



Review Article

# Unraveling the dark matter, long non-coding RNAs, in male reproductive diseases: A narrative review

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## Abstract

Recent advances in human transcriptome have revealed the fundamental and functional roles of long non-coding RNA in the susceptibility to diverse diseases and pathological conditions. They participate in wide range of biological processes such as the modulating of chromatin structure, transcription, translation, and post-translation modification. In addition, based on their unique expression profiles and their association with clinical abnormalities such as those of related to male reproductive diseases, they can be used to develop therapeutic methods and biomarkers for screening of the diseases. In this study, we will review the identified lncRNAs and their molecular functions in the pathogenesis of male reproductive diseases such as prostate cancer, benign prostatic hyperplasia, prostatitis, testicular cancer, varicocele, and sperm abnormalities.

**Key words:** Long noncoding RNA, Prostate cancer, Prostatic hyperplasia, Prostatitis, Varicocele, Sperm abnormalities.



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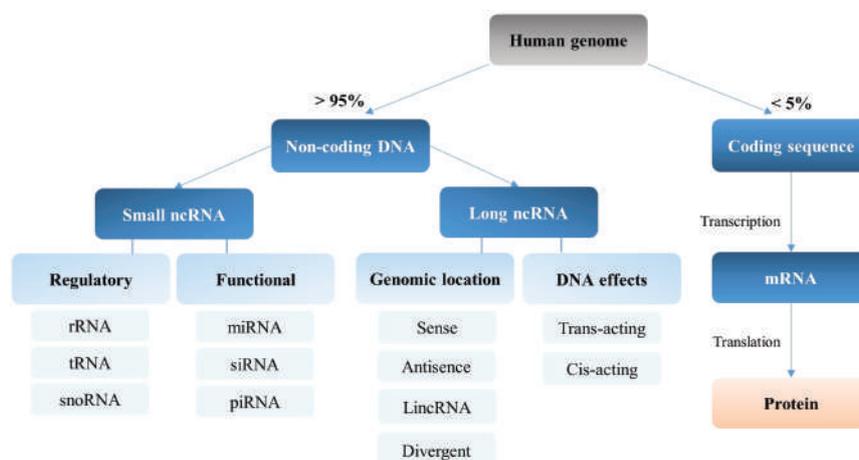
## 1. Introduction

The prevalence of infertility is 15% worldwide, and according to the global data, 20-70% of the total infertility cases is attributed to male infertility (1). Male infertility is characterized by heterogeneous and multifactorial conditions among which genetics factors encompass approximately 40% of cases with idiopathic infertility (2). The most common clinical abnormalities associated with male infertility are prostate cancer (PCa), prostatitis, benign prostatic hyperplasia (BPH), testicular cancer (TCa), varicocele, and inability to produce normal sperm (azoospermia, oligozoospermia, asthenozoospermia (AZS), and teratozoospermia). Although the main molecular mechanisms involved in the pathogenesis of these abnormalities are unknown, all of them have genetic background (3-6).

