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Review Article

Physiological and Pathological Roles for MicroRNAs: Implications for Immunity Complications

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MicroRNAs (miRNAs) are small non-coding regulatory RNAs molecules with a size of approximately 22 nucleotides that are implicated in regulating gene expression at the post-transcriptional regulatory levels. Inflammatory disorders especially autoimmune diseases (ADs) occur from an abnormal immune response of body against cells of their own specific tissues or multiple organ systems leading to chronic and sustain inflammatory responses and thus contribute to cell damage. Some recent studies have reported that several miRNAs may be expressed differentially in ADs and other inflammatory diseases which can have a critical role in immune response modulation and autoimmunity. This review is focused on the role of miRNAs in the pathogenesis and progression of several autoimmune diseases.

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Introduction

MicroRNAs (miRNAs) are short non-coding regulatory RNAs molecules with about 22 nucleotides that are implicated in regulating gene expression at the post-transcriptional levels [1]. miRNAs are found in living organisms such as plants, animals and some viruses which act through the suppression of target genes and RNA silencing in post-transcriptional regulation of gene expression [2]. It has been said that miRNAs are conserved evolutionally in phylogenetic taxons, from worms to humans [3] and the number of miRNAs is 1000 in human genome which regulate over 30% of the total human genes [4].

It was twenty years ago that, for the first time, researchers reported there are elements of human genome that have no functional role but enjoy a gene regulatory function [5]. The first miRNAs was detected in 1993 while an oligonucleotide small RNA was produced by the lin-4 locus in the nematode Caenorhabditis elegans that encoded and translated a protein which modulated protein lin-14 in the developmental timing manner [6]. Therefore, this locus has been shown as a critical part of the non-coding DNA that plays an important role in regulating gene complex in the most cell processes in different species [7]. miRNAs are transcripted by RNA polymerase II as a long primary transcript considered by hairpin structures (pri-miRNAs) and processed in nucleus by RNAase III Drosha and produced 70-100 nucleotide pre-miRNAs [8]. RNAase III Drosha is 160 kDa enzymatic protein conserved in different species containing two RNAase III domains and one double-strand RNA-binding domain. Drosha forms a large complex of 650 kDa in Homo sapiens called microprocessor [5]. The second pathway of miRNA biogenesis called Mirtron manner is regulatory RNAs which gets processed and forms pre-microRNAs via splicing procedures without RNAse III Drosha- mediated cleavage [5, 9, 10]. The initiated precursor molecules are translocated to the cytoplasm through Exportin 5-mediated mechanisms with an additional step conducted by the RNase III Dicer on originated precursor molecules [11]. RNase III Dicer works in association with transactivating response to RNA-binding protein (TRBP) and forms a double-strand RNA with 22 nucleotides extended, miRNA/ miRNA* including the mature miRNA as a guide and the complementary traveler strand, miRNA* [12]. More miRNAs are originated from independent miRNA genes or introns of genes that code proteins. In fact dicer enzyme trims the pre- miRNA and removes the hairpin loop, leaving a double stranded miRNA duplex molecule. Meanwhile, one of the miRNA double complex strands joins a multiprotein complex, forms miRNA-protein complex, is named small RNA-induced silencing complex (RISC) and conducts RISC to the 3’ untranslated regions (UTRs) of target mRNAs. The supplementary strand that is identified as a passenger strand is generally discarded. In plant cells, the miRNA is typically totally complementary to its target mRNA molecule [13, 14]. The miRNA will bind with mRNA, leading to deactivation of

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the mRNA and thus its break down. In animal cells, the miRNA nucleotides usually do not pair up with the mRNA nucleotide as well and their base pairing often follows a pattern though. The miRNA-protein complex presents blocks translation and speeds up deadenylation that breaks down the poly-A tail thus triggering mRNA to be degraded faster and translated less which causes suppression of target protein expression [15]. Several studies reported that miRNAs is complicated in various physiological procedures and controls cellular processes including differentiation, proliferation and cell death [16]. Recent studies have shown that miRNAs plays an important role in autoimmune diseases (ADs) such as rheumatoid arthritis (RA), systemic lupus erythematous (SLE), type 1 diabetes mellitus (T1DM), multiple sclerosis (MS), Sjogren's syndrome (SS), inflammatory bowel disease (IBD), psoriasis (PS), primary biliary cirrhosis (PBC), idiopathic thrombocytopenia purpura (ITP) and other immune diseases [17,18].

