DOI: 10.20514/2226-6704-2023-13-6-413-421
УДК: 616.379-008.64
EDN: LLKGAF

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ВЗАИМОСВЯЗЬ МИКРОРНК С ТРАНСПОЗОНАМИ В РАЗВИТИИ САХАРНОГО ДИАБЕТА 1 ТИПА

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Relationship of MicroRNAs with Transposable Elements in Type 1 Diabetes Development

Резюме

В обзорной статье представлены данные об участии эпигенетических факторов в этиопатогенезе сахарного диабета 1 типа. Это отражается, в первую очередь, в изменениях экспрессии микроРНК, которые влияют на транскрипцию генов, вовлеченных в аутоиммунные реакции, разрушение бета-клеток островков Лангерганса и продукцию инсулина. Однако причина наблюдаемых эпигенетических изменений до сих пор не ясна. В эволюции источниками генов микроРНК являются транспозоны, занимающие до 45 % всей последовательности ДНК человека и являющиеся драйверами эпигенетической регуляции в онтогенезе. Они являются источниками последовательностей транскрипционных факторов и сайтов связывания с ними. Особенности распределения транспозонов в геноме могут стать причиной изменения количества 5'VNTR (variable number of tandem repeats) — повторов промоторной области гена инсулина и инсерций HERV в область генов *HLA*, что отразится на характере их экспрессии. В связи с этим сделано предположение, что причиной развития сахарного диабета 1 типа может служить дисбаланс активации транскрипции транспозонов, что способствует изменению экспрессии специфических микроРНК и белок-кодирующих генов, а также способствует развитию аутоиммунного ответа. Провоцирующими факторами могут быть индивидуальные особенности распределения транспозонов в геноме, вирусные инфекции и стрессовые воздействия. Анализ научной литературы подтверждает предложенные механизмы развития болезни, поскольку доказаны глобальная роль ретроэлементов в гормональной регуляции, чувствительность транспозонов к экзогенным вирусным инфекциям и стрессовым воздействиям, экспрессия эндогенных ретровирусов HERV-W у большинства больных сахарным диабетом 1 типа с активацией аутоиммунного ответа. Анализ базы данных MDTE DB (miRNAs derived from transposable elements database) показал происхождение от транспозонов 12 ассоциированных с сахарным диабетом 1 типа микроРНК (miR-192, miR-224, miR-31, miR-320c, miR-326, miR-340, miR-342, miR-44661, miR-548c, miR-652, miR-95), использование которых может стать основой таргетной терапии.

Ключевые слова: *аутоиммунные реакции, инсулин, микроРНК, ретроэлементы, транспозоны, сахарный диабет 1 типа, эндогенные ретровирусы*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 05.10.2023 г.
Принята к публикации 28.11.2023 г.

Для цитирования: Мустафин Р.Н. ВЗАИМОСВЯЗЬ МИКРОРНК С ТРАНСПОЗОНАМИ В РАЗВИТИИ САХАРНОГО ДИАБЕТА 1 ТИПА. Архивъ внутренней медицины. 2023; 13(6): 413-421. DOI: 10.20514/2226-6704-2023-13-6-413-421. EDN: LLKGAF

Abstract

The review article describes the involvement of epigenetic factors in type 1 diabetes mellitus (T1DM) etiopathogenesis. The disease is characterized by changes in expression of microRNAs that affect the transcription of genes involved in autoimmune reactions, destruction of beta cells and insulin production. However, the cause of the observed epigenetic changes is still unclear. In evolution, the sources of microRNA genes are transposable elements, which occupy up to 45% of the entire human DNA sequence and are drivers of epigenetic regulation in ontogenesis. They are sources of transcription factor sequences and binding sites for them. Features of the genome distribution of transposable elements can cause changes in

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the number of 5'VNTR (variable number of tandem repeats) — repeats of insulin promoter region and HERV insertions into HLA genes, which affects their expression. Therefore, I assume that the cause of the development of type 1 diabetes mellitus may be an imbalance in transcription activation of transposons, which contributes to changes in the expression of specific microRNAs and protein-coding genes, and also contributes to autoimmune response development. Triggers for this may be individual features of genome distribution of transposons, viral infections and stress. An analysis of the scientific literature confirms my proposed mechanisms for T1DM development, since the global role of retroelements in hormonal regulation, the sensitivity of transposable elements to exogenous viral infections and stress, and HERV-W expression of the majority of patients with T1DM with activation of the autoimmune response have been proven. Analysis of the MDTE DB (miRNAs derived from transposable elements database) database showed the transposon origin of 12 T1DM-associated microRNAs (miR-192, miR-224, miR-31, miR-320c, miR-326, miR-340, miR-342, miR-44661, miR-548c, miR-652, miR-95), the use of which can become the basis for targeted therapy for T1DM.