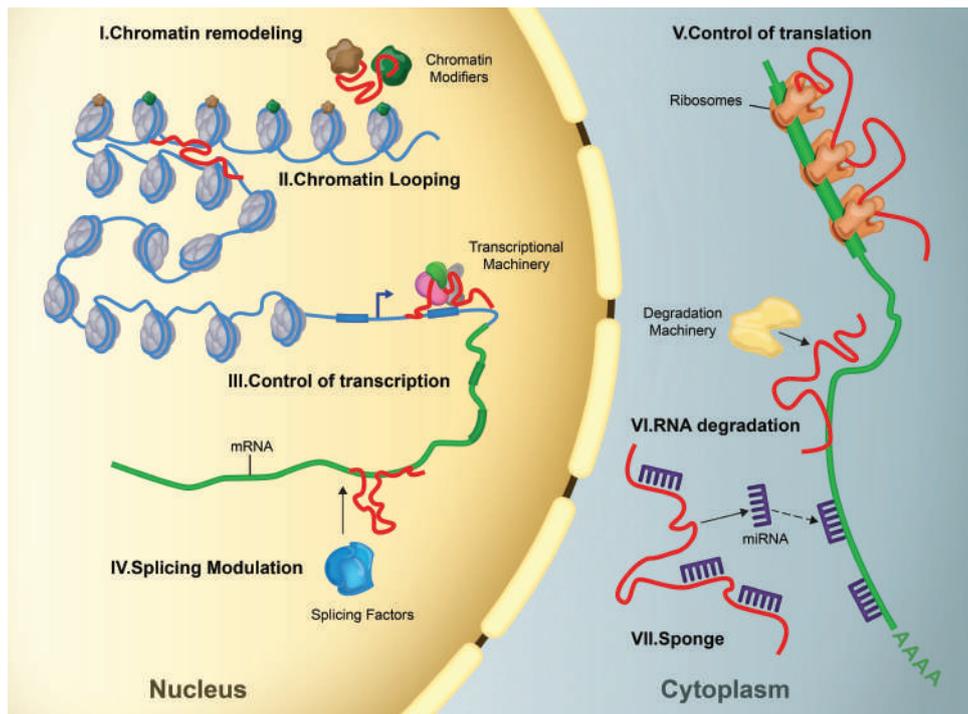
While more than 85% of the human genome is transcribed, only a low proportion of these transcribed RNAs encode proteins (7). Non-coding RNAs (ncRNAs) are categorized into two broad groups based on their size. Short ncRNAs are < 200 nucleotides (nts) in length and include microRNAs (miRNAs), piwi-interacting RNAs (piRNAs), and small nuclear RNAs (snoRNA) (8), while long ncRNAs (lncRNAs) are > 200 nts in length (Figure 1). lncRNAs are involved in several mechanisms such as chromatin remodeling, chromatin looping, recruitment of transcription factors. They can also be involved in RNA splicing and control of translation. Furthermore, they can also modulate

RNA degradation as well as act as a miRNA sponge and sequester them to control gene expression (Figure 2) (9).

The gene regulatory process can occur at any stage such as RNA transcription, translation, and post-translational modification. This process includes DNA methylation, histone modification (methylation, phosphorylation, ubiquitylation, acetylation, and sumoylation) and tissue-specific transcription factors (TFs) (10, 11). In addition, ncRNAs have also been identified as prominent regulatory elements in gene expression (12). The dark matter of the genome, lncRNAs, was previously considered as transcriptional noise (13). However, advances in genomic technologies such as high-throughput sequencing technologies have led to the identification of thousands of lncRNA in different diseases including male reproductive ones. lncRNAs are involved in differentiation, proliferation, and self-renewal of spermatogonial stem cells (SSCs) (14). Furthermore, they modulate apoptosis, invasion, cell cycle, and cell signaling pathways in the male reproductive tract. Therefore, lncRNAs could be considered as a potential biomarker to detect any abnormalities in male reproductive tract. In this review, we will provide a short summary about the role of lncRNAs and their pathways in the pathogenesis of male reproductive-associated diseases such as PCa, prostatitis, BPH, TCa, varicocele, and sperm abnormalities (azoospermia, oligozoospermia, asthenozoospermia, and teratozoospermia).



**Figure 1.** The components of the human genome. Less than 5% of the genome consists of coding sequences, which can ultimately be translated to proteins. More than 95% of genome encompasses non-coding DNA, which is transcribed into two broad groups including small ncRNA and lncRNA. Small ncRNAs are categorized into regulatory (rRNA: 121-5070 nts, tRNA: 73-93nts, snoRNA: 70-200 nts) and functional RNAs (miRNA: 21-25 nts, siRNA: 20-25 nts, piRNA: 24-31 nts). lncRNAs can act as cis-acting lncRNA (affect nearby genes in same chromosome) or trans-acting lncRNA (affect distant gene on other chromosomes). lncRNA can originate from sense, antisense strand, intergenic (lincRNA), and opposite direction to nearby protein (divergent).



