REVIEW ARTICLE

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The Importance of miRNAs in The Immune System

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Abstract
miRNAs act as post-transcriptional regulators of protein synthesis. It is known that miRNAs, which are members of the non-coding RNAs class, are effective in the regulation of post-transcriptional gene expression and the hereditary and adaptive immune response. miRNAs bind to target mRNAs to regulate gene expression by mRNA degradation or translational inhibition. miRNAs have functions in the formation or development of many diseases such as cancer, viral and autoimmune diseases in which epigenetic mechanisms play a role. With the development of miRNA-based therapeutic and diagnostic approaches in recent years, miRNA research has gained importance. In this review, general information about miRNA is emphasized, its role in some diseases and the relationship between immunity and miRNA are examined.

Keywords: Cancer, immunity, miRNA.

INTRODUCTION

Micro-ribonucleic acids (miRNAs) belong to the class of non-coding small RNA molecules that modulate the expression of multiple protein-coding genes at the post-transcriptional level. It has been demonstrated that miRNAs play an important role in cell proliferation and differentiation, gene expression and the pathogenesis of inflammatory and autoimmune diseases, regulation of many genes and pathways, adaptive and specific immunity, immune system diseases, viral diseases, cancer and many other cellular processes. By investigating the roles of irregular miRNAs involved in inflammatory autoimmune pathogenesis and miRNA functions that regulate autophagy and immune response, different miRNA expression patterns can be identified and miRNA-based therapeutic approaches, vaccines, potential diagnoses, prognostic markers and new therapeutic strategies for the treatment of inflammatory autoimmune diseases can be developed in the future.

Discovery and Properties of miRNAs

miRNAs are functional RNA molecules with a length of 20-25 nucleotides, non-coding, functional RNA molecules that play a role in post-transcriptional gene regulation (Rusca & Monticelli, 2011). These small gene expression regulators have tissue developmental stage and disease-specific patterns, and are thought to play essential roles in cell differentiation and preservation of tissue type identity (Carissimi et al., 2009). miRNAs can be transcribed in intron regions that do not encode protein or exon regions encoding protein in the genome, but can not be translated into protein (Karagün et al., 2014).

The first miRNA was discovered in 1993 by Lee et al. and was determined that the gene called lin-4 in *Caenorhabditis elegans* (roundworm) did not encode any protein, but transcribed a small RNA of 22 nucleotides. Reinhart et al. (2000) also discovered another 22 nucleotide miRNA in *Caenorhabditis elegans*, which called let-7 and regulates the development timing. Over the years, many small RNA molecules similar to let-4 and let-7 have been discovered in various eukaryotic organisms and have been named as miRNA since 2001 (Çoğul, 2013; Karagün et al. 2014).

miRNAs are of endogenous origin and predominantly bind to the 3'UTR region or open reading frame (ORF) of the target mRNA, affecting translational regulation and/or causing a decrease in target mRNA levels (Vodala et al., 2012). miRNAs are important regulators of gene expression for humans, animals, viruses and plants, and have important effects on cell cycle differentiation, apoptosis, autoimmunity, immune functions, regulation of cellular processes, antibody production, antiviral defense and inflammatory mediator release (Kobazi, 2013). In addition, they play a fundamental role in almost all biological processes, including development, hormonal signaling, and biotic and abiotic stress response (Zhang et al.2012).

