Endocrine nuclear receptors and long non-coding RNAs reciprocal regulation in cancer (Review)

MONICA CANTILE[1*], MARGHERITA CERRONE[2*], MAURIZIO DI BONITO[2], PASQUALE MOCCIA[2], MAURA TRACEY[3], GERARDO FERRARA[2] and ALFREDO BUDILLON[1]

[1]Scientific Directorate; [2]Pathology Unit and [3]Rehabilitation Medicine Unit, National Cancer Institute INT-IRCCS Fondazione G. Pascale, I-80131 Naples, Italy

Received April 20, 2023; Accepted September 26, 2023

DOI: 10.3892/ijo.2023.5595

Abstract. Nuclear receptors (NRs) are transcriptional regulators involved in different aspects of normal cell physiology. Their deregulation is associated with aberrant expression, gene mutations and/or epigenetic alterations that can be related to the pathogenesis of various human diseases, and especially in cancer. In particular, a complex genomic network involved in the development and progression of NR-mediated cancer has been highlighted. Advanced genomic technologies have made it possible to understand that the expression of any particular NR in a given cancer subtype is only one component of a larger transcriptional machinery that is controlled by multiple associated NRs and transcription factors. Additionally, their ability to regulate and to be regulated by molecules of non-coding RNAs, microRNAs as well as long non-coding RNAs, is opening new scenarios for understanding the role of NRs in cancer initiation and progression. In the present review, the authors aimed to outline the reciprocal interactions that exist between the main NRs and long non-coding RNAs in different tumor diseases, to suggest new diagnostic biomarkers as well as therapeutic strategies for these tumors.

Contents

Correspondence to: Dr Monica Cantile, Scientific Directorate, National Cancer Institute INT-IRCCS Fondazione G. Pascale, 53 Via Mariano Semmola, I-80131 Naples, Italy
E-mail: m.cantile@istitutotumori.na.it

*Contributed equally

Key words: nuclear receptors, long non-coding RNAs, cancer progression

1. Introduction

Nuclear receptors (NRs) are ligand-activated transcription factors involved in main cellular processes including homeostasis, metabolism, growth, differentiation and development (1). These receptors interact with specific DNA sequences in the promoter and enhancer regions of their target genes modulating their transcription by co-binding to a series of co-factors/coregulators belonging to transcription initiation machinery (2). The NR superfamily can be divided into three classes based on the type of ligand: Endocrine, metabolic and orphan NRs (3). The endocrine NR subfamily includes estrogen receptors (ERs) αlpha (ERα or ESR1) and ERβ (ERβ or ESR2), androgen receptors (AR), progesterone receptors, glucocorticoid receptors, mineralocorticoid receptors, vitamin D receptors (VDRs), retinoic acid receptors (RARs), as well as thyroid hormone receptors (THRs) (1).

Numerous factors contribute to the regulation of NRs, especially the recruitment of coregulatory proteins, post-translational modifications and interactions with other transcription factors.

Dysregulated NR signaling can promote a large series of pathological processes. In particular, mutation or aberrant expression of NR and/or of their coregulators may influence both the development and progression of several human diseases including cancer (4). Moreover, epigenetic regulation, especially by activation of non-coding RNA molecules (ncRNAs), represents an element of complexity in the modulation of NR-dependent gene expression.

Long non-coding (lnc) RNAs are non-coding molecules longer than 200 bp, able to interact with mRNA, DNA, protein and microRNA (miRNA or miR) (5). They have different regulatory functions in humans: i) Regulation of histone modifications at the chromatin level by interaction with histone-modified complexes or enzymes; ii) transcriptional regulation and post-transcriptional regulation; iii) miRNA

sponge; iv) RNA stability; v) Protein relocalization and vi) post-translation modifications (6).

During cancer evolution, lncRNAs may regulate cell proliferation, apoptosis, migration, invasion, stem-like phenotype and remodeling of the tumor microenvironment (TME) (7). Previous studies have shown that lncRNAs can function as positive or negative regulators of NR-dependent gene expression, and in turn, NRs can regulate different lncRNAs. This crosstalk appears to be particularly important in the modulation of oncogenic processes (8,9).

