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REVIEW

Long Non-Coding RNA *JPX*: Structure, Functions, and Role in Chromatin Architecture

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Abstract—Long non-coding RNAs (lncRNAs) are a novel class of regulators of key cellular processes and biomarkers of various pathologies. The lncRNA *JPX* is a multifunctional RNA involved in the regulation of transcription, translation, and chromatin architecture. *JPX* influences transcription and enhancer-promoter communication by regulating binding of proteins to DNA, particularly by interacting with the chromatin architectural protein CTCF. Additionally, *JPX* can interact with microRNAs, repressor proteins, or mRNA stabilizers, regulating translation in pathogenesis of oncological and other diseases. This review summarizes the accumulated knowledge about the structure, evolutionary origin, and functions of the long non-coding RNA *JPX* in normal and pathological conditions.

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INTRODUCTION

Although the protein-coding exons constitute only about 1.5% of the genome, more than 75% of the genome is transcribed, including non-coding RNAs (ncRNAs) [1]. Initially, ncRNAs were identified as RNAs lacking an apparent open reading frame and were considered to be mere byproducts of transcription. However, hundreds of long non-coding RNAs (lncRNAs) essential for cell survival have since been identified [2]. Traditionally, lncRNAs are defined as ncRNAs longer than 200 nucleotides [3], but according to a newer classification, lncRNAs are ncRNAs longer than 500 nucleotides [4, 5]. Most lncRNAs are characterized by relatively low expression levels (with notable exceptions such as NEAT1 or MALAT1 [6, 7]), tissue specificity, low evolutionary conservation, and the presence of isoforms resulting from alternative splicing [5, 8-10].

The recently accumulated experimental data have expanded our understanding of lncRNAs as important regulators of cellular processes. For example, lncRNAs can facilitate recruitment or displacement of the transcription factors, chromatin remodeling complexes, and transcription repressors from chromatin [11-15]. Additionally, lncRNAs are involved in establishing the specific spatial structure of chromatin, which directly affects gene expression in eukaryotes. In mammalian cells, genome topology is largely determined by architectural proteins such as cohesin and CTCF, whose binding can be regulated by specific lncRNAs [16-18]. lncRNAs can regulate chromatin architecture at different levels – from loops to the structure of entire chromosomal territories. This is achieved through the rich protein interactome of these molecules [19-21]. For example, during X chromosome inactivation (XCI), the lncRNA *Xist* recruits transcription repressors (such as SPEN) and architectural proteins (such as SMCHD1) and displaces RNA polymerase II, cohesin,

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and CTCF [22]. All these interactions contribute to chromatin restructuring at the chromosomal level and overall inactivation of transcription on the X chromosome.

Moreover, the transcribed lncRNA genes can act as enhancers of transcription for other genes, forming spatial contacts with them [23-25]. In some cases, knockdown of the lncRNAs themselves does not affect expression of the regulated genes, unlike the inhibition of transcription or deletion of structural elements of lncRNA genes [3, 4]. In this case, lncRNAs may be mere "byproducts" of the act of transcription, which itself plays a regulatory role. Such hypothesis has been proposed in the literature for a number of enhancer RNAs [3]. However, it is worth noting that at least sometimes, lncRNAs transcribed from enhancers are involved in establishing enhancer–promoter contact and transcription regulation [4]. In general, despite the differences in stability and modifications of such enhancer-associated lncRNAs and "typical" enhancer RNAs (many of which apparently do not have any functions), a clear division of these RNA classes is currently absent [4].

lncRNAs also regulate expression at the translation level, for example, by binding to the 5′ end of the target RNA and recruiting polysomes [26, 27], or by directly binding to mRNA, increasing their stability. Finally, lncRNAs can bind microRNAs (miRNAs), preventing their access to mRNA and thus promoting translation of the latter [28-30]. One lncRNA can bind several miRNAs, simultaneously acting as a regulator of many biochemical pathways [31].

The lncRNA *JPX* (just proximal to *XIST*, primate lncRNA) is an example of a multifunctional RNA involved in regulation of transcription, translation, and chromatin architecture. Initially, its role in X chromosome inactivation was discovered, but later its functional repertoire was significantly expanded. In particular, it has been shown that, at least in certain cell types, this RNA determines chromatin conformation and controls cell development programs through interaction with the architectural protein CTCF. In addition, *JPX* can directly activate many genes by recruiting transcription activators or displacing repressors. Finally, through interaction with many proteins and miRNAs, *JPX* influences onset and progression of dozens of different pathologies.

STRUCTURE AND EVOLUTIONARY ORIGIN OF THE *JPX* GENE

The *JPX* gene (human Ensembl ID: ENSG0000022547, NCBI ID: 554203; house mouse *Mus musculus* Ensembl ID: ENSMUSG00000097571, NCBI ID: 70252) is located on the X chromosome and is the closest to the *XIST* gene (separated from it by ~10 kb in mice and ~90 kb in humans) [32, 33] (Fig. 1). Other names of the *JPX* gene include *ENOX* (expressed neighbor of *XIST*), *LINC00183*, *DCBALD06*, or *NCRNA00183* in humans and *Enox*, *2010000I03Rik*, or *2510040I06Rik* in house mice. In both mice and humans, this gene is transcribed to form multiple isoforms produced by alternative splicing. Discovered independently by two research groups, this gene was annotated both as a three-exon variant with polyadenylation signal after the third exon [32] and as a five-exon variant with two alternative polyadenylation signals in the region of the 3′ end of the fifth exon [33]. The predicted exon positions coincide with those in the RefSeq database; in humans, the main isoform is 1692 nucleotides long, consisting of five exons (Fig. 1b). In humans and mice, this lncRNA is expressed from both the active and inactive X chromosomes, as demonstrated in various human tissues [34] (Fig. 2). Like other lncRNA genes in the X chromosome inactivation center (XIC), the *JPX* gene in placental mammals has originated from a protein-coding gene [35, 36] (Fig. 2).

To date, 124 isoforms of *JPX* and 100 isoforms of *Jpx* (rodent lncRNA) have been annotated in the Ensembl database based on the MGI sequencing data. However, contribution of the vast majority of these remains unstudied. The NCBI RefSeq database contains only one experimentally validated isoform of *JPX* (highlighted in red in Fig. 2) and *Jpx*. Nevertheless, the publicly available RNA-seq data indicate expression of the alternative *JPX* isoforms in many tissues (Fig. 2, human example). It should also be noted that in the studies where *JPX*/*Jpx* knockdown was performed, antisense oligonucleotides and primers for expression level verification were generally selected for the exons present in dozens of isoforms [37-39]. Because of this, it was impossible to determine the physiological role (and the expression level) of individual isoforms. To improve understanding of the role of specific isoforms, more research is needed, including overexpression or knockdown of individual isoforms.

Both initial studies identified an extended unmethylated CpG island near the exon 1 of *Jpx* and showed gene expression in many mouse tissues [32, 33]. The gene was found to be conserved in mice, humans, and cattle, with exon 1 being the most conserved (Fig. 3). Additionally, the exons 2 and 3 were likely derived from the mobile genetic elements (MGEs) [32].

Formation of pseudogenes from the protein-coding genes played a crucial role in the emergence of all ncRNAs in the XIC of the common ancestor of placental mammals [40]. XIC is involved in the mechanism of random X chromosome inactivation, in which either the paternal or maternal X chromosome could be inactivated. The relative arrangement of genes within the XIC locus is conserved, although the gene sizes,

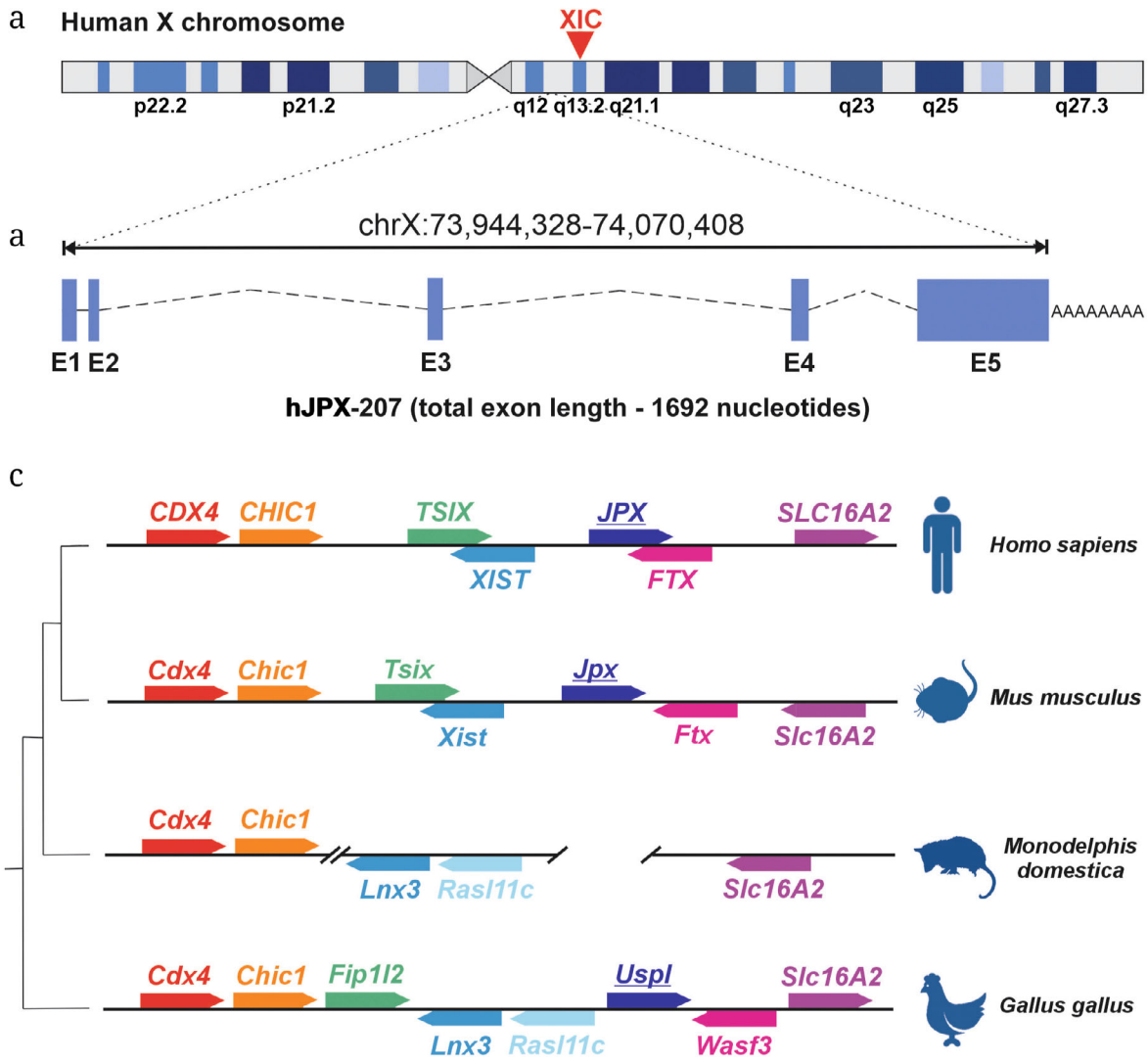

Fig. 1. Structure and evolutionary origin of the *JPX* gene. a) Location of the inactivation center on the human X chromosome. b) Exon-intron structure of the *JPX* isoform ENST00000602772.5. Exons are indicated by rectangles, introns by dashed lines. c) Genomic organization and comparison of the X chromosome inactivation center region in different species: *Gallus gallus* – chicken; *Monodelphis domestica* – gray short-tailed opossum; *Mus musculus* – house mouse; *Homo sapiens* – human. Non-coding genes localized within the XIC originated from protein-coding genes: *XIST*, *JPX*, and *FTX* from *Lnx3*, *Uspl*, and *Wasf3*, respectively (adapted from [35, 36], with modifications based on NCBI and UCSC databases).

distances between them, or transcription orientation have repeatedly changed during evolution due to insertion of MGEs [35] (Fig. 1c).

