Review Article

Biological functions and affected signaling pathways by Long Non-Coding RNAs in the immune system

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ABSTRACT

Recently, the various regulative functions of long non-coding RNAs (LncRNAs) have been well determined. Recently, the vital role of LncRNAs as gene regulators has been identified in the immune system, especially in the inflammatory response. All cells of the immune system are governed by a complex and ever-changing gene expression program that is regulated through both transcriptional and post-transcriptional processes. LncRNAs regulate gene expression within the cell nucleus by influencing transcription or through post-transcriptional processes that affect the splicing, stability, or translation of messenger RNAs (mRNAs). Recent studies in immunology have revealed substantial alterations in the expression of lncRNAs during the activation of the innate immune system as well as the development, differentiation, and activation of T cells. These lncRNAs regulate key aspects of immune function, including the manufacturing of inflammatory molecules, cellular distinction, and cell movement. They do this by modulating protein-protein interactions or through base pairing with RNA and DNA. Here we review the current understanding of the mechanism of action of lncRNAs as novel immune-related regulators and their impact on physiological and pathological processes related to the immune system, including autoimmune diseases. We also highlight the emerging pattern of gene expression control in important research areas at the intersection between immunology and lncRNA biology.

1. Introduction

Long non-coding RNAs (LncRNAs) (more than 200 nucleotides) are considered a type of genome transcript, usually determined by non-protein transcripts, that regulate many biological aspects of human disease [1–3]. Genomes with extensive transcription lead to the production of thousands of lncRNAs, which are not translated into practical proteins. This broad definition includes a large and heterogeneous set of transcripts that have differences in terms of biogenesis and genomic origin. According to GENCODE data, the human genome includes over 16,000 lncRNA genes, although other sources estimate the number of human lncRNAs exceeds 100,000 [4,5]. These primarily consist of lncRNAs transcribed by both RNA polymerase II and other RNA polymerases [1,6]. LncRNAs regulate gene expression through multiple mechanisms. RNA, proteins, and DNA interactions allow lncRNAs to influence chromatin structure and function, transcription of nearby and distant genes, RNA splicing, stability, and translation, among other

aspects of gene expression regulation (Fig. 1) [7,8]. Additionally, lncRNAs can affect the splicing, stability, and translation of RNA molecules. In addition, lncRNAs participate in the establishment and modulation of organelles and nuclear condensates [1].

The interaction of LncRNAs in cancer is well-known in various processes including cell cycle, proliferation pathways, and microbial balance [9–11]. In addition, LncRNAs could tightly control the development, homeostasis, and innate/acquired immune responses via macrophages, monocytes, mast cells, dendritic cells, neutrophils, eosinophils, innate lymphoid cells (ILCs), basophils and, B or T lymphocyte. Hence, LncRNAs could have key roles in immune-related diseases such as auto-immune disorders and inflammatory pathways [12]. Precise regulation of immune system gene expression depends on an organism's capability to develop a strong immune response against pathogens without identifying self-antigens [13,14]. Previous studies have explained the surface receptor functions, secreted cytokines, and transcription factors involved in this process, but relatively little information is available on the function of RNA [15]. Moreover, the process

provided a list of rapid annotation and LncRNAs functional analyses in the genome with more than 58,000 estimations of LncRNAs [24]. So far, the function of a limited number of LncRNAs has been reported and the rest are probably just "noise" transcriptions [25]. However, different functions associated with gene transcription and protein regulation are performed by many LncRNAs [26]. Recently, the positive functions of LncRNAs associated with the immune system have been presented [27]. In vivo and in vitro studies define cellular functions and phenotypes and manipulate accessible cellular components at both molecular and cellular levels. Hence, the potential of LncRNAs in the immune system control offers highly organized biological systems [26,28,29]. Here, we try to review the recent advances in the mode of action related to LncRNAs during the immune system based on the biological functions in immune system-related disease with an emphasis on circular RNA (circRNA), RNA editing, RNA modification, and the extent of their expression. Also, we tend to emphasize the importance of future immunologic prospects to fill the gaps in LncRNA biology and its specific functions.
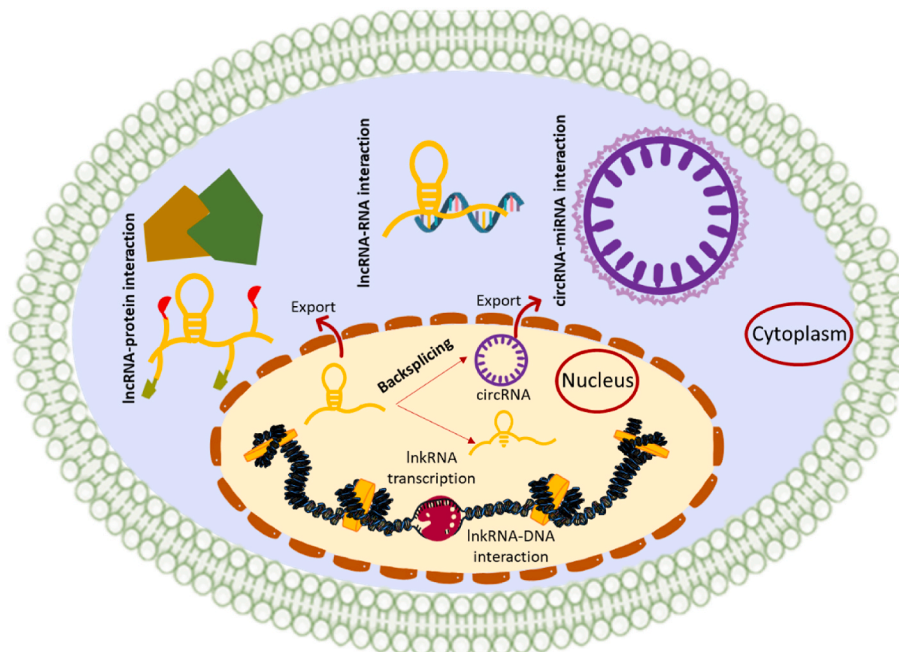
2. Long non-coding RNAs

2.1. Potential of LncRNAs in the immunogenetic events regulation

Fig. 1. LncRNA mechanism and function via binding with DNA, RNA, and proteins. LncRNAs have modular domains that allow them to interact with DNA, RNA, or proteins, often through higher-order RNA structures. The mere process of transcribing lncRNAs can itself exert regulatory effects on gene expression, such as by altering chromatin accessibility or sequestering transcription factors at target gene promoters.

related to cancer immunity such as exposure/recognition of antigen and immune infiltration is mediated by LncRNAs significantly [16].

In this line, various studies reported that LncRNAs are dysregulated in the onset and development of cancers such as LncR-SNHG1 which helps breast cancer to escape from the immune system [17]. Another example is referred to LncR-NKILS which promotes apoptosis on cytotoxic T lymphocytes and consequently prevents tumor immunity [18]. The function of RNA as a passive carrier of DNA codes into proteins has been proved and now the researchers are focused on its active roles in different processes during gene expression such as transcription, translation, and post-translational modification (PTMs) [19]. According to the results of scientists' studies, more than 70 % of the mammalian genome is transcribed, but the majority of these transcripts do not ultimately translate into proteins [20–23]. Finally, these results have

In recent years, the biological functions of various LncRNAs have been investigated such as Xist (turning off the X chromosome), H19 (genomic printing), LincRNA-RoR (embryonic stem cells differentiation (ESCs), and HOTAIR (metastatic breast cancer). The dominant molecular archetype was not found for LncRNAs but is able to bind with DNA, RNA, and proteins using modular domains or higher-order RNA structures, respectively like protein scaffolds (Fig. 2). The vital role of LncRNAs in the immune system regulation is proven but because of their complexity, an understanding of different regulatory functions is still challenged. The level of LncRNAs in various immune cells is found in their development, differentiation, and activation process [30,31]. Restrictive activity of immune-related LncRNAs is determined especially in RNA/protein or RNA/DNA binding. This information mentions the worthwhile effect of immune-related LncRNAs which are near the
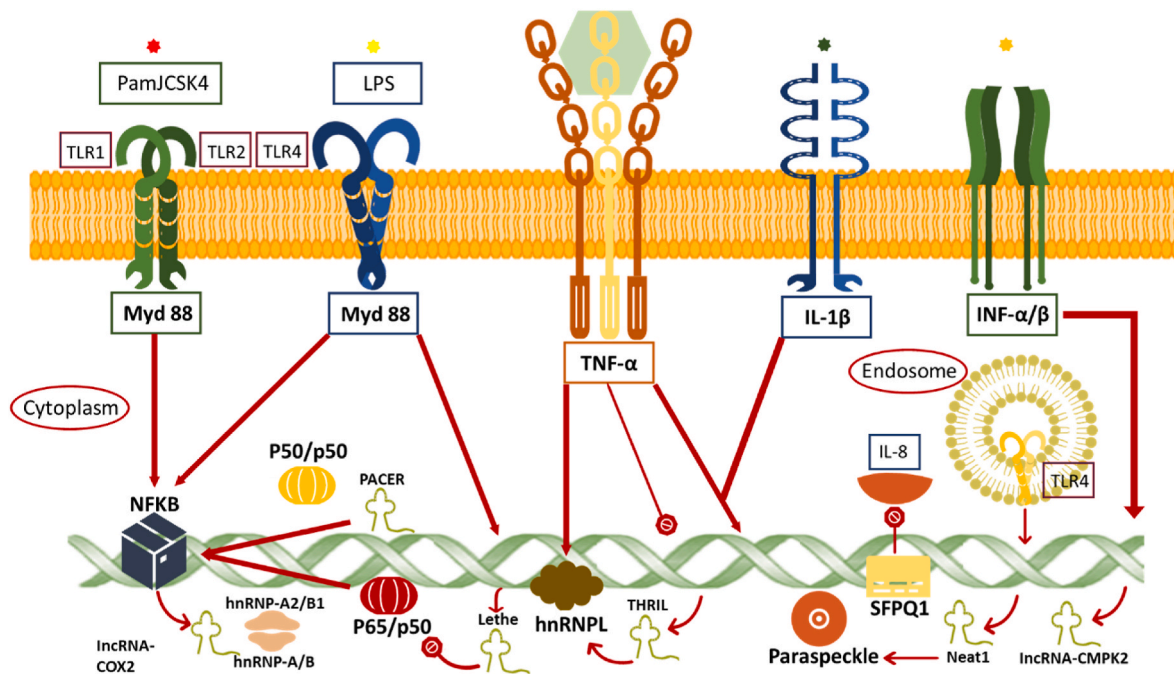
Fig. 2. Overview of LncRNAs linked with immune system that are involved in the modulation of deoxyribonucleic acid, red arrows indicated their association as nursing or inhibition interactions, respectively. IL: interleukin, hnRNP: heterogeneous nuclear ribonucleoproteins.

