



Long non-coding RNAs: Mechanism of action and functional utility



Shakil Ahmad Bhat^a, Syed Mudasir Ahmad^{a,*}, Peerzada Tajamul Mumtaz^a,
Abrar Ahad Malik^a, Mashooq Ahmad Dar^a, Uneeb Urwat^a, Riaz Ahmad Shah^a,
Nazir Ahmad Ganai^b

^a Division of Biotechnology, Faculty of Veterinary Sciences and Animal Husbandry, Shuhama, Sher-e- Kashmir University of Agricultural Sciences and Technology, Kashmir, 19006, India

^b Division of Animal Breeding and Genetics, Faculty of Veterinary Sciences and Animal Husbandry, Shuhama, Sher-e- Kashmir University of Agricultural Sciences and Technology, Kashmir, 190006, India

ARTICLE INFO

Article history:

Received 7 September 2016
Received in revised form
9 November 2016
Accepted 10 November 2016
Available online 12 November 2016

Keywords:

LncRNA
X-chromosome inactivation
Genome imprinting
Transcription regulation
Cancer
Immunity

ABSTRACT

Recent RNA sequencing studies have revealed that most of the human genome is transcribed, but very little of the total transcriptomes has the ability to encode proteins. Long non-coding RNAs (lncRNAs) are non-coding transcripts longer than 200 nucleotides. Members of the non-coding genome include microRNA (miRNA), small regulatory RNAs and other short RNAs. Most of long non-coding RNA (lncRNAs) are poorly annotated. Recent recognition about lncRNAs highlights their effects in many biological and pathological processes. lncRNAs are dysfunctional in a variety of human diseases varying from cancerous to non-cancerous diseases. Characterization of these lncRNA genes and their modes of action may allow their use for diagnosis, monitoring of progression and targeted therapies in various diseases. In this review, we summarize the functional perspectives as well as the mechanism of action of lncRNAs.

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1. Introduction

The overwhelming use of technologies and new discoveries has led to the understanding of functional properties of what was once considered as junk DNA. The International Human Genome Sequencing Consortium 2004 surprised everyone after revealing that there are only 20,000 protein-coding genes in the human genome, that is just about >2% of the total genomic sequences. Through the extensive annotation efforts, some dedicated consortiums such as the ENCODE project, have broadened our knowledge of what lies in the dark recesses of the genome [1]. These findings in relation to previous studies have underscored the pervasiveness of genome transcription [2,3], and it became clear that nonprotein-coding regions too have various functions and regulatory roles. A mere number of protein-coding genes probably can't explain the organizational complexity of organisms, as there are other less complex eukaryotes with a more or less similar number of protein-coding genes (e.g., *Caenorhabditis elegans*). This increased

complexity may be explained by pre-mRNA splicing of protein-coding transcripts and post-translational modification of proteins, which increase the diversity and functionality of the proteome. The human genome sequencing has provided an opportunity for the systematic survey of genomic regions for their biological activity. As a first logical proxy for activity, many groups began their quest by mapping observed transcriptional events in the genome [4,5]. A project called FANTOM3 identified approximately 35,000 non-coding transcripts from approximately 10,000 distinct loci bearing many signatures of mRNAs, including capping, splicing, and poly-adenylation, but has little or no open reading frames (ORF) [6]. Thousands of long non-coding RNA (lncRNA) transcripts were identified that did not appear to be coding for proteins due to these early efforts [7,8].

lncRNAs are up to ~100 kilobases (kb) long, more specifically their nucleotide span range from 200 nt to 100 kilobases (kb). These are mRNA-like transcripts, but lack stable open reading frames. Like other protein coding genes, lncRNAs are probably transcribed by RNA polymerase II (RNA pol II) and are polyadenylated [9,10]. Generally, the extent or levels of expression of lncRNAs appear to be lower than protein-coding genes [11–14], and specific to the tissues [15]. Although the function of most of the lncRNAs is unknown, the

* Corresponding author.

E-mail address: mudasirbio@gmail.com (S.M. Ahmad).

number of characterized lncRNAs is increasing. Studies suggest their role in regulation of gene expression at transcriptional as well as at post-transcriptional level in development, differentiation, and human diseases, that could be negative or positive [16–18]. It has been reported that many lncRNAs function as key regulators of translational output (also transcriptional) and therefore affect cell identity and function [19–22]. In a short period, lncRNAs have emerged as legitimate, major new class of genes, as more and more functions are being attributed to them. In the near future, more functions associated with them will emerge.