**Figure 2.** Functions of lncRNAs, (I) lncRNAs (in red) recruit chromatin modifiers such as activator (brown) or repressive (green) Histon remarks to change chromatin organizational pattern. (II) They can act as a structure to create chromatin looping through which, cis-regulatory sequences such as enhancers and silencers interact with target promoters. (III) lncRNAs control transcription by interacting with transcriptional activators and repressors. (IV) lncRNAs can modulate splicing pattern of RNA by interacting with splicing factors and junctions. (V) lncRNAs control translation by inhibiting or favoring the loading of polysome to mRNAs. (VI) lncRNAs protect RNA from degradation or subject them to degradation machinery. (VII) lncRNAs also act as molecular sponge by interacting with their complementary miRNA. They can also occupy their binding sites on RNA molecules.

## 2. Materials and Methods

The current narrative review study aimed to provide the latest information about the lncRNAs involved in the susceptibility to different male reproductive diseases and summarizing lncRNAs functions in the development of the related diseases. It was conducted through a comprehensive search in electronic databases, including PubMed, Scopus, and Google Scholar using Keywords such as lncRNA, prostate cancer, prostatic hyperplasia, prostatitis, testicular cancer, varicocele, sperm abnormalities. After evaluating 122 related articles including original, review, and meta-analysis, 93 articles were finally used in this study.

## 3. Diseases

### 3.1. Prostate cancer

PCa as a complex and noncutaneous malignancy is the second cause of cancer-associated death among men (15). Several studies have implicated the role of differentially expressed lncRNAs affecting pathological, treatment, and prognosis of PCa. In addition, lncRNAs can act as oncogene and tumor suppressor molecules in PCa tumorigenesis (16, 17). We will discuss some principal oncogenic lncRNAs later in the article. Table I mentions the further oncogenic lncRNAs with their summary of functions.

**Table I.** Other\* known oncogenic lncRNAs involved in PCa

lncRNA	Genomic location	Summary of functions	Reference
<b>SAP30L-AS1</b>	5q33.2	Binds to promoter of SAP30L and represses it. It promotes PCa cell proliferation and inhibits apoptosis	(18)
<b>FALEC</b>	1q21.2	Up regulated in hypoxic environment. It promotes invasion, proliferation and migration in vitro	(19)
<b>MYU/VPS9D1-AS1</b>	16q24.3	Promotes expression of c-Myc by competitive binding to mir-184. It induces proliferation of PCa	(20)
<b>PCSEAT/PRCAT38</b>	21q22.3	By acting as a sponge for miRNA-143-3p and miRNA-24-2-5p, regulates EZH2. It increases the motility and growth of PCa	(21)
<b>FOXC2-AS1</b>	16q24.1	Targets 3'UTR of miR-1253 and binds to complementary site in EZH2. It promotes cell proliferation and PCa growth in vivo and in vitro	(22)
<b>LINC01116</b>	2q31.1	Knock down of this lncRNA with siRNA increases the expression of genes such as GAPDH (regulates glycolysis), MAP1LC3B2 (autophagy) and H2AFY (chromatin structure). It increases cell proliferation of PCa	(23)
<b>LOC400891</b>	22q11.2	Up regulated in PCa tissue. It is associated with proliferation, migration and invasion in PCa tissues and independent predictor of biochemical free-survival	(24)
<b>ncRNA-ROR</b>	18q21.31	Acts as ceRNA and Competes with miR-145 binding in HuPCaSCs (human prostate cancer stem cells), miR-145 decreases cell proliferation in PCa by suppressing Oct4 expression. It promotes cell proliferation in PCa	(25)
<b>PCA3/DD3</b>	9q21-22	Knock down of this lncRNA in LNCap cells regulates genes encoding AR cofactors and EMT marker. It increases viability of PCa cells	(26)
<b>SPRY4-IT1</b>	5q31.3	Highly upregulated in PCa. Knockdown of this lncRNA in PC3 cells inhibits cell proliferation and invasion of cells	(27)
<b>LOC440040</b>	11p11.12	Upregulated in PCa tissues, high expression of this lncRNA is associated with advanced clinical features and shorter overall survival. Its expression is independent prognostic factor in patients	(28)
<b>ZEB1-AS1</b>	10p11.22	Recruits methyltransferase MLL1 to promoter of ZEB1 and increases expression of ZEB1 by inducing H3K4me3. It increases proliferation and migration of PCa cells	(29)
<b>TRPM2-AS</b>	21q22.3	Overexpressed in PCa. In addition, it regulates TRPM2 gene and genes related to cell cycle and survival such as FYN and AKT1	(30, 31)

