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Signaling through estrogen receptors modulates long non-coding RNAs in prostate cancer

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ABSTRACT

Prostate cancer (PCa) is a sex-steroid hormone-dependent cancer in which estrogens play a critical role in both initiation and progression. Recently, several long non-coding RNAs (lncRNAs) have been associated with PCa and are supposedly playing a pivotal role in the biology and progression of this type of cancer. In this review, we focused on some lncRNAs that are known for their androgen and estrogen transcriptional responsiveness in PCa. Specifically, we summarized recent pieces of evidence about lncRNAs NEAT1, H19, MALAT1, and HOTAIR, in estrogen signaling, emphasizing their role in PCa progression and the acquisition of a castration-resistant phenotype. Here, the reader will find information about lncRNAs present in estrogen-dependent transcriptional complexes. The potential role of lncRNA/estrogen signaling as a novel pathway for PCa treatment will be discussed.

1. Introduction

In this review, we will discuss the biological effects of estrogens and the genomic and non-genomic activities (Hamilton et al., 2017) mediated by the estrogen receptors α and β (ERα and ERβ). The classical mechanism of ER action involves ligand binding to the receptor that induces the dimerization with another ER. The complex (homodimers or heterodimers) recognizes a specific DNA sequence, named estrogen-responsive element (ERE), present on the promoters of target genes regulating their transcription. ER also controls gene expression without binding the DNA but modulating the function of other classes of transcription factors through protein-protein interactions. In this indirect or "tethered" mechanism, ER interacts with existing transcription factors (e.g., Fos/Jun) while associating with their respective response elements retaining the hormone-responsiveness. Therefore, the presence of ER in these transcription complexes makes the whole complex sensitive to the estrogen. Nevertheless, the ER genomic activities might also be regulated by estrogen-independent pathways involving protein kinases, which induce phosphorylation and activation of nuclear ERs independently of the hormone (Zhao et al., 2019).

The ERs non-genomic activities involve a small portion of the intracellular ER pool and precisely that located in the proximity of the plasma membrane, in structures called caveolae, associated with other proteins like the scaffold protein caveolin-1 or Src, Ras and PI3-kinases (Bjornstrom and Sjoberg, 2005). This ER subgroup responds to estrogens with the rapid activation of a signaling cascade, including the generation of calcium currents, cAMP, inositol phosphate generation, and the stimulation of protein kinase activity. Of note, these diverse mechanisms of action are not mutually exclusive but rather complementary, and once active, they both contribute to the regulation of gene transcription in response to estrogen stimulation (Bjornstrom and Sjoberg, 2005).

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1.1. The role of sex steroid hormone signaling in prostate cancer: an outline

PCa is the second leading cause of cancer death among men in western countries (Bray et al., 2018). Androgen deprivation therapy, radiation, and radical prostatectomy are the best therapeutic approaches, but about one-third of patients develop a lethal androgen-independent disease (Cattrini et al., 2017). For this reason, finding new molecular markers or targets is the most urgent need in the field as well as the identification of more effective therapies for the prevention and treatment of metastatic and therapy-resistant PCa. The role of the sex hormone receptors is continuously under evaluation to understand how their role in PCa may elicit new therapeutic solutions. Herein, we shall briefly summarize some of the most critical features of estrogen receptors in the context of the healthy prostate and their role in PCa (Auchus and Sharifi, 2020). However, for a more thorough discussion about the role of sex hormone receptors in the prostate and, in particular, that of androgens, the reader is referred to other recent and more specialized articles (Zhao et al., 2019; Fujita and Nonomura, 2019; Truong and Lange, 2018).