2. Mechanism of action

2.1. LncRNAs as chromatin regulators

The number of lncRNAs with described functions is steadily increasing, and most of the reports revolve around their regulatory capacity. lncRNAs often function as important cis and trans-acting modulators for the expression of protein-coding genes [23,24]. lncRNAs can mediate epigenetic modification by recruiting chromatin-remodelling complex to a specific chromatin locus (Fig. 1A). At least 38% of the lncRNAs present in several tissues bind to the polycomb repressive complex 2 or the chromatin modifying proteins, CoREST and SMCX [24]. Others bind to trithorax

chromatin-activating complexes and/or activated chromatin [25]. The well-characterized lncRNAs, ANRIL, XIST, HOTAIR and KCNQ1OT1 are able to recruit epigenetic modifiers to specific loci for reprogramming the chromatin state. For example, KCNQ1OT1 binds to PRC2 and the methyl-transferase G9A (also known as EHMT2), whereas ANRIL binds to PRC1 and PRC2 [26,27]. HOTAIR and other lncRNAs function as scaffolds (Fig. 1B) coordinate the targeting of specific repressive histone modifying complexes to target loci [26]. However, within this framework, the detailed mechanism of how specific DNA regions are targeted by lncRNAs remains unclear. An example of such principle approaches together is the XIST locus that controls the X chromosome dosage compensation. XIST, in many ways can be considered as a model example of lncRNA biology, and the dissection of its mechanism of action can serve as a guide for deeper and thorough future lncRNA studies. Principally, X chromosome inactivation is due to ablation of the DNA and promoter of XIST [27,28], yet such models can't undermine the effect of the local act of transcription.

2.2. Transcriptional regulation

Long non-coding RNAs act as co-factors to modify the activity of transcriptional factor. For example, the ncRNA Evf2 is transcribed from conserved distal enhancer and recruits the transcription

