Emerging role of long non-coding RNA JPX in malignant processes and potential applications in cancers

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Abstract

Long non-coding RNAs (lncRNAs) reportedly function as important modulators of gene regulation and malignant processes in the development of human cancers. The lncRNA JPX is a novel molecular switch for X chromosome inactivation and differentially expressed JPX has exhibited certain clinical correlations in several cancers. Notably, JPX participates in cancer growth, metastasis, and chemoresistance, by acting as a competing endogenous RNA for microRNA, interacting with proteins, and regulating some specific signaling pathways. Moreover, JPX may serve as a potential biomarker and therapeutic target for the diagnosis, prognosis, and treatment of cancer. The present article summarizes our current understanding of the structure, expression, and function of JPX in malignant cancer processes and discusses its molecular mechanisms and potential applications in cancer biology and medicine.

Keywords: Biomarker; Cancer; JPX; Long non-coding RNA; Therapeutic target

Introduction

Cancer is a major disease that threatens human life and health, and presents rapidly growing morbidity and mortality burdens worldwide.[1] Although several approaches have been employed for cancer management, including radiotherapy, chemotherapy, surgery, targeted therapy, and immunotherapy,[2,3] treatments have remained restricted, given that cancer formation is a complicated multi-factorial and multi-step processes. Therefore, there remains an urgent need for detailed studies examining molecular mechanisms underlying cancer development.

Human genome sequencing has revealed that only 2% of the transcribed gene sequences eventually encode proteins, while the remaining 98% do not encode proteins.[4,5] In recent years, long non-coding RNAs (lncRNAs) with lengths greater than 200 nt have received considerable attention.[6] LncRNAs were initially considered genomic transcriptional "noise," a byproduct of RNA polymerase II transcription with no biological function.[7] However, on further exploration, lncRNAs have been found to perform critical functions in gene expression regulation and physiological/pathological processes.[8-15] In addition, the aberrant expression of lncRNAs has been closely associated with disease onset and progression, particularly in malignant tumors. For example, Hox transcript antisense intergenic RNA,[16,17] metastasis-associated lung adenocarcinoma transcript 1,[18] and prostate cancer-associated transcript 1 [19] were identified as oncogenes, while growth arrest specific transcript 5,[20] long intragenic non-coding RNA p53-induced transcript,[21] and maternally expressed gene 3 [22] were reported as tumor suppressors. Dysregulated lncRNAs can promote the biological behavior of malignant tumors through several mechanisms, for example, by serving as microRNA (miRNA) sponges, protein scaffolds, and transcript decoys.[23-25] Notably, lncRNAs can also work as potential therapeutic targets and biomarkers for cancer treatment and diagnosis.[26,27]

JPX, a lncRNA on chromosome X, is located ~10-kb upstream of Xist and acts as a molecular switch for X chromosome inactivation.[28] Gene expression profiling interactive analysis (http://gepia.cancer-pku.cn/detail.php?gene=JPX) showed differential expression of JPX across all tumor samples and paired normal tissues, as well as the clinical correlation between JPX expression and

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survival of patients with certain cancers. A growing number of studies have identified an important role for JPX in cancers. In the present study, we review the recent findings on the biological functions, molecular mechanisms, and clinical significance of JPX, providing new insights into its clinical potentials for the diagnosis, prognosis, and treatment of cancers.

