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Regulatory Effects of Long Non-coding RNAs on Th17/Treg Differentiation and Imbalance

Reza Dabbaghipour[1,2], Elham Ahmadi[2], Mona Entezam[1], Omid Rahbar Farzam[2], Amir Baghbanzadeh[2], Ali Saber Sichani[3], Nazila Jalilzadeh[2], Mahdi Jafarlou[2], and Behzad Baradaran[2,4]

[1] Department of Medical Genetics, Shiraz University of Medical Sciences, Shiraz, Iran
[2] Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3] Department of Biology, Texas A&M University, College Station, Texas, USA
[4] Department of Immunology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

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ABSTRACT

Scientific research over the past decades has proven the pivotal role of long non-coding RNAs (LncRNAs) in regulating gene expression. The immune responses are controlled through the interaction of pro-inflammatory (predominance of T helper 17 cells (Th17)) and anti-inflammatory cytokines excretion (predominance of Regulatory T cells (Treg)). Recent studies have marked the impact of many diverse LncRNAs on Treg/Th17 imbalances. Moreover, some of the roots and causes of human diseases can be associated with the alterations in the Th17/Treg ratio. In this review study, we overviewed the association between LncRNAs and Th17/Treg, with the potential of providing novel prognostic and diagnostic biomarkers and promising therapeutic targets in various diseases, particularly cancer.

Keywords: Long non-coding RNA; Regulatory T cells; T helper 17 cells

INTRODUCTION

Recently, researchers have discovered a new class of RNAs that are longer than 200 nucleotides, have 5′-end 7-methyl guanosine (m7G) caps and 3′-end polyadenylated (poly (A)) tails, and are not translated into protein products. LncRNAs with numerous functions in different areas of genome regulation and homeostasis assure genome stability and maintenance.[1] Some examples of the regulatory activities of LncRNAs include chromatin structure and function organization,[2] transcriptional regulation,[3] nuclear scaffolding, organization, and condensation,[4] as well as post-transcriptional regulation for producing functional peptides.[5] Furthermore, there are some other critical roles for LncRNAs in genome regulation that cause physio-pathological disorders,[6] like neuronal differentiation and disorders,[7] hematopoiesis and immune responses,[8] and carcinogenesis.[9]

CD4+ helper T (Th) cells are essential for coordinating cellular elements and components of the immune response. The main subsets of CD4+ Th cells include T_h1, T_h2, T_h17, regulatory T (Treg) cells and follicular helper T cells, which originated from naive peripheral precursors.[10] Interleukin 17 (IL-17) cytokines

Corresponding Author: Behzad Baradaran, PhD; Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. Tel: (+98 41) 3337 1440, Fax: (+98 41) 3337 1311, E-mail: behzad_im@yahoo.com, baradaranb@tbzmed.ac.ir

consist of six family members originating from IL-17, namely IL-17A, IL-17B, IL-17C, IL-17D, IL-25, and IL-17F.[11] The main lineage of T_h17 is typified by secreting IL-17A and IL-17F cytokines.[12] RORγt (factors retinoic acid receptor-related orphan receptor γt) as a distinct Th17 cell marker is significant for Th17-cell lineage commitment and function.[13] Th17 cells produce pro-inflammatory IL-17A and IL-17F, which are crucial for host defensive responses against infection in tissues and against external pathogens by recruiting neutrophils and macrophages.[14] Th17 cell function is related to autoimmune and inflammatory diseases, like multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), psoriasis, allergy, and asthma.[15] Only 5–7% of CD4+ T cells are Tregs which develop directly in the thymus (tTreg cells) and periphery (pTreg cells). FOXP3 (forkhead box P3), as the main regulator (immune-suppressive) of Treg cells, induces a specific gene expression program and epigenetic signature during Treg cell development. Among the chemokine receptor expression, T_h17 immune responses are highly controlled by Treg cells under RORγ expression.[16]

The immune responses are controlled through the secretion of a wide variety of pro-inflammatory (predominance of Th17) and anti-inflammatory cytokines (predominance of Treg). The balance between Th17 and Treg cells is controlled by activating the transcription factors like RORγt and STAT3 (signal transducer and activator of transcription 3) or FoxP3 and STAT5.[17-19] A balance between regulatory T cells and pro-inflammatory T helper subsets is a functional key preventive checkpoint to the pathophysiology of autoimmune diseases.[20] According to studies, the balance between Th17 and Treg cells is influenced by many factors engaging in signaling pathways initiated by T cell receptors (TCR), cytokines signals, Foxp3 stability, metabolic pathways, and the intestinal microbiota. The imbalance between Th17 and Treg cells is responsible for the pathogenesis of diseases like human leukocyte antigen B27-associated acute anterior uveitis (a distinguished increase of Th17 cells and a significant dramatic decrease of Treg cells),[21,22] chronic obstructive pulmonary disease (COPD) exacerbation (an increase of Th17 cells),[23] systemic lupus erythematosus (SLE),[24] the pathogenesis of Moyamoya disease (MMD),[25] psoriasis, IBD, RA, MS,[26] and atherosclerosis.[27]

This study aimed to review the latest progress in understanding the role of different long non-coding RNAs in regulating Th17/Treg differentiation and their balance impact on various diseases.