miRNAs and the Immune System

In general, immunity is all the reactive reactions that the organism develops against all harmful and foreign substances (proteins, polysaccharides, microorganisms, etc.). The organism's self-protection mechanisms include phagocytic cells in blood and tissues, physical barriers, and various blood-derived molecules, and are grouped as non-specific (hereditary) immune system and specific (acquired) immune system (Paul, 2003). The non-specific immune system constitutes the first stage in the defense mechanism, and at this stage, the organism's own hereditary structure and foreign substance can be distinguished, while one pathogen type cannot be distinguished from the others (Litman et al., 2005) Specific or acquired immunity is a defense system that continues to develop throughout life, can separate substances that are foreign to the organism, and respond specifically to different pathogens and foreign molecules. White blood cells, called lymphocytes, play an important

role in immune system defense and contain T lymphocytes that contribute to cellular immunity and B lymphocytes that contribute to humoral immunity (Songu and Katilmis, 2012). miRNAs have very important roles in preventing many diseases such as autoimmune diseases and cancer and in regulating the immune system. It also has important effects on the development of immune cells and regulation of immune response, and specific miRNAs such as miR-21, miR-146a, miR-155 miR-301a, miR-9, miR-147b, miR-125a, miR-10a, miR-17-92, miR-181a, miR-182, miR-29a/b, miR-17-92, miR-34a, miR-150, miR-181b, miR-125b, miR217 play a regulatory role in the immune system. It has been reported that miR-223 may be the main determining factor of hematopoietic proliferation and differentiation (Zardo, 2012).

Relationship of Non-Specific and Specific Immune System with miRNA

Nonspecific immunity is a phylogenetically ancient biological system in which multicellular organisms evolved to protect themselves from invading pathogens. Non-specific immune system consists of granulocyte and monocyte-derived macrophages and dendritic cells. miRNAs have important functions in the development and control of innate immune cells (Çoğul, 2013). Nuclear miRNAs have the ability to regulate the activation of immune cells by regulating the expression of cellular cytokines (Liu et al., 2018). Transcription growth factor-1, which plays an important role in the formation of granulocytes from natural immune system cells, suppresses the expression of some miRNAs by binding to the promoter regions. These cells, which make up a large part of the peripheral white blood cells, connect by recognizing microbial products such as TLR (Toll-like receptors) and PMAPs (Pathogen-related molecular patterns), thus stimulating the signaling pathway that creates the immune response. Toll-like receptor (TLR) signaling has been reported to induce the expression of various miRNAs, including miR-155, miR-146a, and miR-21 (Taganov et al., 2007). Three miRNAs (miR-146, miR-132 and miR-155) were identified that were rapidly upregulated in response to microbial lipopolysaccharides (LPS) in human monocytic cells. In addition, miR-146 acts as a negative feedback regulator of TLR signaling by targeting tumor necrosis factor receptor-associated factor 6 (TRAF6) and interleukin-1 receptor-associated kinase 1 (IRAQ-1) (Taganov et al., 2007). Lederhuber et al. (2011) determined that differences between the negative regulatory role for miR-146a are clearly evident in neonatal and adult TLR4 signaling, and a statistically higher significant increase in umbilical cord blood monocytes compared to adults.miR-146a has important functions as a modulator of differentiation of innate cells and adaptive immunity (Rusca & Monticelli, 2011). In addition, miR-146a is effective in establishing endotoxin tolerance in monocytes and regulating TNF-α production (Nahid et al., 2009). Besides, when the expression level of miR-146a in human Langerhans cells (LC) compared with the level of expression in interstitial dendritic cells (intDC), it was found that it was structurally expressed at higher levels in LC cells (Jurkin et al., 2010).

miR-150 expression increases during the maturation stages of B and T cells, while miR-150 expression decreases during the separation of pure T cells into Th1 or Th2 subtypes (Monticelli et al., 2005). In addition, ectopic miR-150 expression in B cell progenitors in mice inhibits B cell development at the pro-B cell stage and decreases the B1 cell level, a subset of mature B cells present (Xiao et al., 2007). It has been reported that miR-150 expression is higher in B cells than lymphoma cells (Lawrie et al., 2007).

miRNAs are expressed in immune cells, play a role in regulation of specific and non-specific immune response, form regulatory networks in innate immunity, regulate the functions of immune cells such as monocytes, dendritic cells (DC), macrophages, neutrophils, natural killer (NK) cells, megakaryocytes and granulocytes. In addition, in adaptive immunity, they regulate immune signaling pathways, involve in T and B cell development, differentiation, and functions of central and peripheral tolerance (Billeter et al., 2014; Chandan et al., 2020). miR - 146a, miR - 155, miR - 21, and miR - 132 are important miRNAs negatively regulating host inflammatory pathways triggered by Toll-like receptor (TLR) signaling in myeloid cells. It has been determined that miR-155 induced by TLR ligands suppresses negative regulators of TLR signaling such as SHIP1 and SOCS1 in mouse macrophage (Billeter et al., 2014).

