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Review

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Discovering the Role of Long non-coding RNAs in Regulation of Steroid Receptors Signaling in Cancer

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ABSTRACT

Long non-coding RNAs (lncRNAs) are a major group of transcripts with fundamental roles in almost all physiological aspects of cell. They can regulate expression of genes via different mechanisms. In addition, they have been shown to modulate cancer related signaling pathways. Most of lncRNAs are localized in the nucleus and exert their role through recruitment of chromatin modifiers to DNA. Several lines of evidence suggest their participation in steroid hormone receptor (SHR) signaling. Steroid hormones exert their physiological and pathological functions via modulation of gene expression. Through a computerized search of the MEDLINE/PUBMED, Web of Knowledge, Scopus, ProQuest and Google Scholar databases with key words lncRNA, steroid receptor, estrogen receptor, androgen receptor and glucocorticoid receptor, we found published studies within the maximal date range until July 2017. Many lncRNAs have been shown to regulate or be regulated by SHRs. Numerous treatment strategies in common cancers such as breast and prostate cancer modulate SHR functions. Accordingly, identification of the regulatory network of SHR would pave the way for designing more effective treatment modalities for cancer especially for endocrine therapy unresponsive cancers. The critical role of lncRNAs in this regulatory network potentiates them as therapeutic targets for such common cancers.

Key words: lncRNA, Androgen receptor, Estrogen receptor, Glucocorticoid receptor.

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1. INTRODUCTION

Recent data provide evidences supporting the active transcription of at least 90% of the genome in spite of extremely low proportion of regions encoding protein coding genes. Long non-coding RNA (lncRNA) genes are among the non-coding RNAs whose roles in almost all aspects of cellular function have been elucidated (1-3). As stated by GENCODE consortium there are 9640 lncRNA loci, representing 15,512 transcripts most of them being located between genes and called long intergenic ncRNAs (lincRNAs). In addition to lincRNAs, overlapping, antisense, and intronic lncRNAs exist (4). The majority of lncRNAs are localized in the nucleus and exert their role through recruitment of chromatin modifiers to DNA. The chromatin modifiers are categorized based on their function to repressive modifiers such as polycomb repressor complex (PRC), activating modifiers and nuclear organization factors. Other lncRNAs participate in regulation of gene expression via binding to certain proteins and making scaffolds within ribonucleoprotein complexes, producing sponges for microRNAs (miRNAs) to prevent the actions of miRNAs on mRNAs and modulate the half-life of mRNAs (5). Figure 1 shows the function of a subset of lncRNAs which are localized in the nucleus. Many of lncRNAs have been shown to have differential expression in tumoral samples compared with the adjacent non tumoral samples which implies their role in tumorigenesis process (6-10).

