cells [15].

The genes in the MHC region are highly polymorphic, meaning that there are many alternative forms existing in each gene, called alleles. Because class I, II and II genes lie close together in the MHC loci, they are inherited together, making recombination rare. Individuals inherit these alleles as a set together, and that set of linked alleles is called a haplotype [15]. As of July 2024, there are 38,627 unique HLA alleles reported ([IPD-IMGT/HLA Database \(ebi.ac.uk\)](https://www.ebi.ac.uk/ipd/imgt/hla/)). And, although there are many of these alleles reported, more than 90% of them are rare, having been reported twice, or only once, while the remaining alleles are designated as common and well-documented [16].

The exact biological mechanism by which HLA genes are contributing to T1DM are difficult to determine. The highest risk is conferred by DR and DQ loci from class II HLA region [10]. Two main high-risk haplotypes are DR3-DQ2 (DRB1*03:01-DQA1*05:01-DQB1*02:01) and DR4-DQ8 (DR4-DQA1*03:01-DQB1*03:02), located in HLA class II region, where about 90% of patients carry one of those two haplotypes, and were 30% of patients carry both. Class I contribute, but less strongly to T1DM. Significant risk factor for T1DM is HLA-B*39 allele, connected to being diagnosed with T1DM at younger age, while HLA-A*02 allele is also connected to the higher likelihood of developing T1DM and has the frequency of >60% in people with T1DM (Klak et al., 2020). Some haplotypes are protective, such as DRB1*04:03 and is present at a frequency of ~3.5% in individuals with Asian descent, and only about 0.5% in individuals of European descent. The DRB1*07-DQA1*02:01-DQB1*02:02 is also protective in Europeans, but it's closely-related version, DRB1*07:01-DQA1*:03:01-DQB1*02:02, found in African population, is predisposing to T1DM. The DR3 version, DRB1*03:02-DQA1*04:01-DQB1*04:02, found in Africans is protective, but it's common haplotype, DRB1*03:01-DQA1*05:01-DQB1*02:01, which is found in most populations, is predisposing to T1DM [16].

2.1.2. INS gene

The INS gene is found on chromosome 11p15.5, and contributes about 10% towards T1DM susceptibility [17]. The short repeated variable number of tandem repeats (VNTR) region in the INS gene showed significant association with the progression of T1DM. The rs698 and rs3842753 loci also showed association with T1DM. The polymorphism in these regions have been divided into three classes, from class I to class III, with class I having the least number of repeats, and class 3 having the most. Class I VNTRs are associated with the higher risk of T1DM, while for class III it is believed to be protective (Bauer et al., 2021; Klak et al., 2020).

Recent studies showed that besides being transcribed in the β -cells, the INS gene is also expressed in the thymus, with the transcription level correlating with the allelic variation at the INS-VNTR. Class III haplotypes, which are protective against T1DM was reported to be associated with 2 to 3- higher increase in mRNA levels of INS gene in human thymus than class I haplotype. The higher level of class III haplotype of the INS gene is thought to facilitate immune tolerance induction, by negatively selecting insulin specific T lymphocytes [19].

The predominant hypothesis of how VNTR regulates insulin expression is by affecting binding of the transcription factor AIRE (autoimmune regulator) to its promoter region. Thus, class I VNTR will induce lower transcription of insulin and its precursors in the thymus, which will lead to reduced tolerance and the development of T1DM [20].

2.1.3. CTLA4 gene

The cytotoxic T-lymphocyte antigen (CTLA-4) gene is located on chromosome 2q33. It is a 40-kDa transmembrane glycoprotein expressed on non-lymphoid cells and resting and activated T cells [21], [22]. The activation of T lymphocytes by the T cell receptor (TCR) complex after recognizing an antigen requires additional signals from cluster of differentiation (CD) 28 (CD28). CTLA-4 delivers inhibitory signals to reduce T-cell activation by competing with CD28 for B7 ligands. CTLA-4 can also directly interact with the TCR complex to inhibit TCR signaling, acting as an intracellular phosphatase. Blocking CTLA-4 with anti-CTLA-4 mAb can increase (interleukin) 2 IL-2 (IL-2) mRNA expression and secretion of IL-2, promoting T-cell proliferation. Consequently, genetic variations affecting the CTLA4 gene's function may influence susceptibility to autoimmune diseases by altering the inhibitory effect on T-cell activity [23].