Stimulation with interferon-β and TLR ligands causes induction of miR-155 via both the nuclear factor-κB pathway and the Jun N-terminal kinase pathway. Stimulation with interferon-β and TLR ligands causes induction of miR-155 by both nuclear factor-κB and Jun N-terminal kinase pathways. It has been reported that increased expression of miR-21 and miR-196 suppressed the formation of granulocytes in bone marrow cells of rats (Velu et al., 2009). In addition, miR-223 plays a role in granulocyte differentiation and acts as a negative regulator (Çoğul, 2013). miR-17~92 family consists of six miRNAs processed from a common leader transcript and grouped according to their functions (Davidson-Moncada et al., 2010). Fontana et al. (2007) determined that miR-17~92 family is effective in monocyte differentiation. Subsequently, Zhang et al. (2020) reported that three paralogous clusters of the miR-17~92 family in genetically modified mice collectively suppressed IL-12 production in macrophages.

miRNA and Autoimmune Diseases

Antibodies are produced by the immune system against foreign substances in the body. In general, autoimmune diseases occur as a result of the immune system perceiving the tissues and organs in the body as foreign and developing an immune response. The cause of autoimmune diseases is not known in deeply, but it is thought to be of genetic origin (Ceccarelli et al., 2017). It is known that expressions of miRNAs are different in autoimmune diseases and miRNA regulation may affect the development of autoimmune diseases or prevent diseases (Iborra et al., 2012). Overexpression or under-expression of miRNAs can affect specific targets and pathways, leading to autoimmune disease phenotypes. miR-146a is deregulated and altered in autoimmune diseases (Ceribelli et al., 2012).

Abnormal expression of miR-155 is observed in many autoimmune diseases such as rheumatoid arthritis (RA), multiple sclerosis (MS), and systemic lupus erythematosus (SLE). Multiple Sclerosis (MS) is a multifactorial, chronic autoimmune disease of the central nervous system with inflammatory demyelinating character that occurs in young adults with genetic and environmental factors. It has been determined that miR-146a, miR-10a and miR-155 have an important role in development of multiple sclerosis and miR-10a may be important in diagnosis of the disease (Sarıdaş, 2018). Liu et al. (2015) reported that expression of miR-126 in IFN pathway was effective in the pathogenesis of systemic lupus erythematosus (SLE) autoimmune disease (Liu et al., 2015).

Type 1 diabetes is an autoimmune disease in which insulin deficiency occurs as a result of the destruction of the beta cells of the pancreas. It was determined that expressions of miR-24, miR-25, miR-26a, miR-29a, miR-152 increased in children with type 1 diabetes (Bolkent, 2018).In rheumatoid arthritis (RA), miR-146a and miR-223 have been reported to be higher activated rheumatoid arthritis patients compared to patients with mild activation of miR-146a and miR-223 (Bakay, 2018) and a positive correlation was observed between the expression of miR-301a-3p and the Th17 cell count in patients.

