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MicroRNA-mediated regulation of T helper type 17/regulatory T-cell balance in autoimmune disease

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Summary

T helper type 17 (Th17) cells and regulatory T (Treg) cells are two distinct T-cell subsets with opposite effects on immune functions. While Th17 cells are a key effector in the immune response and play critical roles in the development of autoimmunity and inflammation, Treg cells orchestrate the overall immune response and maintain peripheral immune tolerance by regulating the activity of the effector T cells. However, the developmental pathways for Th17 and Treg cells are reciprocally interconnected and there is a significant amount of plasticity between them. Disturbed Th17/Treg balance contributes to the development of autoimmune diseases, like experimental autoimmune encephalomyelitis and multiple sclerosis. MicroRNAs (miRNAs) are small non-coding RNA molecules that post-transcriptionally regulate gene expression. Recently, emerging evidence demonstrates that miRNAs play an important role in regulating the pathogenesis of autoimmune diseases through the modulation of Th17/Treg balance. This review will provide an overview of the dysregulated miRNAs and their functions in modulating the Th17/Treg balance in autoimmune diseases.

Keywords: autoimmune disease; immune regulation; microRNAs; T helper type 17/regulatory T balance.

Introduction

$CD4^+$ T cells play critical roles in mediating adaptive immunity and are crucial in achieving an effective immune response to pathogens. After interaction with an antigen–MHC complex, naive $CD4^+$ T cells differentiate into different effector cell subsets including T helper type 1 (Th1), Th2, follicular helper T, Th17 and regulatory T (Treg) cells. These T-cell subsets have distinct cytokine profiles and different effects on immune functions.[1] Th17 and Treg cells are two distinct T-cell subsets with opposing actions. Whereas Th17 cells represent a pro-inflammatory subset, Treg cells have an antagonist effect. The balance between these two cell populations is essential for immune homeostasis, and the disturbed equilibrium of Th17 and Treg cells has been implicated in a variety of autoimmune and inflammatory diseases.[2] Since the discovery of Th17 and Treg cells, many factors have been identified that regulate the differentiation and function of Th17 and Treg cells. MicroRNAs (miRNAs) are a well-studied class of non-coding RNA molecules, which post-transcriptionally regulate gene expression by targeting mRNAs for degradation or by repressing the translation of mRNAs. During the past few years, many miRNAs have been found to play important roles in regulating the function of the immune system, including immune tolerance and autoimmunity. Particularly, miRNAs have been considered as an important new factor in the regulation of Th17/Treg balance that contributes to the development and progression of autoimmune diseases.[3] This review will focus on the dysregulated miRNAs leading to disturbed Th17/Treg balance during the development of autoimmune diseases.

Th17, Treg cells and Th17/Treg balance

An overview of Th17 and Treg cells

The Th17 cells require specific cytokines, such as transforming growth factor-β (TGF-β), combined with

interleukin-6 (IL-6) or IL-21 for their differentiation.[4] At the molecular level, the differentiation of Th17 cells requires a unique lineage-specific transcription factor, retinoid-related orphan receptor γt (RORγt).[5] Th17 cells secrete a characteristic profile of cytokines including IL-17A, IL-17F, IL-21 and IL-22, which recruit and activate neutrophils and macrophages to fight against extracellular microbial organisms or mediate the development of autoimmune disease.[6] Although roles for Th17 cells in promoting inflammation and autoimmune disorders have been extensively demonstrated, it is still controversial whether and how Th17 cells influence tumour immunity.

Regulatory T cells are another lineage of $CD4^+$ T cells with immunosuppressive properties. They require the specific cytokine TGF-β and the transcription factor Foxp3 for their differentiation.[7] In addition, IL-2 is important for the generation and expansion of Treg cells.[8] The Treg cells come in at least two forms according to the site of their maturation: naturally occurring $CD4^+$ $CD25^+$ Treg (nTreg) cells and inducible Treg (iTreg) cells. Although nTreg cells suppress inflammation and immune responses mainly in a cell-contact-dependent manner, iTreg cells secrete inhibitory cytokines IL-10 or TGF-β to exert their suppressive effects.[9] The Treg cells play an important role in the prevention of autoimmunity and in the regulation of immune responses against infections and cancer.

