Insight: Biology (2017) Volume 1, pp.16–20.

ORIGINAL RESEARCH ARTICLE

Research progress of microRNA in immune system

Lingyan Cheng, Jianpeng Lv, Yaling Sun

Life Sciences College, Shantou University of Science and Technology, Guangdong, China

ABSTRACT

MicroRNA (miRNA) is a single-stranded small molecule RNA of non-coding proteins with a length of about 18-24 nucleotides in eukaryotic cells. It is widely found in multicellular organisms and viruses. The miRNA itself is not encoding protein which is mainly through the nucleic acid sequence complementary pairing to a specific target mRNA and inhibit the target mRNA translation process or degradation of target mRNA, thereby inhibiting protein synthesis and regulation of gene expression. According to reports, microRNAs are widely involved in the physiological and biochemical immune response process and their dysfunction may lead to tumorigenesis, viral infection, abnormal expression of hematopoietic cells and immune diseases (RA, SLE) and other pathological phenomena. This paper describes the related mechanisms of mirna and some progress in the immune system.

***Keywords**: microRNA (miRNA); target gene; immune system*

Introduction

MicroRNA (miRNA) is a class of non-coding small RNAs with an endogenous length of about 22 nucleotides that regulates mRNA expression at post-transcriptional levels which is widely found in viruses, nematodes, plants, and animals. Mature miRNAs can complement the specific target mRNA by nucleic acid sequence to degrade or inhibit its translation, thereby inhibiting the synthesis of protein and achieving the purpose of regulating gene expression. MiRNA genes are present in the genome in a variety of forms such as single copy, multiple copies or gene clusters, and most of them are located in the gene spacer. Their transcription is independent of other genes. The expression of these small RNA molecules has spatial and temporal specificity and is an important molecule for regulating the expression of other functional genes. It has been found that more than 100 kinds of miRNA sequences are expressed by immune cells in more than 800 kinds of miRNA sequences. It is involved in cell production, differentiation, apoptosis, natural immune, and acquired immune response.

Discovery of miRNA

In 1993, Lee et al. had found that the first gene-regulated gene lin-4[1] which was moderately regulated embryos and was discovered in 1998. American scientists Andrew Fire and Craig C. Mello found that dsRNA could induce gene silencing. In 2000, Reinhart in the nematode found a second isochronous switch gene let-7[2]. 2001 'Science' reported dozens of small RNA genes similar to lin-4 from nematodes, fruit flies and human clones, namely miRNAs. Up to now, according to miRNA registry published data miRNA entries include 103 species, more than 9,000, of which 851 people are involve. (Release 13. 0, March, 2009)

Biosynthesis and mechanism of action of miRNA

Most of the miRNA primary transcription products (pri-miRNAs) were first synthesized under the action of RNA polymerase II and the Pri-miero RNA molecule was formed in the nucleus by double-stranded RNA-specific nuclease Rnasel II-Drosha (Pre-microRNAs) from 7 0 to 100 n t and then

the Pre-miRNAs were transported to the cytoplasm under the action of the transporter-5 which was replaced by another double-stranded RNA. The nuclease RnasellI - Dice r recognizes and further cleaves the small molecule RNA which is about 2 2 nt, that is, mature miRNAs. Mature miRNAs, under the guidance of RNA-induced silencing complex R I S C are completely or incompletely matched with the complementary target mRNA which degrades the target mRNA or regulating its post-transcriptional translation[3].

The role of miRNAs in the immune system

The immune system is the protective system of the body to protect itself and protect against foreign invasion. It can detect and remove the factors such as foreign matter, foreign pathogenic microorganisms and so on. Its function in hyperthyroidism will be on their organ or tissue damage. CD4 + T cells play an important role in many diseases caused by autoimmunity. The immune system is composed of immune organs, immune cells and immune molecules which are divided into two categories of innate immunity and adaptive immunity. The mechanism of its play complex and diverse has not yet fully elucidated. The present study has found that miRNAs play a significant role in the immune system through complementary base pairs. The miRNAs are mainly expressed in terms of the number and extent of their target gene levels which are capable of fine tuning at all levels of the immune response.

miRNA is involved in the development and differentiation of immune cells

miRNAs are spatially expressed in tissue-specific miRNAs that may be associated with histiocytosis and can play a physiological role similar to tissue-specific transcription factors. In 2004, Chen[4] reported that miRNAs may be associated with immune cell differentiation. It is found that mir-142a, mir-181a and mir-223 are expressed in immune cells, miR-181a is expressed in B lymphocytes, miR-223 is expressed in bone marrow cells, whereas miR-142a was expressed with B lymphocytes and bone marrow cells. This initial finding suggests that miRNAs may be involved in the maturation, proliferation, differentiation, and activation of immune cells.

