Emerging Role of Non-Coding RNAs in Regulation of T-Lymphocyte Function

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T-lymphocytes (T cells) play a major role in adaptive immunity and current immune checkpoint inhibitor-based cancer treatments. The regulation of their function is complex, and in addition to cytokines, receptors and transcription factors, several non-coding RNAs (ncRNAs) have been shown to affect differentiation and function of T cells. Among these non-coding RNAs, certain small microRNAs (miRNAs) including miR-15a/16-1, miR-125b-5p, miR-99a-5p, miR-128-3p, let-7 family, miR-210, miR-182-5p, miR-181, miR-155 and miR-10a have been well recognized. Meanwhile, IFNG-AS1, lnc-ITSN1-2, lncRNA-CD160, NEAT1, MEG3, GAS5, NKILA, lnc-EGFR and PVT1 are among long non-coding RNAs (lncRNAs) that efficiently influence the function of T cells. Recent studies have underscored the effects of a number of circular RNAs, namely circ_0001806, hsa_circ_0045272, hsa_circ_0012919, hsa_circ_0005519 and circHIPK3 in the modulation of T-cell apoptosis, differentiation and secretion of cytokines. This review summarizes the latest news and regulatory roles of these ncRNAs on the function of T cells, with widespread implications on the pathophysiology of autoimmune disorders and cancer.

Keywords: miRNA, lncRNA, circRNA, T cell, cancer, autoimmune

INTRODUCTION

T-lymphocytes (T-cells) play a central role in adaptive immunity and are involved in the pathogenesis of immune-related disorders and cancer, thus several therapeutic strategies have been developed to stimulate their effector functions (1). During the process of maturation in the thymus, T cells express T cell receptors (TCR) on their surface. Moreover, they can express either CD8 or CD4 glycoproteins, thus being categorized as glycoprotein on their surface and are called CD8+ (cytotoxic) or CD4+ cells (helper) T cells (2). Based on the distinctive cytokine profiles, T helper (Th) cells can be categorized to Th1, Th2, Th9, Th17, Th22, regulatory T cells (Tregs), and follicular helper T cells (Tfhs) subtypes (3). Each cell type can be recognized by epigenetic and genetic signatures. For instance, Treg cells are described by over-expression of the FOXP3
transcription factor (4) Demethylation of the intronic conserved non-coding sequence 2 is required for maintenance of FOXP3 expression and regulation of stability of Tregs upon re-exposure to cytokines (5). In Tregs, this intronic sequence acts a sensor for IL-2 and STAT5 (5). The expression of a number of transcription factors has been shown to be altered in CD8+ T cells during clearing an Bacterial or Viral infection (6). Notably, it is possible to predict the potential of these cells to make memory cells based on gene signatures (6). For instance, expressions of Blc-2 and Cdh-1 have been shown to be surged in the memory subset of CD8+ T cells (6). In addition, chromatin configurations have been found to influence the function of T cells (6). Non-coding RNAs (ncRNAs) carry a regulatory function in several biological processes including implications in immune checkpoint inhibitor treatment (7). Recent studies have highlighted the impact of different classes of non-coding RNAs in T cell functions. In this review, we highlight the function of microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) in regulation of T cells. These three classes of ncRNAs have regulatory effects on expression of mRNA coding genes. In fact, lncRNAs and circRNAs can sequester miRNAs and decrease availability of miRNAs. Since miRNAs can inhibit expression of target mRNAs, the sequestering effects of circRNAs and lncRNAs on miRNAs release miRNA targets from inhibitory effects of miRNAs (8).

miRNAs AND T CELL REGULATION

miRNAs are about 22 nucleotides in length and regulate expression of their target transcripts mostly through binding to their 3’ UTR (9, 10). These small molecules are generated in the forms of precursors by RNA polymerases II and III. The mature miRNA is generated through a series of cleavage events in the nucleus and cytoplasm (9). Given their various regulatory functions, miRNAs are important players in the regulation of several physiologic and pathophysiologic processes (11). As for the regulation of T-cell differentiation, several examples of important miRNAs have been reported. For instance, mir-15/16 hampers T cell cycle, their survival and differentiation to memory T cells. Experiments in miR-15/16 deficient T cells have shown that these miRNAs directly inhibit the expression of a broad network of genes contributing in the regulation of cell cycle progression, survival, and development of memory cells (12). Another study has shown miR-15a/16-1 silencing in CD4+ T cells leads to the production of higher levels of IL-22, while up-regulation of miR-15a/16-1 results in down-regulation of the IL-22 expression through suppression of thearyl hydrocarbon receptor. miR-15a/16-1 silenced CD4+ T cells were superior to wild-type CD4+ T cells in terms of tissue repair capacity because of their higher capability in production of IL-22. Furthermore, IL-22 has been shown to decrease miR-15a/16-1 levels through activation of phosphorylated STAT3-c-myc signaling (13).

A high throughput miRNA profiling in human peripheral γδ T cells of healthy subjects has led to identification of 14 differentially expressed miRNAs between αβ and γδ T cells. While miR-150-5p, miR-450a-5p, miR-193b-3p, miR-365a-3p, mir-31-5p, miR-125b-5p and miR-99a-5p have been up-regulated in γδ T cells, miR-34a-5p, miR-16-5p, miR-15b-5p, miR-24-3p, miR-22-3p, miR-22-5p and miR-9-5p have had the opposite trend (14). Notably, mir-125b-5p and mirR-99a-5p have been found to attenuate the activity of γδ T cells and decrease their cytotoxic effects against tumor cells. Up-regulation of miR-125b-5p or miR-99a-5p in γδ T cells was shown to suppress the activity of γδ cells and induce their apoptosis. Moreover, miR-125b-5p silencing has increased cytotoxic effects of γδ T cells against tumor cells through enhancing the production of IFN-γ and TNF-α (14). Overexpression of mir-125b has also promoted Treg cells differentiation and suppressed Th17 cell differentiation (15). In addition, miR-125a, a miRNA which has only recently been reported to be involved in myelogenous leukemogenesis (16), could inhibit production of proinflammatory cytokines in CD4+ T cells and Th1/Th17 cell differentiation by targeting ETS-1 (17).