Plasticity of Th17 and Treg cells

Accumulating evidence indicates that $CD4^+$ T cells are more plastic than previously described, particularly Th17 and Treg cells. Although Th17 and Treg cells play opposite roles in the regulation of autoimmunity and inflammation, the TGF-β pathway is shared by both Th17 and Treg cells for their differentiation. TGF-β promotes Th17 and iTreg cell development by inducing the expression of both Foxp3[10] and RORγt[4] in T-cell receptor (TCR)-stimulated naive $CD4^+$ T cells. These cells can shuttle towards a pro-inflammatory Th17 phenotype or a regulatory iTreg cell phenotype depending on the surrounding cytokine environment. In the absence of IL-6 or IL-21, TGF-β alone is unable to initiate Th17 differentiation. Foxp3 is able to physically bind RORγt to suppress its transcriptional activity, resulting in the inhibition of Th17 differentiation and favouring the development of the Treg cell lineage. In the presence of IL-6 or IL-21, Foxp3 is released from RORγt and then Th17 differentiation can be initiated.[11,12] Therefore, IL-6 and IL-21 play a critical role in driving the Th17 differentiation by controlling the Foxp3/RORγt balance. In addition, the cytokine IL-2 is a potent inducer of Foxp3 but inhibits Th17 cell differentiation via a signal transducer and activator of transcription 5 (STAT5) -dependent mechanism.[13]

Because the developmental pathways for Th17 and Treg cells are reciprocally interconnected, these two cell subsets can interconvert under specific conditions. Foxp3-expressing Treg cells can convert into IL-17-secreting cells and lose their suppressive function under inflammatory conditions.[14] Inflammatory Th17 cells can convert into IL-10-producing cells, which possess immunosuppressive properties but lack Foxp3 expression.[15] In addition, subpopulations of $CD4^+$ $Foxp3^+$ $ROR\gamma t^+$ Treg cells that have the capacity to produce IL-17 have been reported in both humans[16] and mice.[17] These cells represent a transient population that displays the functional features of both Th17 and Treg cells.

Th17/Treg balance and autoimmune diseases

An imbalance between Th17 cells and Treg cells is often associated with certain autoimmune diseases,[2] infectious and allergic diseases,[18] as well as cancer.[19] Th17 cells with specificity for self-antigens are highly pathogenic and lead to the development of inflammation and severe autoimmunity. In animal models, the implication of Th17 cells was described in different autoimmune diseases, including experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis. In humans, Th17 cells and their cytokines are also associated with several autoimmune and inflammatory diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), psoriasis and inflammatory bowel disease.[20] On the other hand, a reduction in Treg cell numbers and/or a loss of Treg cell function has been observed in many human autoimmune diseases and animal models of autoimmunity.[21] So maintaining Th17/Treg balance appears to be critical for the prevention of the development of autoimmune diseases.

MicroRNAs regulates Th17/Treg imbalance in autoimmune diseases

miRNAs that are dysregulated in autoimmune diseases and regulate Th17/Treg balance

Multiple miRNAs have been reported to be dysregulated in autoimmune diseases. Among them, a number of miRNAs are involved in the regulation of Th17/Treg cell balance (Table 1). The miRNAs could regulate Th17/Treg in a T-cell intrinsic way. Alternatively, miRNAs expressed by non-T cells could be responsible for the disturbed Th17/Treg balance.