MALAT-1

LncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1), located on chromosome 11q13, contains more than 8000 nucleotides expressed in various healthy tissues. LncRNA MALAT-1 is regarded as a prognostic biomarker for detecting early-stage non-small-cell lung carcinoma (NSCLC) patients at risk of metastasis.[28] MALAT-1 expression is elevated in numerous cancers, affecting various tumor features.[29] MALAT-1 is also remarkably up-regulated in patients with MS, especially in secondary progressive MS (SPMS), which can be a good diagnostic biomarker.[30] Research on experimental autoimmune encephalomyelitis (EAE) mice demonstrated that MALAT-1 expression was down-regulated in the tissues of the central nervous system (CNS), exacerbating autoimmune neuro-inflammation.[30] Besides, MALAT-1 down-regulation is associated with the polarization of macrophages toward the M1 profile, a shift in T-cell differentiation toward Th-1 and Th-17, and a reduction in the differentiation of Treg cells.[31] Wu et al, showed an up-regulated MALAT-1 expression level in graft-infiltrating cells of tolerated cardiac allografts.[32] In addition, results from the adaptive transfer of MALAT-1 overexpressing dendritic cells showed prevention of acute allograft rejection after cardiac transplantation. MALAT-1 overexpression is associated with the induction of tolerogenic dendritic cells (DCs) and Tregs via the miRNA-155/dendritic cell-specific intercellular adhesion molecule-3 grabbing non-integrin (DC-SIGH)/IL10 axis.[32] Xue et al, reported that silencing up-regulated MALAT-1 in mice with acute viral myocarditis (AVMC) reduced the severity of coxsackievirus B3 (CVB3)-induced AVMC through the inhibition of Th17 cell differentiation and decreased the expression of the RORγt.[33]

NEAT1

Long non-coding RNA nuclear-enriched abundant transcript RNA 1 (lncRNA NEAT1), cytogenetically located on chromosome 11, encoding two transcriptional variants, namely NEAT1-2 and NEAT1-1, is up-regulated in different types of cancer.[4] NEAT1 is essential for the nucleus' function and assemblage of paraspeckle.[34,35] LncRNA NEAT1 expression is

positively linked to Th17 and Th1 cell proportions and the following corresponding cytokine secretion levels in sepsis patients. As a result, lncRNA NEAT1 is a possible applicable biomarker for sepsis.[36] Since lncRNA NEAT1 overexpression has been demonstrated in the peripheral blood mononuclear cells (PBMC) sample of RA patients, lncRNA NEAT1 knockdown prevents the differentiation of CD4+ T cells towards Th17 by decreasing the STAT3 protein level, a pivotal molecule for Th17 differentiation and a downstream target for NEAT1.[37] LncRNA NEAT1 upregulation has been reported in the CD4+ T cells of peripheral blood samples from patients with preeclampsia (PE). LncRNA NEAT1 silencing promotes Treg/Th17 balance via the mir-485-5p/absent in melanoma 2 (AIM2) axis in PE.[38] Karimi et al noted that up-regulation of lncRNAs NEAT1 and KCNQ1OT1 was associated with Th17/Treg imbalance in patients with relapsing-remitting MS (RR-MS).[39] Line of evidence suggests that lnc-NEAT1 silencing in DCs promotes immune tolerance by increasing Tregs and decreasing the amount of Th17 cells, inhibiting T cell proliferation, and reducing inflammatory cell infiltration in experimental autoimmune myocarditis (EAM) and heart transplantation mouse models.[40] Figure 1 outlines some of the main lncRNAs influencing the Th17/Treg imbalance.

GAS5

The long non-coding RNA growth arrest-specific 5 (lncRNA GAS5) is a member of the 5′-terminal oligopyrimidine (5′TOP) gene family, containing 12 exons. The conserved intronic sequences of GAS5 express ten box C/D small nucleolar RNAs (snoRNAs). The biological activity of GAS5 is partially dependent on snoRNAs.[41] LncRNA GAS5 has a tumor-suppressive role and is down-regulated in several types of cancer.[42] Low expression of GAS5 in patients with sepsis is negatively correlated with Th17 and IL-17A, and possibly has an inhibitory effect on the inhibition of Th17 cell differentiation.[43] It was also observed that GAS5 expression declined in the PBMCs of immune thrombocytopenia (ITP). Increased GAS5 expression alleviates ITP through TRAF6-mediated degradation of STAT3, inhibiting Th17 differentiation.[44] In a study by Chi et al, while GAS5 expression and Treg cells' percentage decreased, Th17 cells' percentage increased in patients with pneumonia. Since GAS5 overexpression in pneumonia, CD4+ T cells promote Treg targeting the miR-217/STAT5 axis, GAS5 lncRNA downregulation causes Th17/Treg inequity in childhood pneumonia.[45]

