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Prospects for the study of transposons in the pathogenesis of autoimmune diseases

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Abstract

One of the mechanisms for the development of autoimmune diseases is changes in epigenetic regulation, the root causes of which have not yet been established. At the same time, data on the role of transposons as sources of long noncoding ribonucleic acids (RNA) and microRNAs involved in the development of immune pathology have been accumulated. In evolution, transposable elements have become the basis for the emergence of V(D)J recombination and regulation of HLA genes. Pathological transposon activation has been revealed in type 1 diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, Aicardi–Goutieres and Sjögren's syndromes. The influence of exogenous viruses on the development of autoimmune diseases may be due to their interactions with transposons. Transposable elements themselves are able to activate the antiviral immune response, stimulating the hyperproduction of interferon. An assumption about changes in the activation of transposons as drivers of autoimmune pathology was made, which is reflected in the expression of non-coding RNAs, which are key epigenetic factors. The analysis of the transposon-derived microRNA database (MDTE DB) made it possible to identify 13 microRNAs associated with autoimmune diseases: systemic scleroderma (miR-31, miR-609, miR-3162), juvenile rheumatoid arthritis (miR-151), systemic lupus erythematosus (miR-198, miR-342), psoriasis (miR-224, miR-378) and myasthenia gravis (miR-421, miR-551a, miR-612, miR-891b), multiple sclerosis (miR-584), which serves as a proof of the proposed hypothesis. Since changes in epigenetic factors under the influence of transposons are reversible and are reflected in the expression of certain non-coding RNAs, targeted therapy using microRNAs and their analogues as tools is a promising direction in the development of specific treatment for autoimmune diseases.

Keywords: autoimmune response, viruses, long non-coding RNAs, interferon, microRNAs, transposons, epigenetics.

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Abbreviations

ADAR, adenosine deaminase RNA; AID, autoimmune diseases; DNA, deoxyribonucleic acid; ERV, endogenous retroviruses; IFN, interferon; IRF3, interferon regulatory factor 3; LINE, long interspersed nuclear elements; lncRNA, long noncoding RNA; ncRNA, non-coding RNA; RAG, recombination-activating genes; RNA, ribonucleic acid; SINE, short interspersed nuclear elements; TE, transposable elements, transposones; TIR, terminal inverted repeats.

Background

Autoimmune diseases (AIDs) are characterized by the increased reactivity of the immune system against self-antigens, which causes tissue damage. The etiology of AIDs remains unknown; however genetic, microbial, environmental, and psychological factors may be decisive. In this case, epigenetic changes, such as the methylation of deoxyribonucleic acid (DNA) cytosine and histone modifications, are signaling mediators between the genome and the environment.

Impaired epigenetic regulation has been identified in numerous studies of patients with AID compared with healthy people [1]. Important epigenetic factors are non-coding RNAs (ncRNAs), which are subdivided into long ncRNAs (lncRNAs, at least 200 nucleotides in length) and small ncRNAs, including the best known microRNAs. They regulate gene expression at the post-transcriptional level and serve as "guides" for the distribution of specific epigenetic marks throughout the genome using RNA-directed DNA methylation. This phenomenon, originally discovered in plants, was also found in humans [2].

MicroRNAs also affect histone modifications because of interactions with histone deacety-

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lase [3]. That is, ncRNAs represent the basis for changes in DNA methylation and modification of chromatin in ontogenesis, which is reflected in the dynamic transformations of gene expression. Transposable elements (TE) distributed in the genome are higher-order drivers, which are sources of microRNAs [4] and lncRNAs [5]. Many lncRNAs are formed directly from TE transcripts [6, 7].

A comprehensive study revealed that more than 2/3 of the human genome consist of TEs and their residues [8]. In evolution, they originated from many germinal insertions of viruses that are integrated into the genome and lost the ability to infect [9]. TEs are classified into DNA-TEs and retroelements. The latter is subdivided into autonomous ones, namely, endogenous retroviruses (ERV) and long interspersed nuclear elements (LINE) and non-autonomous ones, namely, short interspersed nuclear elements (SINE), including the most common Alu elements [10].

