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LncRNA as a Therapeutic Target for Angiogenesis

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Abstract: Background: Out of 3 billion base pairs in human genome only ~2% code for proteins; and out of 180,000 transcripts in human cells, about 20,000 code for protein, remaining 160,000 are non-coding transcripts. Most of these transcripts are more than 200 base pairs and constitute a group of long non-coding RNA (lncRNA). Many of the lncRNA have its own promoter, and are well conserved in mammals. Accumulating evidence indicates that lncRNAs act as molecular switches in cellular differentiation, movement, apoptosis, and in the reprogramming of cell states by altering gene expression patterns. However, the role of this important group of molecules in angiogenesis is not well understood. Angiogenesis is a complex process and depends on precise regulation of gene expression.

Conclusion: Dysregulation of transcription during this process may lead to several diseases including various cancers. As angiogenesis is an important process in cancer pathogenesis and treatment, lncRNA may be playing an important role in angiogenesis. In support of this, lncRNA microvascular invasion in hepatocellular carcinoma (MVIH) has been shown to activate angiogenesis. Furthermore, lncRNA-Meg3-knockout mouse showed increased expression of vascular endothelial growth factor pathway genes and increased cortical microvessel density. Overall, there is strong evidence that lncRNA is an important class of regulatory molecule, and a number of studies have demonstrated that these can be targeted to change cellular physiology and functions. In this review, we have attempted to summarize these studies and elucidate the potential of this novel regulatory molecule as a therapeutic target.

Keywords: Epigenetic regulation, gene expression, intervening noncoding RNA, LncRNA, Linc-MD1.

1. INTRODUCTION

Until recently, small molecules (pharmacological agents), peptides, proteins, antibodies, and small interfering RNA (siRNA), and microRNA (miRNA) targeting protein-coding genes were considered as therapeutic agents. Recent evidence indicates that long non-coding RNA (lncRNA) is rapidly emerging as a promising drug target and/or candidate [1-4]. LncRNA is a group of non-coding RNAs that is more than 200 base pairs and may have their own promoters and may lie between protein-coding genes (intergenic) [5]. Specifically, these long intergenic non-coding RNA (lincRNA) are conserved in various species [5]. Pathway for lncRNA biogenesis is similar to that of protein-coding RNAs *i.e.* histone modification profiles, splicing signals and exon/intron lengths [6]. Similar to mRNA most of these lncRNA has a poly A tail; however, they cannot be translated into proteins. Importantly, the expression level of lncRNA is lower than mRNA in tissues except brain where lncRNA is expressed higher than mRNA [6]. LncRNAs are predominantly located in the nucleus and few are located in the cytoplasm, which underscores their regulatory role in gene transcription. Although, few lncRNAs are located in both nucleus and cytoplasm [7, 8].

LncRNAs were considered earlier as “dark matter” or “transcriptional noise” with no biological functions [9], however, whole genome transcriptomic analysis revealed large number of dynamically expressed lncRNAs, many of which are involved in variety of biological activities [10]. For example, lincRNA-RoR regulates reprogramming of human induced pluripotent stem cells [11], lincRNA ES1, ES2, and ES3 promote pluripotency and neuronal differentiation by association with chromatin modifiers and transcription factors indicating a major role in human brain development [12]. Muscle-specific linc-MD1 regulates muscle differentiation by acting as competing-endogenous RNA in mouse and human myoblasts [13]. Linc-MD1 “sponges” micro RNA-133 and -135 to regulate the expression of transcription factors MAML1 and MEF2C that activate muscle-specific gene expression [13]. LncRNAs are also involved in regulating the synapse formation by modulating the expression of genes related to synapse formation and maintenance [14]. Recent evidence indicates that lncRNAs are also involved in the gene regulation of inflammation [15]. LncRNA lnc13 downregulation was observed in small intestinal biopsy samples from patients with celiac disease [15]. Lnc13 regulates gene expression by binding to heterogeneous nuclear ribonucleoproteins (hnRNPs) [15].

