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 miRNAs to regulate gene expression by miRNA 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. Reinhar 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 cell-mediated immunity and humoral immunity. In the latter, antibodies are produced that bind to foreign substances and contribute to the elimination of these substances. Antibodies are produced by B lymphocytes, which are activated by antigens through the interaction of their surface immunoglobulin receptors. Antigen-antibody complexes or activated T lymphocytes activate B lymphocytes to differentiate and produce the appropriate antibodies. These antibodies are produced in the form of immunoglobulin and are secreted into the blood and tissue fluids. The antibodies then bind to foreign substances and facilitate their elimination. The antibodies can also neutralize toxins or complete the process of complement activation, leading to the lysis of foreign substances. Additionally, some of the antibodies can also activate phagocyte cells, which play a key role in the destruction of foreign substances. Phagocytes are a type of white blood cell that engulf and destroy foreign substances, such as bacteria and viruses.
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, miR-217 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 (Çoğlu, 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, form regulatory networks in innate immunity, control 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 SHP1 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 (Çoğlu, 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 detail, 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 (Ibora 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 (Sardea, 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 (Li et al., 2018).

Ectopic expression of miR-483 causes an increase in tumor cell proliferation, migration, invasion and tumor colony formation as well as upregulation of IG2 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).

**miRNA, Viruses and Bacteria**

It has been observed that miRNA expression is 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 PRRV virus, Dengue virus, Hepatitis C virus, Influenza B virus (Hsu et al., 2007). 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

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