The body has many defense systems that prevent TE activation. These include epigenetic factors (LINE1 promoter methylation, RNA interference by microRNAs, histone modification by specific proteins such as retinoblastoma protein), interferon-I (IFN-I), SAMHD1-mediated stress granule formation, interactions with DNA repair enzymes, transcriptional and posttranscriptional regulations by members of the SOX and MOV10 helicase families, and hypermutation of LINE1 transcripts via APOBEC cytidine deaminase [11].

Although TEs are parts of the human genome, which have been preserved over millions of years of evolution, they represent a potential immunogenic danger, particularly when new mutations arise in them, which increase their foreignness for defense mechanisms. However, unaltered TE transcripts are pathogenic because they tend to form double-stranded Z-conformational structures (Zα-domains), which are recognized by the ZBP-1 protein. Thus, activated ZBP-1 stimulates the production of IFN-I through IFN regulatory factor 3 (IRF3) [12].

Retroelements are sources of complementary DNA, for which pattern recognition receptors serve as pathogen-associated molecular patterns that induce the synthesis of IFN and other cytokines that induce AID [13]. Several cellular sensors are involved in the recognition of foreign RNA and DNA, namely, melanoma differentiation-associated gene 5, RNA-activated protein kinase, DNA-activated protein kinase, and DNA sensor cyclic GMP-AMP synthetase[1]. Additional sensors are DDX1, DDX21, DDX36, DDX41, IFI16, and Aim2. Extracellular DNA or RNA entering the cell through receptor-mediated endocytosis is recognized by Toll-like receptors 3, 7, 8, and 9 in the endosome. These pathways primarily promote IFN-I production by activating IRF3 and related transcription factors [14].

Although several systems protect the genome from TE activity, TE dysregulation is highly probable because they function as drivers of epigenetic regulation of gene expression [15].

Epigenetic changes in AIDs

Immune system cells express various lncRNAs specific for their types, which has been revealed for $CD4^+$ and $CD8^+$ T-lymphocytes and $CD11c^+$ dendritic cells. Upon induction, macrophages produce various lncRNAs located near the protein-coding genes of the innate immune system [16], which is crucial in viral destruction. Its increased activity leads to AIDs and is under the regulatory control of lncRNAs. IFN signaling by lncRNAs is essential for the body's antiviral response [17].

Several IFN-induced lncRNAs have been identified to regulate the IFN response, which is impaired in AID, by the feedback principle. For example, systemic scleroderma is characterized by the activation of IFN-associated lncRNAs and the antiviral response in an IFN-dependent manner in human monocytes in response to TLR4 activation (which stimulates the production of transforming factor-β, which promotes fibrosis). A clinical study of patients with systemic scleroderma revealed overexpression of these lncRNAs compared with the control. Among them, the levels of lncRNA negative regulator of the IFN response (NRIR) in vivo in monocytes significantly increased with a pronounced correlation of the IFN response. Fifteen target genes for NRIR have been identified, including two genes for IFN-related chemokines CXCL10 and CXCL11 that are involved in the pathogenesis of systemic scleroderma [18].

LncRNAs were found to play a role in the development of various AIDs, such as rheumatoid arthritis (lncRNAs: *GAS5* and *HOTAIR*), systemic lupus erythematosus (*GAS5, NEAT1, Linc0949,* and *Linc0597*), multiple sclerosis (*GAS5* and *Linc-MAF-4*), psoriasis (*PRINS* and *PSORS1C3*), Hashimoto's thyroiditis (*TMEVPG1 aka, NeST aka,* and *IFNG-AS1*), and diabetes mellitus (*FlicR*) [19]. LncRNAs and their specific epigenetic marks can be used as potential biomarkers for determining AID status, prognosis, and treatment response and as targets for targeted therapy [1]. For example, adenosine deaminase RNAs (ADAR RNAs), which diversify the transcriptome by modifying

[1] GMP, guanosine monophosphate; AMP, adenosine monophosphate.

RNA molecules, are used for primate-specific adenosine-inosine (A-to-I) editing of RNA of Alu-elements. ADAR1 expression and A-to-I RNA editing rate are significantly high in rheumatoid arthritis in the synovium and blood of patients with active disease. Moreover, a good clinical effect of the treatment was noted as a decrease in the rate of A-to-I editing of Alu-element transcripts [20].

