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MicroRNA signature of regulatory T cells in health and autoimmunity

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ABSTRACT

MicroRNAs (miRNAs) are small RNA molecules with regulatory functions on the expression of genes through binding directly to target messenger RNA (mRNA) transcripts, eventuating in gene expression suppression via translational hindrance and/or target mRNA cleavage. These molecules have been established to participate in numerous critical cellular settings, including differentiation, development, and function of immune cells. As an important suppressor cell of immune system, regulatory T cells (Tregs) are important in modulating the immune homeostasis as well as tolerance to self-antigens. Despite identification of numerous transcription factors, cytokines, and other mediators regulate the biology of Tregs, investigations have demonstrated that noncoding RNAs are involved in several mechanisms of the regulation of Treg cells. On the other side, dysregulation of expression of several miRNAs has been reported in Tregs, implicating to the impaired function of these regulatory cells, resulting in autoimmune and other immune-based disorders. In this review, we aim to go through the overall microRNA network and specific miRNAs that are involved in the development, differentiation, and function of Tregs. Moreover, an overview was provided with respect to the role of aberrant expression of miRNAs in Tregs of autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, diabetes, and psoriasis.

1. Introduction

A number of regulatory mechanisms is required to orchestrate the immune homeostasis and ensure the immune tolerance against harmful and uncontrolled inflammation. Through suppressing the active T cells, regulatory T cells (Tregs) play an important role in regulating immune homeostasis and maintaining the self-tolerance. As the unique transcription factor of Tregs, Foxp3 has been demonstrated to be the major player of Treg development as well as its function. Despite identification of several transcription factors and mediators in regulation of Tregs, researchers have initiated to concentrate on the role of noncoding RNAs such as microRNAs (miRNAs) in Treg regulation [1,2].

MiRNAs are characterized as a group of conserved and small noncoding RNA molecules which are comprised of approximately 22 nucleotides. The master role of MiRNAs is regulation of gene transcription at the posttranscriptional level, which is considered as an epigenetic regulatory mechanism, through cleaving or blocking messenger RNAs (mRNAs) from further translation. After identification of first miRNA in the nematode Caenorhabditis elegans [3], more than 1000 miRNAs have been characterized in both humans and mice with implications to diseases as well as the normal cell physiology. It is said that over 60% of protein-coding genes in humans are regulated by miRNAs, implying to the important and central role of miRNAs in the regulation of gene expression [4]. Researches have disclosed that miRNAs are key regulators in numerous physiological cellular processes like maturation, differentiation, and apoptosis. With respect to clinical viewpoint, miRNAs are efficiently involved in a wide spectrum of human disorders and hold a promising diagnostic and prognostic potential to be a marker or therapeutic target [5].

On the other side, miRNAs take part in the regulation of several processes during innate and adaptive immune system development. MiRNAs, for example, play a major role in modulation of development, homeostasis, as well as the function of immune cells, including Th17 cells, natural killer (NK) cells, and Tregs. Furthermore, impairments in regulation of microRNA biogenesis components, such as Drosha and Dicer, eventuates in autoimmune manifestations in mice [6]. In this review paper, we intent to focus on the role of the microRNAs in the regulation of Tregs in normal condition as well as some autoimmune disorders.

2. MicroRNA biogenesis

Small RNAs are categorized into various classifications according to their origin or the components they bind [7]. These small RNA

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categories are miRNAs, trans-acting siRNAs (tasiRNAs), small-interfering RNAs (siRNAs), small scan RNAs (scnRNAs), Piwi-interating RNAs (piRNAs), and repeat-associated siRNAs (rasiRNAs). siRNAs are long and double-stranded RNA molecules that function as silencing genes through cleaving target mRNAs that they bind [8]. As an epigenetic regulatory mechanism of gene expression, small non-coding RNAs play single function in cellular physiology, regardless of their size and type [9].

In human, miRNAs are coded by introns of coding genes as well as by both introns and exons of non-coding genes. In the process of miRNA maturation, primary miRNAs (pri-miRNAs) from long primary transcripts underlie a number of endonucleolytic maturation process. Pri-miRNAs are composed of a 5′, 7- methylguanosine cap and contain 3′ poly (A) tail. These pri-miRNAs are transcribed by RNA polymerase II, while other non-coding RNA molecules are transcribed by RNA polymerase III [10]. Afterwards, The Drosha and DGCR8 (DiGeorge syndrome critical region 8 homologue) microprocessor enzymes recognize and cleave the pri-miRNA to produce an approximately 70nt intermediate RNA molecule containing stem-loop hairpin folding, which is precursor miRNAs (pre-miRNAs) located in the nucleus [11,12]. Afterwards, pre-miRNAs are transported to the cytoplasm by means of the RanGTP-dependent dsRNA-binding protein Exportin 5 [12], and then further processed via the cytoplasmic RNAase III enzyme Dicer to an about 22nt double-stranded miRNA structure [13]. In this double-strand structure, one strand plays role as the guide strand, which is integrated into a large protein complex, namely miRNA-induced silencing complex (miRISC). The RISC complex is composed of components like Dicer, human immunodeficiency virus 1-transactivating response RNA-binding protein (TRIB), and Argonaute protein-2 (Ago2). The miRISC product is mature and functional miRNA. After that, the miRISC is transported by importin 8 towards its target mRNA. Ultimately, miRNA can be settled into specific organelles within the cell [9] and the other strand, which is determined as the passenger strand, underlies degradation (Fig. 1).

