International Journal of Medical Laboratory 2016;3(3):150-158.

International Journal of Medical Laboratory
Shahid Sadoughi University of Medical Sciences

Review Article

Role of miR-146a in Immune System and Autoimmunity

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Article history
Received 14 June 2016
Accepted 29 Sep 2016
Available online 28 Oct 2016

Key words
Adaptive immunity
Autoimmune disease
Innate immunity
MicroRNA

A B S T R A C T

MicroRNAs (miRNAs) are small preserved non-coding RNA molecules that regulate gene expression post-transcriptionally by targeting the 3' UTR of mRNAs for translational repression or degradation. The rising evidence has established the significant role of miRNAs within the regulation of immune system and the prevention of autoimmunity. MiR-146a has obtained an importance as a modulator of differentiation and the function of cells of the adaptive, as well as innate immunity rapidly. In this paper, we summarize the recent understanding of the role of miR-146a in adaptive and innate immune responses, as well as in autoimmunity.

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Introduction

MicroRNAs (miRNAs) are non-coding RNAs which have a function in post-transcriptional regulation of gene expression by binding to sequences in the 3' untranslated region (UTR) of specific target mRNAs [1]. They have emerged as the novel molecular regulators of numerous genes involved in normal immune responses, and the pathogenesis of inflammatory and autoimmune diseases. Also, they are known to regulate immune cells processes such as apoptosis, differentiation, and maturation [2, 3]. In 2010 two reports revealed the correlation between miR-146a and autoimmune diseases [4, 5]. Also, miR-146a has been shown to be an important modulator of innate as well as adaptive immunity cells [6-8]. In this review, we will discuss the recent understanding of the role of miR-146a in adaptive and innate immune responses, as well as autoimmunity.

1. MiR-146a pathway

Transcriptional factors, inflammatory mediators including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB),and microbial components such as bacterial lipopolysaccharides (LPSs) can activate miR-146 expression [9, 10]. Taganov et al. have shown that the up-regulation of miR-146a was observed in response to inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β stimulation within LPS stimulation in human monocyte cells. miR-146 was also quickly up-regulated, and negatively regulated toll-like receptors (TLRs) signaling by targeting TNF receptor-associated factor (TRAF) 6 and Interleukin-1 receptor-associated kinase (IRAK)-1, which are crucial for proinflammatory signaling [9].

To understand the biological role of miR-146a, the mice have been created with a targeted deletion of this gene. MiR-146a is expressed mainly in immune tissues, and its expression can be induced in immune cells upon cell maturation or activation. Lack of miR-146a expression results in hyper-responsiveness of macrophages to LPSs, and also leads to an exaggerated inflammatory response in mice with endotoxin-challenged. The overexpression of miR-146a in monocytes has the reverse effect, contrary. Mice with deletion of miR-146a develop a spontaneous autoimmune disorder, characterized by multi organ inflammation, lymphadenopathy, and splenomegaly [11].

Monocytes overexpressing miR-146a shows a reducing inflammatory response. In contrast, stimulation of LPS was resulted in significantly diminished production of proinflammatory cytokines, including TNF, IL-6, and IL-12 in miR-146a knockout macrophages. These studies show that overexpression of miR-146a in cell lines will result in the reducing of proinflammatory responses [12, 13]. This data support the proposition that miR-146a plays a negative role in the control of inflammation in macrophages.