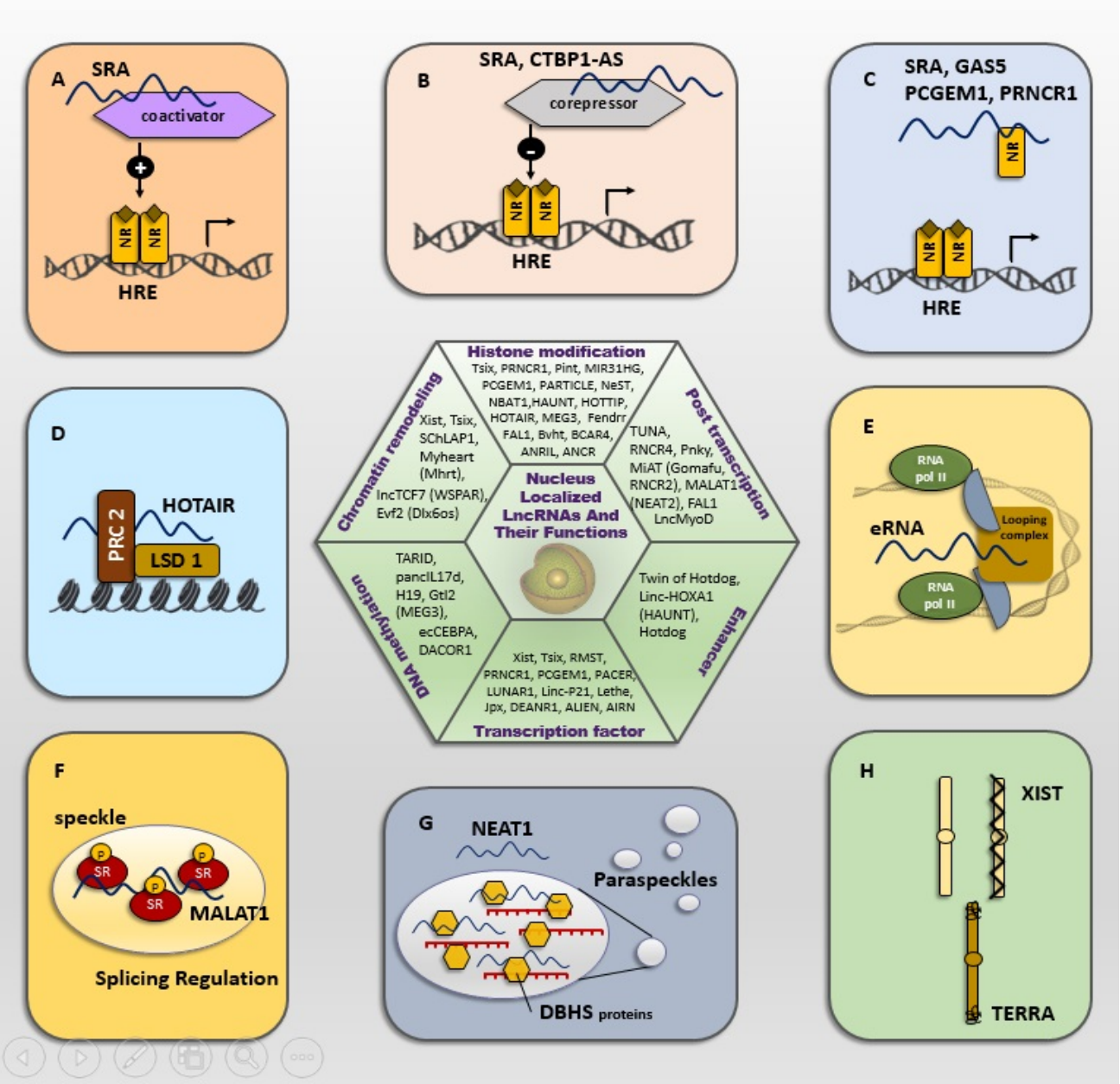

Figure 1. Nuclear lncRNAs and their functions. LncRNAs can regulate gene expression through interaction with coativators (A) or corepressors (B), direct interaction with receptors (C), recruitment of epigenetic regulator complexes (D), chromatin looping (E), participation in nuclear speckles and interaction with splicing factors (F), localization in paraspeckles and involvement in RNA or protein retention (G), and participation in dosage compensation and telomere biology (H)

In addition, several single nucleotide polymorphisms within lncRNA coding genes have been demonstrated to be associated with the risk of certain malignancies (11, 12). The steroid hormone receptors (SHRs) are ligand-dependent intracellular transcription factors whose role in the development of many kinds of human cancer has been elucidated. The majority of their physiological and pathological functions are thought to be performed via modulation of gene expression. SHRs transmit signals from a steroid hormone to the target genes through cooperation with specific response element DNA sequences and multiple coregulatory proteins including both activators and repressors. As coactivators and corepressors are located in the same complex, SHRs can regulate gene transcription in an effective manner. Several upstream signaling networks control the expression and function of SHRs (13). SHRs belong to the class I nuclear receptors which include androgen receptor (AR), estrogen receptor (ER), progesterone receptor (PR) and glucocorticoid receptor (GR) (14). The functional domain of these receptors include a hormone-independent activation domain AF-1 in N-terminal, a DNA binding domain and a C-terminal region encompassing both the ligand binding domain and a ligand-dependent activation domain AF-2 (Figure 2).