Key words: *autoimmune reactions, insulin, microRNA, retroelements, transposable elements, type 1 diabetes mellitus, endogenous retroviruses*

Conflict of interests
The authors declare no conflict of interests

Sources of funding
The authors declare no funding for this study

Article received on 05.10.2023
Accepted for publication on 28.11.2023

For citation: Mustafin R.N. Relationship of MicroRNAs with Transposable Elements in Type 1 Diabetes Development. The Russian Archives of Internal Medicine. 2023; 13(6): 413-421. DOI: 10.20514/2226-6704-2023-13-6-413-421. EDN: LLKGAF

BCP — beta cells of pancreas, DM — type 1 diabetes mellitus, HERV — human endogenous retrovirus, HLA — human leukocyte antigen, *INS* — insuline gene, Treg — regulatory T-cells (CD8+ lymphocytes), UTR — untranslated region, VNTR — variable number of tandem repeats

Introduction

According to the International Diabetes Federation (IDF), diabetes affects 8.8 % of the adult world population. 10–15 % of cases are type 1 diabetes mellitus (DM1) [1], which is characterised by uncontrolled immune response to beta cells of pancreas (BCP) and their depletion [2]. Autoantibody synthesis starts several years before clinical manifestations of DM1 with inflammatory processes in pancreas, infiltration with T-lymphocytes and other immune BCP cells [3]. One method to develop new therapies for DM1 can be the study of genetic factors of this disease, since DM1 heritability is assumed to be 88 %, and monozygotic twins concordance — 70 % [4]. 2 % of DM1 patients are diagnosed with a monogenic disease causes by MODY (Maturity-Onset Diabetes of the Young) gene mutations [5], with the most common mutations being in genes *HNF4A, GCK, HNF1A, HNF1B* [6].

Genetic testing, such as genome-wide association study (GWAS), made it possible to identify association between DM1 and polymorphic variants of a number of various genes: *GSDMB* (encodes gasdermin B), *C1QTNF6* (a protein associated with C1q and tumour necrosis factor), *ZPBP2* (zona pellucida-binding protein 2), *CTSH* (catepsin H), *SIRPG* (signal-regulating protein gamma). Besides, the association of DM1 with allelic variants of the following genes has been identified: *AFF3* (a coding protein, a member of AF4/FMR2), *RPS26* (ribosomal protein S26), *DEXI* (dexamethasone 1), *CFDP1* (craniofacial development protein 1), *ORMDL3* (ORM1-like protein 3), *SMARCE1* (SWI/SNF-bound, matrix-associated actin-dependent chromatin regulator), *UBASH3A* (ubiquitin-associated SH3 domain-containing protein A) [7]. DM1 is also associated with allelic variants of the following genes: *PTPN22* (a protein product — nonreceptor thyrosine phosphataze, type 22), *CTLA-4* (T-lymphocyte-associated cytotoxic protein), *IL2RA* (interleukin 2 receptor alpha-subunit), *PTPN2* (nonreceptor thyrosine phosphataze, type 2), *IFIH1* (interferon-induced helicase), *BACH2* (main leucine zip-per transcription factor), *UBASH3A* (ubiquitin-associated SH3 domain-containing protein A), *GLIS3* (Gli-like protein 3) [8]. However, it is currently not possible to explain the impact of such a number of genes and, moreover, to use obtained data to develop diagnostic panels and new therapies. A study of the role of epigenetic factors in DM1 aetiopathogenesis is far more promising, because changes caused by these factors are reversible; therefore, they can be targeted in order to correct and treat DM1. Epigenetic factors include DNA methylation, histone modification and RNA interference using non-coding RNAs [9].