Recent studies have also demonstrated that lncRNA play a major regulatory role in angiogenesis. LncRNA can regulate the various processes involved in angiogenesis directly

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or indirectly by regulating various molecules which plays a vital role in angiogenesis such as vascular endothelial growth factor (VEGF) [16]. There is strong evidence that lncRNA is an important class of regulatory molecule, and a number of studies have demonstrated that these can be targeted to change cellular physiology and functions. In this review, we have attempted to summarize these studies and elucidate the potential of this novel regulatory molecule as a therapeutic target with emphasis on vascular pathologies.

2. CLASSIFICATION OF LncRNA

More and more lncRNAs are discovered due to high-throughput sequencing techniques and computational methods. Based on their nearest protein-coding gene, lncRNAs can be classified in five different classes (Fig. 1) [9] (1) Sense, or (2) Antisense, lncRNAs that are located on the same strand or the opposite strand, respectively, of the nearest protein-coding genes, and overlap at least one protein-coding exon; (3) Bidirectional lncRNAs are transcripts that initiate in a divergent fashion from the promoter of a protein-coding gene; the precise distance cutoff that constitutes bidirectionality is not defined but is generally within a few hundred base pairs; (4) Intronic lncRNAs initiate within an intron of a protein-coding gene in either direction and terminate without overlapping exon, and (5) intergenic lncRNA (also termed large intervening noncoding RNAs or lincRNAs), lncRNAs that locate in the interval regions between two protein-coding genes, have their own promoter with separate transcriptional units from protein-coding gene.

3. MECHANISMS OF LncRNA FUNCTIONS

LncRNA acts by three major mechanisms of action (Fig. 2). 1. LncRNA can fold into a tertiary structure and provide a scaffold for the formation of a quaternary structure for proteins and other regulatory RNA [17]. For example, lncRNA participates in gene silencing by regulating polycomb repressive complex 2 activity [17], which has histone methyltransferase activity and primarily methylate histone H3 on lysine 27 (H3K27me3) a mark of transcriptionally silent chromatin. 2. LncRNA also regulates the gene expression at post-transcriptional level in the cytoplasm by affecting the stability of mRNAs, altering the translation efficacy of target mRNAs and may function as a precursor for microRNAs or compete for microRNA-mediated inhibition, leading to increased mRNA expression [18]. 3. LncRNAs may also directly bind DNA sequences and form RNA-DNA triplex complex [18]. This can trigger the expression of genes by providing a more open chromatin domain for mRNA transcription. LncRNAs can also silence the gene expression by occupying the transcription factor binding sites [19]. In the nucleus, lncRNAs also control the epigenetic state of particular genes, involved in transcriptional regulation and splicing [10]. It is well established that biochemically-purified chromatin contains a significant amount of RNA, which may influence chromatin structure and gene regulation [20, 21] and/or DNA methylation [22].

4. LncRNA AND ANGIOGENESIS

Angiogenesis is a complex process and depends on the precise regulation of gene expression. Dysregulation of transcription during this process may lead to several diseases

during pregnancy (placental insufficiency), newborn (hemangioma, growth restriction), and adult (corneal neovascularization, tumors, non-healing wounds). Inhibition of angiogenesis can be beneficial in disorders such as hemangioma, corneal neovascularization, cancer; whereas, stimulation of angiogenesis can be beneficial in disorders such as placental insufficiency, wound repair, tissue engineering, and regenerative diseases. At present, genetic pathways regulated during angiogenesis are not completely understood. Importantly, the angiogenic response is regulated by a coordinated transcriptional and translational regulation of angiogenesis genes. As angiogenesis is an important process in cancer pathogenesis and treatment, novel therapeutic targets are needed to inhibit angiogenesis and lncRNA can be invaluable in this regard.