Autoimmune diseases are chronic disease conditions created from the deficiency of immunological tolerance to auto-antigens following a pathological status that is imposed on the target organs or numerous organ systems. The prevalence rate of autoimmune diseases is higher than 3% more than 80% of whom are women [19]. Recently it has been reported that the expression of several miRNA has been changed in ADs [18]. We review the role of miRNAs in the pathogenesus and progression of several autoimmune disease.

Discussion

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic autoimmune defect primarily introduced by the inflammatory responses of synovial tissue hence leading to bone and cartilage damage [20]. Numerous studies have reported that miR-146a and miR-155 are over-expressed in peripheral blood mononuclear cells (PBMCs) [21], synovial fibroblasts and fluids [22], $CD4^+$ T-cells derived from PBMCs, as well as Th-17 cells in RA patients [23, 24]. While defective apoptosis of fibroblast in synovial fluid is serious in pathogenesis of RA, the effect of miRNAs on programmed cell death regulation is rarely identified. Some recent studies have identified that miR-34a and miR-34 are involved in modulation of apoptotic pathways. Immature miR-34a* triggers apoptosis in FasL-stimulated RA synovial fibroblasts; however, the up-regulation of miR-34a protects cells from FasL-mediated apoptosis [25]. miRNA that is complicated in cell proliferation regulates cyclin-dependent kinase 2 (CDK2) and monocyte protein-1 (MCP). Over-expression of miR-346 in RA-synoviocytes has also been reported [26]. Also, miR-346 can indirectly modulate IL-18 secretion. miR-203 is over-expressed in RA-synovial fibroblasts, therefore up-regulation of miR-203 causes secretion of MMP-1 and IL-6 through the NF-κB pathway in synovial fibroblasts. Thus it is said that miR-203 is a pro-inflammatory factor in RA [27].

Another study has indicated that miR-146a, miR-132 and miR-16 are up-regulated but miR-363, miR-498 and Let-7a are down-

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regulated in RA patients PBMCs [21,23]. The over-expression of miR-155 in PBMCs and fibroblast-like synoviocytes has a protective effect against the inflammation so that it reduces IKBHE expression [28]. Moreover, it is reported that plasma concentration of miR-24 and miR-125a-5p is a possible diagnostic marker in patients with RA [29]. Additional marker is miR-140 that is proposed to down-regulate in chondrocytes. miRNA-140 is involved in controlling pathways that regulate cartilage development and response to Interleukin (IL)-1 [30]. Also another study indicated that miR-323-3p that is located on chromosome 14 is over-expressed in synovial fibroblast and can be a biomarker for inflammatory responses and immune modulations [31].

Type 1 Diabetes Mellitus

Diabetes type 1 is caused by insulin deficiency due to T cell mediated destruction of β-cells which produces insulin from human pancreas islets. Recent studies reported that several miRNA are related to T1DM. miR-375 has an important role in glucose homeostasis, α- and β-cell return and adaptive β-cell growth in reply to insulin request after insulin resistance, therefore, miR-375 knockout mice is glucose intolerant and pancreatic β-cell mass decreases due to reduced proliferation [32,33]. Thus, it has been proposed that miR-375 can have an indirect effect on diabetes type 1. Recently circulating miRNAs is recognized to cause unrestricted beta cell destruction in children with diabetes type 1 [34]. It has also been reported that 12 miRNAs is over-expressed in T1DM condition, therefore some of them are involved in apoptosis and β-cell gene expression complexes. For examples, it has been identified that tissue-specific miR-25 is implicated in glucose metabolism and homeostasis that is documented as a prognostic biomarker in the new onset of T1D in children [35].