LncRNAs are usually designated from the names of neighboring protein-coding genes [16] and are divided into five classes [17]:

1) Long intergenic transcripts

2) Introns

3) Bidirectional, which are transcribed in the opposite direction relative to the promoter of protein-coding genes

4) Antisense RNAs transcribed from the opposite DNA strand of exons of protein-coding genes;

5) LncRNAs of the pseudogenic type

According to the NONCODE database, the human genome contains 96,000 lncRNA genes [19]. Despite the name "non-coding," many of them are capable of translation (because of noncanonical open reading frames) to form peptides that perform various functions, including participation in the immune response [21]. This indicates the evolutionary role of lncRNA genes in the emergence of protein-coding genes that retain the properties of their phylogenetic precursors, that is, the functionality of their transcripts [22]. Thus, the *p53* gene mRNA contains a site locus for direct binding to the domain of the Mdm2 ubiquitin ligase, which degrades the p53 protein. The interaction of these molecules leads to Mdm2 inactivation and enhances p53 synthesis [23]. Many other protein-coding genes have similar bifunctionality [22].

In addition to lncRNAs, microRNAs are significant in AID development. In patients with early-stage rheumatoid arthritis, miR-16, miR-24, miR-125a, and miR-223 levels in the blood serum increase, whereas miR-22 and miR-103a are predictors of disease development. The expression of miR-223 is high during the activation and relapse of rheumatoid arthritis [24] and juvenile rheumatoid arthritis. This microRNA controls myeloid cell differentiation, similar to miR-26a, which is also high in juvenile rheumatoid arthritis. T-lymphocyte regulation involves miR-21, miR-146, miR-150, and miR-151, whose expression levels are increased in this disease. The levels of miR-223 and miR-16 are associated with disease activity. In the blood plasma of patients with juvenile rheumatoid arthritis, the concentrations of microRNAs miR-132 and miR-155 decreased, whereas in peripheral monocytes, the concentrations of miR-98a, miR-21, and miR-133a are also noted. In addition to the above microRNAs, high levels of miR-145 are noted in the blood plasma and miR-99a, miR-100, miR-125a, miR-146a/b, miR-150, miR-155, miR-181c, and miR-223 in monocytes in juvenile rheumatoid arthritis [25].

High levels of miR-96 and miR-183, which target *EGR-1* and *PTEN*, are expressed in $CD4^+$ T-lymphocytes of patients with Graves' orbitopathy [26]. MicroRNAs have a unique potential to determine the pathogenesis of systemic scleroderma. The miR-29 and miR-let-7 families downregulate the expression of collagens and fibrosis-associated transcription factors. Mir-145 inhibits SMAD3, also exerting an anti-fibrotic effect. Thus, in systemic scleroderma, their levels are reduced. Enhanced expression is characteristic of miR-483-5p and miR-21 (suppresses SMAD7, promoting fibrosis). The latter is also involved in vasculopathy, along with miR-31 and miR-155 [27].

In addition, according to a meta-analysis conducted in 2016, overexpression of miR-16, miR-34b-3p, miR-146a/b, miR-181, miR-200b-3p, miR-223, miR-300, miR-609, miR-768-3p, miR-877-3p, miR-3162-3p, and miR-4701-5p and low expression of miR-574 and miR-200b-5p are also associated with systemic scleroderma. miR-16, miR-132, miR-146a, and miR-301a-3p are associated with rheumatoid arthritis; miR-26b-5p, miR-142-3p, miR-146a, miR-155, miR-223, miR-224, miR-378, and miR-424 (overexpression) and miR-99a, miR-125b, miR-181a, and miR-193b (underexpression) are associated with psoriasis; miR-21, miR-61, miR-78, miR-142-3p, miR-189, miR-198, miR-298, miR-299-3p, miR-342, miR-410, miR-516a-3p, miR-525-5p, and miR-629 (overexpression) and miR-17-5p, miR-112, miR-126, miR-141, miR-146a, miR-155, miR-184, miR-196a, miR-383, and miR-409-3p (underexpression) are associated with systemic lupus erythematosus; miR-146a-3p, miR-146a-5p, miR-155, and miR-210 are associated with antiphospholipid syndrome; miR-21, miR-27a, miR-150, miR-155, miR-146a/b, miR-326 [28], miR-22, miR-145, miR-155, miR-223/-3p, miR-584 [29] and miR-214, miR-140-5p, and miR-572 (underexpression) are associated with multiple sclerosis [28].