The effect of miRNA on hematopoietic cells

A number of recent reports have investigated the role of miRNAs in mammalian hematopoiesis. MiRNA analysis of hematopoietic cells in mice and humans revealed that not only the expression of miRNAs in hematopoietic and non-hematopoietic cells was different, but the expression of miRNAs in different hematopoietic cells was different[5]. If hematopoietic stem cells were differentiated into different stages of immune cell differentiation, miRNA expression will change accordingly[6,7]. For instances, TNF-[alpha] stimulation of mouse Raw 264. 7 cells can cause miR-125b and miR-155 expression levels change, this change will lead to the corresponding NF-κB transcriptional activity changes. The expression levels of miR-16, miR-142-3p, miR-142-5p, miR-150, miR-15b and let-7f were compared with naïve T cells during antigen-induced CD8 + T lymphocyte differentiation down-regulation of effector T cells. Although most of these miRNA functions are not known, some have been confirmed the growth and function of lymphocytes play an important role[8].

Effects of miRNA on bone marrow cells

MiR-155 plays an important role in the proliferation and differentiation of bone marrow cells. It has been shown that miR-155[9] is elevated in patients with acute myeloid leukemia (AML) and miR-155 can inhibit the expression of related genes in hematopoietic system diseases. Down-regulation of some transcription factors can regulate the role of miR-155 in hematopoietic development such as CuII, Arntl, Picalm, Jarid2, Csflr, HIF1a.

Fontana and other human umbilical cord blood CD34 hematopoietic progenitor cells found that mir-17-29 reduction can also lead to acute myeloid leukemia-1 (AML-1), the hematopoietic core binding factor (CBF) increased in which CBF can promote bone marrow cell differentiation related genes. It is speculated that miRNAs may have far-reaching value in the diagnosis and treatment of human hematopoietic diseases. Johnnidis[10] and other tests found that mir-223 knockout mice after LPS stimulation, neutrophils increased and lung Spontaneous inflammation. Further studies have found that mir-223 by down-regulation of transcription factor Mef-2c and then on the proliferation and differentiation of neutrophils play a regulatory role[11]

Effects of miRNA on T lymphocytes

Recent studies have found that miRNAs are involved in antigen-induced T cell differentiation. The level of miR-150 expression was significantly increased in the process of T cell maturation but the expression level of miR-150 was decreased rapidly after further differentiation into Th1 and Th2 subgroups. In contrast, miR-146 expression levels increased in Th1 cell subsets and decreased in Th2 cell subsets[13]. Li[14] and other miR-181a study

found that the expression level of T lymphocytes with the sensitivity of the antigen is consistent. Neilson et al.[15] T lymphocyte development process in the various stages of small RNA sequences, including DN1, DN3, DN4, DP, CD4 + and CD8 + T lymphocytes were found to be highly expressed in CD4 + CD8 + DP stage compared with DN or mature CD4 + T lymphocytes and CD8 + T lymphocytes. MiR-181a can promote the affinity of mature T cells to antigens and found that decreased levels of miR-181a expression in immature T cells can inhibit the affinity of T cells to antigens. In short, miR-181a had a higher level of expression in the early stage of T-cell differentiation, whereas the level of miR-181a was significantly lower in the double-positive and later stages. This indicates that miR-181a plays an important role in positive selection and negative selection. It is known that the target molecules of R-181a are various phosphatases such as SHP2, PTPN22, DUSP5 and DUSP6, so miR-181a can affect the signal of TCR. Therefore, miR-181a can reduce the level of TCR activation by adjusting the expression level of T-cell surface inhibitory co-stimulatory molecules and down-regulating the levels of various phosphatases that negatively regulate TCR signaling pathway.

Effects of miRNA on B lymphocytes

It has been reported that miR-150 expression is significantly up-regulated in mature B cells from spleen-derived cells, whereas the same phenomenon is not seen in bone marrow-derived pro-B cells. Early development of mi R-150 transgenic mice B cell development was destroyed, while in miR-150 deletion of transgenic mice B lymphocytes were highly expressed. Studies have found that miR-150 abnormal expression through the target gene c-Myb to prevent pro-B cells into pre-B cells[16]. Neilson[17] and other studies have found that miRNA-181A also plays a positive role in B cell differentiation. MiR-181a is preferentially expressed in thymus, low expression in undifferentiated progenitor cells and highly expressed in differentiated B lymphocytes. In vitro, hematopoietic progenitor cells ectopic overexpression of miR-181a, even without the effect of T cells induced, B lymphocyte number also increased by 2 times. This indicates that miR-181a is a positive regulator of B lymphocyte specificity in the bone marrow of mice[18]. These indicate that miR-181a plays an important role in the differentiation of B lymphocytes.