The A49G polymorphism was shown to be the most associated with T1DM of all CTLA4 SNPs, and it is the only polymorphism that changes the primary amino acid sequence. In vitro studies of this polymorphism showed that this form of CTLA4 is aberrantly processed in the endoplasmic reticulum, which leads to its reduced expression on the surface of the cells. Two more other variants that were discovered, C to T transition at the 319 position of the promoter region, and (AT)_n dinucleotide repeat polymorphism at the position 642 of the 3'UTR region did not show strong association with T1DM. Although the exact mechanism by which these polymorphisms affect the function of CTLA4 gene is not clear, for humans, the predominant hypothesis is that the allelic variants are lowering the levels of mRNA of the soluble CTLA4 splice variant [13], [20] and posttranslational modification [23].

2.1.4. PTPN22 gene

Protein tyrosine phosphatase, non-receptor type 22 (PTPN22) gene is located on chromosome 1p13 and encodes a 110-kDa protein, lymphoid-specific phosphatase (Lyp) which have a critical role as a negative regulator of T-cell activation (S. Tang et al., 2012).

PTPN22 affects different types of immune cells and signaling pathways, having both positive and negative regulatory effects. It downregulates T-cell signaling, and mutants in the gene results in B-cell receptor (BCR) and TCR hyper-responsiveness. It also has various roles of T-cell regulation and signaling, B-cell and BCR signaling, and is involved in various innate immunity and inflammatory processes in different immune cells. PTPN22 genetic variants contribute to many autoimmune diseases, and it is hypothesized that its role depends on the affected tissue by the autoimmune disorder [25].

Src and Syk kinases are substrates of PTPN22 protein and are governing the immune-receptor signaling. By interacting with the C-terminal Src tyrosine kinase (Csk), the negative regulatory kinase of the T-cell, it is downregulating it. The rs2476601 risk allele A (R620W mutation) is decreasing the ability of binding the phosphatase to SH3 domain of Csk. PTPN22 gene is also a target for forkhead box P3 (FOXP3) transcription factor, and expression of FOXP3 inhibits PTPN22 upregulation, making possible for the polymorphism to affect the development of T regulatory (Treg) cells, their function and homeostasis. Risk allele A of this variant is associated with increase of frequencies of total and naïve CD4⁺CD25⁺CD127^{low}FOXP3⁺ Treg. This mutation can be used as a marker to predict the progression of T1DM [26], [27].

A study in an isolated Armenian population found a close association between rs1310182 c.2054-852C>T polymorphism with T1DM, and limited contribution of the rs2476601 c.1858C>T polymorphism with the prototypic gain of function. The rs1310182 polymorphism is not much understood. It was found out to be associated with various autoimmune diseases. A missense point mutation in rs2476601 polymorphism causes a LYP variant with a gain-of-function. The mutation occurs in the P1 linkage domain, decreasing its affinity to CSK threefold and leading to increased activity of C-terminal Src kinase (CSK). LYP works in a way that it is binding to Src homology domain (SH3) in CSK, and when dissociated from CSK it is downregulating B-cell receptor and T cell receptor signaling [28].

A study conducted by Ferjeni et al., in the Tunisian population, showed that rs2488457 (-1123G/C) SNP, is associated with T1DM. It is located in the promoter region of the PTPN22 gene, and affecting the transcription rate of Lyp. This SNP was shown to be associated with T1DM in Japanese, but not in Caucasians [29]. The

association between T1DM and G allele and GG genotype of rs1310182 and A allele and AG genotype of rs2476601 SNPs were shown in Emirati population [30]. And, a meta-analysis conducted by Tang et al., revealed that there is a significant association of +1858C/T polymorphism with T1DM in people from America and Europe [24].