miRNA and Cancer

In general, malignant cell proliferation, as a result of abnormalities in cell division and differentiation processes due to changes in gene expression is called cancer. It is known that epigenetic mechanisms involving miRNAs are effective in the carcinogenesis process. In CLL (chronic lymphocytic leukemia), which is the adult form of leukemia, it has been reported that approximately 50% of the patients experience deletion of the 13q14 region and miR-15a and miR-16-1 genes are localized in this deletion region (Calin et al., 2002). Low-expressed tumor suppressor miRNAs in cancer cells are called TS-miR, and highly expressed miRNAs are called onco-miR. (Ertürk, 2012). Nuclear miRNAs have an important place in tumor formation and apoptosis processes. Nuclear miRNAs, mainly acting on promoter regions, affect the expression profile of oncogenes, tumor suppressors or other cancer-related genes during the cancer initiation process (Liu et al., 2018). Ectopic expression of mirR-483 causes an increase in tumor cell proliferation, migration, invasion and tumor colony formation as well as upregulation of IGF2 expression (Zhang et al., 2017). There is a connection between some miRNAs in cancerous tissues in breast cancer and the clinical features of the disease and the development stage of the cancer. In breast cancer tissue miRNA genes such as miR-9-1, miR-124a-3, miR-148, miR-152 and miR-663 are hypermethylated (Lehmann et al., 2007).

Tumor-associated macrophages (TAMs) express an alternatively activated phenotype that includes largely immunosuppressive and tumor-supporting properties. Reprogramming TAMs towards a conventionally activated phenotype (M1) can block the tumor-associated immunosuppression ion and elicit anti-tumor immunity. Conditional deletion of the miRNA processing enzyme DICER in macrophages leads to M1-like TAM programming characterized by the hyperactive IFN-γ/STAT1 signal (Baer et al., 2016). Cancer cells have developed some mechanisms to evade immune system interventions, and hence, difficulties are experienced in treatment and immune response formation may occur. MDSCs (Myeloid Origin Suppressor Cells) are the main myeloid cells responsible for the immune escape mechanism of cancer miRNAs are identified as important determinants for TAM pro-tumor activity as well as the accumulation, expansion, and tumor-supporting function of MDSCs. Destruction of miR-155 in myeloid cells causes faster tumor growth, reduction of M1-macrophages and enrichment of pro-tumor cytokines in the tumor environment. miR-4942, whose expression was induced by tumor-derived factors, increases CXCR4-mediated chemotaxis of MDSCs,modulating the intrinsic apoptotic pathway by targeting the phosphatase and tensin homolog (PTEN) (Chaudhuri et al., 2011; Curtale, 2018;). Irregular miR-155 expression is associated with increased cancer risk (Leng et al.2011). miR-205 targets promoters in prostate carcinoma cells activates IL-24 and IL-32, members of the cytokine family that act as tumor suppressors (Majid et al., 2010). Treatment of bone marrow derived mesenchymal stem cells (MSC) with diazoxide (DZ) has been reported to increase the expression of miR-146a and cell survival. In addition, down-regulation of miR-146a expression by antisense inhibitors abolished the cytoprotective effects caused by diazoxide(Suzuki et al., 2010). The miR-125 family plays important roles in hematopoiesis and immune cell function, and may have an oncogenic or tumor suppressor effect depending on the miR-125a and miR-125b cell types. Therefore, chemotherapy with miR-125a and miR-125b may increase drug resistance or sensitivity and miR-125a and miR-125b may be used as potential diagnostic or prognostic markers (Wang et al., 2019).

