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Long Noncoding RNAs and Human Osteosarcoma

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Abstract

Osteosarcoma is the most commonly diagnosed malignancies in children and adolescents, pathologically characterized by spindle cells and deviant osteoid formation. Although significant evidences in therapeutic strategies have been accomplished, the conclusion is still unclear for the critical metastatic or persistent osteosarcoma. Therefore, it is essential to develop novel and effective biomarkers or therapeutic targets for diagnosis of osteosarcoma. Long noncoding RNAs (lncRNAs), as a novel class of noncoding RNA, are composed of transcripts longer than 200 nucleotides and play critical roles in development and progression of various cancers including osteosarcoma. LncRNAs are mainly involved in different biological process such cell growth, transcription, translation, epigenetic regulation, splicing, chromosome dosage compensation, imprinting, nuclear, cytoplasmic trafficking and cell cycle control. LncRNAs may act as oncogenic or tumor suppressive that can modulate osteosarcoma pathogenesis including cell growth, migration, proliferation, metastasis, invasion and cell apoptosis. In this review, we summarize the current knowledge of lncRNAs and its critical role in progression of osteosarcoma. It will be helpful for researchers to evaluate the functional role of lncRNAs in the development of osteosarcoma and enhance the efficacy of therapeutic treatment modalities.

Keywords: LncRNAs; Osteosarcoma; Progression; Metastasis; Mechanisms

Introduction

Osteosarcoma is the highly aggressive malignant bone tumor and the second leading cause of death in adult and children worldwide [1]. Osteosarcoma is characterized as tumor that produce osteoid matrix with multinucleated cells [2,3]. About 10% - 25% of patients were associated with lung metastasis, temporarily pulmonary damage were the major causes of osteosarcoma mediated death [4]. Inclusive treatments such as chemotherapies and surgery resection have significantly improved the treatment strategy and survival rate of osteosarcoma patients [5]. Currently the 5-year survival rate of osteosarcoma patients has been enhanced to 70% [6,7]. However several osteosarcoma patients posses resistance to suitable chemotherapeutics and then die due to huge metastasis and tumor relapse, which is essential impediment for successful osteosarcoma treatments [8]. In spite of advance research to identify some novel therapeutic approaches, the overall diagnosis ratio of osteosarcoma patients has still reached a low level in past 30 years [9]. Based on biological characteristic of osteosarcoma, there exist a large scale of fuzzy regions that are involved in the exploration of molecular mechanisms associated with osteosarcoma metastasis, origination and chemo-resistance. Hence, suitable biomolecules that act as prognostic or diagnostic biomarkers and specific therapeutic targets are predictable to be identified and may intensely progress therapeutic efficacy as well as clinical outcomes for osteosarcoma patients. Inspiringly, several lncRNAs have recently been identified to play crucial role in osteosarcoma development.

Along coding genes, large numbers of lncRNAs transcripts exist in human genome. LncRNAs are transcribed in a precise manner during cell development, differentiation, cancer progression and other diseases [10-12]. Non coding RNAs (ncRNAs) are endogenously RNA molecules with no capability of coding protein. According to size of nucleotides, ncRNAs can be classified as small non coding RNAs (sncRNAs, <200 nt) and lncRNAs (>200 nt) [13]. The small ncRNA such as microRNAs (miRNAs), transfer RNAs, small interfering RNAs (siRNAs), some ribosomal RNA and piwi-interacting RNAs, have been investigated to function in the tumorigenesis, metastasis and chemo-resistance. The wide spreading catalogue of lncRNAs is initially observed during the functional studies of human genome. LncRNAs are considered to have equivalent chromatin signatures to the coding genes. More and more recent researches have pointed out differences in the existence of specific histone letters [14-16] and splicing capability [15,17] among lncRNAs and coding genes, as well as with other lncRNAs according to chromatin structure [13,18].