Angiogenesis induction is vital for cancer growth and it also helps in activating invasion and metastasis [23, 24]. The major signaling molecule for angiogenesis is vascular endothelial growth factor (VEGF) [16] and it is highly expressed in disease conditions like cancer [25]. Hypoxia strongly induces expression of VEGF [26] via hypoxia inducible factor-1 α (HIF-1 α) [27], which in turn activates VEGF receptor 2 (VEGFR2) to stimulate tip cell migration from arteries to initiate angiogenesis. VEGFR2 signaling is potentiated by coreceptor neuropilin-1 (Nrp1) for promoting the tip cell

function, which plays a major role in the separation of arteries and veins [28]. Another pro-angiogenic signaling mediator is Notch [29], which plays a role in coordinating the tip cells and stalk cells proliferation and migration. Notch components pathway is highly expressed in arteries compared to veins [30]. All these signaling molecules are regulated by lncRNAs. LUNAR1 is a specific Notch-regulated lncRNA [31], which has the ability to enhance insulin like growth factor 1 receptor (IGF1R) mRNA expression and promote angiogenesis and cell survival.

Maternally expressed gene 3 (MEG3) encodes a lncRNA, which is expressed in many normal tissues [32]. Loss of MEG3 lncRNA gene expression is reported in tumor cells and this could be due to multiple mechanisms like gene deletion, promoter hypermethylation, and hypermethylation of intergenic differentially methylated region [33]. Re-expression of MEG3 lncRNA is reported to suppress the tumor growth in both *in vitro* and *in vivo* animal models [33]. Inactivation of MEG3 lncRNA gene is reported to increase the expression of angiogenesis promoting genes and microvessel formation in the brain [34]. Moreover, in MEG3-knockout mouse quantitative PCR and immunohistological staining showed increased expression of VEGF pathway genes and increased cortical microvessel density [35]. A recent report indicates that another lncRNA HOTAIR promotes angiogenesis through directly activating the transcription of VEGFA as well as indirectly through GRP78 mediated upregulation of VEGFA and Ang2 expression in both *in vitro* and *in vivo* nasopharyngeal carcinoma studies [36]. Thus, MEG3 and HOTAIR may play an important role in the control of angiogenesis.

LncRNA associated with microvascular invasion in hepatocellular carcinoma (lncRNA MVIH) is known to play a major role in hepatocellular carcinoma by inducing angiogenesis [37]. It is predicted that MVIH activate tumor-inducing angiogenesis by inhibiting the secretion of phos-

Types of LncRNA

Fig. (1). Demonstrates the five major classes of LncRNA.

Major Mechanisms of Action of LncRNA

Fig. (2). Demonstrates the three major mechanisms of action of LncRNA.

phoglycerate kinase 1 (PKG1), which is correlated with reduced serum PKG1 levels and increased microvessel density in hepatocellular carcinoma patients [37]. A recently published report indicates that tyrosine kinase containing immunoglobulin and epidermal growth factor homology domain-1 gene (tie-1) is regulated by lncRNA tie-1AS in endothelial cells. Tie-1AS lncRNA selectively binds to tie-1 mRNA and regulates tie-1 mRNA transcription, resulting in specific defects in endothelial cell contact junctions and tube formations [38].

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is another lncRNA, which plays an essential role in angiogenesis [39]. MALAT1 is significantly upregulated

by hypoxia and hyperglycemia in endothelial cells [40]. *In vivo* experiments with genetic deletion of MALAT1 gene have demonstrated reduced retinal vascular growth and endothelial growth [41]. Importantly, pharmacological inhibition of MALAT1 decreased blood-flow recovery and capillary density after hind-limb ischemia by impairing the expression of various cell cycle regulators [42, 43]. MALAT1 chiefly influences the alternative splicing by controlling the distribution and activity of sarcoplasmic reticulum protein expression [44]. MALAT1 expression is also upregulated in retina and kidney of diabetic mice [40]. Whereas, silencing of MALAT1 resulted in inhibition of diabetic retinopathy by regulating pericyte loss, capillary degeneration, and microvascular leakage [43]. Moreover, endothelial cells stimulated

with hyperglycemia shows the involvement of MALAT1 in angiogenesis and inflammation. Knockdown of MALAT1 shows decreased cell proliferation, migration, and tube formation in endothelial cells stimulated with hyperglycemia [40, 42, 43].