The most common non-coding RNA is micro-RNA. They are short RNA molecules of 18–25 nucleotides, which regulate gene expression at the posttranscriptional level. The majority of micro-RNA genes is localised in introns, however, they can also be localised in intergenic sequences, untranslated regions (UTR) and exons. They primarily down-regulate mRNA transmission in their target genes due to complementary binding with 3'UTR. Exceptions are miR-10a, which binds with c 5'UTR in ribosomal mRNA and up-regulates its translation; and miR-21, which positively regulates expression of mitochondrial cytochrome (mt-Cytb) [2]. Micro-RNA can affect DM1 development in several ways: causing BCP depletion and functional changes, suppressing insulin

gene expression and stimulating immune response to beta cells (Fig. 1). These effects are implemented by inhibiting or stimulating specific targets with micro-RNA molecules — mRNA genes involved in various signal paths and mechanisms. Paediatric patients with DM1 have increased blood levels of miR-21, which causes BCP apoptosis due to stimulation of caspase-3 production [10]. Similar effects on BCP are observed with miR-375, targeting genes *Aifm1, Gephyrin, Ywhaz, Mtpn*, that participate in insulin exocytosis. Besides, it was noted that miR-375 can down-regulate insulin gene expression [11]. miR-29, the levels of which are increased in serum of DM1 patients [12], stimulates apoptosis by suppressing expression of antiapoptotic proteins [13].

Serum of DM1 patients demonstrates increased levels of miR-26 [12], which targets mRNA of histone methyltransferase gene Ezh2, suppressing regulatory T-cell (Treg) proliferation [14]. Thus, Ezh2 inhibition causes an increase in synthesis of Treg participating in immune response. DM1-associated miR-25 (increased serum expression) down-regulates insulin gene expression (*INS*) [12]. Plasma of DM1 patients demonstrates significantly higher miR-181 expression, which negatively regulates expression of gene *SMAD7,* effecting BCP function [15]. In 2017, Assmann et al. conducted a systemic review and bioinformatic analysis of available scientific information on the role of micro-RNA in DM1 development. As a result, they identified a reliable dysregulation of 11 specific micro-RNAs in DM1 patients as compared to controls: miR-21-5p, miR-24-3p, miR-100-5p, miR-146a-5p, miR-148a-3p, miR-150-5p, miR-181a-5p, miR-210-5p, miR-342-3p, miR-375, miR-1275. miR-21-5p, miR-181a, miR-375 were involved in BCP apoptosis due to inhibition of mRNA of genes *PI3K* and *AKT*with suppression of mTOR pathways; miR-146a-5p — due to inhibition of transcription factor NFκB. miR-24-3p and miR-210-5p targeted cytokines IL6R, LIFR, IL2RB, IFNLR1. Micro-RNAs miR-148a-5p, miR-100-5p, miR-150-5p target mRNA of genes *NFκB, MAPK, PI3K-Akt* in pathways of ubiquitin-mediated protein cleavage [16].

A meta-analysis of data on the association between circulating micro-RNA in serum and plasma of DM1 patients, conducted in 2021, demonstrated a highly reliable increase in expression of 2 micro-RNAs (miR-181, miR-210) and reduction in expression of 1 microRNA (miR-375) vs. healthy controls [17]. Blood mononuclear leukocytes of patients with DM1 had significantly higher expression of miR-326, which promotes autoimmune response due to the impact on mRNA, proteins of which are immune modulators. They include homotype 1 of erythroblastosis tumour virus E26 and vitamin D receptor [18]. Low miR-146 levels in peripheral mononuclear leukocytes are associated with immune response in DM1, evidencing the protective action of this micro-RNA [19]. Autologous-reactive CD8+ T-cells of DM1 patients demonstrate increased expression of miR-510 [20], miR-23b, miR-590 and miR-98, targeting apoptosis regulating genes *Fas, Faslg, Trail, Trail-R2,* effecting increased proliferation of diabetogenic T-cells [21]. Patients with type 1 pre-diabetes demonstrate higher miR-31 expression in CD4+ T-cells, facilitating immune response due to inhibition of transcription factor Foxp3 involved in immune reactions [14].

Based on the above, DM1 development can be impacted by changes in expression of specific micro-RNAs both in pancreatic tissue itself (facilitating BCP apoptosis, impaired insulin synthesis and autoimmune response activation), impacting circulating micro-RNA levels, and in blood cells stimulating their autoimmune response. Therefore, micro-RNAs can be successfully