immune system genes and organize their activity in cis/trans manner such as IL1 -RBT46 [32], lnc-IL7R [33–35] and lincRNA-Ccr2-5′ AS [36]. Generally, a standard promoter region is needed for LncRNAs and mRNAs to two direct transcriptions. The immune-related LncRNAs are transcribed at antisense direction which are usually overlapped with genes that are produced proteins [37]. Recently, several LncRNAs are determined to manage the transcription mechanisms in both cis or trans manner such as HOTAIR act in trans and is placed in intergenic regions [38]. Whereas alternative LncRNAs have been able to regulate their adjacent genes proteins in cis effect such as PACER [39], lnc-IL7R [33], THRIL [40], and lincR-Ccr2-50 A S [35]. It is essential to clarify in what manner immune-related LncRNAs affect targets using dedicated transcription factors that are chargeable for inflammatory intermediary production [31,41]. Moreover, the role of several LncRNAs in inflammation and response is discovered such as various several pathways NF-kB, arachidonic acid, JAK/STAT, and MAPK signal [42]. Also, the molecular functions and responsible processes of various LncRNAs have been explained based on sequencing technologies. Furthermore, the involvement of lncRNAs with RNA, DNA, or RNA-Protein are precisely determined [35]. Moreover, LncRNAs could manage the gene expression at different processes connected to transcription, splicing, translation, and degradation of nucleic acid. With regarding different assays like microarray and RNA-Sequencing, the LncRNAs functions in innate immunity became the attraction subject, and discovered numerous important LncRNAs involved in immune gene expressions for example Lethe, PACER, THRIL, and NEAT1 [36] (Table 2). Recent research has demonstrated that Long non-coding RNAs play a functional role in both the innate and adaptive immune system [43]. While the regulation of adaptive immunity, including B and T cell biology, has traditionally been studied from a protein and microRNA perspective [44–46], the emergence of LncRNAs as a new class of non-coding RNAs has shed light on their impact on key factors in lymphocyte biology, such as NOTCH, PAX5, MYC, and EZH2. These LncRNAs have been found to modulate lymphocyte activation by influencing pathways like NFAT, NFκB, MYC, interferon, and TCR/BCR signaling (NRON, NKILA, BCALM, GAS5, PVT1), as well as cell effector functions (IFNG-AS1, TH2-LCR). The increasing body of evidence suggests that LncRNAs, similar to miRNAs and proteins, play critical and essential roles in the physiology of B and T

cells, with potential implications for autoimmune diseases and malignancies [43] (Table 3).

LncRNAs have recently emerged as an important component of the adaptive immune system, participating in regulatory networks that govern the development, activation, and differentiation of lymphocytes. The key regulators that drive lymphocyte development also control the expression of numerous lncRNAs, indicating the crucial role of these non-coding RNAs in the maturation of T and B cells [35]. LncRNAs, like IFNG-AS1, Morrbid, and lncRNA-AS-GSTT1, have been shown to directly impact T cell responses and influence T helper cell polarization. These lncRNAs collaborate with key transcription factors involved in T cell polarization, enhancing cytokine production essential for cellular effector functions. Dysregulation of lncRNAs may also lead to an imbalance in Th cell populations, which can contribute to the development of autoimmune diseases [47,48]. The production of antibodies has been linked to lncRNA expression in B cells. Similarly, lncRNAs expressed by other cells in the local environment can affect antibody production by B cells, as indicated by the NEAT1-BAFF axis. Furthermore, lncRNAs play a crucial role in the germinal center reaction by supporting the functions of activation-induced cytidine deaminase and promoting class switch recombination [49]. LncRNAs also play a role in regulating the overall biology of B cells by modulating the signals that promote B cell survival during activation. Disrupting the normal expression of lncRNAs can influence various signaling pathways and contribute to the development of lymphoma, while certain lncRNAs can collaborate with well-known oncogenes like MYC in malignant B cells [50–52]. The genetic abnormalities observed in hematological cancers are associated with distinct lncRNA expression patterns, which may be useful for differentiating disease subtypes. The genomic aberrations and other alterations present in hematological malignancies are likely to disrupt the normal expression of lncRNAs, and this has been shown in certain cases [53]. LncRNAs play a crucial role in various stages of both cellular and humoral immune responses. Akin to the insights gained from studying microRNA (miRNA) functions, investigating lncRNAs can uncover novel molecular mechanisms. Consequently, the established literature on adaptive immunity will require re-evaluation from the emerging perspective of lncRNAs.

Table 1
Exosomal lncRNAs associated with autoimmunity disorders.

Exosomal LncRNA	Expression level	Description	Ref.
NEAT1	Up-regulated	It causes M2 polarization of macrophages and reduces joint inflammation.	[62]
Hotair	Up-regulated	Inducing an immune response	[63]
LUST	Up-regulated	They probably perform a role in the pathogenesis of RA.	[64]
anti-NOS2a	Up-regulated		
MEG9	Up-regulated		
SNHG4	Up-regulated		
TUG1	Up-regulated		
H19	Up-regulated	probably causes the progression of the entire cholestatic autoimmune disease.	[65]
lincRNA-Cox2	up-regulation	Following microbial challenge, it induces the expression of pro-inflammatory genes	[66]
HAR1B	Up-regulated	Its high expression in blood mononuclear cells (BMCs) of RA patients.	[63]
PRINS	Down-regulated	Its low expression in blood mononuclear cells (BMCs) of RA patients.	
HOXA3as	Down-regulated		
TRAFD1-4:1	Up-regulated	It affects CXCL-1 target gene expression by inhibiting miR-27a-3p.	[67]
LYRM4-AS1	Down-regulated	It plays a regulatory role in cartilage apoptosis.	[68]
PCGEM1	Up-regulated	–	[69,70]
OANCT	Up-regulated	It can intensify joint inflammation by increasing macrophages to M1 type polarization.	[71]
LINC01015	Up-regulated	Involved in inflammation	
ENST00000584157.1	Up-regulated	–	[72]
KLF3-AS1	Down-regulated	It inhibits apoptosis in cartilage cells.	[73]

Table 2
LncRNAs associated with innate immunity.

LncRNA	Expression level in innate immunity	Description	Ref.
ANRIL	Down-regulated	Controls proliferation of cells by TNF-α and NF-κB	[74,75]
Linc-MAF-4	Up-regulated	induces differentiation of TH1 by repressing MAF expression	[76,77]
AS-IL1α	Up-regulated	Regulates IL-1α transcription via RNAP-II (RNA Polymerase II)	[78]
FIRRE	Down-regulated	controls inflammatory genes expression like NFkB-dependent expression and increases the VCAM1	[79,80]
H19	Up-regulated	Setting the insulin-like growth factor pathway	[81]
IL-1b-RBT46	Down-regulated	regulate IL-1 and CXCL8 by NF-kB	[82]
IL7-AS	Down-regulated	Affected the IL-6 level by NF-kB pathway	[83]
Lathe	Up-regulated	Regulate various processes: NF-kB, production of ROS, and NOX2 gene level by interaction with the RelA	[84,85]
LincRNACOX2	Down-regulated	Controls the COX2 gene's activity to control the NF-kB gene's expression.	[86–88]
Lnc-DC	Up-regulated	Affected the differentiation of DC using STAT3 to inhibit the de-phosphorylation of Y705 by SHP1	[89]
LincRNA-EPS	Down-regulated	- prevents IRGs expression and interacts with hnRNPL - suppresses the inflammatory response via regulating nucleosome positioning at IRG	[82]
LncHSC-1	Up-regulated	Affects the differentiation of myeloid	[90]
LncHSC-2	Up-regulated	Regulates the self-renewal and differentiation via hematopoietic TF E2A	[90]
Lnc-IL7R	Down-regulated	Deposits the H3K27me3 genes regulates the IL-6, IL-8 expression, E-selectin, and VCAM-1	[33]
LncITPRIP-1	Up-regulated	Binds to the C-terminus of MDA5 and induces the IFN signaling	[91]
Lnc-LsM3b	Down-regulated	stops the activity of RIG-1 and the production of IFNs-I	[92,93]
LncRNA-Mirt2	Up-regulated	Impacts the polarization of macrophage via inhibition of K63-ubiquitination	[94]
LincRNA-Tnfaip3	Down-regulated	Regulates the NF-kB genes by raising the modification of histone H3	[95]
MALAT1	Up-regulated	Affects the inflammatory genes via inhibition of NF-kB	[96,97]
MIR3142HG	Up-regulated	- control the level of CCL2 and IL-8 mRNA and its protein - regulate the survival rate of inflammatory cells by modulation of proapoptotic gene Bim (Bcl-2)	[98–101]
NEAT1	Up-regulated	Regulates the expression of IL-8 via SFPQ which activates IL-8 transcripts	[102]
NEAT1v2/eRNA 07573	Up-regulated	Regulates antibacterial immune responses via preventing the exosome/NEXT components	[103]
NKILA	Up-regulated	Regulate the KLF4 level via NF-kB-mediated DNA methylation	[104]

(*continued on next page*)

2.2. Exosomal LncRNAs and their role in the immune system

Numerous evidence shows the LncRNAs potential which are released into the circulation (known as circulating LncRNAs) which are stable in peripheral blood and body fluids (urine) however, they are also found as exosomal LncRNAs [54,55]. Exosomes are kind of extracellular vesicles, small (nano-sized), bio-vesicles that are released from several cells (e.g., immune cells) into blood, and urine, breast milk, saliva, and sperm (body fluids) [56]. These molecules are associated with several cellular functions that could modulate the immune system, signal transduction, and antigens presentation [56,57]. Exosomes contain lipid bilayer plasma membrane, cytoplasmic proteins, coding/non-coding RNAs, and lipids [56,58]. Previous studies have presented exosomes and their biological activity as cargos or disease indicators, and specific bio-markers for novel diseases [57]. The exosomes are detected in various biofluids and participated in several pathological processes, such as immune modulation highlighting their importance in acting as biological equipment in the prognosis, determination, and immunological disorders treatment [59,60]. These vesicles are released continuously at a high level by B/T cells, dendritic cells, mast cells, liver cells, stem cells, and tumor cells [60]. Concerning the potential of LncRNAs in the immune related diseases (such as autoimmune diseases) (Table 1), their potential to distinguish healthy or patient cases, and the existence in

Table 2 (*continued*)

LncRNA	Expression level in innate immunity	Description	Ref.
NRIR	Up-regulated	Controls the interferon-induced genes and CXCL10 and CCL8 production	[105]
PACER	Up-regulated	induces *COX2* expression after binding with p50 NF-kB subunit of COX2 promoter.	[39]
PTPRJ-as1	Up-regulated	It is a tyrosine phosphatase that has tumor suppressor-like activity.	[106]
THRIL	Down-regulated	controls the level of CSF1, CCL1, IL-8, TNF-α and CXC10 by hnRNPL complex.	[107]
NRAV	Down-regulated	It epigenetically inhibits the ISGs transcription, and increases IAV replication.	[108]
lincRNA VIN	Up-regulated	Viral protein synthesis and support for IAV replication.	[109]
lncRNA-CMPK2	Up-regulated	It causes HCV replication and regulates the protein-coding ISGs negatively.	[110]
Morrbid	Down-regulated	Induces by pro-survival cytokines involved in short-lived myeloid cells Its inhibition leads to raising the short-term myeloid cell death.	[111]
AS-IL-1a	Up-regulated	It is highly produced in RAW and peritoneal macrophages following LPS stimulation. It suppresses the expression of IL1b	[112]
lncBST2/BISPR	Up-regulated	Up-regulate BST2 mRNA expression	[113]
LincRNA-COX2	Up-regulated	Stimulated in BMDC by LPS and Pam3CSK via TLR4, and TLR2, respectively. Manage the expression of inflammatory genes	[86,114]

Table 3

LncRNAs in adaptive immunity.

lncRNA	Expression level in adaptive immunity	Description	Ref.
GAS5	Down-regulated	Involved in mTOR and glucocorticoid response pathways and stopped the growth arrest	[115,116]
lincR-Ccr2-5'AS	Down-regulated	Associated with chemokine response and Ccr1,2,3,5 genes and increases the migration of CD45⁺ cells	[35,46]
lncRNA Rmrp	Up-regulated	Linked with cytokines response (IL17a)	[117]
NeST	Up-regulated	Associated with INF-γ related response, production of IL-2	[118–120]
NRON	Down-regulated	Controlled the NFAT-dependent genes	[121]
NTT	Down-regulated	Associated with differentiation of macrophages	[122,123]
TH2-LCR	Up-regulated	Regulates the gene transcription encoding TH2 cell cytokines, such as IL-4, IL-5, and IL-13	[124]
lncRNA-CD244	Down-regulated	prevents the IFNG expression and TNF downstream of CD244	[125]
Gata 3-AS	Up-regulated	Co-expressed with GATA3 at Th2-polarizing status	[126]
Fas-AS1	Down-regulated	It enhances apoptosis via Fas/FasL in B/T cells	[127]
LincR-Ccr2-5'AS	Down-regulated	controls Ccr1, Ccr2, Ccr 3, and Ccr 5 as Th2-specific gene expression system	[35]
Flicr	Up-regulated	FoxP3 and Flicr partially overlap when produced in Tregs. Removal of FoxP3lo decrease the Tregs in NOD mice to preserve against diabetes. Negative regulation by IL-2.	[128]

exosomes fractions, both circulating and exosomal LncRNAs could be served as non-invasive diagnosis biomarkers at early stages of immunodeficiency and autoimmunity disorders [61].