A large number of lncRNAs have been identified in various types of species as well as in tissues [19]. Some of lncRNAs are critical for organism development [20,21] and cancer progression [22]. LncRNAs are essential for certain biological processes such as transcription, translation, epigenetic regulation, splicing, chromosome dosage compensation, imprinting, nuclear and cytoplasmic trafficking and cell cycle control [23,24]. Advance research and investigation significantly disclose the roles of lncRNAs in the prognosis and pathogenesis of different human diseases such as osteoarthritis [25] and osteosarcoma [26]. Li et al. [26] reported the expression profile of lncRNAs in osteosarcoma and showed that approximately 25,733 lncRNAs consist of 789 downregulated and 403 upregulated lncRNAs. Further study showed that 32 pathways were downregulated transcripts and 34

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pathways were upregulated transcripts. Recent studies implied that abnormal expressions of lncRNAs are directly involved in certain diseases including progression, invasion and metastasis of cancers [27,28]. In this review, based on characteristics and function of lncRNAs, we summarized the recent acquaintance among its pathological role in the pathogenesis of osteosarcoma. This article insights future research and helps the scientists to further elevate lncRNAs therapeutic roles in progression of osteosarcoma to develop noval diagnostics/prognostic biomarkers for treatment of osteosarcoma.

Characteristics of lncRNAs

Long non-coding RNAs (lncRNAs) are known as larger class of noncoding RNA constitutes as a size of 200nt-100kb long transcripts without open-reading frame [29,30]. Its transcription processes are mostly occurred by RNA polymerase II and regulated by the transcriptional activators of the chromatin remodelers known as switching defective/sucrose non-fermenting (SWI/SNF). LncRNAs can be categorized into several broad groups such as sense lncRNAs, antisense lncRNAs, intronic lncRNAs, bidirectional lncRNAs, intergenic lncRNAs, untranslated region (UTR) associated lncRNAs and promoter-associated lncRNAs [10,31].

LncRNAs are mostly spliced, capped and polyadenylated in a same way as mRNA molecules [32]. LncRNAs are characterized as a large and highly heterogeneous set of ncRNAs. LncRNAs expression usually depend on both cellular and tissues context [14,33]. After discovery of *H19* and *XIST* lncRNAs in 1990s [34,35], lncRNAs was considered as transcriptional noise with almost no or extremely slight functions [36]. LncRNAs can be existed in all cellular contexts especially with high proportion identified in the cytoplasm and nucleus [37]. The secondary structure of lncRNAs includes stem loops and hairpins, produced by posttranscriptional modifications, which allows their association with chromatin and other proteins as well as essential for lncRNAs' vast group of functions [38].

Biological Function of lncRNAs

The key function of lncRNAs has been ascribed to regulate the expression of coding genes by manipulating its adjacent genes (in cis) or modifying distinct genes on other chromosomes (in trans) [39]. At different levels of gene functions including transcription, translation, and protein function, lncRNAs can regulate individual genes or gene expression process by altering the basic transcription mechanism or through epigenetic mechanism. Unambiguously, the functions of lncRNAs are as follows: (1) LncRNAs located at the upstream promoter region can alter gene expression at downstream promoter area through chromatin remodeling and histone modification. (2) LncRNAs can regulate genes expression with the help of microRNA or siRNA and serve as a precursor for small RNA. (3) LncRNAs has closed association with special proteins and adjust protein activity (4) LncRNAs constitute various product due to alternative splicing [40].

Moreover, lncRNAs are associated with main cellular pathways regulating differentiation, proliferation and apoptosis that are concerned with pathogenesis of various human cancers [41,42]. During transcriptional or posttranscriptional stages, lncRNAs control various gene including oncogenes and tumor suppressor genes and also affect cellular processes such as cell proliferation, angiogenesis, apoptosis, migration, invasion and metastasis (Figure 1) [43-45].

LncRNAs and Osteosarcoma

LncRNAs and osteosarcoma development and metastasis

Osteosarcoma is lethal because of pulmonary metastasis with widespread progression that leads to respiratory failure. Tumor metastasis and invasion are multistep complex process in which tumor cells alter cell- extracellular matrix (ECM) associations at the primary tumor site to invade adjacent tissues and thus translocated through the vascular vessels to other systems to form secondary tumors [46]. Matrix metalloproteinases (MMPs) are family of proteolytic enzyme that plays an essential role in tumor metastasis and invasion by breaking the ECM and basement membrane. It has been investigated that during osteosarcoma cell migration and invasion, several lncRNAs promote or suppress cell proliferation, metastasis and invasion via modulating MMP-2 and MMP-9 secretion [47].