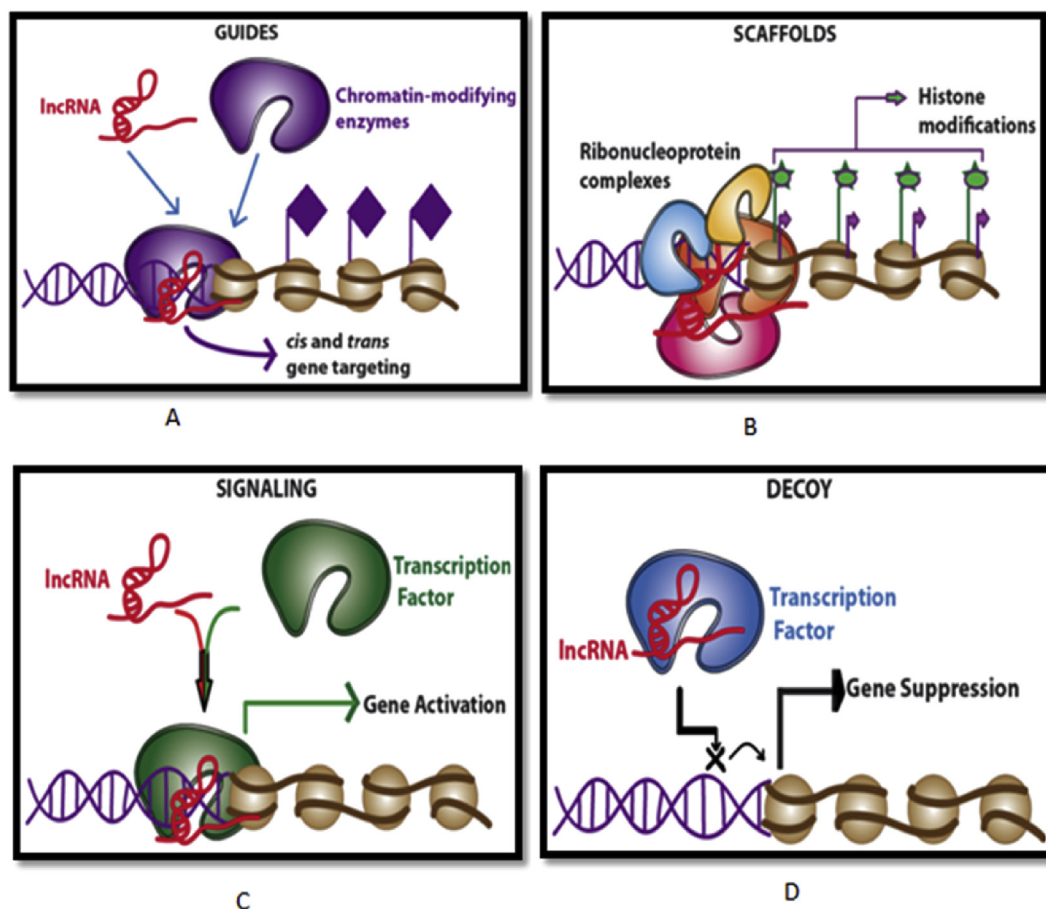


Fig. 1. lncRNA-mediated transcriptional regulation. Long non-coding RNAs (lncRNAs; red solid lines) regulate gene transcription through three main mechanisms: (A) Interaction with and recruitment of chromatin-modifying enzymes (e.g., histone methylases, acetylases, and deacetylases) to the target gene locus. Modulation of the chromatin state by these enzymes leads to activation or repression of local genes. (B) Interaction with other RNA-binding factors such as hnRNPs to form RNA–protein complexes (RNPs). RNPs can either promote transcription by recruiting key proteins to the target gene promoters or repress gene transcription by binding to existing gene repressors. (C) lncRNAs also have enhancer functions and help to change the chromatin architecture and recruit transcriptional machinery proteins to adjacent target gene locus to promote its transcription. (D) lncRNAs are also involved in the repression of some pro-apoptotic genes, such as FAS and BIK, by acting as a decoy for the transcription factor (NF- κ B).

factor (Fig. 1C) DIX2 to the same enhancer to induce expression of adjacent protein-coding genes [29]. Various developmental genes are regulated in a similar fashion by transcribing the enhancers in the cells in which they are active [30]. LncRNAs can modify RNA polymerase (RNAP) II activity by interplaying with the initiation complex to steer promoter choice e.g., in the humans transcription of a ncRNA from an upstream region of the dihydrofolate reductase (DHFR) locus to form a triplex in the major promoter of DHFR inhibits the binding of the transcriptional co-factor TFIID31. This could be a general mechanism for controlling the usage of the promoter, as thousands of these triplex structures exist in eukaryotic chromosomes [31]. Long lncRNAs may also affect global changes by interacting with some basic components of the RNAP II-dependent transcription machinery. LncRNAs interacting with RNAP II machinery are primarily transcribed by RNAP III, thereby delinking their expression from the RNAP II-dependent transcription reaction they regulate. For example, transcription of Alu elements in response to heat shock, they bind tightly to RNAP II to rule out the formation of active pre-initiation complexes [32]. Alu elements can independently mediate polymerase binding and repression by their respective domain interaction. Due to their abundance and distribution in the mammalian genome, these functional domains might have been co-operated into other ncRNAs during evolution [33].

2.3. Post-transcriptional regulation

The ability of ncRNAs to identify complementary sequences allows some specific interactions capable of regulating post-transcriptional processing of mRNAs like capping, splicing, editing, transport, translation, degradation, and stability at various control sites. For example, MALAT1 affects alternate splicing by interacting with splicing factors. Another lncRNA, Gomafu/MIAT, which is localized to a nuclear domain and has a neuron-specific expression, may block spliceosome formation and affect the mRNA splicing by sequestering splicing factor 1 (SF1) [34,35]. The NAT lncRNAs also plays an essential role in regulating mRNA dynamics (Fig. 1D). About 61–72% of all transcribed regions possess lncRNAs in antisense orientation (NATs) [36]. Unlike classical NAT lncRNAs to the imprinting genes (Tsix, Air, HOTAIR, and Evi-2) which are responsible for recruiting repressor complexes like PRC2 to the target site, certain NATs result in RNA duplexes to inhibit cis-regulatory elements, leading to an alternate splicing pattern of the paired gene. For example, the Zeb2/Sip1 NAT complementary binds to the 5' splice site of an intron in the 5'-UTR of the zinc finger Hox mRNA Zeb2, which plays a crucial role in epithelial-mesenchymal transition (EMT). Expression of the Zeb2 NAT upon EMT masks the splice site, hence preventing spliceosome action. Subsequently the translation machinery can then recognize and bind to an internal ribosome entry site (IRES), resulting in more efficient Zeb2 translation.