Androgen receptor (AR) is a ligand-dependent trans-acting regulatory protein belonging to the steroid receptor in the nuclear receptors superfamily. Usually, androgens, especially dihydrotestosterone and testosterone, combine with AR and cause its dissociation from heat shock protein-90 complex. Subsequently, AR undergoes to homodimerization, nuclear translocation, and in the presence of a ligand, binding to the androgen-responsive elements encompassing the regulatory genomic regions of androgen-responsive genes. Depending on the type of ligand, agonist or antagonist, the hormone-receptor complex may stimulate an activating or inhibitory response of the target genes transcription affecting in turn, the differentiation process of prostatic epithelial cells (Siegel et al., 2014; Koochekpour, 2010). AR-mediated androgen signaling pathways play an essential role in regulating life and death of prostate epithelial cells and, in general, the function of male reproductive system. AR plays a significant role in the development of an insidious form of PCa, the castration-resistant prostate cancer (CRPC), which is defined by the progression of the disease despite androgen depletion therapy (ADT). This condition may be recognized by a continuous rise in serum prostate-specific antigen (PSA) levels and the appearance of new metastases (Wang et al., 2018; Hettel et al., 2018). About 80% of CRPC patients showed increased expression of AR whereas only 20–30% exhibit lack of AR (Chen et al., 2017).

The estrogen receptor (ERα and ERβ) family is activated upon binding with estrogen, and in dimeric form recognizes the estrogen response elements in the genome to regulate the expressions of target genes. ERα is highly expressed in female reproductive organs, whereas ERβ is abundantly expressed in many organs, including the prostate. ERα is consistently upregulated during the malignant transformation of prostate epithelium and, subsequently, in high-grade (primary tumors characterized by pathological Gleason score > 7) and metastatic PCa (Bjornstrom and Sjoberg, 2005). In CRPC, ERα expression was increased by androgen-deprivation therapy (ADT), suggesting a role for this receptor in prostate oncogenesis (Wang et al., 2018). Indeed, the genetic inactivation of ERα prevented the development of the high-grade Prostatic Intraepithelial Neoplasia (PIN), a pre-malignancy lesion, believed to precede the development of prostate adenocarcinoma, the most common form of prostate cancer (Banerjee et al., 2018) or PCa induced by chronic exposure to testosterone and estradiol (Russell et al., 2017). Based on these findings, ERα inhibitors such as anti-estrogens and ERα antagonists have been investigated in early-stage clinical trials demonstrating antitumor activity in PCa (Dunn and Ford, 2007).

On the contrary, there are conflicting results about the role of ERβ. This molecule, involved in the differentiation of prostatic epithelial cells and numerous antiproliferative actions on prostate cancer cells, is commonly considered a tumor-suppressor gene (Bonkhoff, 2018). However, hormone naïve PCa (characterized by no prior hormonal therapy or ADT), unlike high-grade PIN, shows elevated ERβ expression in different locations, including lymph node and bone metastasis (Bonkhoff, 2018). This evidence is in favor of a tumorigenic role for ERβ, possibly depending on the cancer stage (Di Zazzo et al., 2016). This scenario is further supported by the evidence that ERβ appears extensively expressed in luminal cells, both in benign and neoplastic lesions and in PCa stem cells (Bonkhoff, 2018; Di Zazzo et al 2016, 2018). Altogether, these findings suggest that both ERs may represent prevention and therapeutic targets for PCa.

Of interest is the evidence that hormone receptor interacts or regulates some long non-coding RNAs (lncRNAs) having an impact at different levels on prostate physiology and pathophysiology. This matter is discussed below, with particular attention paid to lncRNAs involved in PCa.

2. Prostate-cancer associated lncRNAs and their role in estrogen receptor signaling

LncRNAs are RNA transcripts longer than 200 nucleotides with no or limited protein-coding capability. The biology of lncRNAs is multifaceted acting, mainly as modulators, at both the transcriptional and translational levels, in several biological functions putting in place a complex array of mechanisms. Growing evidence indicates that lncRNAs play a significant role in rewiring multi-layered gene expression in which lncRNAs act as a scaffold or guide. LncRNAs are targeted to chromatin by proteins having dual RNA and DNA binding capabilities (Mishra and Kanduri, 2019). It is increasingly evident that lncRNAs form functional layers of the cancer genome (Chi et al., 2019; Jiang et al., 2019). According to recent studies, lncRNAs exhibit aberrant expression patterns in various types of cancer, playing an essential role in both cancer incidence and spreading. This concept also applies to PCa, in which lncRNAs accomplish critical functions in cancer initiation, development, and progression (Ramnarine et al., 2019; Xu et al., 2019). Fig. 1 summarizes a subset of lncRNAs highly expressed in PCa, suggesting potential for a clinical application in diagnosis, prognosis, and prediction (Ramnarine et al., 2019; Xu et al., 2019; Lim et al., 2018). Some of them are involved in estrogen signaling in PCa context as candidate novel biomarkers representing potential therapeutic targets. This concept (detailed in paragraph 2.3) is based on some original reports from our and other groups (Aiello et al., 2016; Bhan et al., 2014). In particular, HOX transcript antisense RNA (HOTAIR) and metastasis-associated lung adenocarcinoma transcript-1 (MALAT1) can associate with both ERα/ERβ at the chromatin level (Aiello et al., 2016). This finding supports a novel molecular mechanism expanding our knowledge of hormone action. The interaction with ERs appears to be necessary for complete estrogen responsiveness, as indicated by HOTAIR and MALAT1 depletion experiments determining abrogation of estrogen sensitivity of the estrogen target gene pS2, in both PCa cell lines and Organotypic Slice Cultures (OSCs).