2.1.5. IL2RA gene

The interleukin 2 receptor alpha (IL2RA) which is also known as CD25 is located on chromosome 10p15. It is encoding the α chain of the IL-2 receptor complex and binds to IL-2, which is key player in proliferation of T reg cell, with high affinity. The proliferation of CD4⁺ FOXP3⁺ Tregs reliant on IL-2/IL-2RA is crucial for maintaining immune homeostasis. In T1DM, the dysfunction of CD4⁺ FOXP3⁺ Tregs is largely due to the ineffective induction and maintenance of these cells, which is linked to deficiencies in IL-2/IL-2RA signaling [21], [31].

Lowe et al., identified ss52580101 to be the most closely related to T1DM, of 288 analyzed SNPs. The SNPs that had the weakest associated had increased level of soluble IL2RA. They suggested the possible biological mechanism for autoimmunity is through reduced binding of IL-2 [32]. Qu et al., genotyped 949 nuclear family trios (1 affected offspring and 2 parents) of mixed European descent and found that rs28360490 and rs706778 SNPs were significant association with T1DM [33].

2.1.6. IFIH1 gene

Interferon induced with helicase C domain 1 (IFIH1) gene, which is also known as melanoma differentiation-associated gene-5 (MDA-5) encodes a cytoplasmic receptor that is responsible for recognizing double stranded RNA (dsRNA). When dsRNA binds to the IFIH1, proinflammatory cytokines are released by the immune cells, particularly interferons (INFs), which results in the apoptosis of the virus-infected cells [34]. IFIH1 also increase the expression of HLA class I genes, making the cells more visible to the immune system. This causes the destruction of β -cells, leading to T1DM [22].

GWAS studies identified non-synonymous variants in the IFIH1 locus, rs1990760 and rs3747517, mediating susceptibility to T1DM by increasing the production of type I interferon. Four rare SNPs, rs35667974, rs35337543, rs35732034 and rs35744605, are associated with the protection from T1DM [35].

2.2. Other genes

2.2.1. SUMO4 gene

SUMOylation is a process of post-translational modification (PTM), which includes several proteins, among them small ubiquitin-like modifier (SUMO), and enzymes that catalyze the conjugation/remove conjugated SUMO from substrates. PTM affect protein in various ways, such as localization, stability, and transcriptional regulation, which affects cellular processes and can contribute to the both health and disease [36]. Sumoylation can inhibit protein degradation by 26S proteasomes. Protein factors, which include NF κ B are reported to be the main targets of sumoylation. If 26 proteasome does not degrade sumoylated I κ B α , it will influence the activity of NF κ B [37].

There are four SUMO members which have been identified in humas. SUMO1, SUMO2, SUMO3 and recently SUMO4. SUMO4 is reported as a T1DM susceptibility gene, and is located on chromosome 6q25 (Li et al., 2005; Wang & She, 2008).

The M55V substitution within the gene is associated with the increased risk of T1DM (Wang & She, 2008). It is hypothesized that M55V substitution could results in higher capacity of stimulation of the cellular immune response, leading to higher levels of activated NF κ B, activating transcription of genes which are implicated in the T1DM development [41].

2.2.2. GLIS3 gene

Gli-similar 3 (GLIS3), located on chromosome 9p24.2 [42] is a member of Kruppel-like zinger family of transcription factors. It plays a role in beta cell mass maintenance and regulation the expression of INS gene in adults. GWAS have identified GLIS3 as one of the few genes related to both T1DM and T2MM [43]. GLIS3 is

highly expressed in a developing pancreas, and is involved in the development of the kidneys, livers, eyes and thyroid. Having a function as an activator or repressor, it possesses critical roles in regulating various cellular processes [44].

GLIS3 has been shown to play a central role in the development of islets, as well as the generation of functional β -cells and maintenance of their cellular identity, and is therefore a prime candidate gene for understanding the development and possible treatment of diabetes [45].