Exosomes, which can transport various biological components such as proteins, nucleic acids, microRNAs, and long non-coding RNAs, are commonly recognized as mediators of cell-cell communication, facilitating the transmission of biological signals [129,130]. Exosome-mediated signaling between cells occurs in normal physiological processes like embryonic development and metabolic regulation, as well as during tumor progression [131]. Numerous studies have suggested that exosomes perform a crucial role in modulating immune responses and help create an immunosuppressive tumor microenvironment [132]. Exosomes expressing CD73 in the serum of melanoma patients can suppress the immune response of T cells, thereby increasing resistance to immunotherapy [133]. Exosomes released by melanoma cells can limit the entry of CD8⁺ T cells into the tumor microenvironment [134]. Pancreatic cancer-derived exosomes can promote the transformation of tumor-associated macrophages into the immunosuppressive M2 subtype, thereby facilitating tumor metastasis [135]. Colorectal cancer-derived exosomes stimulated the proliferation of regulatory T cells, creating an immunosuppressive tumor microenvironment that facilitates tumor progression and resistance to chemotherapy [136]. These studies have shown that exosomes can regulate the innate and adaptive immune cells within the tumor microenvironment, thereby influencing tumor progression and treatment. A systematic understanding of how exosomes target the immune response in cancer could be beneficial in exploring potential therapeutic approaches.

This finding further supports their conclusion that the NEAT1

contained within exosomes released by peripheral blood mononuclear cells may contribute to the development of rheumatoid arthritis and could potentially be used as a diagnostic marker going forward [65]. Exosomal long non-coding RNA TRAFD1-4:1 from fibroblast-like synoviocytes can degrade the extracellular matrix of chondrocytes, influence the movement of chondrocytes, and lead to permanent harm to the joints [67]. CXCL-1 contributes to the progression of joint inflammation in rheumatoid arthritis by stimulating the release of inflammatory cytokines like IL-6 and IL-17 [137,138]. Ren et al. found that the non-coding gene TRAFD1-4:1 was highly expressed in rheumatoid arthritis. This gene affected the expression of the target gene CXCL-1 by inhibiting miR-27a-3p, which in turn accelerated the breakdown of the cartilage matrix in the joints and hindered the joint-protective function of the cartilage [67]. The exosomal long non-coding RNA NEAT1 has been associated with the abnormal growth of fibroblast-like synoviocytes and the inflammation of the synovial tissue through various signaling pathways. The NF-κB signaling cascade is recognized as a crucial player in the development of rheumatoid arthritis, and the phosphorylated p65 subunit is a widely used marker of NF-κB pathway activation [62,139]. Rao et al. reported that exosomal NEAT1 from peripheral blood mononuclear cells participates in the development of rheumatoid arthritis through the NF-κB signaling pathway. By analyzing differentially expressed lncRNAs, they determined that NEAT1 levels were considerably higher in the rheumatoid arthritis group compared to healthy controls [62]. NEAT1 and its downstream genes had a synergistic effect on the development of rheumatoid arthritis through the NF-κB signaling pathway. Additionally, the researchers observed increased cell viability of fibroblast-like synoviocytes, elevated levels of inflammatory factors, and higher phosphorylation of p65 in the serum of RA patients compared to the control group. Furthermore, the injection of NEAT1-loaded exosomes in a mouse model of RA yielded similar results as in human fibroblasts [65]. The authors' findings suggest that the

Table 4
LncRNAs associated with Crohn's disease.

lncRNA	Expression level in Crohn's disease	Description	Ref.
DQ786243	Down-regulated	Correlation with DQ786243 and CD severity is associated with regulation of Treg function through CREB and Foxp3 expression.	[152]
GUSBP2	Up-regulated	GUSBP2 interaction with KLRK1 and association with HMGN1 and WDFY1 can be related to immunity/inflammation.	[156, 157]
RP5-968D22.1	Up-regulated	RP5-968D22.1 has been reported to be significantly upregulated in LUSC tissues compared to adjacent tissues.	[156, 158, 159]
		as biomarkers for the diagnosis of CD.	[156, 160]
ALOX12P2	Down-regulated	ALOX12P2 overlaps a lot with the ALOX12-AS1 gene, and the protein encoding ALOX12 gene is surrounded by the ALOX12-AS1 gene.	[156, 161]
DDX11-AS1	Up-regulated	DDX11-AS1 is overexpressed in most malignant tumors including gastric cancer, osteosarcoma, bladder cancer, NSCLC, liver cancer, colorectal cancer.	[156, 162]
RP11-68L1.2	Up-regulated	There is no additional information about this.	[156]
AF113016	Down-regulated		
RP11-428F8.2	Up-regulated		
AC009133.20	Up-regulated		
AGSK1	Down-regulated		
LOC283761	Down-regulated		
LOC729678	Down-regulated		
XLOC_005955	Up-regulated		
AC064871.3	Down-regulated		
XLOC_005807	Up-regulated		
RP11-923I11.5	Up-regulated		
RP11-510H23.3	Down-regulated		
GAS5-AS1	Up-regulated		
XLOC_010,037	Down-regulated		
CTC-338M12.3	Down-regulated		

exosomal NEAT1 originating from peripheral blood mononuclear cells may play a role in the development of rheumatoid arthritis and could potentially be used as a diagnostic indicator in the future.

2.3. LncRNAs and their effect on homeostasis and innate immune cell development

Little information about the LncRNAs effects on innate immune cells is presented. For example, HOTAIRM1 is more expressed in human granulocytes that is associated with retinoic acid throughout myeloid differentiation [140,141]. The absence of HOTAIRM1 leads reduction of CD11b and CD18 levels and hence white cell lines are disrupted [140]. HOTAIRM1 is transcribed between the two genes, HOXA1 and HOXA2. Based on the functional studies, it was revealed that granulocytic differentiation could be impaired after HOTAIRM1 knockdown, and the level of differentiated genes (ITGAM, CD18, HOXA1, and HOXA4) are decreased. Recently, researchers found the role of Morrbid LncRNA in the moderating of neutrophils, eosinophils, and Ly6Chi monocytes by controlling the BcL2l11 (as a pro-apoptotic molecule (named Bim) [101]. Morrbid is extracted from unstable myeloid cells corresponding to survival cytokines and suppressed the transcription of Bcl2l11 after the promotion of PRC2 inhibitor. In addition, without Morrbid, cell apoptosis is started via activation of Bcl2l11 [101].

Also, a high level of MORRBID was found in eosinophils obtained from hyper-eosinophilic syndrome (HES) patients and a set of disorders determined using a modified period of leukocyte AN [101]. Taken along, this information recommended that dysregulated Morrbid-Bcl2l11 axis could also be a crucial component in HES and different disorders of dysregulated myeloid periods like auto-inflammation and cancer. In mouse embryonic stem cells, the linc 1405 is expressed in the upstream locus of the Eomes factor and the promoter/locus elimination results in a reduction of its expression level [142]. Recently, Rroid identified a cis-regulatory component and its critical role during the balance and activation of clustered innate lymphoid cells (ILCs), but no ILC2 or ILC3 was found. Interestingly, it was found that various LncRNAs are expressed near to locus of transcription factors or main lineage-specific cytokines. These are cis-regulatory components in different processes of developing, balancing, and functionalizing immune cell subtypes [143].

2.4. LncRNAs in auto-immune disease

LncRNA dysregulation can affect autoimmune disorders such as rheumatoid arthritis (RA), psoriasis, Sjogren's syndrome (SS), Crohn's disease (CD), and Systemic lupus erythematosus (SLE) which are explained below.

2.5. LncRNA in Crohn's disease (CD)

Crohn's disease is a persistent and recurring inflammatory condition that has the potential to impact any portion of the digestive tract [144]. The incidence of CD is on the rise across both developing and developed nations, posing a significant global healthcare challenge and serving as a captivating area of research [145,146]. However, the precise mechanism behind CD remains unclear. Genetic predisposition, immune response, and environmental factors are believed to play a role [147]. While the use of 5-aminosalicylic acid, prednisone, and anti-inflammatory agents has advanced the treatment of CD, their effects are primarily palliative and occasionally ineffective for refractory CD [148].

As a result, there is an urgent need to develop new treatments for CD, and discovering the mechanisms of CD is of great clinical importance. Recent studies based on genome-wide association have revealed new susceptibility genes for CD and emphasized the important role of genomic factors [149]. Nonetheless, the majority of these studies have centered on protein-coding genes and overlooked non-coding RNAs. Thanks to the advancement of high-throughput technologies, many non-coding RNAs have been discovered, with many of them found to be involved in maintaining cellular and tissue homeostasis. Recent research has shown that lncRNAs play a fundamental role in the regulation of immune function and the progression of autoimmune diseases, including CD (Table 4). According to the results of the study conducted by Mirza et al. the perspective of lncRNA transcription was revealed in inflammatory bowel disease [150]. Furthermore, Qiao et al. identified high levels of lncRNA DQ786243 and its effect on the function of regulatory T lymphocytes through modulation of CREB and Foxp3 levels in CD patients [151,152]. The association with DQ786243 and CD severity has been linked to regulating Treg function through the expression of CREB and Foxp3 [152,153]. While CREB was initially thought to directly affect the upregulation of Foxp3, the results of this study suggest that CREB phosphorylation may play a more important role in this process [151,154]. These findings also indicate a close relationship between the expression of DQ786243 and cAMP response element binding protein, which plays an important role in the activity of the TCR response element in Foxp3, and also plays a key role in the function and development of regulatory T cells as a major transcription factor [155].

2.6. LncRNA in systemic lupus erythematosus (SLE)

SLE is known as chronic autoimmune disorder in multiple organs

Table 5
LncRNAs in Systemic lupus erythematosus.