T-cell intrinsic miRNAs

During the pathogenesis of autoimmune diseases, many miRNAs are dysregulated in T cells and contribute to the disturbed Th17/Treg balance. MS is a chronic inflammatory autoimmune disease that damages the central nervous system and has been characterized by demyelinated

Table 1. Dysregulated miRNAs in autoimmune diseases that associated with Th17/Treg balance

Autoimmune disease	miRNA	Cell types	Dysregulation	Function	References
EAE and MS	miR-20b	Th17	↓	Th17↓	22
	miR-30a	Th17	↓	Th17↓	23
	miR-146a	Th17	↓	Th17↓	24
	miR-214	$CD4^+$ T cell	↓	Th17↓	25
	miR-26a	PBLs	↓	Th17↓	26
	miR-17-92	T cell	↑	Th17↑	27
	miR-326	Th17	↑	Th17↑	28
	miR-384	$CD4^+$ T cell	↑	Th17↑	29
	miR-181c	$CD4^+$ T cell	↑	Th17↑	30
	miR-21	Th17	↑	Th17↑	31
	miR-132/212	Th17	↑	Th17↑	32
	miR-155	Sera	↑	Th17↑	33
	miR-27a	$CD4^+$ T cell	↑	Th17↑	25
	miR-590	Th17	↑	Th17↑	34
	miR-448	Th17	↑	Th17↑	35
	miR-141	$CD4^+$ T cell	↑	Th17↑	36
	miR-200a	$CD4^+$ T cell	↑	Th17↑	36
	miR-223	$CD4^+$ T cell	↑	Th17↑	37
	miR-223	Dendritic cell	↑	Th17↑	49
	miR-182	$CD4^+$ T cell	↑	Treg↓	38
	miR-let-7i	Circulating exosomes	↑	Treg↓	53
RA	miR-301a-3p	PBMC	↑	Th17↑	39
	miR-16	PBMC	↑	Th17↑ and Treg↓	40
	miR-21	PBMC, $CD4^+$ T cell	↓	Th17↑ and Treg↓	41
	miR-146a	Treg	↓	Treg↑	42
	miR-155	Treg	↓	Treg↑	42
	miR-155	$CD14^+$ cell, macrophage	↑	Th17↑	50
	miR-363	Dendritic cell	↓	Th17↓	51
SLE	miR-873	Th17	↑	Th17↑	43
	miR-326	Treg	↑	Treg↓	44
	miR-142-3p	Dendritic cell	↑	Th17↑ and Treg↓	53
	miR-663	BMSC	↑	Treg↓	52
EAM	miR-155	PBMC, $CD4^+$ T cell	↑	Th17↑	45
PV	miR-200a	$CD4^+$ T cell	↑	Th17↑ and Treg↓	46
	miR-210	$CD4^+$ T cell	↑	Treg↓	47
ITP	miR-125a-5p	$CD4^+$ T cell	↓	Th17↑ and Treg↓	48

Th17; T helper type 17; Treg, regulatory T; miRNA, microRNA; EAE, experimental autoimmune encephalomyelitis; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; EAM, experimental autoimmune myocarditis; PV, psoriasis vulgaris; ITP, immune thrombocytopenic purpura; PBLs, peripheral blood lymphocytes; PBMC, peripheral blood mononuclear cell; BMSC, bone-marrow-derived stroma cell; ↓, Decrease , ↑ Increase; Th17↑, promotes Th17 cell differentiation; Th17↓, inhibits Th17 cell differentiation; Treg↑, promotes Treg cell differentiation; Treg↓, inhibits Treg cell differentiation.

regions in the white and grey matter of the brain and spinal cord. As of now, most T-cell intrinsic miRNAs that regulate Th17/Treg balance were found during the development and progression of MS and EAE. Although miR-20b,[22] miR-30a,[23] miR-146a,[24] miR-214[25] and miR-26a[26] were down-regulated in $CD4^+$ T cells or Th17 cells during the process of demyelination disease in both patients with MS and EAE mice, the expression of miR-17-92,[27] miR-326,[28] miR-384,[29] miR-181c,[30] miR-21,[31] miR-132/212,[32] miR-155,[33] miR-27a,[25] miR-590,[34] miR-448,[35] miR-141,[36] miR-200a[36] and miR-223[37] was markedly increased. As a consequence, the dysregulation of these miRNAs contributes to the increased Th17 response. On the other hand, up-regulation of miR-182 in $CD4^+$ T cells promotes the development of EAE through the inhibition of Treg cell development.[38]