Given that GLIS3 mRNA is moderately expressed in the human thymus, it is proposed that the T1DM risk allele identified by GWAS might reduce GLIS3 expression in the thymus. This reduction could lead to T1DM autoimmunity by allowing GLIS3-reactive T-cells to escape negative selection. Additionally, the GLIS3 risk allele might enhance the diabetogenic T-cell response following β -cell apoptosis, whether physiological or pathological. It was found that the low-frequency A908V variant significantly protected against T1DM, despite predictions from SIFT and PolyPhen-2 suggesting it is unlikely to be functional. It was suggested that it is possible that the epitope containing 908V may induce central or peripheral tolerance more effectively than 908A, thereby reducing autoimmune reactions to β -cells. However, further immunological and functional studies are necessary to confirm this hypothesis and to clarify the precise mechanisms linking GLIS3 to T1DM [46].

It is hypothesized that GLIS3 might serve as an autoantigen in T1DM because GLIS3 mRNA is moderately expressed in the human thymus. Consequently, GLIS3 risk alleles that reduce GLIS3 expression in the thymus could contribute to T1DM autoimmunity by allowing GLIS3-reactive T-cells to evade negative selection. Furthermore, the diabetogenic T-cell response following β -cell apoptosis could be amplified by these GLIS3 risk alleles [43].

The rs7020673 and rs10758593 SNPs were the most studied SNPs in GLIS3 gene, regarding their susceptibility to T1DM. But the meta-study conducted by Duarte et al., however, showed no significant association between these two SNPs and T1DM [47].

2.2.3. Cathepsin H gene

Cathepsin H (CTHS) is located on chromosome 15q25.1 [42] encodes cathepsin, a member of papain-like cysteine proteases primarily involved in MHC class II antigen presentation, endolysosomal protein degradation, and activation of other proteins. It is expressed in β -cells of the pancreas, and APC, but not in T-cells. CTHS was associated with T1DM by GWAS. Patients with risk variants in this gene, had early onset of the disease, rapid decline of β -cell function, and increased CTHS transcription. Transcriptional dysregulation of this gene promotes the apoptosis of β -cells [48].

Most significant SNP in the CTSH gene which is related to T1DM susceptibility is rs3825932. The T allele of this gene is associated with lower CTSH expression in human lymphoblastoid cell lines and pancreatic tissue. The TT genotype has lower protein levels. Carriers of this genotype require higher insulin dose in order to maintain glycemic control and have higher IDA1c levels, which indicates the negative effect the TT genotype has on the function of residual β -cells in patients with T1DM. Patients with TT genotype also have faster disease progression, which leads to more prominent dysfunction of β -cells. Flyøel et al., suggested that, as higher CTSH expression in β -cells may preserve its function and protect against immune-mediated damage, it could be a possible therapeutic target. [11].

2.2.4. SIRPG gene

The signal regulatory protein gamma (SIRPG) is located on the chromosome 20p13. It is expressed on NK cells, T-cells, and a small subset of CD19+ B-cells. It has been linked to T1DM in multiple GWAS studies, but its contribution still remains unclear, with only a small number of studies trying to address its biological function. SIRPG is one of the ligands for CD47, and its binding to it facilitates cell adhesion, apoptosis, proliferation in response to the stimulation by superantigen and *trans*-endothelial migration of T-cells. Engagement of CD47 of APCs to SIRPG on T-cells has been shown to enhance the proliferation of antigen-specific T-cells [49], [50].

In GWAS, two *cis*-pQTL of the SIRPG gene have been associated with T1DM: rs2281808 (C>T, in the intron) and rs6043409 (G>A, A263 V). The T allele in rs2281808 is a risk allele, having the association with the reduced expression of SIRPγ on T cells in human, which leads to a hyperactivated state with lower threshold of activation in healthy donors [51]. The major allele at rs6043409 SNP is the risk allele for T1DM. This allele results in increased expression of SIRPγ on the surface of T-cells. The minor allele A in this SNP is associated with the reduced risk of T1DM [50].