Let-7 family miRNAs are also involved in the regulation of T cells functions. In vivo experiments demonstrated that, let-7g-5p may attenuate the frequency of Th17 cells of rheumatoid arthritis (RA) and block Th17 differentiation (18). Let-7f-5p inhibits Th17 differentiation through targeting STAT3. This miRNA has been found to be downregulated in CD4+ T cells of patients with multiple sclerosis (MS) (19). Finally, let-7d-3p regulates the expression of IL-17 in CD4 + T cells by targeting AKT1 and modulation of AKT1/mTOR signaling pathway (20). miR-210 is another miRNA whose deletion enhances T cell differentiation and Th17 polarization under hypoxic situation through modulation of HIF-1α expression (21). Expression of this miRNA has also been found to be over-expressed in both psoriasis patients and psoriasis animal models where it stimulates Th17 and Th1 cell differentiation but suppresses Th2 differentiation via inhibiting expressions of STAT6 and LYN. Ablation of miR-210 in animals and intradermal injection of miR-210 antagonist has reversed the immune imbalance and blocked the development of psoriasis-like inflammatory response in an animal model of psoriasis. TGF-β and IL-23 have been shown to increase the expression of miR-210 through the induction of HIF-1α, and subsequent recruitment of P300 and enhancement of histone H3 acetylation in miR-210 promoter (22).

miR-181c has been shown to enhance Th17 differentiation and promote autoimmunity through targeting Smad7 and modulating TGF-β pathway and IL-2 expression (13). Overexpression of mir-181c has suppressed activation of T cell, impaired cytoskeleton arrangement in T cells by targeting BRK1 (23). Meanwhile, miR-181a has been reported to restrict IFN-γ production by targeting Id2 so regulating IFN-γ-mediated CD8+ T cell responses mediated by (24). This miRNA also promotes expression of TGF-β and IL-10 and inhibits function of Tregs through modulating the PI3K/Akt pathway (25). Figure 1 illustrates the role of various ncRNAs in regulating the differentiation of T cells via the PI3K/Akt/mTOR and MAPK/ERK signaling pathways. Table 1 summarizes the impact of miRNAs on regulation of function of T cells.
LncRNAs AND T CELL REGULATION

LncRNAs are typically longer than 200 nucleotides and may also be several kilobases long (69). They exert diverse effects on chromatin structure, transcription of genes and post-transcriptional regulation of gene expression (70). These effects are exerted through both chromatin-based mechanisms and the interaction with other types of transcripts. Moreover, by serving as decay, scaffold, and enhancers, LncRNAs influence genes expressions though various mechanisms (71). Several LncRNAs have been found to influence the function of T cells. For instance, IFNG-AS1 is up-regulated in the intestinal tissue of patients with active inflammatory bowel disease (IBD). Specific over-expression of IFNG-AS1 in T cells has led to significant enhancement of inflammatory cytokines, while attenuation of production of anti-inflammatory cytokines. Media from IFNG-AS1-overexpressing T cells has induced a potent inflammatory response in primary human peripheral blood mononuclear cells (PBMCs) (72). Lnc-ITSN1-2 is another LncRNA that affect T cells differentiation. This LncRNA has been shown to increased proliferation and activation of CD4+ T Cells and promote their differentiation to Th1/Th17 through targeting miR-125a and upregulating IL-23R (73).

The regulatory role of NEAT1 on T cells functions has been validated in different contexts, including sepsis, primary Sjögren’s syndrome, RA and hepatocellular carcinoma (HCC) (74, 75). Downregulation of NEAT1 has restricted immune response in mouse model of sepsis and induced T cell apoptosis through modulating miR-125/MCEMP1 axis (76). This LncRNA has been shown to promote expression of CXCL8 and TNF-α and activate MAPK signaling pathway. NEAT1 expression has been up-regulated in CD4+ and CD8+ T cells of patients with primary Sjögren’s syndrome (34). Similarly, this LncRNA has been found to be up-regulated in peripheral blood mononuclear cells of RA patients. Its silencing has led to inhibited differentiation of Th17 cells from CD4+ T cells by downregulating STAT3 through modulating its ubiquitination (77). Finally, NEAT1 has been found to be up-regulated in PBMCs of HCC patients parallel with up-regulation of Tim-3. NEAT1 silencing has blocked apoptosis of CD8+ T cells and increased their cytolysis function. Further, NEAT1 has been shown to exert such effects through miR-155/Tim-3 pathway. Taken together, NEAT1 has been suggested as an important target for enhancing the efficiency of immunotherapy (78).

MALAT1 is another LncRNA with prominent role in the regulation of T cell function. This LncRNA regulates Th1/Th2 ratio by sponging miR-155 and modulating expression of CTLA4 (79). On the other hand, MEG3 has been found to enhance proportion of Th17 cells and regulate Treg/Th17 ratio by sponging miR-17 and upregulating RORγt (80). Moreover, this LncRNA decreases proliferation of CD4+T cell and inhibits Th1 and Th17 differentiation by absorbing miR-23a and modulating expression of TIGIT (81). Figure 2 represents the role of various LncRNAs in regulating the JAK2/STAT3 and NF-κB signaling pathways in the regulation of function of T cells. Table 2 summarizes the impact of LncRNAs on T cell function.