3. LncRNAs: a functional perspective

Though they are different from mRNAs exported to the cytoplasm for translation, few lncRNAs are known to be restrained in certain sub-nuclear compartments [37–39], which suggest potential functions in these compartments.

3.1. X chromosome inactivation

Epigenetic regulation of allelic expression (process of dosage compensation and genomic imprinting) is the best-studied function of lncRNAs. XCI (X chromosome inactivation) compensates the imbalance between XX and XY with respect to X-linked genes by

inactivation of one of the X chromosomes in females through hetero-chromatinization [40]. Two different types of XCIs occur in placental mammals, the first one is the imprinted XCI, in the embryo, where the paternal X chromosome is always inactivated and another type is the random XCI, which occurs in the inner cell mass where epigenetic markers have been silenced after embryo implantation [41]. In random XCI, either the paternal or the maternal X chromosome is randomly inactivated, producing a mosaic female. XCI in placental mammals is regulated by a cluster of lncRNA loci which is known as the X-inactivation centre (Xic) [42]. The Xi-specific transcript (Xist) is highly expressed from Xi (X inactive) during the onset of XCI, but not from Xa (X active) chromosome. Xist RNA recruits silencing factors like Polycomb repressive complex 2 (PRC2) [43] by forming a “Xist cloud” around the X chromosome [44]. As it turns out, Xist is regulated by other lncRNAs. Tsix, which is transcribed in antisense orientation from a promoter downstream of Xist, is expressed at a higher level before initiating XCI and then goes silent from the future Xi chromosome, but persists on the presumptive Xa chromosome, thus exhibiting the reverse pattern as Xist expression. Tsix has a role in coordinating X chromosome pairing to bring epigenetic asymmetry within the Xist locus and to downregulate Xist by different mechanisms [45].

3.2. Regulation of allelic expression: genomic imprinting

LncRNAs also play their role in genomic imprinting by expression of a gene monoallelically according to its line of descent [46,47]. Like XCI, imprinting is also controlled by some specific genomic loci, known as imprinting control regions. Depending on parental origins, differentially methylated regions, unmethylated DNA imprinting control regions (ICRs), result in specific expression of nearby lncRNAs genes and suppression of neighbouring genes in cis [48]. Most of the imprinted clusters are associated with protein coding genes and some specific lncRNAs which are inversely expressed, e.g., Air and Kcnq1ot1/LIT1 (Kcnq1 opposite transcript 1, or long QT intronic transcript 1) cause suppression of paternally inherited genes. Precisely, Kcnq1ot1/LIT1 is involved in repression of several protein-coding genes in cis by interacting with repressive chromatin-modifying complexes [49,50]. Kcnq1ot1/LIT1 is an imprinted region with at least eight genes expressed exclusively or preferentially from the maternal allele [51]. Kcnq1ot1/LIT1 acts as an organizer on a tissue/lineage-specific nuclear domain, involving in epigenetic silencing of the Kcnq1 imprinting control region [51–54] other examples being Igf2r/Air [26], Dlk1/Gtl2 [27], Nesp/Nespas/Gnas [55], and the Beckwith–Wiedemann syndrome (BWS) associated Kcnq1/Kcnq1ot1 [56]. These lncRNAs regulate the expression of imprinted genes by recruiting epigenetic factors, such as PRC2 and G9a [57]. H19 was one of the first lncRNAs to be identified and is reported to be the most highly expressed transcripts within the embryo [58]. It is inversely imprinted with Igf2. However, it has been observed that H19 does not seem to function as a lncRNAs [59], but acts as miRNA precursor [60].

4. LncRNAs in cancer

Cancer is a condition where gene expression is aberrant. The study of genetic background of cancer has revealed that the majority of the cancers are attributed to non-coding regions of the genome. Recent developments indicate that several cancer loci are transcribed into lncRNAs and that these transcripts play key roles in tumorigenesis. LncRNAs contribute to cancer development through diverse mechanisms. LncRNAs are reported to be implicated in serial steps of cancer development [61]. These lncRNAs interact with nucleic material and protein molecules and/or their combinations and act as an essential regulator of chromatin organization,