Recently, three new lncRNAs have been identified in endothelial cell differentiation and angiogenesis. These three lncRNAs (Terminator, Alien and Punisher) are induced during differentiation of endothelial cell from human pluripotent stem cell [45]. LncRNA Terminator is mainly expressed during the pluripotent cell period, whereas, Alien is expressed in cardiovascular progenitors, and Punisher is expressed specifically in human endothelial cells. Zebrafish and mice have shown similar trends. Knockdown of Terminator influences genes related to pluripotent maintenance. Alien knockdown mainly affects cell adhesion, extra cellular matrix remodeling, angiogenesis, and blood vessel development. Knockdown of Punisher influences mitosis, cell adhesion, and extracellular interaction [45].

Recent studies have demonstrated that two new intergenic lncRNAs called linc00323-003 and MIR503HG are induced by hypoxia in endothelial cells, which contribute to angiogenesis [46]. Silencing either of these lncRNAs transcripts lead to angiogenic defects, including the repression of growth factor signaling followed by the inhibition of angiogenic sprouting. Both lncRNAs inhibit the expression of the endothelial expression factor GATA2, there by potentially controlling the cell proliferation [46]. However, the *in vivo* function of these lncRNAs is unclear, their role in angiogenesis need to be examined.

Recent reports indicate that lncRNAs are induced in hypoxic [41] or hyperglycemic conditions [40], which provide new leads regarding endothelial cell survival. Nuclear factor of activated T-cells (NFAT) plays a significant role in endothelial cell survival and angiogenesis [47]. Specifically, dephosphorylated NFAT moves into the nucleus to function as a transcriptional factor [48]. Cytoplasmic lncRNA non-coding repressor of NFAT (NRON) has been identified as a critical regulator of NFAT dephosphorylation [49]. It forms the NRON complex by binding to various regulatory proteins such as KPNB1, PPP2R1A, PSMD11, and IQGAP1. NRON inhibits NFAT nuclear distribution by acting as a decoy [49, 50]. Furthermore, accumulation of Ets-1 in the cytoplasm could competitively displace NFAT from NRON complex, which leads to inhibition of NRON function [51]. Additionally, NRON over-expression inhibits NFAT expression, which reduces endothelial cells proliferation, tube formation, and migration [52]. Importantly, NRON inhibition through siRNA results in activation of NFAT, which promotes endothelial cells proliferation, tube formation, and migration [52].

Not only endothelial cells but also vascular smooth muscle cells (VSMC) are regulated by lncRNA. RNA-seq analysis of Ang II-stimulated rat aortic VSMC identified a novel lncRNA named Lnc-Ang362, which promotes VSMC proliferation [53]. Lnc-Ang362 is located proximal to miR-221 and miR-222, which are known regulator of VSMC proliferation and neointimal hyperplasia [54]. Knocking down of Lnc-Ang362 reduced the miR-221 and miR-222 expression and inhibited VSMC proliferation [53].

LncRNAs have been implicated in other aspects of vascular development [45]. Initial reports of stem cell-based studies have highlighted the involvement of lncRNA *Braveheart* (AK143260; Bvht) in cardiac development [55]. LncRNA *Fendrr* a lateral-mesoderm specific lncRNA has been shown to play a functional role in chromatin modifications, and thereby control the developmental signaling in the heart in a mouse knockout study [56]. This study showed *Fendrr* is an essential regulator of heart and body wall development in mouse. *Kcnq1ot1*, a new lncRNA regulates *Kcnq1* transcription through modulating chromatin flexibility and access of transcriptional machinery to its enhancer [57]. *Kcnq1* is reported to play a key role in the heart development during embryogenesis [57].