In particular, the ancestor of the *JPX* gene is the ubiquitin-specific protease gene *Uspl*, which is functional in marsupials [40] (Fig. 1c). The first exon of *JPX* originated from the first exon of *Uspl*, the second exon of *JPX* from the fifth exon of *Uspl*, and one of the alternative exons of *JPX* transcripts from the seventh exon [36]. The first exon of *JPX* is conserved in mice and humans and generally exhibits the highest evolutionary conservation (Fig. 3).

Interestingly, the ribosome profiling data indicate intense ribosome binding in the first exon containing a short open reading frame (sORF) and translation of the first exon in various human and mouse tissues [41]. The region around this frame is highly conserved among the placental mammals and vertebrates in general [36, 41]. The functions of sORF include regulation of transcription and translation. Although the 5′ end of *JPX* (containing the promoter and the first two exons) can efficiently initiate transcription of the luciferase gene when cloned into an expression construct as a promoter, mutation in the start codon of sORF reduces mRNA production [41]. A similar effect of this mutation is observed on transcription of the *JPX* gene in the endogenous context. Despite the fact that the mutation in the start codon of the sORF reduces transcription, it nevertheless promotes production of luciferase, enhancing translation of its mRNA [41].

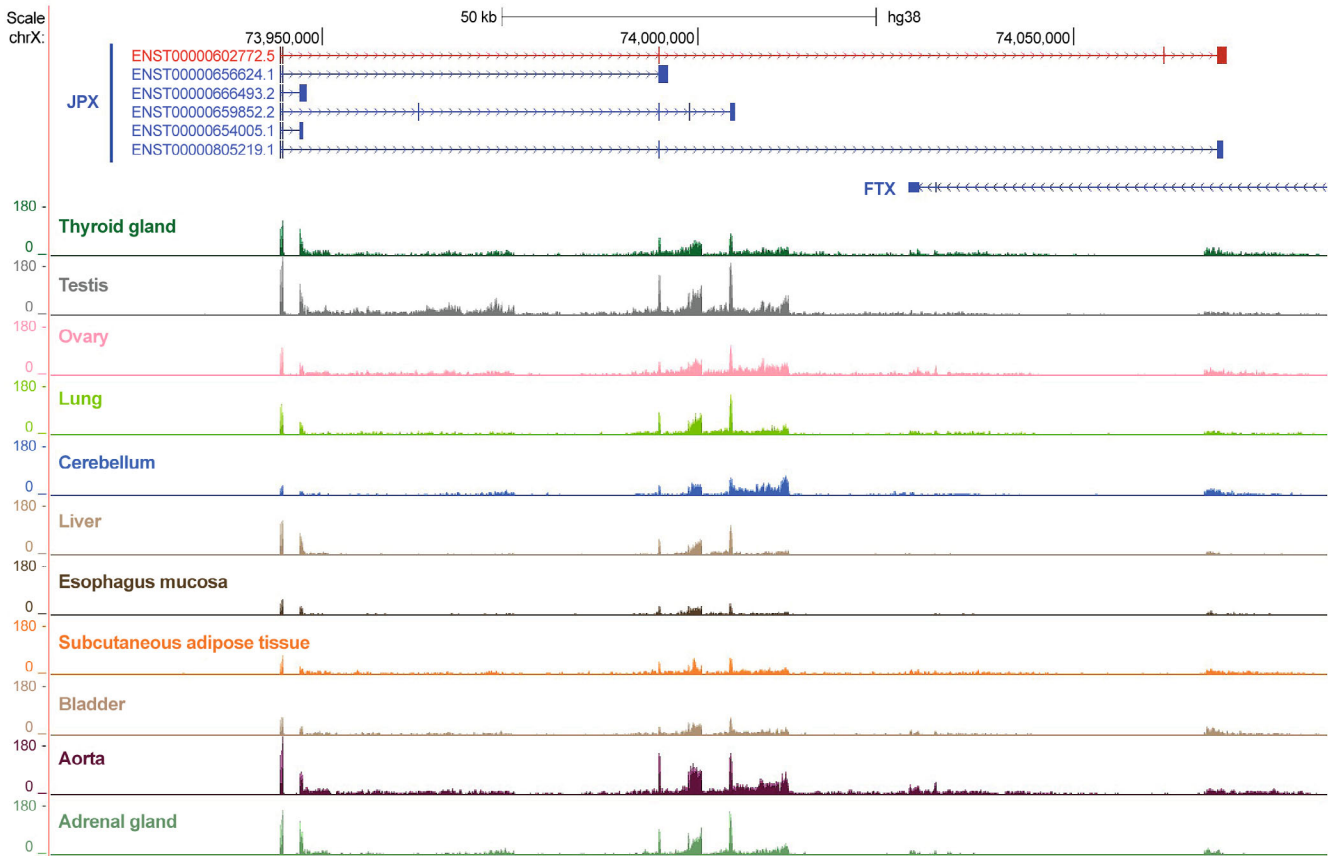

Fig. 2. Some isoforms of the lncRNA *JPX* and its expression profile in various human tissues, according to the Genotype-Tissue Expression Project (GTEx). Visualization was performed in the UCSC Genome Browser (https://genome.ucsc.edu/). The only isoform present in the NCBI RefSeq database as a validated transcript is highlighted in red (https://www.ncbi.nlm.nih.gov/nuccore/NR_024582.1). Purple highlights isoforms from the GENCODE v48 database with exons corresponding to the regions of active expression, according to GTEx.

This indicates that the wild-type sORF suppresses translation of the subsequent ORF of luciferase. One of the mechanisms of this suppression could be competition for ribosome binding. However, these observations, made in model experiments, do not answer whether translation of the sORF *JPX* is important for realization of the function of this RNA.

Excluding the first exon, the *JPX* sequence is not conserved even among placental mammals [42]. This is explained by the fact that most of *JPX* arose through insertion of the MGEs in a species-specific manner [35, 41, 42]. For example, in mice, the exons 2 and 3 have pronounced homology with the MGEs of the LTR/MaTR class, while in cattle these two exons demonstrate the homology with SINE and LINE, respectively. In humans, the third exon arose from the integration of SINE [32]. The fourth and fifth exons of the mouse *Jpx* gene have pronounced homology with the exons 2-7 of the protein-coding gene *Ebag9* and may have arisen through retrotransposition [33]. Insertion of MGEs has also determined the species-specific arrangement of the genes. For example, in humans, the *JPX* gene overlaps with the *FTX* gene, which is transcribed in the opposite direction, while in mice, these genes do not overlap. Most of the region between the 5′ end of the mouse *Jpx* gene and the last exon of *Ftx* is absent in humans and is represented by the species-specific MGEs of the SINE and LTR classes [42].

Structural and functional conservation of transcripts of the mouse *Jpx* gene and the human *JPX* gene was investigated in a recent study [43]. It was shown that the human lncRNA *JPX* tends to evolve in a different direction than the lncRNA *Jpx* in rats and mice, potentially acquiring new functions. Despite the abundance of stem-loop structures, mouse and human RNAs do not have pronounced similarity in the secondary structure, and their overall spatial structure differs significantly (Fig. 4). However, it was shown that expression of a fragment containing the first three exons of the lncRNA *JPX* or *Jpx in trans* compensates for the effect of deletion of the mouse *Jpx* gene and increases survival of the mouse cells [43].

Thus, the *JPX* gene produces multiple transcript isoforms, is poorly conserved, and emerged through two mechanisms: pseudogenization of the protein-coding genes and insertion of MGEs.

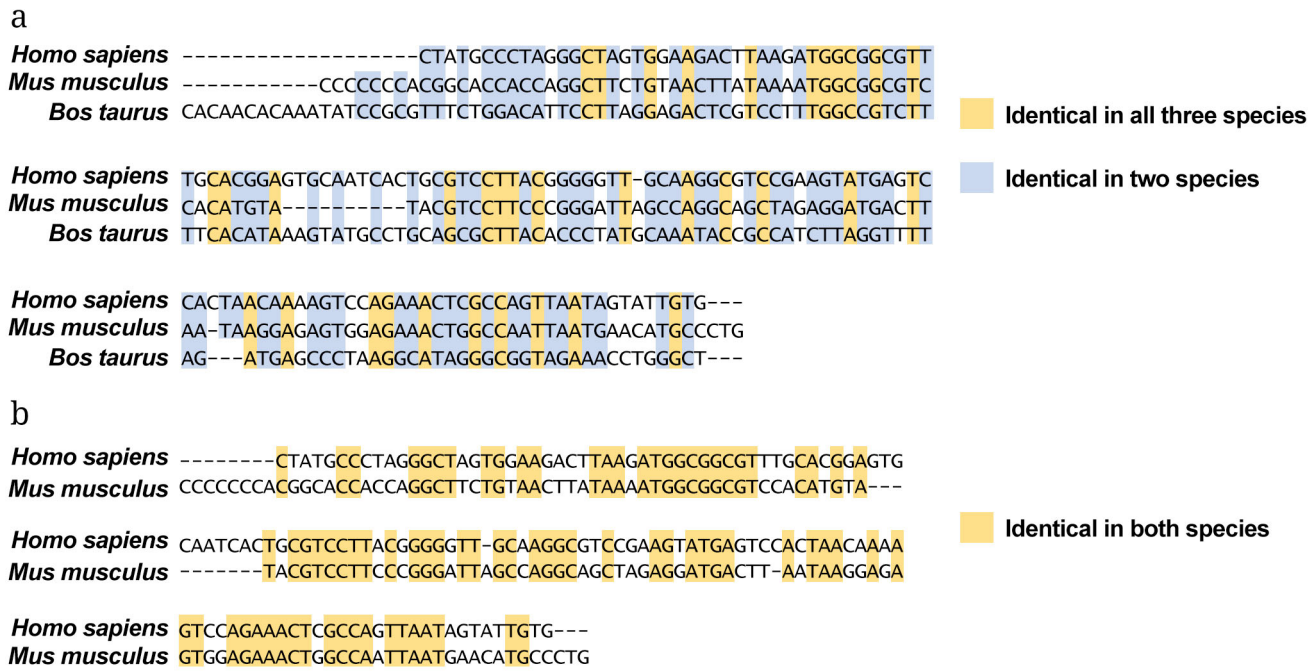

Fig. 3. Alignment of the first exon sequence of *Jpx* from different mammalian species. a) Comparison of the sequences of this exon in humans (*Homo sapiens*), mice (*Mus musculus*), and cattle (*Bos taurus*). Regions of complete sequence identity are shown in yellow, and regions of partial identity are shown in blue. b) Comparison of the sequence of this exon in mice and humans. Regions of identity (60%) are highlighted in yellow. Alignments were performed using the CLUSTALW program (https://www.genome.jp/tools-bin/clustalw).