Structure of Human LncRNA JPX

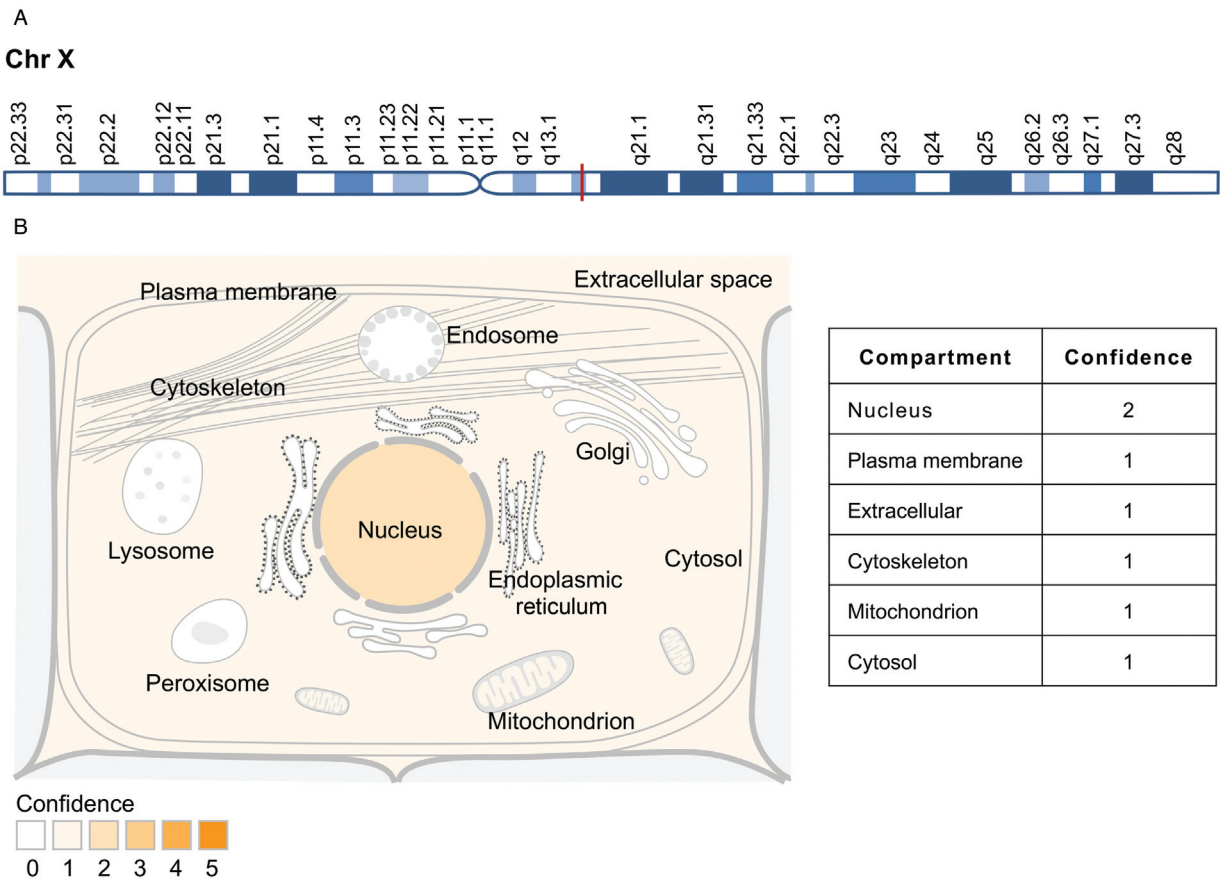
JPX was originally discovered as a novel conserved noncoding gene by sequencing the X-inactivation center region in mice, humans, and bovines.[29] The gene annotation of human lncRNA JPX showed a linear structure containing five exons and was 1696 bp in length (Gene ID: 554203, RNA sequence: NR_024582). The GeneCards database (https://www.genecards.org/) indicates that *JPX* gene is located on chromosome Xq13.2 [Figure 1A]. Cellular localization revealed that JPX was mainly located in the nucleus, as well as in plasma membrane, cytoplasm, cytoskeleton, extracellular domain, and mitochondria [Figure 1B].

Expression of JPX in Human Cancers

Recent studies have revealed that JPX is aberrantly expressed in at least 12 types of cancers. JPX is highly expressed in non-small cell lung cancer (NSCLC),[30-32] gastric cancer (GC),[33] oral squamous cell carcinoma (OSCC),[34] cervical cancer (CC),[35] ovarian cancer (OC),[36] osteosarcoma (OS),[37] and glioblastoma multiforme (GBM).[38] Conversely, low JPX expression has been detected in breast cancer,[39] prostate cancer,[40] uveal melanoma,[41] acute myeloid leukemia,[42,43] and hepatocellular carcinoma (HCC). [44,45] Specifically, Ma *et al*[45] first identified the low expression of JPX in the plasma of patients with HCC, demonstrating the diagnostic value of JPX. Interestingly, the expression of lncRNA JPX was also upregulated in exosomes, single nucleated cells, and granulocytes of female patients with HCC.[46] Aberrant JPX expression plays an important role in cancer development.

JPX and Clinical Features

Growing evidence has revealed a strong correlation between lncRNA expression and clinical features.[47-50] These findings may provide a reliable basis for developing guidelines for the diagnosis, prediction of prognosis, and treatment of various types of cancer. Differentially expressed JPX showed potential clinical correlations in multiple cancers [Table 1]. For example, high JPX expression was strongly correlated with lung cancer (LC) tumor size, lymph nodes metastasis, and tumor node metastasis (TNM) stage.[30-32] Similarly, JPX expression was associated with age, the International Federation of Gynecology and Obstetrics stage, tumor size, vaginal infiltration, and lymph node metastasis in patients with



Compartment	Confidence
Nucleus	2
Plasma membrane	1
Extracellular	1
Cytoskeleton	1
Mitochondrion	1
Cytosol	1

Figure 1: Structure of JPX. (A) Gene location of JPX on human chromosome. (B) Subcellular locations of JPX in a human cell. Chr X: Chromosome X.

Table 1: Clinical correlations of JPX in various types of cancer.