CircRNAs AND T CELL REGULATION

CircRNAs are another group of ncRNAs that can be occasionally translated into proteins. The enclosed structure of circRNAs has endowed them a certain resistance to RNases and thus increases the stability in different body compartments.
| microRNA          | Expression pattern | Disease                        | Sample                                      | Cell line                  | Interaction | Signaling pathway    | Function                                                                 | Reference |
|-------------------|--------------------|--------------------------------|---------------------------------------------|----------------------------|-------------|----------------------|--------------------------------------------------------------------------|-----------|
| miR-15/16         | –                  | miR-15/16 deficient mouse model| CD4(+) T cells obtained from mice           | –                         | –           |                       | Constrains formation of memory T cells and confines T cell survival and cell cycle through modulating complex network of their target genes implicated in cell cycle and survival Decreasing IL-22 secretion of CD4+ T cells through targeting AHR upregulation inhibits activation of γδ T cells and cytotoxicity to tumor cells by decreasing secretion of IFN-γ and TNF-α overexpression promotes Treg cells differentiation and suppresses Th17 cell differentiation. Inhibited production of proinflammatory cytokines in CD4+ T cells and Th1/Th17 cell differentiation by targeting ETS-1 silencing represses activation of T cells by upregulating TNFAIP3 and inhibiting NF-κB signaling pathway Uregulation attenuates Th17 frequency in RA mouse model and blocks Th17 differentiation. Overexpression inhibits Th17 differentiation through targeting STAT3. Regulates expression of IL-17 in CD4+ T cells by targeting AKT1 and modulation of AKT1/mTOR signaling pathway overexpression was associated with lowered EGR-1 expression and augmented | (12)      |
| miR-15a/16-1      | –                  | C57BL/6 mice                   | Naïve CD4+ T cells                          | AHR                       | –           |                       | Pathway                                                                  | (13)      |
| miR-125b-5p       | Downregulated      | Peripheral blood obtained from 21 healthy donors | αβ T cells and γδ T cells purified from peripheral blood | –                         | –           |                       | Pathway                                                                  | (14)      |
| miR-99a-5p        | Downregulated      | Peripheral blood obtained from 21 healthy donors | αβ T cells and γδ T cells purified from peripheral blood | –                         | –           |                       | Pathway                                                                  | (15)      |
| miR-125b          | Downregulated (in PBMCs and CD4+ T cells of patients) | Juvenile idiopathic arthritis (JIA) | Blood samples from 216 JIA patients and 22 healthy volunteers, 24 male DBA/1J mice | CD4+ T cells              | –           |                       | Pathway                                                                  | (16)      |
| miR-125a          | Downregulated (in PBMC of IBD patients) | Inflammatory bowel diseases (IBD) | Blood samples from 106 IBD patients and 16 healthy controls, Female C57BL/6 mice | CD4+ T cells              | ETS-1†      |                       | Inhibited production of proinflammatory cytokines in CD4+ T cells and Th1/Th17 cell differentiation by targeting ETS-1 silencing represses activation of T cells by upregulating TNFAIP3 and inhibiting NF-κB signaling pathway Uregulation attenuates Th17 frequency in RA mouse model and blocks Th17 differentiation. Overexpression inhibits Th17 differentiation through targeting STAT3. Regulates expression of IL-17 in CD4+ T cells by targeting AKT1 and modulation of AKT1/mTOR signaling pathway overexpression was associated with lowered EGR-1 expression and augmented | (17)      |
| miR-128-3p        | Upregulated (in T cells RA patients) | Rheumatoid arthritis (RA) | Blood samples from 20 patients with RA and 20 healthy subjects, C57BL/6 mice | Patient derived T cells   | TNFAIP3     | NF-κB signaling pathway | Pathway                                                                  | (35)      |
| let-7g-5p         | Downregulated (in plasma of RA patients) | Rheumatoid arthritis (RA) | Plasma samples from RA patients and healthy controls, C57BL/6 mice, DBA 1/J mice | CD4+ T cells              | –           |                       | Pathway                                                                  | (18)      |
| let-7f-5p         | Downregulated (in CD4+ T cells of patients with MS) | Multiple sclerosis (MS) | Blood samples from 16 RRMS patients and 16 healthy controls, Female C57BL/6J mice | CD4+ T cell               | STAT3†      |                       | Pathway                                                                  | (19)      |
| miR-let-7d-3p     | Upregulated (in patients' T cells and Graves' orbitopathy (GO)) | Primary Sjögren's syndrome (pSS) | Blood samples from pSS patients and healthy controls | CD4+ T cells              | AKT1        | AKT1/mTOR signaling pathway | Pathway                                                                  | (20)      |
| miR-183           | Upregulated       | Blood samples from patients with GO and normal subjects, TCR-HA/Thy.1.1 transgenic mice, INS-HA/Rag2KO | CD4(+) T cells from human blood samples and mice | –                         | EGR-1       |                       | Pathway                                                                  | (21)      |
| miR-96            |                    |                                |                                             |                           |             |                       | Pathway                                                                  | (22)      |