JPX-MEDIATED ACTIVATION OF *XIST* DIFFERS AMONG PLACENTAL ORDERS

The *JPX*-mediated activation of *XIST* is best studied in the orders Rodentia and Primates. The mechanisms of this activation appear to vary both between and within these orders.

In humans, the *JPX* gene is located near the *XIST* gene and forms a spatial contact with it, acting as a strong enhancer that transfers RNA polymerase II to the *XIST* promoter (regulation *in cis*) [44]. Transcription of the *JPX* locus is necessary to maintain *XIST* transcription in human cells after XCI, while mature, spliced *JPX* transcripts are not required for *XIST* expression. Thus, in humans, *XIST* activation is regulated by transcription of the *JPX* gene (Fig. 4a).

In the phylogenetically distant common marmoset (*Callithrix jacchus*), the *JPX* gene does not play an obvious role in the activation of the *XIST* gene and does not form a spatial contact with it [45]. In the more closely related rhesus macaque (*Macaca mulatta*), the *JPX* gene is already involved in the activation of *XIST*, although the main role in this process is played by the macaque-specific enhancer [45]. Apparently, in the order Primates, the activator role of *JPX* is strengthened during evolution.

In the order Rodentia, the function of the *Jpx* gene has been studied in mice and voles. Interestingly, in the order Rodentia, the expression pattern of *Jpx* differs, which could indicate different mechanisms of activation of the *Xist* gene. For example, in voles, unlike in mice, the *Jpx* gene is expressed only from the active X chromosome [46], is not spliced, and is transcribed as a single exon of 1.5-2 kb [46, 47]. Such a transcript is present only in voles and has no homologs in other studied rodent species [47]. Finally, the *Jpx* gene in voles is transcribed equally efficiently in both directions [46, 47]. Despite the listed differences in *Jpx* expression between mice and voles, the exact mechanisms of *Xist* regulation in voles require clarification.

In mice, the mechanism of lncRNA *Jpx*-mediated regulation of the *Xist* gene is well studied. Unlike in humans, in mice, transcription of *Xist* is activated by the lncRNA *Jpx*, not by its gene (regulation *in trans*) [48] (Fig. 4b). Knockout of *Jpx* in the female embryonic stem cells negatively affects expression of *Xist* and XCI, impairing differentiation [48]. The effect of knockout is reproduced by the *Jpx* knockdown and is compensated by its ectopic expression [48]. In addition, the efficiency of XCI is proportional to the level of expression of the *Jpx* transgene [49, 50].

A possible explanation for the difference in the mechanisms of XCI initiation between mice and humans may be found in the chromatin organization of this locus, particularly in the different linear distance between the *JPX* gene and the *XIST* promoter [44].

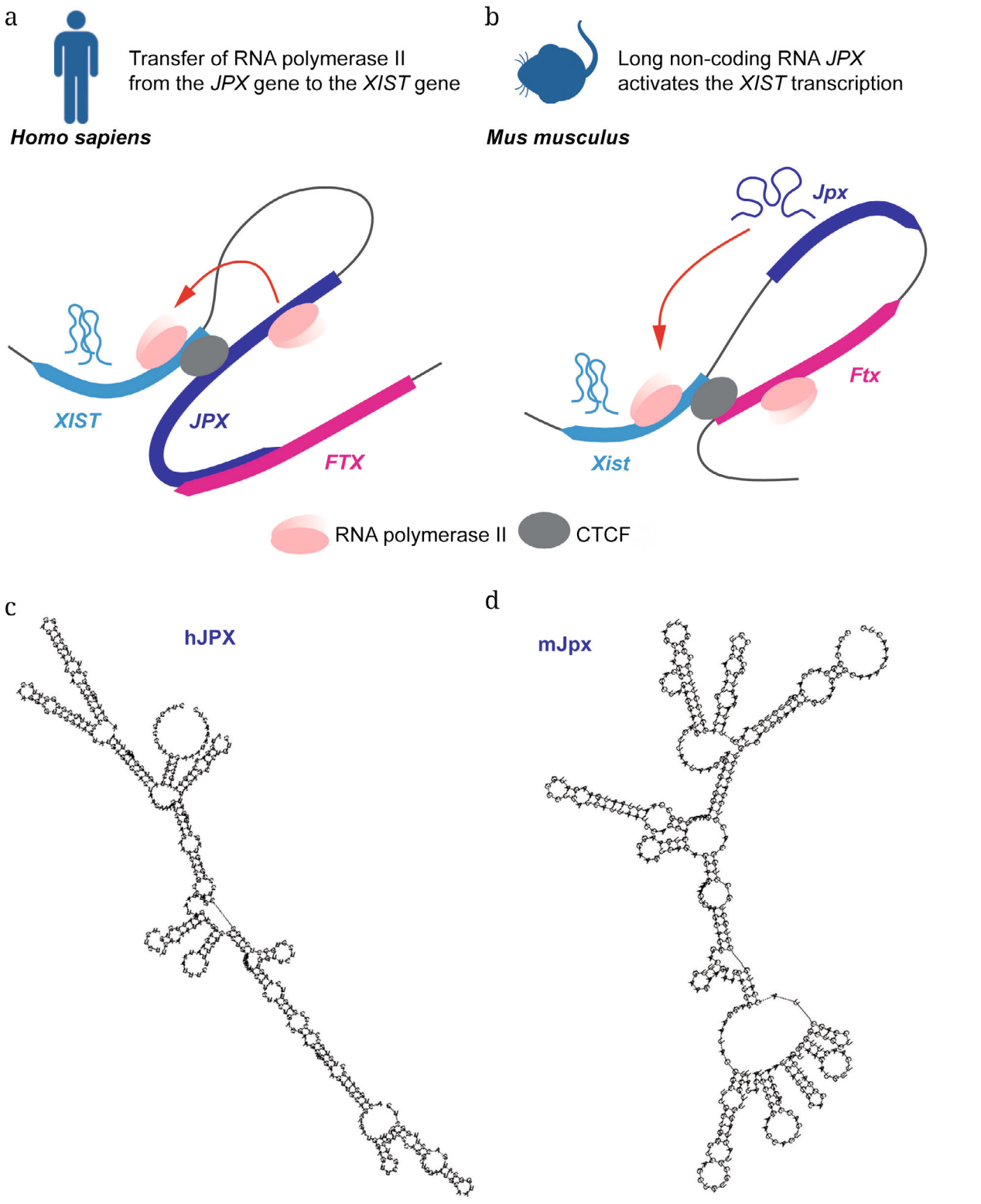

Fig. 4. Regulation of *XIST*/*Xist* gene transcription in humans and mice. a) In humans, the actively transcribed *JPX* gene acts as an enhancer, supplying the RNA polymerase II to the *XIST* gene. The transcript of *JPX* is not important for the activation of *XIST*. b) In mice, the *Jpx* transcript itself plays a key role. Thus, in humans, the *XIST* gene is activated by the *JPX* gene *in cis*, while in mice, *Xist* is activated by the *Jpx* transcript *in trans* (based on [4], with modifications). c) Secondary structure of the fragment of human lncRNA *JPX* (isoform ENST00000602772.5). The image was obtained using the RNAfold Webserver online service (http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi). d) Secondary structure of the fragment of mouse lncRNA *Jpx* (isoform ENSMUST00000181020.11). The image was obtained using the RNAfold Webserver online service (http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi).

In mice, *Jpx* activates *Xist* by displacing from its promoter the CTCF protein, a key and multifaceted regulator of transcription and chromatin architecture [49]. However, it should be noted that at least in the mouse cells, *Jpx* is able to interact with CTCF beyond the X chromosome.

Jpx REGULATES CTCF BINDING ON THE X CHROMOSOME AND BEYOND

The CTCF protein is considered the main architectural protein of chromatin in vertebrates and exhibits high conservation among *Bilateria*. CTCF consists of unstructured terminal regions and a centrally located cluster of 11 C2H2-type zinc fingers; five of these fingers specifically bind to the CTCF binding motif, which is conserved among mammals [51-53]. Knockout of the *Ctcf* gene leads to early embryonic lethality in mice [54-56], indicating the critical importance of this protein for cellular differentiation and embryonic development.

Tens of thousands of CTCF binding sites are located throughout the genome. Acting as a barrier to DNA loop extrusion, CTCF serves as a key moderator of enhancer–promoter communication. On the one hand, by binding near enhancers and promoters, CTCF could facilitate formation of the regulatory chromatin contacts. On the other hand, CTCF acts as an insulator capable of limiting enhancer action and preventing aberrant activation of transcription. For this reason, for some genes, CTCF binding in the promoter region promotes transcription activation, while for others, it promotes transcription repression [57, 58]. CTCF has at least three RNA-binding domains, and its ability to participate in loop formation depends on these domains [59, 60].

In mice, CTCF represses *Xist* expression by binding to its promoter region during the XCI. The mouse lncRNA *Jpx* promotes *Xist* activation by reducing CTCF levels at the promoter by approximately twofold during differentiation [49]. The results of RNA immunoprecipitation (RIP) indicate direct interaction between CTCF and *Jpx*, with the first three exons of *Jpx* playing a key role in the CTCF binding [37, 49]. A model has been proposed in which *Xist* activation is determined by the ratio of *Jpx* and CTCF molecules in the nucleus [49]. In the male cells, which have a single allele of the lncRNA *Jpx* gene, its concentration is insufficient to prevent CTCF binding, which is expressed from the two autosomal alleles. At the same time, in the female cells, both CTCF and *Jpx* are expressed from two alleles, allowing *Jpx* to displace CTCF from the *Xist* promoter, initiating XCI [49].

Jpx is able to bind to CTCF and regulate gene expression beyond the X chromosome. For example, after induction of development in the mouse embryonic stem cells, *Jpx* begins to bind to chromatin throughout the genome, displacing CTCF predominantly from the weak CTCF binding sites at the promoters and enhancers of the genes involved in differentiation [37] (Fig. 5). This *Jpx*-mediated dissociation of CTCF from the weak binding sites leads to the redistribution of cohesin, enhancer–promoter contacts, and changes in the gene expression profile. This also occurs when *Jpx* binds to the CTCF binding site in the *Xist* promoter. Knockdown of *Jpx* restores the CTCF-dependent spatial contact between the *Xist* promoter and *Ftx*, characteristic of undifferentiated embryonic stem cells.

The regulatory role of *Jpx* is not limited to embryonic development. In the hepatocytes isolated from the starved adult mice, the level of CTCF association with chromatin is diminished by twofold, despite the increased level of *Ctcf* gene expression [61]. This decrease is especially evident among the promoters of genes induced under starvation conditions. These include, for example, genes of carbohydrate and lipid anabolism [61]. The observed decrease can be reversed by knockdown of *Jpx* RNA, whose gene also increases expression in the mouse hepatocytes during starvation [61].