In myasthenia gravis, the expression of miR-7 is decreased by epithelial cells of the thymus (controls CCL21 production), and an increase in miR-125a (regulates the transcription of FoxP3 and various signaling pathways of inflammation) was determined. In addition, miR-1-3p, miR-34c-5p, miR-125a-5p, miR-375-3p, miR-421-3p, miR-429-3p, miR-486-5p, miR-509-3p, miR-551a-3p, miR-574-3p, miR-612-5p, miR-760-3p, miR-767-3p, miR-875-3p, miR-890-5p, miR-891b-5p, miR-892a-3p, miR-4465-3p, and miR-4500-3p are dysregulated in this disease [30].

Table 1. Transposon-derived microRNAs associated with autoimmune diseases

Source of microRNA	microRNA	Disease	Reference
LINE2	miR-31	Systemic scleroderma (overexpression)	[27]
LINE2	miR-151	Juvenile rheumatoid arthritis (overexpression)	[25]
SINE (MIR3)	miR-198	Systemic lupus erythematosus (overexpression)	[28]
DNA transposon MER135	miR-224	Psoriasis (overexpression)	[28]
SINE	miR-342	Systemic lupus erythematosus (overexpression)	[28]
SINE	miR-378	Psoriasis (overexpression)	[28]
LINE2	miR-421	Myasthenia gravis (underexpression)	[30]
LINE1	miR-551a	Myasthenia gravis (underexpression)	[30]
DNA transposon hAT-Blackjack	miR-584	Multiple sclerosis (overexpression)	[28]
LINE2	miR-609	Systemic scleroderma (overexpression)	[28]
SINE	miR-612	Myasthenia gravis (overexpression)	[30]
SINE	miR-891b	Myasthenia gravis (underexpression)	[30]
LINE2	miR-3162	Systemic scleroderma (overexpression)	[28]

Note: DNA, deoxyribonucleic acid; LINE, long interspersed nuclear elements; RNA, ribonucleic acid; SINE, short interspersed nuclear elements

An analysis of the results of GWAS 12 of AID conducted in 2018 showed an association of Crohn's disease and rheumatoid arthritis with f miR-1908-5p expression and an association of Crohn's disease with miR-3614-5p [31].

The association of ncRNAs supports the assumption of the role of TE dysregulation in the etiopathogenesis of AID because TEs are important sources of lncRNAs [5, 7] and microRNAs [4]. A database of microRNAs derived from TEs has been created, according to which 2583 different microRNAs are originated from TEs. In this regard, this information system was analyzed according to the above-described microRNAs associated with AID. As a result, 13 of these microRNAs originated from TEs (Table 1), which confirms the involvement of TEs in AID development.

Relationship of transposons with viruses in immunopathology

A close evolutionary relationship was found between viruses and TE. Moreover, a study revealed their interconversions and the existence of intermediate life forms that combine the properties of viruses and TEs [32]. Human retroelements are involved in antiviral defense, which explains their activation in response to viral infections [10, 15]. In the life of the organism, the relationship between exogenous viruses and TEs can become one of AID factors. In chronic idiopathic urticaria, stable remission can be achieved after therapy with a retroviral integrase inhibitor (raltegravir) [33]. Various viruses can induce the expression of ERVs adjacent to antiviral response genes. Moreover, the activity of some TEs increases almost immediately after infection, even before the increase in IFN production [10].

Patients with rheumatoid arthritis have high levels of antibodies to the Epstein–Barr virus in comparison with the control, whereas a violation of antibodies specific to the virus is typical. The disease predisposition allele HLA-DRB1*0404 was found to be associated with a low frequency of gp110-glycoprotein-specific T cells, which is necessary for infection control [34].

Epstein–Barr virus infection is also associated with multiple sclerosis. Moreover, patients have an increased response to the viral antigens. Using solid-phase epitope mapping, antibodies from patients with multiple sclerosis recognize the peptide region of the EBNA-1 protein (covers amino acids from 411 to 426), cross-reacting with myelin basic protein [35].