Cancer	Number of cases or tissues	Expression	Correlations with clinical features	Reference
LC	116 pairs of LC tissues and corresponding adjacent tissues	Upregulation	Tumor size, TNM stage, metastasis	[32]
NSCLC	55 pairs of NSCLC tissues and adjacent normal tissues	Upregulation	Tumor size, lymph node metastasis, TNM stage, overall survival	[30]
	45 pairs of the NSCLC tissues and corresponding normal tissues	Upregulation	Tumor size, TNM stage, lymph node metastasis	[31]
GC	32 pairs of GC and adjacent non-tumor tissues	Upregulation	Overall survival	[33]
CC	39 pairs of CC tissues and corresponding adjacent non-carcinoma tissues	Upregulation	Age, FIGO stage, tumor size, vaginal invasion, lymph node metastasis	[35]
OC	32 cases of ovarian cancer tissues and corresponding adjacent tissues	Upregulation	Poor prognosis (3-year survival rate), tumor size, lymph node metastasis	[36]
GBM	GEPIA database (tumor, 163; normal, 207)	Upregulation	Poor overall survival	[38]
BC	GEO database (tumor, 79; metastasis, 63; normal, 20)	Downregulation	Not reported	[39]
HCC	40 pairs of HCC specimens and adjacent non-cancerous specimens (20 HCC stage I–II patients and 20 HCC stage III–IV patients)	Downregulation	TNM stage	[44]
	68 HCC tissues and adjacent normal tissues; blood samples from 42 patients with HCC and 68 healthy controls	Downregulation	Histological grade, TNM stage, poor overall survival	[45]
	Exosomes, mononuclear cells, and granulocytes of female patients	Upregulation	Not reported	[46]
PC	43 pairs of prostate tumoral and non-tumor tissue	Downregulation	Not reported	[40]

BC: Breast cancer; CC: Cervical cancer; FIGO: International Federation of Gynecology and Obstetrics; GBM: Glioblastoma multiforme; GC: Gastric cancer; GEO: Gene expression omnibus; GEPIA: Gene expression profiling interactive analysis; HCC: Hepatocellular carcinoma; LC: Lung cancer; NSCLC: Non-small cell lung cancer; OC: Ovarian cancer; PC: Prostate cancer; TNM: Tumor node metastasis.

CC.[35] In addition, JPX expression was significantly lower in TNM III–IV HCC specimens than in TNM I–II specimens.[44] Moreover, reduced JPX expression in HCC was markedly correlated with histological grade.[45] Collectively, JPX was significantly associated with distinct clinical features, including tumor size, TNM stage, lymph node metastasis, histological grade, and prognosis.

Role of JPX in Cancer Malignant Processes

Cancer development usually occurs by modulating gene expression, which alters normal cellular physiological processes to promote malignant cancer progression, including cell adhesion, motility, proliferation, and differentiation.[51] Based on accumulating evidence, lncRNAs are recognized as an important class of regulators of tumorigenesis and cancer progression.[52,53] Collectively, JPX reportedly exhibits different functional roles in malignant cancer processes [Table 2].

JPX in cancer growth

Tumorigenesis is a multi-gene, multi-step process characterized by several important pathological markers, including uncontrolled cell proliferation and apoptosis.[54] Cancer cells can not only proliferate indefinitely but also escape apoptosis, allowing them to gain immortality.[55] LncRNAs play a critical regulatory role in cancer cell growth.[56,57] The *in vitro* functional assays have revealed that JPX might play a dual role in cancer growth. Conversely, JPX overexpression could promote cell proliferation and inhibit apoptosis, suggesting an oncogenic role in NSCLC,[31,32] GC,[33] OSCC,[34] CC,[35] OC,[36] OS,[37] and GBM.[38] In contrast, JPX overexpression significantly inhibited cell proliferation and induced apoptosis, suggesting a tumor suppressor role in HCC.[44] The *in vivo* effect of JPX on tumor growth demonstrated that JPX could promote or suppress tumor growth in a subcutaneous xenotransplanted cancer model in nude mice.[30,32,35,44] Therefore, JPX can influence cancer progression by affecting cancer cell growth.

JPX in cancer metastasis

Cell invasion and migration are key phenotypic hallmarks of cancers and are closely associated with tumor metastasis.[58,59] Epithelial cell-mesenchymal transition (EMT) is characterized by poor cell adherence and improved migratory capacity. It has been shown that JPX knockdown inhibits cancer cell migration and invasion, while JPX overexpression promotes these phenotypes in NSCLC,[31,32] GC,[33] OSCC,[34] CC,[35] OC,[36] and OS.[37] For example, JPX knockdown increased the expression of E-cadherin, and decreased

Table 2: Functional roles of JPX in various types of cancer.