transcriptional and posttranscriptional regulation. Their mis-expression confers the cancer cell potential to initiate tumour growth, and metastasis. A review demonstrating the roles of lncRNAs in cancer diagnosis and therapy, reported different expression profiles for numerous lncRNAs in urothelial cancer [62]. Various evidences suggest that most of the lncRNAs result in epigenetic changes by recruiting various chromatin modifying agents [63,64], like polycomb repressive complex 2 or the chromatin modifying proteins CoREST and SMCX [65]. The best studied lncRNAs (Table 1); ANRIL, MALAT1, HOTAIR and KCNQ10T1, Taurine-upregulated gene 1 (TUG1), LINC00152, RP11-385J1.2 and TUBA4B which recruit epigenetic modifiers to their respective specific loci to regulate the chromatin state and their misexpression are linked to diverse cancers such as ANRIL: prostate cancer, HOTAIR: breast cancer KCNQ10T1: colorectal cancer, TUG1: esophageal cancer, LINC00152: gastric cancer, RP11-385J1.2 and TUBA4B: non-small cell lung cancer [66–70]. One of the first lncRNAs described to have a functional role in the development of cancer is the metastasis-associated HOX Antisense Intergenic RNA (HOTAIR). HOTAIR lncRNAs promotes cancer metastasis by inducing epigenetic variations in the chromatin state of cancer cells [71]. The mechanism of action is well demonstrated in Fig. 2. It was observed to be highly up-regulated in metastatic and primary breast tumours, about 2000 times over the normal breast tissue. The upregulation of HOTAIR could be associated with poor prognosis in breast, liver, colorectal, GIT, and pancreatic cancers. Meanwhile, it may probably contribute to promote the tumour invasiveness and metastasis [72–77]. A substantial growth of primary tumours was observed in mouse mammary fat pads by the grafting cells expressing HOTAIR [78]. Interestingly, certain reports indicate various lncRNAs emanating from the HOX locus suggesting its global regulatory role [79]. Taurine-upregulated gene 1 (TUG1) has shown significant over expression in esophageal squamous cell carcinoma (ESCC) tissues, and *in vitro* silencing of TUG1 inhibits the proliferation and migration of ESCC cells [80]. POU3F3 (Linc-POU class 3 homeobox 3) acts as a regulator in ESCC, which promotes the methylation of POU3F3 by interacting with EZH2 [67,68]. Another significant lncRNA (LINC00152) has been associated with the development of gastric cancer (GC) and can be used as biomarker for GC diagnosis [69]. Recent comprehensive studies have shown that wide range of lncRNAs are significantly associated with non-small cell lung cancer (NSCLC). Important among these, RP11-385J1.2 and TUBA4B, and are aberrantly over expressed lncRNAs, thus exhibit an important developmental role in NSCLC [70]. The MALAT1 gene, or the metastasis-associated lung adenocarcinoma transcript 1, is associated with metastatic potential and is widely expressed in various human tissues [81,82] and was also found to be up-regulated in various types of cancers like breast, prostate, colon, liver and uterine cancers [83]. Some lncRNAs are constituents of macromolecular complexes involved in RNA processing. MALAT1 is proposed to be acting at a post-transcriptional level by controlling the alternative splicing of pre-mRNA molecules. It modulates the activity of serine/arginine (SR) splicing

factors [84]. MALAT1 is up-regulated in various cancer types and is over-expressed in metastatic cells of lung and colorectal cancers [85].

Many tumor suppressor genes are known to carry antisense transcripts [86]. For example, p15, a cyclin-dependent kinase inhibitor implicated in leukemia, possesses an antisense transcript, which silences its transcription in cis and trans by inducing heterochromatin formation without changing the DNA methylation in a Dicer-independent manner [87–90]. It is possible that these antisense transcripts directly bind and recruit chromatin-modifying complexes to their associated sense transcripts [91].

In summary, lncRNAs can act through different mechanisms to regulate cancer state. Although the molecular mechanisms of various lncRNAs functions are well studied, but their modes of action mostly remain unclear. A comprehensive study of the lncRNA mechanism and their functions will aid in better understanding of their role in cancer and will open up new therapeutic possibilities to modulate their function.