The following are a few relevant examples of specific lncRNAs as effectors of estrogens/estrogen receptor signaling in prostate cancer pathophysiology (Fig. 1).

2.1. NEAT1: a ERα target involved in castration-resistance

The nuclear enriched abundant transcript 1 (NEAT1) is a structural constituent of paraspeckles and is dysregulated in cancer. NEAT1 regulates apoptosis, cell growth, proliferation, invasion, and metastasis (Ghafouri-Fard and Taheri, 2019; Klec et al., 2019), acting also as competing endogenous RNAs (ceRNA) through targeting and recruiting microRNA (miR). For example, in ovarian cancer, lncRNA (NEAT1) functions as a ceRNA for miR-506 to promote cell proliferation and migration (Yong et al., 2018). Chakravarty and colleagues (Chakravarty et al., 2014) revealed that NEAT1 is a specific transcriptional target of ERα in PCa and is significantly overexpressed in prostate cancer versus benign prostate. Once activated, NEAT1 acts as a transcriptional

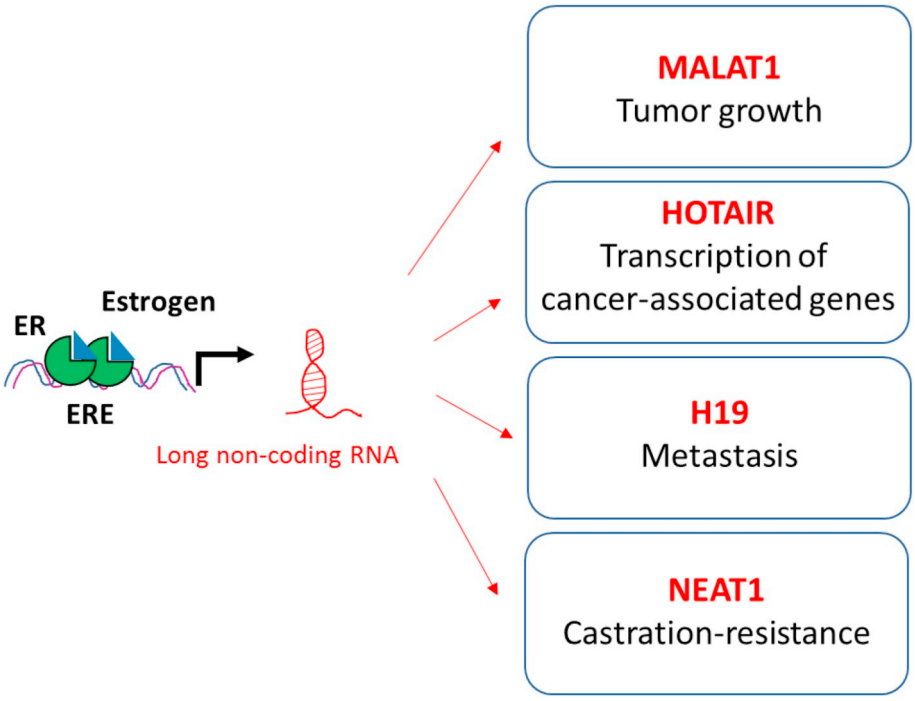

Fig. 1. LncRNAs play a distinctive role in PCa progression. MALAT1 appears to be associated with tumor growth and survival; HOTAIR is involved in the transcriptional regulation of cancer-regulated genes because of its association with Polycomb; H19 and NEAT1 might play a role in PCa metastatic progression and acquisition of a castration-resistance phenotype.