LncRNA	Expression level in SLE	Description	References
Linc0597	Up-regulated	–	[165,166]
Lnc-DC	Down-regulated	Lnc-DC is negatively correlated with CRP disease.	[167]
Linc0949	Down-regulated	It has a strong positive correlation with C3 levels, but a negative correlation with SLEDAI-2K and LN.	[166]
Gas5	Down-regulated	Gas5 is negatively correlated with CRP disease and plays a key role in regulating the development of this disease by inducing antigen exposure and producing autoantibodies.	[167]
NEAT1	Up-regulated	NEAT1 regulates the expression of inflammatory chemokines via the protein kinase pathway.	[168]
NR_103776.1	Down-regulated	. NR_103776.1 has a significant and negative correlation with inflammatory indices (CRP and ESR).	[169]
TUG1	Down-regulated	The level of complement C3 was positively correlated with TUG1 expression.	[170]
uc001ykl.1	Down-regulated	The expression level of uc001ykl.1 correlates with erythrocyte sedimentation rate (ESR) and C-reactive protein.	[171]
ENST00000448942	Down-regulated	There is a significant correlation between ENST00000448942 levels with ESR and anti-Smith antibodies.	[171]
Lnc-FOSB-1:1	Down-regulated	Its function can be as a miRNA sponge and interfere with the function of several other miRNAs in regulating the mTOR pathway in neutrophils.	[171]
lincRNA-p21	Down-regulated	Decreased expression of this lncRNA can increase the level of miR-181a, which is beneficial for IL-2 recovery.	[171]
LINC00176	Up-regulated	It may promote the growth and binding of $CD4^+$ T cells in SLE by reducing WIF1 expression and stimulating WNT5a signaling pathway.	[171]
FAS-AS1	Up-regulated	It has a role in supporting Fas-mediated cell death through apoptosis.	[171]
PVT1	Down-regulated	Serum PVT1 showed a negative correlation with both age and ESR level in individuals with systemic lupus erythematosus.	[171]
NONHSAT101022.2	Down-regulated	This might worsen SLE by stimulating NK cells to produce IFN-γ through the cis-regulation of LMBRD2, thus increasing β2-AR signal transduction.	[171]
IL21-AS1	Down-regulated	A positive correlation is seen between IL21-AS1 and the ratio of PBMCs of SLE patients.	[171]
LncRNA H19	Up-regulated	This leads to a decrease in the suppressive function of Treg cells, which are	[171]

Table 5 (*continued*)

LncRNA	Expression level in SLE	Description	References
		important for regulating the immune response. As a result, the overall immune response may be altered, potentially impacting various immune-related conditions and diseases.	
AC007278.2	Up-regulated	AC007278.2 plays a role in the expansion of SLE by causing a decrease in CCR7 expression and facilitating the maturation of Tfh cells into B cells.	[171]
LncRNA MIAT	Up-regulated	LncRNA MIAT functions as a competitive inhibitor of miR-222, leading to the promotion of SLE through the upregulation of CFHR5 expression via the degradation of miR-222 in living organisms.	[171,172]
LincRNA00892	Up-regulated	This lncRNA is efficient in promoting the production of IgG through the activation of $CD4^+$ T cells.	[171]
Linc 02009	Up-regulated	No functional studies have been performed for this lncRNA.	[171]
Gm20513	Up-regulated	lncRNA Gm20513 is positively associated with SLE-related H2-Aa gene expression in kidney tissues.	[171]
Linc 00513	Up-regulated	This led to an increase in the activation of STAT1 and STAT2, ultimately resulting in the upregulation of the type I interferon pathway.	[171]
RP11-2B6.2	Up-regulated	This specific lncRNA plays an important task in promoting the activation of IFN-I signaling pathway. It does this by epigenetically suppressing SOCS1 expression and increasing JAK1, TYK2, and STAT1 phosphorylation.	[171]

characterized by loss of self-tolerance to antigens, and dysregulation of interferon responses. One of the distinctive features of SLE is circulated autoantibodies against ds-DNA (*anti*-ds-DNA) and proteins that bind to nuclear RNA (like as *anti*-Sm, and *anti*-RNP) [163]. It was determined that development of SLE is dependent on genetic and environmental risk factors with high prevalence in women, especially in childbearing years [164]. Lately, it was recommended that level of lnc-DC GAS5 in the SLE patients was reduced but the level of linc0597 in plasma was increased [165]. The lnc-DC (intergenic LncRNAs) was identified that produced by DCs at high level, and showed the role of DCs to inducing T-cells activity, hence its important function in the pathogenesis of SLE was determined [164,165]. In addition, different LncRNAs such as lnc-DC, GAS5, and linc0597 suggested to be potential lupus biomarkers [164](Table 5).

Interestingly, the LncRNAs function in the SLE pathogenesis was found in mouse models like as growth arrest-specific 5 (GAS5) which also GAS5 could be a genetic candidate for the development of SLE in humans located at 1q25 chromosome [165]. The level of linc0949 along with linc0597 was decreased in SLE patients and linc0949 can be used as a biomarker in these patients during diagnosis and evaluation of treatment response [165,173]. Also, in SLE cases the remarkable raising of GAS5 and miR-21 was reported in T-cells $CD4^+$. In SLE patients with ulcers, T-cells produced a high level of GAS5 compared to patients without SLE related ulcers [116](Fig. 3).
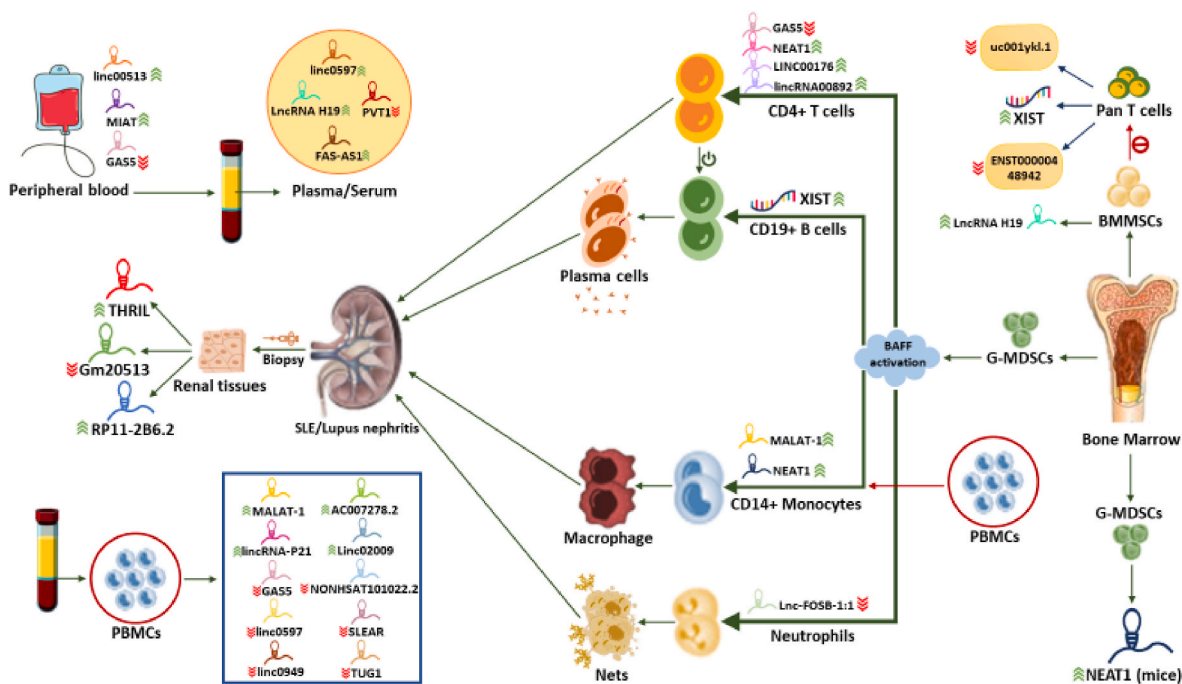
Fig. 3. The following lncRNA have been reported to be altered in peripheral blood and renal tissue samples from patients with systemic lupus erythematosus (SLE): upregulated, ↑: downregulated↓.
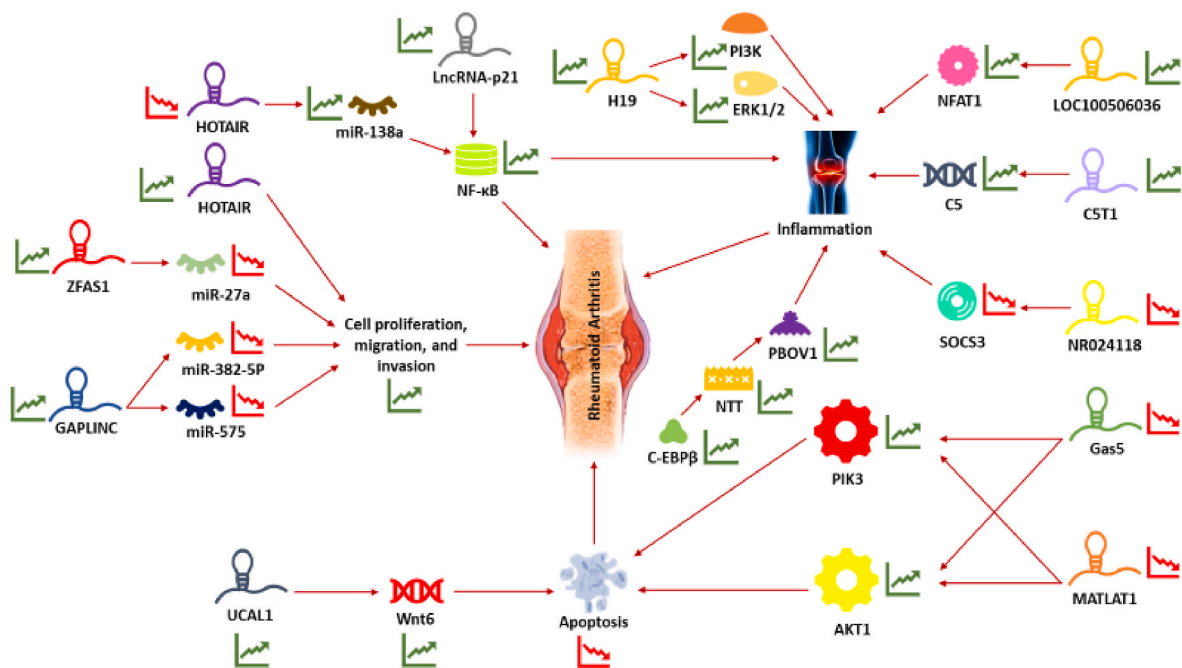

Fig. 4. The network of lncRNAs in rheumatoid arthritis has been extensively studied. These lncRNAs include NR024118, also known as LincRNA-p21, UCA1, GAPLINC, MALAT1, ZFAS1, and Gas5 in synoviocytes and HeLa cells, as well as NTT in monocytes and THP-1 cells, H19 in synoviocytes, and HOTAIR in chondrocytes. Additionally, LncRNA C5T1 has been identified in T cells and Jurkat cells, and LOC100506036 in synoviocytes. Due to the prominent role of these lncRNAs in the pathogenesis of rheumatoid arthritis, they are potential targets that can be useful in the treatment path.

Long non-coding RNAs (lncRNAs) derived from peripheral blood mononuclear cells of systemic lupus erythematosus patients have been a focus of research due to their abundant presence and diverse nature. Abnormal PBMC counts and functions are strongly associated with the pathogenesis of SLE [174,175]. A study utilized microarray technology to identify 137 long non-coding RNAs (lncRNAs) derived from peripheral blood mononuclear cells that were differentially expressed between normal controls and patients with systemic lupus erythematosus. Of these, 83 lncRNAs were upregulated and 54 were downregulated in SLE patients compared to normal controls. Two lncRNAs, ENST00000604411.1 and ENST00000501122.2, were notably elevated, while lnc-HSFY2-3:3 and lnc-SERPINB9-1:2 was significantly reduced in patients with systemic lupus erythematosus [176]. The study found that the upregulated ENST00000604411.1 lncRNA could contribute to the

Table 6

LncRNAs associated with RA.