Cancer	Cell lines	Expression	Regulated targets	Regulatory axis/ signaling	*In vitro* effect	*In vivo* effect	Reference
LC	Normal cell (BEAS-2B); LC cells (SPC-A-1, LTEP-a-2, A549, NCI-H1299)	Upregulation	miR-33a-5p, E-cadherin, GSK-3β, N-cadherin, Vimentin, Twist1, β-catenin	JPX/miR-33a-5p/ Twist1, Wnt/ β-catenin signaling	Cell growth↑, proliferation↑, migration↑, invasion↑, EMT↑	Tumor growth↑, metastasis↑	[32]
NSCLC	Normal cell (16HBE); NSCLC cells (A549, H1299, H292, H460, SPCA-1)	Upregulation	miR-145-5p, CCND2	JPX/miR-145-5p/ CCND2	Cell proliferation↑, migration↑, cell cycle progression↑	Tumor growth↑	[30]
	Normal cell (BEAS-2B); NSCLC cells (NCI-H1299, A549, NCI-H460)	Upregulation	miR-5195-3p, E-cadherin, N-cadherin, vimentin, VEGFA	JPX/miR-5195-3p/ VEGFA	Cell proliferation ↑, invasion↑, migration↑, EMT↑, apoptosis↓	Tumor growth↑	[31]
GC	Normal cell (GES-1); GC cells (NCI-N87, MKN-45)	Upregulation	miR-197, CXCR6, Beclin1, p62	JPX/miR-197/ CXCR6, autophagy	Cell activity↑, migration↑, invasion↑	Not reported	[33]
OSCC	Normal cell (NOK); OSCC cells (SCC-15, SCC-25, HSC-2, SCC-9)	Upregulation	miR-944, CDH2	JPX/miR-944/ CDH2	Cell proliferation↑, migration↑, invasion↑, apoptosis↓	Not reported	[34]
CC	Normal cervical cells (End/E6E7); CC cells (MS751, C33A, HeLa, Caski, SiHa)	Upregulation	miR-25-3p, SOX4	JPX/miR-25-3p/ SOX4	Cell proliferation↑, migration↑, invasion↑	Tumor growth↑	[35]
OC	Normal cell (OSE); OC cells (SKOV3, OVCAR3)	Upregulation	Bax, Bcl-2, Caspase-3, p-PI3K, p-Akt, p-mTOR	PI3K/Akt/mTOR	Cell proliferation↑, migration↑, invasion↑, apoptosis↓	Not reported	[36]
OS	Normal osteoblast cell line (hFOB1.1); OS cells (Saos-2, MG63, U2OS)	Upregulation	β-catenin, MYC, Axin2, Cyclin D1	Wnt/β-catenin	Cell proliferation↑, cell viability↑, migration↑, invasion↑	Not reported	[37]
GBM	Normal astrocyte NHA cells; GBM cells (U251, LN229, SHG-44, LN18)	Upregulation	PDK1, FTO	JPX/FTO/PDK1; m6A methylation	Cell proliferation↑, TMZ chemoresistance↑, DNA damage repair, aerobic glycolysis	Not reported	[38]
BC	Breast non-tumorigenic cells (M10, MCF10A); tumorigenic cells (MCF7, MDA-MB-468); metastatic cells (MDA-MB-231, Hs578T)	Downregulation	Xist, p-Akt	AKT phosphorylation	Cell viability↑	Not reported	[39]
HCC	HCC cell (HepG2)	Downregulation	XIST, miR-155-5p, SOX6, PTEN	JPX/XIST/miR-155-5p/SOX6 and PTEN	Cell proliferation↓, apoptosis↑	Tumor growth↓	[44]
	Mononuclear cells and granulocytes of female patients	Upregulation	XIST, CTCF	JPX/XIST/CTCF	Not reported	Not reported	[46]
UM	Normal cells (FPC1, APRE19); UM cells (MUM2B, OCM1)	Downregulation	CANT1, XIST, H3K4	CANT1-JPX/FTX-XIST	Not reported	Not reported	[41]

BC: Breast cancer; CANT1: Calcium-activated nucleotidase 1; CC: Cervical cancer; CCND2: Cyclin D2; CDH2: Cadherin 2; CTCF: CCCTC-binding factor; CXCR6: C-X-C motif chemokine receptor 6; EMT: Epithelial cell-mesenchymal transition; FTO: Fat mass- and obesity-associated; FTX: Fiveprime to Xist; GBM: Glioblastoma multiforme; GC: Gastric cancer; GSK-3β: Glycogen synthase kinase 3β; H3K4: Histone demethylase; HCC: Hepatocellular carcinoma; LC: Lung cancer; m6A: N6-methyladenosine; miR: MicroRNA; NSCLC: Non-small cell lung cancer; OC: Ovarian cancer; OS: Osteosarcoma; OSCC: Oral squamous cell carcinoma; p-Akt: Phosphylated Akt; PDK1: Phosphoinositide dependent kinase-1; p-mTOR: Phosphylated mammalian target of rapamycin (mTOR); p-PI3K: Phosphylated phosphatidylinositol3-kinase (PI3K); PTEN: Phosphatase and tensin homolog deleted on chromosome ten; SOX: Sex-determining region Y-box; TMZ: Temozolomide; UM: Uveal melanoma; VEGFA: Vascular endothelial growth factor A; Xist: X-inactive-specific transcript; ↑: Increase; ↓: Decrease.

expression levels of both N-cadherin and vimentin, thereby indicating that JPX promoted the EMT process and then facilitated the metastasis and invasion of NSCLC cells.[31,32] There is considerable evidence suggesting that exosomes are key players in intercellular communication and cancer metastasis by transmitting intracellular cargoes such as DNA, RNA, and proteins.[60-62] Interestingly, JPX was found to be upregulated in exosomes and could be delivered from cancer cells to blood cells to activate Xist expression in female patients with HCC.[46] These findings suggest that exosome-transmitted JPX is involved in cancer metastasis.