(Continued)
| microRNA | Expression pattern | Disease | Sample | Cell line | Interaction | Signaling pathway | Function | Reference |
|----------|--------------------|---------|--------|-----------|-------------|------------------|----------|-----------|
| miR-210  | Upregulated (in activated T cells) | Chronic colitis | Mr210 conditional knockout mice | Naive T cells, TH17 cells | HIF-1α | – | proliferation while their downregulation had reverse effects. Deletion potentiates T cell differentiation and TH17 polarization by modulation of HIF-1α expression. | (21) |
| miR-210  | Upregulated (in psoriasis patients) | Psoriasis | Blood samples and skin tissues specimens from 63 psoriasis patients and 80 normal volunteers, C57BL/6J and BALB/c mice | CD4+ T | STAT6, LYN | – | Enhances Th1 and Th17 differentiation and represses Th2 differentiation by targeting STAT6 and LYN. | (22) |
| miR-182-5p | Downregulated (in Th17 cells of EAU mice) | Uveitis | Blood samples from 15 patients with Behcet’s disease with uveitis, 15 patients with active sympathetic ophthalmia with uveitis and 15 healthy subjects, C57BL/6 mice | CD4+ T-cells, EL4 murine T cell line | TAF15 | STAT3 signaling pathway | inhibits Th17 development and lowers disease severity in experimental autoimmune uveitis by targeting TAF15 and modulating STAT3 pathway. | (37) |
| miR-182  | Upregulated (in CD4+ T cells of RRMS patients) | Relapse and remitting multiple sclerosis (RRMS) | Blood samples from RRMS patients and healthy controls, female C57BL/6 mice | CD4+ T cells | HIF-1α | – | Its overexpression led to promoted differentiation of naive T cells to Th1 and Th17 through targeting HIF-1α and rising IFN-γ expression. | (38) |
| miR-181c | – | Multiple sclerosis (MS) | Female C57BL/6 mice | CD4+ CD62L+ T helper cells | Smad7 | TGF-β signaling pathway | Enhanced Th17 differentiation and promoted autoimmunity through targeting Smad7 and modulating TGF-β pathway and IL-2 expression. | (13) |
| miR-181c | Downregulated (in activated T cells) | – | – | MCF7, HeLa, CD3+ T cells, Jurkat T cells | BRK1 | – | Its overexpression suppressed activation of T cell, impaired cytoskeleton arrangement in T cells by targeting BRK1. | (23) |
| miR-181a | – | – | C57BL/6J mice | CD8+ T cell | Id2 | – | Restrict IFN-γ production by targeting Id2 so regulated CD8+ T cell responses mediated by IFN-γ expression. | (24) |
| miR-181a | – | Allergic rhinitis (AR) | C57BL/6 mice | CD4+ T cells, Treg cells | P38K/Akt pathway | – | Promoted expression of TGF-β and IL-10 and inhibited function of Tregs through | (25) |
| microRNA | Expression pattern | Disease | Sample | Cell line | Interaction | Signaling pathway | Function | Reference |
|----------|--------------------|---------|--------|-----------|-------------|------------------|----------|-----------|
| miR-202-5p | Upregulated (in PBMCs, Tregs, and CD4+ T cells of AR patients) | Allergic rhinitis (AR) | Blood samples from 30 AR cases and 10 normal controls | Tregs cells, CD4+ T cells | -- | -- | modulating PI3K/Akt pathway | 
|           |                    |         |        |           |             |                  | Repressed differentiation of Tregs by targeting MATN2 | (39) |
| miR-155 | -- | Allergic rhinitis (AR) | C57BL/6 mice | CD4+ T cells, Treg cells | -- | SOCS1 and SIRT1 signaling pathway | Elevated proliferation of Treg cells by modulating SOCS1 and SIRT1 signaling pathway | (25) |
| miR-155 | Upregulated (in donor T cells in aGVHD patients) | Acute graft versus host disease (aGVHD) | C57BL/6 (B6, H2b), C57BL/6-Tg(CAG-EGFP)1Osb/J (B6 GFP, H2b), Cg-miR-155tm1.1Rsky/j (miR-155−/−, H2b), B6D2F1 (F1, H2b/H2d), BALB/c (H2b), and C3.SW-H2b/SnJ (H2b) | -- | -- | -- | Its expression in CD8+ and CD4+ T cells is necessary for pathogenesis of aGVHD through regulation of migration, expansion and effector function of T cell | (40) |
| miR-155 | -- | Viral infection | C57BL/6, Mir-155−/−, wild-type (WT) and ovalbumin-specific Tcrα/Tcrβ transgenic (OTII) mice | CD4+ T | -- | -- | Its overexpression is implicated in regulation of proliferation, activation and cytokine production of CD4+ T | (41) |
| miR-155 | -- | Vitiligo | Blood samples from one vitiligo patient and one healthy donor | naive T and CD8+ T cells | -- | -- | Its overexpression decreased proliferation of CD8+ T cells and enhanced Treg percentage | (42) |
| miR-155 | -- | Glioma | C57BL/6 mice | GL261, T cell | FoxO3a | Akt and Stat5 signaling pathway | Its upregulation promoted proliferation and activation of T cells and increased their cytotoxicity by targeting FoxO3a and modulating Akt and Stat5 signaling pathway | (43) |
| miR-149-3p | Downregulated (in CD8+ T cells overexpressing PD-1) | Breast cancer | Female BALB/c mice | 4T1, CD8+ T cell | -- | -- | Its overexpression reduced T cell apoptosis and expression of T cell inhibitor receptors, also promoted activation of T cells | (39) |
| miR-143 | Upregulated (in naive and memory T cells compared with effector T cells) | Esophageal squamous cell carcinoma (ESCC) | 13 tumor tissues and adjacent normal tissues from 13 ESCC patients and blood samples from 10 healthy donors | CD8+ T cell, HER2-CAR T cells | Glut-1 | -- | Its upregulation promoted differentiation of CD8+ T cell to memory T cells, raised T cell cytotoxicity and decreased apoptosis by | (44) |
| microRNA | Expression pattern | Disease | Sample | Cell line | Interaction | Signaling pathway | Function | Reference |
|----------|--------------------|---------|--------|-----------|-------------|------------------|----------|-----------|
| miR-17-92 | – | Chronic graft-versus-host disease (cGVHD) | miR-17-92 conditional knockout (KO) mice | CD4+ T | – | – | targeting Glut-1 and regulation of metabolism | (45) |
| miR-10a | – | – | 3 Adipose Tissue healthy subjects, female C57BL/6 mice | Naïve CD4+ T cell, adipose tissue derived mesenchymal stem cells (AD-MSCs) | – | – | Transfection with miR-10a-loaded exosomes derived from AD-MSCs elevated expression of RORγt and Foxp3 and reduced expression of T-bet and led to differentiation of naive T cells to Th17 and Treg | (46) |
| miR-10a-3p | Downregulated (in PBMC of LN patients) | Lupus nephritis (LN) | Blood samples from 94 LN patients and 38 healthy subjects | – | REG3A† JAK2/STAT3 pathway | Its upregulation enhanced Treg cells and lessened Th17/Treg ratio and alleviated renal function by targeting REG3A | (47) |
| miR-633 | Downregulated (in CD4+ T cells of SLE patients) | Systemic lupus erythematosus (SLE) | Blood samples from 20 SLE patients and 19 healthy controls | CD4+ T cells, Jurkat cells | AKT1† AKT/mTOR pathway | Its downregulation increased IL-17, and IFN-γ production and activated AKT/mTOR pathway in CD4+ T cells | (48) |
| miR-142-3p | Upregulated (in CD4+ T cells of T1D patients) | Type 1 diabetes (T1D) | Blood samples form T1D patients, CBy.PL(B6)-Thy1°/ScJ (CD90.1 BALB/c), Balb/cByJ (CD90.2 BALB/c), Balb/c.Cg-Foxp3tim2TcR/J (BALB/c Foxp3GFP), and NOD/ShLttJ mice, NOD.Cg-Pkdchsd101−/− H2-Ab1°/° NOD.Cg-Prkdcscid H2-Ab1°/° Il2ra°/° Il2rg°/° HLA-DQA1,HLA-DQB1 1Dv/Sz mice | CD4+ T cells | Tet2 | Inhibited differentiation of Treg cells and decreased stability of Tregs by targeting Tet2 and its depletion collapsed islet autoimmunity in mouse models of diabetes | (49) |
| miR-142-3p | – | Acute graft versus host disease (GVHD) | Blood samples from volunteer donors, NOD/SCID/mice | Thymic-derived regulatory T cell (tTreg) (CD4+ CD25 + CD127- tTreg) | ATG16L1 | – | Its knockout enhances survival and proliferation of Tregs by upregulating expression of ATG16L1 and modulating autophagy | (50) |
| miR-142-3p | – | – | Blood samples from healthy volunteers, NOD | Naïve CD4+CD45RA+ T cells | KDM6A | – | Its knockout improved regulatory | (51) |
| microRNA | Expression pattern | Disease | Sample | Cell line | Interaction | Signaling pathway | Function | Reference |
|----------|--------------------|---------|--------|----------|-------------|-------------------|----------|-----------|
| miR-26b-5p | Downregulated (in HCC tissues and CD4+ and CD8+ T cells) | Hepatocellular carcinoma (HCC) | 42 HCC tissues and ANTs, SPF C57BL/6 and nude mice | CD4+ and CD8+ T cells | PIM-2 | – | Its overexpression improved cytokine secretion of CD4+ and CD8+ T cells by targeting PIM-2 | (48) |
| miR-34a | Downregulated (in tumor-infiltrating T cells) | Gastric cancer (GC) | Blood samples from 73 GC patients and 58 healthy controls | Jurkat cell | LDHA | – | Its overexpression decreased lactate level in T cells and increased IFN-γ expression through targeting LDHA | (53) |
| miR-140-5p | Downregulated (in encephalomyelitic CD4+ T cells) | Experimental autoimmune encephalomyelitis (EAE) | Female C57BL/6 mice | CD4+ T cells | – | – | Its upregulation constrained Th1 differentiation through regulating methylation of STAT1 and Tbx and modulation of mitochondrial respiration | (17) |
| miR-130a-3p | Downregulated (T cells AS patients) | Ankylosing spondylitis (AS) | Blood samples from 30 HLA-B27-positive AS patients and 30 HLA-B27-negative healthy controls | Jurkat T cells | HOXB1 | – | Its overexpression resulted in increased proliferation and decreased apoptosis rate in T cells through targeting HOXB1 | (54) |
| miR-126 | – | Acute autoimmune colitis | Friend leukaemia virus B (FVb)/N miR-126 knockdown mice | CD4+ T cells | IRS-1 | AKT and NF-κB pathways | Its knockdown was associated with elevated proliferation and activation of CD4+ T cells and augmented expression of IFN-γ Promoted Th17 differentiation from CD4+ T cells through targeting Foxo1 | (55) |
| miR-425 | Upregulated (in PBMC of IBD patients) | Inflammatory bowel disease (IBD) | Blood samples from 124 IBD patients and healthy controls, Female BALB/c mice | CD4+ T cells | Foxo1↓ | – | Promoted Th17 differentiation from CD4+ T cells through targeting Foxo1 | (56) |
| miR-219a-5p | Downregulated (in CD4+ T cells of IBD patients) | Inflammatory bowel disease (IBD) | Blood samples from 33 IBD patients and 23 healthy individuals, female BALB/c mice | CD4+ T cells | ETV5↑ | – | Its overexpression inhibited Th1/Th17 cell differentiation by targeting ETV5 and | (57) |

