Rheumatol Int (2013) 33:557–560
DOI 10.1007/s00296-012-2559-1

REVIEW ARTICLE

MicroRNA-155 as a therapeutic target for inflammatory diseases

Naghmana Kanwal · Peter John · Attya Bhatti

Received: 9 April 2012 / Accepted: 21 October 2012 / Published online: 14 December 2012

Abstract MicroRNAs are short non-coding molecules expressed in different tissues and regulate the transcription of different genes. They are highly specific in their action. Upregulation or downregulation of specific microRNAs has been observed during different diseases like cancers, embryogenesis, organogenesis, apoptosis and arthritis. They are also known to be involved in autoimmune diseases. MicroRNAs are also found to be stable and easy to validate. Differential expression of microRNA-155 has been studied by different groups in inflammatory diseases including arthritis along with other miRNAs. This suggests that it can be used as a potential biomarker or therapeutic in the autoimmune diseases, especially rheumatoid arthritis. Experimental studies are needed to explore their role as biomarker or therapeutic.

Keywords Rheumatoid arthritis · MicroRNAs · Diagnostic marker · Pathogenesis

MicroRNA-155 in inflammatory diseases

MicroRNAs are a class of short, non-coding, evolutionary conserved RNA molecules that can modulate the transcription of other genes [1]. miRNAs are highly conserved among mammals [2]. In silico studies and gene mapping suggest that miRNAs regulate 30 % genes of human genome. miRNAs are highly specific for every cell type and developmental stage [3]. They control the basic biological functions, such as apoptosis, organogenesis, proliferation, embryogenesis, antiviral response and the stress [4]. MicroRNA abnormal levels are lined with cancers in humans [5], haematopoiesis [6], metabolism [7] and cardiac hypertrophy [8]. miRNAs are also found to modulate T-cell receptor sensitivity and T-cell selection [9] as well as Treg cell development [10], which could suggest the involvement of miRNA in the autoimmunity development. They act by binding to the 3′UTR and act as post-transcription modulators.

miRNA-155 is encoded within B-cell integration (Bic) gene located on chromosome 21. Its expression was observed during many autoimmune diseases like multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus. Moreover, it serves as potential regulator of immune cells which target specific miRNAs. Since immune cells play important role in human autoimmune disease pathogenesis, miR-155 might be a good therapeutic target [12].

miRNA-155 individually controls autoimmune destructive arthritis in two ways: it inhibits the generation of self-reactive T- and B-cell responses and controls the development of local bone destruction. So, these types of interactions make it a novel target for the treatment of RA [13]. Generally, miRNA-155 together with miR-146 is induced by proinflammatory stimuli like tumour necrosis factor α (TNFα), Toll-like receptors (TLRs), LPS, pam3CSK4 and interleukin 1 by the activation of transcription factors like MAP kinases such as JNK and NF-kB. miRNA-155 is also known to regulate the Th1 cells and positively regulate the TNFα mRNA. It was also

N. Kanwal · P. John (✉) · A. Bhatti
Atta-ur-Rahman School of Applied Biosciences (ASAB), National University of Sciences and Technology (NUST), Sector H-12, Islamabad, Pakistan
e-mail: pjohn72@hotmail.com

N. Kanwal
e-mail: naghmanakanwal@gmail.com

A. Bhatti
e-mail: attyabhatti@gmail.com

studied based on genetically modified mice that miR-155 is a key regulator of B-cell maturation by controlling the AID-mediated myc-IgH translocation process.

miRNA-155 positively regulates the production of TNFα, which is the first cytokine involved in the pathogenesis of inflammatory diseases. This makes it a potential therapeutic target for treating such diseases [14].