JPX in cancer chemoresistance

Currently, chemotherapy is a therapeutic strategy for cancer management. However, chemoresistance remains a major challenge in chemotherapy. JPX knockdown enhanced temozolomide (TMZ) sensitivity and significantly suppressed phosphoinositide dependent kinase-1 (PDK1) expression in GBM cells. Meanwhile, upregulation of PDK1 partially recovered JPX-induced chemoresitance to TMZ.[38] These results indicated that JPX could promote TMZ chemoresistance by targeting PDK1 at the post-transcriptional level. In addition, JPX was notably upregulated following phorbol 12-myristate 13-acetate-treatment of Dami cells (megakaryoblastic cells) and was predicted to affect the growth and differentiation of megakaryoblastic leukemia cells by acting as a decoy for miRNAs, titrating them away from transforming growth factor β (TGF-β) receptor messenger RNAs (mRNAs).[43] Taken together, these findings indicate that JPX is not only closely associated with chemoresistance, but also a potential target for precision oncology.

Mechanisms of JPX in Cancers

LncRNAs contribute to cancer development through various molecular mechanisms. JPX is reportedly involved in various biological processes of cancer progression by sponging miRNAs, interacting with proteins, and regulating specific signaling pathways.

JPX acts as a competing endogenous RNA (ceRNA) for miRNA

In recent years, ceRNA networks have been reported to participate in cancer progression.[63,64] The ceRNA hypothesis suggests that miRNAs are negative regulators of gene expression and can influence the expression of targeted mRNAs. If long-stranded RNAs, including lncRNAs and mRNAs, have the same miRNA binding sites, these RNAs can compete for miRNA uptake and thus regulate their respective expression.[65] Thus, lncRNAs, miRNAs, and mRNAs form large and complex ceRNA regulatory networks in eukaryotic cells.[66,67] JPX was found to act as a ceRNA to regulate the expression of different mRNAs by competing with multiple miRNAs, thereby affecting downstream signaling pathways and participating in the malignant biological phenotypes of cancers. For example, Pan *et al*[32] showed that JPX was upregulated and affected cell proliferation, migration, and invasion, as well as tumor growth and metastasis in LC. Another study revealed that JPX functioned as a ceRNA for Twist1 mRNA, a switch in EMT, by sponging miR-33a-5p and thereby regulating the Wnt/β-catenin signaling pathway [Figure 2A]. Similarly, JPX competitively binds to miR-145-5p and upregulates the expression of cyclin D2 to promote cell proliferation, migration, and cell cycle progression in NSCLC[30] [Figure 2B]. Furthermore, JPX could also sponge miR-5195-3p to upregulate the expression of vascular endothelial growth factor A expression to promote cell proliferation, invasion, migration, and EMT and inhibit cell apoptosis in NSCLC[31] [Figure 2C]. In CC, JPX promoted cancer progression by modulating the miR-25–3p/sex-determining region Y-box 4 axis[35] [Figure 2D]. In OSCC, JPX competitively binds to miR-944, thereby increasing cadherin 2 expression and promoting cell proliferation, migration, and invasion[34] [Figure 2E]. In GC, JPX was found to bind miR-197, thereby affecting the expression of its targeted gene, C-X-C motif chemokine receptor 6, and exerting oncogenic functions[33] [Figure 2F]. In acute megakaryoblastic leukemia, JPX was predicted to interact with three known oncogenic miRNAs (miR-9-5p, miR-17-5p, and miR-106-5p) and regulate the expression of TGF-β receptor mRNA[43] [Figure 2G]. Collectively, JPX is a long-stranded ncRNA that may provide additional binding sites for miRNAs involved in tumor progression through ceRNA regulatory networks.

JPX interacts with proteins

In addition to competitively binding to miRNAs, lncRNAs have been identified to interact with proteins, participating in molecular regulation, such as chromosomal regulatory complexes, transcription factors (TFs), and RNA binding proteins.[68-70] An RNA immunoprecipitation assay revealed that JPX interacted with fat mass- and obesity-associated (FTO) protein, a major N6-methyladenosine demethyltransferase, and enhanced FTO-mediated PDK1 mRNA demethylation.[38] Thus, JPX enhanced PDK1 mRNA stability in an FTO-dependent manner [Figure 3A]. In addition, JPX binds to TFs to regulate the transcription of downstream molecules. Sun *et al*[71] found that JPX competitively binds with CCCTC-binding factor (CTCF) at the Xist P2 promoter to activate XIST expression in trans-acting elements. A similar study showed that exosome-derived JPX could activate XIST expression by inhibiting the trans-regulatory effect of CTCF in HCC[46] [Figure 3B]. Collectively, these findings indicate that JPX RNA can interact with proteins involved in cancer progression.