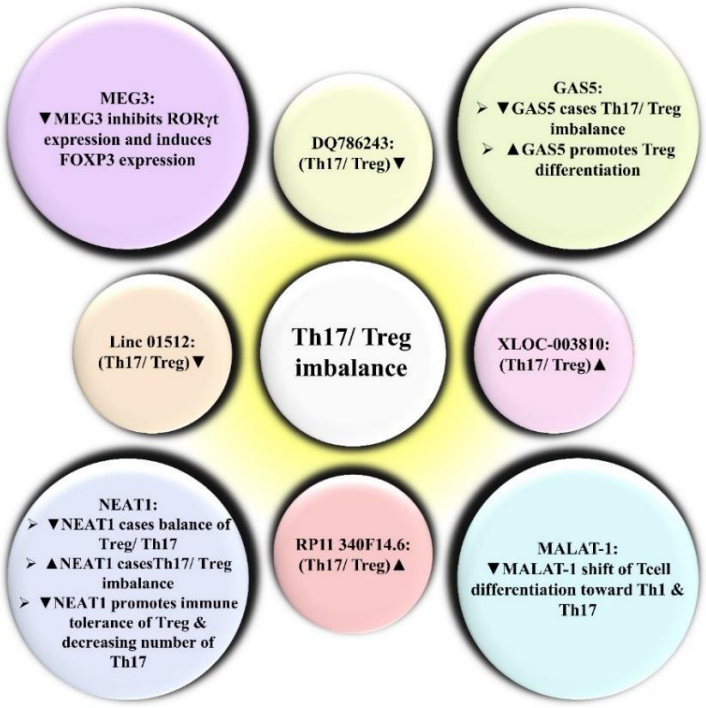

Figure 1. Effects of long non-coding RNAs on Th17/Treg imbalance.

MEG3

Human maternally expressed gene 3 (MEG3) is a lncRNA with monoallelic expression located on the 14q32.3 chromosome region. Several studies have recommended a tumor-suppressive function for this lncRNA. Upregulation of LncRNA-MEG3 has been reported in the CD4+ T cells of peripheral blood samples from patients with asthma and those with ITP.[46-48] Qiu et al, found that MEG3 lncRNA knockdown diminished the Th17 cells' percentage, RORγt protein and mRNA levels, and Th17-associated cytokines with no effect on the Tregs' percentage, Treg-related cytokines, and FOXP3 level.[47] LncRNA-MEG3 regulates Treg/Th17 balance in asthma patients by competing for endogenous RNA, sponging microRNA-17, and increasing the RORγt expression.[47] Moreover, lncRNA-MEG3 induces Treg/Th17 immune imbalance via miR-125a-5p decoy. LncRNA-MEG3 knockdown inhibits RORγt expression and induces Foxp3 expression. The downstream target of miR-125-5p is CXC chemokine ligand-13 (CXCL13). Dexamethasone administration indicated the opposite effect on the MEG3/miR-125a-5p/CXCL13 axis.[48,49]

LncRNA PVT1

LncRNA plasmacytoma variant translocation 1 (PVT1), located on the 8q24 chromosomal region, is associated with oncogenic function in various cancers.[50] ITP is a platelet-related blood disorder that changes the Treg/Th17 balance by shifting CD4+ T-cell differentiation to Th1 and Th17.[51] In primary ITP, the Treg/Th17 cell ratio is associated with diseased activity.[52] Yu et al indicated that the lncRNA PVT1 level was lowered, whereas the number of Th17 cells was elevated in patients with ITP.[53] Increased expression of PVT1 leads to decreased Th17 cell number and differentiation through increased ubiquitination and degradation of NOTCH1, introducing an appropriate therapeutic target for ITP treatment.[53] Lu et al, revealed that since PVT1 overexpresses the TNF receptor-associated factor (TRAF) 6 by sponging miR-146a, lncRNA PVT1 upregulation leads to increased Treg cell autophagy to suppress heart transplant rejection.[54]

LncRNA DQ786243

DQ786243 overexpression, for the first time, was discovered in hepatocellular carcinoma (HCC).[55] Then, the up-regulatory function was reported for some types of cancers like colorectal cancer,[56] gastric cancer (GC),[57,58] ovarian cancer,[59]and HCC.[60,61] Yu Qiao et al, (CD) patients compared with healthy controls or clinically inactive CD patients. LncRNA DQ786243, related to the severity of CD, regulates the performance of Tregs by affecting CREB and Foxp3 expression in CD. However, cAMP response element binding protein (CREB) is a chief member of the group of bZIP-containing transcription factor that is overexpressed in a wide range of tumors and is not the only mediator of DQ786243 for Foxp3 upregulation.[62,63] Wang et al, found that DQ786243 lncRNA and Foxp3 were intensely expressed in CD4+ cells of oral lichen planus (OLP) patients (64). DQ786243 overexpression in normal CD4+ cells stimulates Foxp3 expression, increases the number of Foxp3+ Tregs, increases the Tregs' suppressive function via the Foxp3-miR-146a-NF-κB axis, and inhibits both the Th1 and Th17 functions by decreasing IFN-γ and IL-17 levels.[64]