A 2016 analysis of a study of 4.5 million people (1977–2012) confirmed the association between infections (including viral ones) and 29 AIDs [36]. All patients with autoimmune Guillain–Barré syndrome have antibodies, namely, class G immunoglobulins against Zika and Dengue viruses, and 69% of cases had antibodies against the chikungunya virus [37]. Human herpesvirus type 6 is associated with endocrine AIDs. A comparative study revealed a more pronounced expression of glycoprotein-B of this virus in the pancreas of patients with type 1 diabetes mellitus compared with people without diabetes but were positive for autoantibodies [38].

The role of hepatotropic viruses in the etiology of autoimmune hepatitis has been discovered.

Half of the patients with viral hepatitis E have at least one type of autoantibodies, and 17% of patients have two types (antinuclear autoantibodies in 33%, antibodies against smooth muscle fibers in 21%, and antineutrophil cytoplasmic antibodies in 14% of cases) [39].

Moreover, 40%–70% of patients with hepatitis C experience at least one extrahepatic pathology of rheumatic nature (arthralgia, arthritis, vasculitis, or Sjögren's syndrome) with positive tests for rheumatoid factor or other autoantibodies (antinuclear, anti-DNA, antibodies to extractable nuclear antigen, antineutrophil cytoplasmic antibodies, antiphospholipids, and antibodies to cyclic citrulline peptide) [40].

Viruses mediate their effects on AID through the induction of heat shock proteins and virus-mediated conversion of epithelial cells into virgin de novo professional antigen-presenting cells. Heat shock protein induction leads to molecular mimicry, where epitopes on heat shock proteins can be mistaken for viral peptides and presented by antigen-presenting cells to autoreactive T-cell receptors with subsequent apoptosis of antigen-presenting cells and mediated MHC[2] class II-DR apoptosis of operational antigen-presenting cells with an outcome in autoimmune processes [41]. However, the influence of exogenous viruses on AID development is most probably based on their effect on TEs [10], whose imbalance is involved in the pathogenesis of these diseases because viruses activate TEs [10, 15].

Role of transposons in immunopathology development

With evolution, TEs were found to be the most important sources of regulatory sequences and protein-coding genes, including those involved in the immune system [15, 32]. The system that provides the formation of antigen-specific immunity in vertebrates has two main features of DNA-TE. These features include the presence of recombinase (encoded by *RAG1* and *RAG2*, recombination-activating genes) and mobile DNA (limited to specific sites recognized by recombinase). RAG proteins are homologous to the transposase of the *Tc1* element [42]. Coaptation of RAG1/2 (recombination-activating genes) for the arrangement of variable, joining, and diversity (V(D)J) antigen receptor genes was a decisive event in the emergence of adaptive immunity in jawed vertebrates. The discovery of ProtoRAG from the DNA-TE family in the lancelet provided evidence of the origin of RAG1/2 in evolution from TE.

Typical ProtoRAGs are flanked by 5-bp long target site duplications and two terminal inverted repeats (TIRs) similar to the V(D)J recombination signal sequences. Between TIRs, RAG1-like and RAG2-like genes are located, containing an intron and are oriented tail-to-tail. ProtoRAG was active in the lancelet germline, and lancelet RAG1/2-like proteins can mediate TIR-dependent TE excision, host DNA recombination, transpositions, and low-efficiency TIR reunions using mechanisms similar to vertebrate RAGs [43].

ERVs have formed the evolution of the transcriptional network that underlies the IFN response. In various clades of mammals, independently of each other, ERVs formed numerous IFN-inducible enhancers [44]. ERVs are also involved in the regulation of the human immune system because they are enhancers of *HLA-G* [45].

HERV integration within or near critical immune factor genes is responsible for the polymorphic variability in humans, such as the insertions of the provirus HERV-K (HML10) into the major histocompatibility complex region. Owing to the persistence of HERVs in the human genome and their basal expression in most healthy tissues, the immune system must prevent its HERV-mediated activation. However, HERV expression products can still affect the host immune system, being the most important factor in the functioning of human innate immunity [9].

Long-term IFN responses in human AID, including relapsing–remitting multiple sclerosis, may be caused by the transcripts of LINE and Alu retroelements, which induce an IFN response by activating pattern recognition receptors [46]. The overexpression of retroelements can be an activating mechanism of AID development [1].