LncRNAs play essential roles in the osteosarcoma development, progression, prognosis, diagnosis and management [46]. LncRNAs can affect and modulate cellular processes such as cell cycle, differentiation, proliferation, and apoptosis [48]. Consequently, progression of cancer can be characterized by transcriptomics to distinguish among progression, metastasis and recurrence of human cancers including osteosarcoma. It has been investigated that *metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) / microRNA 376A (MIR376A) / transforming growth factor alpha (TGFA)* play critical roles in the progression of osteosarcoma. MALAT1 initiated osteosarcoma development by suppressing *MIR376A* and promoting *TGFA* expression [49].

The *HOX antisense intergenic RNA (HOTAIR)*, a well characterized lncRNA, which concerned in the progression and pathogenesis of different tumors. *HOTAIR* is most highly expressed in osteosarcoma and thus linked with advanced tumor stages, high histological grades, and poor survival. Therefore, *HOTAIR* may be a significant target in the diagnosis of human osteosarcoma [50]. Moreover, *small nuclear RNA host gene 12* (*SNHG12*) induced cell proliferation and migration by overregulating *angiomotin* [5] gene expression in human osteosarcoma cells, which controls the expression of MMP-2/MMP-9 [51]. LncRNA (*H19*) may act as oncogenic or tumor suppressor in the progression of osteosarcoma. Recent evidences suggested that *H19* is concerned with the pathogenesis mechanisms of osteosarcoma and acts as an oncogenic lncRNA [52,53].

LncRNA and Osteosarcoma Prognosis

Interestingly, certain amount of oncogenic and tumor suppressive lncRNAs have been recognized in osteosarcoma pathogenesis, such as cell growth, apoptosis, proliferation, migration, invasion and metastasis. Here, we can recapitulate the possible roles and underline mechanisms of certain lncRNAs that are associated with osteosarcoma pathogenesis as shown in Table 1.

Overexpression of lncRNA *Taurine Up-regulated Gene 1* (*TUG1*) in osteosarcoma initiated cell proliferation, inhibited cell apoptosis and arrest cell cycle at G0/G1 through underline function mechanisms with sponges miR-9-5p to downregulate the expression of *POU domain class 2 transcription factor 1* (*POU2F1*). *TUG1* has also close association with disease status. Therefore, *TUG1* acts as a possible therapeutic target and as sovereign prognostic factor in osteosarcoma patients [54-56]. Increase expression of *HOTTIP* results to enhanced cell proliferation, invasion that associated with advance Enneking stage, metastasis and poor survival of osteosarcoma [57]. Upregulation of *Fibroblast Growth Factor 3 antisense transcript 1* (*FGFR3-AS1*) in osteosarcoma