JPX regulates specific signaling pathways

Aberrant signaling has been identified as a key mechanism in cancer.[72] Recent studies have showed that JPX mediates at least two signaling pathways, Wnt/β-catenin signaling and phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR), known to be involved in cancer progression.[32,36,37] It is well-known that aberrant Wnt/β-catenin signaling plays a critical role in diseases, including cancer.[73-75] Pan *et al*[32] observed that β-catenin was downregulated upon JPX knockdown, while glycogen synthase kinase 3β, a key regulator of the Wnt/β-catenin signaling, was upregulated; JPX overexpression induced the opposite effects. These findings suggest that JPX positively regulates the Wnt/β-catenin signaling, thereby promoting the malignant process of LC. In OS, overexpression of JPX significantly increased the expression of β-linked protein, MYC, Axin2, and cyclin D1 proteins, and activated the Wnt/β-catenin pathway to mediate cancer growth and metastasis[37] [Figure 2H]. PI3K signaling affects cancer cell growth, survival, motility, and metabolism.[76] Li *et al*[36] reported that JPX facilitated the proliferation, invasion, and migration of OC cells through PI3K/Akt/mTOR signaling [Figure 2I]. Dahariya *et al*[43] showed that JPX contributed to the activation of

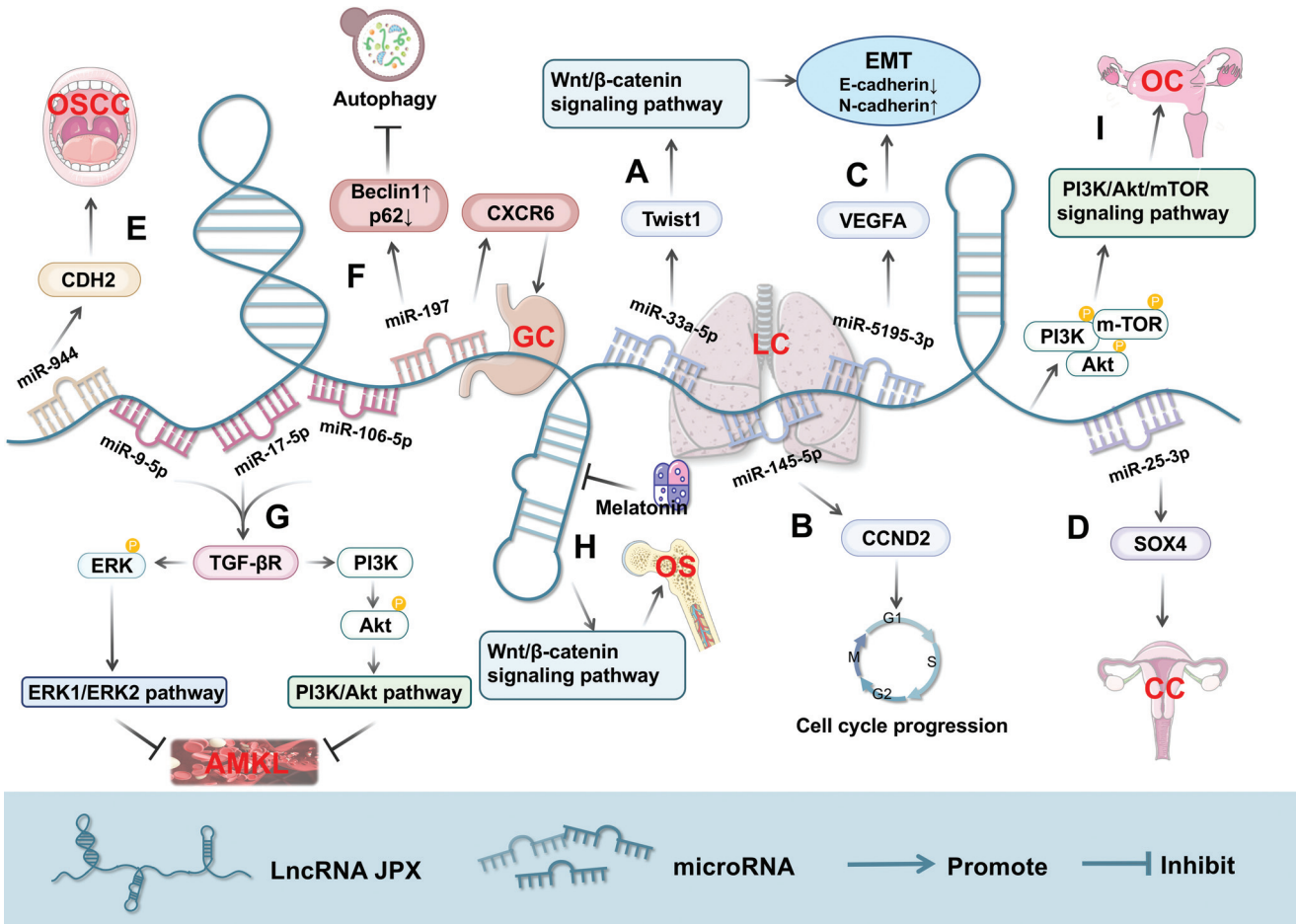


Figure 2: Possible molecular mechanisms of JPX in human cancers. (A) JPX regulated miR-33a-5p/Twist1-mediated EMT progression by activating Wnt/β-catenin signaling in LC. (B) JPX functioned as a ceRNA for miR-145-5p to regulate cyclin D2 (CCND2) expression, and then promoted cell cycle progression in NSCLC. (C) JPX regulated NSCLC EMT by modulating miR-5195-3p/VEGFA axis. (D) JPX promoted CC progression by modulating miR-25-3p/SOX4 axis. (E) JPX was overexpressed in OSCC and promoted malignancy via miR-944/cadherin 2 (CDH2) axis. (F) JPX promoted GC progression by regulating C-X-C motif chemokine receptor 6 (CXCR6) and autophagy via inhibiting miR-197. (G) JPX contributed to the activation of extracellular signal-regulated kinase 1/2 (ERK1/2) and phosphatidylinositol3-kinase (PI3K)/AKT pathways via miRNAs/transforming growth factor β receptor (TGF-βR) axis, thus enhancing polyploidization and terminal maturation of megakaryocytes. (H) Anticancer effects of melatonin