Positive regulation of TNFα and increased levels of TNFα by miRNA-155 are associated with RASF; thus, it may be concluded that increased levels of this miRNA may lead towards disease pathogenesis [15]. miRNA-155 is also shown to involve in a large number of biological activities. It was initially discovered to be involved in cancers and neoplastic diseases [16] in modulation of haematopoiesis and in immune system [17–19]. miRNA-155 has also been shown to be induced in colons and activated CD4+ T cells [20].

miRNA-155 has a key role in autoimmunity. In the haematopoietic compartment, it promotes the development of inflammatory T cells. It has also been shown to be involved in the cytokine production (IL-6, IL-17 and IL-22) and local bone destruction [21]. Experiments with knockout mice demonstrate the absence of miRNA-155 results in the impaired memory response, which is the indication that it might regulate generation of memory B-cells [22].

miRNA-155 regulates several immune responses. Activated B and T cells and activated macrophages showed its higher expression. Its expression is also associated with B-cell malignancies. Together, this information suggests its role in normal functioning of B and T lymphocytes and dendritic cells [23].

In a study, it was observed that during experimental autoimmune encephalomyelitis (EAE), miRNA-155 expression was upregulated in CD4+ T cells. Furthermore, miRNA-155 knockout mice showed less inflammation in CNS and reduced severity of disease, which may be due to the decrease in Th1 and Th17 responses in the CNS and peripheral lymphoid organs. The scientists confer from these experiments miRNA as a new target for therapeutic intervention in multiple sclerosis [25].

Generally, miRNAs mediate disease pathology via coordinated regulation of molecular effectors pathways. Unravelling miR disease-related activities will facilitate future therapeutic interventions.

miRNAs are found in dried biological fluids such as semen, saliva, vaginal secretions and menstrual blood. It is also found that in the plasma, miRNA is protected from endogenous RNase activity and is stable enough that it does not degrade at room temperature for 24 h and can be stored at −20 °C for up to 7 days, so it can serve as a biomarker [29].

Multiple tests are used to diagnose the autoimmune diseases, such as CT scan, X-ray, ESR, white blood cell count, C-reactive protein, antinuclear antibodies (ANA) and serum rheumatoid factor in case of RA. But miRNAs can be used as biomarker due to their stability and expression in multiple tissues, and the fact that they can be easily targeted. Furthermore, miRNA-based gene therapies can also be used to treat autoimmune diseases. Still further studies are needed to further explore their role as therapeutics in future.

MicroRNA-155 in rheumatoid arthritis

MicroRNAs (miRNAs) regulate the immunoinflammatory response. So, inflammation may alter miRNA levels in joints of RA patients. During inflammation, upregulated TLRs may involve in miRNA pathway. RT-PCR and microarray analysis showed comparable expression levels of 12 miRNAs including hsa-miR-155 [11].

Microarray analysis of TNF-treated RASFs showed significant upregulation of miRNA-155 as compared to patients with osteoarthritis (OA). It was also analysed that miR-155 expression can be induced by TNF, interleukin-1, lipopolysaccharide, poly (I–C) and bacterial lipoprotein. The expression of miR-155 in RA synovial tissue was higher than in OA synovial tissue.

It has been studied that if expression of miRNA-155 is higher in synovial fibroblasts derived from patients with RA (RASFs), then it can repress the expression of matrix metalloproteinase 3 (MMP-3) and MMP-1 via TLR ligands and cytokines that may lead to tissue destruction in joints. In RA patients, higher miRNA-155 levels were observed in synovial fluid as compared to monocytes [3]. Moreover, another study showed that RA PBMCs exhibit much higher expression of miR-155 as compared to normal individual PBMCs [24]. It could suggest that this microRNA can have therapeutic potential for the treatment of joint destruction in RA.

In arthritis synovial fluid macrophages, it was observed that with the increased expression of miRNA-155, the expression of Src homology 2-containing inositol phosphatase-1 (SHIP-1) was downregulated, which is an inhibitor of inflammation, and the expression of pro-inflammatory cytokines like IL-6 (which is an inducer for the development of the autoreactive Th17 cells) and TNF-α (mediator of chronic inflammation) was upregulated. Both IL-6 and TNF are validated clinical therapeutic targets in RA. Moreover, it was also observed that miR-155 knockout mice showed reduced levels of TNF-α and other chemokines and was resistant to collagen-induced arthritis, so it can be a good therapeutic target in case of arthritis. But further studies are required to explore the involvement of these miRNAs in different cellular pathways before exploring their roles as therapeutics.