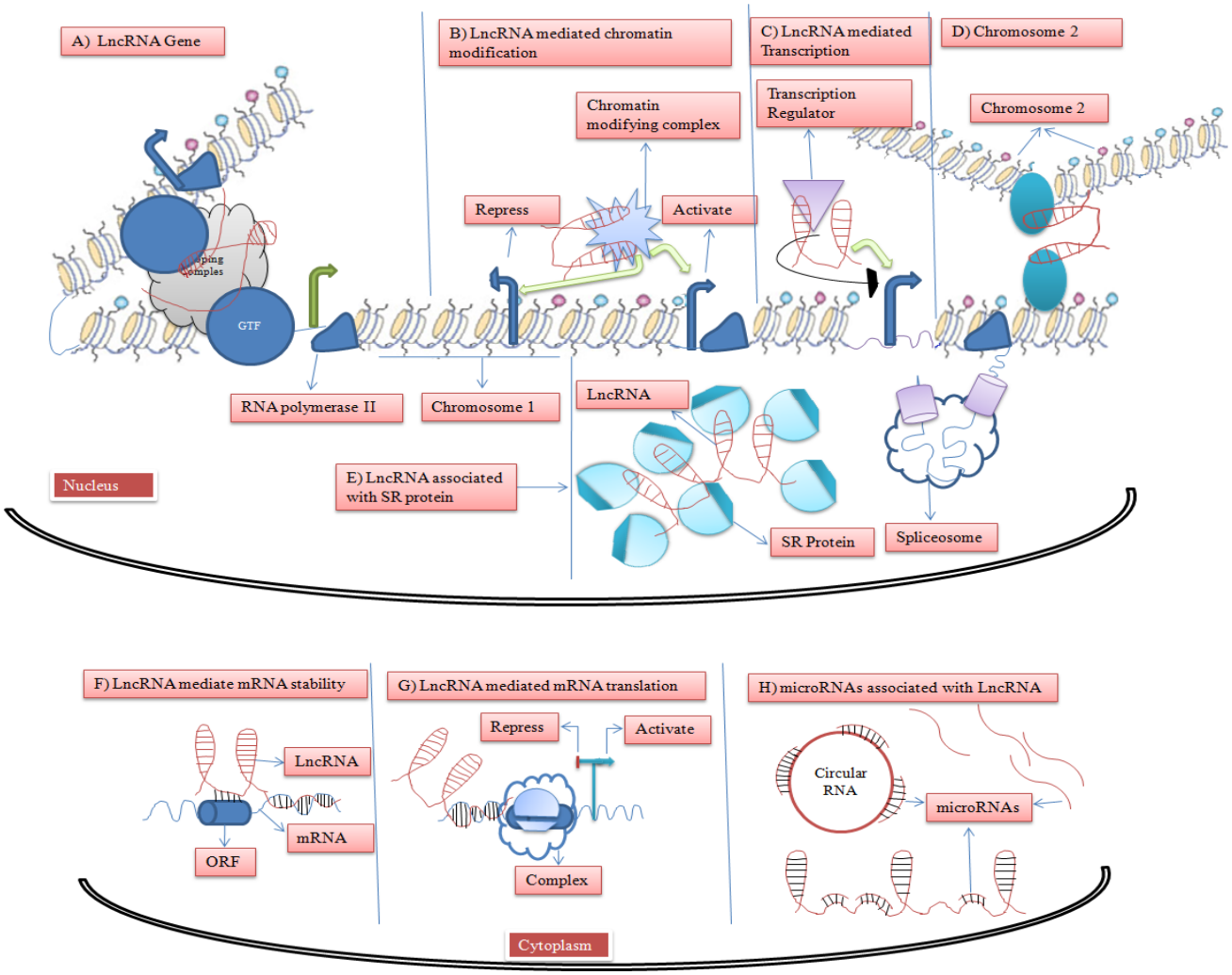

Figure 1: LncRNAs concerned with various cellular functions that act in different way such as to regulate gene expression and other different mechanism. (A) LncRNA gene associated complex (B) LncRNAs regulate gene expression at epigenetic level through binding chromatin modifying complexes to specifics genomics loci (C) LncRNAs modulate gene expression by changing the function of transcription factor and act as co activator or repressor (D) LncRNAs established interchromosomal linkage between two chromosomes (E) LncRNAs associated with splicing regulatory protein to regulate gene expression (F) LncRNAs closely linked with mRNA to increase mRNA stability and protect it from degradation (G) LncRNAs associated with mRNA to activate or repress its translation and regulate gene at posttranscriptional level (H) LncRNAs compete with miRNAs and act as miRNAs sponges in the regulation of miRNAs level and gene expression.

is closely linked with increase tumor size, advance clinical stage and poor prognosis [58]. It has been investigated that aberrant expression of *highly up-regulated in liver cancer* (*HULC*) is directly related with clinical stages, distant metastasis and poor prognosis of osteosarcoma [59]. Overexpression of *Breast Cancer Anti-Estrogen Resistance 4* (*BCAR4*) in osteosarcoma is connected with large tumor size, progressed enneking stage and unfavorable survival [60].

