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Review

Integrative computational mRNA–miRNA interaction analyses of the autoimmune-deregulated miRNAs and well-known Th17 differentiation regulators: An attempt to discover new potential miRNAs involved in Th17 differentiation

Mohammad Amin Honardoost [a,1], Reza Naghavian [a,1], Fereshteh Ahmadinejad [b,1], Aref Hosseini [a], Kamran Ghaedi [a,*]

[a] Division of Cellular and Molecular Biology, Department of Biology, Faculty of Sciences, University of Isfahan, Isfahan, Iran
[b] Cellular and Molecular Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

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ABSTRACT

Th17 cells are a lineage of CD4$^+$ T helper cells in immune system which differentiate from naïve CD4$^+$ T cells and have demonstrated to play a critical role in the pathogenesis of different autoimmune disorders. miRNAs are a novel group of non-coding RNAs which participate in post-transcriptional regulation of gene expression mostly by pairing with 3′UTR of their mRNA targets and inhibition of its translation. It has been demonstrated that miRNAs function in various cellular processes such as differentiation, proliferation, and apoptosis. By now, several signaling pathways and their downstream positive and negative regulators involve in Th17 differentiation have been discovered. Several studies have reported the aberrant miRNA expression profile in patients with autoimmune disease called autoimmune-deregulated miRNAs. Here, using integrative miRwalk database which assembles the data gathered from ten different bioinformatics databases designed to predict miRNA-target interaction, we analyzed possible targeting effect of "autoimmune-deregulated miRNAs" on prominent positive and negative regulators of Th17 differentiation. Our resulting mRNA-miRNA network simply nominated several miRNAs with strong possibility which probably may have inducing (miR-27b, miR-27a, miR-30c, miR-1, and miR-141) or inhibitory (miR-20b, miR-93, miR-20a, miR-152, miR-21, and miR-106a) role in Th17 differentiation by targeting negative or positive regulators of Th17 differentiation, respectively.

Contents

Abbreviations: IBD, inflammatory bowel disease; miRNAs, microRNAs; MS, multiple sclerosis; PBMCs, peripheral blood mononuclear cells; PS, prediction score; RA, rheumatoid artists; RAR, retinoic acid receptor; RRMS, relapsing-remitting MS; RXR, retinoid X receptor; SLE, systemic lupus erythematosus; TCR, T-cell receptor; Tfh, T follicular helper; TFs, transcription factors; Th, T helper; UC, ulcerative colitis.

* Corresponding author at: Division of Cellular and Molecular Biology, Department of Biology, Faculty of Sciences, University of Isfahan, Azadi Sq., Hezar Jerib Ave., Postal Code: 81746-73441 Isfahan, Iran.
E-mail addresses: kamranghaedi@yahoo.com, kamranghaedi@sci.ui.ac.ir (K. Ghaedi).
[1] These authors contributed equally to this article.

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1. Introduction

Autoimmune disorders refer to a group of diseases arising due to aberrant immune responses against self-antigens. Like immune responses against foreign antigens, autoimmune responses recruit the same major components of immune system including innate (i.e. macrophage, neutrophils, monocytes) and adaptive immune cells (such as B cells and $CD4^+$/$CD8^+$ T cells). These responses against self-antigens could involve either the whole body or a specific organ resulting in systemic or organ-specific autoimmunity, respectively (Cotsapas and Hafler, 2013; Vyse and Todd, 1996).

T helper 17 (Th17) lineage is a well-known $CD4^+$ T cell lineage which is characterized by secreting inflammatory cytokines such as IL-17A, IL-17F, IL-22, and IL-21 and also expressing lineage-specific transcription factor, RORC. On the other hand, induced-regulatory T (iTreg) lineage is an anti-inflammatory $CD4^+$ T cell lineage which differentiates from the same naïve $CD4^+$ T cells. This lineage participates in regulation of immune responses through suppressing differentiation and function of other effector $CD4^+$ T cells such as Th17 cells. In addition, iTreg cells play a central role in induction of self-antigen tolerance. ITreg cells are characterized by the expression of master transcription factor, FOXP3 and secretion of anti-inflammatory cytokines including IL-10 and TGF-β (Chen et al., 2003; Davidson et al., 2007; Burchill et al., 2008; Yao et al., 2007).

