GAVIN PUBLISHERS

Journal of Vaccines, Immunology and Immunopathology

Short Communication

Sharma VK, et al. J Vaccines Immunol: JVII-123.
DOI: 10.29011/2575-789X. 000023

Upregulated Expression of miR-301a Stimulates Inflammation in Inflammatory Bowel Disease: Recent update

Varun Kumar Sharma[1*], Saba1, Mohit Kumar[1], A. Geetha Bhavani[2], Jayanand Manjhi[1,2]

[1]Department of Biotechnology & Microbiology, School of Sciences, Noida International University-NIU, Uttar Pradesh, India

[2]Department of Chemistry, School of Sciences, Noida International University-NIU, Uttar Pradesh, India

[*]**Corresponding author:** Varun Kumar Sharma, Department of Biotechnology and Microbiology, School of Sciences, Noida International University-NIU, Sector-17 A, Yamuna Expressway Gautam Budh Nagar -201308, Uttar Pradesh, India. Tel: +911204862200; Email: varun1.sharma@niu.ac.in

Citation: Sharma VK, Saba, Kumar M, Bhavani AG, Manjhi J (2018) Upregulated Expression of miR-301a Stimulates Inflammation in Inflammatory Bowel Disease: Recent update. J Vaccines Immunol: JVII-123. DOI: 10.29011/2575-789X. 000023

Received Date: 16 December, 2017; **Accepted Date:** 05 January, 2018; **Published Date:** 12 January, 2018

Keywords: Autoimmunity; Crohn's Disease; IL-17; Inflammatory Bowel Disease; miR-301a; Pro-Inflammatory Cytokines; T Cells; TNF- α; Ulcerative Colitis

Commentary

CD4 T cells act as a key regulator of adaptive immunity and critically involves in the function of the immune system. CD4 T cells interact with various immune cells and suppress a broad range of pathogenic conditions via coordinating immune responses. CD4 T cells also play a major role to maintain immunogenic tolerance to avoid undesired immune response to self antigens. The activation and differentiation of naïve CD4+ T cells into distinct subsets such as T_H1, T_H2, T_H17 and regulatory T cells (Tregs) are accomplished by various signals obtained from antigen-loaded MHC class II molecules, co-stimulatory molecules and polarizing cytokines. Diminished in number or defective in nature (phenotype) of CD4 T cells linked with various autoimmune diseases and pathological condition [1,2]. The autoimmunity is a multi defective immune cell process which is mainly associated with failure in central immune-tolerance with amendment of self-antigen expression levels. Recent studies suggest the development of autoimmune diseases such as Crohn's Disease (CD), Ulcerative Colitis (UC), Inflammatory Bowel Disease (IBD), Systemic Lupus Erythematosus (SLE), Multiple Sclerosis (MS) and Rheumatoid Arthritis (RA) are linked with CD4 T subset cells [1-4]. Additionally, dysregulated immune system in autoimmune diseases are linked with various pro-inflammatory cytokines, which are mediated by CD4 T subset cells. For instance CD patients has been remarkably noticed with T_H1 cell-mediated disease with high levels of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ). Another example, UC patients have been reported to be linked with T_H2 cells. Additionally, recent evidence suggests that various autoimmune diseases, including IBD have been associated with T_H17 cells [4,5].

T_H17 cells are a distinct lineage of CD4 helper T cells, which secrete specific cytokines such as IL-17A, IL-17F, IL-21, GM-CSF and IL-22 and play a critical role in the pathogenesis of several autoimmune and allergic diseases. IL-17A producing T_H17 express the surface IL-23 receptor (IL-23R) and lineage specific transcription factor RORC (RORγt in mice). RORC is key transcription factor play pivotal role in the differentiation T_H17 cells [6, 7]. IL-17 is a pro-inflammatory cytokines and reported to be over expressed in a large set of autoimmune disease. Recent studies suggest that various microRNAs (miR-301a, miR-155 and miR-21) are directly or indirectly involve in T_H17 differentiation and modulate the IL-17 production [4,8-15].

MicroRNAs (miRNAs) are conserved non-coding RNA sequences, approximately 18-25 nucleotides in length. miRNAs are fine tuners which act as negative regulator of the target genes via binding to 3'-untranslated region of mRNAs, leading to mRNA degradation or inhibition of mRNA translation [2]. miRNAs are tiny in size but effectively regulates various cellular and physiological processes and aberrant expression of miRNA has been linked to various pathologies including autoimmune diseases. Recent observations by various research groups determine the role of various miRNAs in the function of the immune system and also provide evidences linked the development of autoimmunity and inflammatory diseases. Additionally, In recent years, significant efforts have been made the association of miRNAs with autoimmune disease, in particular IBD with T_H17 mediated abnormal production pro-inflammatory cytokines. Recent observation published by Liu and colleagues suggests that induced expression of miR-301

promotes T_H17 cell differentiation via suppressing the expression of SNIP1 in inflamed mucosa of IBD patients [4]. Idiopathic IBD is a chronic inflammation of the human digestive tract. CD and UC are the two main clinical type linked with IBD [4-7] (Figure 1).