LncRNA	Expression level in RA	Description	References
TRAFD1–4:1	Up-regulated	This lncRNA can lead to upregulating CXCL1 through miR-27a-3p sponging.	[67]
OIP5-AS1	Up-regulated	miR-410–3p/Wnt7b signaling axis OIP5-AS1 is involved in miR-410–3p/Wnt7b signaling axis.	[198]
XIST	Up-regulated	By binding to GATA1, it can upregulate CCN6.	[199]
BZRAP1-AS1	Down-regulated	Inhibiting the function of miR-1286 through competing endogenous RNA (ceRNA) activity leads to an upregulation of COL5A2 expression.	[200]
THRIL	Up-regulated	This upregulation of matrix metalloproteinase 1, MMP-3, and MMP-13 is induced by elevated levels of interleukin-1β (IL-1β).	[201]
PICSAR	Up-regulated	sponging miR-4701–5p	[202]
NEAT1	Up-regulated	Through controlling miR-338–3p	[203]
IFNG-AS1	Up-regulated	Increased IFNG-AS1 is a significant factor in RA because it controls IFNG.	[204]
Lnc-IL7R	Up-regulated	Through interaction with EZH2, Lnc-IL7R encourages FLS development.	[205]
LINC00152	Up-regulated	FOXM1 stimulates the activation of Wnt signaling and activates the expression of LINC00152.	[206]
GAPLINC	Up-regulated	GAPLINC encourages FLSs' biological tumor-like characteristics like miRNA sponging in RA patients.	[207]
DILC	Down-regulated	By causing FLSs to undergo apoptosis and reducing the production of IL-6, DILC takes role in RA.	[208]
UCA1	Down-regulated	FLSs' capacity to survive is impacted by UCA1 by altering Wnt 6 expression.	[209]
GAS5	Down-regulated	GAS5 overexpression inhibits IL-18 and causes FLSs to apoptosis.	[210]
ZFAS1	Up-regulated	MiR-27a-dependent ZFAS1 increased FLS invasion and migration	[211]
RP11–83J16.1	Up-regulated	RP11-83J16.1 can increase inflammation, proliferation, migration and invasion in FLS by controlling URI1 activity.	[212]
PICSAR	Up-regulated	By acting as a sponge for miRNA-4701–5p, PICSAR can facilitate the movement, multiplication and penetration of FLSs.	[202]
LINC01197	Down-regulated	LINC01197 up-regulates THBS2 expression and inactivates TLR4 NF-κB and acts as a sponge for miR-150.	[213]
THRIL	Down-regulated	It induces FLS growth and regulates the inflammatory response through activation of PI3K/AKT signaling.	[201]
C5T1lncRNA	Up-regulated	This lncRNA is located in the associated region and affects C5 transcript levels.	[214]
NTT	Up-regulated	Overactivation of lncRNA NTT/PBOV1 axis induced monocytic differentiation of RA.	[122]
MEG3	Down-regulated	This lncRNA can inhibit AKT/mTOR RA signaling pathway through miR-141.	[215]
HOTAIR	Down-regulated	HOTAIR attenuates RA pathological development by	[216]

Table 6 (*continued*)

LncRNA	Expression level in RA	Description	References
		targeting miR-138 and NF-kB pathway.	
LINC01882	Down-regulated	LINC01882 has been associated with the activation of T cells and has been identified to play a significant role in rheumatoid arthritis. Its involvement in modulating T cell function underscores its potential as a target for therapeutic intervention in RA.	[217]
NEAT1	Up-regulated	NEAT1 was found to enhance the transformation of CD4+ T cells into Th17 cells.	[218]
HIX003209	Up-regulated	HIX003209 is involved in promoting inflammation in rheumatoid arthritis through TLR4/NF-kB signaling pathway by acting as a sponge for miR-6089.	[219]
H19	Up-regulated	This activation of DDR-2 results in the upregulation of H19, which in turn interacts with miR-103a and facilitates its degradation.	[220]
LERFS	Down-regulated	This lncRNA is involved in the suppression of FLS motility, invasion and growth.	[221]
FER1L4	Down-regulated	FER1L4 plays a role in RA regulation by potentially targeting NLRC5. This suggests that FER1L4 may significantly influence RA regulation through its interaction with NLRC5.	[222]
ncRNA-p21	Down-regulated	Methotrexate triggers the production of the lncRNA-p21, leading to decreased NF-κ B activity in cells treated with TNFα.	[223]
uc.477	Up-regulated	This modulation of lncRNA uc.477 closely influences the regulation of HQT on RA.	[224]

development of systemic lupus erythematosus by protecting the active X chromosome from inappropriate silencing. Additionally, the levels of ENST00000604411.1 and ENST00000501122.2, two upregulated lncRNAs, were positively correlated with the clinical disease activity index in SLE patients, indicating that these lncRNAs could serve as potential biomarkers to assess disease activity in SLE [176]. The lncRNA TCONS_00483,150 was significantly reduced in peripheral blood mononuclear cells of systemic lupus erythematosus patients compared to healthy controls. Additionally, its expression was significantly correlated with anti-ribosomal P protein (anti-Rib-P) autoantibodies, suggesting it may serve as a novel biomarker for SLE diagnosis [177]. Furthermore, other lncRNAs, including taurine-upregulated gene 1, linc0949, nuclear-enriched plentiful transcript 1, and linc0597, were also expressed at reduced levels in the PBMCs of SLE patients [166,168, 177]. Among patients with lupus nephritis, levels of the long non-coding RNA TUG1 were notably decreased and inversely linked with disease state. Additionally, NEAT1 is recognized as a lncRNA that responds rapidly to lipopolysaccharide stimulation and can regulate innate immunity through the toll-like receptor signaling cascade [102,178]. The study found that NEAT1 expression levels in PBMCs of SLE patients were significantly elevated and positively related to disease activity. Additionally, NEAT1 was observed to modulate the Inflammatory chemokines expression and cytokines by actuating the belatedly mitogen-activated protein kinase signaling pathway. This regulation of the immune response of T and B cells could contribute to the expansion of SLE, suggesting NEAT1 as a potential therapeutic target for this condition [168]. Other study indicated that elevated NEAT1 levels were

Table 7
LncRNAs associated with MS.

LncRNA	Expression level in MS	Description	References
lncDDIT4	Up-regulation	Th17 cell differentiation	[231]
MALAT1	Up-regulation	Oncogenic role	[232]
NEAT1	Up-regulation	Regulation of CXCL8 expression	[233,234]
lnc-DC	Up-regulation	lnc-DC controls dendritic cell differentiation and maturation.	[232]
IFNG-AS1 (Tmevpg1)	Down-regulated	IFNG-AS1 transcript level is positively correlated with high IFNG level.	[235]
NRON	Down-regulated	NRON can be described as a cytoplasmic scaffold for an RNA-protein complex that regulates NFAT activity and localization in T cells.	[236]
TUG1	Down-regulated	TUG1, by participating in the p53 pathway, restores DNA damage caused by bup in ganglion cells and is also involved in the cell cycle.	[236]
PANDA	Up-regulated	p53 protein stabilization	[234]
linc-MAF-4	Up-regulated	Th1/Th2 cell differentiation	[237]
FAS-AS1	Down-regulated	Regulation of soluble Fas receptor	[238]
THRIL	Up-regulated	Regulative role in innate immunity	[238]
PVT1	Down-regulated	Control pf IL-6 release	[238]
OIP5-AS1	Up-regulated	Cell division	[239]
RN7SK RNA	Up-regulated	Regulation of CD4$^+$ T lymphocytes	[233]
APOA1-AS	Up-regulated	Negative transcriptional regulator of ApoA1	[240]
AC007278.2	Up-regulated	Regulation of Th1 cell development	[241]
IFNG-AS1-001	Up-regulated	IFNG-AS1-001 transcript level is positively correlated with high IFNG level.	[241]
IFNG-AS1-003	Up-regulated	It causes IFN-γ transcription/expression in Th1 cells.	[241]
AL928742.12	Down-regulated	Not determined	[242]
RP11-530C5.1	Up-regulated	Potential cis-regulatory	[242]
LincR-Gng2-5′AS	Up-regulated	Immune regulatory function	[243]
LincR-Epas1-3′AS	Down-regulated		
RP11-29G8.3 GAS8-AS1 LINC00293	Up-regulated	Not determined	[244]
LRRC75A-AS1	Down-regulated		

inversely related to the Th1/Th2 balance, potentially influencing the development and progression of systemic lupus erythematosus [179]. Consequently, the long non-coding RNAs NEAT1, linc0949, and linc0597 are anticipated to serve as promising diagnostic biomarkers for SLE, while TUG1 is predicted to be a useful marker for clinical diagnosis and disease activity in SLE.

The severe manifestation of SLE is lupus nephritis (LN) and leads to mortality and complications in patients. Progression of SLE patients with LN (~10–30 %) to end-stage renal disease (ESRD) has been observed. Renal outcome could be predicted by renal biopsy as an invasive method to assess glomerular damage [180], non-invasive biomarkers such as exosome-derived and/or circulating markers would be a major improvement. Pisitkun et al. identified and characterized exosomes in human urine. The next studies are focused on the urine exosomes in patients with renal, systemic, and urogenital diseases that aim to detect urinary biomarkers [181–184]. Platelets, endothelial cells, and leukocytes of SLE patients could release circulating exosomes in plasma, and their key roles in SLE pathogenesis were proved [185,186] such as linc0597 and linc0949, which able to control the induction of the

pro-inflammatory cytokines [40,187,188].

2.7. LncRNA in Rheumatoid arthritis (RA)

Another chronic inflammatory disease is RA with uncontrolled synovial tissue proliferation and most multisystem comorbidities. Its prevalence is about 0.8 % worldwide, which is 2-fold more in women than men. Also, RA predominantly changed the multiple peripheral joints and caused damage to the irreversible joints. The diagnosis and progression rate of RA can be done by laboratory tests and imaging studies, but primarily detection of RA needs a clinical diagnosis, and there is no single definitive diagnostic assessment confirming the RA diagnosis [189].

Thus, early diagnosis and detection of RA by biomarkers such as exosome-derived and/or circulating markers would be a potential therapeutic target. Increasing pieces of evidence confirmed the different LncRNA expression profiles in RA patients and healthy individuals, which determined their effects on the disease pathogenesis, the disease severity, and potential as RA indicators [190–193]. A study by Qing Luo et al. based on microarray technology, showed the heightened expression of 2410 LncRNAs and decreased expression of 2635 LncRNAs in RA patients. The 139 dysregulated LncRNAs were involved in signaling pathways related to the T-cell receptors and ALAS2 and KCNMB3 were identified as significant deregulated LncRNAs. The results of this study suggested that different LncRNAs patterns could provide new insights into RA pathogenesis [194]. In addition, it was found that various cytokines, such as IL-6 and TNF-a act as inflammatory intermediates and could be involved in RA pathogenesis [195].