Recently, increasing number of studies have revealed a pathogenic role of Th17 lineage in development or progression of different organ-specific autoimmune diseases including, multiple sclerosis (MS), rheumatoid artists (RA), psoriasis, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), allergy and asthma (Waite and Skokos, 2011). Accordingly, numerous studies have been carried out to shed light on the precise molecular mechanisms and signaling pathways involved in induction of pathogenic Th17 differentiation and to find the best therapeutic targets for the suppression of its differentiation. Furthermore, it is beneficial to find therapeutic targets that induce iTreg differentiation, while suppressing pathogenic Th17 differentiation, since it has been observed that iTreg cells population decreases during pathogenesis of above-mentioned autoimmune diseases (Afzali et al., 2007). Nevertheless, the first step to get to this goal is to attain a precise and comprehensive knowledge of signaling pathways and molecular mechanisms to determine the fate of differentiation to Th17 and/or iTreg lineages.

MicroRNAs are a class of endogenous small (18–22 nucleotide) non-coding RNA which play a crucial role in regulation of various cellular processes such as cell cycle, mitosis, apoptosis, differentiation and so forth (Bartel, 2004). Hence, up/down-regulation of miRNA expression could result in numerous abnormalities and dysfunction of cellular activities (Bartel, 2004; Garzon et al., 2010). Until now, several studies have reported miRNAs up/down-regulation during pathogenesis of different autoimmune diseases. Interestingly, a number of these miRNAs have been accounted for differentiation and pathogenesis of Th17 cells. Although, in recent years many studies have been carried out to decipher the molecular mechanism of Th17 differentiation, little is known about the precise role of miRNAs in differentiation of Th17 cells. Few studies have investigated the possible role of miRNAs in

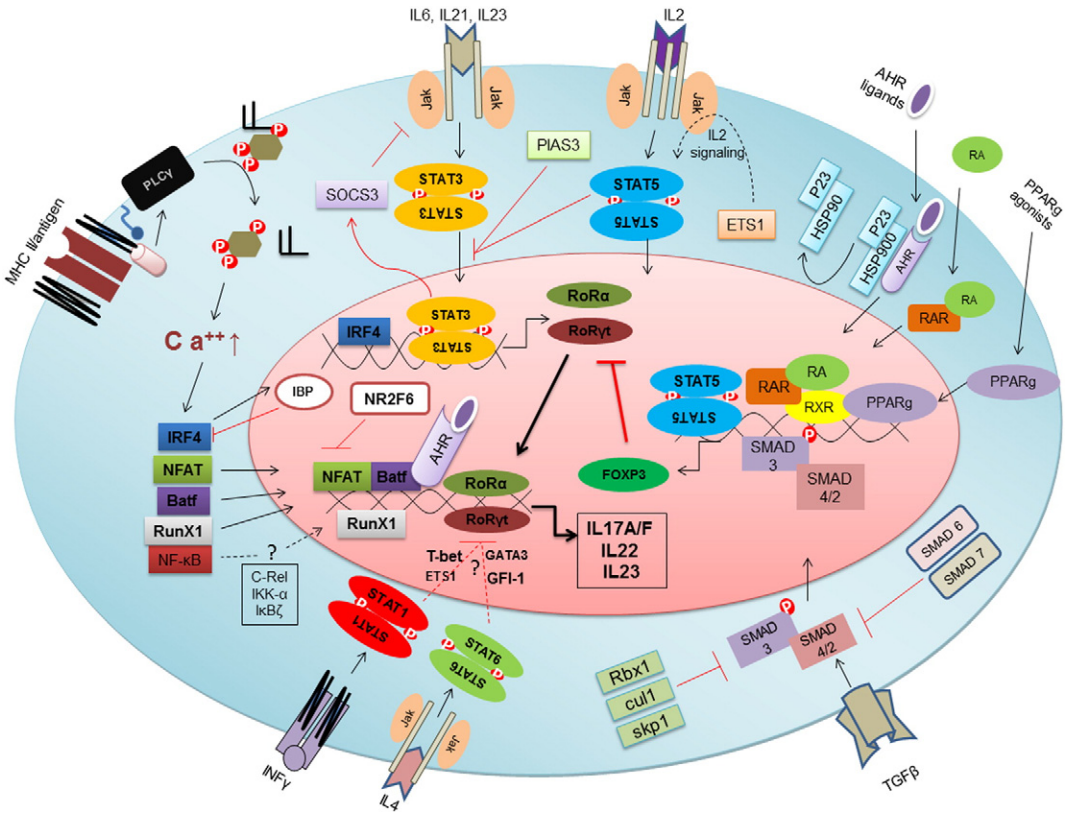

Fig. 1. Non-metabolic signaling pathways of naïve CD4 + T cells differentiation to Th17 lineage namely, TCR signaling pathway, retinoic acid receptor signaling pathway, cytokine signaling pathway, and AHR receptor signaling pathway.