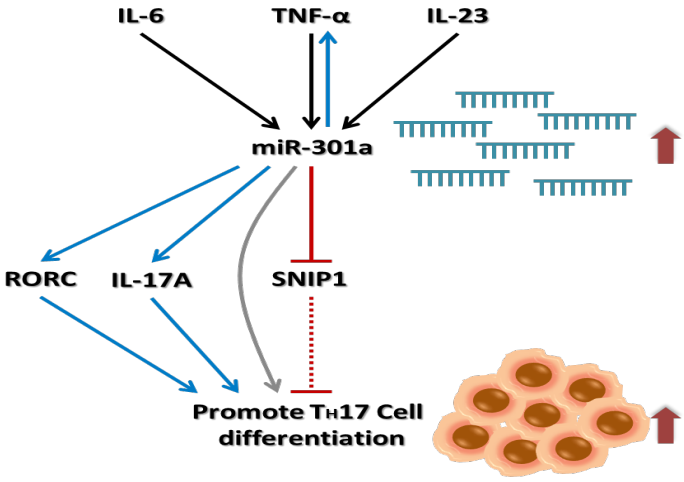

Figure 1: Regulation of miR-301a in Inflammatory Bowl Disease (IBD): Under pathological condition, miRNA regulation modulates. In IBD, expression of miR-301a were upregulated in all patients, which could positively regulated by inflammatory cytokines, such as Interleukin (IL)-6, IL-23 and TNF-α. Upregulated miR-301a promotes T_H17 differentiation via inducing the expression of RORC, IL-17a, and suppressing the expression of SNIP1 (negative regulation of T_H17 differentiation). Interestingly, miR-301a also regulates TNF-α production via positive feed-back loop. In conclusion, miR-301a play as a key regulator which modulates pro-inflammatory cytokine production in IBD.

Chong He et al. first investigated the expression of miR-301 in the inflamed mucosa and PBMC of patients with IBD and observed that miR-301 is over expressed in the inflamed mucosa and PBMC of both patients with CD and patients with UC compared with Healthy Controls (HC). Further, they examined the expression of miR-301 in inflamed and unaffected mucosa from the same patients and identified over expression in inflamed mucosa compared with the unaffected mucosa of the same patients. miR-301 expression is induced in CD4 T-cells compare with other subsets of immune cells in HC. Additionally, they also observed the expression of miR-301 was induced in CD4 T-cells and Intestinal Epithelial Cells (IECs) compare to B cells and Dendritic Cells (DCs) in normal intestinal mucosa patients with colon cancer.

As evidence suggested that various pro-inflammatory cytokines expression such as TNF-α, IL-23 and IL-6 have been induced in mucosa of patients with IBD. The authors next aimed to understand the mechanism by which miR-301 was induced in IBD and identify the effect of cytokine on the miR-301 regulation. For this purpose, they stimulated CD4 T-cells (isolated from HC) using anti-CD3/CD28 in presence of selected cytokines such as TNF-α, IL-17A, IL-23, IL-6, IFN-γ, IL-10 or IL-12. They observed that miR-301 expression was significantly induced in stimulated CD4 T-cells in the presence of IL-23, IL-6 and TNF-α (highest), suggested that miR-301 expression might be mediated by TNF-α. To examine this hypothesis Chong He et al. focused to understand the expression of miR-301 in mucosa of CD patients with pre and post anti-TNF-α mAb (IFX) treatment. They observed miR-301 expression was suppressed with IFX treatment nd results suggested the correlation between miR-301 and TNF-α in patients with active CD.