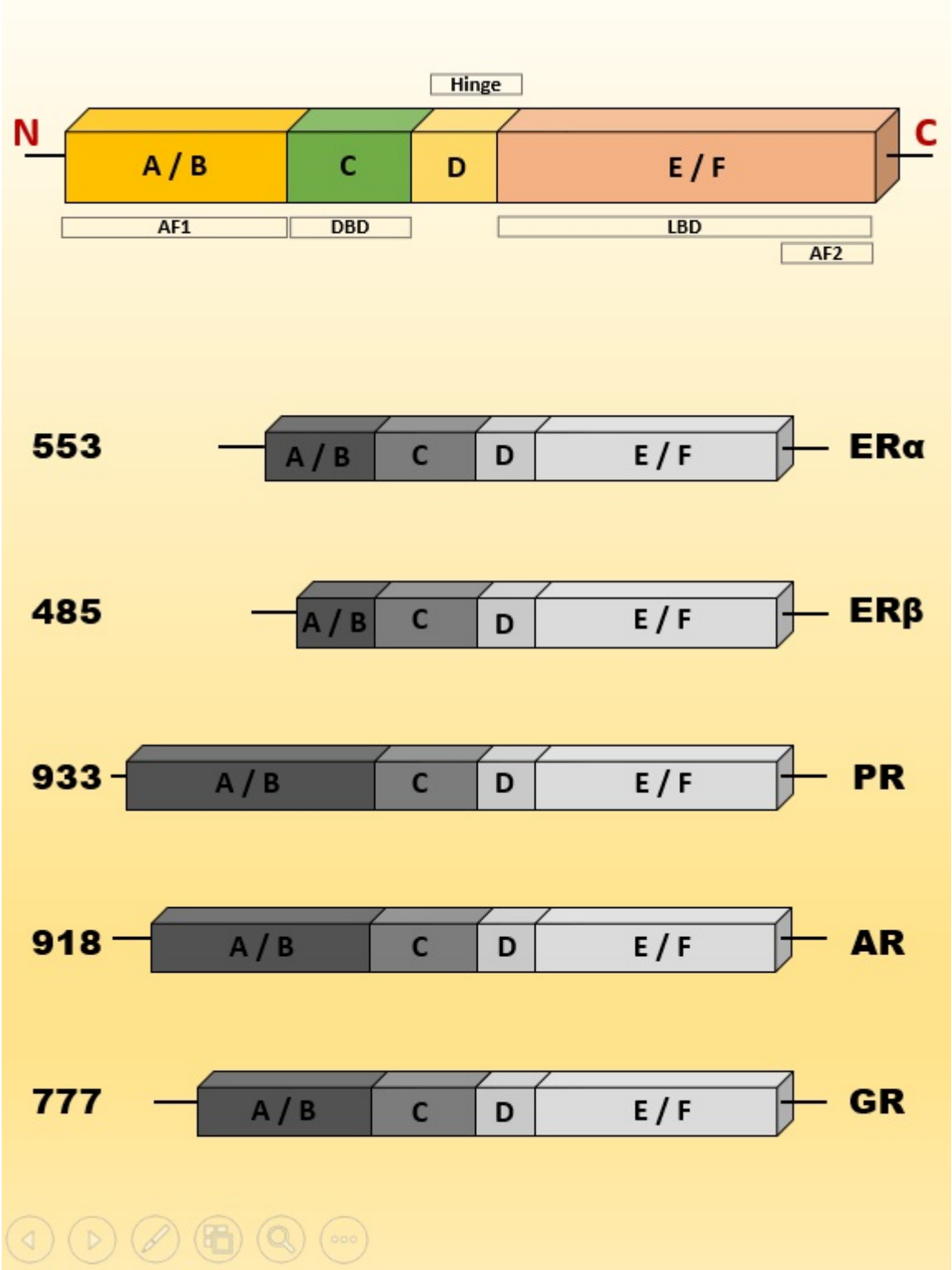

Figure 2. Structures and functional domains of steroid receptors. The A/B domain codes for a ligand-independent transcriptional activation function 1 (AF1). The C domain codes for two zinc fingers produced by four cysteine residues which make the DNA binding domain (DBD). The COOH-terminal E/F domain has a ligand binding domain (LBD) with a ligand-dependent transcriptional activation function 2 (AF2) domain

Ligand binding leads to conformational alterations and dimerization of receptors which in turn result in specific recognition of hormone responsive elements (HRE) upstream of target genes (15). Numerous treatment strategies in common cancers such as breast and prostate cancer are focused on modulation of SHR functions. Consequently, elaboration of the regulatory network of SHR would pave the way for designing novel effective treatment modalities for cancer especially cancers that are unresponsive to the endocrine therapy or become resistance during treatment course. LncRNAs as important modulators of gene regulation have crucial roles in modulation of endocrine functions leading to cancer development or participating in treatment response. LncRNAs and transcription factors such as SHR constitute important parts of an interaction network which contributes in several aspects of tumorigenesis process. The function and expression pattern of lncRNAs with putative role in modification of SHR signaling have been shown in Table 1 and are explained in the following sections. As shown in

Figure 3 SHRs have similar as well as distinctive roles in the development of individual cancers. Consequently, the role of SHR-targeted lncRNAs should be assessed distinctively in each cancer type. The relative position of lncRNAs in upstream or downstream of SHRs has been depicted in Figure 4.

Table 1.The function and expression pattern of lncRNAs with putative role in modification of steroid hormone receptor signaling

LncRNA	*Relate steroid receptor*	*Chromosome Location*	*Transcript type*	*Cancer name*	*Correlation with steroid receptor*	*Expression pattern in cancer*	*Validation Method*	*Function*	*Ref*
PCGEM1	AR	2q32.3	lincRNA	prostate cancer	Induced by AR	Up-regulated	qPCR microarray RNA-seq	regulates metabolic programming, enhances activation of c-Myc and AR	(16)
PRNCR1 (PCAT8)	AR	8q24.21	Pseudo gene	prostate cancer	Induction of AR	Up-regulated	qPCR, RIP	plays a vital role in directing the transcriptional activity of AR	(17)
PlncRNA-1(CBR3-AS)	AR	21q22.12	Antisense Intron Overlapping	prostate cancer	Induction of AR	Up-regulated	qPCR, Western blot	regulates AR expression	(18)
PCA3(DD3)	AR	9q21.2	Antisense, Intron Overlapping	prostate cancer	Induction of AR	Up-regulated	qPCR, Northern bolt, RNA-seq	increases cell growth and viability through modulation of cell cycle arrest and apoptosis	(19, 20)
PCAT10 (CTBP1-AS)	AR	4p16.3	-	prostate cancer	Repression of AR	Up-regulated	qPCR, Western bolt, Northern bolt, RIP	transcriptional corepressor of AR	(21)
GAS5	GR	1q25.1	Intron Overlapping lincRNA Antisense	mesothelioma	Repression of GR	Down-regulated	real-time PCR, Western blots, ChIP, RNA in-situ hybridization, Immunohistochemistry, quantitative PCR	interacts with the activated GR suppressing its transcriptional activity	(22)
	AR	1q25.1	Intron Overlapping lincRNA Antisense	breast cancer	Repression of AR	Down-regulated	RT–PCR, real-time RT–PCR	may act as a decoy by interacting with the AR DNA binding domain thus preventing the binding of AR to its target AREs, and restricts the expression of cell survival genes	(23)
				prostate cancer		Up-regulated / Down-regulated	qPCR, RNAi		(24)
PCAT18 (Loc728606)	AR	18q11.2	-	prostate cancer	Induced by AR	up-regulated	microarray, qPCR, RNAi	unknown	(25)
PCAT29	AR	15q23	-	prostate cancer	Repressed by AR	Down-regulated	qPCR, RT-PCR, Microarray	unkown	(26)
SOCS2-AS1	AR	12q22	Antisense Intron Overlapping	prostate cancer	Induction of AR	up-regulated	RNA-seq, qPCR, ChIP, RIP	promotes androgen signaling by modulating the epigenetic control for AR target genes	(27)
DRAIC (LOC145837)	AR	15q23	Intron Overlapping	prostate cancer	Repressed by AR	Down-regulated	qPCR, Western blot	unknown	(28)
RP1-4514.2	AR	8q11.23-q12.1	Intron Overlapping	prostate cancer	Induced by AR	Down-regulated	RNA-Seq	unknown	(29)
LINC01138	AR	1q21.2	lincRNA	prostate cancer	Induced by AR	Down-regulated	RNA-Seq	promotes the proliferation and inhibits apoptosis	(29)
SUZ12P1	AR	17q11.2	Intron Overlap	prostate cancer	Induction by AR	Down-regulated	RNA-Seq	promotes the proliferation	(29)