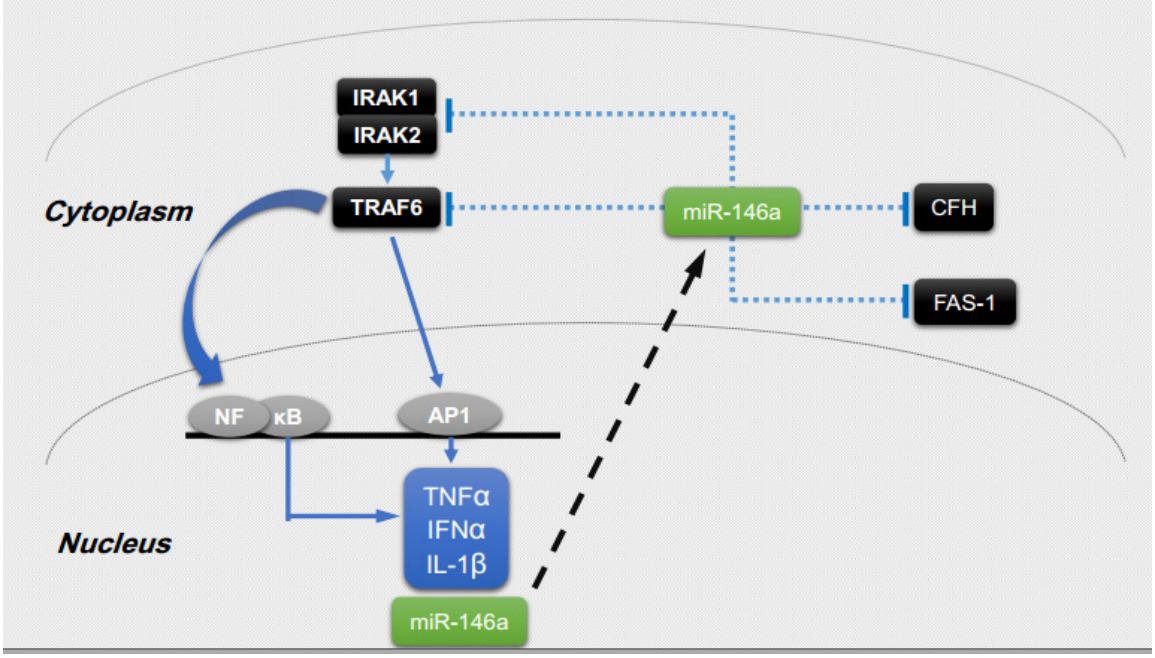

Fig. 1. MiR-146a pathway

2. MiR-146 in the innate immunity

The innate immunity is responsible for the initial defense against infection by external pathogens such as microbial components; and it is predominantly mediated via myeloid cells. The presence of pathogens is generally detected by tissue antigen-presenting cells (APCs) via receptors binding to nonself-antigens such as microbial products. However, many families of receptors are been known, the best categorized are the TLR and the IL-1 receptors. The APC is activated by the NF-κB pathway and ligation of pathogens to receptors leading to the production of type 1interferons (IFNs) [14, 15].

MiRNA biogenesis is regulated via Inflammation through cytokines, antigens, or TLR ligands which can regulate specific transcription factors for modulating miRNA expression levels [14, 16, 17]. MiR-146a was reported as a key factor modulating the innate immune response. MiR-146a acts as a negative feedback regulator in LPS stimulation and virus infection; and suppresses TLR signaling pathways by targeting TRAF6 and IRAK1/2 in various innate cells such as microglial cells, lung epithelial alveolar cells, and monocytes [8, 9, 13, 18].

MiR-146 is induced in response to cytokines and pathogen products such as LPS in dendritic cells (DCs) and macrophages [9, 18, 19]. It is transcriptionally induced by these NF-κB in cells [9]. NF-κB has been reported to play a critical role in regulation of DC immune functions and maturation [20, 21]. Moreover, NF-κB mediates the protection of DC from apoptosis [22]. Interestingly, miR-146a is known to silence TRAF6 and IRAK1/2 [9, 12, 18, 23], resulted in inhibition of NF-κB activation [23, 24]. Moreover, miR-146 has been proposed to be an anti-

inflammatory miRNA in DCs [9, 18]. Interestingly, miR-146a is known to silence complement factor H (CFH), a key repressor of the innate and immune response [25].

3. MiR-146a and adaptive immune responses

The adaptive immune system involves the selective recognition and the removal of non-self by the T cell receptors on T cells and antibodies produced by B cells. The activation of T and B cells are complex processes tightly controlled at different points including miRNA-mediated gene regulation [26]. MiR-146a is much more abundant in various differentiated lymphocyte in comparison with naive B or T lymphocytes [27].