Previous observation performed by another group suggested that miR-301a could induce T_H17 cell differentiation in EAE [8]. The authors were aimed to address the effect of miR-301 on CD4 T-cell activation isolated from IBD or HC. For this purpose authors were primarily transduced CD4 T-cells with lentivirus-miR-301a or lentivirus-anti-miR-301a and then stimulated with anti-CD3/CD28. They obtained miR-301a conditional upregulation results in enhanced the expression of IL-17a, RORC and TNF-α in stimulated-CD4 T-cell in IBD and HC compare to control, and also observed down-regulated expression of these molecules with suppressed expression of miR-301a using lentivirus-anti-miR-301a. These observations revealed that the expression of miR-301a was positively correlated with IL-17a, RORC and TNF-α. Furthermore, the authors identified the SNIP1 as a putative target of miR-301a which they further validated using relative expression analysis in aforementioned experimental setups and additional method termed as dual-luciferase reporter assays, in *in-vitro*. These observations were further validated in *in-vivo* active patients with IBD (both, CD and UC) as well as clotis mice model. To understand the physiological effect of SNIP1, Authors performed forced suppression in the expression of SNIP1 using Lentivirus-SNIP1 siRNA in stimulated CD4 T-cells and observed that suppressed expression of IL-17a, RORC and TNF-α. Conditional suppression of SNIP1 promotes T_H17 cell differentiation.

To summerise, these observations provide evidence induced expression of miR-301a in IBD facilitates the intestinal mucosal inflammation via promoting the induced expression of IL-17a, RORC and TNF-α. These observations also implicate that elevated expression of miR-301a in IBD regulates T_H17 cell differentiation via suppressing the expression of SNIP1. Conclusive remarks of these observations are revealing that the miRNA-mediated regulation play pivotal role in IBD pathogenesis, and it would be worth to modulate the miR-301a expression and use in the treatment of IBD.

References

1. Zhu J, Yamane H, Paul WE (2010) Differentiation of effector CD4 T cell populations (*). Annu Rev Immunol 28: 445-489.

2. Sharma VK, Kaveri SV, Bayry J (2016) Impaired regulatory T cell function in autoimmune diseases: are microRNAs the culprits? Cell Mol Immunol 13: 135-137.

3. Cader MZ and Kaser A (2013) Recent advances in inflammatory bowel disease: mucosal immune cells in intestinal inflammation. Gut 62: 1653-1664.

4. He C, Shi Y, Wu R, Sun M, Fang L, et al. (2015) miR-301a promotes intestinal mucosal inflammation through induction of IL-17A and TNF-α in IBD. Gut 2015.

5. Yang J, Sundrud MS, Skepner J, Yamagata T (2014) Targeting Th17 cells in autoimmune diseases. Trends Pharmacol Sci 35: 493-500.

6. Maddur MS, Vani J, Hegde P, Lacroix-Desmazes S, Kaveri SV, et al. (2011) Inhibition of differentiation, amplification, and function of human TH17 cells by intravenous immunoglobulin. J Allergy Clin Immunol 127: 823-830.

7. Maddur MS, Miossec P, Kaveri SV, Bayry J (2012) Th17 cells: biology, pathogenesis of autoimmune and inflammatory diseases, and therapeutic strategies. Am J Pathol 181: 8-18.

8. Mycko MP, Cichalewska M, Machlanska A, Cwiklinska H, Mariasiewicz M, et al. (2012) MicroRNA-301a regulation of a T-helper 17 immune response controls autoimmune demyelination. Proc Natl Acad Sci U S A 109: E1248-1257.

9. Wei B and Pei G (2010) MicroRNAs: critical regulators in Th17 cells and players in diseases. Cell Mol Immunol 7: 175-181.

10. Gaffen SL, Jain R, Garg AV, Cua DJ (2014) The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. Nat Rev Immunol 14: 585-600.

11. Tian L, De Hertogh G, Fedeli M, Staats KA, Schonefeldt S, et al. (2012) Loss of T cell microRNA provides systemic protection against autoimmune pathology in mice. J Autoimmun 38: 39-48.

12. Baumjohann D and Ansel KM (2013) MicroRNA-mediated regulation of T helper cell differentiation and plasticity. Nat Rev Immunol 13: 666-678.

13. Ma L, Xue HB, Wang F, Shu CM, Zhang JH (2015) MicroRNA-155 may be involved in the pathogenesis of atopic dermatitis by modulating the differentiation and function of T helper type 17 (Th17) cells. Clin Exp Immunol 181: 142-149.

14. Yi J, Wang D, Niu X, Hu J, Zhou Y, et al. (2015) MicroRNA-155 Deficiency Suppresses Th17 Cell Differentiation and Improves Locomotor Recovery after Spinal Cord Injury. Scand J Immunol 81: 284-290.

15. Murugaiyan G, da Cunha AP, Ajay AK, Joller N, Garo LP, et al. (2015) MicroRNA-21 promotes Th17 differentiation and mediates experimental autoimmune encephalomyelitis. J Clin Invest 125: 1069-1080.