miRNA, Viruses and Bacteria

It has been observed that miRNA expressionis affected by some bacterial and viral pathogens (Zhou et al., 2018). To date, as a result of the analysis of 228 human viruses, it has been determined that 62 viruses belonging to six different viral families contain target regions for human miRNA (Watanabe et al., 2007).miR-146a plays a role in the regulation of vesicular stomatitis virus (VSV) infection (Hou et al., 2009). In addition, in recent years, it has been determined that DNA and RNA viruses produce viral miRNAs (v-miRNAs) to avoid the host's immune response (Mishra et al.2019). Viral miRNAs are expressed similarly to eukaryotic miRNAs in simian poliomaviruses and human adenoviruses, most of them in dsDNA viruses of herpesvirus families(Gottwein and Cullen, 2008; Mishra et al., 2019). The first v-miRNAs were identified in 2004 by cloning small RNAs from the Burkitt lymphoma cell line infected with *Epstein-Barr virus* (EBV) (Pfeffer et al., 2004). miR-21 modulates the TLR signal by targeting MyD88 and IRAQ1 during hepatitis C virus (HCV) infection, which leads to suppression of type I interferon production (Chen et al., 2013). Some miRNAs determined to directly suppress mammalian viruses are listed in Table 3. MiR-146 is expected to have antiviral effect due to the binding site of miR-146 in many virus genomes such as *PFV-1 virus*, *Dengue virus*, *Hepatitis C virus*, *Influenza B virus* (Hsu et al., 2007).*Helicobacter pylori* is a gram (-), microaerophilic bacterium capable of colonization in the human stomach and duodenum, responsible for many stomach diseases.

H. pylori infection is effective in the early stages of gastric cancer pathogenesis by induction of chronic gastritis, and changes miRNA expressions and increased miR-155 expression in gastric mucosal tissues have been observed as a result of infection in gastric cells (Zhou et al., 2018).

RESULT

The discovery of miRNAs has revealed a new regulation of gene expression with high effect in biological systems. Recent studies show that miRNAs are effective in specific and non-specific immune system cells, cell development and functions, and act as oncogenes or tumor suppressors in many tumor and cell types. In many diseases such as cancer, autoimmune, autoinflammatory diseases, miRNA expression levels are important to understand the epigenetic mechanism of the disease and show a significant increase or decrease. Changing the expression levels of miRNAs with external effects and the emergence of unexpected results emphasize the importance of miRNAs once again. It will probably take time to understand the full effects of miRNAs on the immune system, but it is predicted that they have much more functions in biological systems in light of the

accumulations obtained. By understanding the effect of microRNAs in cellular processes and biological systems, biomarkers and therapeutic targets can be developed for the diagnosis and treatment of many diseases for humans, animals and plants.

Conflict of Interest

The authors declare that there is no conflict of interest in the content of the article

REFERENCES

Baer C, Squadrito ML, Laoui D, Thompson D, Hansen SK, Kiialainen A, Hoves S, Ries CH, Ooi CH, De Palma M. 2016. Suppression of microRNA activity amplifies IFN-γ-induced macrophage activation and promotes anti-tumour immunity. Nat Cell Biol, 18, 790–802.

Bakay U. 2018. Romatoid Artrit' e mikroRNA-146a, mikroRNA-223 Düzeyleri, Sensitive ve Spesifiteleri, Diğer Hastalık Paramereleri ve Biyolojik Ajan Tedavisiyle İlişkisi. Fırat University Faculty of Medicine, Department of Physical Medicine and Rehabilitation PhD Thesis.

Billeter AT, Hellmann J, Roberts H, Druen D, Gardner SA, Sarojini H, Galandiuk S, Chien S, Bhatnagar A, Spite M, Polk Jr. HC. 2014. MicroRNA-155 potentiates the inflammatory response in hypothermia by suppressing IL-10 production. FASEB J. 2014;28(12), 5322-5336.

Bolkent S. 2018. Tip1 ve Tip2 Diyabet ile ilişkili miRNA'lar. Türkiye Klinikleri J Med. Sci 2018;38(3), 266-74.

Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, Aldler H, Rattan S, Keating M, Rai K, Rassenti L, Kipps T, Negrini M, Bullrich F, Croce CM. 2002. Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc.Natl.Acad.Sci 2002;99, 15524-15529.

Carissimi C, Fulci V, Macino G. 2009. MicroRNAs: Novel regulators of immunity. Autoimmunity Reviews, 8(6): 520-524.

Ceccarelli F, Agmon-Levin N, Perricone C. 2017. Genetic Factors of Autoimmune Diseases. J Immunol Res. 2789242.