			ping, lincRNA					and inhibits apoptosis	
KLKP1	AR	19q13.33	Intron Overlapping, lincRNA	prostate cancer	Induction by AR	Up-regulated	RNA-Seq	unknown	(29)
H19	PR-A ERα	11p15.5	lincRNA Intron Overlapping	breast cancer	Induction	Up-regulated	qPCR, Western blot, RNAi	accelerates cell cycle progression and increases cell proliferation	(30)
				prostate cancer		Down-regulated	qPCR, Western blot	unknown	
HOTAIR	ERα and ERβ	12q13.13	Antisense lincRNA	breast cancer	Induction of ER, Repressed by ER	Up-regulated	qPCR, Western blot, RIP, ChIP	promotes ligand-independent ER activities and contributes to tamoxifen resistance	(31)
	AR			prostate cancer	Induction of AR	Up-regulated	RT-PCR ChIP-seq	binds to the AR protein to block its interaction with the E3 ubiquitin ligase MDM2, thereby preventing AR degradation	(32)
NEAT1	ERα	11q13.1	lincRNA	prostate cancer	Induced by ER	Up-regulated	ChIP, RNA seq, ISH, microarray	a downstream target in the ERα signalling pathway and a mediator of ERα signalling in prostate cancer cells	(33)
DSCAM-AS1	ERα	21q22.2	Antisense	breast cancer	Induction of ER	Up-regulated	qRT-PCR	cell survival and proliferation, epithelial-mesenchymal transition	(34)
SPRY4-IT1	ER	5q31.3	Intronic Antisense	breast cancer	Induction of ER	Up-regulated	microarray, qPCR, Western blot, RNAi	cell proliferation and apoptosis inhibition	(35)
BC200 (BCYRN1)	ER	2p21	lincRNA	breast cancer	Induced by ER	Up-regulated	qPCR, ChIP	inhibits apoptotic cell death through regulating Bcl-xL expression	(36)
MALAT1	ERβ	11q13.1	lincRNA	prostate Cancer	Repression of ER	Up-regulated	RNA-ChIP, qRT-PCR	repressor of gene transcription	(37)
lincRNA-BC5	PR	Xq24	lincRNA	breast cancer	Induced by PR	Up-regulated	real-time qPCR, RPIseq	unknown	(38)
lincRNA-BC8	PR	13q34	lincRNA	breast cancer	Repressed by PR	Down-regulated	real-time qPCR, RPIseq	unknown	(38)
SRA1	ER, PR, GR, AR	5q31.3	Intron Overlapping	breast cancer	Induction of ER	Up-regulated	-	increases estradiol induced gene transcription	(15)
PVT1	ERα	8q24	lincRNA	breast cancer	Repression of ER	Up-regulated	qPCR, Western blot	reduces ERα expression	(39)
	AR			prostate Cancer	Induction of AR	Up-regulated	qPCR	unknown	(40)
SOX2OT	ER, PR	3q26.33	Intron Overlapping	breast cancer	Repression	up-regulated	qPCR, Western blot	induces SOX2 expression	(41)