Regulation of miRNA on immune cell signal transduction

miRNA and the relationship between intrinsic immune response

Intrinsic immune response in the body of non-specific anti-infective immune process is of great significance and it is the body resistance to pathogens of the first line of defense. Many miRNAs are thought to be associated with the regulation of innate immune responses. The recognition of 'self' and 'non-self' receptors is known as pattern recognition-related receptor (PRR) which is also known as pathogen-associated molecular patterns (PAMP). The body through the identification of PAMP to start the inherent immune defense to prevent the invasion of pathogens or timely removal of invasive pathogens to prevent its further spread and can mediate the follow-up organ adaptive immune response. Taganov et al.[19] stimulated the human monocyte cell line THP-1 with LPS and detected the expression of 200 mature miRNAs by chip technique and found that miR-132, miR-146 and miR-155 levels were elevated. There are two different miR-146 subtypes, miR-146a and miR-146b, which can bind to the same target gene. However, the results of LPS stimulation showed that although both subtypes were induced by LPS, both TNF-α and IL-1β could induce miR-146 expression, but only miR-146a production was dependent on activation of NF2-κB. In addition, studies have shown that[20], toll-like receptor (TLR) pathway involved in the activation of miR-146a activation, TLR2, TLR4 and TLR5 ligands can significantly stimulate miR-146 expression upregulation. It has been demonstrated that TRAF6 and IRAK1 are direct target molecules of miR-146. MiRNA-146 can reduce the expression of IRAK1 and TRAF6 in two important components of TLR pathway and thus regulate the immune signal transduction. This suggests that miR-146 can be used as a potential drug target for the intervention of systemic disorders such as septic shock, or local damage such as rheumatoid arthritis due to an excessively active immune response.

Relationship between miRNA and adaptive immune response

Adaptive immunity is a highly specific defense mechanism for the development of the immune system in the evolutionary process for specific antigenic substances, including T cell-based cellular immunity and B cell-based humoral immunity. Protein recognition and antigen presentation of monocytes and dendritic cells are an important

component of adaptive immunity. Rodriguez and other studies have found that macrophages and dendritic cells by TLR ligand stimulation, through the NF-KB and JNK pathway, induced miR-155 production, miR-155 deletion of dendritic cells cannot play the antigen delivery and co-stimulatory effect cannot induce effector T cell activation, indicating that mir-155 has an important role in TLR signaling pathway. This regulatory pathway may be a positive regulator of TLR signaling pathway by inhibiting PUI, indirectly reducing the expression of DC-SIGN and further reducing its ability to bind to pathogens. MiR-155 has a positive regulatory effect on TLR signaling pathway.

The relationship between miRNA and immune disease

MiRNAs are not only associated with normal immune responses, but also related to abnormal immune responses such as inflammation and autoimmune diseases. Recently, many studies have revealed that miRNAs play an important role in immune system diseases such as psoriasis and hereditary allergic eczema skin miRNA expression profiles Healthy and noninflammatory skin miRNA expression is very different, there is also a difference between the two. (MiR-203, miR-146 and miR-125b) have been shown to have differences in miRNA expression between psoriasis and atopic eczema in different levels of inflammation such as Sonkoly[21]. These mirRNA are inflammatory response and cytokine signaling regulation. Psoriasis-specific miRNAs: miR-203, miR-146a, miR-203 target molecule cytokine signal transduction factor-3 (SOCS-3), whereas miR-146 direct targets TRAF6 and IRAK1 are TNF- Signal pathway regulators, and TNF-α signaling pathways have been shown to be an important pathway in the pathogenesis of psoriasis[22]. MiR-146a can reduce the release of inflammatory factors by regulating TLR / IL-1β signaling pathway TRAF6 and IRAK1[23]. This suggests that miR-146 can be used as a potential drug target for the intervention of inflammatory diseases. MiR-203 can target the translation of cytokine signaling 3 (SOCS-3)[24,25]. The expression of SOCS-3 was inhibited in the skin of patients with psoriasis and was consistent with the high expression of miR-203. SOCS-3 is a negative regulator of IL-6 and IFN-γ-induced signaling pathways. SOCS-3 deficiency causes IL-6-induced activity of STAT3 to persist. Therefore, miR-203 inhibits SOCS-3 to increase skin inflammatory response or prolonged response time. Overexpression or downregulation of miRNA and the pathogenesis of inflammatory diseases are closely related. In addition to psoriasis and hereditary allergic eczema, miRNAs are associated with other inflammatory or autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