LINE1 can be an endogenous trigger for the activation of innate immunity by stimulating IFN production [47]. Accordingly, the role of TE in AID pathogenesis is reflected by the high level of IFN-I in these diseases because RNAs and complementary DNAs of retroelements can be recognized as foreign [14]. As early as 1985, using mouse models with type 1 diabetes mellitus, more severe manifestations of the disease develop in women whose β-cells produce type C retrovirus in the form of intra- and extracellular vacuoles [48]. In model mice, insulin autoantibodies cross-reacted with the p73 protein (IAP gag gene product) of ERV, which is associated with molecular mimicry between insulin and p73. Autoantibodies that cross-react with p73 and insulin are also detected in 65% of people with type 1 diabetes mellitus, which indicates the role of ERV in the development of this pathology [49].

[2] MHC: major histocompatibility complex.

In rheumatoid arthritis, transcriptional activation of HERV-K occurs [50], resulting in the production of antibodies against its proteins, particularly env-$su_{19–37}$ [51]. The role of TEs in the development of rheumatoid arthritis is confirmed by the increased production of ADAR1, which edits Alu transcripts and may be associated with protection from their overexpression [20]. A study also revealed the correlation of antibodies against p40 (ORF1 product of LINE1 retroelement) with the development, severity, and activity of systemic lupus erythematosus [52]. The effect of ERV on lupus nephritis in mice has been demonstrated. ERVs are sources of nephritogenic retroviral immune complexes gp70-anti-gp70 following TLR7 activation [53, 54]. Among ERVs, mice with lupus express a significantly higher number of modified polytropic retroviruses that are controlled by the Sgp3 locus [53].

AID includes the neurodegenerative Aicardi–Goutières syndrome, in which, as in systemic lupus erythematosus, the dysfunction of the antiviral enzyme TREX1 (a repair exonuclease with three primary groups) can occur. In models of Aicardi–Goutières syndrome in TREX1-deficient mice, large amounts of extrachromosomal complementary DNA LINE1 elements were found in nerve cells and astrocytes, which caused inflammation due to increased IFN-I secretion [55]. LINE1 inhibitors suppressed this activation of the immune system, which include the TREX1 and ADAR1 proteins associated with Aicardi–Goutières syndrome. Disease pathogenesis may be associated with *TREX1* and *ADAR1* mutations; as a result, they lose their ability to inhibit LINE1 retrotranspositions [47].

The role of LINE1 overexpression due to their hypomethylation in the pathogenesis of Sjögren's syndrome and systemic lupus erythematosus has been proven. LINE1 transcripts in these diseases increased the synthesis of IFN-I, which contributes to the autoimmune response [11]. Similar processes occur during human physiological aging, when pathological activation of LINE1 stimulates IFN-I production, causing the development of aseptic inflammation [56]. This may explain the increased synthesis of autoantibodies with age, despite the progressive weakening of immune system functions [57].

Conclusion

AIDs, which may be caused by mutations in the coding regions of active TEs, are involved in the regulation of genome functioning in ontogenesis. Consequently, the immunogenicity of these TEs is increased, which contributes to their recognition as "foreign" ones, causing autoimmune reactions. Other mechanisms may be pathological insertions of TEs into the immune system genes, which contribute to altered protective reactions, and the movement of TEs in the region of protein-coding genes with a change in their antigenic structure while maintaining functionality leads to the stimulation of immune responses against them.

The initiating moment for AID may also be an overexpression of unchanged TEs, which transcripts stimulate the IFN response, and can be processed into ncRNAs involved in the immune pathology. The role of TEs in AID development indicates the possibility of developing new treatment methods aimed at suppressing the increased activity of TEs. For example, an inhibitor of retroviral integrase (raltegravir) in the clinic contributed to the stable remission of chronic idiopathic urticaria [33].

The use of specific microRNAs, which repress pathologically activated TEs, is the most promising. Moreover, microRNAs can be used to determine AID response to treatment, as has been revealed for miR-125b and miR-223 in rheumatoid arthritis [24]. MiR-29, which has an antifibrotic effect, is promising for the treatment of systemic scleroderma [27]. MicroRNA analogs or antagonists have already been proposed for the treatment of rheumatoid arthritis [24].

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