LncRNA RP11 340F14.6

Huang et al, exhibited that the increased expression of RP11 340F14.6 lncRNA in the PBMC sample of patients with juvenile idiopathic arthritis (JIA) caused the shift of T-cell differentiation toward the Th17 subset, increasing Th17/Treg ratio by bonding to its neighbor, P2X7R. Therefore, RP11 340F14.6 could be a therapeutic biomarker for JIA.[65]

Lnc-DDIT4

DNA damage-inducible transcript 4 (DDIT4) is a cytoplasmic and tumor-associated protein that is up-regulated under stressful conditions like DNA damage, chemotherapy, and hypoxia.[66] The mammalian target of rapamycin (mTOR), a serine/threonine kinase protein that controls immune responses and inflammatory processes, including glial function modulation and mTOR inhibitors (like rapamycin), improves various experimental models of MS.[67] Zhang et al, stated that the mRNA expression of lncDDIT4 and DDIT4 in PBMCs and CD4+ T cells in MS patients was higher than in healthy groups.[68] LncRNA DDIT4 (lncDDIT4) upregulation in patients with MS is linked with the inhibition of DDIT4/mTOR pathway and Th17 differentiation by targeting DDIT4. Moreover, lncDDIT4 expression in healthy individuals inhibits Th17 differentiation.[68]

LncRNA MIAT

MIAT is located on chromosome 22q12.1, primarily recognized as a susceptible locus for myocardial infarction. It has been argued that MIAT involves other diseases such as cancer, endocrine system diseases, nervous system diseases, and cardiovascular system diseases.[69] Ma et al, found that MIAT expression levels were elevated in the nasal mucosa of allergic rhinitis mice.[70] Furthermore, MIAT overexpression promoted allergic inflammatory symptoms and responses by increasing the differentiation of Th-17 cells via miR-10b-5p sponges.[70]

XLOC_003810

LncRNA XLOC_003810 increases the frequency of activated CD4+ T-cells and a range of pro-inflammatory cytokines such as IFN-γ, TNF-α, and IL-1β in patients with myasthenia gravis-related thymoma (MG-T).[71] It also inhibits the expression of PD-1/PD- L1 (71). Niu et al, documented that the level of LncRNA XLOC_00381 was significantly high in CD4+ T cells of thymic samples from patients with MG-T.[72] Lentivirus-mediated studies of XLOC_003810 silencing and up-regulation in CD4+ T cells showed that increased expression of XLOC_003810 was associated with a high Th17/Treg imbalance, which should be considered a therapeutic target in future studies.[72]

CRNDE

Colorectal neoplasia differentially expressed (CRNDE)**,** located on chromosome 16, was initially found to be excessively expressed in colorectal cancer. Its overexpression has also been reported in several types of cancer.[73] Sun et al, mentioned that transmitting lncRNA CRNDE-h in colorectal cancer (CRC) patients' serum-driven exosomes to CD4+ T cells increased the Th17 cell differentiation, IL-17 promoter activity, and RORγt expression. Some regulatory functions of CRNDE, such as inhibiting ubiquitination and degradation of RORγt, are accomplished by binding to the PPXY motif of RORγt, ultimately increasing RORγt expression and elevating IL-17 promoter activity.[74]

LncRNA LINC01512

LINC01512 lncRNA is located on the 6P21.1 chromosomal region and overexpressed in patients with lung adenocarcinoma, correlating to the increased progression of lung adenocarcinoma.[75] Gao et al, indicated that LINC01512 expression is enhanced by its upstream regulator, melatonin, via the AMPK signaling pathway. LINC01512 stimulates Treg differentiation and interferes with Th17 differentiation by enhancing SIRT1 expression, resulting in a Treg/Th17 imbalance in necrotizing enterocolitis.[76]

IFNA-AS1

IFNG-AS1, known as TMEVPG1, is located in a cytokine gene cluster that controls *Ifng* gene expression.[77] Luo et al, found that IFNA-AS1 increased the ratio of the Treg subset and decreased the Th1 subset ratio by regulating the expression level of their transcription factors. However, they indicated a slight impact on the Th17 and Th2 subsets ratio in an experimental autoimmune myasthenia gravis (EAMG) model.[78]

Lnc-ITSN1-2

Long non-coding RNA intersectin 1–2 (lnc-ITSN1-2), placed on chromosome 21, is markedly up-regulated in patients with RA, and its plasma level is associated with the inflammatory index and disease activity.[79] Blood lnc-ITSN1-2 is elevated in the PBMCs of patients with sepsis disease. Expression of lnc-ITSN1-2RNA has been positively correlated with increased Th17 cells, inflammation, and multiple organ dysfunction in sepsis patients.[80] Another study showed that lnc-ITSN1-2 functions as a ceRNA to up-regulate IL-23R expression through sponging miR-125a in IBD CD4+ T cells.[81] Furthermore, lnc-ITSN1-2 promotes IBD CD4+ T cell proliferation and activation and IBD CD4+ T cell differentiation toward Th1/Th17 cells, indicating a direct link between risk and disease activity in IBD patients.[81] Figure 2 outlines some of the main lncRNAs influencing the Th17 differentiation.