In contrast to mice, the effect of human lncRNA *JPX* on CTCF binding to chromatin is less studied. The first three exons of human *JPX* are able to bind CTCF *in vitro*, and its ectopic expression in the mouse cells can partially rescue the effect of *Jpx* knockout [43]. However, presence of *JPX* interaction with CTCF in the living cells remains questionable. In particular, there are conflicting data regarding displacement of CTCF from the *XIST* promoter. On the one hand, *JPX*, secreted by the hepatocellular carcinoma cells in exosomes, can approximately halve the CTCF binding levels at the *Xist* promoter and intensify transcription of the luciferase gene under the *Xist* promoter in HeLa cells transfected with this construct [62]. On the other hand, in the human embryonic stem cells, knockdown of *JPX* does not increase the level of CTCF binding at the *XIST* promoter [44]. The question of the ability of *JPX* to regulate CTCF binding on human autosomes requires further study. However, in addition to CTCF, *JPX* can mediate interactions of many other human proteins with chromatin.

OTHER PROTEIN PARTNERS OF *JPX*

In addition to CTCF, the protein partners of *JPX* in the regulation of gene expression include several transcription activators and repressors.

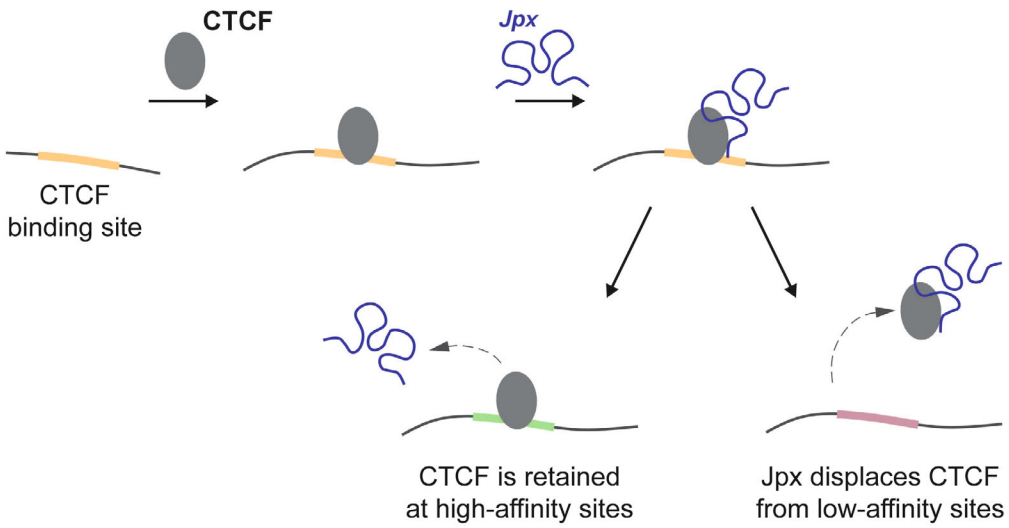

Fig. 5. Regulation of CTCF binding by lncRNA *Jpx*. In mouse cells, lncRNA *Jpx* binds CTCF and promotes its dissociation from the weak binding sites. The strong binding sites retain the ability to bind CTCF. Dissociation of CTCF leads to local genome restructuring (adapted from Oh et al. [37], with modifications).

For example, in the human smooth muscle cells, the lncRNA *JPX* regulates immune response by activating transcription of the interferon cascade genes [63]. Expression of the immune genes positively correlates with the *JPX* expression, which binds in their promoter regions. The RIP results showed that *JPX* directly interacts with the BRD4 and p65 proteins, which are key regulators of these genes. Knockdown of *JPX* significantly reduces binding of BRD4 and p65 to the interferon response genes [63]. These data suggest that *JPX* forms a complex with p65 and BRD4 and recruits them to the immune response genes.

In addition, *JPX* is involved in the recruitment of the SWI/SNF chromatin remodeling complex BRG1. This remodeler binds to hundreds of tissue-specific enhancers and maintains chromatin in an "open" state [64, 65]. In the cultures of human endothelial cells HUVEC, knockdown of *JPX* significantly reduces the level of BRG1 at enhancers and, accordingly, their activity [38]. Thus, *JPX* can activate transcription by recruiting key coactivators and chromatin remodeling complexes.

Furthermore, *JPX* can activate genes by preventing their binding to the repressive Polycomb complexes (PRC1 and PRC2). In the human cardiomyocytes, the EZH2 subunit (H3K27 methyltransferase) of the PRC2 complex co-immunoprecipitates with *JPX* [66]. Knockdown of *JPX* increases the EZH2 recruitment and the level of the H3K27me3 mark (histone H3 methylated at position K27) at the promoter of the *SERCA2A* gene. This gene is actively expressed in cardiomyocytes and is necessary to maintain Ca^{2+} ion concentration in the cytosol [66]. An increase in the Ca^{2+} concentration following *JPX* knockdown leads to apoptosis. Thus, *JPX* promotes cell survival by derepressing vital genes.

In cytoplasm, *JPX* also regulates gene expression at the translational level in at least three ways: by destabilizing translation repressor proteins, regulating chemical modifications of mRNA, and interacting with miRNAs.

For example, adenine methylation at position N6 is recognized by the YTHDF2 protein, which causes degradation of BMP2 mRNA in the human skin melanoma cells [67]. By directly interacting with YTHDF2 and destabilizing it, *JPX* increases synthesis of the BMP2 protein, which is necessary for cell proliferation [67]. The level of YTHDF2 is regulated through proteasomal degradation, from which it is protected by the deubiquitinating protease USP10. Binding of the YTHDF2 protein to *JPX* prevents it from interacting with USP10, which ultimately promotes proteolysis of YTHDF2 and synthesis of the BMP2 protein.

In addition, *JPX* promotes demethylation of N6-methyladenine in the mRNA of phosphoinositide-dependent kinase-1 (PDK1), which is necessary for aerobic glycolysis – the main source of energy in glioblastoma multiforme cells [68]. In these cells, *JPX* binds to the alpha-ketoglutarate-dependent RNA demethylase FTO and recruits it to the PDK1 mRNA. Knockdown of *JPX* negatively affects demethylation of PDK1 mRNA and its interaction with FTO, which negatively affects survival of the glioblastoma multiforme cells [68].

In summary, *JPX* regulates the binding of proteins to chromatin, thereby affecting enhancer-promoter communication and transcription, and interacts with repressor proteins, regulating transcription, or with mRNA-stabilizing proteins, regulating translation (Fig. 6). *JPX* also interacts with miRNAs, thereby regulating key signaling cascades in various human

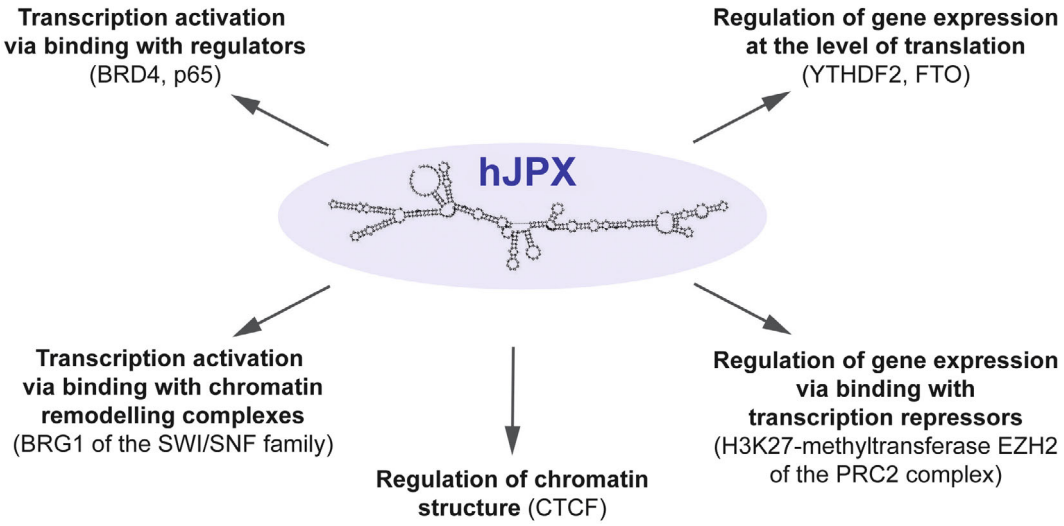

Fig. 6. Mechanisms of gene expression regulation mediated by lncRNA *JPX* (*hJPX*) in humans.

cell types. This aspect of *JPX* biology is of particular interest, as modulation of signaling cascades is often associated with the development of pathologies.

JPX AND miRNAs IN NORMAL PHYSIOLOGY AND PATHOLOGY

miRNAs are a group of small non-coding RNAs with a wide range of functions. miRNAs bind to the 3′-UTR of mRNAs, thereby stimulating their degradation or blocking their binding to ribosomes [69, 70]. lncRNAs can complementarily bind miRNAs and inhibit their action (competing endogenous RNAs, or "miRNA sponges") [71-73]. Acting as a "miRNA sponge," *JPX* enhances translation of the regulated mRNAs.

The expression level of *JPX* is elevated in many types of cancer cells [74], and its artificial overexpression stimulates proliferation of tumor cultures [39, 75, 76] and growth of xenografts *in vivo* [77-79] (Table 1). The expression level of *JPX* negatively correlates with the expression level of some miRNAs, whose ability to interact with *JPX* is confirmed by the RIP data with antibodies against the AGO2 protein [77, 78, 80]. Acting as a "sponge" for miRNAs, *JPX* increases expression of oncogenes [81-83]. Knockdown of *JPX* leads to the significant decrease in survival and proliferative activity of tumor cells both *in vitro* and in mouse models *in vivo* [74, 77, 84]. The effects of knockdown can be partially reproduced using synthetic inhibitors of *JPX* and neutralized using synthetic inhibitors of those miRNAs that interact with *JPX* [78, 80, 84].

There are also examples of non-oncological diseases where *JPX* functions as a competing endogenous RNA in pathogenesis or disease prevention. For example, in a healthy individual, *JPX* facilitates the survival of nucleus pulposus cells of intervertebral discs by binding miR-18a-5p and thus maintaining the level of the HIF-1α protein [85]. Pathological reduction of HIF-1α levels makes human nucleus pulposus cells (HNPC) susceptible to hypoxia and leads to the intervertebral disc degeneration; the original state can be restored by overexpressing *JPX* [85]. Similarly, increasing the expression level of *JPX* promotes the survival of cardiomyocytes in the ischemia-reperfusion syndrome, where *JPX* binds miR-146b and increases the level of the anti-apoptotic protein BAG-1 [86]. Another example is osteoarthritis, characterized by massive apoptosis of chondrocytes due to inflammatory processes. In chondrocytes, under the influence of the inflammatory mediator interleukin-1β, the expression level of *JPX* increases, which binds the miR-25-3p. The target of miR-25-3p in chondrocytes is the mRNA of peptidyl-prolyl isomerase PPID, whose overexpression mediated by the miR-25-3p inactivation stimulates chondrocyte apoptosis [87]. An additional example is allergic rhinitis, where overexpression of *JPX* in the $CD4^+$ cells can disrupt the balance between the progeny of these cells and be one of the causes of this disease. By binding miR-378g, *JPX* increases the level of CCL5, which leads to an imbalance between the populations of Treg and Th17 lymphocytes, differentiating from $CD4^+$ [88].