(Continued)
| microRNA | Expression pattern | Disease | Sample | Cell line | Interaction | Signaling pathway | Function | Reference |
|----------|-------------------|---------|--------|-----------|-------------|-------------------|----------|-----------|
| miR-22  | Upregulated (in intestinal tissues and CD4+ T cells of IBD patients) | Inflammatory bowel disease (IBD) | Intestinal tissues and blood samples from 99 IBD patients, 15 intestinal tissues from patients with colonic polyps and 20 blood samples from healthy controls | CD4+ T cells | HDAC4 | – | regulating phosphorylation of STAT3 and STAT4 Elevated Th17 differentiation and inflammatory cytokines production by targeting HDAC4 | (58) |
| miR-21-5p | Downregulated (in PBMC of vitiligo patients) | Vitiligo | Blood samples from 15 vitiligo patients and 15 healthy controls | CD4+ T cells | STAT3↓ | – | Its overexpression increased Treg cells proportion and decreased effector T cells (Teff), so balanced Treg/Teff ratio by targeting STAT3 | (59) |
| miR-223-3p | Upregulated (in Th17 cells) | Experimental autoimmune uveitis | Female C57BL/6 | CD4+ T cells | FOXC3 | – | Induced autoreactive Th17 responses by targeting FOXC3 and modulation of IL-23 receptor expression | (60) |
| miR-669b-3p | – | – | C57BL/6 (H-2b) and BALB/c (H-2d) mice | CD4+ T cells | – | – | Increased proliferation of CD4+ T cells and restrained apoptosis of these cells by negative regulation of IDO | (61) |
| miR-146a | Upregulated (in CD27-γδ T cells) | – | C57BL/6J and CD45.1 mice, Rag2−/− mice, Il17a-GFP knock-in mice, miR-146a−/− mice, Nod1−/− and Atf2−/− mice | CD27-γδ T cells and CD27+ γδ T cells, CD4+ T cells | NOD1 | – | Decreased IFN-γ production and restricted functional plasticity of γδ T cells through targeting NOD1 | (62) |
| miR-29b | Upregulated (in CD4+ T cells of OLP patients) | Oral lichen planus (OLP) | Blood samples form 18 OLP patients and 18 age-and gender-matched controls | CD4+ T cells | – | – | Inhibited IFN-γ expression and secretion in CD4+ T cells, also suppressed expression of DNMT1 induced global DNA hypomethylation in CD4+ T cells to Th1 responses | (63) |
| miR-31 | Upregulated (in peripheral blood of CHD patients) | Coronary heart disease (CHD) | Blood samples from 56 CHD patients and 47 non-CHD individuals | CD4+ T cells | Bach2 | – | Increased Th22 differentiation by targeting Bach2 | (64) |
| miR-653 | Downregulated (in thymic tissues of MG mice) | Myasthenia gravis (MG) | Thymic tissues from 42 MG patients, BALB/c male nude mice | Thymocytes obtained from thymic tissues | TRIM9 | – | Its overexpression decreased viability of thymocytes and induced cell cycle arrest and apoptosis in these cells by targeting TRIM9 | (65) |
| miR-192 | Downregulated (in plasma and CD4+ of children with childhood asthma) | – | Blood samples from 18 children with childhood asthma | CD4+ T cells | CXCR5 | – | Its overexpression impeded activation | (66) |

(Continued)
miR-23a-intergenic circRNAs (110). The impact of this group of circRNAs, circRNAs from introns, exon-intron circRNAs and intergenic circRNAs (109). Four categories of circRNA shave been identified: exonic circRNAs, circRNAs from introns, exon-intron circRNAs and intergenic circRNAs (110). The impact of this group of transcripts on T cell functions has been discovered during the recent decade. Several studies have shown that circRNAs can bind with miRNAs, thus decreasing bioavailability of miRNAs and releasing miRNA targets from their inhibitory effects. This kind of interactions between circRNAs and miRNAs has critical biological impacts. A high-throughput screen study found down-regulation of circ_0012919 in patients with cryptococcal meningitis as compared to healthy controls. Circ_0012919 silencing has increased the intensity of fungal infection in the animal models and decreased their survival. Circ_0012919 has been suggested to regulate molecular cascades associated with the host antimicrobial response in T cells. Functionally, circ_0012919 has been shown to increase ADM level, decrease cell apoptosis and reverse G1/S arrest in T cells through sequestering miR-126. Thus, circRNA-12919 has an essential role in the regulation of cell cycle and apoptosis in T cells (111).