Lnc-SGK1

A high salt diet (HSD) promotes tissue inflammation, and the pathogenic differentiation of Th17 cells accelerates the progress of autoimmunity due to SGK1 increased expression in the presence of salt and following IL-23R increased expression by inactivating Foxo1.[82] One study declared that in mice fed with a diet high in salt, a more intense form of EAE was observed due to an increased number of pathogenic IL-23-dependent Th17s. The development of Th17 cells could be disrupted by gene silencing or chemical inhibition of p38/MAPK, NFAT5, or SGK1.[83] Yao et al, found that SGK-1 and long non-coding RNA SGK1 (lnc-SGK1) expression were increased in the presence of

Helicobacter pylori infection and HSD in patients with stomach cancer. The SGK1 promoter region upstream lnc-SGK1 stimulates Th17 and Th2 cell differentiation and reduces Th1 cell differentiation by triggering the SGK1/JunB signaling pathway, which is regarded as a valuable prognostic indicator in GC patients.[84]

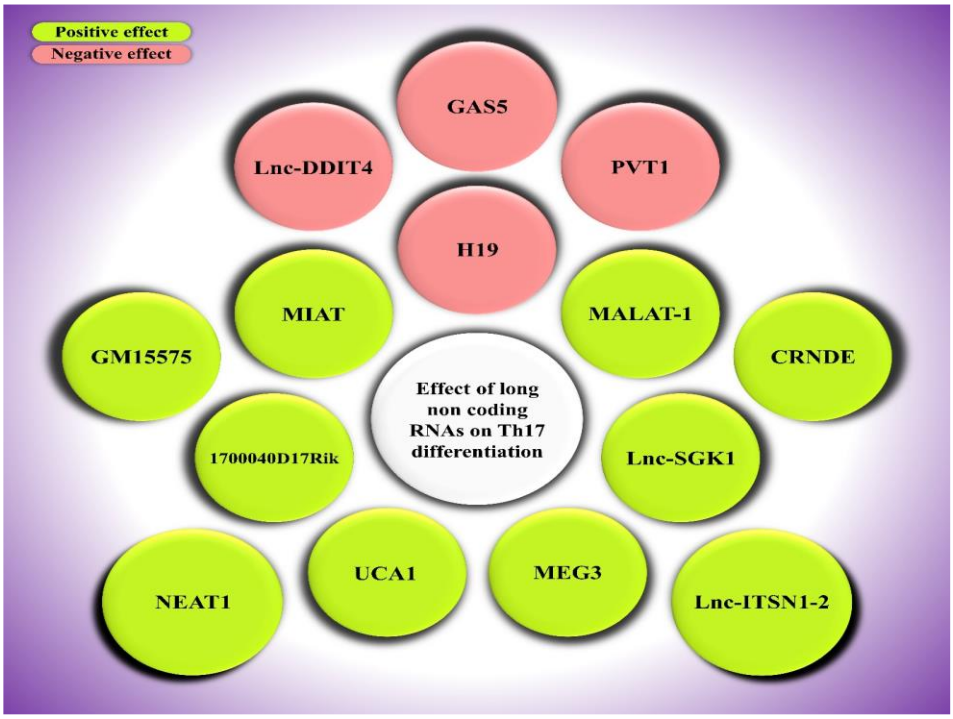

Figure 2. Effects of long non-coding RNAs on Th17 differentiation.

LncRNA H19

LncRNA H19 belongs to an imprinted cluster located on the 11p15 chromosome region. H19 is only transcribed from the maternal chromosome in healthy tissues since the paternal chromosome promoter is methylated and not expressed.[85] Liu et al, discovered the H19 downregulation in peritoneal fluid mononuclear cells (PFMC) from endometriosis (EMS) patients with Th17 differentiation. The increased expression of LncRNA H19 promotes IER3 expression via miR-342-3p sponging, inhibits Th17 cell differentiation, and decreases IL-17 levels and proliferation of endometrial stromal cells (ESCs).[86]

LncRNA UCA1

Long non-coding RNA Urothelial Carcinoma Associated 1 (UCA1), located on chromosome 19p13.12, is a member of the human endogenous retrovirus H family identified as an oncogenic lncRNA in many cancers.[87] Ren et al, revealed that the UCA1 level was increased in $CD4^+$ T cells of patients with acute ischemic stroke. Consequently, it can be considered a prognostic indicator because its elevation is positively associated with the enhanced Th-17 cell proportion, inflammation-related cytokines, and disease severity.[88]