\*Refers to lncRNAs which are not mentioned in the main text

Abbreviations: SAP30L: 30-kDa Sin3-associated Protein, EZH2: Enhancer of zeste homolog 2, UTR: Untranslated region, siRNA: Small interfering RNA, GAPDH: Glyceraldehyde 3-phosphate dehydrogenase, MAP1LC3B2: Microtubule-associated proteins 1A/1B light chain 3 beta 2, H2AFY: H2A histone family member Y, HuPCaSCs: Human prostate cancer stem cells, LNCap: Lymph node carcinoma of the prostate, AR: Androgen receptor, EMT: epithelial-mesenchymal transition, MLL1: myeloid/lymphoid or mixed-lineage leukemia 1, ZEB1: Zinc finger E-box binding homeobox 1 TRPM2: Transient receptor potential cation channel subfamily M member 2

### 3.1.1. Oncogenic lncRNAs in PCa

Prsenter and colleagues identified 121 unannotated ncRNA transcript in a cohort of 102 prostate tissues and cell lines using high-throughput RNA sequencing and named them as prostate cancer-associated ncRNA transcripts (PCATs) based on their fold-change in PCa samples compared to normal tissue. PCAT-1, ~ 1.9 kb lncRNA, is located upstream of the c-Myc gene at chromosome 8q24 (32). Its expression is significantly high and upregulated in most PCa cells especially metastatic samples; furthermore, it is mostly found in cytoplasm and in a small amount in the nucleus of PCa cells. It has also been reported that lncRNA PCAT-1 represses BRCA2 involved in homologous recombination (HR), resulting in unrepaired Double-stranded DNA breaks (DSBs) (33). Another study revealed that PCAT-1 with microRNAs (miR-3667-3p and miR-34a) upregulates the c-Myc protein level, which is essential for cell cycle progression, leading to proliferation of prostate tumor cell (34). PCAT-5 is another oncogenic lncRNA that is regulated by transcription factor ERG (ETS-related gene) and is significantly associated with cell proliferation and invasion of PCa cells. In addition, it is upregulated in castration-resistant prostate cancer (CRPC) tissue compared to normal prostate cells (35). The lncRNA Prostate Ovary Testis Expressed Family member Antisense 1 (POTEF-AS1) is the androgen-dependent regulator that is involved in apoptosis and toll-like receptor signaling pathways by interacting with TLR3 and TNFSF10. In addition, it has a fundamental role in the progression of docetaxel-treated cells by repressing apoptosis, resulting in chemoresistance (36).

HOXD antisense growth-associated lncRNA (HOXD-AS1) is upregulated in PCa. A study has reported that HOXD-AS1 regulated the expression of target genes and promoted cell proliferation

by recruiting WDR5. This molecule is part of the MLL1/MLL complex and has a key role in histone H3 lysine 4 tri-methylation (H3K4me3) which is associated with transcriptional activation (37). Li and coworkers in 2017 reported that small nucleolar RNA host gene 1 (SNHG1) lncRNA promotes cell proliferation and is upregulated in PCa. By acting as ceRNA (competing endogenous RNA), this lncRNA suppresses the activity of miR-199a-3p that promotes the expression of its target, CDK7, resulting in increased cell proliferation and cell cycle progress in PCa (38). SOCS2-AS1 (Cytokine signaling 2-antisense transcript 1) is an androgen-induced lncRNA and regulates genes TNFSF10, FOXM1, and CENPF, which are involved in apoptosis and cellular proliferation in PCa. Moreover, by repressing apoptosis, it plays a fundamental role in the progression of CRPC (39).