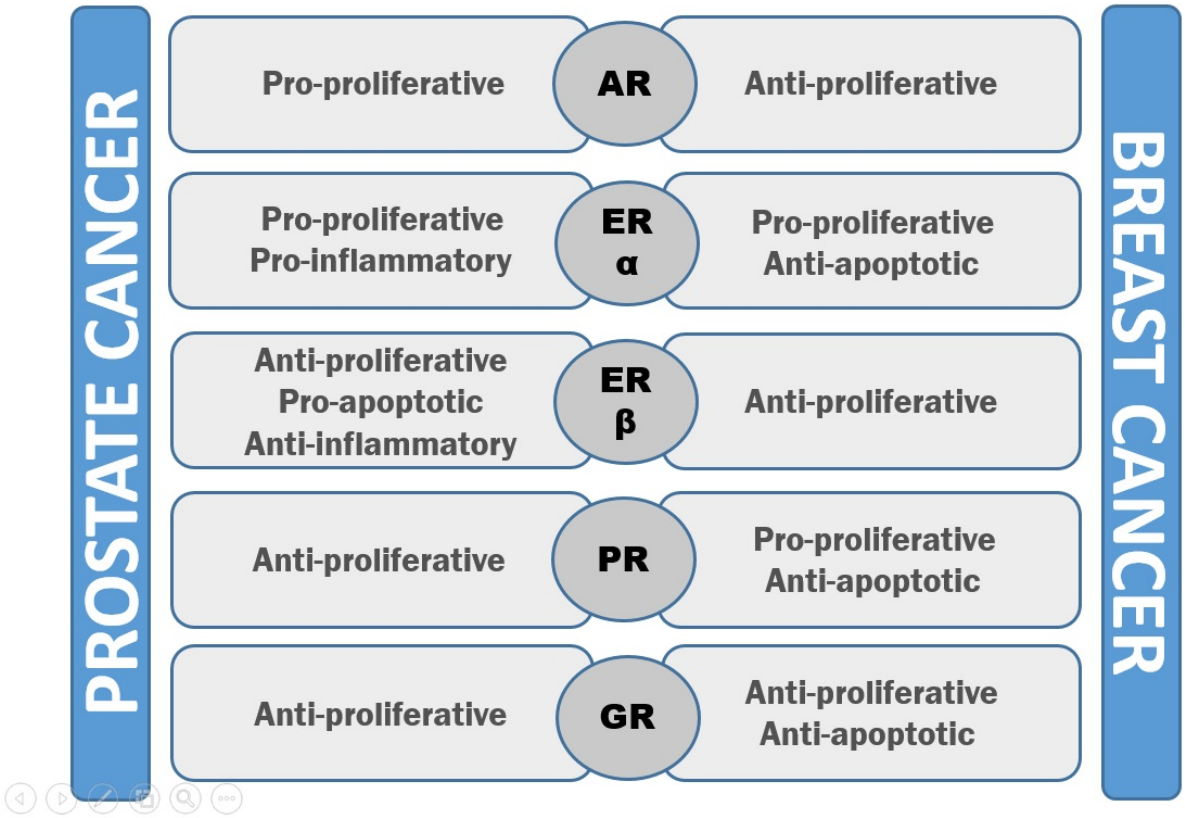

Figure 3 Examples of steroid hormone receptor functions in breast and prostate cancers

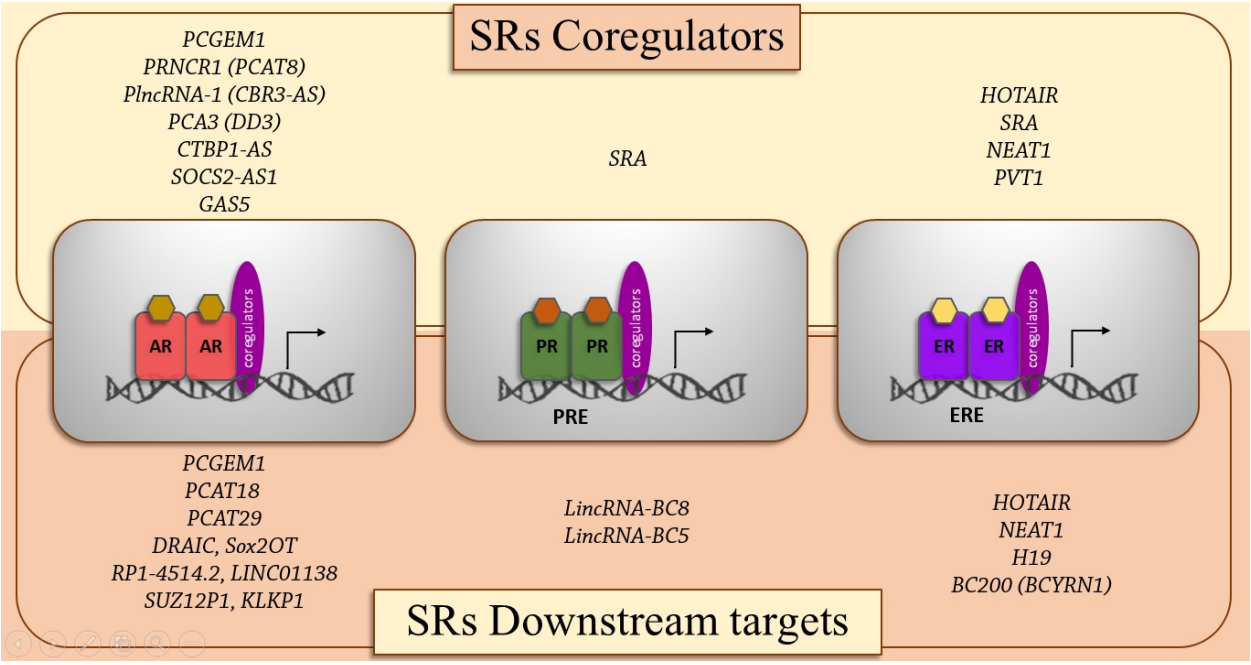

Figure 4 The relative position of lncRNAs in upstream or downstream of steroid hormone receptors

2. Evidence acquisition

Through a computerized search of the MEDLINE/PUBMED, Web of Knowledge, Scopus, ProQuest and Google Scholar databases with key words lncRNA, steroid receptor, estrogen receptor, androgen receptor and glucocorticoid receptor we found published studies within the maximal date range until July 2017.