According to the microarray analysis obtained from RA PBMCs, 2099 dysregulated LncRNAs were found them the main four dysregulated LncRNAs are ENST00000456270, NR_002838, NR_026,812, and uc001zwf.1. The level of IL-6 and TNF-a are associated with ENST00000456270 expression and the Simplified Disease Activity Index (SDAI) of RA cases, which suggested it as a novel diagnosis LncRNA [196]. The up-regulated of several LncRNAs including RNA143598, HIX0032090, IGHCgamma1, RNA143596, and XLOC_002730, have been identified in serum samples of RA (43 individuals) and control group (40 healthy people). The disease stages and development of ESR levels are linked to RNA143598 and HIX0032090 expression as well. Moreover, the expression of XLOC_002730 and HIX0032090 were found to be associated with the levels of RF, and RNA143596, RNA143598, and HIX0032090 were linked to *anti*-CCP antibody levels. Regarding these results, the association between these five LncRNAs with inflammatory response and autoimmunity could be suggested, and also be considered new targets for RA [192]. In another study, LncRNA: lnc-ITSN1-2 in plasma samples of 30 R A cases was found to be extremely up-regulated compared to healthy individuals and it had a positive correlation with ESR, CRP (clinical parameters), and DAS28 (Fig. 4).

Totally, these outcomes have presented the role of this lncRNA as a factor in the management and diagnosis of RA patients [197]. Circulating lncRNA expression levels were described by numerous studies, and this evidence identified that these LncRNAs have crucial functions in RA pathogenesis and deserve as novel non-invasive RA biomarkers to detect the disease (Table 6).

2.8. Multiple Sclerosis (MS)

Disabling disorder, MS be categorized as neurodegenerative disease and immune-mediated process [225,226]. The central nervous system (CNS), spinal cord, were affected and different impairments of mobility, visual, sensory, and cognitive deficits have been observed in MS people [225,226]. Due to the heterogeneity of the relapsing and subsequent progressive course of patients with MS, the identification, and discovery of long-term predictive tools with confidence such as potential exosome-derived and/or circulating biomarkers could be promising
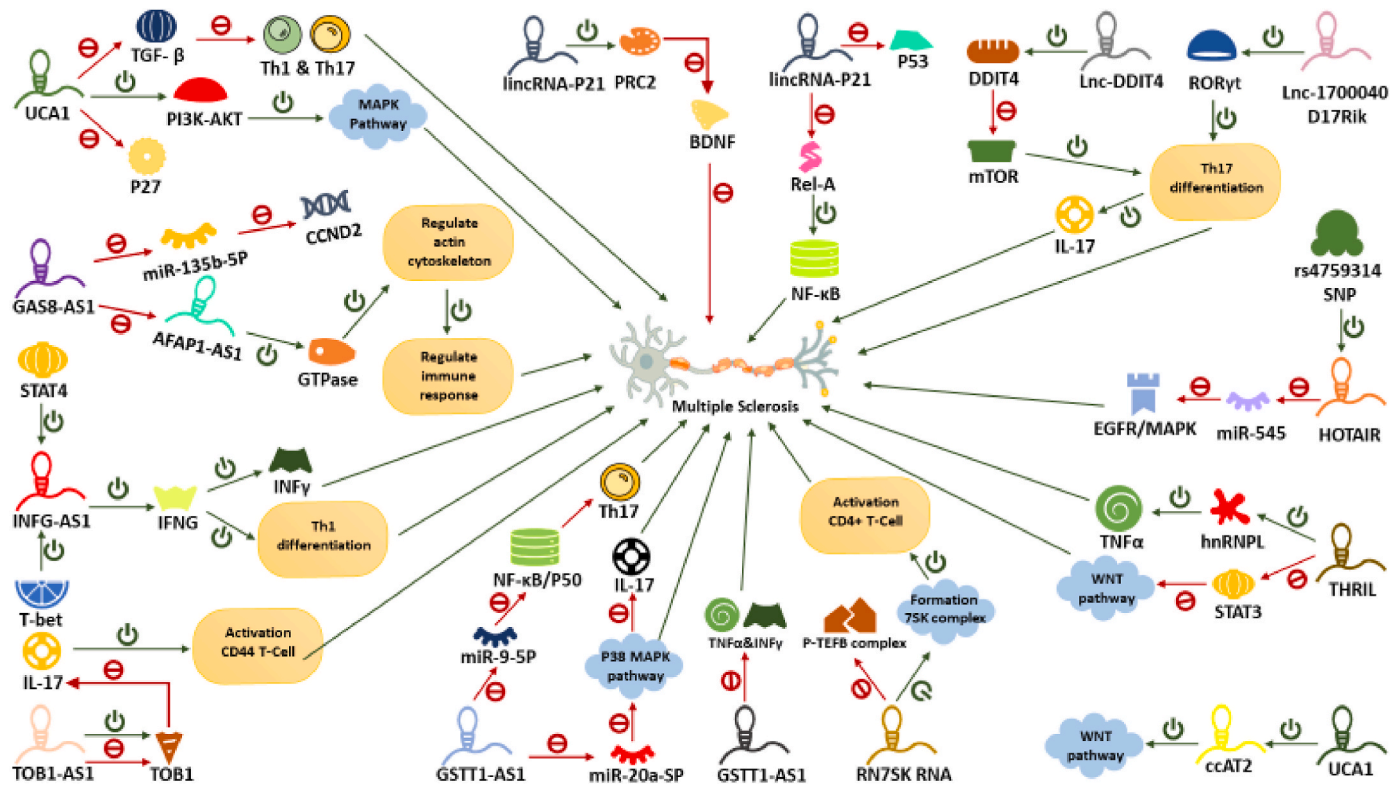
Fig. 5. The role of several lncRNAs as a schematic diagram of involvement in the adjustment of major molecular cascades in MS. Among the main pathophysiological mechanisms associated with MS are T cell subsets (regulatory T cells (Treg), Th1, Th2, and Th17). The activation of inflammatory cascades and cytokine secretion occurs due to the disruption in regulating these subsets and ultimately causes demyelination in the brain, spinal cord, and nerve damage. Lnc-DC is upregulated in PBMCs of MS patients. By transforming this lncRNA, it activates Toll-like receptor 4 (TLR4) and TLR9. The secretion of inflammatory cytokines, including IL-1, IL-6 and IL-17, is one of the main functions of TLR4, which leads to the suppression of Treg cells. Also, TLR4 inhibits miR-30a, which causes Th17 differentiation [232, 246]. In addition, lnc-DDIT4 is upregulated in peripheral blood mononuclear cells (PBMCs) found in MS subjects. This particular lncRNA interacts with DDIT4 and is responsible for regulating the immune response and differentiation of Th17 cells [231]. BDNF-AS plays an important role in inhibiting the neuroprotective factor BDNF and recruiting PRC2. GSTT1-AS1 prevents MS progression by inhibiting IFN-g and TNF-a secretion [235]. The p38 MAPK signaling pathway is activated by TUG1 through miR-20a-5p repression, thus TUG1 downregulation reduces Th17 differentiation. UCA1 is involved in the regulation of PI3K-AKT, ERK1/2 and MAPK cascades and Th17 differentiation. Also, the interaction between this lncRNA and another lncRNA, CCAT2, induces WNT cascade signaling and increases inflammatory cytokine production [233,234].

strategies [227]. Information about CNS couldn't be accessed without the use of invasive techniques, and immune cell polarization toward auto-reactive cells and mechanisms underlying immune cell activation outside the CNS remain to be clarified [228]. Grazyna et al. identified that serum-derived exosomes might significantly contribute to MS immune reactions and they might provide novel biomarkers of disease activity [229].

The association of LncRNAs with autoimmune and neurological diseases has been demonstrated by numerous studies. There is also evidence of changes in LncRNAs expression in peripheral blood and PBMCs of MS cases than in healthy people. These studies suggested the LncRNAs association with MS pathogenesis and their biomarker potential for diagnosis of disease stages. Also, high level of TUG1, LINC00293, ENST00000518278, RP11-29G8.3 (ENST00000563635) was found in the serum of 16 secondary progressive and 12 primary progressive MS (PP-MS) patients when compared to healthy individuals. This study indicated the regulatory function of LncRNAs in autoimmune and inflammatory responses in MS cases, and their highlighted activity in the progressive MS disease [230] (Table 7).

Heterogeneous nuclear ribonucleoprotein L (THRIL) plays a role in innate immunity. LncRNA PVT1 resides in risk chromosomal rearrangement loci that are preferred sites for different diseases including MS, and FAS-AS1 with the regulation of apoptosis during the development of lymphocyte and immune processes. Recently, Eftekharian et al. reported down-regulation of PVT1, FAS-AS1, and THRIL up-regulation in 50 RRMS blood and 50 control individuals, which confirmed their

roles in the MS pathogenesis and suggested as circulating predication biomarkers of disease or treatment response [225]. Zhang et al. through a wide microarray assay identified up-regulation (ENSG00000231898.3, lncRNA XLOC_009626, and lncRNA XLOC_010, 881) and down-regulation (ENSG00000233392.1, lncRNA ENSG00000259906.1, and lncRNA XLOC_010,931) in PBMCs of RR-MS patient than healthy control, this study recommended that dys-regulated LncRNAs could participate in the MS pathogenesis [245](Fig. 5).

2.9. LncRNA in psoriasis

Psoriasis is an ordinary chronic and hyper-proliferative disease of the skin because of genetic, environmental, and immune factors, affecting around 2 % of the population. The plaque (also called Vulgaris), erythrodermic, pustular, and guttate are the four main clinical types of psoriasis. Plaque, a common psoriasis form is affects 85%–90 % of patients [247]. Patients with psoriasis also could develop a variety of complications for example psoriatic arthritis (PsA), cardiovascular diseases, metabolic syndromes, and skin lesions [247]. Psoriasis is usually diagnosed based on the evaluation of the appearance and clinical morphology of a skin lesion. There are no special diagnosis blood tests or clearly-defined diagnostic criteria for this disease. Analysis of skin biopsy is invasive and may be aching and itching that is considered a common and efficient clinical diagnosis procedure [248]. Therefore, discovering the non-invasive diagnostic methods or highly sensitive and specific biomarkers for psoriasis are major challenges. PsA affects

Table 8

LncRNAs associated with Psoriasis.