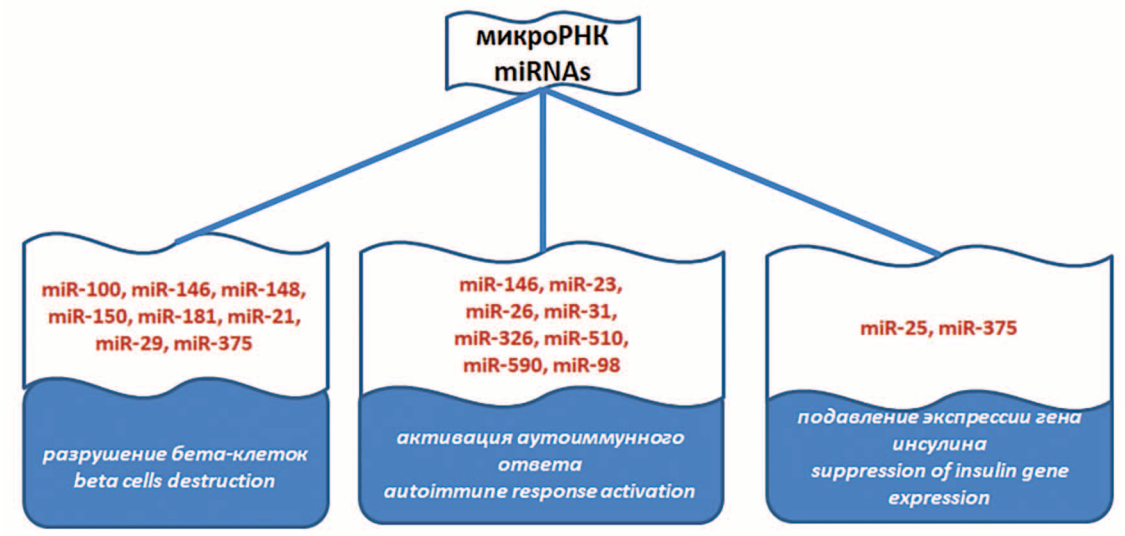

Figure 1. *Scheme of the mechanisms of microRNAs influence on T1DM development*

used as an object for epigenetic therapy impacting both T-cells (inhibiting differentiation of their pathogenic phenotypes) and BCP (facilitating their functional restoration). In particular, low miR-146 levels in mononuclear leukocytes are associated with severe DM1. Administration of miR-146 mimetics in animal models alleviates diabetes and inhibits autoimmune processes [22]. It is possible to use such mimetics and other micro-RNAs, such as miR-191 and miR-342, expression of which is reduced in regulatory T-cells of patients with DM1 [20]. It is also necessary to search for root causes, that cause imbalance in expression of micro-RNAs and other factors activating production of anti-BCP autoantibodies.

Micro-RNAs and transposones in the development of type 1 diabetes mellitus

Transposones have become an unexpected important source of micro-RNA genes during evolution [23]; they are scattered all over human genome and are able to move within genome, including gene introns. Together with their repeats, transposones account for over 2/3 of all human DNA sequences [24]. MDTE DB, a database on the origin of human micro-RNAs from transposones, has been formed [23]. Transposones are classified as retroelements (they form repeats from their own cDNA transcripts, which are integrated into a new gene locus) and DNA-transposones (they move within the genome using "cut and paste" mechanism). Retroelements can have long terminal LTR repeats (including endogenous retroviruses (HERV)) or cannot have them (non-LTR retroelements). Autonomous non-LTR retroelements (encoding own reverse transcriptase and endonuclease, which are essential for transpositions) are LINE1, LINE2, PLE, DIRS. Non-autonomous retroelements using enzymes of other transposones include SINE (also Alu) and SVA (SINE-VNTR-Alu) [25]. A comparative analysis of micro-RNAs presented in MDTE DB with scientific literature allowed identifying 12 micro-RNAs originating from transposones, the expression of which is specifically changed in patients with DM1. Three micro-RNAs (miR-335, miR-340, miR-548c) out of 44 presented in a paper by Takahashi et al. [26] originated from transposones [23]. Two micro-RNAs (miR-342 и miR-652) out of 41 published in a study by Ferraz et al. originated from transposones [27]. Out of 22 micro-RNAs identified by Morales-Sanchez et al., miR-31 and miR-4661 originated from retroelements [28].

For some micro-RNAs, which originate from transposones, the expression of which is changes in DM1 patients (Table 1), the mechanism of impacting the disease has been identified. For example, miR-326 targets mRNA of genes modulating immune system: *VDR* (vitamin D receptor) and *ETS-1* (homotype of erythroblastosis tumour virus E26) [29]. miR-31 targets mRNA

Table 1. *Expression changes of transposable elements-derived miRNAs in patients with T1DM*