Ceribelli A, Satoh M, Chan EK. 2012. MicroRNAs and autoimmunity. Current opinion in immunology, 24(6), 686-691.

Chandan K, Gupta M, Sarwat M. 2020. Role of Host and Pathogen-Derived MicroRNAs in Immune Regulation During Infectious and Inflammatory Diseases. Frontiers in Immunology, 10, 3081.

Chaudhuri AA, So AY, Sinha N, Gibson WS, Taganov KD, O'Connell RM, Baltimore D. 2011. MicroRNA-125b potentiates macrophage activation. J. Immunol, 187, 5062–5068.

Chen Y, Chen J, Wang H, Shi J, Wu K, Liu S, Liu Y, Wu J. 2013. HCV-induced miR-21 contributes to evasion of host immune system by targeting MyD88 and IRAK1. PLoS Pathogens, 9, e1003248.

Curtale G. 2018. MiRNAs at the Crossroads between Innate Immunity and Cancer: Focus on Macrophages. Cells 2018, 7(2), 12.

Çoğul K. 2013. Ankilozan Spondilit' te Kan Mikro-RNA Düzeylerinin Araştırılması ve Hastalık Aktivitesi İle Fonksiyonel Kapasite Arasındaki İlişkisi. Mersin University Faculty of Medicine Department of Physical Medicine and Rehabilitation PhD Thesis.

Davidson-Moncada J, Papavasiliou FN, Tam W. 2010. MicroRNAs of the immune system: roles in inflammation and cancer. Ann N Y Acad Sci, 1183, 183-194.

Ertürk E. 2012. Meme Kanseri Gelişiminde miRNA' ların Rolünün Araştırılması. Uludağ University Institute of Health Sciences, Department of Medical Biology, Master's Thesis.

Fontana L, Pelosi E, Greco P, Racanicchi S, Testa U, Liuzzi F, Croce CM, Brunetti E, Grignani F, Peschle C. 2007. MicroRNAs 17–5p-20a-106a control monocytopoiesis through AML1 targeting and M-CSF receptor upregulation. Nat Cell Biol, 9, 775–787.

Gottwein E, Cullen BR. 2008. Viral and Cellular MicroRNAs as Determinants of Viral Pathogenesis and Immunity. Cell Host & Microbe, 3(6), 375-387.

He J, Zhao J, Zhu W, Qi D, Wang L, Sun J, Wang B, Ma X, Dai Q, Yu X. 2016. MicroRNA biogenesis pathway genes polymorphisms and cancer risk: a systematic review and meta-analysis. PeerJ, 4, e2706.

Hou J, Wang P, Lin L, Liu X, Ma F, An H, Wang Z, Cao X. 2009. MicroRNA-146a feedback inhibits RIG-I-dependent type I IFN production in macrophages by targeting TRAF6, IRAK1, and IRAK2. Journal of Immunology, 183(3), 2150–2158.

Hsu PW, Lin LZ, Hsu SD, Hsu JB, Huang HD. 2007. ViTa: Prediction of host microRNAs targets on viruses. Nucleic Acids Res, 35, 381-385.

Iborra M, Bernuzzi F, Invernizzi P, Danese S. 2012. MicroRNAs in autoimmunity and inflammatory bowel disease: Crucial regulators in immune response. Autoimmunity Reviews, 11(5), 305-314.

Jurkin J, Schichl YM, Koeffel R, Bauer T, Richter S, Konradi S, Gesslbauer B, Strobl H. 2010. miR-146a is differentially expressed by myeloid dendritic cell subsets and desensitizes cells to TLR2-dependent activation. Journal of Immunology, 184(9), 4955–4965.

Karagün BŞ, Antmen B, Şaşmaz İ, Kılınç Y. 2014. Mikro RNA ve Kanser. Türk Klinik Biyokimya Derg, 12(1), 45-56.