3.1 MiR-146a and T cell

The autoimmunity in miR-146a knockout mice correlates mechanistically with a loss of peripheral T cell tolerance. Activation of peripheral T cells in naive mice is often an indication of a break in immune tolerance. It is usually found in mice models of autoimmune diseases, which is determined in miR-146a knockout mice. The T cell lineage examination in miR-146a knockout mice has shown that a large fraction of peripheral T cells displayed an activated, effector status. Thus, it seems that lack of miR-146a expression can lead to a loss of peripheral T cell tolerance over time which correlates with the development of an autoimmune disorder in miR-146a–null mice [11]. MiR-146a is barely expressed in naive T cells In human lymphocytes, although it is highly expressed in memory T cells, and is induced upon T-cell receptor stimulation [28].

The regulatory T cells (Tregs) known as suppressor T cells, are a subpopulation of T cells, which maintain tolerance to self-antigens, modulate the immune system, and abrogate autoimmune disease. Tregs are immunosuppressive, and generally down-regulate or suppress proliferation and induction of effector T cells [29]. Repression of miR-146a expression increases numbers of Treg cells, and also impairs their function leading to breakdown of immunological tolerance with tissue infiltration in several organs, and massive lymphocyte activation [6]. Also, miR-146a has been shown to be up regulated in Th1 cells and abolished in Th2 cells throughout T-cell differentiation [30]. Recently a study has shown that miR-146a is highly expressed in Tregs and targets STAT-1. Consequently, it controls Treg-mediated suppression of IFNγ-dependent Th1 responses and inflammation selectively [6]. In Jurkat T cells, miR-146a has been reported to target Fas-Associated protein for modulating activation-induced cell death and IL-2 expression [7].

3.2 MiR-146a and B cell

JunMei et al. reported that miR-146a inhibition had no effect on the expression of IRAK1 and TRAF6 in B cells. This data suggest that the function of miR-146a in B cells does not include these two target molecules [31]. However, Boldin et al. stated that expression of mature miR-146a was found relatively high in peripheral $CD19^{+}$ B

cells, the functional roles of miR-146a remained unknown in these B cells [11].

4. Multiple Sclerosis and miR-146a

Immune system damages the myelin of nerve cells of brain and spinal cord in Multiple Sclerosis (MS) [32]. The patients with MS have auto reactive T cell, mediating autoimmune response to myelin antigens, which results in both axonal degeneration and inflammation [33].

miR-146, which is related with immune responses, is at least two fold more abundant than in normal brain white matter in active MS lesions [34]. MiR-146a controls TLR through a negative feedback regulation loop involving down regulation of TRAF6 and IRAK1 levels [9]. In neuroinflammation, and TLR activation modulate the release of inflammatory cytokines [35]. Additionally, TLRs are expressed on cells of the central nervous system; and there is a marked increase in expression of TLRs in MS brain lesions and cerebrospinal fluid mononuclear cells [36, 37]. Further, both CFH and IRAK-1 deficiencies are observed in MS and in other hand, miR-146a targets signaling proteins involved in the innate immunity, including CFH and IRAK-1 [9, 25, 38, 39]. Interestingly, glial cells, which are responsible for axonal myelination have had significantly increased expression of miR-146a [40- 42]. Of further interest, viral infections of brain cells up-regulate NF-kB and by neurotropic viruses, as a result of over expression of miR-146a[43].

5. Systemic lupus erythematosus and miR-146a

Systemic lupus erythematosus (SLE), also known as lupus, is an autoimmune disease in which the immune system attacks the connective tissue. Type I IFN plays a very important role in the pathogenesis of SLE [44, 45]. Recently a study has revealed that miR-146a is a negative regulator of the type I IFN pathway by targeting the multiple key signaling proteins including, TLR-7/9, STAT1, TRAF6 and IRAK-1 in peripheral circulating leukocytes of SLE patients [5]. MiR-146a was profoundly decreased in patients with SLE against healthy controls. The overexpression of miR-146a in normal peripheral blood mononuclear cells greatly reduced the induction of IFN-α/β, and the inhibition of endogenous miR-146a increased the production of IFN-α/β in response to the activation of TLR-7. Additionally, there's a negative correlation between miR-146a levels and disease activities [5]. These data reveal that miR-146a levels may potentially offer a therapeutic target to SLE patients.