2.2.5. BACH2 gene

BTB and CNC homology 1 (BACH2) is located on chromosome 6q15 and acts as a transcription factor in the immune system, with its role implicated in regulating immunoglobulin class switching, formation of Treg cells, maintenance of T-cell state, regulation of B-cells towards plasma cell differentiation. It is expressed and modulated by proinflammatory cytokines in both human and rodent pancreatic cells. The SNPs in this gene might contribute to development of T1DM, because the gene is related to the control of T-cells and differentiation of B-cells, plays role in anti-apoptosis in β-cells, and modulates the balance between immunity and tolerance [52], [53]. Increased expression of BACH2 gene in peripheral blood of children which are positive for β-cell antibodies could predict their progression to T1DM. Dysregulation of BACH2 is directly implicated in the pathogenesis of T1DM. Inhibition of BACH2 leads to cytokine-induced apoptosis of human and rodent β cells through the activation of the JNK1/BIM pathway and anti-apoptotic members of the BCL-2 family. The overexpression of BACH2 protects these cells from apoptosis. Therefore, BACH2 appears to be a critical factor in safeguarding β-cells against apoptosis induced by cytokines [52].

2.2.6. TYK2 gene

The tyrosin kinase 2 (TYK2) gene, located on chromosome 19p13.2, is encoding a tyrosine kinase, a part of Janus kinase (JAK) family. It has an essential role in the signaling of intracellular signal transducer and activator of transcription (STAT), stimulated by cytokines, which includes type-I interferons (IFN-I). The IFN-I signaling contributes to the development of T1DM by upregulating the expression and antigen presentation of class I MHC, which in turn directs cytotoxic autoimmune responses towards β-cells. The rs2304256 SNP in this gene is causing a missense mutation, which leads to decreased function of the gene, is associated with higher risk of developing T1DM. The rs34536443 and rs2304256 SNPs, which induce a partial inhibition of the expression of the TYK2 gene are associated with the protection against T1DM and other autoimmune diseases [14], [42]. Furthermore, this gene confers a possible link with susceptibility to virus-induced T1DM, which was also confirmed by the study conducted by Izumi et al., which showed that the lower expression of this gene in β-cells of the mice [54], [55].

3. Non-coding RNAs

About 50% of the loci with T1DM susceptibility belong to different classes of non-coding RNAs (ncRNA), with their roles still needed to be explained. The ncRNAs can be divided into two groups: small ncRNA, for example, microRNAs (miRNAs), and long ncRNAs (lncRNA) [56].

miRNA are short nucleotide RNAs (about 22 nucleotides long) that act as posttranslational regulator by binding to 3' UTR region of target mRNA, which causes translational repression or degradation of mRNA. They are essential for maintaining β-cell function and normal development and differentiation of the pancreas. Several miRNAs are regulated by glucose or pro-inflammatory cytokines in β-cells and pancreatic islets where they modulate insulin transcription/secretion, proliferation, or apoptosis. The SNPs connected to the T1DM susceptibility can alter the seed-sequence in loci-associated miRNA, or the target sites of protein-coding genes by miRNA. Furthermore, SNPs in miRNA can change the structure of region by flanking them, which is influencing the accessibility of binding of the miRNA. Some SNPs can alter the target sites of miRNA in several of the susceptibility loci [56]. For example, when miRNA-21 (miR-21) is overexpressed, it was shown to disrupts the development of β-cells in animal models. As it regulates the caspase levels, by its overexpression, the caspase-3 levels are increased, which leads to the reduction of cell count and viability. Studies also reported

that elevated levels of this gene lead to increased apoptosis of β -cells in T1DM development by targeting the translocation of *blc-2* gene. When the levels of miR-29 were increased in human and mouse pancreatic cells, it was found to impair the glucose-induced insulin secretion. It promoted β -cells destruction, leading to pancreatic dysfunction in early stages of the development of T1DM by targeting myeloid cell leukemia-1 (Mcl1) antiapoptotic protein. In patients with T1DM, miR-181 was found to be overexpressed compared to the control, and as it has negative correlation with SMAD7 and C-peptide levels, studies suggested that it could have a potentially significant role in the dysfunction of β -cells. Two miRNAs, miR-7 and miR-124, are negative regulator of the differentiation of β and α -cells, with miR-7 inhibiting pair box 6 (*pax6*) gene, and miR-124 targeting the forkhead box A2 (*Foxa2*) transcription factor [57].

