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Review

The role of microRNAs in the pathogenesis of autoimmune diseases

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ABSTRACT

MicroRNAs (miRNAs) are single-stranded, endogenous non-coding small RNAs, ranging from 18 to 25 nucleotides in length. Growing evidence suggests that miRNAs are essential in regulating gene expression, cell development, differentiation and function. Autoimmune diseases are a family of chronic systemic inflammatory diseases. Recent findings on miRNA expression profiles have been suggesting their role as biomarkers in autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome. In this review, we summarize the characteristics of miRNAs and their functional role in the immune system and autoimmune diseases including systemic lupus erythematosus, primary Sjögren's syndrome, rheumatoid arthritis, systemic sclerosis, multiple sclerosis and psoriasis; moreover, we depict the advantages of miRNAs in modern diagnostics.

Contents

1. Introduction

MicroRNAs (miRNAs) constitute a recently discovered family of small RNAs, ranging from 18 to 25 nucleotides in length. They are single-stranded, endogenous non-coding RNAs playing critical roles in regulating gene expression [1,2].

miRNAs regulate approximately 90% of protein-coding genes, and play a central role in various biological processes including immune call lineage commitment, differentiation, proliferation, apoptosis and maintenance of immune homeostasis. It is not surprising that alterations in the expression of miRNAs potentially contribute to the development of certain pathological conditions and clinical disorders.

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Nowadays, the pathogenetical role of miRNAs is most intensively studied in malignant diseases as well as autoimmune conditions. Changes in miRNA expression profiles have been identified in different autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Sjögren's syndrome (SS) [3–5]. In this review, we summarize the characteristics of miRNAs and their functional role in the immune system and autoimmune diseases including SLE, primary SS, RA, systemic sclerosis (SSc), multiple sclerosis (MS) and psoriasis.

2. The biology of miRNAs

The majority of miRNA genes derived from the intergenic regions or in oriented antisense to form independent transcription units. Most of the others reside in the intron region of protein-coding genes [6]. Human miRNAs are not always genomically isolated; sometimes several miRNAs are assembled as clusters for further transcription and expression [7].

The miRNA biogenesis and maturation occur first in the nucleus and then in the cytoplasm with the help of several proteins and enzymes (Fig. 1). The first step in the miRNA biogenesis is the generation of primary miRNA transcripts (pri-miRNAs) from DNA molecules in the nucleus of the cell. Most miRNA genes are transcribed by RNA polymerase II to produce a few hundred to thousand nucleotide-long pri-miRNA [6]. The pri-miRNAs are both capped and polyadenylated with a typical hairpin structure [8]. These pri-miRNAs are recognized by an enzyme–protein complex and further cleaved into 70–100 nucleotide-long precursor miRNA (pre-miRNA). This complex is composed of Drosha and DiGeorge syndrome critical region gene 8 (DGCR8) and denoted as microprocessor complex [9]. Drosha is one of the two members of the RNase III family while DGCR8 is the double-stranded RNA-binding protein which is deleted in DiGeorge syndrome [10]. The pre-miRNA then exported to cytoplasm through exportin 5, which is a member of the karyopherin family of nucleocytoplasmic proteins. The exportin 5 recognizes a two-nucleotide overhang left by Drosha at the 3′ end of the pre-miRNA hairpin, requiring the GTP-bound form of the Ran GTPase for providing energy [11].

The noncanonical miRNA biogenesis pathway bypasses the microprocessor complex cleavage processing for another sort of pre-miRNAs, known as mirtrons, which directly spliced out of introns by spliceosome. The branched pre-mirtrons then undergo lariat-mediated debranching to mimic the structural features of pre-miRNAs [12,13]. Interestingly, mirtrons can not only be found in *Caenorhabditis elegans* and Drosophila, but also reported in mammals [14].

The pre-miRNAs have further processing to yield mature miRNA in the cytoplasm. The second member of the RNase III family named Dicer interacts with both 5′ and 3′ ends of the pre-miRNA and cleaves the hairpin loop, processing to a 19–25 nucleotides miRNA/miRNA* duplex [15,16]. The miRNA* was regarded as passenger strand since it is less-stable, while the miRNA as guide strand. The miRNA/miRNA* duplex releases the helix structure after loaded into the argonaute (Ago) proteins. The guide strand remains the interaction with Ago to generate the RNA-induced silencing complex (RISC), which facilitate miRNAs binds to their targets [17]. The passenger strand as complementary strand of the guide strand is degraded as a RISC complex substrate. However recent study demonstrates that several miRNA* are stably expressed and may play an important role, as well [18].