RA is an autoimmune disease characterized by arthritis associated with articular cartilage and bone destruction. Stanczyk[26] and other studies found that compared with the OA control group, RA patients with synovial fibroblasts miR-155, mir-146 expression increased and mir-155 in RA synovial tissue expression was significantly higher than OA Synovial tissue and speculated that MMP-13 may be a potential target gene for mir-155, indicating that miR-155 may have a modulatory effect on bone destruction in RA patients. Nakasa[27] and other normal and OA patients with synovial tissue study found that miR-146a in RA patients with synovial tissue overexpression. Through in situ hybridization studies have found that miR-146a is mainly expressed with RA synovial CD68 macrophages. Murata[28] found that plasma levels of miR-16 in RA patients were closely related to DAS28, and the level of mir-16 in synovial fluid was significantly higher than that in OA and RA plasma levels. In addition, the expression of miR-146a in PBMCs could enhance the function of T h l cells, indicating that miR-146a may affect the development of RA disease through TNF-a and other inflammatory factors.

SLE is an autoimmune-mediated, diffuse connective tissue disease characterized by acute inflammation. In 2007, Dai et al.[30] found that the expression of multiple miRNAs (mir-196a and mir-17-5p) in SLE PBMCs was down-regulated compared with normal PBMCs in 23 SLE and 10 healthy volunteers, While the expression of 9 miRNAs increased (mir-189 and mir-61). Zhou et al.[31] studied the SLCpDC type I interferon. It was found that miR-155 promoted / inhibited the production of interferon by targeting IRAKM or TAB2, indicating that synergistic effect was achieved at different stages of pDC activation and was helpful for SLE disease Provide treatment direction.

Conclusion

In conclusion, miRNAs are involved in multiple aspects of the immune response. MiRNAs regulate the immune response and inflammatory response in a large, networked manner. A single miRNA can have multiple regulatory functions at the same time. And each target gene can be regulated by multiple miRNAs. Therefore, the miRNA on the physiological function of the regulatory role is very complex, with the miRNA research to further deepen, help us from the source to understand some of the autoimmune

disease etiology and morbidity. Mechanism for clinicians to fundamentally prevent and control these diseases to provide a new entry point.