LncRNAs are long RNA about 200 nucleotides in length. They can regulate the expression of the genes both positively and negatively. More than 1100 islet-specific and in most cases, β -cell-specific lncRNA have been identified in humans. Loci associated with T1DM in lncRNAs could potentially be regulators of their host protein-coding candidate genes [56]. MEG3 has been verified to have participation in the development of the T1DM pathogenesis. It can alter insulin secretion by modulating the expression of *Sin3 α* , *Smc3*, and *Rad21*, through EZH-2 associate H3K27 methylation. TUG1 is involved in retinal development, and compared to other tissues, it is overexpressed in pancreatic tissue. The silencing of TUG1 leads to reduced insulin production in β -cells and higher rates of apoptosis. Some lncRNAs contribute to the complication associated with T1DM. MALAT1 was shown to be increased in T1DM patients. It inhibits the acetylation of H3 histone of *PDX1* gene and decreases its expression. *PDX1* is a transcription factor and contributes to insulin expression enhancement. The lnc13 is thought to be involved in T1DM pathogenesis by enhancing β -cells inflammatory responses. A SNP in rs917997 in lnc13 has been shown to regulate the expression of *STAT1*. The individuals with CC genotype have higher *STAT1* expression in their islets compared to those carrying heterozygous. SNPs in *PVT1* and *MEG3* has also been shown to influence the T1DM risk (Taheri et al., 2020).

4. Epigenetics

Epigenetics provides a link between the development of T1DM and the environment as the environmental factors can induce epigenetic changes. They work by influencing the gene expression and the function of the cell without changing the DNA sequence. Epigenetic modifications can be divided into three groups: DNA methylation, histone modification and microRNA [59].

The DNA SNP-CpG methylation patterns were found to be potentially relevant for the genetic association secretion of insulin and/or insulin expression in the pancreatic islets in humans. In *CD4⁺* cells in T1DM, the regions of *FOXP3* gene were hypermethylated, which lead to decreased expression of the gene, and reduced production of Treg cells. As for histone modification, in *CTLA4* gene, there was increased level of H3K9me2, which has been linked to the activation of T-cells. The trichostatin-A, well known histone deacetylase inhibitor (HDACi) was suggested to enhances the production of IFN- γ , and increases the transcription activity of *Tbx21* in T lymphocytes, which in result leads to reducing the inflammatory damage of islet cells [60]. The role of microRNA was explained in the chapter above.

5. Environment

Over the past 30 years, the incidence of T1DM has increased by several times, with the only possible explanation for it being the changes in lifestyle or environment. Some factors were proposed to act as a trigger in genetically predisposed individuals, such as infections, gut microbiota, vaccines, dietary factors such as vitamin D, breastfeeding, cow's milk, cereals and solid foods, and polysaturated fatty acids; toxins and other chemical compounds and of β -cells stress; as well as the hygiene hypothesis [61].

6. Conclusion

Type 1 diabetes mellitus is a complex disease, characterized by the autoimmune destruction of pancreatic β -cells. Its development is an interplay of genetics, epigenetic and environmental factors. There are many genes

involved in genetic susceptibility, with MHC complex (HLA in humans) being the main one, but not enough to cause T1DM on its own. The INS, CTLA4, PTPN22, IL2RA and IFIH were discovered shortly after. With GWAS more than non-HLA 120 genetic variants connected with T1DM were identified. Genes connected to T1DM susceptibility does not just change the protein structure, but some of them changes the expression of other genes. Furthermore, epigenetic changes are also discovered in connection to T1DM, changing the expression. Lastly, genes themselves are not enough to cause T1DM, but a certain environmental factor needs to act as a trigger.

Additional studies of genes connected to the T1DM susceptibility might provide a greater insight into prevention and management of T1DM. By identifying genetic markers and understanding their roles in disease development, researchers can develop targeted therapies and personalized treatment plans.

Declaration of competing interest

The authors declare that they have no known financial or non-financial competing interests in any material discussed in this paper.

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