Epstein barr virus (EBV) infections have been implicated in SLE pathogenesis. EBV infection induced NF-kB dependent expression of miR-146a [46, 47]. These data suggest the potential role of this miRNA in EBV-mediated autoimmune pathogenesis.

6. Rheumatoid arthritis and miR-146a

Rheumatoid arthritis (RA) is an inflammatory disorder that primarily affects joints [48]. TNF-α and IL-1β, which are inflammatory cytokines, play an important role in RA pathogenesis [49, 50]. Up-regulation of miR-146a is reported in various cell types in RA,

where it is supposed to negatively regulate proinflammatory cytokines such as TNF-α and IL-17 [3, 4, 51]. Recent reports revealed that miR-146a expression was increased in $CD4^+$ T cells, and was positively correlated with the levels of the TNFα and IL-17. Moreover, the increase in miR-146a expression may contribute to RA pathogenesis by suppressing T-cell apoptosis and enhancing the differentiation of IL-17 cells, respectively [2, 3]. Furthermore, miR-146a expression in $CD4^+$ T cells negatively correlates with Fas-associated factor 1(FAS-1) that regulates T-cell apoptosis [2]. Similarly, Curtale et al. [28] showed that miR146a is an anti-apoptotic factor which is modulating activation induced cell death [4]. In addition, TRAF6 and IRAK-1 were similarly expressed in RA and healthy patients, in spite of higher levels of miR-146 in RA patients. Consequently, miR-146 is unable to efficiently regulate TRAF6/IRAK-1, and as a result leads to the prolonged TNF-α production in RA patients [52]. A positive correlation between miR146a expression levels and disease activity, suggests the potential utility of miR-146a as a RA disease activity biomarker [4].

7. Sjögren's syndrome and miR-146a

Sjögren's syndrome (SS) is a systemic chronic inflammatory disorder which affects the glands that make moisture [53]. Pauley et al. found that miR-146a expression was increased in the peripheral blood mononuclear cells and salivary glands of the SS mouse, and it was expressively increased in SS patients compared to healthy controls [54]. MiR-146a was supposed to inhibit the production of inflammatory cytokines. Therefore, SS patients should decrease the production of inflammatory cytokines such as IL-1β and IL-18 under the existence of increased levels of miR-146a. In contrast, both cases were increased [55- 57]. Similarly, Zilahi et al. showed that miR-146a expression was increased in SS patients. However, interestingly, the significant overexpression of TRAF6 was observed, while the down-regulation of IRAK1 gene in peripheral blood mononuclear cells was reported[55]. MiR-146a accumulation in this autoimmune disease cannot be explained by its immunosuppressive nature in innate cells. Thus, more investigations are still needed to understand the role of miR-146a in SS.

Conclusions

The discovery of miRNAs has revealed a new side of regulation of gene expression with a deep impact on many biological systems. Studies in recent years have shown that miRNA-146a has a unique expression profile in cells of the innate and adaptive immune system. There is now increasing indication to suggest that miR-146a can be an important player in autoimmune diseases. In this review, we described the role of miR-146a as an important regulator of inflammation, and significant factor in pathogenesis of autoimmune diseases and valuable diagnostic markers. Furthermore, deregulated miR-146a expression has been related with several

autoimmune diseases such as MS, SLE, RA, and SS. However, miR-146a was decreased in peripheral blood mononuclear cells from human patients with lupus; it was increased in peripheral blood mononuclear cells from human patients with RA. Thus, the unique roles of miR-146a have to be recognized based on the cell type or disease type, not generalized items. Transgenic mouse with deletion of miR-146a can be used to investigating the role of this miRNA in the pathogenesis of autoimmune diseases. Besides, it will then be an important to determine whether manipulating the levels of expression of miR-146a has therapeutic benefits.

Conflict of Interest

The authors have no conflicts of interest.

Acknowledgement

There is no Acknowledgement to declare.

References

[1]. Alexandrov PN, Dua P, Lukiw WJ. Up-regulation of miRNA-146a in progressive, age-related inflammatory neurodegenerative disorders of the human CNS. Frontiers in neurology 2014; 29(5): 181.

[2]. Anglicheau D, Muthukumar T, Suthanthiran M. MicroRNAs: small RNAs with big effects. Transplantation 2010; 90(2): 105-12.