LncRNA	Expression level in Psoriasis	Description	References
FABP5P3	Up-regulated	By enlisting human antigen R (HuR), it keeps KMT2C overexpressed and improves the downstream response to proliferation and inflammation.	[251]
GAS5	Down-regulated	In autoimmune diseases, GAS5 interacts with the DNA binding domain of glucocorticoid receptors (GRs).	[252]
PRINS	Up-regulated	Through the regulation of GIP3 protein, it maintains the increase in proliferation of keratinocytes in psoriasis and through direct contact with mRNA, it reduces the level of various pro-inflammatory factors in inflammatory keratinocytes.	[253,254]
KLHDC7B-DT	Up-regulated	By binding to ILF2, KLHDC7B-DT activates JAK-STAT and MAPK signaling pathways and can cause inflammation and excessive proliferation in keratinocytes.	[255]
RP6-65G23.1	Up-regulated	Through simultaneous stimulation of the ERK and AKT pathways, it encourages keratinocyte growth. Bcl 2 and Bcl-xl are downregulated, which inhibits apoptosis.	[256]
SPRR2C	Up-regulated	Its function is to increase the proliferative and inflammatory effects of IL-22 in HaCaT.	[257]
MIR31HG	Up-regulated	MIR31HG increases proliferation under the condition of NF-κB activation.	[258]
ANRIL	Down-regulated	By activating inflammatory factor transcripts, it may contribute to the response to induction of NF-κB and transcription factor (YY1).	[259,260]
HOTAIR	Up-regulated	HOTAIR may mediate inflammatory genes (IL-6, iNOS, TNF-α, MIP-1B) by activating the expression of cytokines and NF-kB.	[261–263]
MALAT−1	Up-regulated	By interacting with NF-κB, it inhibits lps-induced maturation of DCs, reduces T cell proliferation, and induces the generation of Treg cells. It also suppresses inflammatory reactions.	[96,264, 265]
AGAP2-AS1	Up-regulated	It stimulates the AKT/mTOR pathway by upregulating AKT 3, which in turn promotes keratinocyte growth.	[266]
MSX2P1	Up-regulated	Binding to miR-6731–5p as a ceRNA represses S100A7 to drive keratinocyte proliferation and other proliferative cytokines levels.	[267]

Table 8 (*continued*)

LncRNA	Expression level in Psoriasis	Description	References
SLC6A14–1:1	Up-regulated	It plays an important role in the function of cells such as Treg, NF-κB, mTOR and MAPK and has an important effect on the release of chemokines, cytokines and also the JAK-STAT signaling pathway.	[268]
HSFY2–10:1	Up-regulated	It can promote proliferation and inflammation by controlling the pathway through which it is mediated and the competitive binding of miR-145.	[268]
PRANCR	Up-regulated	Promote proliferation	[269]
LINC00941	Down-regulated	It leads to the inhibition of keratinocyte primary differentiation.	[270]
H19	Down-regulated	It increases the level of S1PR3 and acts as a sponge for miR-766–3p. It can also control the proliferation of psoriatic keratinocytes and skin inflammation through the AKT/mTOR pathway.	[271]
LOC285194	Down-regulated	It causes negative regulation in miR-616, and through its direct binding to the 3′ untranslated region of GATA3, it reduces the expression of GATA3.	[272]
ST7OT	Down-regulated	ST7OT mediates histone methyltransferase activity by binding to Polycomb 2 chromatin repressor complex) PRC2 (.	[272,273]
NONHSAT044111	Down-regulated	By affecting the release of cytokines and chemokines and the JAK-STAT signaling pathway, it plays a task in the differentiation and function of Treg cells, NF-κB, mTOR, MAPK.	[268]
LncRNAAL162231.4	Down-regulated	It can be involved in various mechanisms such as chemokine signaling pathway, skin barrier, immune response and epidermal growth.	[274]

approximately 10–30 % of patients with psoriasis, which leads to skin symptoms as well as enthesitis synovial-related inflammation, and bone erosions in the joint [249].

The differentially expressed genes (DEGs) expressed LncRNAs have been indicated in psoriasis patients. Followed by inducing IL-17 A in keratinocytes cells (KCs). The investigation showed that the level of LncRNA-MSX2P1 in clinical psoriatic lesions is higher than in normal skin samples [250]. Also, the epidermis of patients had high levels of MIR31HG and lncRNA-RP6- 65G23.1. These LncRNAs are able to regulate different processes during the proliferation of KCs, apoptosis, and inflammation responses in psoriasis (Table 8).

The lncRNA-MSX2P1 acts as an endogenous sponge RNA and is able to prevent miR-6731–5p which causes increasing the pro-inflammatory cytokines and S100A7 and consequently manifests psoriasis [267]. Besides, when KCs were treated with NF-kB inhibitor, the level of MIR31HG decreased which presented its impact on the regulation of psoriatic KCs and its therapeutic target [275]. It was found that RP6-65G23.1 expression was increased when induced by a different mix of cytokines. Prevention of cell proliferation, arresting the cell cycle (in
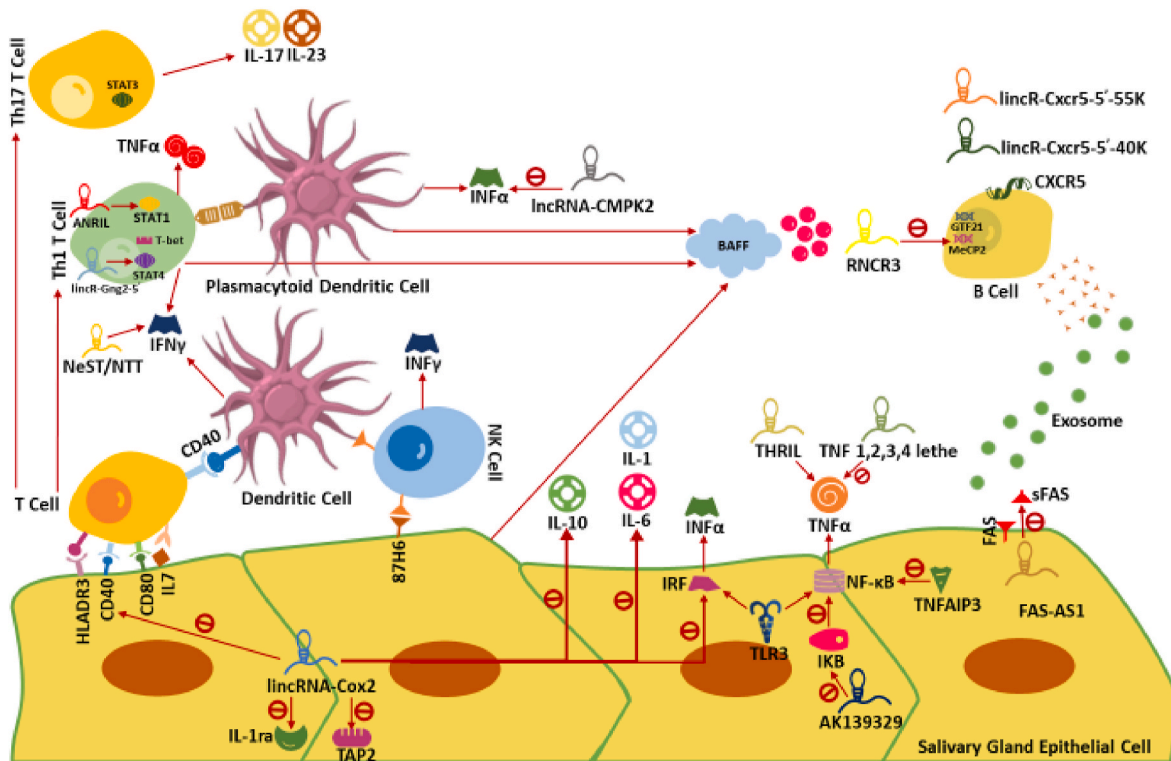
Fig. 6. The proposed hypothesis suggests that lncRNAs could play a significant role in the pathophysiology of SS. Empirical data supports this hypothesis, indicating specific regulatory instances where lncRNAs are involved. In the context of SS, the lncRNAs associated with the condition are highlighted in red rimmed boxes.

G1/S phase), and apoptosis have happened after RP6-65G23.1 Knockdown. Also, KC proliferation was induced by a high level of this lncRNA via AKT and ERK1/2 pathways as well as onset apoptosis by an increased expression of Bcl-2 and Bcl-xl, to develop psoriasis [256].

Another LncRNA, HOTAIR has a high level in HaCaT cells after UV irradiation. After receiving the UV, the high level of HOTAIR leads to a low cell survival rate, promotes apoptosis-related genes (Bax, Caspase 3, 9), prevents Bcl 2, and induces the level of TNF-a, and IL-6 protein. These pathways impacted apoptosis after UV induction and inflammation by increasing the level of PKR in KCs [276].

2.10. LncRNA in Sjögren's syndrome (SS)

Exocrine gland destruction (especially in salivary and lachrymal glands) creates SS as an autoimmune disease that leads to symptoms such as deterioration of tear tissue and dry lips, eyes, and mouth. In patients with SS, B cell hyperactivity was seen in exocrine glands that were exposed by circulating immune responses, generation of autoantibodies against SSA or SSB, and hypergammaglobulinemia [277,278]. The SS pathogenesis is multifactorial and has not been fully comprehended. The diagnosis and appearance or onset of SS symptoms are delayed, and disease diagnosis is dependent on invasive methods including the analysis of minor salivary glands biopsy. Although several diagnoses and therapeutic biomarkers have been implicated in SS, discovering the circulating biomarkers that could potentially ameliorate the disease diagnosis is a major issue [279]. It is reported that exosomes have main roles in SS pathogenesis due to the presentation of intracellular auto-antigens to immune cells, and for the first time, it is reported that RNA-containing exosomes from salvia could serve as a potential detector for disease conditions in SS patients [280–282](Fig. 6). Recent studies have revealed numerous genetic factors associated with this illness. These factors have been identified through various approaches such as focused candidate studies, expression studies, and unbiased genome-wide association studies [283–286]. In particular, genes such as

IL12A and TNFAIP3, which are linked to the innate and adaptive immune systems, as well as inflammatory signaling pathways and cytokines, have been implicated [284]. The transcription of these genes is influenced by epigenetic factors, which leads to coordinated activity in the immune and inflammatory pathways in response to external stimuli. Additionally, noncoding RNAs, including micro RNAs (miRNAs), are known to play a role in gene regulation and are closely linked to the disease processes. Furthermore, it is increasingly apparent that lncRNAs may mediate the crosstalk between genes through epigenetic modification of their respective loci. Recent research has highlighted the involvement of these ncRNAs in the development of different inflammatory conditions such as SS. These studies have underscored their task in regulating inflammatory responses, the function of proinflammatory cytokines, and the MHC protein complex [287] (Table 9) NEAT1, a lncRNA, plays a crucial role in regulating cytokine production and the immune response [102,288]. Research by Zhang P et al. found that NEAT1 promotes the activation of several inflammasomes, making it an important player in the innate immune response [289]. Additionally, Gast M et al.'s study confirmed NEAT1's role as a novel immunoregulatory factor, influencing the secretion of various chemokines and interleukins, ultimately impacting monocyte-macrophage function and T-cell differentiation. Also, according to previous studies, NEAT1 was found to be overexpressed in multiple sclerosis patients compared to healthy individuals, which emphasizes the importance of NEAT1 in immune-related processes [290,291].

2.11. LncRNA in type one diabetes mellitus (T1DM)

The main autoimmune chronic disease, Diabetes, in which the level of blood sugar is high (hyperglycemia) because of insulin deficiency. In fact, the damage of insulin-producing cells by T cells in pancreatic islets leads to insufficient secretion of insulin. It affected 415 million individuals globally and is estimated to up 642 million by 2040 [299,300]. Determination of autoantibodies for pancreatic β-cells or C-peptides

Table 9
LncRNAs associated with SS.