3. LncRNAs with putative role in SHR signaling

3.1. Carboxyl terminal binding protein 1-antisense (CTBP1-AS)

It is an lncRNA coded from the antisense region of *CTBP1*. Global transcriptome analysis of prostate cancer cells has led to identification of this lncRNA. Its expression is promptly induced by androgen treatment. It is localised in the nucleus of cancer cells and enhances androgen-

dependent and castration-resistant tumour growth. The mechanism by which *CTBP1-AS* regulates epigenomic transcription in the nucleus involves its interaction with an RNA-binding transcriptional and splicing factor named the Splicing Factor Proline-Glutamine Rich (SFPQ/PSF). Through this interaction it inhibits cell cycle regulators or AR coregulators such as CTBP1 leading to increased cell proliferation (21).

3.2. HOX transcript antisense RNA 1 (HOTAIR)

It is an androgen-repressed lncRNA which is significantly induced after androgen deprivation treatment and in castration-resistant prostate cancer (CRPC). *HOTAIR* bounding with the AR protein prevents its interface with the E3 ubiquitin ligase MDM2, thereby avoiding AR ubiquitination and protein degradation. Accordingly, *HOTAIR* expression is adequate to trigger androgen-independent AR activation and induces the associated transcriptional program even in androgen deprivation status. In addition, it has a promoting effect in prostate cancer cell growth and invasion (42). *HOTAIR* inhibits expression of numerous tumor and metastasis suppressor genes including PR (43). Another study has demonstrated positive effect of *HOTAIR* on modulation of estrogen-target genes which is exerted through estrogen-modulated chromatin remodeling (37). A recent study has confirmed its role as a direct target of ER-mediated transcriptional repression. Elevated *HOTAIR* expression has been associated with breast cancer cell proliferation, while its knockdown considerably inhibits cell survival and decreases tamoxifen-resistant cell growth (31).

3.3. RP1-4514.2

It has been recognized as an AR-targeted lncRNA through data mining of public available gene expression datasets in addition to microarray experiment to detect genome-wide lncRNAs' expressions following dihydrotestosterone (DHT) induction in LNCaP cells. The obtained results have been further validated in prostate cancer samples and cell lines. Its expression has been suppressed after DHT treatment while being induced following AR silencing, suggesting the involvement of AR in androgen-mediated regulation of its expression. A notable increase of AR binding to the chromatin of assumed androgen response elements (AREs) in RP1-4514.2 has been demonstrated in LNCaP cells following treatment with DHT (29).

3.4. Long intergenic non-protein coding RNA 1138 (LINC01138)

A similar approach with *RP1-4514.2* has led to detection of this lncRNA as an AR-targeted gene. It has been also among lncRNAs whose direct interaction with AR has been confirmed by Chromatin immunoprecipitation (ChIP)-PCR. In addition, its expression in prostate cancer patients has been associated with Gleason score and pathologic tumor (pT)-stage. Its pro-proliferative and anti-apoptotic effects have been confirmed experimentally in prostate cancer cells. It has been among the top three up-regulated lncRNAs after AR knockdown. In addition, it enhances proliferation and suppresses apoptosis of prostate cancer cells. In brief, the functional studies as well as expression studies in patients' samples suggest an oncogenic effect for this lncRNA in spite of its repression by AR activity in androgen-dependent tumors. Consequently, there may be other pathways for regulation of its expression in prostate cancer cells (29).

3.5. SUZ12 polycomb repressive complex 2 subunit pseudogene 1 (SUZ12P1)

This lncRNA is an AR-targeted lncRNA whose function has been validated by ChIP-PCR. It is an androgen-reduced lncRNA as its expression has been up-regulated after AR knockdown. Its expression has been associated with Gleason score and pT-stage in prostate cancer samples in a way that it was expressed at lower levels in tumors with a low Gleason score (≤ 7), compared with tumors with Gleason score ≥ 8. Besides, its expression level was significantly higher in invasive extraprostatic tumors as compared with intraprostatic localized tumors. Functional studies have confirmed its role in proliferation enhancement and apoptosis inhibition (29).

3.6. Kallikrein pseudogene 1 (KLKP1)

This lncRNA is an AR-targeted lncRNA which has been detected through a similar approach with *RP1-4514.2* and was confirmed as directly AR-targeted lncRNA by ChIP-PCR. It has been among five lncRNAs whose expressions have been elevated following DHT treatment. In addition, *KLKP1* expression was decreased significantly after AR knockdown implying the participation of AR in androgen-mediated modulation of its expression (29).

3.7. Prostate cancer gene 3 (PCA3, DD3)

It is an lncRNA whose elevated expression has been demonstrated in prostate cancer tissues compared with normal tissues. In addition, *PCA3* is a urinary marker which can be applied for the prediction of biopsy outcome in several studies in various populations. Its application in screening programs has increased the specificity of screening and decreased unnecessary biopsies (44). In a more recent study conducted in Italian patients, the PCA3 test has been confirmed to have diagnostic priority compared to total PSA and free/total PSA tests leading to better assortment of high-risk patients that may need a saturation prostatic biopsy. In addition, the prognostic value of PCA3 has been confirmed by the observation of the association of upper PCA3 score values with greater tumor aggressiveness (45).