Rheumatoid arthritis is an autoimmune disease characterized by a chronic inflammation of the joint synovium membrane leading to bone and cartilage destruction. The chronic inflammatory process in RA indicates that immune regulation in the joint is disturbed and that may be caused by an excessive inflammatory response

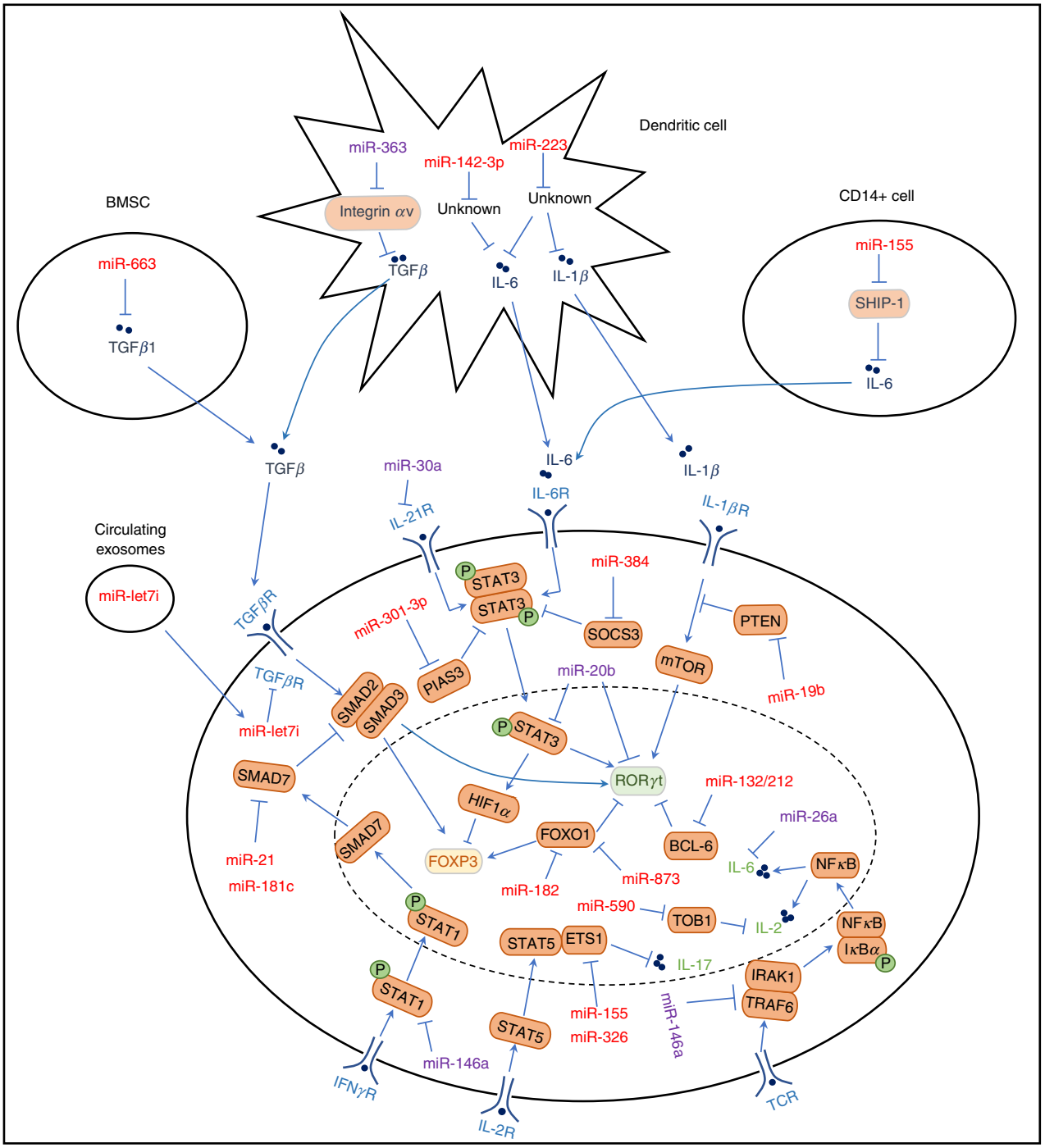

Fig. 1. Targets of dysregulated microRNAs (miRNAs) that are involved in the regulation of T helper typ 17 (Th17)/regulatory T (Treg) cell balance. Red colour represents miRNAs that increase the ratio of Th17/Treg; Purple colour represents miRNAs that decrease the ratio of Th17/Treg cells

associated with a deficiency in the control of the immune response. The expression of miR-301a-3p,[39] miR-16[40] and miR-21[41] was found to be increased in peripheral blood mononuclear cells from RA patients. The up-regulation of these miRNAs leads to increased Th17 cell frequency and impaired Treg cell development. It has been reported that miR-146a[42] and miR-155[42] promote Treg cell development. In RA patients, decreased expression of miR-146a and miR-155 has been associated with reduced frequency of Treg cells.

Several T-cell intrinsic miRNAs were also found to be dysregulated during the pathogenesis of other autoimmune diseases. The expression of miR-873[43] and miR-326[44] expression in patients with SLE, miR-155 in

patients with experimental autoimmune myocarditis,[45] miR-200a[46] and miR-210[47] in patients with psoriasis vulgaris, and miR-125a-5p in patients with immune thrombocytopenic purpura[48] were all dramatically increased. The dysregulation of these miRNAs contributes to the disturbed Th17/Treg balance through the promotion of Th17 cell development and/or suppression of Treg cell development.