Iain McInnes and colleagues report that miRNA-155 has a critical role in antigen-dependent arthritis and cytokine-driven joint inflammation. So, aberrant cytokine expression in RA may be blocked by targeting miRNA-155 [26]. In vitro and mouse studies suggest antagonizing miR-155 could help treat RA [27].

Researchers from the University of Florida have recently found out that specific miRNA upregulation in the blood mononuclear cells of patients can be used as potential marker for RA diagnosis and therapy response. They have measured the upregulation of different miRNAs in RA patients and healthy controls. Expression of miR-146a, miR-155, miR-132 and miR-16 was 1.8- to 2.6-fold higher in RA patients as compared to healthy controls [28]. Joanna Stanczyk in 2008 [3] specifically showed the upregulation of miR-155 in the synovial fibroblasts (RASFs) and synovial tissues of RA patients by real-time PCR. So, these types of studies suggest that it is a novel target for the treatment of RA [13].

Conclusions

Several studies showed the differential expression of microRNA-155 in the inflammatory diseases. It has also been shown that microRNA-155 was upregulated in the activated macrophages and activated B and T cells. Variable expression of microRNA-155 also observed in various experiments in RA patients suggests that it can be used in the diagnosis and treatment of inflammatory diseases including rheumatoid arthritis.

References

1. Bartel DP (2004) MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 116(2):281–297
2. Chen K, Rajewsky N (2007) The evolution of gene regulation by transcription factors and microRNAs. Nat Rev Genet 8:93–103
3. Stanczyk J, Pedrioli DM, Brentano F, Sanchez-Pernaute O, Kolling C, Gay RE, Detmar M, Gay S, Kyburz D (2008) Altered expression of microRNA in synovial fibroblasts and synovial tissue in rheumatoid arthritis. Arthritis Rheum 58(4):1001–1009
4. Kloosterman WP, Plasterk RH (2006) The diverse functions of microRNAs in animal development and disease. Dev Cell 11(4):441–450
5. Calin GA, Croce CM (2006) MicroRNA signatures in human cancers. Nat Rev Cancer 6:857–866
6. Chen CZ, Lodish HF (2005) MicroRNAs as regulators of mammalian hematopoiesis. Semin Immunol 17(2):155–165
7. Krützfeldt J, Stoffel M (2006) MicroRNAs: a new class of regulatory genes affecting metabolism. Cell Metab 4(1):9–12
8. Carè A, Catalucci D, Felicetti F, Bonci D, Addario A, Gallo P, Bang ML, Segnalini P, Gu Y, Dalton ND, Elia L, Latronico MV, Høydal M, Autore C, Russo MA, Dorn GW 2nd, Ellingsen O, Ruiz-Lozano P, Peterson KL, Croce CM, Peschle C, Condorelli G (2007) MicroRNA-133 controls cardiac hypertrophy. Nat Med 13(5):613–618
9. Li QJ, Chau J, Ebert PJ, Sylvester G, Min H, Liu G, Braich R, Manoharan M, Soutschek J, Skare P, Klein LO, Davis MM, Chen CZ (2007) MiR-181a is an intrinsic modulator of T cell sensitivity and selection. Cell 129(1):147–161
10. Cobb BS, Hertweck A, Smith J, O'Connor E, Graf D, Cook T, Smale ST, Sakaguchi S, Livesey FJ, Fisher AG, Merkenschlager M (2006) A role for Dicer in immune regulation. J Exp Med 203(11):2519–2527
11. Xie YF, Shu R, Jiang SY, Liu DL, Zhang XL (2011) Comparison of microRNA profiles of human periodontal diseased and healthy gingival tissues. Int J Oral Sci 3:125–134