Distinctly upregulation of *Zinc finger E-box binding homeobox 1 antisense 1* (*ZEB1-AS1*) in osteosarcoma has close association to tumor size, progressed clinical stage and poor prognosis via activating transcription of *ZEB1* gene [61]. LncRNA *maternally expressed gene 3* (*MEG3*) regulates *p53* expression and is closely associated with osteosarcoma survival [62]. Similarly, upregulation of *Forkhead box protein C2* antisense 1 (*FOXC2-AS1*) is correlated with favorable survival for osteosarcoma patients [63]. LncRNA *loc285194* is initially recognized in osteosarcoma but the underline functional mechanism remains unknown. Liu et al. [64] has reported that *loc285194* may take a potential diagnostic role in various cancers such as colon cancer and osteosarcoma. Moreover, some additional lncRNAs have been recognized as autonomous prognostic biomarkers in osteosarcoma. Flockhart et al. [65] initially discovered *BRAF-activated noncoding RNA* (*BANCR*) in melanoma cells which is approximately 693bp in length. Overexpression of *BANCR* is significantly associated with large tumor size, distant metastasis, advanced clinical stage and poor prognosis of osteosarcoma [66]. Increased expression of *urothelial carcinoma associated 1* (*UCA1*) has close association with positive distant metastasis, large tumor size and advanced clinical stage and acts as an autonomous prognostic indicator for poor survival of osteosarcoma [67].

Similarly, upregulation of *antisense H19 transcript* (*91H*) has also significant correlations with large tumor size, progressed clinical stage and post-operative chemotherapy and acts as an autonomous prognosis

Lncrnas	Size	Genomic Location	Relative Expression	Molecular Mechanism	Reference
HULC	500bp	6p24.3	Upregulated	Inhibition of *HULC* by a siRNA lead to reduces the proliferation, invasion and migration capacities of OS.	[66,70,71]
MALAT1	8.7 kb	11q13.1	Upregulated	Strong activation of wnt/beta-catenin signaling pathway through loss of PCDH10 tumor suppressor. Promotes motility and invasion via *MALAT1/miR-124/RBG2* signaling. Modulates P13K/AKT signaling. Associated with Rho/ROCK Pathway	[46,49,66, 69,72]
PACER	793 bp	1q31.1	Upregulated	promotes cell proliferation and migration by regulating *COX-2* gene in a NFκB-dependent way	[66,73]
BANCR	693bp	9q21.11-12	Upregulated	Associated with large tumor size, distant metastasis, and advanced clinical stage an independent predictor of poor survival	[66,74]
UCA1	2.3 kb	19p13.12	Upregulated	Serve as a decoy by acting sponge and sink for miRNAs, which results in inducing carcinogenesis or drug resistance.	[66,67]
BCAR4	118bp	16p13.13	Upregulated	Increase proliferation and metastasis of osteosarcoma by activating GLI2-depended gene expression.	[60]
HOTAIR1	2.2-kb	12q13.13	Upregulated	Promotes cellular invasion and migration through upregulating the transcription of *cyclin E, Bcl-2, caspase-3* and *-9,* and matrix metalloproteinase (MMP) 9 and 3.	[47,50,75]
TUG1	7.5 kb	22q12.2	Upregulated	Promotes cell proliferation, migration, via associating with sponges' miR-9-5p to downregulates *POU2F1* expression.	[54,55,66]
H19	2.3 kb	11p15.5	Upregulated	Induces osteosarcoma development via associated with miR-141. Also concern with Hedgehog signaling pathway	[2,52]
MFI2	951 bp	3q29	Upregulated	Promotes cell proliferation and migration by inducing expression of *FOXP4*	[66]
SNHG12	1.3 kb	1p35.3	Upregulated	Promotes cell proliferation and migration via increase expression of *angiomotin* gene	[51]
91H	120 kb	11p15.5	Upregulated	Correlated with advanced clinical stage, chemotherapy after surgery, and tumor size >5 cm, an independent prognostic factor for overall survival	[66,68]
ODRUL	319 bp	16q24.1	Upregulated	Associated with doxorubicin resistance through induces expression of *ABCB1* (*multidrug resistance gene*)	[66]
HOTTIP	4.6 kb	7p15.2	Upregulated	Associated with WDR5/MLL complex to activates Wnt/β-catenin signaling pathway	[57,66]
HNF1A-AS1	2.4 kb	12q24.31	Upregulated	Modulate with cell proliferation and metastasis by regulating Wnt/β-catenin signaling pathway	[66]
FOXC2-AS1	319 bp	16q24.1	Upregulated	Associated with upregulation of *ABCB1*, *HIF1A* and *FOXC2* expression.	[63]
ZEB1-AS1	2.6 kb	10p11.22	Upregulated	Promote cell proliferation and metastasis though binding and selection of p300 to the *ZEB1* promoter region, that activates *ZEB1* transcription	[61]
LINCOO161	1 kb	21q21.3	Upregulated	Promote cisplatin-induced apoptosis by interacting with sponges endogenous miR-645 that regulates *IFIT2* expression	[66]
loc285194	>2 kb	3q13.31	Downregulated	Interact with miR-211 to regulates cell growth by activating *p53* expression	[64]
HIF2PUT	2.8 kb	2p21	Downregulated	Promote cell proliferation and migration by upregulating *HIF-2α* expression	[66,75]
TUSC7	>2 kb	3q13.31	Downregulated	Promotes cell proliferation and increases colony formation in vitro	[66]
MEG3	1.6 kb	14q32.2	Downregulated	Positively regulates the expression of *p53*	[62]