5. LncRNA AND VASCULAR PATHOLOGIES

LncRNA has also been shown to be involved in pathological vascular conditions such as atherosclerosis [58], microvascular disorders [59], diabetic retinopathies [60], pulmonary hypertension [61], and myocardial infarction [62]. LncRNA ANRIL is transcribed from INK/ARF locus, which is expressed in atherosclerotic tissues and cells such as primary coronary smooth muscle cells, vascular endothelial cells, human monocyte-derived macrophage cells, and carotid myocytes [59]. Increased expression of ANRIL transcripts was reported to correlate directly with the severity of atherosclerosis [63]. Transforming growth factor beta 2 overlapping transcript 1 (TGFβ2-OT1) is another lncRNA involved in atherosclerosis. TGFβ2-OT1 is transcribed from the 3' UTR of TGFβ2 coding gene. Lipopolysaccharide and oxidized low-density lipoproteins regulate the expression of TGFβ2-OT1 in the pathology of atherosclerosis [64]. Microarray profiling of the overexpression of TGFβ2-OT1 indicates that three miRNAs (miR-3960, miR-4488 and miR-4459) are regulated by TGFβ2-OT1 and acts as an endogenous competing RNA bound to miRNAs [65]. Furthermore, the overexpression of these three miRNAs resulted in the repression of their downstream targets: ceramide synthase 1 (CERS1), N-acetyltransferase 8-like (NAT8L), and Laribonucleoprotein-domain-family-member 1 (LARP1) [66]. These are primarily involved in endothelial cell autophagy, inflammation and in endothelial injury, and regulation of angiogenesis [65, 66]. Another study reported that smooth muscle specific osteogenic transcription factor RUNX2 is regulated by TGFβ and bone morphogenic protein (BMP) [67]. RUNX2 is an essential regulator of vascular calcification [67]. Further, it has been reported that activation of RUNX2 induces the overexpression of miR-3960 and miR-3960, which promotes the vascular calcification by increasing the osteoblast differentiation markers alkaline phosphatase (ALP) and osteocalcin [68]. Considering together the above-results suggest that overexpression of TGFβ2-OT1 and subsequent downregulation of miR-3960 may prove a novel way to specifically target RUNX2 signaling in the pathology of atherosclerosis and vascular calcification [65, 68]. Moreover, *in vitro* studies in human THP-1 foam cells indicate that upregulation of lncRNA nuclear factor 1A-AS1 (NF1A-AS1) leads to reduced expression of nuclear factor 1A (NF1A). Lentiviral-mediated overexpression of lncRNA NF1A-AS1 in a "mouse model" affected the markers of atherosclerosis such as the ratio of high-density lipoprotein

(HDL) to low density lipoprotein (LDL) in the circulation as well as reduced inflammatory cytokines such as IL-1 β , IL-6, TNF- α , and C-reactive protein in the circulation [69]. Overall, accumulating evidence indicates that lncRNA plays an important role in atherosclerosis.

Myocardial infarction-associated transcript (MIAT) lncRNA is associated with angiogenesis following microvascular disease and myocardial infarction [62]. Hyperglycemic endothelial cells as well as diabetic retinæ also have shown increased MIAT levels [60]. Of note, knockdown of MIAT could prevent endothelial cell proliferation, migration and tube formation [60]. Studies indicate that knockdown of MIAT attenuates diabetes-induced pericyte loss, capillary degeneration, and microvascular leakage. The mechanism of action of MIAT could be through miR-150, which is a repression target of VEGF. MIAT acts as a decoy for miR-150 and upregulates VEGF [62].

Other than atherosclerosis and heart diseases, because of their significant involvement in angiogenesis, lncRNA has been implicated in various cancers. An important lncRNA, which plays a key role in angiogenesis and tumorigenicity is H19 [70]. H19 is a conserved lncRNA expressed in both human and rodents [71]. A recent study reported that H19 harbors both canonical and noncanonical binding sites for the let-7 family of miRNAs. It is also reported that H19 modulates let-7 availability by acting as a 'molecular sponge' reducing the level of free let-7, which binds to its target mRNA [72]. *In vivo* studies in rats indicate that lncRNA H19 was undetectable in uninjured carotid arteries; however, 7 and 14 days post-injury H19 levels were significantly upregulated and localized to the neointimal area following *in situ* analysis [73]. Recently, increased levels of plasma lncRNA H19 has been reported as a novel biomarker in gastric cancer [74].