CTBP1-AS, an androgen-responsive lncRNA, is located in the AS region of C-terminal-binding protein 1, which works as a corepressor for the androgen receptor. By recruiting the RNA-binding transcriptional repressor PSF and HDAC (Histon deacetylase), this lncRNA can repress the expression of the CTBP1 gene. Low expression of this gene is associated with overexpression of androgen-related genes and aberrant cell proliferation in prostate cells which causes PCa (40). PVT1 (Plasmacytoma Variant Translocation 1) lncRNA was identified to be associated with miR-146a expression. This lncRNA decreases the miR-146a expression by increasing methylation in CpG Island in the promoter of miR-146a. The silencing of miR-146a suppresses apoptosis and promotes cell viability in PCa (41). Another study by Yang and co-authors revealed that the level of PVT1 expression was notably high in PCa compared to normal prostate cells. In addition, they did knockdown this lncRNA in PCa cell lines and found the expression of cleaved caspase-3 and c-Myc was upregulated and downregulated, respectively. Therefore, this

lncRNA increases cell growth in PCa in vitro and in vivo (42).

The gene encoding TTTY15 (Testis-specific transcript Y-linked 15) lncRNA is located at Yq11.2. Some studies revealed that the fusion of the TTTY15 gene with USP9Y (Ubiquitin Specific Peptidase 9 Y-linked) gene is a potential carcinogen in some cancers particularly in PCa (43, 44). Xia and colleagues found that this lncRNA is upregulated in patients with PCa compared to normal cases. They used the CRISPR-Cas9 technique to knock down this lncRNA and reached the conclusion that it suppressed the growth of PCa cells in vitro and in vivo. Moreover, TTTY15 increases CDK6 and FN1 expression by acting as a sponge for microRNA let-7 (45). A single study reported that the expression level of THBS4-003 (Thrombospondin 4) is significantly higher in PCa cells compared to non-tumor ones. It also revealed that knockdown of this lncRNA suppressed the invasive and migratory capability of PCa cell, the expression level of MMP-9 (matrix metalloproteinase-9) as well as p38 (3). Further, Jiang and colleagues found that lnc-MX1-1 (MX Dynamin like GTPase 1) is upregulated in PCa cells compared to adjacent normal prostate cells using array expression profiling. By using RNAi in LNCaP and 22Rv1 cell lines, they suppressed the expression of this lncRNA and identified proliferation and invasiveness of the cells were significantly reduced. In addition, their result indicated the significant association of this lncRNA with clinical features of patients with PCa such as PSA, metastasis, Gleason score, and recurrence-free survival (17).

### 3.1.2. Suppressive lncRNAs in PCa

Some of the identified lncRNAs are tumor-suppressive which show reduced expression in PCa cell and decrease the proliferation and

migration of PCa cells through different molecular pathways. Some main suppressive lncRNAs will be discussed as follows. Table II presents the further suppressive lncRNAs with their summary of functions. BDNF-AS (brain-derived neurotrophic factor antisense), a naturally-occurring RNA antisense against BDNF, is downregulated in cancers such as retinoblastoma and lung cancer (46, 47). It was also downregulated in PSA-positive, PSA-negative PCa cell lines as well as PCa human tissue. Further investigation revealed that increasing the expression of this lncRNA using lentivirus-mediated BDNF-AS suppressed PCa cell development, invasion, and proliferation in two aforementioned PCa cell lines. This study also suggested the overexpression of this lncRNA could be considered as a potential method for therapeutic drug for PCa (48). GAS5 (Growth Arrest Specific 5) gene encodes a snoRNA from its intron and a lncRNA from its exonic sequence. The increased level of this lncRNA promotes apoptosis and inhibits the anti-apoptotic abilities of glucocorticoids by binding to the DNA-binding domain of glucocorticoids (49).