Table 1: Different lncRNAs and the related regulation mechanism concerned with osteosarcoma

factor with poor outcomes of osteosarcoma patients [68]. Increased expression of *MALAT1* correlated with distant metastasis, advance clinical stage and poor prognosis of osteosarcoma patients and acts as a self-determining predictive factor of patients' survival situation Table 1 [69].

The Mechanism of Lncrnas Regulating Osteosarcoma

Targeting mRNA

Short- lived mRNA called *c-myc* or *c-los* mRNA, plays a critical role in maintaining normal function and its dysregulation will lead to oncogenesis [70-76]. Zhu et al. [63] documented three groups of doxorubicin-resistant MG-63/DXR cells and their paired parental MG-63 cells and recognized 3465 lncRNAs (1761 up regulated and 1704 downregulated) and 3278 mRNAs (1607 upregulated and 1671 downregulated) that were aberrantly transcribed in MG-63/DXR cells. The coexpression association among lncRNAs and mRNA was identified, such as NR-036444 and ENST00000563280 that cooperated with certain genes including *ABCB1 FOXC2 and HIF1A*, and might have significant roles in doxorubicin resistance in osteosarcoma.

LncRNAs associated messenger RNAs (mRNAs) are usually less copious than normal protein-coding mRNAs but possessing stronger tissue and cell-specific lncRNAs expression platforms [50,51]. It has been studied that the *SNHG12* enhances cell migration and proliferation via upregulating the expression of *angiomotin* [5] gene in human osteosarcoma cells. In addition, Ruan W et al. [51] identified that *SNHG12* mRNA transcription was upregulated in osteosarcoma cell lines and tissues as compared with normal cell and tissues. Mammalian genomes encode several natural antisense RNAs that are complementary to their target sense RNAs. *FGFR3 antisense transcript 1* (*FGFR3- AS1*) enhanced *FGFR3* mRNA constancy and upregulated *FGFR3* transcript through antisense associated with *FGFR3* 3′-UTR. Enhanced expression of *FGFR3-AS1* is closely associated with large tumor size, advanced clinical stage, metastasis and poor outcomes of osteosarcoma. Hence lncRNA *FGFR3-AS1* induced osteosarcoma growth via modifying its antisense transcript *FGFR3* [58].

Activating signal pathways

Signaling Pathways as a molecular mechanism to play critical role in development of osteosarcoma has been elucidated as follow.

Chan et al. [2] investigated that aberrant Hh signaling in mature osteoblasts lead to pathogenesis of osteoblastic osteosarcoma. However, upregulation of Hh signaling promote *Yap1* expression which is responsible for aberrant lncRNA *H19* expression in malignant osteosarcoma. To date, limited studies investigated the basic roles of lncRNAs in osteosarcoma osteogenesis, development, metastasis, invasion, or chemotherapy resistance. It has been mentioned in a report that when lncRNAs were expressed differentially in osteosarcoma they were found to be involved in many of the pathways showing that lncRNAs can work as therapeutic targets in osteosarcoma [26]. When *P50- associated COX-2 extragenic RNA* (*PACER*) was overexpressed in osteosarcoma tissues and cell lines influenced the *COX-2* gene was activated in an NF-κB-dependent manner and worked as an oncogene in osteosarcoma (Figure 2) [73].