T-cell extrinsic miRNAs

Non-T cells, such as dendritic cells (DCs) and macrophages, also express miRNAs that are able to modulate Th17/Treg balance. miR-223, a myeloid cell-specific miRNA and one of the most up-regulated miRNAs in patients with MS, can promote DC-induced activation of the pathogenic Th17 response.[49] miR-155 is up-regulated significantly in the RA synovial compartment, particularly in $CD68^+$ macrophages and $CD14^+$ cells. This up-regulation promotes the development of autoreactive Th17 cells.[50] The decreased expression of miR-363 in DCs from patients with RA leads to increased levels of IL-6, IL-17 and TGF-β in the serum.[51] In addition, it has been reported that miR-663 in bone marrow-derived mesenchymal stem cells and miR-142-3p in monocyte-derived DCs suppress Treg cell development during the pathogenesis of SLE.[52] Recently, studies found that the expression of miRNA let-7i in circulating exosomes is markedly increased in patients with MS and this leads to the suppression of Treg cell development.[53]

Mechanisms through which dysregulated miRNAs modulate Th17/Treg balance

During the development of autoimmune diseases, dysregulated miRNAs regulate Th17/Treg balance through targeting the positive or negative regulators of Th17 and/or Treg cell differentiation. In this section, we will summarize different mechanisms through which dysregulated miRNAs modulate Th17/Treg balance during the development of autoimmune diseases (Fig. 1).