12. 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
13. Blüml S, Bonelli M, Niederreiter B, Puchner A, Mayr G, Hayer S, Koenders MI, van den Berg WB, Smolen J, Redlich K (2011) Essential role of microRNA-155 in the pathogenesis of autoimmune arthritis in mice. Arthritis Rheum 63(5):1281–1288
14. Luo X, Tsai LM, Shen N, Yu D (2010) Evidence for microRNA-mediated regulation in rheumatic diseases. Ann Rheum Dis 69(Suppl I):i30–i36
15. Sheedy FJ, O'Neill LA (2008) Adding fuel to fire: microRNAs as a new class of mediators of inflammation. Ann Rheum Dis 67:70–73
16. Tam W, Dahlberg JE (2006) MiR-155/BIC as an oncogenic microRNA. Genes Chromosom Cancer 45(2):211–212
17. Georgantas RW 3rd, Hildreth R, Morisot S, Alder J, Liu CG, Heimfeld S, Calin GA, Croce CM, Civin CI (2007) CD34+ hematopoietic stem-progenitor cell microRNA expression and function: a circuit diagram of differentiation control. Proc Natl Acad Sci 104(8):2750–2755
18. Rodriguez A, Vigorito E, Clare S, Warren MV, Couttet P, Soond DR, van Dongen S, Grocock RJ, Das PP, Miska EA, Vetrie D, Okkenhaug K, Enright AJ, Dougan G, Turner M, Bradley A (2007) Requirement of bic/microRNA-155 for normal immune function. Science 316(5824):608–611
19. Thai TH, Calado DP, Casola S, Ansel KM, Xiao C, Xue Y, Murphy A, Frendewey D, Valenzuela D, Kutok JL, Schmidt-Supprian M, Rajewsky N, Yancopoulos G, Rao A, Rajewsky K (2007) Regulation of the germinal center response by microRNA-155. Science 316(5824):604–608
20. Chen DF, Gong BD, Xie Q, Ben QW, Liu J, Yuan YZ (2010) MicroRNA155 is induced in activated CD4(+) T cells of TNBS-induced colitis in mice. World J Gastroenterol 16(7):854–861
21. Ceribelli A, Yao B, Dominguez-Gutierrez PR, Nahid MA, Satoh M, Chan EK (2011) MicroRNAs in systemic rheumatic diseases. Arthritis Res Ther 13(4):229
22. Tili E, Michaille J, Costinean S, Croce CM (2008) MicroRNAs, the immune system and rheumatic disease. Nat Clin Pract Rheumatol 4(10):534–541
23. Galeazzi M, Balistreri E, Giannitti C, Sebastiani GD (2012) MicroRNA in autoimmunity and autoimmune diseases. Reumatismo 64(1):7–17
24. Long L, Shi J, Li LZ (2009) Altered expression of mir-155 and mir-181a in periphery blood mononuclear cells of rheumatoid arthritis. Arthritis Rheum 60:1647
25. Murugaiyan G, Beynon V, Mittal A, Joller N, Weiner HL (2011) MicroRNA-155 ameliorates experimental autoimmune encephalomyelitis. J Immunol 187(5):2213–2221
26. Kurowska-Stolarska M, Alivernini S, Ballantine LE, Asquith DL, Millar NL, Gilchrist DS, Reilly J, Ierna M, Fraser AR, Stolarski B, McSharry C, Hueber AJ, Baxter D, Hunter J, Gay S, Liew FY, McInnes IB (2011) MicroRNA-155 as a proinflammatory regulator in clinical and experimental arthritis. Proc Natl acad Sci USA 108(27):11193–11198

27. Chang S et al (2011) MicroRNA-155 (miR-155). SciBX 4(39):1085
28. MicroRNAs May Aid in the Diagnosis of Rheumatoid Arthritis (2008) Medi news. Available from: http://www.medinewsdirect.com/?p=579 (cited 16 Nov 2011)
29. Murata K, Yoshitomi H, Tanida S, Ishikawa M, Nishitani K, Ito H, Nakamura T (2010) Plasma and synovial fluid microRNAs as potential biomarkers of rheumatoid arthritis and osteoarthritis. Arthritis Res Ther 12(3):R86