Another high throughput circRNA profiling in patients with systemic lupus erythematosus (SLE) has led to identification of 127 differentially expressed circRNAs in T cells of these patients. Among them, circRNA hsa_circ_0012919 has been reported to be the down-regulated. Functional studies have shown that hsa_circ_0012919 silencing increases early apoptosis of Jurkat cells and enhances production of IL-2 by activated Jurkat cells. Binding of this circRNA with hsa-miR-6127 has been validated through functional studies (112). Hsa_circ_0012919 has been reported to be up-regulated in CD4+ T cells of SLE patients in two independent studies. In a microarray study of circRNAs signature in these patients, hsa_circ_0012919 has been among differentially expressed circRNAs between SLE patients and healthy subjects.

Expression of this circRNA has been associated with SLE features. Down-regulation of hsa_circ_0012919 has enhanced expression of DNMT1, decreased CD70 and CD11a levels and inverted the DNA hypomethylation of these genes in CD4+ T cells of SLE. Hsa_circ_0012919 has been found to regulate expressions of KLF13 and RANTES through sequestering miR-125a (113). This circRNA has also been found to increase the expression of MDA5 in CD4+ T cells through downregulating mir-125a-3p (114). Hsa_circ_0005519 is another circRNA influencing T cell function. This circRNA has been found to be up-regulated in CD4+ T cells of asthmatic patients. Expression of this circRNA has been inversely correlated with hsa-let-7a-5p levels. Expression of hsa_circ_005519 in CD4+ T cells has been correlated with fraction of exhaled nitric oxide and eosinophil ratio in the circulation of these patients. Hsa_circ_0005519 has been predicted to sequester hsa-let-7a-5p and release IL-13/IL-6 from its inhibitory effect (115). Being up-regulated circRNA in nasal mucosa of patients with allergic rhinitis, circHIPK3 has been found to promote differentiation of CD4+ T cells to Th2 by targeting miR-495 and increasing expression of GATA-3 (116). Figure 3 illustrates the role of different ncRNAs in Th2-cell differentiation through modulating the IL-4-STAT6-GATA3 axis. Table 3 shows the impact of circRNAs on T cell function.

### SUMMARY

Numerous miRNAs, lncRNAs and circRNAs have been found to influence activity, survival or differentiation of T cells under physiologic or pathologic conditions. These molecules can affect pathophysiology of autoimmune conditions such as MS, SLE, RA, IBD and asthma via this route. Moreover, several of these non-coding RNAs influence immune evasion of cancer cells and their response to immunotherapeutic modalities.
Notably, both lncRNAs and circRNAs can serve as sponges for miRNAs. Through this molecular mechanism, lncRNAs and circRNAs bind with certain miRNAs to decrease their bioavailability. Thus, circRNAs and lncRNAs can indirectly affect expression of miRNAs targets. Circ_0001806/miR-126, hsa_circ_0045272/hsa-miR-6127, hsa_circ_0012919/miR-125, hsa_circ_0005519/hsa-let-7a-5p, circHIPK3/miR-495 are examples of circRNA/miRNA axes regulating T cell functions. In addition, Inc-ITSN1-2/miR-125a, NEAT1/miR-125, NEAT1/ miR-155, MALAT1/miR-155, MEG3/miR-17, MEG3/miR-23a, Gm15575/miR-686 are examples of lncRNA/miRNA pairs in this regard. These examples not only indicate the intricate network between these classes of transcripts, but also provide clues to find the most important modules in the regulation of T cell functions. Contribution of miR-125, miR-155, MEG3 and NEAT1 in more than one of these molecular axes suggests their significance in the regulation of T cell function. Most notably, all of these four non-coding RNAs have essential roles in cancer development or suppression (118–120), further highlighting the intercalation of cancer-related and immune-related molecular pathways.

GATA3, RORγ, NF-κB, SIRT1, STAT3 and FOXO3 as major regulators of T cell function have been shown to be influenced by non-coding RNAs. For instance, GATA3 is influenced by Dreg1 and GATA3-AS1 IncRNAs; RORγ is regulated by MEG3; SIRT1 is modulated by miR-155 and miR-23a-3p; STAT3 is regulated by let-7f-5p, miR-182-5p and miR-10a-3p, miR-21-5p and NEAT1; and FOXO3 is controlled by mir-155. Therefore, non-coding RNAs affect T cell functions through different routes.

Consistent with the important roles of lncRNAs, circRNAs and miRNAs in the regulation of function of T cells and their impact on differentiation of different classes of T cells, therapeutic targeting of these ncRNAs represent an efficient tool for management of disorders related with abnormal function of T cells. Forced up-regulation or silencing of these transcripts can affect signaling pathways that modulate T cell responses, thus alleviating tissue damage caused by abnormal T cell responses. Moreover, assessment of ncRNAs signature is a probable strategy for prediction of course of T cell-related disorders.

Taken together, the significant impact of non-coding RNAs on differentiation, survival, cytokine production and activity of T cells potentiates these molecules as important targets for treatment of various disorders, particularly cancer. Moreover, non-coding RNAs participate in the pathogenesis of autoimmune disorders via affecting epigenetic regulation of genes with crucial roles in the regulation of effector T cells as well as Tregs (121). Thus, identification of the role of these transcripts in the regulation of T cell functions can provide new modalities for treatment of this kind of disorders as well. High throughput sequencing method and assessment of the competing endogenous RNA network through bioinformatics methods is an efficient strategy in identification of appropriate targets for therapeutic interventions.