4.1. Role of lncRNAs in immunity

The role of non-coding RNAs in the regulation of gene expression in immune cells is still poorly understood [92]. Reports suggest their role in T cell development, differentiation, and activation of adaptive and innate immunity. lncRNAs are reported to be present in various immune cells like monocytes, macrophages, dendritic cells, neutrophils, T cells and B cells. The role of lnc-DC in the differentiation of monocytes to dendritic cells has been well established [93,94]. Many lncRNAs like Lethe [95] and lnc-IL7R [96] have been reported to possess immune system associated functions. Moreover, recent reports reveal that the regulatory functions of many of these lncRNAs are in RNA-protein binding [97,98], chromatin remodeling [99, 100] and in interactions with transcriptional factors and signaling molecules [101] as described in Fig. 1D. Although the functions of most of the lncRNAs in infections are still unknown, recent reports suggest that many lncRNAs may be playing a pivotal role in gene regulation at transcriptional and posttranscriptional level during innate immune responses. Their role in gene expression regulation in macrophages and other innate immune cells has also been reported. Such discoveries suggest that lncRNAs may contribute to gene regulatory networks governing host–pathogen interactions. Similarly, inflammatory mediation or cytokine regulation by lncRNAs is also poorly understood. The innate immunity is the frontline defense response of a cell. The Innate immune response is important to the host to defend itself from the invasion of various pathogenic organisms like bacteria or viruses. As cells encounter pathogens, an innate immune response is triggered by the production of inflammatory mediators or cytokines through transcription factors, such as AP1, NF- κ B, and miRNAs [102, 103]. The innate immune response also triggers adaptive immune responses by recognizing pathogens by certain specific receptors known as TLRs (Toll-like receptors) resulting in the elimination of the pathogen. It has been found that TLRs are a major

Table 1
lncRNAs in cancer.

S.No.	lncRNA	Function	Reference
1	ANRIL	Transcription control by chromatin modifications	[52]
2	MALAT1	Promotes cancer by controlling the alternative splicing of pre-mRNA molecules	[67,68,69]
3	HOTAIR	Promotes cancer metastasis and progression through epigenetic variations in the chromatin state	[61]
4	KNCQ10T1	Promoting cancer progression	
5	TUG1	Promoting proliferation, migration, cell cycle	[53,54,66]
6	LINC00152	Promoting cancer progression	[55]
7	RP11-385J1.2	Suppressing proliferation and invasion	[56]
8	TUBA4B	Promoting proliferation, migration, invasion	[56]

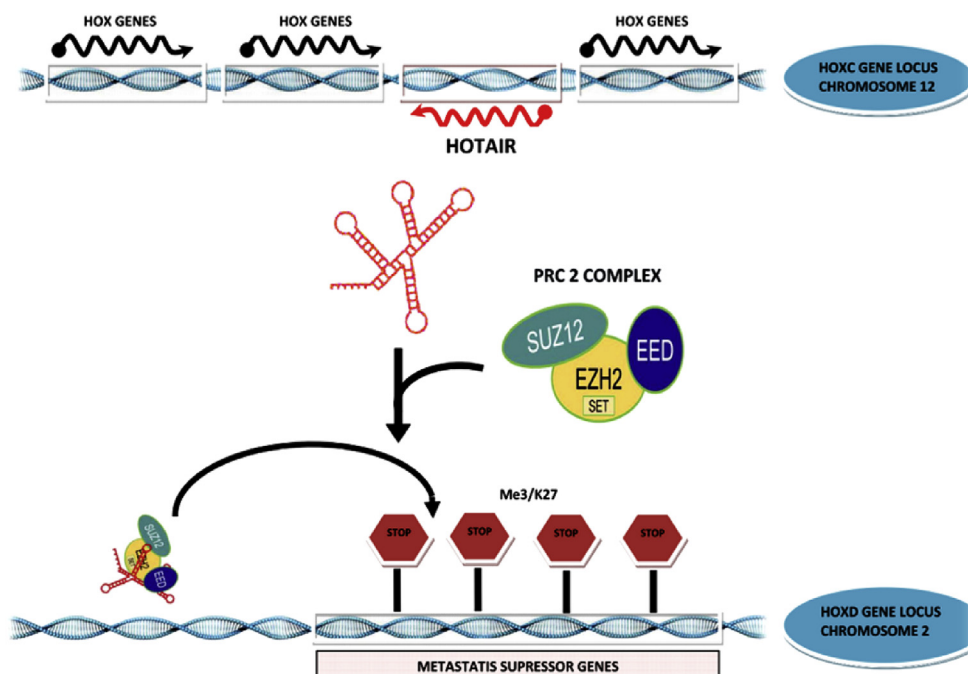


Fig. 2. Model of long noncoding RNA (lncRNA) HOX transcript antisense RNA (HOTAIR) regulating expression of HOX genes in trans. lncRNA HOTAIR transcribed from the HOXC cluster of genes (chromosome no.2) binds PRC2 complex of polycomb-group of proteins and targets it to the HOXD cluster (chromosome no.12) leading to H3K27 methylation and silencing of neighboring HOXD genes.