via regulating JPX/Wnt/β-catenin signaling pathway in human OS cells. (I) JPX promoted the progression of ovarian cancer through PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway. CC: Cervical cancer; ceRNA: Competing endogenous RNA; EMT: Epithelial-mesenchymal transition; GC: Gastric cancer; LC: Lung cancer; LncRNA: Long noncoding RNA; miR: MircoRNA; NSCLC: Non-small cell lung cancer; OS: Osteosarcoma; OSCC: Oral squamous cell carcinoma; P: Phosphorylation; VEGFA: Vascular endothelial growth factor A.

extracellular signal-regulated kinase 1/2 and PI3K/AKT pathways, thus enhancing the polyploidization and terminal maturation of megakaryocytes. Typically, specific signaling pathways are involved in primary mechanisms underlying JPX-mediated cancer development.

Potential Biomarkers and Therapeutic Targets of JPX for Cancer Treatment

In the era of precision oncology, lncRNAs can be used as biomarkers for the diagnosis or prognosis of cancers at an early stage. Additionally, lncRNAs serve as targets for cancer treatments.

JPX as a diagnostic biomarker

Growing evidence indicates the superiority of lncRNAs as biomarkers for the early diagnosis of cancer.[77,78] The potential role of JPX as a diagnostic biomarker has been demonstrated in the early stages of several cancers. In particular, the area under the receiver operating characteristic (ROC) curve (AUC) of JPX for HCC diagnosis was approximately 0.814 (specificity, 52.4%; sensitivity, 100%). Furthermore, the authors suggested that JPX could be used to distinguish patients with HCC from healthy controls.[45] To a certain extent, JPX exhibits good diagnostic value as a biomarker.

JPX as a prognostic biomarker

Prognostic biomarkers are crucial for predicting tumor behavior and survival time, as well as for guiding treatment decisions. Notably, the expression levels of lncRNAs have been found to correlate with cancer prognosis.[79,80] The role of JPX as a prognostic biomarker has been investigated in several cancers [Table 1]. For example, the 3-year survival rate was substantially lower in the JPX high-expression group than that in the JPX low-expression group in patients with OC.[33] Furthermore, a multivariate analysis of differentially expressed lncRNAs in 117 patients with thymoma revealed that overall survival was independently associat-