Multiple sclerosis

Multiple sclerosis is a chronic autoimmune disease that involves the central nervous system and causes autoimmune demyelination of nerve fibers and neurodegeneration and characteristically leads to progressive neurological disorders and motor and sensory disabilities [36]. Some new studies using new techniques such as miRNA arrays have confirmed the association of miRNAs in people with MS [37-40]. miRNAs play a critical role in T helper (Th)-17 contradiction and pathogenesis of MS. The clinical and experimental studies have shown that miR-326 which is Th-17 cell-specific miRNA, is over-expressed in MS patients and animal models with experimental autoimmune encephalomyelitis (EAE). Therefore, disease intensity of MS is correlated to miR-326 expression. In experimental model of EAE which is a similar animal model of MS, down-regulation of miR-326 by specific siRNA reduces the number of Th-17 cells leading to mild EAE while the over-expression of miR-326 increases the quantity of Th-17 cells that contribute to acute EAE. It has been reported that miR-326 via pointing Ets-1 can stimulate Th-17 differentiation [37]. miR-18b, miR-599 and miR-493 are over-expressed in patients with relapsing-remitting multiple sclerosis

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(RRMS) compared with a control group [38]. Microarray studies have shown 10 miRNAs to be meaningfully unregulated in whole blood samples of RRMS patients [41]. Also 3 types of miRNAs are up-regulated in active plaques of MS patients that seem to target the 3' un-translated regions of CD47 gene [39]. Serum-miRNA expression analysis from PRMS, SPMS and PPMS indicates that miR-21 and miR-106b are over-expressed in patients with MS. In addition, miR-17-92 profile was reported to get down-expressed in the B-cells in MS patients [42]. Furthermore, analysis of 23 miRNAs from RRMS patients shows that expression of these miRNA is different in CD4 and CD25-positive T regulatory cells compared with the control group [43]. Totally, the expression of miRNAs in mononuclear cells of RRMS patients (from 365 miRNAs that were investigated in microarray analysis) revealed that miR-17-5p, related to autoimmunity, was over-expressed in the CD_4^+ T regulatory cells of RRMS patients [40].

Sjogren's syndrome

Sjogren's syndrome is an autoimmune disease defined by chronic inflammation which implicates the exocrine glands [44]. People with SS have a chronic progressive period and in most cases they do not need immunosuppressive drugs. Microarray analysis has shown that miRNA expression profiles in the salivary glands are different between SS patients and healthy people. Also, expression patterns of miRNAs are changed in SS patients with low and high- grade of inflammation. Furthermore, cluster profile of miR-17-92 which is exported from microarray analysis has demonstrated down-regulation of miR-17-92 cluster category of patients with SS compared with the controls [45]. Another study has reported up-regulation of miR-146 in the SS patients. It has been said that miR-146 leads to increased phagocytic process and reduces pro-inflammatory cytokine production [46]. Hence miR-146 can serve as a prognostic and diagnostic marker in the beginning and during the progression of SS [35].

Systemic lupus Erythematous

Systemic lupus erythematous is a chronic and prolonged autoimmune disease the causes of which are unknown and has various clinical signs [47]. microRNA expression profiling using microarrays from peripheral blood mononuclear cells of patients with SLE has shown 16 miRNAs to be over-expressed in SLE patients [48]. Data have also reported that miR-146a is down-regulated in SLE patients. It has been established that miR-146a is a negative regulator of natural immunity which directly represses the downstream transactivation of type 1 interferon and targets interferon regulatory factor 5 (IRF-5) and STAT in JAK/STAT signaling pathway. IRFs are a family of transcription factors that result in the transcriptional activation of specific genes and regulate expression of pro- and anti-inflammatory genes [49]. miR-146a expression is necessary for regulation of natural immunity in normal conditions; therefore, the promoter variant of miR-146a has indicated lower binding capacity to Ets-1 [50]. Ets-1 is necessary for the development of natural T regulatory cells and regulation of Foxp3, therefore, Ets-1 transcription factor