activator of well-characterized PCa genes and NEAT1 silencing compromised the expression of ERα target genes, suggesting that NEAT1 is not only a downstream target but also a mediator of ERα signaling in prostate cancer cells. Of note, the ERα-NEAT1 axis might operate in the absence of AR or during androgen deprivation therapy. In this context, it may have clinical implications, specifically in the acquisition of castrate-resistant phenotype, facilitating the onset of refractory disease by overcoming the androgen/AR signaling (Chakravarty et al., 2014; Lin, 2016).

2.2. H19: an ERβ target with a role in tumor metastatization

The oncofetal H19 lncRNA is involved in several steps of tumorigenesis from the early stages up to metastasis. H19 exerts either oncosuppressor or oncogenic activity widely depending on the cancer type and tumor microenvironment (Raveh et al., 2015). Aberrant epigenetic modifications in IGF2/H19 locus in PCa tissues were firstly described gene by Paradowska (Paradowska et al., 2009). Overexpression of this lncRNA in metastatic prostate cell lines repressed cell migration by increasing the level of miR-675 embedded in the first exon of H19 (Zhu et al., 2014). Moreover, recent evidence highlighted the role of lncRNAs in cancer progression, depending on the tumor microenvironment (Botti et al., 2019).

H19 is among the lncRNAs most sensitive to estrogens (Adriaenssens et al., 1999) and hypoxia (Matouk et al., 2007), two stimuli exerting a pro-tumoral role in PCa. Bacci and colleagues (Bacci et al., 2019) highlighted H19-dependent mechanisms by which estrogen and hypoxia signaling favor the acquisition of an aggressive phenotype. In PCa cells, H19 was independently upregulated by estrogen or hypoxia, whereas it was transcriptionally inhibited upon a combined treatment, estrogen *plus* hypoxia. In turn, H19 may act as a transcriptional repressor of several cell adhesion molecules by recruiting EZH2 Polycomb subunit increasing histone 3, tri-methyl lysine 27 (H3K27me3) level at the promoter region. In particular, E-cadherin, β3 and β4 integrin subunits are regulated by this mechanism. The following events occurred in PCa depending on the tumor microenvironment. In essence, under estrogen stimulation or in the presence of hypoxia, H19 was upregulated, while E-cadherin (CDH1) was downregulated following induction of epithelial-mesenchymal transition (EMT) that favors single-cells migration (Bacci et al., 2019).

Conversely, in the presence of combined stimuli, H19 was downmodulated with increasing of CDH1 as well as β3 and β4 integrins expression exhibiting a hybrid epithelial/mesenchymal phenotype where cells retain epithelial traits of the cell to cell adhesion and simultaneously gain mesenchymal characteristics of migration and invasion allowing them to move collectively as clusters (Jolly et al., 2015). The co-regulation of CDH1 and β integrins under combined estrogens and hypoxia stimuli satisfies the characteristics of the cohesive metastatic phenotype described by Harryman et al. (Harryman et al 2016). According this study the aggressive and metastatic PCa proceeds through a cluster of invasive cells expressing both integrins and cadherins, for extracellular matrix remodeling during migration as well as for the cell-to-cell cohesion, supporting the so-called “collective migration”, respectively.

These data underline the crucial role of the lncRNA H19 in estrogen signaling and its potential impact on the tumor microenvironment: the switch from EMT to a β integrin-mediated invasion. This phenomenon is crucial for the acquisition of an aggressive and metastatic phenotype. It might depend on the presence of both estrogen and hypoxia leading to specific inhibition of H19 transcription.

2.3. MALAT1 and HOTAIR are ERβ partners in PCa

The lncRNAMALAT1 plays an essential role in cancer biology, mainly acting as tumor-promoting (Schmitt and Chang, 2016). In cancer, MALAT1 is widely investigated for its functional activity and therapeutic potential. MALAT1 is involved in the modulation of several cellular processes, including proliferation, cell death, cell cycle progression, migration, invasion, immune response, angiogenesis, and tumorigenicity (Li et al., 2018). Among mechanisms associated with MALAT1, the regulation of transcription was described *via* its interaction with the Polycomb Repressive Complex 1 subunit Pc2/CBX4 (Yang et al., 2011).