A study by Pickard and colleagues using GAS5-encoding plasmids or GAS5 siRNAs in PCa cell lines showed that the low expression of this lncRNA is significantly associated with increased apoptosis and decreased survival rate in PCa (50). In addition, a study found that this lncRNA targets mir-103 leading to inactivation of PI3K/AKT-mTOR signaling pathway, low PCa cell growth, and proliferation (51). A single study reported that IGF2-AS (insulin growth factor 2 antisense) lncRNA was downregulated in PCa cell line and human PCa tissues. Lentivirus-induced IGF2AS overexpression decreased xenograft development in vivo, invasion, and proliferation of PCa cells in vitro. Through inverse regulation of IGF2, this lncRNA acted as an epigenetic tumor suppressor in PCa (16). lncRNA FENDRR (FOXF1 Adjacent

Non-Coding Developmental Regulatory RNA) is located at 16q24.1. This lncRNA has a fundamental role in modifying chromatin by interacting with Trithorax group/MLL protein complexes (TrxG/MLL) and polycomb repressive complex 2 (PRC2) (52, 53). Zhang and colleagues identified that this

lncRNA can also act as ceRNA for miR-18a-5p which upregulates the RUNX1 expression, resulting in decreased progression of PCa cell. Their study also indicated that there was a negative correlation between this lncRNA and the prognosis of PCa (54).

**Table II.** Other\* known suppressive lncRNAs involved in PCa

lncRNA	Genomic location	Summary of functions	Reference
<b>DRAIC</b>	15q23	Knock down of this lncRNA decreases cell proliferation. It decreases the transformation of cuboidal epithelial cells to fibroblast-like. In addition, it decreases cellular migration	(55)
<b>LncRNA625</b>	15p13	Downregulated in PC3 cell line compared to normal cells. It targets miR-432 and decrease its expression, and regulates Wnt/ $\beta$ -catenin pathway. The overexpression of this lncRNA prevents cell growth, induces cell cycle arrest at the G1/S phase and apoptosis in PC3 cells	(56)
<b>LOC284454</b>	19p13.13	Downregulated in PCa samples	(57)
<b>LINC00844</b>	10q21.1	Induces AR binding to the chromatin and regulates androgen-regulated gene transcription. It activates the expression of NDRG1, which is fundamental metastasis suppressor. Furthermore, it prevents PCa progression and invasion	(58)
<b>PCAT29</b>	15q23	Regulated by FOX1 and AR. It suppresses PCa migration and metastasis	(55)
<b>PCAT14</b>	22q11.23	Down regulation of this lncRNA is associated with metastatic progression and Gleason score	(59)
<b>MEG3</b>	14q32.2	Its expression is low in PCa cells compared to normal cells. It decreases the expression of Bcl-2, increases BAX and activates caspase3, leading to inhibition of intrinsic cell survival pathway. It also inhibits cyclinD1 and induces cell cycle arrest in G0/G1 phase	(60)

\*Refers to lncRNAs which are not mentioned in the main text

Abbreviations: AR: Androgen receptor, NDRG1: N-MYC downstream-regulated gene-1

### 3.2. lncRNAs in the discrimination of BPH from PCa

BPH, another common prostate-associated disease, is non-cancerous enlargement of prostate characterized by over-proliferation of stromal and epithelial cells of the transition zone (61). It affects About 50% of males in the age range of 51-60 yr and reaches up to 70% among the age range of 61-70 (62). The measurement of prostate-specific antigen (PSA) has been used widely for screening PCa; however, its level can be increased by BPH

as well (63). Therefore, using PSA is controversially debatable (64), and finding biomarkers that can exactly determine PCa from BPH would help clinicians to use proper therapeutic methods for these diseases. Several studies reported that because of tissue-specific expression pattern of lncRNAs, they could be considered as biomarkers to efficiently discriminate BPH from PCa. A study by Bayat and co-authors investigating four lncRNAs, Prcat17.3, Prcat38, Prcat47, and Cat2184.4, revealed low expression of lncRNA Cat2184.4 in PCa samples compared to BPH ones.

In contrast, lncRNAs PRCAT17.3 and PRCAT38 showed significant upregulation in PCa samples compared to BPH ones. In addition, lncRNA PRCAT47 showed increased expression in PCa but not statistically significant compared to BPH samples. They concluded that this lncRNA can be considered as potential biomarkers to differentiate BPH from PCa (65).