LncRNA Gm15575

Identified for the first time by Bian et al, Gm15575Z is a novel lncRNA up-regulated in the spleen tissue and Th17 cells of EAE mice and could be related to the pathogenesis of MS.[89] LncRNA Gm15575 regulates the differentiation and function of Th17 cells by upregulating pro-inflammatory chemokine C–C motif of chemokine ligand 7 (CCL-7) through sponging miR-686, and CCL7 chemokine then recruits Th cells, particularly Th17 cells.[89]

1700040D17Rik

Guo et al, recognized a new long non-coding RNA in mice, lncRNA-1700040D17Rik, located on mouse genomes close to the RORγt gene. LncRNA-1700040D17Rik is operated only in cis and is down-regulated in CD4+ T-cells isolated from spleens of EAE

mice compared to normal mice and remarkably expressed following treatment with rhIL23R-CHR. 1700040D17Rik promotes Th17 cell differentiation in EAE mice via positive RORt expression regulation, indicating a possible role for lncRNA-1700040D17Rik in MS pathogenesis.[90]

LncRNA HULC

Hepatocellular carcinoma up-regulated lncRNA (HULC) is approximately 500 nucleotides long and cytogenetically located on chromosome 6p24.3, including two exons. HULC is a lncRNA most strongly expressed in hepatocellular carcinoma with an oncogenic effect on several cancers.[91] Du et al, found that HBV X protein (HBx), originating from the hepatitis B virus genome, induces upregulation of HULC, which promotes hepatoma cell proliferation by P18 expression inhibition.[90] Furthermore, Zhao et al, reported that HULC was overexpressed in Tregs of peripheral blood from patients with HBV-related liver cirrhosis and that CD4+ CD25+ FoxP3+ Tregs were abundant in these patients' blood.[91] Consequently, HULC promotes the differentiation and function of Tregs by directly inhibiting p18 expression.[91] Figure 3 outlined some of the main lncRNAs influencing the Treg differentiation.

LncRNA HOXA-AS2

LncRNA homeobox A cluster antisense RNA 2 (HOXA-AS2) is an oncogenic lncRNA between the HOXA3 and HOXA4 genes in the HOXA cluster, which is extremely expressed in several types of cancer.[92] Zhong et al, reported higher expression of HOXA-AS2 in tumor tissues of glioma patients and glioma cell lines.[92] HOXA-AS2 upregulation in glioma patients brought about poor outcomes. LncRNA HOXA-AS2, by sponging of miR-302a, activates the lysine demethylase 2A (KDM2A)/jagged 1 (JAG1) axis pathway, promoting the differentiation and proliferation of Tregs and immune tolerance in the gliomas.[92,93]

Linc-POU3F3

The long intergenic non-protein-coding RNA POU3F3 (Linc-POU3F3), with a length of 747-bp, is located on chromosome 2q12 on the reverse strand next to the POU3F3 gene. Increased expression of Linc-POU3F3 has been ascertained in several types of cancer, including esophageal squamous cell carcinoma, glioma, and colorectal cancer.[94-96] Xiong et al, indicated that the elevated expression of linc-POU3F3 in peripheral blood T-regs of GC patients caused elevated T-reg differentiation and GC cell proliferation by activating the TGF-beta signal pathway.[97]

LncRNA FEZF1-AS1

The 2653 bp long FEZ family Zinc Finger 1-Antisense RNA 1 (FEZF1-AS1) lncRNA is located on chromosome 7q31.32. It has been proposed that this newly detected lncRNA with oncogenic effects is vastly expressed in several malignancies.[98] Hong et al, discovered higher levels of FOXP3 and FEZF1-AS1 expression and lower levels of miR-149-3p expression in colon cancer cell lines and tissues from colon cancer patients. Higher levels of FEZF1-AS1 were correlated with poor prognosis and unfavorable conditions like the immuno-escape of CC cells due to the effect on Treg differentiation in patients with colon cancer. FEZF1-AS1 silencing reduced the progression of CC cells by elevating miR-149-3p to suppress FOXP3 expression.[99]

LncRNA HCP5

The long non-coding RNA human histocompatibility leukocyte antigen (HLA) Complex P5 (HCP5) is a cancer-related lncRNA with an oncogenic role that is up-regulated in several cancers. However, it may be tumor-suppressive in cutaneous melanoma.[100] Yang et al, revealed that long non-coding RNA HCP5 expression is diminished in nasal tissues, PBMCs, CD4+ T cells, and isolated Tregs from the peripheral blood of allergic rhinitis (AR) patients compared with the normal group. LncRNA HCP5 increases ATXN2L expression by miR-16 sponging, resulting in Treg proliferation, differentiation, and inflammatory response inhibition in nasal epithelial cells of AR patients.[101]