The mature miRNA interacts with the 3′-UTR of specific messenger RNA (mRNA) to regulate gene expression. Target mRNA is recognized by the 2–7 nucleotides of the 'seed' region of the miRNA [19]. The complementary degree of the base pairing between the miRNA seed region and mRNA defines the mechanism of gene regulation [20]. When the complementary base pairing is perfect or near-perfect, Ago protein of the RISC complex induces the endonucleotic cleavage of the target mRNA resulting in deadenylation and degradation of mRNA fragments. When the base pairing is incomplete, the formation of double-stranded RNA, resulting from the binding of miRNA, leads to translational repression [2,21,22]. Repressed mRNAs aggregate in cytoplasmic foci called P-bodies, which are known sites of mRNA destabilization [23,24].

3. miRNAs in immune system

The miRNAs play critical roles not only in the development of immune system but also the regulation of both innate and adaptive immunity [5,25]. MiRNAs function as translational repressors during stem cell fate and differentiation [26]. MiR-181, miR-223 and miR-142s are strongly expressed in hematopoietic cells and shown regulatory roles during hematopoietic lineage differentiation [27,28].

3.1. Innate immunity

The innate immune system is the first line of host defense and important in mechanisms against invading microorganisms; moreover, it forms the basis of the development of adaptive immunity. Host cells express diverse pattern recognition receptors (PRRs), including toll-like receptors (TLRs), C-type lectin-like receptors (CLRs), retinoic acid-inducible gene (RIG)-I-like-receptors (RLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs). These can recognize a wide range of pathogen-associated molecular patterns (PAMPs). These mechanisms trigger the intracellular signaling pathways, which results in releasing of proinflammatory cytokines, chemokines, and interferons (IFNs), as well as lead to the expression of co-stimulatory molecules [29]. TLRs are the most characterized PRRs, which are capable of potently activating different cell types, which could be highly expressed on most immune cells [30]. Their downstream signaling pathways lead to the production of a wide range of immune-stimulatory cytokines and chemokines. Aberrant activation of TLRs may result in unrestricted inflammatory responses therefore the family of TLRs may play a pivotal role in the development of autoimmune diseases [31]. Among all ten TLR subtypes, TLR1, TLR2, TLR4, TLR5, TLR6 and TLR10 are generally regarded as extracellular receptors, while the family of TLR3, TLR7, TLR8 and TLR9 are intracellular receptors located in endosomal compartments and responsible for the recognition of nucleic acids derived from viruses, bacteria and the host [32–35]. TLR4 can recognize lipopolysaccharides (LPSs), which is the typical endotoxin for gram-negative bacteria. The LPS-mediated inflammatory responses consequently induce overexpression of miR-146a/b, miR-132 and miR-155. Upregulation of miR-146 leads to translational repression of its target genes interleukin-1 receptor-associated kinase (IRAK) 1 and tumor necrosis factors receptor associated factor (TRAF) 6 [36]. miR-146 was recognized as a negative regulator of RLRs in the *in vitro* model of mouse macrophages through targeting IRAK1, IRAK2 and TRAF6 [37]. Exposure to LPS stimulates tumor necrosis factors (TNF)-α secretion. Overexpression of miR-155 and lower expression of miR-125b may relate with elevated level of TNF-α. It was indicated that miR-155 targets transcript coding gene for several proteins enhancing TNF-α translation, including Fas-associated death domain protein (FADD), IkappaB kinase epsilon (IKKepsilon) and TNFR superfamily-interacting serine–threonine kinase 1 (Ripk1), while miR-125b targets the 3′-UTR of TNF-α transcripts [38]. In miR-147 knockout mice, increased inflammatory cytokine expression found in macrophages upon TLR stimulation such as ligands to TLR2, TLR3 and TLR4. Thus miR-147 was regarded as a negative regulator in TLR-activated inflammatory responses [39]. The miR-1303 production is also regulated by the NF-κB pathway. A recent study revealed negative regulation of mycobacteria-induced Atg2B protein production related with autophagy process [40].

The miR-146a and miR-155 influence IFN-type I synthesis in plasmacytoid dendritic cells mediated by TLR-7 and TLR-9, while in T and B cells, group of miRNAs including miR-21, miR-126, miR-146a, miR-155, miR-1246 and others might correlate with epigenetic modifications, support abnormal cytosine release, differentiation of cell subsets, B cell hyperactivity and autoantibody production [41].