МикроРНК/ MiRNA	Характер изменения экспрессии при СД1 (ткань)/ Expression change in T1DM (tissue)	Транспозон — источник возникновения/ Transposable element — source of origin	Автор исследования/ Reference
miR-192	повышение (кровь)/ increase (blood)	LINE2	[35]
miR-224	повышение (моча)/ increase (urine)	ДНК-транспозон MER135 DNA-transposon MER135	[34]
miR-31	понижение (кровь)/ decrease (blood)	LINE2	[28, 30]
miR-320c	повышение (кровь)/ increase (blood)	LINE1	[33]
miR-326	повышение (ткань БКПЖ)/ increase (pancreatic islet tissue)	ДНК-транспозон hAT-Tip100 DNA-transposon hAT-Tip100	[18]
miR-335	повышение (кровь)/ increase (blood)	SINE-MIR	[26]
miR-340	повышение (кровь)/ increase (blood)	ДНК-транспозон TcMar-Mariner DNA-transposon TcMar-Mariner	[26]
miR-342	повышение (кровь)/ increase (blood)	SINE/tRNA-RTE	[27]
miR-4661	понижение (кровь)/ decrease (blood)	LTR-Gypsy	[28]
miR-548c	повышение (кровь)/ increase (blood)	ДНК-транспозонTcMar-Mariner DNA-transposon TcMar-Mariner	[26]
miR-652	повышение (кровь)/ increase (blood)	ДНК-транспозон hAT-Tip100 DNA-transposon hAT-Tip100	[27]
miR-95	повышение (моча)/ increase (urine)	LINE2	[32]

of gene of transcription factor FOXP3, which regulates development and functions of regulatory T-cells [30]. miR-95, which originates from LINE2 [23], also interacts with FOXP3 [31]. Increased miR-95 levels are observed in patients with DM1 and are significantly higher in a high risk of severe diabetic nephropathy progression [32]. miR-320c targets mRNA of genes *STAT4, CCR7, RASGRP1, SH2B3,* the expression products of which are involved in regulation of endocytosis, cell cycle and signal pathway of transforming growth factor TGF-beta. Therefore, increased miR-320c levels in DM1 are associated with damaged BCPs [33]. Urine of DM1 patients demonstrate higher levels of miR-224 targeting mRNA of gene *SMAD4,* involved in TGF-beta pathways and cell proliferation regulation [34]. DM1-associated miR-192 activates TLR7/8 pathways, promoting T-cell proliferation [35].

The data in Table 1 make it possible to suspect a role played by transposones in DM1 development, a potential manifestation of which is modified expression of transposone-originated micro-DNAs connected with them in single gene networks. Moreover, it is likely that transposones are primary drivers of epigenetic processes in DM1, causing global changes in regulatory networks of the genome and resulting in modified expression of complementary micro-RNAs. It is caused by high sensitivity of transposones to stresses [36, 37] and viral infections [38, 39], which initiate pathologic activation of transposones and result in DM1. An important role can be participation of transposones in endocrine system functioning (Fig. 2). Domestication of retroelement MIR-b in the gene of insulin-like growth factor 1 (*IGF-1*) promoted production of a functional domain of its protein product [40]; retroelement ASR (Alu/snaR-related) has been used to form a beta subunit of chorionic gonadotropin [41]. Nuclear receptors of progesterone [42], vitamin D [43] and oestrogens [44] evolved as a result of retroelement exaptation. It is worth mentioning that LINE1 served as a basis for 80 % of sites for binding to transcription factors of all protein-encoding human genes [45]. Besides, transposones were a primary source of transcription factors during evolution [46]. Prolactin gene promoter *Prl* originated from ERV *MER39* [47], arginine-vasopressin 1a gene (*AVPR1A*) — from SVA [48]. ERV was the source of gene enhancers for proopiomelanocortin(*POMC*) [49] and corticoliberin