receptor type for pathogen recognition [104]. Following this ligand recognition by these receptors, lncRNAs like Nest/tmvp1 [105,106], IL1 β -eRNA [107] and IL1 β -RBT46 [108] recruit transcription activators through RNA–protein complex formation or remove repressors of transcription, leading to rapid expression of cytokines. This also involves transcriptional and post-transcriptional gene regulation via transcription factors (API and NF- κ B, and miRNAs) [109]. Phagocytes such as macrophages and polymorphonuclear neutrophilic granulocytes (PMNs) represent the first line of defense against invading pathogens. Macrophages are key components of host defense mechanisms against invading pathogens. Many lncRNAs were also found to be up-regulated in macrophages exposed to Toll-like receptor 2 (TLR2) ligands [110]. It has been found that a large number of lncRNAs are involved in regulation of interferon stimulated genes (ISG) like PACER [111], NRON [112,113], antisense transcript of IL1 β and a long intergenic non-coding RNA (lincRNA) Cox2 [114,115] (Table 2). lincRNA Cox2 was found to have a role in TLR-induced expression of interleukin-6 (IL6) [116]. TNF and HNRNPL-related immunoregulatory lincRNA (THRIL) were reported to regulate expression of tumor necrosis factor (TNF) in human monocytes through interactions with HNRNPL [117,118]. In addition to the phagocytosis and secretion of

pro-inflammatory mediators by macrophages, autophagy is the most recent mechanism of the immune response to bacterial infection. Although, the role of lncRNAs in autophagy response to the intracellular bacteria is still unknown [119], it has been reported that IFN- γ induced autophagy in infected macrophages resulted in sustained lncRNA MEG3 down-regulation and lack of IFN- γ allowed for counter-regulation of lncRNA MEG3 by viable *M. bovis* BCG. Knockdown of lncRNA MEG3 in macrophages resulted in autophagy and enhanced removal of intracellular *M. bovis* BCG [120, 121]. It has also been reviewed that lncRNAs may have a function in a variety of human polygenic diseases from cancers of different organs to non-cancerous diseases, such as Alzheimer's disease [122–125]. Further research may enable us to better understand their infectious and inflammatory pathologies and may provide a new insight for effective therapeutics.

5. Conclusion

Despite the fast increase in understanding the functional role of lncRNA, this field is still in its infancy and many questions and challenges are debatable. Their role in human diseases is a mystery. Undoubtedly, in this review article we tried to explain how lncRNAs

Table 2
lncRNA in immunity.

S.No.	lncRNA	Function	Reference
1	lincRNA-COX2	Role in TLR-induced expression of interleukin-6	[114,115]
2	Lnc-DC	Required for the differentiation of monocytes to dendritic cells	[93]
3	NRON	Transcription regulator for immune regulation	[112,113]
4	Lnc-IL7R	Epigenetically regulates inflammation	[96]
5	NeST/Tmvp1	Epigenetically regulates the adaptive immunity through IFN-gamma	[105,106]
6	IL1 β -eRNA	Overexpressed in LPS induced inflammation	[107]
7	PACER	Involved in multiple processes related to regulation of immunogene expression	[111]
8	THRIL	regulate expression of tumour necrosis factor (TNF) in human monocytes	[117]
9	IL1 β -RBT46	Regulates the homeostasis of IL-1 β in monocytes	[108]
10	lethe	Upregulated during inflammation	[95]

play a diverse role in biological processes and contribute in physiological processes of the cell. A better understanding of chromosomal architecture and affiliation between the organization of RNA structure and protein recruitment as well as gene regulation shall help in prognosis and design novel therapeutics to target gene expression for the treatment of many dreadful human diseases. Many of the lncRNAs are reported to have diverse functions, identified through genomic and transcriptomic approaches. The Much deeper study is needed to discover many more lncRNAs that have their functions annotated. Another challenge in lncRNA research is to explore their coding prospective. The possibility that code for short peptides has not been ruled out as of now.

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