LncRNA RP11-357H14.17

LncRNA RP11-357H14.17 is intensely expressed in diffuse-type GC and patients with endometrial carcinoma. RP11–357H14.17 expressional upper levels are also directly linked to the poor prognosis of both cancers.[102,103] Xiaoli et al, found that excessive expression of lncRNA RP11-357H14.17 in GC tissues was associated with a poor prognosis. Oncogenic functions of lnc-RNA RP11-357H14.17 were correlated to ATF2 (homo sapiens basic leucine zipper transcription factor, ATF-like 2) signaling and immune system inhibition by increasing the differentiation of Tregs. Therefore, RP11-357H14.17 could be a valuable prognostic biomarker for GC.[104]

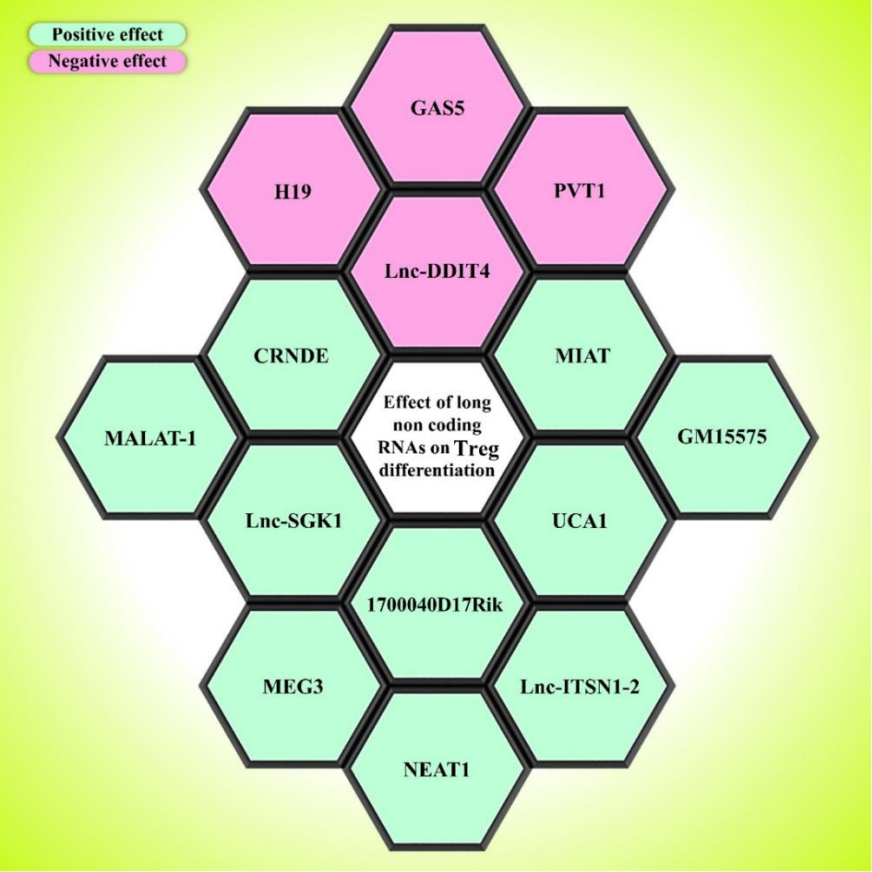

Figure 3: Effects of long non-coding RNAs on Treg differentiation.

LncRNA lnc-EGFR

Jiang et al, discovered a novel cancer-associated lncRNA by high-throughput screening of Treg cells in HCC, named lnc-epidermal growth factor receptor (EGFR). Lnc-EGFR stimulates Treg cell differentiation and CTL activity inhibition, stopping EGFR ubiquitination and degradation by c-CBL and the downstream AP-1 and NF-AT1 stimulation, resulting in HCC tumor growth and immunity escape.[105] Furthermore, Lnc-EGFR promotes proliferation and inhibits apoptosis in human tongue cancer by positively regulating EGFR.[108]

Lnc-Smad3

Xia et al, discovered that two opposing critical epigenetic modifiers, lnc-Smad3, and H3K4 methyltransferase Ash1, regulating TGF-β-mediated iTreg cell polarization. The interaction of lnc-Smad3 with the histone deacetylase HDAC1 leads to Smad3 transcriptional silencing, whereas Ash1l enhances Smad3 expression through the direct targeting of the Smad3 promoter that increases the local H3K4 trimethylation.[106]

LncRNA HAGLR

The HOXD antisense growth-associated long non-coding RNA (lncRNA HAGLR), known as HOXD-AS1, placed between the HOXD3 and HOXD1 genes on chromosome 2, is expressed differentially in numerous types of cancer.[107] Yan et al, showed that in patients with dermatomycosis (DM), the expression levels of HAGLR lncRNA and Foxp3 were elevated, but the amount of Tregs and RUNX3 protein levels were decreased. Therefore, HAGLR LncRNA silencing promoted the differentiation of Tregs via the runt-related transcription factor (RUNX3)/Foxp3 axis.[108]