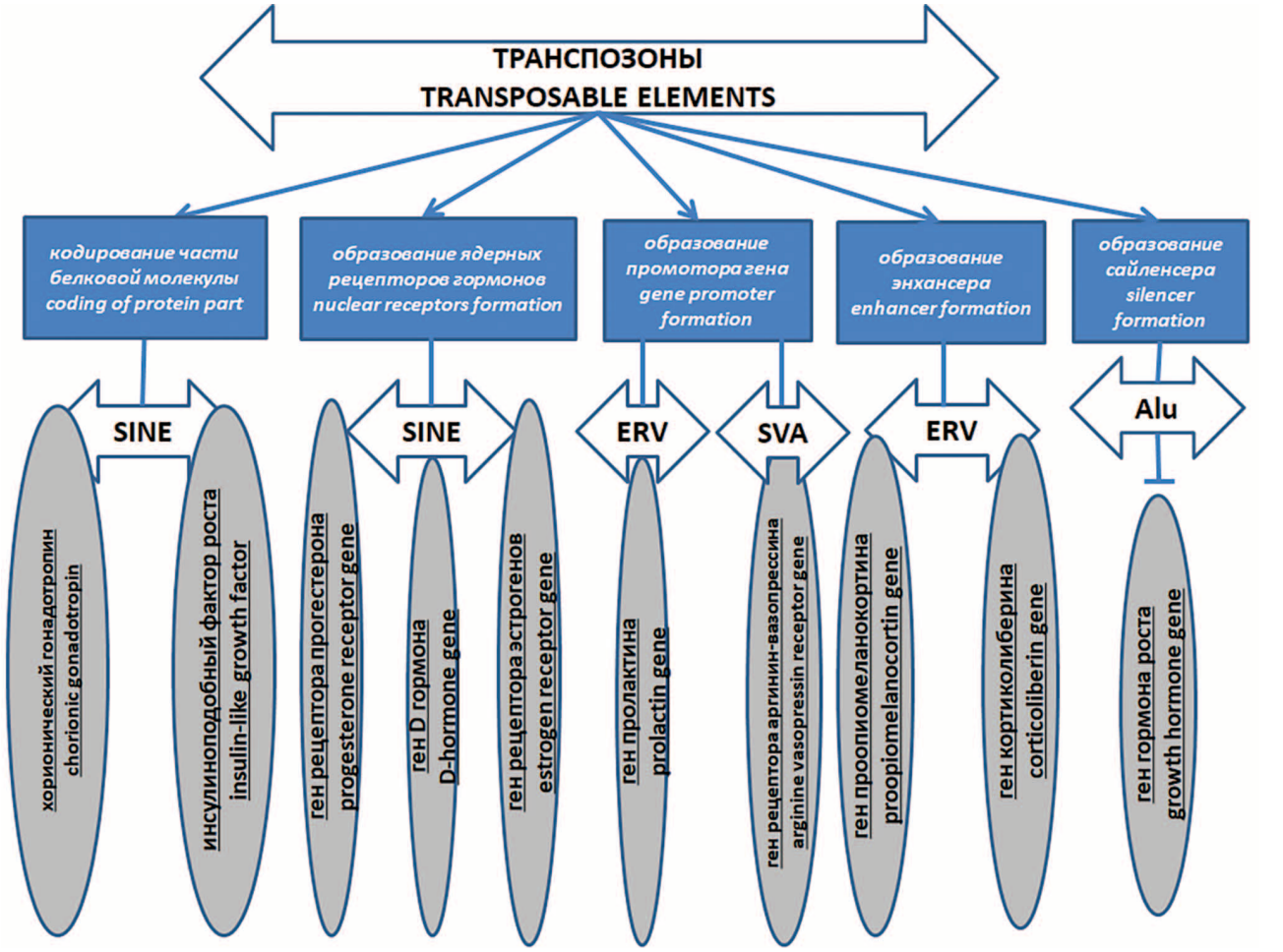

Figure 2. *Role of transposable elements in hormonal regulation*

(*CRH*) [50]. In humans, the gene of growth hormone *GH* is next to 44 *Alu*, a part of which serve as silencers [51]. Description of the role of transposones in DM1 aetiopathogenesis requires more attention.

Role of transposones in the development of type 1 diabetes mellitus

Transposones participate in DM1 aetiopathogenesis via various pathways: serving as autoimmune antigens for stimulation of anti-BCP immune response, inhibiting insulin gene expression or having toxic effect on beta cells. Besides, susceptibility to DM1 depends on the features of SVA distribution in promotor regions of genes HLA and insulin. Results of clinical studies in DM1 patients demonstrate the role of retroelements in maintaining autoimmune processes in this pathology. Since transposones can be activated by exogenous viruses [38, 39], DM1 can be initiated by DM1-associated infections caused by enteroviruses [52, 53] and Epstein-Barr virus [54]. It has been demonstrated that exogenous viruses stimulate HERV-K18 expression and interferon production. In turn, HERV-K18 is a source of superantigen, which stimulates autoimmune T-cells [38].