[3]. Bartel DP. MicroRNAs:genomics, biogenesis, mechanism, and function. Cell 2004; 116(2): 281-97.

[4]. Bartel DP. MicroRNAs:target recognition and regulatory functions. Cell 2009;136(2): 215-33.

[5]. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 2006; 441(7090): 235-38.

[6]. Bhaumik D, Scott GK, Schokrpur S, Patil CK, Campisi J, Benz CC. Expression of microRNA-146 suppresses NF-κB activity with reduction of metastatic potential in breast cancer cells. Oncogene 2008;27(42): 5643-647.

[7]. Boldin MP, Taganov KD, Rao DS, Yang L, Zhao JL, Kalwani M, et al. miR-146a is a significant brake on autoimmunity, myeloproliferation, and cancer in mice. The Journal of experimental medicine 2011;208(6): 1189-201.

[8]. Bresnihan B, Alvaro-Gracia JM, Cobby M, Doherty M, Domljan Z, Emery P, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum.1998;41(12): 2196-204.

[9]. Buchanan MM, Hutchinson M, Watkins LR, Yin H. Toll like receptor 4 in CNS pathologies. Journal of neurochemistry 2010;114(1): 13-27.

[10]. Cameron JE, Yin Q, Fewell C, Lacey M, McBride J, Wang X, et al. Epstein-Barr virus latent membrane protein 1 induces cellular MicroRNA miR-146a, a modulator of lymphocyte signaling pathways. Journal of virology 2008; 82(4): 1946-958.

[11]. Ceribelli A, Nahid MA, Satoh M, Chan EK. MicroRNAs in rheumatoid arthritis. FEBS letters 2011; 585(23): 3667-674.

[12]. Crow MK..Type I interferon in systemic lupus erythematosus, in Interferon: The 50th Anniversary. Springer 2007: 359-86.

[13]. Cui JG, Li YY, Zhao Y, Bhattacharjee S, Lukiw WJ. Differential regulation of interleukin-1 receptor-associated kinase-1 (IRAK-1) and IRAK-2 by microRNA-146a and NF-κB in stressed human astroglial cells and in Alzheimer disease. Journal of Biological Chemistry 2010; 285(50): 38951-8960.

[14]. Curtale G, Citarella F, Carissimi C, Goldoni M, Carucci N, Fulci V, et al. An emerging player in the adaptive immune response: microRNA-146a is a modulator of IL-2 expression and activation-induced cell death in T lymphocytes. Blood 2010; 115(2): 265-73.

[15]. Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ. Processing of primary microRNAs by the Microprocessor complex. Nature 2004; 432(7014): 231-35.

[16]. Eriksson P, Andersson C, Ekerfelt C, Ernerudh J, Skogh T. Relationship between serum levels of IL 18 and IgG1 in patients with primary Sjögren's syndrome, rheumatoid arthritis and healthy controls. Clinical & Experimental Immunology 2004;137(3): 617-20.