Another study investigated the expression pattern of exosomal circulating lncRNAs in PCa, BPH and normal samples (66). It is worth mentioning that exosome is vesicle with 40-100 nm diameter, which has fundamental roles in the cell-to-cell communication and cell signaling by binding to their receptor on cells. Furthermore, they can carry a wide variety of molecules such as proteins, miRNAs, and lncRNAs. This structure keeps aforementioned molecules safe from degradation (67). This study revealed that exosomal lncRNA SAP30L-AS1 (SAP30L Antisense RNA 1 (Head To Head)) were significantly upregulated in BPH. However, their result showed that another exosomal lncRNA SChLAP1 (SWI/SNF Complex Antagonist Associated with Prostate Cancer 1) were upregulated in PCa samples compared to BPH and normal ones. The latter one is more useful as biomarker for discriminating BPH from PCa when PSA concentration is in a gray zone (66). lncRNA-p21 is another exosomal lncRNA which its expression pattern had been investigated in urine samples from patients with BPH and PCa. It is found in high level in urine samples of patients with PCa compared to samples from BPH patients (68).

### 3.3. Prostatitis

Prostatitis is inflammation of the prostate gland that has important roles in the male reproductive system. Although it is amendable, its main pathophysiology and treatment in male

infertility are still unknown. It also can affect the assisted reproduction; therefore, finding the main pathogenesis of prostatitis and its negative impact on sperm quantity and quality including apoptosis and DNA integrity is indispensable (69). A recent study by Xu and colleagues examined the association of lncRNA GAS5 (growth arrest-specific transcript 5), located at 1q25.1, with chronic non-bacterial prostatitis (CNP). Their study revealed that the expression of this lncRNA was decreased in prostatitis tissues. In addition, they found that this lncRNA prevented cell proliferation in prostatitis by downregulation of COX2 expression, an enzyme producing prostaglandins. Their study in the GAS5-overexpressed CNP rat model showed the overexpression of this lncRNA decreased prostate volume, inflammatory cells count, and locomotion score. Therefore, the overexpression of lncRNA can reduce the injury of CNP in vivo (4).

### 3.4. Testicular cancer

Although TCa is generally a rare form of cancer, with the annual incidence of approximately 1%, it is the most prevalent cancer among men with the age range of 14 to 44 years. Testicular germ cell tumors (TGCT) represent nearly 98% of TCa, while the remaining comprise stromal tumors including Sertoli cell tumors, Leydig cell tumors, and other more poorly defined histologic types (70, 71). Newly identified TC are responsive to treatment; however, therapeutic outcomes of these tumors in high stages are not sufficient (72, 73). Therefore, finding molecular pathways and their regulatory elements involved in the progression and growth of TCa cells such as lncRNA would lead to the identification of the best treatment for TCa. A recent study used NCCIT cell lines (Human testicular embryonic carcinoma cells), a pluripotent extragonadal germ cell tumor cell line, to determine the effect of lncRNA Gm2044 on the growth and proliferation

of TCa cells. It revealed that the overexpression of this lncRNA prohibited cell proliferation *in vitro*. In addition, its results showed this effect was mediated by the miR-202-Rbfox2 pathway (74). lncRNA OIP5-AS1 (Opa-interacting protein 5 antisense RNA 1), located at 15q15.1, is another lncRNA that was shown to be overexpressed and promote cell proliferation in many cancers (75). This lncRNA is highly overexpressed in TGCT compared to other many cancers such as thyroid, prostate, pheochromocytoma, and paraganglioma (76). Based on the study by Rezaie and co-authors lncRNA LINC-ROR (Long Intergenic Non-Protein Coding RNA, Regulator Of Reprogramming) was highly expressed in testicular tumor tissues compared to control cell lines (NT2) (77). This lncRNA is located at 18q21 and is involved in embryonic stem cells (ESC) maintenance (78). Moreover, this lncRNA interacts with heterogeneous nuclear ribonucleoprotein I and suppresses p53 activated by DNA damage (79).