LncRNA HOTAIR is highly expressed in a broad spectrum of cancers and is associated with metastasis and poor prognosis (Qu et al., 2019). HOTAIR governs fundamental biochemical and cellular processes to promote proliferation, invasion, survival, drug resistance, and metastasis, and several studies are highlighting its use as a circulating

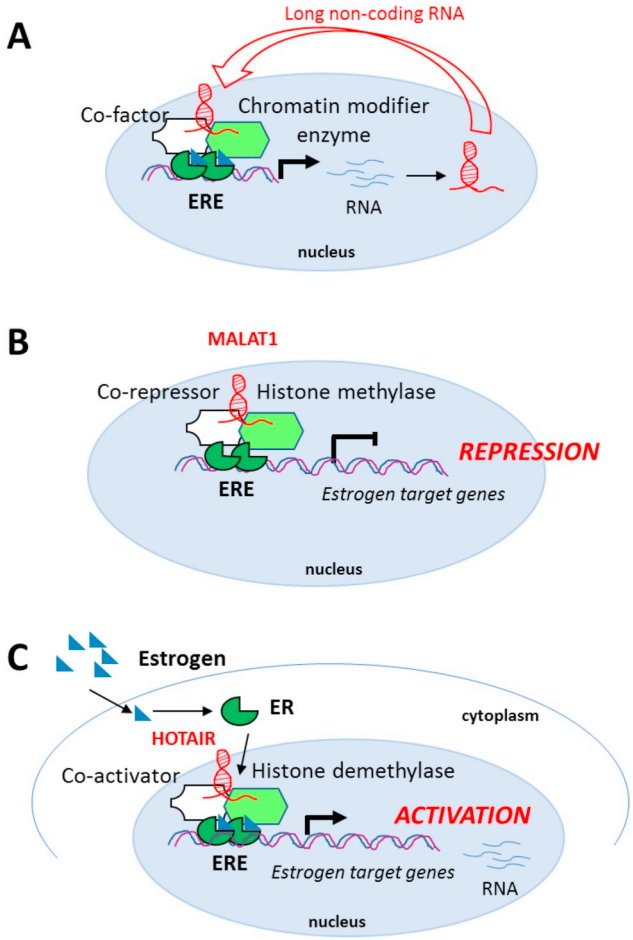

Fig. 2. Modeling of MALAT1 and HOTAIR action in estrogen signaling. A) Estrogen activated lncRNAs act on chromatin as partners of ERs, contributing to either positive or negative gene expression regulation. B) In the absence of estrogen, MALAT1 interacts with ERs and some corepressors to silence transcription. C) In an estrogen-dependent mode, HOTAIR recruits co-activators to promote transcription.

biomarker (Botti et al., 2019). HOTAIR is capable of interacting with many targets, mainly acting as a regulator of chromatin states by binding Enhancer of Zeste homolog 2 (EZH2), the methyltransferase specific to histone 3 lysine 27, and the lysine-specific demethylase 1 (LSD1), a central player in epigenetic regulation (Gupta et al., 2010).

Regarding the role of MALAT1 and HOTAIR in estrogen receptor signaling, Aiello and colleagues (Aiello et al., 2016) identified a molecular mechanism in which both lncRNAs are involved in estrogen-dependent transcription, although with apparently opposite roles (Fig. 2).

In particular, they demonstrated that in PCa, MALAT1 and HOTAIR were associated with the estrogen ERβ on the promoter region of genes bearing an ERE (Fig. 2A). In the absence of estrogen, MALAT1 acts as a repressor of transcription (Fig. 2B). Upon estrogen treatment, as ERβ binds to EREs, the MALAT1 transcript decreased while HOTAIR density significantly augmented (Fig. 2C). These changes were paralleled by a reduction of repressive complexes identified by the Polycomb subunit CBX4 and increased recruitment of lysine demethylases, including the lysine demethylases 1 and 4 (KDM1; KDM4). This phenomenon leads to Histone 3 lysine 9 trimethylation (H3K9me3) and Histone 3 lysine 9 dimethylation (H3K9me2) rarefaction at the promoter level of target genes which are transcriptionally activated. These data suggest a mechanism by which MALAT1 acts as a transcription repressor of estrogen-dependent genes, whereas HOTAIR is more involved in the recruitment of lysine demethylases necessary for the epigenetic modification associated with transcriptional activation.