Kim JK, Lee HM, Park KS, Shin DM, Kim TS, Kim YS, Jo EK, et al. 2016. MIR144* inhibits antimicrobial responses against Mycobacterium tuberculosis in human monocytes and macrophages by targeting the autophagy protein DRAM2. Autophagy, 13(2), 423-441.

Kim H, Iizasa H, Kanehiro Y, Fekadu S, Yoshiyama H. 2017. Herpesviral microRNAs in Cellular Metabolism and Immune Responses. Front Microbiol, 8, 1318.

Kobazi G. 2013. Koyun (Ovis aries) Genomunda mikroRNA Analizleri. Ege University Institute of Science, Department of Biology, Master's Thesis.

Lawrie CH, Soneji S, Marafioti T, Cooper CD, Palazzo S, Paterson JC, Cattan H, Enver T, Mager R, Boultwood J, Wainscoat JS, Hatton CS. 2007. MicroRNA expression distinguishes between germinal center B cell-like and activated B cell-like subtypes of diffuse large B cell lymphoma. Int J Cancer, 121(5), 1156-61.

Lederhuber H, Baer K, Altiok I, Sadeghi K, Herkner KR, Kasper DC. 2011). MicroRNA-146: Tiny Player in Neonatal Innate Immunity?. Neonatology, 99, 51-56.

Lehmann U, Hasemeier B, Römermann D, Müller M, Langer F, Kreipe H. 2007. Epigenetic inactivation of microRNA genes in mammary carcinoma. Verhandlunger der Deutschen Gesellschaft für Pathologie, 91, 214-220.

Leng RX, Pan HF, Qin WZ, Chen GM, Ye DQ. 2011. Role of microRNA-155 in autoimmunity. Cytokine Growth Factor Rev, 22(3), 141-147.

Litman G, Cannon J, Dishaw L. 2005. Reconstructing immune phylogeny: new perspectives. Nat. Rev. Immunol, 5, 866-79.

Liu YJ, Fan WJ, Bai JZ. 2015. microRNA-126 expression and its mechanism of action in patients with systemic lupus erythematosus. Eur Rev Med Pharmacol Sci, 19(20), 3838-3842.

Liu H, Lei C, He Q, Pan Z, Xiao D, Tao Y. 2018. Nuclear functions of mammalian MicroRNAs in gene regulation, immunity and cancer. Mol Cancer, 17, 64.

Liu D, Tan Q, Zhu J, Zhang Y, Xue Y, Song Y, Liu Y, Wang Q, Lai L. 2019. MicroRNA-33/33* inhibit the activation of MAVS through AMPK in antiviral innate immunity.' Cell Mol Immunol, https://doi.org/10.1038/s41423-019-0326-x.

Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, Downing JR, Jacks T, Horvitz HR, Golub TR. 2005. MicroRNA expression profiles classify human cancers. Nature, 435, 834-838.

Lu LF, Liston A. 2009. MicroRNA in the immune system, microRNA as an immune system. Immunology, 127(3), 291-298.

Mishra R, Kumar A, Ingle H, Kumar H. 2019. The Interplay Between Viral-Derived miRNAs and Host Immunity During Infection. Front Immunol, 10, 3079.

Majid S, Dar AA, Saini S, Yamamura S, Hirata H, Tanaka Y, Deng G, Dahiya R. 2010. MicroRNA-205–directed transcriptional activation of tumor suppressor genes in prostate cancer. Cancer, 116, 5637–49.

Monticelli S, Ansel KM, Xiao C, Socci ND, Krichevsky AM, Thai TH, Rajewsky N, Marks DS, Sander C, Rajewsky K, Rao A, Kosik KS. 2005. MicroRNA profiling of the murine hematopoietic system. Genome Biol, 6, R71. (doi:10.1186/gb-2005-6-8-r71.

Nahid MA, Pauley KM, Satoh M, Chan EKL. 2009. miR-146a is critical for endotoxin-induced tolerance: implication in innate immunity. Journal of Biological Chemistry, 284 (50), 34590–34599.