Thus, by interacting with different miRNAs in populations of various cells, the lncRNA *JPX* could be an important participant in the processes occurring in many types of cancer and other diseases.

CONCLUSION

lncRNAs are key regulators of cellular processes in normal and pathological conditions. The range of processes regulated by the lncRNA *JPX* includes

Table 1. Role of lncRNA *JPX* in oncological diseases

Disease	Cellular material	Role of JPX in pathology development	Effect of JPX knockdown on cells	Regulatory axis	Methods	Effect of JPX *in vivo* (on mouse xenografts)	References
Endometrial carcinoma	material from 32 patients with endometrial cancer; cultures of Ishikawa, JEC, HEC-1A, HEC-1B, RL95-2, AN3 CA, hEEC endometrial carcinoma cells	promotes	inhibits proliferation	miR-140-3p/ PIK3CA	RIP, luciferase test, treatment of cells with *JPX* and miR-140-3p inhibitors, knockdown of *JPX* and PI3KC, overexpression of PI3KC	–	[39]
Intervertebral disc degradation	HNPC (human nucleus pulposus cells)	prevents	–	miR-18a-5p/ HIF-1α/ Hippo-YAP pathway	RIP, luciferase test, treatment of cells with *JPX* and miR-18a-5p inhibitors, knockdown of HIF-1α	–	[85]
Lung cancer	healthy bronchial epithelium (BEAS-2B) and lung adenocarcinoma cells (SPC-A-1, LTEP-a-2, A549, NCI-H1299)	promotes	reduces survival and proliferation; decreases Twist1 level	*JPX*/ miR-33a-5p/ Twist1	luciferase test, overexpression of *JPX* and miR-33a-5p	overexpression of *JPX* promotes tumor growth and metastasis	[74]
Head and neck squamous cell carcinoma	CAL27 (human head and neck squamous cell carcinoma cells); tumor samples from 12 patients	promotes	reduces survival and proliferation; stimulates expression of miR-193b-3p and inhibits expression of PLAU	miR-193b-3p/ PLAU	knockdown of *JPX*, overexpression of *JPX* and miR-193b	–	[75]
Non-small cell lung cancer	55 samples from patients; cultures of non-small cell lung cancer cells A549, H1299, H292, H460, SPCA-1, healthy bronchial epithelial cells 16HBE	promotes	reduces proliferation, but does not affect apoptosis	miR-145-5p/ CCND2	RIP, luciferase test, treatment of cells with miR-145-5p inhibitor	knockdown of *JPX* significantly reduced xenograft size	[77]

Table 1 (*cont.*)

Disease	Cellular material	Role of JPX in pathology development	Effect of JPX knockdown on cells	Regulatory axis	Methods	Effect of JPX *in vivo* (on mouse xenografts)	References
Gastric cancer	tumor samples from 32 patients; cultures of gastric cancer cells NCI-N87 and MKN-45 and healthy gastric mucosal cells GES-1	promotes	reduces survival and migration, increases miR-197 level	miR-197/ CXCR6	Beclin1	luciferase test, knockdown of *JPX*, overexpression of Beclin 1, CXCR6 and miR-197 mimics	–
Oral squamous cell carcinoma	cultures of oral squamous cell carcinoma cells (SCC-15, SCC-25, HSC-2, SCC-9) and healthy oral keratinocytes (NOK)	promotes	reduces survival, migration, and proliferation, stimulates apoptosis	miR-944/ CDH2	RIP, luciferase test, overexpression of CDH2 and miR-944, treatment of cells with miR-944 inhibitor	–	[80]
Breast cancer	tumor samples and adjacent tissues from 39 patients	promotes	reduces survival, migration, and proliferation, stimulates apoptosis	miR-25-3p/ SOX4	RIP, luciferase test, overexpression of *JPX*, CDH2 and miR-25-3p, treatment of cells with miR-945 inhibitor	knockdown of *JPX* significantly reduced the size and growth rate of xenografts. The effect could be reversed with a miR-945 inhibitor	[78]
Allergic rhinitis	$CD4^+$ cell samples from healthy individuals and patients with allergic rhinitis	promotes	reduces survival, migration, and proliferation, stimulates apoptosis	miR-378g/ CCL5	RIP, luciferase test, overexpression of *JPX*, CDH2 and miR-25-3p, treatment of cells with miR-946 inhibitor	–	[88]
Osteoarthritis	tissue samples from 20 patients with osteoarthritis and 16 healthy individuals; chondrocyte culture C28/I2	promotes	protects chondrocytes from IL-β-induced damage	miR-25-3p/ PPID	RIP, luciferase test, overexpression of PPID, treatment of cells with miR-25-3p inhibitor	–	[87]

Table 1 (*cont.*)

Disease	Cellular material	Role of JPX in pathology development	Effect of JPX knockdown on cells	Regulatory axis	Methods	Effect of JPX *in vivo* (on mouse xenografts)	References
Osteosarcoma	tumor samples and adjacent tissues from 20 patients; cultures of hFOB1.19 cells (healthy osteoblast model), SAOS-2 and U2OS (osteosarcoma models)	promotes	reduces migration and proliferation of osteosarcoma cells	miR-33a-5p/ PNMA1	RIP, luciferase test, overexpression of miR-33a-5p, treatment of cells with miR-33a-5p inhibitor	–	[84]
Esophageal squamous cell carcinoma	tumor samples and adjacent tissues from 21 patients; cultures of healthy esophageal epithelium Het-1A and esophageal squamous cell carcinoma cells (KYSE150, KYSE450, Eca109, EC9706)	promotes	reduces proliferation of esophageal squamous cell carcinoma cells	miR-516b-5p/ VEGFA	RIP, luciferase test, overexpression of miR-516b-5p and *JPX*	knockdown of *JPX* significantly reduced the size and growth rate of xenografts, while overexpression of *JPX* had the opposite effect	[79]
Apoptosis of cardiomyocytes during ischemia-reperfusion	HL-1 cardiomyocytes	prevents	–	miR-146b	luciferase test, knockdown of *JPX*, inhibition of *JPX*, overexpression of *JPX*	–	[86]
Lung cancer	human A549 cells (lung adenocarcinoma) as a culture and as 3D spheroids	promotes	–	miR-378a-3p/ GLUT1|NRP1| YY1|Wnt5a	luciferase test, overexpression of *JPX*	–	[83]

Note. Based on the data from [82, 83].

enhancer-promoter communication, transcription, translation, and many key signaling cascades.

In mouse cells, *Jpx* affects chromatin architecture by displacing CTCF from DNA. Although human *JPX* is also able to bind CTCF *in vitro*, the question of the ability of this RNA to interact with CTCF *in vivo* and regulate chromatin architecture remains open. Comparative studies are needed to clarify the role of *Jpx* in the regulation of chromatin architecture in other placental mammals.

In addition to CTCF, in human cells, *JPX* regulates the binding of many proteins to chromatin. This allows it to influence transcriptional programs and regulate the course of various pathologies. In the future, it would be interesting to analyze the effect of different isoforms of this lncRNA on interactions with proteins, including CTCF. In addition, the mechanisms of recruitment of *JPX* itself to the regulated genes also remain unstudied.

Current data suggest that *JPX* is not only a fundamental element in maintaining cellular homeostasis but also a promising target for the therapy of various diseases. In oncology, *JPX* is considered a potential biomarker and target for molecular tools [62, 89-96] aimed at inhibiting its interactions with miRNAs to reduce tumor cell proliferation. In non-oncological pathologies, *JPX* can be used to correct disorders in the expression of key proteins involved in cell survival and function. To develop appropriate strategies, more *in vivo* experiments are needed to confirm the results obtained in cell cultures. In addition, although *JPX* appears to be a promising regulator of non-oncological diseases, the question of changes in its expression level in such diseases remains open [85, 87].

In conclusion, studies of *JPX* and other lncRNAs open new horizons in understanding molecular mechanisms of genome regulation. *JPX* serves as an example of how the non-coding RNAs could integrate signals at different levels, becoming key players in the pathogenesis of diseases and promising therapeutic targets. Further study of *JPX* will not only deepen our understanding of fundamental processes of cellular regulation but also could help to develop new approaches to diagnosis and therapy of a wide range of pathologies.

Abbreviations

lncRNA	long non-coding RNA
MGE	mobile genetic elements
JPX	just proximal to *XIST*, primate lncRNA
Jpx	rodent lncRNA
RIP	RNA immunoprecipitation
sORF	short open reading frame
XCI	X chromosome inactivation
XIC	X chromosome inactivation center

Contributions

A. V. Selivanovskiy – literature analysis, writing and editing the article text; A. L. Sivkina – problem formulation, writing and editing the article text, figure preparation; S. V. Ulianov – editing the article text; S. V. Razin – editing the article text.

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Ethics approval and consent to participate

This work does not contain any studies involving human and animal subjects.

Conflict of interest

The authors of this work declare that they have no conflicts of interest.

REFERENCES

1. Palihati, M., and Saitoh, N. (2024) RNA in chromatin organization and nuclear architecture, *Curr. Opin. Genet. Dev.*, **86**, 102176, https://doi.org/10.1016/j.gde.2024.102176.
2. Liang, W.-W., Müller, S., Hart, S. K., Wessels, H.-H., Méndez-Mancilla, A., Sookdeo, A., Choi, O., Caragine, C. M., Corman, A., Lu, L., Kolumba, O., Williams, B., and Sanjana, N. E. (2024) Transcriptome-scale RNA-targeting CRISPR screens reveal essential lncRNAs in human cells, *Cell*, **187**, 7637-7654.e29, https://doi.org/10.1016/j.cell.2024.10.021.
3. Statello, L., Guo, C.-J., Chen, L.-L., and Huarte, M. (2021) Gene regulation by long non-coding RNAs and its biological functions, *Nat. Rev. Mol. Cell Biol.*, **22**, 96-118, https://doi.org/10.1038/s41580-020-00315-9.
4. Ferrer, J., and Dimitrova, N. (2024) Transcription regulation by long non-coding RNAs: mechanisms and disease relevance, *Nat. Rev. Mol. Cell Biol.*, **25**, 396-415, https://doi.org/10.1038/s41580-023-00694-9.
5. Mattick, J. S., Amaral, P. P., Carninci, P., Carpenter, S., Chang, H. Y., Chen, L.-L., Chen, R., Dean, C., Dinger, M. E., Fitzgerald, K. A., Gingeras, T. R., Guttman, M., Hirose, T., Huarte, M., Johnson, R., Kanduri, C., Kapranov, P., Lawrence, J. B., Lee, J. T., Mendell, J. T., Mercer, T. R., Moore, K. J., Nakagawa, S., Rinn, J. L., Spector, D. L., Ulitsky, I., Wan, Y., Wilusz, J. E., and Wu, M. (2023) Long non-coding RNAs: definitions, functions, challenges and recommendations, *Nat. Rev. Mol. Cell Biol.*, **24**, 430-447, https://doi.org/10.1038/s41580-022-00566-8.
6. Ghafouri-Fard, S., and Taheri, M. (2019) *Nuclear Enriched Abundant Transcript 1 (NEAT1)*: a long