Targets of dysregulated miRNAs in T cells

RORγt. The master regulator for Th17 cell differentiation, RORγt was identified as one of the direct targets of miR-20b. miR-20b suppresses the development of EAE through direct targeting of RORγt, which leads to a decreased Th17 response.[22]

Foxo1. Forkhead box O1 (Foxo1) was identified as a Th17 suppressor that can interact with RORγt to negatively regulate IL-17A production[54] and suppress the pathogenicity of Th17 cells through the down-regulation of IL-1R1[55] and IL-23R.[54] miR-873 was found to directly target Foxo1 to facilitate Th17 cell differentiation in patients with SLE.[43] On the other hand, Foxo1 is also essential for the induction of Foxp3 expression in Treg cells.[56] An elevated level of miR-182 and decreased Foxo1 expression were observed during the acute phase of EAE. Further studies showed that miR-182 inhibits Treg cell development through a Foxo1-dependent pathway.[38]

Bcl-6. The miR-132/212 cluster is induced by aryl hydrocarbon receptor activation, which plays critical roles in autoimmune diseases such as EAE. B-cell lymphoma 6 (Bcl-6) is a negative regulator of Th17 differentiation. Further study showed that the miR-132/212 cluster could target Bcl-6 to promote Th17 cell differentiation.[32]

Regulators of IL-21 and IL-6 signalling pathways. Interleukin-21 and IL-6 are two cytokines that can positively regulate Th17 differentiation. miR-30a and miR-26a could inhibit Th17 differentiation through direct targeting of IL-21R and IL-6, respectively.[23,26] Because IL-6 is also a strong suppressor of the TGF-β-driven induction of Foxp3,[57] miR-26a could also promote the development and function of Treg cells. STAT3 activation is important for IL-21 and IL-6 signal transduction. miR-20b could directly target STAT3 to suppress the Th17 response and pathogenesis of EAE.[22] The protein inhibitor of activated STAT3 (PIAS3) is the main cellular inhibitor of STAT3. miR-301a-3p, an inhibitor of PIAS3 expression, promotes Th17 cell differentiation in patients with RA.[39] SOCS3 is an important member of the SOCS family and can negatively regulate the IL-6–STAT3 signalling pathway. miR-384 could promote the differentiation of Th17 cells through the targeting of SOCS3.[29]

Regulators of IL1-β signalling pathway. IL-1β signalling was required for the early stage of Th17 differentiation by converting $Foxp3^+$ T cells into Th17 cells. After polarization, IL-1β also favoured Th17 cells to maintain their function.[58] IL-1β promotes Th17 polarization through the activation of MAPK and the Akt/mTOR pathway, which in turn phosphorylates STAT3 and enhances the transcription of RORγt. Phosphatase and Tensin Homology (PTEN) is an antagonist of the PI3K–AKT–mTOR axis and acts as an important anti-inflammatory mediator by reducing Th17 cell-mediated pathogenesis. miR-19b down-regulates the expression of PTEN, which in turn augments the PI3K–AKT–mTOR axis and promotes Th17 differentiation.[27]

Regulators of TCR signalling pathway. Upon recognition of autoantigens, autoreactive CD4 T cells initiate TCR signalling that leads to nuclear factor- κB (NF-κB) activation. NF-κB induces the production of T-cell autocrine IL-6 and IL-21 cytokines that activate STAT3. TRAF6 and IRAK1 are the NF-κB signalling transducers. miR-146a

targets TRAF6 and IRAK1 and then inhibits the development of pathogenic Th17 cells by blocking the production of IL-6 and IL-21 during the development of EAE.[24]