### 3.5. Varicocele

Varicocele, a main abnormality contributing to male infertility, is an abnormal dilation of pampiniform venous plexus in the scrotum and is prevalent among 20% of adult and adolescent male (80). It causes increased oxidative stress, apoptosis, venous pressure, and temperature resulting in testicular and sperm damage (81). Although many genetics factors such as chromosome alteration and epigenetic changes have been identified to be associated with Varicocele, however, its main molecular mechanism is still unknown (82). lncRNAs as a functional modulator of biological processes may have important roles in the pathogenesis of the disease. The lncRNA gadd7 (growth arrested DNA-damage inducible

gene 7), a 754-nt polyadenylated lncRNA, is overexpressed after DNA damage and growth arrest signal. Its overexpression is associated with suppressed cell growth (83, 84). Furthermore, it is the modulator of endoplasmic reticulum stress and lipid-induced oxidative (85). A single study analyzed the expression level of this lncRNA in the ejaculated spermatozoa of patients with Varicocele and found that the expression level lncRNA gadd7 is negatively associated with sperm count. It also used mouse germ cell lines GC-1 and GC-2 transfected with either pcDNA3.1-gadd7 or negative control plasmid to investigate the effect of this lncRNA overexpression on cell features. Its result indicated the overexpression of this lncRNA suppressed cell proliferation and increased cell apoptosis. In addition, the study showed that gadd7 induced by stress can cause cell death through upregulation of Bax and downregulation of Bcl2, which are pro-apoptotic and anti-apoptotic regulators, respectively (86).

### 3.6. Sperm abnormalities

Male infertility can also be ascribed to uniform testicular maturation arrest (MA) and different types of sperm abnormalities such as oligozoospermia, non-obstructive azoospermia, AZS, and teratozoospermia (87). Spermatogenesis is a complex process regulated by different genes, proteins, and transcriptional network including ncRNAs. Based on the wide ability of lncRNA in proliferation, differentiation, and self-renewal of SSC, they have fundamental roles in spermatogenesis regulation (88). lncRNA HOTAIR (HOX Transcript Antisense Intergenic RNA), located at 12q13.13, is one of the well-studied lncRNA in many diseases and involved in chromatin regulation by binding to Polycomb repressive complex 2 (PRC2) (89). In addition, it plays a key role in epigenetic regulation by

interacting with the lysine-specific demethylase 1 (LSD1), Enhancer of Zeste homolog 2 (EZH2), and methyltransferase specific to histone 3 lysine 27 (90). Zhang and colleagues investigated the expression of this lncRNA in the samples from patients with AZS and oligoasthenozoospermia, and found it had a low expression in AZS and oligoasthenozoospermia compared to normal samples. Furthermore, their results indicated that the low expression of HOTAIR is associated with low expression NRF2 (Nuclear factor erythroid 2-related factor 2) gene. HOTAIR is responsible for histone H4 acetylation in the NRF2 gene promoter, which leads to its activation (91). Since the expression level of NRF2 is associated with sperm quality and antioxidant gene expression (92), HOTAIR may protect spermatozoa against antioxidant activity (91). Another study analyzed the expression profile of lncRNA in AZS and normal sperm samples. The gene ontology and pathway analysis revealed that differentially expressed lncRNA in AZS and normal samples were related to sperm function and spermatogenesis. Moreover, among all identified differentially expressed lncRNAs, the expression level of three lncRNA including lnc32058, lnc09522, and lnc98487 were significantly correlated with sperm motility (93).

## 4. Conclusion

In conclusion, this review emphasizes the identified lncRNAs and their functions in male reproductive disorders including PCa, BPH, prostatitis, TCa, varicocele, and sperm abnormalities. With the advent of state-of-the-art molecular and genomics techniques such as high-throughput sequencing, thousands of lncRNA have been identified in susceptibility to different diseases. However, their main mechanisms and molecular pathways are still

unknown and need more functional and in vitro studies. Identification of differentially expressed lncRNA in each disease can pave the way toward developing unique biomarker, approaches to treat diseases, as well as increase efficiency of assisted reproductive technologies. In addition, lncRNA can be considered as precious indicator of sperm quality.

## Conflict of Interest

The authors declare that there is no conflict of interest.

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