non-coding RNA with diverse functions in tumorigenesis, *Biomed. Pharmacother.*, **111**, 51-59, https://doi.org/10.1016/j.biopha.2018.12.070.
7. Arun, G., Aggarwal, D., and Spector, D. L. (2020) MALAT1 long non-coding RNA: functional implications, *Non-Coding RNA*, **6**, 22, https://doi.org/10.3390/ncrna6020022.
8. Nojima, T., and Proudfoot, N. J. (2022) Mechanisms of lncRNA biogenesis as revealed by nascent transcriptomics, *Nat. Rev. Mol. Cell Biol.*, **23**, 389-406, https://doi.org/10.1038/s41580-021-00447-6.
9. Chen, L.-L., and Kim, V. N. (2024) Small and long non-coding RNAs: past, present, and future, *Cell*, **187**, 6451-6485, https://doi.org/10.1016/j.cell.2024.10.024.
10. Deveson, I. W., Brunck, M. E., Blackburn, J., Tseng, E., Hon, T., Clark, T. A., Clark, M. B., Crawford, J., Dinger, M. E., Nielsen, L. K., Mattick, J. S., and Mercer, T. R. (2018) Universal alternative splicing of noncoding exons, *Cell Syst.*, **6**, 245-255.e5, https://doi.org/10.1016/j.cels.2017.12.005.
11. Jégu, T., Blum, R., Cochrane, J. C., Yang, L., Wang, C.-Y., Gilles, M.-E., Colognori, D., Szanto, A., Marr, S. K., Kingston, R. E., and Lee, J. T. (2019) Xist RNA antagonizes the SWI/SNF chromatin remodeler BRG1 on the inactive X chromosome, *Nat. Struct. Mol. Biol.*, **26**, 96-109, https://doi.org/10.1038/s41594-018-0176-8.
12. Chu, H.-P., Cifuentes-Rojas, C., Kesner, B., Aeby, E., Lee, H., Wei, C., Oh, H. J., Boukhali, M., Haas, W., and Lee, J. T. (2017) TERRA RNA antagonizes ATRX and protects telomeres, *Cell*, **170**, 86-101.e16, https://doi.org/10.1016/j.cell.2017.06.017.
13. Daneshvar, K., Ardehali, M. B., Klein, I. A., Hsieh, F.-K., Kratkiewicz, A. J., Mahpour, A., Cancelliere, S. O. L., Zhou, C., Cook, B. M., Li, W., Pondick, J. V., Gupta, S. K., Moran, S. P., Young, R. A., Kingston, R. E., and Mullen, A. C. (2020) lncRNA DIGIT and BRD3 protein form phase-separated condensates to regulate endoderm differentiation, *Nat. Cell Biol.*, **22**, 1211-1222, https://doi.org/10.1038/s41556-020-0572-2.
14. Beltran, M., Tavares, M., Justin, N., Khandelwal, G., Ambrose, J., Foster, B. M., Worlock, K. B., Tvardovskiy, A., Kunzelmann, S., Herrero, J., Bartke, T., Gamblin, S. J., Wilson, J. R., and Jenner, R. G. (2019) G-tract RNA removes Polycomb repressive complex 2 from genes, *Nat. Struct. Mol. Biol.*, **26**, 899-909, https://doi.org/10.1038/s41594-019-0293-z.
15. Tsagakis, I., Douka, K., Birds, I., and Aspden, J. L. (2020) Long non-coding RNAs in development and disease: conservation to mechanisms, *J. Pathol.*, **250**, 480-495, https://doi.org/10.1002/path.5405.
16. Islam, Z., Saravanan, B., Walavalkar, K., Farooq, U., Singh, A. K., Radhakrishnan, S., Thakur, J., Pandit, A., Henikoff, S., and Notani, D. (2023) Active enhancers strengthen insulation by RNA-mediated CTCF binding at chromatin domain boundaries, *Genome Res.*, **33**, 1-17, https://doi.org/10.1101/gr.276643.122.
17. Ren, C., Han, H., Pan, J., Chang, Q., Wang, W., Guo, X., and Bian, J. (2022) DLGAP1-AS2 promotes human colorectal cancer progression through trans-activation of Myc, *Mamm. Genome*, **33**, 672-683, https://doi.org/10.1007/s00335-022-09963-y.
18. Tsai, P.-F., Dell'Orso, S., Rodriguez, J., Vivanco, K. O., Ko, K.-D., Jiang, K., Juan, A. H., Sarshad, A. A., Vian, L., Tran, M., Wangsa, D., Wang, A. H., Perovanovic, J., Anastasakis, D., Ralston, E., Ried, T., Sun, H.-W., Hafner, M., Larson, D. R., and Sartorelli, V. (2018) A muscle-specific enhancer RNA mediates cohesin recruitment and regulates transcription in *trans*, *Mol. Cell*, **71**, 129-141.e8, https://doi.org/10.1016/j.molcel.2018.06.008.
19. Abdalla, M. O. A., Yamamoto, T., Maehara, K., Nogami, J., Ohkawa, Y., Miura, H., Poonperm, R., Hiratani, I., Nakayama, H., Nakao, M., and Saitoh, N. (2019) The Eleanor ncRNAs activate the topological domain of the ESR1 locus to balance against apoptosis, *Nat. Commun.*, **10**, 3778, https://doi.org/10.1038/s41467-019-11378-4.
20. Yeo, S. J., Ying, C., Fullwood, M. J., and Tergaonkar, V. (2023) Emerging regulatory mechanisms of non-coding RNAs in topologically associating domains, *Trends Genet.*, **39**, 217-232, https://doi.org/10.1016/j.tig.2022.12.003.
21. Quinodoz, S. A., Jachowicz, J. W., Bhat, P., Ollikainen, N., Banerjee, A. K., Goronzy, I. N., Blanco, M. R., Chovanec, P., Chow, A., Markaki, Y., Thai, J., Plath, K., and Guttman, M. (2021) RNA promotes the formation of spatial compartments in the nucleus, *Cell*, **184**, 5775-5790.e30, https://doi.org/10.1016/j.cell.2021.10.014.
22. Loda, A., Collombet, S., and Heard, E. (2022) Gene regulation in time and space during X-chromosome inactivation, *Nat. Rev. Mol. Cell Biol.*, **23**, 231-249, https://doi.org/10.1038/s41580-021-00438-7.
23. Winkler, L., Jimenez, M., Zimmer, J. T., Williams, A., Simon, M. D., and Dimitrova, N. (2022) Functional elements of the cis-regulatory lincRNA-p21, *Cell Rep.*, **39**, 110687, https://doi.org/10.1016/j.celrep.2022.110687.
24. Engreitz, J. M., Haines, J. E., Perez, E. M., Munson, G., Chen, J., Kane, M., McDonel, P. E., Guttman, M., and Lander, E. S. (2016) Local regulation of gene expression by lncRNA promoters, transcription and splicing, *Nature*, **539**, 452-455, https://doi.org/10.1038/nature20149.
25. Gil, N., Perry, R. B.-T., Mukamel, Z., Tuck, A., Bühler, M., and Ulitsky, I. (2023) Complex regulation of Eomes levels mediated through distinct functional features of the Meteor long non-coding RNA locus, *Cell Rep.*, **42**, 112569, https://doi.org/10.1016/j.celrep.2023.112569.
26. Carrieri, C., Cimatti, L., Biagioli, M., Beugnet, A., Zucchelli, S., Fedele, S., Pesce, E., Ferrer, I., Collavin, L., Santoro, C., Forrest, A. R. R., Carninci, P., Biffo, S.,

Stupka, E., and Gustincich, S. (2012) Long non-coding antisense RNA controls *Uchl1* translation through an embedded SINEB2 repeat, *Nature*, **491**, 454-457, https://doi.org/10.1038/nature11508.