70 % of DM1 patients have envelope protein HERV-W in their blood, which is not only an autoimmune antigen, but also inhibits insulin expression [55] and has toxic effect on BCP [39]. Protein Env of retroelement HERV-W was found in BCP samples of 75 % of patients with DM1 [56]. Initiation by actively expressing retroelements HERV of autoimmune reactions is evidenced by high titres of antibodies to envelope protein HERV-W-Env in children with DM1 [57]. A study of transcription of genes *pol* of endogenous retroviruses HERV-H, HERV-K, HERV-W in children with newly diagnosed DM1 showed a significantly higher level of expression of genes *HERV-H-pol* and *HERV-W-pol* as compared to healthy controls [3]. In mice experiments with DM1, autoimmune reaction induction by retroelements has also been confirmed: proteins Env and GagERV have been found in BCP microvesicules. DM1 progression was accompanied by an increase in anti-Env antibodies and T-cell stimulation under the influence of antigene Gag [58]. Further experiments demonstrated that Gag antigen is also found in stromal cells of pancreatic islets. DM1-resistant mice have Gag transcription in BCP without formation of a protein product, whereas in DM1 mice, mRNA of gene *GAG* is translated on ribosomes with formation of a protein which is specific to activation of autologous-reactive T-cells [59].

DM1 development depends not only on intragenic mutations in *INS* [6], but also on changes in the variable number of tandem repeats (VNTR) in its promotor region [8]. VNTR is an essential component of retroelements SVA, which, like other transposones, can change the number of tandem repeats [9]. SVA have a lot of GC-repeats, therefore, they can form alternative DNA structures, such as G-quadruplexes (G4), which impact transcription. Over 40 % of human genes contain G4-sequences in their promotor region [48]. Formation of tandem repeats using retroelements is a universal property of all living organisms, it being associated with illegitimate recombination and further amplification by gene conversion [60].

VNTR are located 596 bps upstream of the initiation site of *INS* translation. They are divided into long class III pools (141–209 repeats) and short class I pools (26–63 repeats). The latter are associated with DM1 [8]. It is an evidence of possible impact of retroelement activity on disease progression, since non-autonomous SVA, forming VNTR in the promotor area, have sequences, which are identical to autonomous retroelements LINE, which enzymes they use to translocate in the genome. Allele A of single nucleotide polymorphism — 23HphI (rs689) is in linkage disequilibrium with class I VNTR, whereas allele T — with class III VNTR. Also, allele C-2221MspI is in linkage disequilibrium with class I and subclass IIIB, while allele T — with subclass IIIA. Class III VNTR facilitate enhanced insulin expression in thymus gland with later negative selection of autologous-reactive T-cells to insulin (resulting in immune tolerance to insulin and low risk of autoimmune response to beta cells of pancreas) [61]. Also, blood tests in DM1 patients demonstrated the impact of VNTR length in the promotor region of gene *INS* on formation of proinsulin-specific T-cells participating in autoimmune response [62].

As pointed out above, association of allele variants of gene pools with DM1, observed in various studies, cannot be interpreted in terms of disease aetiopathogenesis. The most understandable is DM1 association with allele variants of genes in the major histocompatibility system *HLA,* since the disease is associated with autoimmune damage to BCPs [3]. Approximately 50 % of family cases of DM1 are associated with HLA region on chromosome 6p21 [8]. It correlates with the role of retroelement activation as an object for autoantibody production [3], because HERV serve as regulatory elements of class I genes of the major histocompatibility system HLA-G [50]. Retroelements can impact immune reactions, facilitating DM1 development, by direct insertions in genes of the major histocompatibility system. Changes in the region of C4 complement gene location impact HLA-DQ-mediated DM1 development. At the same time, a study of 220 families with DM1 demonstrated that 77.7 % of genes *HLA-DQ8* and 52.9 % of genes *HLA-DQ2* have HERV-K (C4) insertions [63], which impact regulation of these genes. Indeed, since genes *HLA-DQ*