LncRNA	Expression level in Sjögren's syndrome (SS)	Description	References
XIST	Up-regulated	XIST, a 19-kb non-protein-coding RNA, and long nuclear element 1 (LINE1) retrotransposon sequences participate in the inactivation process.	[292,293]
MEG3	Down-regulated	Overexpression of MEG3 blocks TNF-α regulation on keratinocytes, including increased inflammation and suppression of autophagy, possibly through PI3K signaling.	[292,294]
TMEVPG1	Up-regulated	TMEVPG1 expression occurs in all types of cells, including NK cells, CD8 T cells, and CD4 T cells, which may have a regulatory effect through the T-bet mechanism in interferon gamma production.	[295]
lincRNA-Cox2	Up-regulated	lincRNA-Cox2 represses IRF7	[86]
CMPK2	Up-regulated	It suppresses the IFN response and acts through the induction of antiviral IFN-stimulated genes (ISGs).	[283]
ENSG00000277999.1 lnc-UTS2D-1:1 ENSG00000225964.5 ENSG00000262979.1 ENSG00000243398 ENSG00000282851.1 XLOC_078,623	Up-regulated Down-regulated	A strong correlation was seen between pSS characteristics and these lncRNAs, including rheumatoid factor (RF), microglobulin β2, and erythrocyte sedimentation rate (ESR).	[292,296]
ENSG00000225964.5 XLOC_102,167 ENSG00000265479.5 ENSG00000272666.1 ENSG00000260114.2 XLOC_167,004	Up-regulated		
TNF1,2,3,4		Overexpression of lncRNA decreases TNF expression.	[297]
Neat1	Up-regulated	NEAT1 regulates MAPK pathway activation and selectively activates the expression of p-p38 and p-ERK1/2 to regulate NEAT1-induced factors.	[298]

Table 10
LncRNAs associated with T1DM.

LncRNA	Expression level in T1DM	Description	References
PVT1 LINC01018 LINC00960	Up-regulated Down-regulated Down-regulated	In diabetes, it can play a role in inflammatory response.	[320]
MALAT1	Up-regulated	This lncRNA is associated with increased expression of MALAT1 in STZ-induced diabetic mice and db/db mice, leading to microvascular dysfunction.	[321]
HI-LNC71	Down-regulated	Transcriptionally regulates the critical pancreatic beta cell transcriptional regulator PDX1 in EndoC-betaH1 cells, primary islet cells, and the murine beta cell line MIN6.	[321]

failure at the disease onset and play potential roles in T1DM development [307].

Diabetic nephropathy (DN) is a diabetic complication that showed progressive kidney disease and progression to ESRD in ~40 % of T1DM patients. The existing evidence has also shown the association of LncRNAs with susceptibility to ESRD (End-Stage Renal Disease) [308]. In recent years, non-coding RNAs containing exosomes-especially LncRNAs, are also known to participate in diabetes development [309]. Moreover, a relationship between exosomes and T1DM has been indicated [310], which could activate the immune cells and immune molecules, and β-cell apoptosis, thereby, contributing to the pathological of T1DM [311,312]. Islet cell transplantation is identified a curative treatment strategy for T1DM with hypoglycemic unawareness or glycemic liability and the function of islet allograft after cell transplantation is monitored by glucose and C-peptide levels. These methods couldn't detect injury of the transplanted islet mass early and accurately [313–315]. Korutla L et al. have shown that circulating transplant islet-specific exosomes are an effective non-invasive diagnosis biomarker for recurring autoimmunity after allogeneic islet cell transplantation [316]. Another study has reported the first list of lncRNAs containing human islet-derived exosomes obtained from a T1DM and 31 LncRNAs were found to be dysregulated under pro-inflammatory cytokine stress, this comprehensive profile may serve as a novel circulating biomarker for T1D [317]. There is evidence revealing LncRNAs are associated with susceptibility to T1DM and β cell function, but information about circulating and exosomal LncRNAs and their application as a novel early diagnostic biomarker for T1DM remains less explored [318,319] (Table 10).

2.12. LncRNA in Autoimmune thyroid disease (AITD)

This complex disease is related to the thyroid gland that is affected by environmental and genetic risk factors. AITD is known as a common autoimmune disorder and a prototype and specific organ that combines with the mediation of both B and T cells [272]. In particular, Graves' disease (GD) and Hashimoto's thyroiditis (HT) are two important clinical signs [322]. Previously the key function of LncRNAs in AITD was reported. The new zinc-finger gene was found in the AITD coding gene in 8q23–q24. The link between T allele of Ex9b-SNP10 was reported as the high risk for AITD. Their results showed that B cell function is affected by this SNP via regulation in the transcription level [323]. It is found that Heg RNA (poly A (−) transcript) and TSH receptor autoantibodies have inversely association with early and untreated GD and as well as with CD14 mRNA in the both healthy cases and treated GD patients. Level of CD14 mRNA in MNC was reduced after adding siRNA and LPS. In addition, it was presented that ssRNA of Heg RNA could decrease the
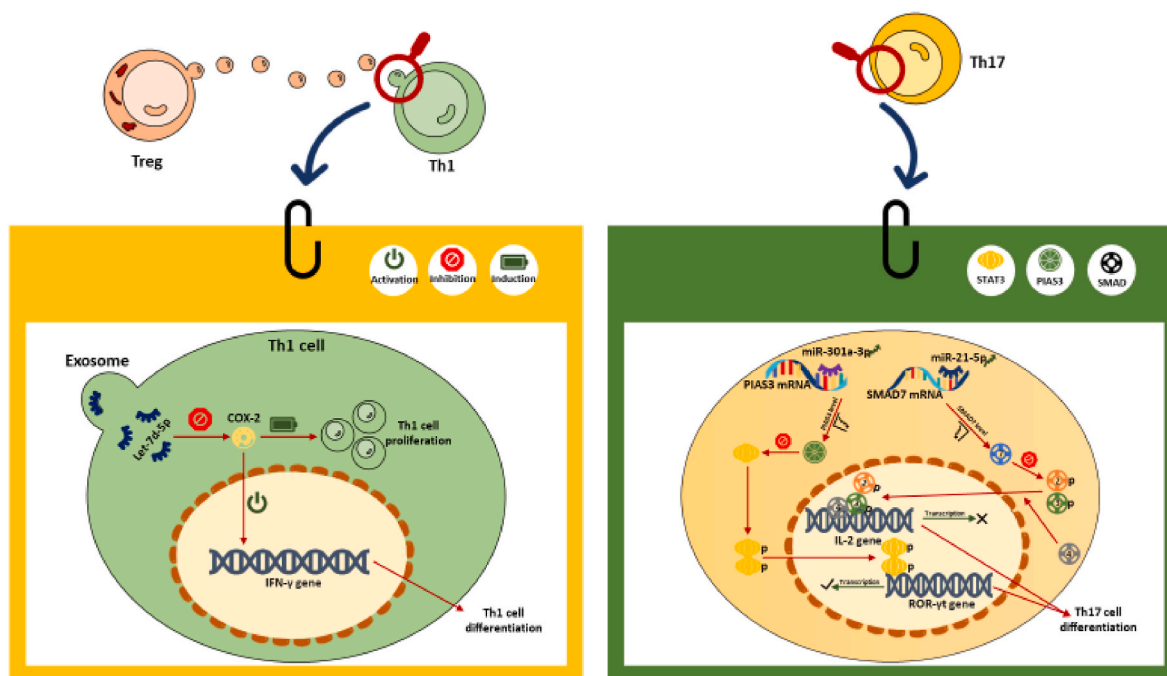
was used to diagnose T1DM, but these methods demand high cost and are time intensive, the sensitivity and specificity of protein-based detection tests are lower than RNA [301]. Furthermore, in the population with a high risk for T1DM, circulating biomarkers could be predictors of stress, dysfunction and death of β-cell in the early pre-symptomatic phase, which suggests that immune-modulatory therapy initiated to help maintain β cell mass effectively [302–304]. Several LncRNAs play potential roles in pancreatic islets, T1DM pathogenesis, and its associated complications [305–307]. A study based on microarray has revealed the profile of LncRNAs expression in the MIN6 cell line before and after cytokine treatment. 467 and 219 LncRNAs were found to be up and down-regulated, respectively. This study has shown that beta cells have sensitized to apoptosis by up-regulation of LncRNA-1, which suggested LncRNAs could contribute to beta cell

Fig. 7. Let-7d-5p is present in exosomes that are derived from regulatory T cells. A decrease in the level of this miRNA is seen in AITD. Combining Th1 cells with exosomes containing Let-7d-5p causes this miRNA to reach the cell. Suppression of IFN-γ and inhibition of TH1 cell proliferation by COX2 occurs through inhibition of Let-7d-5p [326,327]. Also, miR-301a-3p levels are increased in AITD, which binds to the 3'UTR of PIAS3 and represses the translation of PIAS3, which is a repressor of STAT3. STAT3 upregulates RORγT expression to enhance Th17 differentiation [326,328]. Therefore, downregulation of PIAS3 results in increased Th17 differentiation. MiR-21–5p levels are also increased in AITD. The translation of SMAD7, which is an inhibitor of SMAD2/3, is repressed by this miRNA. SMAD2/3 and SMAd 4 downregulate IL-2 expression, thus leading to increased IL-17 levels [326,329].

Table 11
LncRNAs associated with AITD.

LncRNA	Expression level in Autoimmune thyroid disease (AITD)	Description	References
SAS-ZFAT	Down-regulated	It performs a significant task in the functioning of B cells.	[323]
Heg	Up-regulated	It has a negative relationship with TRAb in untreated patients with GD and CD14 mRNA in treated patients and control group.	[324]
NR_038,462	Up-regulated	Functional studies confirmed the role of NR_038,462 in the regulation of critical immune-related pathways in AITD.	[330]
T204821 NR_038,461	Up-regulated	Enrichment of these transcripts occurs mainly in pathways that adjust humoral and cellular immune responses, like those related to antigen presentation and Th1, Th2, and Th17 cell differentiation.	[330,331]
NR_104,125	Up-regulated	Functional studies confirmed the role of NR_104,125 in the regulation of critical immune-related pathways in AITD.	[330,331]
IFNG-AS1	Up-regulated	Increasing the expression of IFNGAS1 in HT patients contributes to the Th1 cell response and may performs a role in the pathogenesis of HT.	[332]

CD14 expression by activating the NF-κB pathway but it needs more detailed studies [324]. In addition, HT patients showed the high level of lncRNA-IFNG-AS1 due to the Th1 cells and high level of IFN-gamma expression. At present, however, the LncRNAs control network affecting the mechanisms of AITD is unclear, and more epigenetic studies are needed [325](Fig. 7) (Table 11).

3. Conclusions

In this study, we investigated the LncRNAs related to the function of immune cells and the development of autoimmune disorders. LncRNAs transcribe RNA transcripts into more than 200 non-protein-coding nucleotides, but have a major impact on immune response diseases such as systemic lupus erythematosus, RA, SS, AITD, T1DM, SS, and human genetic diseases. Despite the growing understanding of the roles of lncRNAs in various biological processes, there remain several key challenges in elucidating the function of lncRNAs in autoimmune disorders. The reasons for the aberrant expression of lncRNAs in autoimmune diseases and the precise mechanisms driving this observation are still not fully understood. The functional differences between lncRNAs and other epigenetic factors remain to be clarified, as well as whether changes in lncRNAs contribute to the progression of disease. Growing evidence conclusively shows that lncRNAs are crucial regulators of diverse biological processes, and their dysregulation is closely associated with the development of autoimmune diseases. Identifying lncRNAs associated with different stages of immune system development would not only serve as a valuable resource for future research exploring the molecular mechanisms underlying natural immune systems but also provide a foundation for understanding the role of lncRNAs in the pathogenesis and progression of diseases. Studying the correlations between long non-coding RNA functions and autoimmune diseases can enhance our understanding of the development and underlying mechanisms of these autoimmune conditions. These studies can provide important molecular targets for the treatment, diagnosis and

management of autoimmune disorders.

CRediT authorship contribution statement

Hossein Ghahramani Almanghadim: Writing – original draft, Investigation, Conceptualization. **Bahareh Karimi:** Writing – original draft, Investigation, Conceptualization. **Sepehr Valizadeh:** Writing – review & editing, Conceptualization. **Kamran Ghaedi:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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