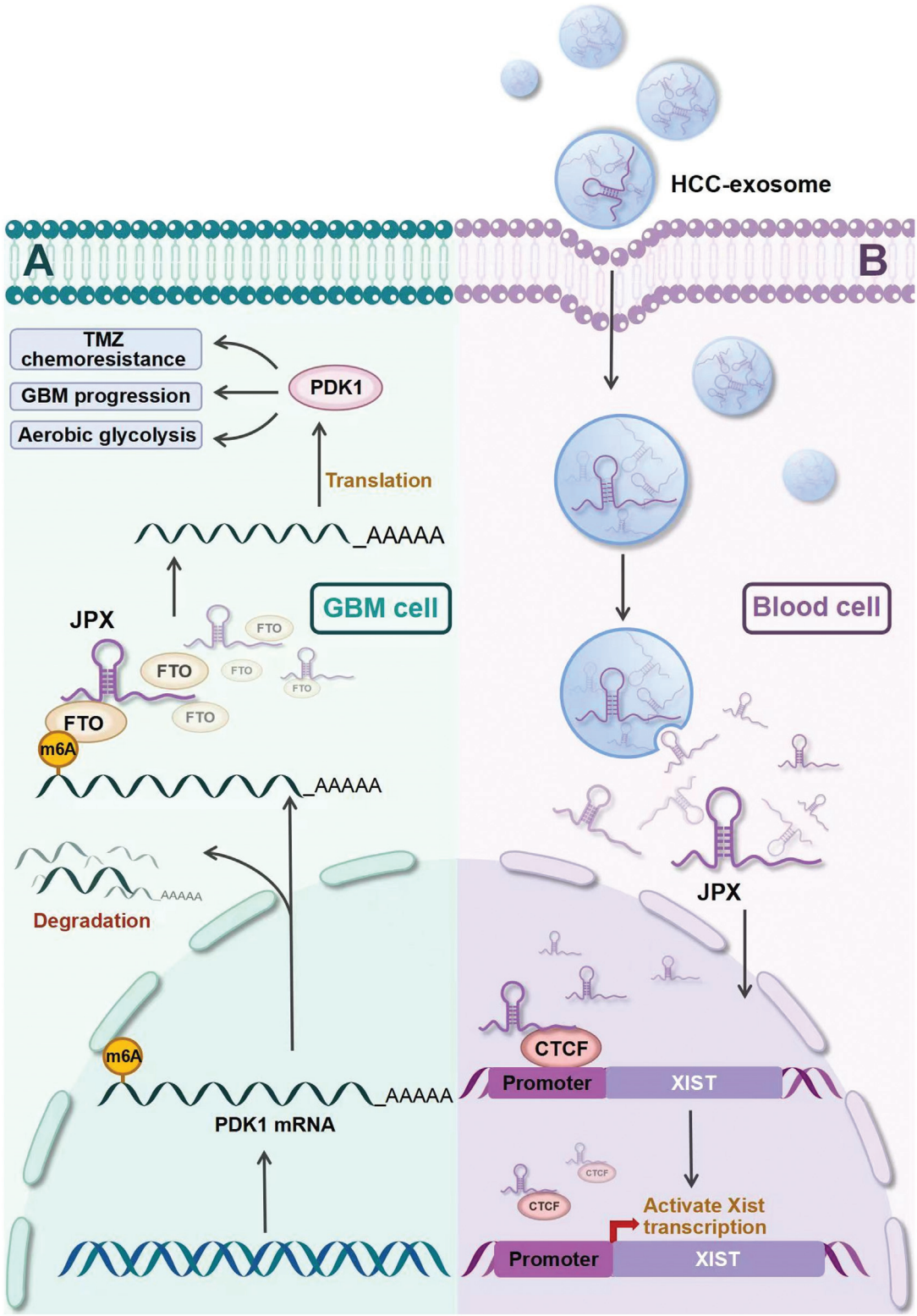


Figure 3: JPX modulates cancer development by sponging RBPs. (A) JPX was delivered from HCC cells to blood cells via exosomes and then activated XIST expression by repressing the trans-regulatory effect of CTCF. (B) JPX maintained PDK1 mRNA stability by reducing m6A methylation of PDK1 mRNA through binding to fat mass- and obesity-associated (FTO) protein, leading to the upregulation of PDK1 expression. Upregulation of PDK1 expression could promote GBM progression, aerobic glycolysis, and TMZ chemoresistance. CTCF: CCCTC-binding factor; GBM: Glioblastoma multiforme; HCC: Hepatocellular carcinoma; m6A: N6-methyladenosine; miRNA: microRNA; mRNA: Messenger RNA; PDK1: Phosphoinositide dependent kinase-1; RBPs: RNA binding proteins; TMZ: Temozolomide; XIST: X-inactive-specific transcript.

ed with JPX expression.[81] These results demonstrate that JPX can be used as a prognostic biomarker in patients with cancer.

JPX as a therapeutic target

Given the growing understanding of the functional roles of JPX in cancer progression, JPX could be employed as a potential therapeutic target. Li *et al*[37] found that the lncRNA JPX was downregulated in melatonin-treated OS cell lines. In addition, experiments have revealed that JPX overexpression promotes cell proliferation, migration, and invasion. However, melatonin treatment can inhibit the JPX-mediated oncogenic effect. These results suggest that JPX may be a key target for OS treatment. Several other studies have shown that JPX is a key regulator of oncogenic signaling pathways in multiple types of cancers.[32,36,37,43] Therefore, JPX could be a potential target for cancer therapy.

Conclusion and Prospective

JPX, a very promising lncRNA, plays an important role in cancer development. In the present study, we provide a comprehensive review of the current understanding of JPX as a key regulator of cancer progression. JPX affects cancer phenotypes by sponging miRNAs or proteins, or by activating cellular signaling pathways. Notably, aberrant JPX expression is closely correlated with clinicopathological features such as lymphatic metastasis, tumor stage, tumor size, and overall survival, suggesting its potential as a biomarker for cancer diagnosis and prognosis. Furthermore, JPX, a downstream molecule of melatonin, shows great potential as a therapeutic target. Despite the progress in clarifying the function of JPX, the precise molecular mechanisms upstream and downstream of JPX need to be comprehensively elucidated. Most studies on JPX are currently based on *in vitro* experiments, and further *in vivo* experiments are urgently needed to reveal the function of JPX in human cancers. Additionally, most experiments have shown that JPX is mainly located in the cytoplasm. The role of JPX in the nucleus remains unclear. Interestingly, JPX can bind to thousands of sites on chromatin and activate transcription. Notably, JPX controls chromatin loop formation by moving the anchor sites.[82] Therefore, we speculated that JPX could influence cancer development through its potential role in the nucleus. Although studies have shown that JPX can be transported via exosomes in HCC, further investigations are warranted, and it remains unknown whether other tumors behave similarly. JPX can serve as a potential therapeutic target; however, robust clinical trials are required to investigate the clinical utility of these molecular approaches. Collectively, the emerging role of JPX study is in its early stages, and more attention should be paid to specific molecular mechanisms and translational medical studies.

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Conflicts of interest

None.

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