Acting as a miRNA sponge

MicroRNAs (miRNAs) are new class of noncoding RNA of about 18-25 nucleotides in sizes. miRNAs can dysregulate gene expression through binding to the 3′-untranslational region (UTR) of their target mRNAs that lead to translation suppression and mRNA degradation [77]. Through negative intervention of their target genes, miRNAs play crucial role in several biological processes such as cell survival, differentiation, proliferation, apoptosis, metabolism, autophagy and motility [78,79]. Moreover, different oncogenes or tumor suppressor genes are also the targets of miRNAs and numerous miRNAs have been involved in tumorgenesis and malignant progression of various human cancers such as osteosarcoma [80,81]. LncRNAs can also regulate gene expression at posttranscriptional levels and can act as endogenous 'sponge' and under regulate a chain of microRNAs. Moreover, a lot of

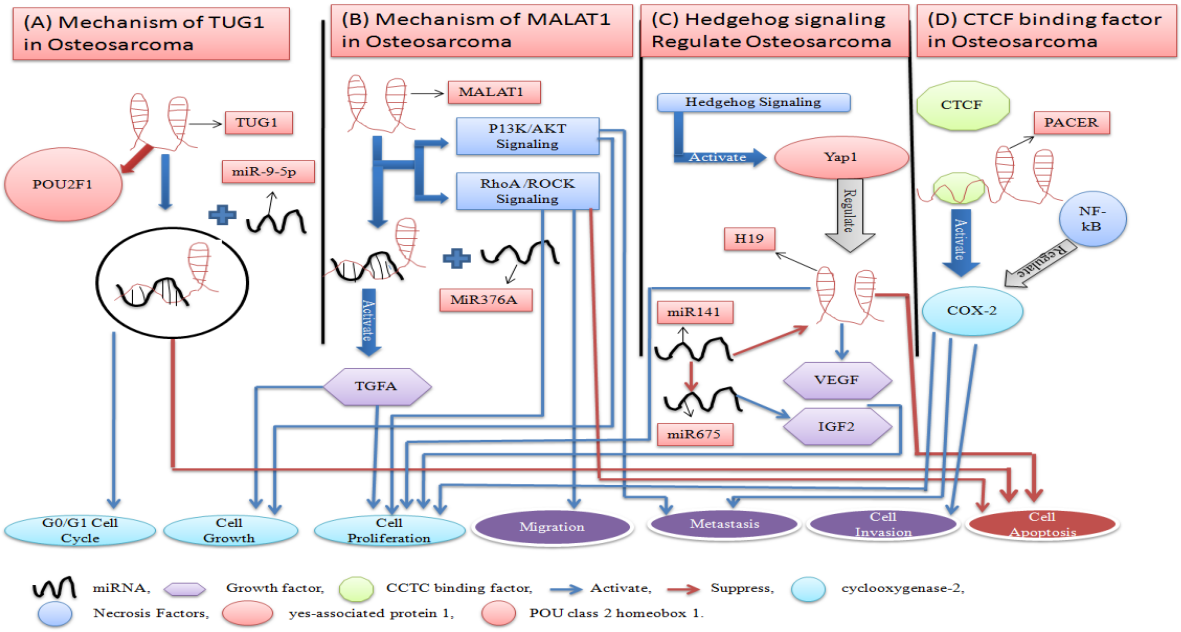

Figure 2: Mechanism of lncRNAs in the pathogenesis of osteosarcoma. (A) TUG1 suppresses POU2F expression and associate with miRNAs to activated cell cycle and cell proliferation but suppress apoptosis. (B) MALAT1 activated signaling pathway and miRNAs mediate its function to control cell growth and proliferation. (C) Hedgehog signaling upregulates H19 along with miRNAs to promote cell proliferation and suppress apoptosis. (D) CTCF binding factors regulates PACER function via targeting COX-2 gene which activate cell proliferation, invasion, and metastasis.