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modulates the development and function of natural regulatory T cells [51]. Some previous studies have reported that regulatory T cells organize a population of CD_4^+ T cells that restrict and control immune responses. Foxo3 is a transcription factor that is involved in the development and function of T regulatory cells. It has also been reported that mice Ets-1() T regulatory cells increase T-cell mediated splenomegaly and systemic autoimmunity [51]. miR-21 is complicated I SLE, so it modulates T-cell response via the regulation of apoptosis [52]. Also, miR-146-a and miR-155 are down-expressed in serum of patients with SLE [53]. Another study reports that miR-21 and miR-148a are involved in reducing DNA methylation in SLE patients [54]. It is assumed that miRNA-126 is implicated in SLE induction by targeting DNA methylation [55]. Similarly, miR-15 is up-regulated in plasma and spleen cells in SLE animal models, therefore, down-regulation of miR-15 can be useful for therapeutic interventions [56].

Inflammatory Bowel Disease

Inflammatory bowel Disease is an inflammatory disease that affects the small intestine and colon [57]. Two major types of chronic inflammatory bowel diseases are Crohn's disease (CD) and ulcerative colitis (UC) which are no key standards for diagnosis of CD and UC and etiological and immunological concepts of these disease are not clear [58]. Some recent studies have demonstrated that miRNA profiles in CD and UC patients are different from those of the control groups, thus some miRNAs are over-expressed while other miRNAs are significantly down-regulated in CD and UC patients. In another study it has been reported that levels of several miRNAs including miR-93, miR- 140, miR- 30e, miR- 20a and let-7b can be identified in CD patients [59]. Gene expression microarrays from platelet-derived miRNAs indicates the expression levels of miRNAs in UC patients to be different compared with those in the control group, hence, several miRNAs such as mir-188-5p, miR-422a, miR-378, miR-500, miR-769-5p and miR-874 are deregulated in UC patients [60]. Also, miR-150 is significantly over-expressed in colonic mocosa of patients with UC [61]. Together, these data suggest that miRNAs may be applied as prognostic and diagnostic markers for IBD detection as well as the factors that are implicated in the pathogenesis of IBD. Furthermore, the cross-interaction between miRNAs and intracellular target genes has been demonstrated. For example, miR-150 targets Myb and miR-143 act as a negative regulator in modulation of K-RAS, API-5 and MEK-2, and miR-145 regulated IRS-1 [62, 63]. Also, another study reports that miR-7 targets CD98 which disrupts the normal growth and differentiation of enterocytes [63]. miR-196 is up-regulated in intestinal epithelial cells of CD patients. It has been said that miR-196 disrupts the protective effect of a GTPase M which plays a protective role in various conditions, therefore, it is revealed that there is a negative association between miR-196 and GTPase M in inflammatory disorders [64]. Altogether, these reports indicate that miRNAs may be considered as a predictive and prognostic

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biomarkers and diagnostic tools in ADs.

Psoriasis

Psoriasis is a typical, chronic, relapsing/remitting and sustained inflammatory immune-mediated skin disease which is marked by red, scaly squares, papules and plaques which frequently itch [65]. The causes of psoriasis are not fully understood but it is likely that PS is a genetic and immunological defect [66]. It is said that miRNAs are involved in pathogenesis of PS, therefore, miRNAs may modulate several intracellular protein expressions and regulate cellular functions. It is reported that miR-203 are over-expressed significantly in the skin of PS patients compared with that of the control groups which inhibits suppressor of cytokine signaling 3(SOCS3). This is a protein that is encoded by the SOCS3 gene. SOCS3 transcripts a member of the STAT-induced STAT inhibitor (SSI) and is considered as a negative regulator of cytokine signaling pathway. SOCS3 expression is triggered by various cytokines such as IL6, IL10 and Interferon gamma. The protein that is encoded by SOCS3 is bound to JAK2 kinase and inhibits it. It has been demonstrated that miR-203, through inhibition of SOCS3, leads to the continued and sustained activation of STAT3 and immune cell mobilization [67]. Besides, the level of miR-146 increases in PS patients who are associated with regulation of innate immune responses [68].