**FUTURE PERSPECTIVES**

High throughput sequencing strategies and identification of differential expressions of lncRNAs, circRNAs, miRNAs...
**TABLE 2 | LncRNAs and T cell regulation.**

| IncRNA          | Expression pattern                                      | Disease                | Sample                                                                 | Cell line                                                                 | Interaction | Signaling pathway | Function                                                                                       | Reference |
|-----------------|--------------------------------------------------------|------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------|-------------|-------------------|-----------------------------------------------------------------------------------------------|-----------|
| IFNG-AS1        | Upregulation (in colonic tissues of IBD patients)        | Inflammatory bowel diseases (IBD) | Colonic tissues from 11 IBD patients, PBMCs from anonymous donors, Jurkat cells | –                                                                          | –           | –                 | Its overexpression augmented inflammatory cytokines expression and decrease anti-inflammatory cytokines expression in T cells. | (72)      |
| Inc-ITSN1-2     | Upregulation (in intestinal mucosa and PBMC of IBD patients) | Inflammatory bowel diseases (IBD) | Blood samples and intestinal mucosa specimens from 120 IBD patients and 30 healthy controls | CD4+ T Cells                                                             | –           | –                 | Increased proliferation and activation of CD4+ T Cells and promoted their differentiation to Th1/Th17 by targeting miR-125a and upregulation of IL-23R | (73)      |
| lncRNA-CD160    | Upregulated (in CD8+ T cells of HBV infected patients)   | Chronic hepatitis B virus (HBV) infection | Blood samples from 164 patients with chronic HBV infection and 67 healthy volunteers, C3H/HeN mice | CD160– CD8 + T cells and CD160+ CD8 + T cells | –           | –                 | Decreased secretion of IFN-γ and TNF-α and repressed function of CD8+ T cells by recruiting HDAC11 to promoters of IFN-γ and TNF-α and elevating methylation of H3K9Me1 | (91)      |
| NEAT1           | –                                                      | Sepsis                 | 130 specific pathogen-free C57BL/6 male mice                             | CD4+ CD25+ T cells                                                       | miR-125, MCEMP1 | –                 | Downregulation of NEAT1 has restricted immune response in mouse model of sepsis and induced T cell apoptosis through modulating miR-125/ MCEMP1 axis | (76)      |
| NEAT1           | Upregulated (in CD4+ and CD8+ T cells of pSS patients)   | Primary Sjögren’s syndrome (pSS) | Blood samples from 20 pSS patients and 10 healthy subjects | CD4+, CD8+, and CD19+ T cells, Jurkat cells                                                                                  | –           | MAPK signaling pathway | Promoted expression of CXCL8 and TNF-α and activated MAPK signaling pathway | (34)      |
| NEAT1           | Upregulated (in the PBMCs of patients with RA)           | Rheumatoid arthritis (RA) | Blood samples from 25 RA patients and 20 healthy controls, Male DBA/1J mice | CD4+ T cell                                                              | STAT3       | –                 | Its silencing prevented differentiation of Th17 cells from CD4+ T cells by downregulating STAT3 through modulating its ubiquitination. | (77)      |
| NEAT1           | Upregulated (in PBMCs of HCC patients)                   | Hepatocellular carcinoma (HCC) | Blood samples from 20 HCC patients and 20 healthy controls               | CD8+ T cells                                                             | miR-155, Tim-3↑ | –                 | Its knockdown decreased apoptosis and raised cytotoxicity of CD8+ T cells by miR-155-mediated downregulation of Tim-3, induced differentiation of Treg cells and impeded CTLs function through stabilizing EGFR by interfering with its ubiquitination. | (78)      |
| Inc-EGFR        | Upregulated (in Treg cells of HCC patients)              | Hepatocellular carcinoma (HCC) | Blood and tissue samples from 70 HCC patients and 55 healthy controls | CD4+ T cells, tumor infiltrated lymphocytes (TIL), 97H, Huh7               | EGFR        | –                 | Induced differentiation of Treg cells and impeded CTLs function through stabilizing EGFR by interfering with its ubiquitination. | (92)      |
| PVT1            | Upregulated (in the CD4+ T cells of patients with SS)    | Sjögren’s syndrome (SS) | Blood samples and labial salivary gland tissues from SS patients and healthy controls, female C57BL/6 mice, NOD/ShLij mice and wild-type ICR mice C57BL/6 (WT), B6.SJL-Ppcre Ppcrs/Boy (B6.SJL), and B6.129S1-Bcl2l11tm1.1Awt/L (Bcl2l11 knock-out) mice, Ifnar1tm1.1Awt/L (Ifnar1)flw, | CD4+ T cell                                                              | Myc         | –                 | Its downregulation decreased CD4+ T cells proliferation and impeded effector function in these cells through downregulation of Myc and controlling glycolysis regulates proliferation, survival and effector functions of CD8+ T cells by modulating Bcl2l11 expression and P3K-AKT signaling pathway | (93)      |
| lncRNA Morrbid  | –                                                      | Viral infection         | –                                                                      | CD8+ T cells                                                             | P3K-AKT signaling pathway | –                 | –                                                                                              | (94)      |