Mechanism Of Gene Regulation	Responsible Lncrnas	Targeted Site or Molecules	References
Trancription Level (targeting mRNA)	*SNHG12*	Upregulate the expression of *angiomotin* (*AMOT*) gene.	[51]
	FGFR3- AS1	Enhance *FGFR3* mRNA constancy and upregulated *FGFR3* transcript through antisense associated with *FGFR3* 3′-UTR.	[58]
	PANDA	Block apoptosis through association with the transcription factor NF-YA to decrease expression of pro-apoptotic genes.	[23,88].
Posttranscription level (As a miRNA sponge)	*linc-MD1*	Interact with miR-133 and MiR-135 to regulate the expression of *MAML1* and *MEF2C*.	[82]
	HULC	Interact with miR-372 to downregulate its expression.	[71]
	loc285194	Posses' reciprocal repression between MiR-211 and *loc285194*.	[64]
	MALAT1	Interact with splicing factors (SR) proteins and enhances their distribution in nuclear speckle domains.	[86]
Epigenetics level	*Xist,*	silencing X-chromosome by interacting with the *polycomb repressive complex 2* (*PRC2*)	[89]
	HOTAIR	Repress transcription in trans of *HOXD* genes. This repressive action is mediated by the interaction of *HOTAIR* with *PRC2*.	[90]
	PCAT-1	As a prostate-specific regulator of cell proliferation, target of *PRC2*, functioning as a transcriptional repressor in a subset of various cancer	[91]

Table 2: Mechanisms of gene regulation and their responsible lncRNAs that target particular site or molecules.

lncRNAs exist that can regulate gene at posttranscriptional levels are as follow (Table 2). *Long intergenic non protein coding RNA-muscle differentiation 1* (*linc-MD1*) regulates the expression of transcription factors such as *mastermind-like 1* (*MAML1*) and *myocyte enhancer factor 2C* (*MEF2C*) with the association of miR-133 and miR-135 [82].

HULC interacts with miR-372 and down regulate its expression [71]. *HULC* plays critical role in progression of human cancer including osteosarcoma [83-91], which may point out the critical reason that miR-372 frequently downregulated in osteosarcoma patients. *Loc285194* may possess reciprocal repression with miR-211 [64]. *GAS5* may act as an endogenous sponge for miR-21 [84]. Hence, lncRNAs also cooperate with certain regulatory system including 'competitive endogenous RNA (CeRNA)' [85] where microRNA response elements may function as outcomes of a new process through which microRNA can modulates both protein coding and non coding genes including lncRNAs. LncRNAs can also serve as key regulator of alternative splicing and pre-mRNA process. For example, *MALAT1* is capable to cooperate with splicing factors serine/arginine [16] proteins and manipulate their allocation in nuclear speckle domains [86]. Since both lncRNAs and miRNAs can act as tumor suppressor or oncogenes in osteosarcoma. The association among miRNAs and lncRNAs intimate the occurrence of competitive RNA regulatory system, which will further help to recognized the molecular mechanism that involved in pathogenesis of osteosarcoma [87].

Conclusion and Future Perspective

In this review, we summarized the feature of lncRNAs, biological function of lncRNAs and their pathological roles concerned with osteosarcoma. Different lncRNAs are closely associated with the pathogenesis and prognosis of osteosarcoma and act as potential diagnostic or prognostic biomarkers. Additionally, lncRNAs promote the development and progression of osteosarcoma via regulating cell growth, proliferation, metastasis, migration, invasion and cell apoptosis. LncRNAs possess various underline mechanisms such as targeting the host related genes, challenging endogenous RNA, association of signaling pathway and so on. Moreover, some lncRNAs act as self governing prognostic predictor and some are concerned in competing to recently existed chemotherapeutics like cisplatin and doxorubicin. Therefore, these result clarified that lncRNAs act as a potential therapeutic target for treatment of osteosarcoma.

LncRNAs has been spotlighted for powerful research, and a broad range of functional roles have already been attributed in the progression of osteosarcoma. However, the absolute abundance and variety of lncRNAs pose a challenge for their classification and role in the regulation of cell cycle, growth, proliferation, metastasis, invasion and prognosis of osteosarcoma. A greater understanding of lncRNAs-to-cell signaling relationship - that is, how and which lncRNAs dictate a cell signaling pathway will be required to initiate osteosarcoma progression. What is the comprehensive mechanism of lncRNAs with the progression and pathogenesis of osteosarcoma? How can lncRNAs regulate the initiation and progression of osteosarcoma? What is the relationship of cell cycle regulatory genes with lncRNAs? What is the exact structure of lncRNAs that interact with specific target proteins to enhance life span of lncRNAs? This could ultimately permit the functional assignation and validation of lncRNAs and might be hugely informative in the hypothesis of lncRNA in the development of osteosarcoma. Given such giant potential, lncRNAs has begun to produce substantial interest in the development and progression of osteosarcoma.

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