Primary Biliary Cirrhosis

Primary Biliary Cirrhosis is an autoimmune disease that involves liver and is identified by chronic and progressive destruction of small, big, and intra-lobular ducts of the liver. Furthermore, these ducts are injured and bile is formed in the liver which is called cholestasis which with time damages the liver leading to scar formation and hepatic cirrhosis. Some recent studies have reported that PBC may affect up 1 in 4000 people, and female to male ratio is at least 9:1. The appearance of specific anti-mitochondrial antibodies (AMA) and auto-reactive cytotoxic T lymphocytes shows PBC to be an auto-immune disorder [96,70]. Some recent studies have, moreover, shown that the levels of miR-299-5p, miR-328 and miR-371 are over-expressed whereas levels of miR-26a, miR-122a and miR-99 are down-expressed at the end stage of PBC patients. Therefore it is proposed that specific miRNAs can be regarded as powerful tools for prognostic and diagnostic measures [71].

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura, known as primary immune thrombocytopenia or autoimmune thrombocytopenic purpura, is characterized by low platelet count (thrombocytopenia) with normal bone marrow and the nonappearance of extra causes of thrombocytopenia. ITP patients suffer from a typical purpuric rash and an increased propensity to hemorrhage [72]. Also patients generate autoantibodies against specific glycoproteins within platelet cell membranes and are affected by destruction of peripheral blood platelets. Several miRNAs are significantly up-regulated and some miRNAs are down-regulated in peripheral blood cells from ITP patients [48]. However, studies are

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insufficient and further studies should be carried out in ITP.

MicroRNA and innate immune system

miRNA and Toll-like receptors (TLR) regulate each other

Recent findings demonstrate the relationship between miRNAs and the TLR-signaling pathways. It is reported that TLR-signaling pathways are regulated by certain miRNAs. It is said that miRNAs regulate TLR-signaling pathways by targeting TLRs, signaling down-stream proteins, regulatory molecules and transcription factors, and cytokines that are induced by TLRs stimulus [73].

Several other studies have demonstrated that molecules complicated in TLR-signaling pathways can control miRNAs expression. On the other hand, miRNAs expression is regulated by the TLR-signaling pathways. Recent studies have also shown that miRNAs expression has been changed following TLRs-signaling stimulation with specific ligand. For example, lipopolysaccharide (LPS) administration, a specific agonist for TLR4, up-regulates expression of miR-146a, miR-155, and miR-132 in human mononuclear cells [74]. Other subsequent studies have shown that the expression of miR-223, miR-147, miR-9, miR-27b and let-7e is provoked after TLRs stimulation by pathogen-associated molecular patterns (PAMPs) and IL-1β [75-77]. Although the expression of particular miRNAs is related to the stimulation TLRs with specific ligands, some of miRNAs such as miR-155, 146 and 21 are competent to affect some molecules complicated in the TLR-signaling pathways [78-81]. It is also identified that miRNAs expression can be induced in a time-course manner. For example, miR-146 and miR-155 are early-response miRNAs because they are up-regulated in a short time after LPS treatment while miR-21 is expressed in a late-response manner since it is highly expressed in macrophage in a longer time after representation to LPS [74, 80, 82].

It has also been reported that miRNA expressions apportion to NF-κB and MAPK pathways that are induced by TLRs activation. For the first time, it is clear that miR-146a expression is correlated to NF-κB pathway in THP-1 monocytes following LPS administration [74]. Other studies have shown that TLR-induced NF-κB-dependent pathway increases the expression of miRNAs. PAMPs or TLRs stimulation can trigger NF-κB pathway and induce expression of many miRNAs including miR-146a, miR-155, miR-132, miR-223, miR-147, miR-9, miR-27b, miR-21, miR-16, miR-23b, miR-30b, miR-301a, miR-125b and let-7e [64, 70, 74, 83-86]. For examples, LPS through the TLR4-MyD88-NF-κB-dependent pathway directly induces the expression of miR-9 in human monocytes and notrophils [58]. Also, LPS and viral latent protein of Epstein - Barr virus can stimulate miR-155 expression in the NF-κB-dependent manner [87, 88]. miR-146a expression is induced in response to pro-inflammatory cytokines such as IL-1β, tumor necrosis factor-(TNF-) α and LPS via NF-κB-dependent pathway [74, 86, 89]. On the opposite site, miR-29b, let-7i, miR-98, miR-107, miR27a and miR-532-5p are down-regulated after TLR4-MyD88-NF-κB-dependent pathway