[17]. Fernández M, Montalban X, Comabella. M. Orchestrating innate immune responses in multiple sclerosis: molecular players. Journal of neuroimmunology 2010; 225(1): 5-12.
[18]. Fox RI. Sjögren's syndrome. *The Lancet* 2005;366(9482): 321-31.
[19]. Gandhi R, Laroni A, Weiner HL. Role of the innate immune system in the pathogenesis of multiple sclerosis. Journal of neuroimmunology 2010; 221(1): 7-14.
[20]. Guo Q, Zhang J, Li J, Zou L, Zhang J, Xie Z, et al. Forced miR-146a expression causes autoimmune lymphoproliferative syndrome in mice via downregulation of Fas in germinal center B cells. Blood 2013;121(24): 4875-883.
[21]. Hill JM, Zhao Y, Clement C, Neumann DM, Lukiw WJ. HSV-1 infection of human brain cells induces miRNA-146a and Alzheimer-type inflammatory signaling. Neuroreport 2009; 20(16): 1500-1505.
[22]. Hou J, Wang P, Lin L, Liu X, Ma F, An H, Wang Z, Cao X. MicroRNA-146a feedback inhibits RIG-I-dependent Type I IFN production in macrophages by targeting TRAF6, IRAK1, and IRAK2. The Journal of Immunology 2009; 183(3): 2150-158.
[23]. Ingram G, Loveless S, Howell OW, Hakobyan S, Dancey B, Harris CL Complement activation in multiple sclerosis plaques: an immunohistochemical analysis. Acta neuropathologica communications 2014;9 (2):53.
[24]. Junker A, Krumbholz M, Eisele S, Mohan H, Augstein F, Bittner R, et al. MicroRNA profiling of multiple sclerosis lesions identifies modulators of the regulatory protein CD47. Brain 2009;132(12): 3342-352.
[25]. Jurkin J, Schichl YM, Koeffel R, Bauer T, Richter S, Konradi S, et al. miR-146a is differentially expressed by myeloid dendritic cell subsets and desensitizes cells to TLR2-dependent activation. The Journal of Immunology2010; 184(9): 4955-965.
[26]. Kasper LH, Shoemaker J. Multiple sclerosis immunology The healthy immune system vs the MS immune system. Neurology 2010;74(Supp 1): S2-S8.
[27]. Kawai T, Akira S. TLR signaling. Cell Death & Differentiation 2006; 13(5): 816-25.
[28]. Kroesen BJ, Teteloshvili N, Smigielska-Czepiel K, Brouwer E, Boots AM, van den Berg, et al. Immuno-miRs: critical regulators of T-cell development, function and ageing. Immunology 2015;144(1): 1-10.
[29]. Kuchen S, Resch W, Yamane A, Kuo N, Li Z, Chakraborty T, et al. Regulation of microRNA expression and abundance during lymphopoiesis. Immunity 2010;32(6): 828-39.
[30]. Li J, Wan Y, Guo Q, Zou L, Zhang J, et al. Research article Altered microRNA expression profile with miR-146a upregulation in CD4+ T cells from patients with rheumatoid arthritis. *Arthritis research & therapy 2010;* 12: R81.
[31]. Li YY, Cui JG, Dua P, Pogue AI, Bhattacharjee S, Lukiw WJ. Differential expression of miRNA-146a-regulated inflammatory genes in human primary neural, astroglial and microglial cells. Neuroscience letters 2011; 499(2): 109-113.
[32]. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. New England Journal of Medicine. 2000;343(22): p. 1594-602.
[33]. Liston A, Linterman M, Lu.-lF. .MicroRNA in the adaptive immune system, in sickness and in health. Journal of clinical immunology 2010; 30(3): 339-46.
[34]. Liston A, Linterman M, Lu LF. Lu.MicroRNA in the adaptive immune system, in sickness and in health. Journal of clinical immunology 2010; 30(3): 339-46.
[35]. Monticelli S, Ansel KM, Xiao C, Socci ND, Krichevsky AM, Thai TH, et al.MicroRNA profiling of the murine hematopoietic system. Genome biology 2005; 6(8): R71.
[36]. Motsch N, Pfuhl T, Mrazek J, Barth S, Grässer FA. Epstein-Barr virus-encoded latent membrane protein 1 (LMP1) induces the expression of the cellular microRNA miR-146a. RNA biolog 2007;4(3): 131-37.
[37]. Nakasa T, Miyaki S, Okubo A, Hashimoto M, Nishida K, Ochi M, et al. Expression of microRNA-146 in rheumatoid arthritis synovial tissue. Arthritis & Rheumatism 2008;58(5): 1284-292.
[38]. Nahid MA, Pauley KM, Satoh M, Chan EK. miR-146a is critical for endotoxin-induced tolerance IMPLICATION IN INNATE IMMUNITY. Journal of Biological Chemistry 2009; 284(50): 34590-4599.
[39]. Niimoto T, Nakasa T, Ishikawa M, Okuhara A, Izumi B, Deie M. MicroRNA-146a expresses in interleukin-17 producing T cells in rheumatoid arthritis patients. BMC musculoskeletal disorders 2010; 11(1): 209.
[40]. O'Connell RM, Rao DS, Chaudhuri AA, Baltimore D. Physiological and pathological roles for microRNAs in the immune system. Nature Reviews Immunology 2010; 10(2): 111-22.
[41]. O'Connell RM, Taganov KD, Boldin MP, Cheng G, Baltimore D. MicroRNA-155 is induced during the macrophage inflammatory response. Proceedings of the National Academy of Sciences 2007;104(5): 1604-1609.
[42]. Pauley KM, Satoh M, Chan AL, Bubb MR, Reeves WH, Chan EK. Upregulated miR-146a expression in peripheral blood mononuclear cells from rheumatoid arthritis patients. Arthritis research & therapy 2008; 10(4): R101.
[43]. Pauley KM, Stewart CM, Gauna AE, Dupre LC, Kuklani R, Chan AL, et al. Altered miR-