References

1. Lee RC, Fein baum RL, Ambros V. The elegans heterochronic gene lin-14 encodes small RNAs with antisense complementarity to lin- 14 [J]. Cell, 1993, 75 (5): 8432854.
2. Reinhart BJ, Slack FJ, Basson M, et al. 21 nucleotide let-7 RNA regulates developmental timing in Caenorhabditis elegaas [J]. Nature, 2000, 403 (6772): 901-906.
3. Suarez Y, Fernandez-Hemando C, Poher J S, et al. Dicer dependent microRNAs regulate gene expression and functions in human endothelial cells [J]. Circ Res, 2007,100 (8): 1164-1173
4. Chen CZ, Li Lodish HF, et al. MicroRNAs modulate hematopoieticlineage differentiation [J]. Science, 2004, 303: 83-86.
5. Wu L, Fan J, Belasco JG. MicroRNAs direct rapid deadenylation of mRNA [J]. ProcNatlAcad SciUSA, 2006, 103 (11): 4034-4039.
6. Felli N, Fontana L, Pelosi E, et al. Micro-RNAs 221 and 222 inhibit normal erythropoiesis and erythroleukemic cell growth via kit receptor down-modulation [J] Proc Natl Acad Sci USA, 2005, 102 (50) : 18081-18086.
7. Chen CZ, Li L, Lodish HF, et al. MicroRNAs modulate hematopoietic lineage differentiation [J]. Science, 2004, 303 (5654): 83-86.
8. Xue Qian, Yang Angang. Progress of miRNAs in the immune system [J]. Journal of Cellular and Molecular Immunology, 2010,26 (1): 223-225.
9. Monticelli S, Ansel KM, Xiao C, et al. MicroRNA profiling of the murine hematopoietic system [J]. Genome Biol, 2005, 6 (8): R71
10. Johnnidis JB, Harris M H, Wheeler R T, et al. Regulation of progenitor cell proliferation and granulocyte function by microRNA-223 [J]. Nature, 2010, 451: 1125-1129
11. Lian Yanling, He Dongyi. MicroRNA on the immune system research progress [J] .Guangdong Medical Journal, 2011,06 (12): 1132-1136
12. Wu H, Neilson JR, Kumar P, et al. MiRNA profiling of native, effector and memory CD8 T cells [J]. PLoS ONE, 2009, (2): 1018-1020
13. Monticelli S, Ansel KM, Xiao C, et al. MicroRNA profiling of the murine hematopoietic system [J]. Genome Biol, 2008,6 (8): R71
14. Li QJ, Chau J, Ebert PJ, et al. MiR-181a is an intrinsic modulator of T cell sensitivity and selection [J]. Cell, 2009,129 (1): 147-161
15. Hung PS, Chen FC, Kuang SH, et al. MiR-181a induces differentiation of periodontal ligament cells [J], J Dent Res, 2010, 89: 252-257
16. Xiao C, Calado DP, Galler G, et al. Mir-150 controls B cell differentiation by targeting the transcription factor c-Myb [J]. Cell, 2007, 131: 146-159
17. Neilson JR, Zheng CX, Burge C B, et al. Dynamic regulation of miRNA expression in ordered stages of cellular development [J]. Genes Dev, 2007,21 (5): 578-589
18. Shivdasani RA. MicroRNAs regulators of gene expression and cell differentiation [J]. Blood 2006,108 (12): 3646-3653
19. Taganov KD, Boldin MP, Chang KJ, et al. NF-kB-dependent induction of microRNA mir146, an inhibitor targeted to signaling proteins of innate immune responses [J]. Proc Natl Acad Sci USA, 2006,103 (33): 12481-12486
20. Wu H, Neilson JR, Kumar P, et al. MiRNA profiling of naïve effector and memory CD8 T cells [J]. PLoS ONE, 2007,2: el020
21. Sonkoly E, Pivarcsi A. Advances in microRNAs: implication for immunity and inflammatory diseases [J]. Cell Mol Med, 2009, 13 (1): 24-38
22. Gunter Maubach, Michelle ChinChia Lim, Jinmiao Chen, Henry Yang, Lang Zhuo. MiRNA studies in vitro and internally activated hepatic stellate cells [J]. World J Gastroenterol, 2011, 17 (22): 2748-2773
23. Taganov KD, Boldin MP, Chang KJ, et al. NF-kB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses [J]. Proc Natl Acad Sci USA, 2006, 33): 12481-12486
24. Ralfkiaer U, Hagedorn PH, Bangsgaard N, et al. Diagnostic microRNA profiling in cutaneous T-cell lymphoma (CTCL) [J]. Blood, 2011, 118 (22): 5891-900
25. Joyce CE, Zhou X, Xia J, Ryan C, Thrash B, Menter A, Zhang W, Bowcock AM. Deep sequencing of small RNAs from human skin variation major alterations in the psoriasis miRNAome [J]. Hum Mol Genet, 2011, 20 (20): 4025-40
26. Stanczyk J, Pedrioli DM, Brentano F, et al. Altered expression of microRNA in synovial fibroblasts and synovial tissue in rheumatoid arthritis [J]. Arthritis Rheum, 2008, 58: 1001-1009
27. Nakasa T, Miyaki S, Okubo A, et al. Expression of microRNA-146 in rheumatoid arthritis synovial tissue [J]. Arthritis Rheum, 2008, 58: 1284-1292
28. Murata K, Yoshitomi H, Tanida S, et al. Plasma and synovial fluid microRNAs as potential biomarkers of rheumatoid arthritis osteoarthritis [J] .Arthritis Res Ther, 2010,12 (3): R86.
29. Guo M, Mao X, Ji Q, et al. MiR-146a in PBMCs modulates Th1 function in patients with acute coronary syndrome [J]. Immunol Cell Biol, 2010,88 (5): 555-564
30. Dai Y, Huang YS, Tang M, et al. Microarray analysis of microRNA expression in peripheral blood cells of systemic lupus erythematosus patients [J]. Lupus, 2007, 16: 939-946
31. Zhou H, Huang X, Cui H, et al. MiR-155 and its star-form partner miR-155 cooperatively regulated type I interferon production by human plasmacytoid dendritic cells [J]. Blood, 2010,116 (26) : 5885-5894