27. Schein, A., Zucchelli, S., Kauppinen, S., Gustincich, S., and Carninci, P. (2016) Identification of antisense long noncoding RNAs that function as SINEUPs in human cells, *Sci. Rep.*, **6**, 33605, https://doi.org/10.1038/srep33605.
28. Cesana, M., Cacchiarelli, D., Legnini, I., Santini, T., Sthandier, O., Chinappi, M., Tramontano, A., and Bozzoni, I. (2011) A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA, *Cell*, **147**, 358-369, https://doi.org/10.1016/j.cell.2011.09.028.
29. Grelet, S., Link, L. A., Howley, B., Obellianne, C., Palanisamy, V., Gangaraju, V. K., Diehl, J. A., and Howe, P. H. (2017) A regulated PNUTS mRNA to lncRNA splice switch mediates EMT and tumour progression, *Nat. Cell Biol.*, **19**, 1105-1115, https://doi.org/10.1038/ncb3595.
30. Wang, Y., Xu, Z., Jiang, J., Xu, C., Kang, J., Xiao, L., Wu, M., Xiong, J., Guo, X., and Liu, H. (2013) Endogenous miRNA sponge lincRNA-RoR regulates Oct4, Nanog, and Sox2 in human embryonic stem cell self-renewal, *Dev. Cell*, **25**, 69-80, https://doi.org/10.1016/j.devcel.2013.03.002.
31. Xia, Q., Shen, J., Wang, Q., Ke, Y., Yan, Q., Li, H., Zhang, D., and Duan, S. (2022) LINC00324 in cancer: Regulatory and therapeutic implications, *Front. Oncol.*, **12**, 1039366, https://doi.org/10.3389/fonc.2022.1039366.
32. Chureau, C., Prissette, M., Bourdet, A., Barbe, V., Cattolico, L., Jones, L., Eggen, A., Avner, P., and Duret, L. (2002) Comparative sequence analysis of the X-inactivation center region in mouse, human, and bovine, *Genome Res.*, **12**, 894-908, https://doi.org/10.1101/gr.152902.
33. Johnston, C. M., Newall, A. E. T., Brockdorff, N., and Nesterova, T. B. (2002) *Enox*, a novel gene that maps 10 kb upstream of *Xist* and partially escapes X inactivation, *Genomics*, **80**, 236-244, https://doi.org/10.1006/geno.2002.6819.
34. Chow, J. C., Hall, L. L., Clemson, C. M., Lawrence, J. B., and Brown, C. J. (2003) Characterization of expression at the human *XIST* locus in somatic, embryonal carcinoma, and transgenic cell lines, *Genomics*, **82**, 309-322, https://doi.org/10.1016/S0888-7543(03)00170-8.
35. Romito, A., and Rougeulle, C. (2011) Origin and evolution of the long non-coding genes in the X-inactivation center, *Biochimie*, **93**, 1935-1942, https://doi.org/10.1016/j.biochi.2011.07.009.
36. Elisaphenko, E. A., Kolesnikov, N. N., Shevchenko, A. I., Rogozin, I. B., Nesterova, T. B., Brockdorff, N., and Zakian, S. M. (2008) A dual origin of the Xist gene from a protein-coding gene and a set of transposable elements, *PLoS One*, **3**, e2521, https://doi.org/10.1371/journal.pone.0002521.
37. Oh, H. J., Aguilar, R., Kesner, B., Lee, H.-G., Kriz, A. J., Chu, H.-P., and Lee, J. T. (2021) RNA regulates CTCF anchor site selection and formation of chromosome loops, *Cell*, **184**, 6157-6173.e24, https://doi.org/10.1016/j.cell.2021.11.012.
38. Oo, J. A., Warwick, T., Pálfi, K., Lam, F., McNicoll, F., Prieto-Garcia, C., Günther, S., Cao, C., Zhou, Y., Gavrilov, A. A., Razin, S. V., Cabrera-Orefice, A., Wittig, I., Pullamsetti, S. S., Kurian, L., Gilsbach, R., Schulz, M. H., Dikic, I., Müller-McNicoll, M., Brandes, R. P., and Leisegang, M. S. (2025) Long non-coding RNAs direct the SWI/SNF complex to cell type-specific enhancers, *Nat. Commun.*, **16**, 131, https://doi.org/10.1038/s41467-024-55539-6.
39. Xiong, H., Zhang, W., Xie, M., Chen, R., Chen, H., and Lin, Q. (2024) Long non-coding RNA JPX promotes endometrial carcinoma progression via janus kinase 2/signal transducer and activator of transcription 3, *Front. Oncol.*, **14**, 1340050, https://doi.org/10.3389/fonc.2024.1340050.
40. Duret, L., Chureau, C., Samain, S., Weissenbach, J., and Avner, P. (2006) The *Xist* RNA gene evolved in eutherians by pseudogenization of a protein-coding gene, *Science*, **312**, 1653-1655, https://doi.org/10.1126/science.1126316.
41. Hezroni, H., Ben-Tov Perry, R., Meir, Z., Housman, G., Lubelsky, Y., and Ulitsky, I. (2017) A subset of conserved mammalian long non-coding RNAs are fossils of ancestral protein-coding genes, *Genome Biol.*, **18**, 162, https://doi.org/10.1186/s13059-017-1293-0.
42. Kolesnikov, N. N., and Elisaphenko, E. A. (2010) Comparative organization and the origin of noncoding regulatory RNA genes from X-chromosome inactivation center of human and mouse, *Russ. J. Genet.*, **46**, 1223-1228, https://doi.org/10.1134/S1022795410100200.
43. Karner, H., Webb, C.-H., Carmona, S., Liu, Y., Lin, B., Erhard, M., Chan, D., Baldi, P., Spitale, R. C., and Sun, S. (2020) Functional conservation of LncRNA *JPX* despite sequence and structural divergence, *J. Mol. Biol.*, **432**, 283-300, https://doi.org/10.1016/j.jmb.2019.09.002.
44. Rosspopoff, O., Cazottes, E., Huret, C., Loda, A., Collier, A. J., Casanova, M., Rugg-Gunn, P. J., Heard, E., Ouimette, J.-F., and Rougeulle, C. (2023) Species-specific regulation of *XIST* by the *JPX/FTX* orthologs, *Nucleic Acids Res.*, **51**, 2177-2194, https://doi.org/10.1093/nar/gkad029.
45. Cazottes, E., Alfeghaly, C., Rognard, C., Loda, A., Castel, G., Villacorta, L., Dong, M., Heard, E., Aksoy, I., Savatier, P., Morey, C., and Rougeulle, C. (2023) Extensive remodelling of *XIST* regulatory networks during primate evolution, *bioRxiv*, https://doi.org/10.1101/2023.12.04.569904.
46. Shevchenko, A. I., Malakhova, A. A., Elisaphenko, E. A., Mazurok, N. A., Nesterova, T. B., Brockdorff, N.,

and Zakian, S. M. (2011) Variability of sequence surrounding the *Xist* gene in rodents suggests taxon-specific regulation of X chromosome inactivation, *PLoS One*, **6**, e22771, https://doi.org/10.1371/journal.pone.0022771.

47. Elisafenko, E. A., Shevchenko, A. I., and Zakiyan, S. M. (2016) Expression profiles of non-coding RNAs in the inactivation center of murid rodents [in Russian], *Genes Cells*, **11**, 82-86, https://doi.org/10.23868/gc120589.
48. Tian, D., Sun, S., and Lee, J. T. (2010) The long noncoding RNA, Jpx, is a molecular switch for X chromosome inactivation, *Cell*, **143**, 390-403, https://doi.org/10.1016/j.cell.2010.09.049.
49. Sun, S., Del Rosario, B. C., Szanto, A., Ogawa, Y., Jeon, Y., and Lee, J. T. (2013) Jpx RNA activates *Xist* by evicting CTCF, *Cell*, **153**, 1537-1551, https://doi.org/10.1016/j.cell.2013.05.028.
50. Carmona, S., Lin, B., Chou, T., Arroyo, K., and Sun, S. (2018) LncRNA *Jpx* induces *Xist* expression in mice using both *trans* and *cis* mechanisms, *PLoS Genet.*, **14**, e1007378, https://doi.org/10.1371/journal.pgen.1007378.
51. Heger, P., Marin, B., Bartkuhn, M., Schierenberg, E., and Wiehe, T. (2012) The chromatin insulator CTCF and the emergence of metazoan diversity, *Proc. Natl. Acad. Sci. USA*, **109**, 17507-17512, https://doi.org/10.1073/pnas.1111941109.
52. Schwalie, P. C., Ward, M. C., Cain, C. E., Faure, A. J., Gilad, Y., Odom, D. T., and Flicek, P. (2013) Co-binding by YY1 identifies the transcriptionally active, highly conserved set of CTCF-bound regions in primate genomes, *Genome Biol.*, **14**, R148, https://doi.org/10.1186/gb-2013-14-12-r148.
53. Liu, F., Wu, D., and Wang, X. (2019) Roles of CTCF in conformation and functions of chromosome, *Semin. Cell Dev. Biol.*, **90**, 168-173, https://doi.org/10.1016/j.semcdb.2018.07.021.
54. Moore, J. M., Rabaia, N. A., Smith, L. E., Fagerlie, S., Gurley, K., Loukinov, D., Disteche, C. M., Collins, S. J., Kemp, C. J., Lobanenkov, V. V., and Filippova, G. N. (2012) Loss of maternal CTCF is associated with peri-implantation lethality of *Ctcf* null embryos, *PloS One*, **7**, e34915, https://doi.org/10.1371/journal.pone.0034915.
55. Heath, H., Ribeiro de Almeida, C., Sleutels, F., Dingjan, G., van de Nobelen, S., Jonkers, I., Ling, K.-W., Gribnau, J., Renkawitz, R., Grosveld, F., Hendriks, R. W., and Galjart, N. (2008) CTCF regulates cell cycle progression of αβ T cells in the thymus, *EMBO J.*, **27**, 2839-2850, https://doi.org/10.1038/emboj.2008.214.
56. Gomez-Velazquez, M., Badia-Careaga, C., Lechuga-Vieco, A. V., Nieto-Arellano, R., Tena, J. J., Rollan, I., Alvarez, A., Torroja, C., Caceres, E. F., Roy, A. R., Galjart, N., Delgado-Olguin, P., Sanchez-Cabo, F., Enriquez, J. A., Gomez-Skarmeta, J. L., and Manzanares, M. (2017) CTCF counter-regulates cardiomyocyte development and maturation programs in the embryonic heart, *PLoS Genet.*, **13**, e1006985, https://doi.org/10.1371/journal.pgen.1006985.
57. Oudelaar, A. M., and Higgs, D. R. (2021) The relationship between genome structure and function, *Nat. Rev. Genet.*, **22**, 154-168, https://doi.org/10.1038/s41576-020-00303-x.
58. Merkenschlager, M., and Nora, E. P. (2016) CTCF and cohesin in genome folding and transcriptional gene regulation, *Annu. Rev. Genomics Hum. Genet.*, **17**, 17-43, https://doi.org/10.1146/annurev-genom-083115-022339.
59. Saldaña-Meyer, R., Rodriguez-Hernaez, J., Escobar, T., Nishana, M., Jácome-López, K., Nora, E. P., Bruneau, B. G., Tsirigos, A., Furlan-Magaril, M., Skok, J., and Reinberg, D. (2019) RNA interactions are essential for CTCF-mediated genome organization, *Mol. Cell*, **76**, 412-422.e5, https://doi.org/10.1016/j.molcel.2019.08.015.
60. Hansen, A. S., Hsieh, T.-H. S., Cattoglio, C., Pustova, I., Saldaña-Meyer, R., Reinberg, D., Darzacq, X., and Tjian, R. (2019) Distinct classes of chromatin loops revealed by deletion of an RNA-binding region in CTCF, *Mol. Cell*, **76**, 395-411.e13, https://doi.org/10.1016/j.molcel.2019.07.039.
61. Sen, D., Maniyadath, B., Chowdhury, S., Kaur, A., Khatri, S., Chakraborty, A., Mehendale, N., Nadagouda, S., Sandra, U. S., Kamat, S. S., and Kolthur-Seetharam, U. (2023) Metabolic regulation of CTCF expression and chromatin association dictates starvation response in mice and flies, *iScience*, **26**, 107128, https://doi.org/10.1016/j.isci.2023.107128.
62. Ma, X., Yuan, T., Yang, C., Wang, Z., Zang, Y., Wu, L., and Zhuang, L. (2017) X-inactive-specific transcript of peripheral blood cells is regulated by exosomal Jpx and acts as a biomarker for female patients with hepatocellular carcinoma, *Ther. Adv. Med. Oncol.*, **9**, 665-677, https://doi.org/10.1177/1758834017731052.
63. Gu, J., Chen, J., Yin, Q., Dong, M., Zhang, Y., Chen, M., Chen, X., Min, J., He, X., Tan, Y., Zheng, L., Jiang, H., Wang, B., Li, X., and Chen, H. (2024) lncRNA JPX-enriched chromatin microenvironment mediates vascular smooth muscle cell senescence and promotes atherosclerosis, *Arterioscler. Thromb. Vasc. Biol.*, **44**, 156-176, https://doi.org/10.1161/ATVBAHA.122.319250.
64. Alver, B. H., Kim, K. H., Lu, P., Wang, X., Manchester, H. E., Wang, W., Haswell, J. R., Park, P. J., and Roberts, C. W. M. (2017) The SWI/SNF chromatin remodelling complex is required for maintenance of lineage specific enhancers, *Nat. Commun.*, **8**, 14648, https://doi.org/10.1038/ncomms14648.
65. Wolf, B. K., Zhao, Y., McCray, A., Hawk, W. H., Deary, L. T., Sugiarto, N. W., LaCroix, I. S., Gerber, S. A.,

Cheng, C., and Wang, X. (2023) Cooperation of chromatin remodeling SWI/SNF complex and pioneer factor AP-1 shapes 3D enhancer landscapes, *Nat. Struct. Mol. Biol.*, **30**, 10-21, https://doi.org/10.1038/s41594-022-00880-x.