Paul WE. 2003. Fundamental Immunology. Philadelphia: Lippincott Williams&Wilkins New York.

Pauley KM, Cha S, Chan EK. 2009. MicroRNA in autoimmunity and autoimmune diseases. J Autoimmun, 32(3-4),189-194.

Pfeffer S, Zavolan M, Grässer FA, Chien M, Russo JJ, Ju J, John B, Enright AJ, Marks D, Sander C, Tuschl T. 2004. Identification of virus-encoded microRNAs. Science, 304(5671), 734-6.

Rusca N, Monticelli S. 2011. MiR-146a in Immunity and Disease. Mol Biol Int, 2011, 437301.

Sarıdaş F. 2018. Multiple Skleroz Gelişimi ile İlişkili miRNA'ların Araştırılması. Uludağ University Faculty of Medicine, Department of Neurology, PhD Thesis.

Songu M, Katılmış H. 2012. Enfeksiyondan Korunma ve İmmün Sistem. J Med Updates, 2(1), 31-42.

Suzuki Y, Kim HW, Ashraf M, Haider H. 2010. Diazoxide potentiates mesenchymal stem cell survival via NF-κB-dependent miR-146a expression by targeting Fas. American Journal of Physiology, 299(4), 1077–1082.

Taganov KD, Boldin MP, Chang KJ, Baltimore D. 2006. NF-{kappa}B-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc. Natl. Acad. Sci, 103, 12481-12486.

Taganov KD, Boldin MP, Baltimore D. 2007. MicroRNAs and immunity: tiny players in a big field. Immunity, 26(2),133-137.

Tang X, Yin K, Zhu H, Tian J, Shen D, Yi L, Rui K, Ma J, Xu H, Wang S. ,2016. Correlation Between the Expression of MicroRNA-301a-3p and the Proportion of Th17 Cells in Patients with Rheumatoid Arthritis. Inflammation, 39(2), 759-767.

Vodala S, Pescatore S, Rodriguez J, Buescher M, Chen YW, Weng R, Cohen SM, Rosbash M. 2012. The Oscillating miRNA 959-964 Cluster Impacts Drosophila Feeding Time and Other Circadian Outputs. Cell Metab, 16(5), 601-612.

Velu CS, Baktula AM, Grimes HL. 2009. Gfi1 regulates miR-21 and miR-196b to control myelopoiesis. Blood, 113(19), 4720-4728.

Zardo G, Ciolfi A, Vian L, et al. 2014. Polycombs and microRNA-223 regulate human granulopoiesis by transcriptional control of target gene expression. Blood, 119(17), 4034-4046.

Zhang L, Hou D, Chen X, et al. 2012. Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA. Cell Res, 22, 107–126.

Zhang Y, Hu JF, Wang H, Cui J, Gao S, Hoffman AR, Li W. 2017. CRISPR Cas9-guided chromatin immunoprecipitation identifies miR483 as an epigenetic modulator of IGF2 imprinting in tumors. Oncotarget, 8, 34177–90.

Zhang X, Smith SM, Wang X, Zhao B, Wu L, Hu X. 2020. Three paralogous clusters of the miR-17~92 family of microRNAs restrain IL-12-mediated immune defense. Cell Mol Immunol, DOI: https://doi.org/10.1038/s41423-020-0363-5.

Wang JK, Wang Z, Li G. 2019. MicroRNA-125 in immunity and cancer. Cancer Letters, 454, 134-145.

Watanabe Y, Kishi A, Yachie N, Kanai A, Tomita M. 2007. Computational analysis of microRNA-mediated antiviral defense in humans. FEBS Lett, 581, 4603–10.

Xiao C, Calado DP, Galler G, Thai TH, Patterson HC, Wang J, Rajewsky N, Bender TP, Rajewsky K. 2007. MiR-150 controls B cell differentiation by targeting the transcription factor c-Myb. Cell, 131(1), 146-59.