To mediate its function, each mature miRNA binds to a specific mRNA basically by pairing of nucleotide sequences in the miRNA to the related complementary sequences in the mRNA located in the 3′ untranslated region (UTR). The function of miRNAs is mediated by either translation suppression or mRNA cleavage. The suppression or degradation of target mRNAs is mainly determined through the match rate between miRNAs and target mRNAs [7,14]. miRNAs are thought to either suppress the translation of mRNA or reduce stability of mRNA after low-match binding rate between the miRNA and the miRNA-recognition elements (MRE) located in the 3′UTR of target genes [15]. There is a spatial and temporal pattern of miRNA's function and expression and function and, as a result, play crucial roles in the modulation of various biological processes in different cellular stages [15,16].

3. Regulatory T cell

Treg cells have been documented to play vital roles in the maintenance of immunological self-tolerance as well as immune homeostasis. Tregs control the quality and quantity of immune responses against non-self-antigens [17–22]. However, various subgroups of Tregs, and their related mechanisms are vital to achieve immunological self-tolerance. Tregs not only are involved in physiological conditions of the body, also participates actively in suppression of immune responses during pathological conditions such as autoimmune and inflammatory disorders, transplant rejection, tumor genesis, and infections [18,23]. First line of studies indicated that Tregs primarily belong to $CD4^+CD25^+$ T cells. As well, FoxP3, a transcription factor, was later introduced as a fundamental component for the Treg development. Studies demonstrate that Foxp3 overexpression has been associated with the suppressive activity of normal non-Treg cells [24]. Moreover, Foxp3 locus knockout in mice is related with impaired self-tolerance process. There are two types of human Tregs: natural and adaptive (or inducible). The development location of natural Tregs (nTreg) are thymus, where these cells mature functionally and other subpopulation of T cells [25,26]. nTregs are present in the periphery with stable function. On the other side, the inducible Tregs (iTregs) are developed from naïve T cells following an antigenic stimulation in the periphery

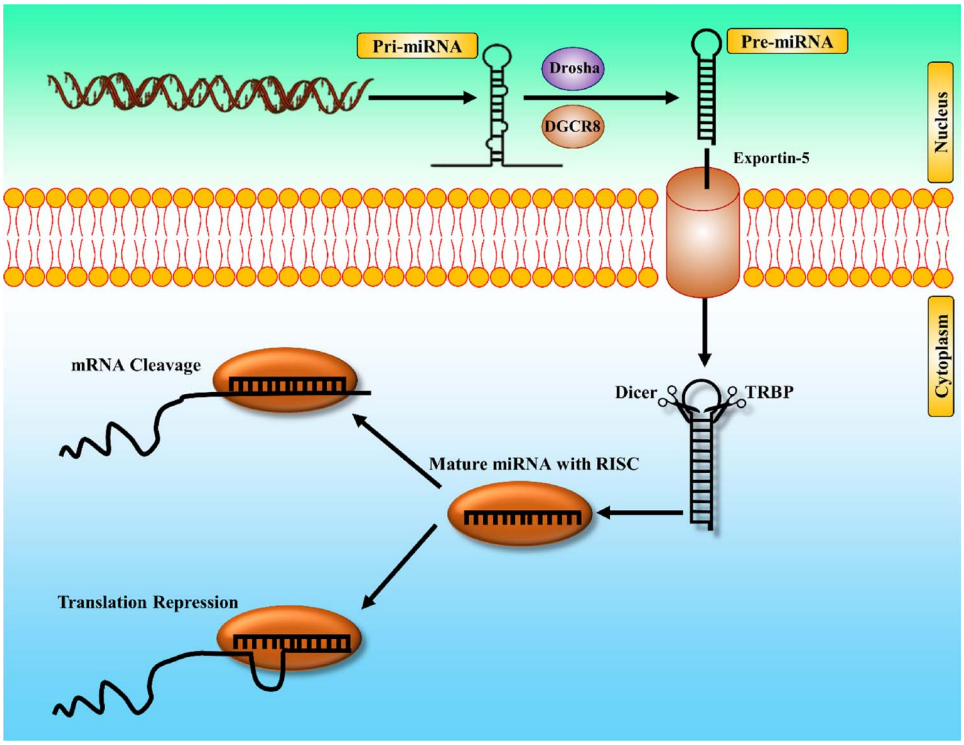

Fig. 1. MicroRNA biogenesis pathway.