3.8. Prostate cancer associated transcript 1 (PCAT1)

This lncRNA has been detected through high-throughput sequencing of polyA+ RNA (RNA-Seq) on a large cohort of prostate tissues and cells lines. Its role in regulation of cell proliferation is possibly exerted through its interaction

with the PRC2. *PCAT-14* expression has been triggered following treatment of androgen responsive VCaP and LNCaP cells with the synthetic androgen. In addition, analysis of prostate cancer samples and their corresponding normal tissues has revealed cancer-specific up-regulation of this lncRNA (46).

3.9. Prostate Cancer Associated Non-Coding RNA 1 (PRNCR1, PCAT8)

It is an lncRNA whose elevated expression has been shown in in aggressive prostate cancer (17). *PRNCR1* silencing by siRNA has decreased the viability of prostate cancer cells and the transactivation activity of AR (47). It binds to the AR together with *PCGEM1*. Such binding intensely augments both ligand-dependent and ligand-independent AR-mediated gene expression profiles leading to pro-proliferation effects in prostate cancer cells. The binding of *PCGEM1* to the AR is thought to be performed secondary to binding of *PRNCR1* to the carboxy-terminally acetylated AR and *PRNCR1* interaction with DOT1L. Overexpression of *PCGEM1* and *PRNCR1* in prostate cancer cells is associated with the forceful induction of both truncated and full-length AR molecules resulting in ligand-independent activation of the AR which implies their crucial role in the pathogenesis of CRPC (17).

3.10. Prostate cancer associated transcript 18 (non-protein coding) (PCAT18)

This lncRNA has been recognized through RNA sequencing on matching metastatic/non-metastatic prostate cancer xenografts originated from patients' samples. It has been shown to be specifically expressed in the prostate compared with a panel of normal tissues and up-regulated in prostate cancer compared to other malignancies. Its expression has been also demonstrated in plasma samples and escalated gradually from healthy persons to patients with localized and metastatic prostate cancer. The *PCAT18*-associated expression signature was considerably associated with AR signaling in a way that AR stimulation has led to a significant induction of *PCAT18* expression. *PCAT18* knockdown has resulted in inhibition of prostate cancer cell proliferation, migration and invasion (25).

3.11. Prostate cancer associated transcript 29 (non-protein coding) (PCAT29)

The role of this lncRNA as an androgen-regulated tumor suppressor has been confirmed in prostate cancer both *in vivo* and *in vitro*. *PCAT29* expression has been shown to be inhibited following DHT treatment and increased upon castration therapy in a prostate cancer xenograft model. Its silencing has led to enhancement of proliferation and migration in prostate cancer cells, while its overexpression inhibited growth and metastases of prostate tumors *in vitro*. In addition, in patients' samples, low *PCAT29* expression was associated with poor prognosis (26).

3.12. Prostate-specific transcript (non-protein coding) (PCGEM1)

It is an lncRNA that binds to AR secondary to binding of *PRNCR1* to the carboxy-terminally acetylated AR. Detection of certain protein modifications by *PCGEM1*-engaged pygopus 2 PHD domain increases discriminating looping of AR-bound enhancers to target gene promoters in prostate cancer cells. Short hairpin RNA mediated knockdown of *PCGEM1* in CRPC cell lines significantly inhibited xenograft tumour growth *in vivo* (17).

3.13. Suppressor of cytokine signaling 2-antisense transcript 1 (SOCS2-AS1)

This lncRNA has been recognized in an attempt for recognition of androgen-induced lncRNAs in AR-positive prostate cancer cells. It has been shown to be overexpressed in CRPC model cells compared with in parental androgen-dependent LNCaP cells. *SOCS2-AS1* enhances castration-resistant and androgen-dependent cell growth. Its knockdown has led to induction of pro-apoptotic genes such as tumor necrosis factor super family 10 (TNFSF10) leading to sensitization of prostate cancer cells to docetaxel therapy. Its role in enhancement of androgen signaling is exerted through altering the epigenetic control for AR target genes such as TNFSF10 (27).

3.14. Steroid receptor RNA activator 1 (SRA1)

SRA1 has been shown to be present in distinctive ribonucleoprotein complexes such as the complex that comprises steroid receptor coactivator 1 (48). *SRA* increases the AF-1 activity of AR, ERα, PR, and GR (49). However, functional analyses carried out with constructions devoid of the AF-1 domains demonstrated coactivatory effect of *SRA1* on the AF-2 regions of ERα and ERβ (15). In addition, it exerts modulatory effects on other nuclear receptors including the vitamin D (VDR) and the retinoic acid (RAR) receptors and the myogenic differentiation factor MyoD as well (15). Although *SRA1* can mediate its coregulatory effects as an RNA molecule, numerous RNA isoforms have been identified that code for SRA protein (SRAP). Both *SRA* and SRAP have been shown to affect steroid hormone signaling pathways and consequently contribute in the pathogenesis of prostate and breast cancers (15). To add extra complexity to the interaction network of *SRA1*, it has been revealed that in breast cancer cells, the unliganded PR interacts with genomic sites and targets a repressive complex comprising *SRA1* to a subset of hormone-inducible genes, keeping these genes suppressed before hormone treatment. *SRA1* interacts with PR and some other components of this complex. Transposition of the repressive complex from target sites facilitates the loading of coactivators leading to induction of a several genes participating in apoptosis and cell proliferation (50).