6. THERAPEUTIC USE

Investigations indicate that lncRNA can be targeted for therapeutic purpose. A novel lncRNA Z38 was found to have high expression in breast cancer [2]. Inhibition of lncRNA Z38 expression by gene silencing reported suppression of cell proliferation and tumorigenesis. Treatment with siRNAs has shown significant induction of apoptosis and inhibition of tumor growth indicating that Z38 can act as a therapeutic target and biomarker in carcinomas [2]. Similarly, knockdown of lncRNA Linc00974 is reported to inhibit the cell proliferation and invasion with activation of apoptosis and cell cycle arrest in hepatocellular carcinoma [4]. The results indicate that Linc00974 has a potential to become a therapeutic target for the prevention of hepatocellular carcinoma progression. Studies have demonstrated that regulatory elements that control lncRNA expression also can be used as a target for cancer therapy. For instance, H19 regulatory gene has been evaluated as a promising and safe targeted therapy agent in phase 1 and 2 studies on pancreatic cancer [3]. A similar vector has already demonstrated as effective in animal studies for bladder cancer therapy [1]. Other circulating lncRNAs also have been investigated as diagnostic markers in various cancers. The plasma levels of lncRNA POU3F3 have been studied as a diagnostic marker in esophageal squamous cell carcinoma [75]. Genome-wide profiling indi-

cated that MALAT-1 and prostate cancer gene 3 (PCA3) were overexpressed in prostate cancer tissues [76]. Another lncRNA SNHG15 is reported as a potential prognostic marker in hepatocellular carcinoma, and increased tissue levels of lncRNA SNHG15 have been reported to worsen the survival rate of hepatocellular carcinoma patients [77]. Studies indicate that lncRNA HOTAIR can be used as a biomarker in various cancers involving breast, liver, gastric, lung, and esophagus [78]. Another lncRNA urothelial carcinoma associated 1 (UCA1) has been reported as a urinary biomarker for bladder cancer in patients [79, 80].

Other than cancers, lncRNA ANRIL has long been investigated as a potential biomarker for atherosclerosis as it is upregulated in plaque and plasma of atherosclerosis patients [63, 81]. Different ANRIL transcripts may vary in their functions; NR_003529 and DQ485454 transcripts specifically correlate with the severity of atherosclerosis [63]. May be ANRIL is playing an important role in atherosclerosis pathogenesis and targeted therapeutically. One of the examples of lncRNA involved in the coronary artery disease (CAD) is lncRNA CoroMarker [82]. It has been used as a biomarker for CAD, and in a clinical study it was successfully able to distinguish 78.05% of CAD out of 221 patients assessed [82]. Since CoroMarker is located mainly in the extracellular vesicle, probably from monocytes, it is stable in plasma and easy to evaluate as a biomarker [83]. Many other lncRNAs are also reported as potential biomarkers for cardiovascular disease [84]. lncRNA LIPCAR has been identified from the plasma of myocardial infarction patients [85]. LIPCAR is consistently detectable in the plasma and is significantly upregulated in patients with cardiac remodeling as well as ischemic and non-ischemic heart failure. Importantly, Higher LIPCAR levels are reported to be an independent predictor of cardiovascular-related death [85]. Another study compared the expression of lncRNAs in the peripheral blood cells between healthy volunteers and myocardial infarction patients. It demonstrated that lncRNA HIF1 α AS2, KCNQ1OT1, MALAT1 were significantly upregulated in myocardial infarction patients [86].

CONCLUSION

Overall, the consensus is building that lncRNAs expression pattern is tissue and disease specific [87–89]. Due to this specificity, lncRNAs may be superior therapeutic targets than existing protein coding genes for various diseases. Additionally, lncRNAs act themselves as a functional molecule and their expression may be a better indicator of disease states [90]. However, at present little is known about the function of most lncRNAs, their role in development, physiology, and disease. Their effective use as therapeutic targets/molecules needs a considerable amount of research. Investigations are needed to examine the toxicity and the pharmacokinetics of lncRNAs. Also, it is important to further evaluate the biological properties of these regulatory RNAs. Nonetheless, lncRNA holds immense promise as a potent regulatory molecule, and because of its cell-type and disease-specific expression it has a great therapeutic potential not only as a biomarker but also as a therapeutic target. Several laboratories are currently investigating the therapeutic potential of these lncRNAs for their diagnostic, prognostic, and curative powers. The research is increasing exponen-

tially in this area and coming decade will teach us more about this important group of regulatory molecule.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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