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induction [90-93]. On the other hand, miR-21, miR146b, miR-155 and miR-146-b-5p are up-regulated via Fos and Jun, and miR-99b is down-regulated in response to several stimuli which indicate that MAPK pathway is complicated in miRNA expression [94-97]. In addition to NF-κB and MAPK pathways that are involved in regulating miRNA expression, other cellular pathways are also responsible for modulating miRNA expression. For example, cyclic AMP response element-binding protein and transcriptional coactivator p300 are involved in miR-132 expression [98, 99]. Activation of Janus kinase 1 (JAK1) and signal transducer and activator of transcription 1 (STAT1) down-regulate miR-143/145 cluster in different cell types [99]. TLR-responsive miRNAs are not only involved in regulating the innate immune responses and host protection, but are also too implicated in the pathogenesis of several infectious diseases. Furthermore, because miRNA and TLRs expression patterns are different in various immune cells, the different distribution of TLRs in different cells could have altered miRNA expressions [73].

Some previous studies have demonstrated that TLR-signaling pathways are necessary to remove PAMPs. Conversely, excess and over-expression of TLRs and downstream signaling pathways may disarrange immune homeostasis and lead to several pathogenic conditions such as autoimmune chronic disorders and inflammatory or cancer [100-102]. So, the defined regulation of TLR-cell signaling pathways is necessary in various conditions [6–12]. Since miRNAs act as a class of main regulators of gene expression, therefore these receptors may be regulated by microRNAs. To date, several types of miRNAs have been reported that regulate TLRs expression. For example, let-7e and let-7i regulate TLR4 expression. Therefore, up-regulation of let-7i causes down-regulation of TLR4 in mice peritoneal macrophage. Knock-down of let-7e by anti-sense miRNA results in up-regulation of TLR4 [62]. Another study has indicated that the myeloid-specific miR-223 can modulate TLR3 and TLR4 expression in granulocytes [83]. Also another study has reported that miR-146a can regulate TLR4 and lead to increase of oxidized low-density lipoprotein accumulation and inflammatory reaction in macrophage [103]. miR-511 acts as an assumed positive regulator of TLR4 under cell cycle arrest situations [104]. miR-26a may negatively control TLR3 signaling pathway as endosomal pattern recognition receptor, by pointing TLR3 expression in rat macrophages, and improve arthritis in rat models [105]. In another study, it has been indicated that miR-105 and miR-146-a negatively regulate TLR2 expression [106, 107]. Also miR-19a/b increases expression of TLR2 in fibroblast-like synoviocytes of rheumatoid arthritis patients. On the other hand, miR-19a/b can reduce TLR2 protein expression and significantly prevent the actions of the TLR2-induced cytokines and kinases [108]. Also miR-43 inhibits the expression of TLR2 that suppress the invasion and migration of human colorectal adenocarcinoma cells [109]. These results indicate that miRNAs have an

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important role in successive expression of TLRs.

Conclusion

MiRNAs constitute a large family of non-coding RNAs with approximately 22 nucleotides that are as endogenous key post-transcriptional regulators in organisms. Since miRNAs are associated with a variety of signaling pathways including programmed cell death, autophagy and inflammatory processes, hence, miRNA are probably involved in the regulation of these pathways. Furthermore, impairment of miRNA expression is associated with the pathogenesis of many inflammatory and autoimmune diseases. On the other hands, a close relationship exists between TLRs and microRNAs so that the disregulation of their expression can play a critical role in pathogenesis of many autoimmune and inflammatory diseases.

Conflict of Interest

The authors declare no conflicts of interest.

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