(Continued)
| IncRNA   | Expression pattern                  | Disease                        | Sample                                                                 | Cell line | Interaction | Signaling pathway                  | Function                                                                 | Reference |
|----------|-------------------------------------|---------------------------------|------------------------------------------------------------------------|------------|-------------|-------------------------------------|---------------------------------------------------------------------------|-----------|
| RP11-340F14.6 | Upregulated (in JIA patients)      | Juvenile idiopathic arthritis (JIA) | Blood samples from JIA and healthy controls                           | T cell     | P2X7R       |                                     | Increased Th17 differentiation and inhibited Treg distribution by binding to P2X7R and inducing its expression | (95)      |
| MALAT1   | --                                 | Asthma                          | Blood samples from 772 asthma patients and 441 healthy controls       | CD4+ T cells | miR-155, CTLA4 |                                    | Regulated Th1/Th2 ratio by sponging miR-155 and modulating expression of CTLA4 | (79)      |
| MEG3     | Upregulated (in CD4+ T cells of patients with asthma) | Asthma                          | Blood samples from 52 asthma patients and 45 healthy controls       | CD4+ T cells | miR-17, RORγt |                                    | Elevated proportion of Th17 cells and regulated Treg/Th17 ratio by sponging miR-17 and upregulating RORγt | (80)      |
| MEG3     | Downregulated (in CD4+ T cells of AA patients) | Aplastic anemia (AA)             | Blood samples from 15 AA patients and 10 healthy controls            | CD4+ T cell | miR-23a, TIGIT |                                    | Its overexpression decreased proliferation of CD4+ T cell and inhibited Th1 and Th17 differentiation by absorbing miR-23a and modulating expression of TIGIT | (81)      |
| DQ786243 | Upregulated (in CD4+ cells of OLP patients) | Oral lichen planus (OLP)         | Blood samples from 10 OLP patients and 10 healthy volunteers         | CD4+ T cell | miR-146a, Foxp3, NF-kB signaling pathway |                                    | Increased Treg cells percentage and Foxp3 expression and promoted suppressive function of these cells by modulating Foxp3-miR-146a-NF-kB axis | (93)      |
| AW112010 | Upregulated (in activated CD4+ T cells) | --                              | Female C57BL/6J mice                                               | CD4+ T cells | KDM5A       |                                    | Induces differentiation of inflammatory T cells through inhibiting expression of IL-10 via interacting with KDM5A and histone demethylation | (96)      |
| GASS     | Downregulated (in CD4+ T cells of HIV infected patients) | AIDS                            | Blood samples from 142 HIV infected patients and 58 healthy controls | CD4+ T cells | --          |                                    | Regulated apoptosis rate and function of CD4+ T cells during HIV infection by modulating miR-21 | (97)      |
| LINC00176| Upregulated (in CD4+ T cells of patients with SLE) | Systemic lupus erythematosus (SLE) | Blood samples from SLE patients and healthy individuals           | CD4+ T cells | WiFi1, WNT5a signaling pathway |                                    | Raised proliferation and adhesion of CD4+T cells by reducing WiFi1 levels and WNT5a pathway activation | (98)      |
| IncRNA028466 | Downregulated (in CD4+ T cells of mice immunized with rEg.P29 antigen) | --                              | Female BALB/c mic                                                    | CD4+ T cell, CD8+ T cell | --          |                                    | Implicated in regulation of cytokine expression from CD4+ T cells | (99)      |
| NONHSAT196558.1 (TANCR) | -- | Blood samples normal volunteers | Primary γδ T cells, Jurkat cells                                    | TRAIL      | --          |                                    | Increased activation and cytotoxicity of γδ T cells by modulating expression of TRAIL in cis manner | (100)     |
| Dreg1    | --                                 | Male C57BL/6 mice                | spleenic CD4+ T cells from mice and human                          | Gata3      | --          |                                    | Its expression was associated with expression of Gata3 during Th2 differentiation and | (101)     |
TABLE 2 | Continued

| IncRNA     | Expression pattern | Disease                | Sample                          | Cell line       | Interaction | Signaling pathway | Function                                                      | Reference |
|------------|--------------------|------------------------|---------------------------------|-----------------|-------------|-------------------|---------------------------------------------------------------|----------|
| Gm15575    | Upregulated (in Th17 cells and spleen tissues of EAE mice) | Multiple sclerosis (MS) | C57BL/6 mice                    | CD4+ T cells    | miR-686, CCL7 | –                 | Promoted Th17 differentiation by sponging miR-686 and upregulating expression of CCL7 | (102)    |
| IncDDT4    | Upregulated (in CD4+ T cells and PBMCs of patients with MS) | Multiple sclerosis (MS) | Blood samples from 36 MS patients and 26 healthy controls | naive CD4+ T cells | DDIT4        | DDIT4/mTOR Pathway | Suppressed Th17 differentiation by targeting DDIT4 and inhibiting DDIT4/mTOR signaling | (103)    |
| linc-MAF-4 | Upregulated (in PBMCs of patients with MS) | Multiple sclerosis (MS) | Blood samples from 34 MS patients and 26 healthy subjects | naive CD4+ T cells | MAF          | –                 | Suppressed Th2 differentiation and promoted Th17 differentiation by inhibiting MAF expression | (104)    |
| NKILA      | Upregulated (in CTLs and TH1 cells of patients with breast and lung cancer) | Non-small cell lung cancer (NSCLC) and breast cancer | Tissue samples and blood samples from 576 invasive breast carcinoma patients and 256 NSCLC patients, blood samples from healthy donors, NOD.SCID mice | CD8+ and CD4+ T cells, cytotoxic T lymphocyte (CTL), Th1, Th2 and Treg | NF-κB        | –                 | Sensitized CTLs and Th1 cells to activation-induced cell death in tumor microenvironment and facilitated tumor immune evasion through suppression of NF-κB activity | (105)    |
| IFNA-AS1   | Downregulated (in PBMCs of patients with MG) | Myasthenia gravis (MG) | Blood samples from 32 MG patients and 20 healthy volunteers, female C57/BL6 mice | CD4+ T cell, Jurkat T cell | HLA-DRB1     | –                 | Is implicated in regulation of Th1/Treg cell proliferation and activation of CD4+ T cells by influencing HLA-DRB1 activity | (106)    |
| GATA3-AS1  | –                  | –                      | Blood samples from healthy volunteers | Human PBMC      | GATA3       | –                 | Regulated polarization of Th2 cells by increasing expression of GATA3 | (107)    |

FIGURE 3 | A schematic diagram of the role of some ncRNAs in modulating the IL-4-STAT6-GATA3 axis in Th2-cell differentiation. Th2 cell differentiation requires considerable metabolic reprogramming. Upon encountering cognate antigen in the lymph node, naive CD4 T helper cells are differentiated into Th2 cells under the effect of the IL-4-STAT6-GATA3 axis. GATA3 could, in turn, alter the IL-4–IL13–IL5 locus to generate a conformation that is reachable by different other transcription factors that are involved in triggering the differentiation of T cells into Th2 cells (117). Growing evidence has confirmed that the interactions between CircHIPK3, LncGAS5, and miR-495 could play a crucial role in the modulation of Th2 differentiation in allergic rhinitis (116). Green arrows indicate upregulation of target genes by ncRNAs (lncRNA, and circRNA), red arrows depict inhibitory effects of by these ncRNAs.
and mRNAs in different stages of T cell development would help in recognition of role of each transcript in development of this group of blood cells. Further knock-in and knock-out studies in different disease conditions can help in identification of specific treatment strategies for related disorders.

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**AUTHOR CONTRIBUTIONS**

SG-F, DB, and JK wrote the draft and revised it. MT and MP designed and supervised the study. OR and MT designed the figures and tables. All authors contributed to the article and approved the submitted version.
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