146a expression in Sjögren's syndrome and its functional role in innate immunity. *European journal of immunology 2011;* 41(7):2029-2039.

[44]. Perry MM, Moschos SA, Williams AE, Shepherd NJ, Larner-Svensson HM, Lindsay MA. Rapid changes in microRNA-146a expression negatively regulate the IL-1β-induced inflammatory response in human lung alveolar epithelial cells. The Journal of Immunology 2008;180(8): 5689-698.

[45]. Pryce G, Ahmed Z, Hankey DJ, Jackson SJ, Croxford JL, Pocock JM, et al. Cannabinoids inhibit neurodegeneration in models of multiple sclerosis. Brain 2003, 126(10): 2191-2202.

[46]. Rescigno M, Martino M, Sutherland CL, Gold MR, Ricciardi-Castagnoli P. Dendritic cell survival and maturation are regulated by different signaling pathways. The Journal of experimental medicine 1998;188(11):2175-180.

[47]. Rom S, Rom I, Passiatore G, Pacifici M, Radhakrishnan S, Del Valle L, et al. CCL8/MCP-2 is a target for mir-146a in HIV-1-infected human microglial cells. The FASEB Journa 2010; 24(7): 2292-2300.

[48]. Rönnblom L1, Eloranta ML, Alm GV. The type I interferon system in systemic lupus erythematosus. Arthritis & Rheumatism. 2006; 54(2): 408-20.

[49]. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. The Lancet 2007; 370(9602): 1861-874.

[50]. Stürner KH, Verse N, Yousef S, Martin R, Sospedra M. Boswellic acids reduce Th17 differentiation via blockade of IL-1β-mediated IRAK1 signaling. European journal of immunology 2014;44(4): 1200-212.

[51]. Szodoray P, Alex P, Brun JG, Centola M, Jonsson R. Circulating cytokines in primary Sjögren's syndrome determined by a multiplex cytokine array system. Scandinavian Journal of Immunolog 2004; 59(6): 592-99.

[52]. Taganov KD, Boldin MP, Chang KJ, Baltimore D. NF-κB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proceedings of the National Academy of Sciences 2006;103(33): 12481-2486.

[53]. Tang Y, Luo X, Cui H, Ni X, Yuan M, Guo Y, et al. MicroRNA-146a contributes to abnormal activation of the type I interferon pathway in human lupus by targeting the key signaling proteins. Arthritis & Rheumatism 2009;60(4): 1065-1075.

[54]. van de Laar L, van den Bosch A, van der Kooij SW, Janssen HL, Coffer PJ, van Kooten CV, et al. A nonredundant role for canonical NF-κB in human myeloid dendritic cell development and function. The Journal of Immunology 2010;185(12): 7252-261.

[55]. Zhao JL, Rao DS, Boldin MP, Taganov KD, O'Connell RM, Baltimore D. NF-κB dysregulation in microRNA-146a–deficient mice drives the development of myeloid malignancies. Proceedings of the National Academy of Sciences 2010;108(22): 9184-189.

[56]. Zhang J, Jia G, Liu Q, Hu J, Yan M, Yang B. Silencing miR-146a influences B cells and ameliorates experimental autoimmune myasthenia gravis. Immunology 2015;144(1): 56-67.

[57]. Zilahi E, Tarr T, Papp G, Griger Z, Sipka S, Zeher M. Increased microRNA-146a/b, TRAF6 gene and decreased IRAK1 gene expressions in the peripheral mononuclear cells of patients with Sjögren's syndrome. Immunology letters 201;141(2): 165-68.