3. Modulation of lncRNAs by selective estrogens receptors modulators (SERMs) as a tool towards *ad hoc* novel therapeutic approaches in PCa

The possibility to modulate estrogen/lncRNAs signaling for the transcriptional regulation of PCa represents an intriguing concept with potential clinical impact. In particular, the application of SERMs might be a promising therapeutic approach. SERMs belong to a family of estrogen receptors binding molecules widely used in a large variety of estrogens-dependent diseases such as osteoporosis and breast cancer. The outcome of the latter disease has been substantially improved by one of the most frequently used among SERMs, namely tamoxifen, which is an ER agonist in the heart and bone but acts as an antagonist in the *breast*. Intriguingly, SERMs may act as agonists or antagonists in a tissue-dependent manner (Haynes and Dowsett, 1999). Indeed, SERMs sustain the normal ER signaling necessary for the maintenance of bone mass and the protection of cardiovascular tissue. However, in some other tissues such as breast and uterus, SERMs may also be ER antagonists, with antiproliferative effects, thus preventing the progression of breast and endometrial cancer, respectively (Patel and Bihani, 2018).

Several studies enlightened the possibility of using SERMs directly against PCa with promising results, as reported by Fujimura and collegues (Fujimura et al., 2018). Their work demonstrated that tamoxifen's analogs, specifically toremifen and raloxifen, do not affect patients' outcome if individually administered. The combined treatment, however, in association with ADT, appears partially to improve patients' prognosis. An explanation for this selective success might be accountable for the extreme heterogeneity of PCa underscoring the need for a personalized medicine. SERMs could also be used indirectly in PCa therapies, modulating ER signaling *via* lncRNAs. Among studies principally focused on breast cancer, there are some reports which suggest modulation of estrogens/lncRNAs signaling through SERMs. In particular, the lncRNA GAS5 enhanced the efficacy of tamoxifen in breast cancer (Gu et al., 2018). In this context, GAS5 caused the down-modulation of the oncogenic miR222, although the mechanism at the origin of this effect is not yet completely understood. Of note, lncRNA modulation might occur *via* phytochemicals (Saghafi et al., 2019). MALAT1 expression, for instance, could be down-modulated by resveratrol (Gehm et al., 1997) a phytoestrogen naturally found in grapes as a major constituent of wine thought to exert both cardioprotective and chemo-preventive activities, in colorectal cancer (Ji et al., 2013). HOTAIR seems regulated by two other phytochemicals, curcumin, and genistein, in renal cell carcinoma and endocrine cancers, respectively. For this work, we focused on the possible role of genistein, a soy isoflavone, on PCa. Chiyomaru and colleagues (Chiyomaru et al., 2013) showed that genistein is regulating HOTAIR and miR-34a, inhibiting cell growth, and migration of PCa cells. Specifically, genistein treatment decreases HOTAIR transcript through the up-regulation of the oncosuppressor miR-34a. Further studies are required to elucidate the precise molecular mechanism by which the phytoestrogen genistein act on non-coding RNAs in the PCa context.

4. Summary and conclusions

LncRNAs are involved in every important biological process and the pathophysiology of a growing number of diseases. In this review, we summarized recent evidence about the role of specific lncRNAs such as NEAT1 and H19 in estrogen signaling leading to PCa progression and acquisition of castration-resistant phenotype. Here, we also reviewed the state-of-art of MALAT1 and HOTAIR transcriptional mechanism and their involvement as ERs partners in estrogen-dependent transcriptional complexes, as proposed initially by Foulds and colleagues (Foulds et al., 2016).

Overall, in response to estrogens, several lncRNAs pathways are activated, leading to genomic and non-genomic regulation of gene expression. The mechanism exerted by lncRNAs in an estrogen-dependent

manner might lead to novel opportunities for the discovery of therapeutic strategies in PCa.

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