66. Bao, J., Zhang, C., Chen, J., Xuan, H., Wang, C., Wang, S., Yin, J., Liu, Y., Li, D., and Xu, T. (2023) LncRNA JPX targets SERCA2a to mitigate myocardial ischemia/reperfusion injury by binding to EZH2, *Exp. Cell Res.*, **427**, 113572, https://doi.org/10.1016/j.yexcr.2023.113572.
67. Luo, D., Tang, H., Tan, L., Zhang, L., Wang, L., Cheng, Q., Lei, X., and Wu, J. (2024) lncRNA *JPX* promotes tumor progression by interacting with and destabilizing YTHDF2 in cutaneous melanoma, *Mol. Cancer Res.*, **22**, 524-537, https://doi.org/10.1158/1541-7786.MCR-23-0701.
68. Li, X. D., Wang, M. J., Zheng, J. L., Wu, Y. H., Wang, X., and Jiang, X. B. (2021) Long noncoding RNA just proximal to X-inactive specific transcript facilitates aerobic glycolysis and temozolomide chemoresistance by promoting stability of PDK1 mRNA in an m6A-dependent manner in glioblastoma multiforme cells, *Cancer Sci.*, **112**, 4543-4552, https://doi.org/10.1111/cas.15072.
69. Shang, R., Lee, S., Senavirathne, G., and Lai, E. C. (2023) microRNAs in action: biogenesis, function and regulation, *Nat. Rev. Genet.*, **24**, 816-833, https://doi.org/10.1038/s41576-023-00611-y.
70. O'Brien, J., Hayder, H., Zayed, Y., and Peng, C. (2018) Overview of MicroRNA biogenesis, mechanisms of actions, and circulation, *Front. Endocrinol.*, **9**, 402, https://doi.org/10.3389/fendo.2018.00402.
71. Agrawal, A., and Vindal, V. (2024) Competing endogenous RNAs in head and neck squamous cell carcinoma: a review, *Brief. Funct. Genomics*, **23**, 335-348, https://doi.org/10.1093/bfgp/elad049.
72. Asadi, M. R., Abed, S., Kouchakali, G., Fattahi, F., Sabaie, H., Moslehian, M. S., Sharifi-Bonab, M., Hussen, B. M., Taheri, M., Ghafouri-Fard, S., and Rezazadeh, M. (2023) Competing endogenous RNA (ceRNA) networks in Parkinson's disease: a systematic review, *Front. Cell. Neurosci.*, **17**, 1044634, https://doi.org/10.3389/fncel.2023.1044634.
73. Xu, J., Xu, J., Liu, X., and Jiang, J. (2022) The role of lncRNA-mediated ceRNA regulatory networks in pancreatic cancer, *Cell Death Discov.*, **8**, 287, https://doi.org/10.1038/s41420-022-01061-x.
74. Pan, J., Fang, S., Tian, H., Zhou, C., Zhao, X., Tian, H., He, J., Shen, W., Meng, X., Jin, X., and Gong, Z. (2020) lncRNA JPX/miR-33a-5p/Twist1 axis regulates tumorigenesis and metastasis of lung cancer by activating Wnt/β-catenin signaling, *Mol. Cancer*, **19**, 9, https://doi.org/10.1186/s12943-020-1133-9.
75. Sun, M., Zhan, N., Yang, Z., Zhang, X., Zhang, J., Peng, L., Luo, Y., Lin, L., Lou, Y., You, D., Qiu, T., Liu, Z., Wang, Q., Liu, Y., Sun, P., Yu, M., and Wang, H. (2024) Cuproptosis-related lncRNA JPX regulates malignant cell behavior and epithelial-immune interaction in head and neck squamous cell carcinoma via miR-193b-3p/PLAU axis, *Int. J. Oral Sci.*, **16**, 63, https://doi.org/10.1038/s41368-024-00314-y.
76. Han, X., and Liu, Z. (2021) Long non-coding RNA JPX promotes gastric cancer progression by regulating CXCR6 and autophagy via inhibiting miR-197, *Mol. Med. Rep.*, **23**, 60, https://doi.org/10.3892/mmr.2020.11698.
77. Jin, M., Ren, J., Luo, M., You, Z., Fang, Y., Han, Y., Li, G., and Liu, H. (2020) Long non-coding RNA *JPX* correlates with poor prognosis and tumor progression in non-small-cell lung cancer by interacting with miR-145-5p and *CCND2*, *Carcinogenesis*, **41**, 634-645, https://doi.org/10.1093/carcin/bgz125.
78. Chen, X., Yang, J., and Wang, Y. (2020) LncRNA JPX promotes cervical cancer progression by modulating miR-25-3p/SOX4 axis, *Cancer Cell Int.*, **20**, 441, https://doi.org/10.1186/s12935-020-01486-3.
79. He, Y., Hua, R., Yang, Y., Li, B., Guo, X., and Li, Z. (2022) LncRNA JPX promotes esophageal squamous cell carcinoma progression by targeting miR-516b-5p/VEGFA axis, *Cancers*, **14**, 2713, https://doi.org/10.3390/cancers14112713.
80. Yao, Y., Chen, S., Lu, N., Yin, Y., and Liu, Z. (2021) LncRNA JPX overexpressed in oral squamous cell carcinoma drives malignancy via miR-944/CDH2 axis, *Oral Dis.*, **27**, 924-933, https://doi.org/10.1111/odi.13626.
81. Kuang, Y., Shen, W., Zhu, H., Huang, H., Zhou, Q., Yin, W., Zhou, Y., Cao, Y., Wang, L., Li, X., Ren, C., and Jiang, X. (2022) The role of lncRNA just proximal to XIST (JPX) in human disease phenotypes and RNA methylation: the novel biomarker and therapeutic target potential, *Biomed. Pharmacother.*, **155**, 113753, https://doi.org/10.1016/j.biopha.2022.113753.
82. Wang, Y., Bai, H., Jiang, M., Zhou, C., and Gong, Z. (2023) Emerging role of long non-coding RNA JPX in malignant processes and potential applications in cancers, *Chin. Med. J. (Engl.)*, **136**, 757-766, https://doi.org/10.1097/CM9.0000000000002392.
83. Mosca, N., Pezzullo, M., De Leo, I., Truda, A., Marchese, G., Russo, A., and Potenza, N. (2024) A novel ceRNET relying on the lncRNA JPX, miR-378a-3p, and its mRNA targets in lung cancer, *Cancers*, **16**, 1526, https://doi.org/10.3390/cancers16081526.
84. Xiong, W., Liu, D., Chen, X., Liu, L., and Xiao, W. (2022) lncRNA JPX modulates malignant progress of osteosarcoma through targeting miR-33a-5p and PNMA1 regulatory loop, *Transl. Oncol.*, **25**, 101504, https://doi.org/10.1016/j.tranon.2022.101504.
85. Yang, H., Wang, G., Liu, J., Lin, M., Chen, J., Fang, Y., Li, Y., Cai, W., and Zhan, D. (2021) LncRNA JPX regulates proliferation and apoptosis of nucleus pulposus cells by targeting the miR-18a-5p/HIF-1α/Hippo-YAP

pathway, *Biochem. Biophys. Res. Commun.*, **566**, 16-23, https://doi.org/10.1016/j.bbrc.2021.05.075.
86. Xu, T., Zhang, Y., Liao, G., Xuan, H., Yin, J., Bao, J., Liu, Y., and Li, D. (2023) Luteolin pretreatment ameliorates myocardial ischemia/reperfusion injury by lncRNA-JPX/miR-146b axis, *Anal. Cell. Pathol. Amst.*, **2023**, 4500810, https://doi.org/10.1155/2023/4500810.
87. Ren, Z., Tang, L., Ding, Z., Song, J., Zheng, H., and Li, D. (2022) Knockdown of lncRNA JPX suppresses IL-1β-stimulated injury in chondrocytes through modulating an miR-25-3p/PPID axis, *Oncol. Lett.*, **24**, 388, https://doi.org/10.3892/ol.2022.13508.
88. Chen, Z., Ke, X., Wang, X., Kang, H., and Hong, S. (2022) LncRNA JPX contributes to Treg/Th17 imbalance in allergic rhinitis *via* targeting the miR-378g/CCL5 axis, *Immunopharmacol. Immunotoxicol.*, **44**, 519-524, https://doi.org/10.1080/08923973.2022.2055566.
89. Xing, Y., Wen, X., Ding, X., Fan, J., Chai, P., Jia, R., Ge, S., Qian, G., Zhang, H., and Fan, X. (2017) *CANT1* lncRNA triggers efficient therapeutic efficacy by correcting aberrant lncing cascade in malignant uveal melanoma, *Mol. Ther.*, **25**, 1209-1221, https://doi.org/10.1016/j.ymthe.2017.02.016.
90. Dahariya, S., Raghuwanshi, S., Sangeeth, A., Malleswarapu, M., Kandi, R., and Gutti, R. K. (2021) Megakaryoblastic leukemia: a study on novel role of clinically significant long non-coding RNA signatures in megakaryocyte development during treatment with phorbol ester, *Cancer Immunol. Immunother.*, **70**, 3477-3488, https://doi.org/10.1007/s00262-021-02937-0.
91. Ma, W., Wang, H., Jing, W., Zhou, F., Chang, L., Hong, Z., Liu, H., Liu, Z., and Yuan, Y. (2017) Downregulation of long non-coding RNAs JPX and XIST is associated with the prognosis of hepatocellular carcinoma, *Clin. Res. Hepatol. Gastroenterol.*, **41**, 163-170, https://doi.org/10.1016/j.clinre.2016.09.002.
92. Lin, X., Huang, Z., Chen, X., Wu, F., and Wu, W. (2018) XIST induced by JPX suppresses hepatocellular carcinoma by sponging miR-155-5p, *Yonsei Med. J.*, **59**, 816-826, https://doi.org/10.3349/ymj.2018.59.7.816.
93. Sajjadi, R. S., Modarressi, M. H., and Tabatabaiefar, M. A. (2021) JPX and LINC00641 ncRNAs expression in prostate tissue: a case-control study, *Res. Pharm. Sci.*, **16**, 493-504, https://doi.org/10.4103/1735-5362.323916.
94. Huang, Y.-S., Chang, C.-C., Lee, S.-S., Jou, Y.-S., and Shih, H.-M. (2016) *Xist* reduction in breast cancer upregulates AKT phosphorylation via HDAC3-mediated repression of PHLPP1 expression, *Oncotarget*, **7**, 43256-43266, https://doi.org/10.18632/oncotarget.9673.
95. Li, J., Feng, L., Tian, C., Tang, Y.-L., Tang, Y., and Hu, F.-Q. (2018) Long noncoding RNA-JPX predicts the poor prognosis of ovarian cancer patients and promotes tumor cell proliferation, invasion and migration by the PI3K/Akt/mTOR signaling pathway, *Eur. Rev. Med. Pharmacol. Sci.*, **22**, 8135-8144, https://doi.org/10.26355/eurrev_201812_16505.
96. Gál, Z., Gézsi, A., Semsei, Á. F., Nagy, A., Sultész, M., Csoma, Z., Tamási, L., Gálffy, G., and Szalai, C. (2020) Investigation of circulating lncRNAs as potential biomarkers in chronic respiratory diseases, *J. Transl. Med.*, **18**, 422, https://doi.org/10.1186/s12967-020-02581-9.