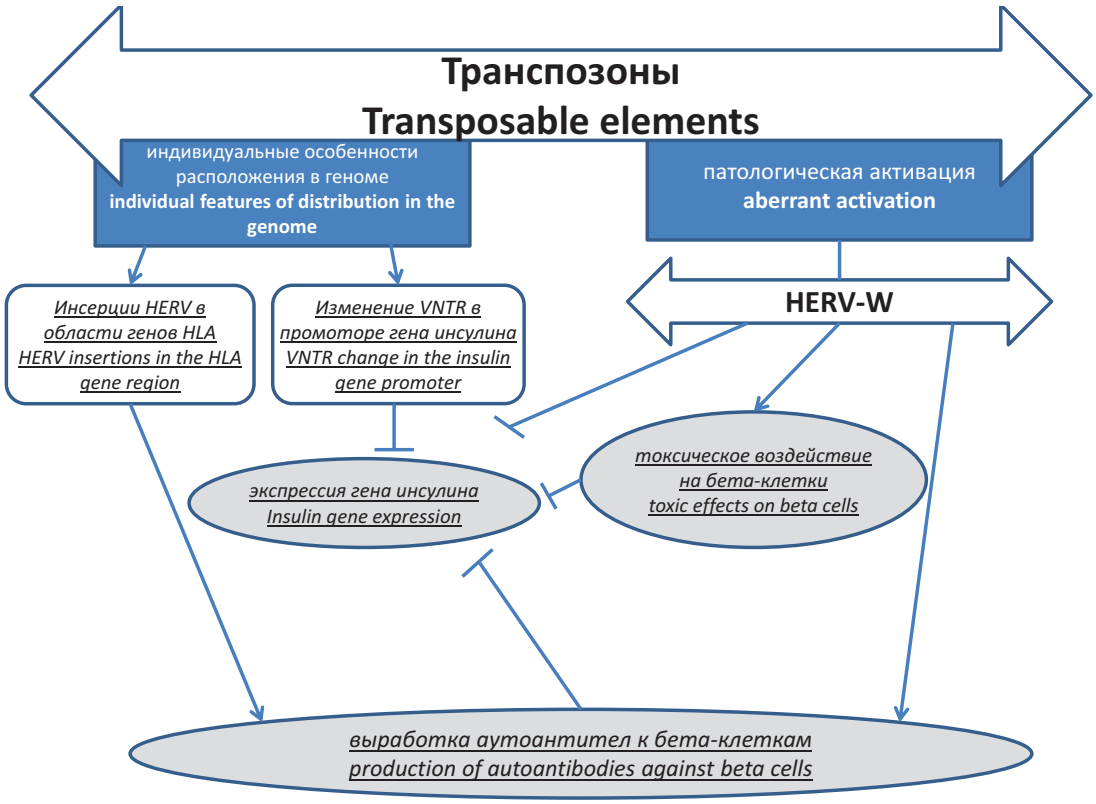

Figure 3. *Scheme of transposable elements effect on the type 1 diabetes mellitus development*

are a factor of DM1 development, the impact of various LTR in this region on disease pathogenesis has been studied. Segregation of LTR located 1,300 bps upstream of *HLA-DQB1* (LTR13) with various HLA-DQ haplotypes was analysed in 284 DM1 patients. It was found out that alleles DQ8/LTR13+ are associated with a risk of DM1 as compared to allele DQ8/LTR13- carriers [64]. In another study of 246 DM1 patients, the association between DQ-LTR3 and disease development was identified. DQ-LTR3 is 90 % homological to HERV-K, evidencing the impact of endogenous retroviruses on the distribution of this sequence [65]. Therefore, pathological transposone activation due to their specific individual location in the genome (affecting VNTR in promotor regions of genes *INS* and HLA group), stresses [36, 37] and exogenous viruses [38, 39] contribute to DM1 development (Fig. 3).

Conclusion

Analysis of scientific literature demonstrated a significant role of heredity in DM1 development. However, studies showed the association between the disease and polymorphic variants or genes, the impact of which cannot be explained. Analysis of data on the impact of epigenetic factors on the disease is of particular interest, because they can be corrected. The change in expression of specific micro-RNAs observed in serum and plasma (circulating micro-RNA), mononuclear leukocytes, T-cells and BCP has been demonstrated. These micro-RNAs impact DM1 development by inducing autoimmune reactions, depleting BCPs and inhibiting insulin production. Experiments demonstrated efficiency of the use of micro-RNA mimetics for DM1 progression suppression, and it can serve as a basis for clinical trials. The root cause of changes in the expression of specific micro-RNAs involved in DM1 pathogenesis is probably pathologic transposone activation. It has been proven that, under the influence of stress factors and exogenous viral infections, individual susceptibility (due to transposone composition and distribution in the genome) facilitates enhanced expression of retroelements. The latter are autoimmune antigens (mainly HERV-W) for production of anti-BCP autoantibodies. Endogenous retroviruses have direct toxic effect on BCPs. Upon activation, transposones show mutual regulation. Retroelements SVA are sources of VNTR in promotor regions of insulin gene, and HERV insertions impact HERV expression. During evolution, sources of genomes of a number of micro-RNAs were transposones. Analysis of literature sources resulted in identification of 12 micro-RNAs originating from them and involved in DM1 development. One can assume that the use of these micro-RNAs as a targeting tool will make it possible to normalise expression of transposones as part of complex therapy of patients with DM1.

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