LncRNA SNHG1

Small nucleolar RNA host gene 1 (SNHG1) functions as an oncogenic element in different types of cancer.[109] Pei et al, observed that excessive expression of LncRNA SNHG1 in CD4+ tumor-infiltrating

lymphocytes (TILs) of breast cancer patients supports the immunity-mediated escape of tumor cells and differentiation of Tregs through the miR-448/IDO axis. Consequently, lncRNA SNHG1 knockdown leads to a dramatic drop in FOXP3 and IL-10 expression.[110]

LncRNA FENDRR

Yu et al stated that lncRNA FENDRR expression, a tumor-suppressor gene, was diminished in HCC tissues and HCC cell lines.[111] As a result, lncRNA FENDRR overexpression in HCC cells induced apoptosis and inhibited proliferation and Treg-mediated immune escape mechanisms by sponging miR-423-5p; it also up-regulated the growth arrest DNA-damage-inducible beta-protein (GADD45B). [111]

LncRNA CDKN2B-AS1

LncRNA cyclin-dependent kinase inhibitor-2B-antisense RNA 1 (CDKN2B-AS1) is a newly found lncRNA with altered expression in several types of cancer. It can be used as a prognostic biomarker or treatment target in many diseases.[112] Lei et al, found that the expression of lncRNA CDKN2B-AS1 was high in patients with cerebral infarction since CDKN2B-AS1 knockdown inhibited the proliferation of Tregs through the up-regulation of MAPKK kinase 1 (MAP4K1) and the decline of transcription factor B-cell lymphoma/leukemia 11A (BCL11A).[113] Therefore, targeting CDKN2B-AS1 can be a potential therapeutic strategy.[113]

LncRNA SNHG16

Small nuclear RNA host gene 16 (SNHG16), known as ncRAN (non-coding RNA expressed in aggressive neuroblastoma), is an oncogenic lncRNA located on chromosome 17q25.1. In addition to its overexpression in invasive neuroblastoma, SNHG16 is unusually expressed in many cancers.[114] In breast cancer, the largest tumor lymphocyte infiltrating cells are CD73+ γδT1 cells, a population of Treg cells with an immunosuppressive function.[115] Researchers found that breast tumor cell-derived exosomes (TDEs) could transfer the lncRNA SNHG16 to Vδ1 T cells. Also, lncRNA SNHG16 up-regulated SMAD5 by decoying miR-16–5p, resulting in CD73 expression in these cells.[115]

LncRNA RP11-323N12.5

Wang et al, mentioned that the most expressed lncRNA in GC, according to the data from the TCGA database, is RP11-323N12.5, which binds to c-MYC in the promoter region of YAP1, up-regulates its expression and induces tumorigenesis and immunosuppression.[116] They revealed that in T cells, RP11-323N12.5 induced Treg differentiation in a YAP1 upregulation-dependent manner.[116]

LINC00301

Long intergenic non-coding RNA 00301 (LINC00301) is pronouncedly expressed in NSCLC, correlated with a poor prognosis. Also, LINC00301 facilitated the proliferation, migration, and invasion of cancer cells and caused Tregs' infiltration and CD8+ T cells' inhibition in the tumor microenvironment (TME) by targeting TGF-β.[117]

LncRNA Flatr

Brajic et al, found a new lncRNA specifically expressed in a subset of activated Tregs, named Foxp3-specific lncRNA anticipatory of Tregs *(*Flatr), cytogenetically located on chromosome 13. Flatr is considered one of the principal members of the Treg lncRNA transcriptome, promoting Treg cell development by enhancing FOXP3 expression.[118]

LncRNA Flicr

Zemmour et al found a mature Treg-specific lncRNA, named Foxp3 long intergenic non-coding RNA (Flicr), located on the human and mouse genomes, very close to the FOXP3 locus, and influencing FOXP3 only in a cis-fashion. T.LncRNA.Flicr disrupts Treg cell differentiation by modifying the accessibility of chromatin at the FOXP3 locus under IL-2 restriction conditions, triggering autoimmunity.[119]

CONCLUSION

This review presented long non-coding RNAs as inhibitory and stimulatory elements that interfered with Treg and Th17cell differentiation, resulting in Treg/Th17 imbalance in several diseases, including cancer. We also reviewed many lncRNAs contributing to the escape of tumor cells from immune responses through the enhancement of Treg differentiation, resulting in their immunosuppressive effects in the tumor microenvironment. Thus, these lncRNAs should be considered as potential targets for several reasons, such as strengthening the immune system in cancer therapy and developing promising

prognostic biomarkers, diagnostic indicators, and therapeutic agents in Treg/Th17 disordered-associated diseases.

Future prospective

Some regulatory functions of current lncRNAs are associated with effects on Th17/Treg expression and differentiation, which play an essential role in the pathophysiology of immune-related disorders and cancer. Finding a comprehensive connection between LncRNAs and their impact on the status of Th17/Treg provides a promising prospect to develop potential therapeutic targets, discover novel cancer biomarkers, and unearth new targets for the treatment of CD4+-mediated pathologies.

STATEMENT OF ETHICS

This study complied with all the related ethical standards.

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There was no funding resource for this review study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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