Regulators of TGF-β signal pathway. The TGF-β signalling plays an essential role in the generation of both Th17 and Treg cells. SMAD (an acronym from the fusion of Caenorhabditis elegans Sma genes and the Drosophila Mad, Mothers against decapentaplegic)-7 inhibits TGF-β-induced transcriptional responses by blocking the activation of SMAD-2/3 and their complex formation with SMAD-4. miR-21 and miR-181c could promote Th17 cell differentiation through direct targeting of SMAD-7.[31,59] Overexpression of miR-21 reduced SMAD-7 expression while up-regulating SMAD-2/3 levels, resulting in enhanced IL-17 production. However, Treg cell differentiation was normal in miR-21-deficient mice. TGF-β signalling regulates Treg cell differentiation and function through both SMAD-dependent and SMAD-independent pathways. Although the SMAD-2/3-pathway dependent TGF-β signalling has been demonstrated to partially regulate iTreg cell differentiation, it has also been shown that a combination of SMAD-2 and SMAD-3 deficiency does not alter Foxp3 expression or the suppressive activity of iTreg cells *in vivo*. It has been reported that the level of IL-2 was enhanced in miR-21-deficient mice. Because IL-2 has been shown to stabilize TGF-β-induced Foxp3 expression, it is possible that enhanced IL-2 expression in miR-21-deficient mice could compensate for the loss of defective SMAD-2/3-dependent TGF-β signalling during Treg cell differentiation.

Regulators of IFN-γ signalling pathway. Interferon-γ mediates the phosphorylation of STAT1, which leads to the expression of T-bet, Smad7 and FasL. T-bet and Smad7 are two negative regulators of Th17 cell polarization. In addition, Smad7 inhibits the regulatory function of Treg cells. STAT1 is a direct target of miR-146a and decreased expression of miR-146a facilitates a pro-inflammatory phenotype of Treg cells because of increased STAT1 activation.[24]

Regulators of IL-2 signalling pathway. STAT5 is an essential downstream transcription factor of IL-2 signalling, which is critical for the survival of T cells but suppresses Th17 cell development.The transcriptional regulator Tob1 (transducer of ERBB2-1) can impair IL-2 production in Th17 cells and plays an important role in the activation of encephalitogenic T cells in central nervous system autoimmunity.[60] It has been reported that miR-590 promotes pathogenic Th17 cell differentiation through targeting Tob1.[34] Other studies showed that Ets-1, a target of miR-155 and miR-326, may form a protein complex with STAT5, and then inhibit IL-17 expression. Thereby, miR-155 and miR-326 could promote Th17 differentiation through direct targeting of Ets-1.[28,45]

Targets of dysregulated miRNAs in non-T cells

The miRNAs could modulate the balance of Th17/Treg in a cell non-autonomous way, that is, through targeting factors important for Th17 and Treg cell development in non-T cells. miR-363,[51] miR-142-3p[61] and miR-223[49] were dysregulated in DCs and could promote Th17 cell differentiation during the pathogenesis of autoimmune diseases. miR-363 suppresses the expression of integrin αv, which is an important positive regulator of TGF-β activation. However, the targets of miR-142-3p and miR-223, which account for the disturbed Th17/Treg balance, have not been characterized yet. In $CD68^+$ macrophages and $CD14^+$ cells, up-regulation of miR-155 leads to decreased expression of SHIP-1, which in turn promotes the production of Th17 inducing cytokine IL-6.[50] Through targeting TGF-β_1, miR-663 in bone-marrow-derived mesenchymal stem cells down-regulates the frequency of Treg cells not only by inhibiting nTreg cell proliferation and iTreg cell differentiation but also by converting Treg cells toward a follicular helper T-cell phenotype.[52] The circulating exosomal miRNA, miR-let7i, which is markedly increased in patients with MS, suppresses the induction of Treg cells by targeting insulin-like growth factor 1 receptor and transforming growth factor β receptor.[53]

Concluding remarks

Although Th17 and Treg cells are both implicated in inflammatory and autoimmune diseases, they are two distinct T-cell subsets with opposing actions. Th17 and Treg cells share common factors for their development and function, and the plastic nature of these two cell subsets emphasizes the importance of Th17/Treg balance during the development of autoimmunity, inflammation and cancer. The miRNAs play crucial roles in the development and function of both Th17 and Treg cells, and shaping the balance between Th17 and Treg cells has significant biological implications for the development of novel miRNA-based therapeutic approaches for the treatment of autoimmune and inflammatory diseases.

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Disclosures

The authors declare no conflict of interest.

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