3.15. Down Syndrome Cell Adhesion Molecule antisense RNA 1 (DSCAM-AS1)

It is the most plentiful Apo-ERα-regulated lncRNAs which is expressed in ERα+ breast carcinoma, but not in pre-neoplastic or adjacent normal tissues. *DSCAM-AS1* silencing can considerably mimic the influence of ERα depletion in breast cancer cells in terms of growth arrest and expression of epithelial-mesenchymal transition (EMT) markers. Consequently, a putative function has been suggested for *DSCAM-AS1* in ERα downstream that is possibly confined to breast carcinoma development (34).

3.16. Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1)

Abnormal expression of *MALAT1* has been shown to correlate with disease course and patients' outcome in various human malignancies including breast and prostate tumors. RNA-ChIP experiments have shown interaction between *MALAT1* and ERβ in prostate cancer cells and between *MALAT1* and ERα in breast cancer cells. *MALAT1* has been considered as an ER transcriptional target as well as ER partner regarding its ability to modulate the estrogen-dependent and independent expression of genes such as pS2, hTERT and PSA (37).

3.17. Nuclear enriched abundant transcript 1 (NEAT1)

NEAT1 has been the most significantly overexpressed lncRNA in prostate cancer which has been detected through a combinatory approach of ChIP and RNA-sequencing data for detection of ERα-specific non-coding transcriptome profile. In addition, its role in the pathogenesis of prostate cancer has been confirmed through assessment of two large clinical cohorts. Its elevated expression in prostate cancer cells has been associated with lack of response to androgen or AR antagonists (33).

3.18. B-ALL associated long RNAs (BALR-2)

This lncRNA is implicated in control of cell survival as its knockdown has resulted in apoptosis induction as well as proliferation decrease. In addition, elevated expression of BALR-2 in B-acute lymphoblastic leukemia (B-ALL) correlates with poor overall survival and decreased response to prednisone therapy. Its knockdown has resulted in up-regulation of numerous genes implicated in the GR signaling pathway which implies that *BALR-2* regulatory effect on apoptosis is mediated through modulation of the GR signaling pathway (51).

3.19. Growth arrest-specific 5 (GAS5)

The elevated expression of this lncRNA has been demonstrated in cells whose growth has been stopped because of insufficiency of nutrients or growth factors. It makes cells sensitive to apoptosis by inhibition of glucocorticoid-mediated induction of numerous responsive genes, such as the one encoding cellular inhibitor of apoptosis 2. By binding to the DNA-binding domain of the GR, *GAS5* functions as a decoy glucocorticoid response element (GRE) contesting with DNA GREs for binding to this receptor (52). *GAS5* has been shown to have a crucial role in normal growth arrest in both leukemic and untransformed human T-lymphocytes. In addition, its expression is regulated by the mammalian target of rapamycin (mTOR) pathway and it is necessary for the suppressive effects of rapamycin and its analogues on T-cells (53). Moreover, *GAS5* can repress PR and AR in a ligand dependent manner (43).

4. Discussion

Despite the great advances in the field of oncology, the function of many lncRNAs in cancer development has not been clarified yet. The interactions between lncRNAs and transcription factors have been predicted by bioinformatics tools and validated in several experiments (54). SHRs are among transcription factors with important roles in development of common cancers. The existence of endocrine treatment modalities for a variety of cancers including breast and prostate cancer as well as emergence of unresponsiveness to these therapies among these patients necessitate the search for identification of factors that modulate response to these therapies. For instance, endocrine therapy resistance has been documented in a subset of ER+ breast cancer cells resulting in hormone-independent proliferation. The induction of a cluster of noncoding RNAs following estrogen withdrawal has been shown to significantly enhance the expression of the ER gene leading to creation of an adaptive environment for breast cancer cells (55). In addition to this well-documented role of non-coding RNAs in induction of resistance, the differential expression of lncRNAs within certain subtypes of cancer patients implies their role in determination of treatment response or patients' prognosis. The role of lncRNAs as therapeutic targets in malignancies has further been highlighted by the observation that lncRNAs mediate induction of androgen-independent AR activity leading to CRPC progression. In addition, some lncRNAs have been shown to contribute in estrogen-responsiveness and regulate the expression of hormone-sensitive genes. The delicate regulation of lncRNA expression and their effect on expression hormone-sensitive genes should be considered in any approach focusing on pharmacological targeting of lncRNAs (37). Besides, several lines of evidence suggest that steroid-responsive as well as SHR modulating lncRNAs can be applied as diagnostic or predictive markers in cancer patients. Consequently, future studies should focus on elaboration of the exact function of lncRNAs and their status in the interaction network consisted of lncRNAs, miRNAs and transcription factors such as SHRs.

5. CONCLUSION

Consistent with the regulatory role of lncRNAs in many

aspects of cell life, lncRNAs are involved in regulation of expression of SHRs. As dysrgulation of SHRs has been implicated in some kinds of common cancers such as breast and prostate cancers, lncRNAs are putative targets for designing new therapeutic options for cancer.

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AUTHORS CONTRIBUTION

Sepideh Farmarzi and Ali Dianatpour contributed in electronic search. Soudeh Ghafouri-Fard designed the study and drafted the manuscript. It is should be noted that first and second authors had equal contributions in this paper.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this paper.

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