The steroid receptor RNA activator (SRA) was identified as the first lncRNA able to bind and increase the activity of steroid receptors (10) (Fig. 1). SRA is able to interact with numerous proteins acting as a 'scaffold' for the assembly of other coregulatory proteins that direct NR-dependent transcription (11-14).

In addition to the role of signaling by NR, numerous studies revealed that SRA is involved in other physiological functions: i) Modulation of adipogenesis via direct binding to and promoting the transcriptional activity of peroxisome proliferator activated receptor γ, ii) regulation of steroidogenesis and adrenal biology by binding and activation of SF-1 as well as dosage-sensitive sex reversal-adrenal hypoplasia protein, iii) promotion of muscle differentiation by increasing the activity of myogenic differentiation 1 protein (12), iv) induction of proliferation and migration of vascular smooth muscle cells by stimulating the phosphorylation of mitogen-activated protein kinase, extracellular signal-regulated kinases and cAMP response element-binding protein CREB (15), v) promotion of melanin pigmentation process by modulation of p38 and phosphoribosyl-anthranilate isomerase gene expression (16); and vi) modulation of insulin signaling and regulation of β-oxidation (17).

Instead, aberrant SRA expression and mutant variants have been identified in several pathological conditions, not only in hormone-driven tumors (Fig. 1) (12). SRA promotes cervical cancer cell migration and invasion via upregulation of matrix metalloproteinase-9, matrix metalloproteinase-2, vascular endothelial growth factor A (VEGFA) expression and NOTCH receptor 1 signaling pathways (18). Park *et al* (19) revealed that SRA is involved in the proliferation, migration and invasion of endometrial cancer cells by increasing the expression of EIF4E-BP1 and Wnt/β-catenin signaling activity. SRA mediates p38 activation, cell invasion along with proliferation, regulates epithelial-mesenchymal transition (EMT) and distant metastasis in melanoma (20) and induces tumor progression as well as drug resistance in colorectal cancer by oxidative phosphorylation pathway genes (21). In hormone-driven cancers, SRA is directly involved in the mechanisms underlying breast tumorigenesis and tumor progression (22), and their isoforms are capable of enhancing AR activities in prostate cancer cells (23).

More recently, Kim *et al* (24) demonstrated that SRA is able to regulate cell migration, proliferation, and invasion of ovarian cancer cells by modulation of EMT and expression of NOTCH-related genes.

Given the importance of NRs in hormone-driven cancers, a deeper understanding of epigenetic regulatory mechanisms in human tumors may offer new scenarios for new diagnostic and predictive biomarkers. In the present review, it was proposed to schematize the crosstalk existing between the main endocrine NR and the lncRNAs in tumor initiation and progression.

2. Crosstalk between ERα and lncRNAs in cancer

Two different ER subtypes were identified: i) The NRs ERα and ERβ, and ii) the membrane receptor G protein-coupled ER 1 (GPER1). Their expression is tissue-specific. ERα, has 3 isoforms and truncated isoforms can suppress ERα activity by heterodimerizing with full-length isoforms (25,26). It is mainly expressed in female sex organs, such as the breast, ovaries and uterus as well as involved in the regulation of cell proliferation in addition to apoptosis in cancer cells (27). Mechanistically, ERα translocates from the cytoplasm to the nucleus, upon binding to 17β-oestradiol (E2), and binds estrogen response elements (EREs) in the ERα-dependent gene promoter (28).

Breast cancer (BC). Most of the data highlights in particular the crosstalk between ERα and lncRNAs in BC. In BC, ERα can be activated by estrogen in luminal subtypes, but its aberrant activity in a hormone-independent manner has also been described in basal-type subtypes (29). Numerous estrogen-regulated lncRNAs have been identified in BC. HOX antisense intergenic RNA (HOTAIR) is transcriptionally induced by E2 and it is involved in the modulation of chromatin-modifying enzymes in addition to the regulation of gene silencing (30). ERs along with a series of coregulators (histone methylases MLL1, MLL3 and CREB-binding protein/p300) bind to the promoter of HOTAIR, containing multiple functional EREs, in an E2-dependent manner (30). This interaction potentially contributes to BC evolution and progression (31,32). Gupta *et al* (33) described that aberrant expression of HOTAIR can affect cell motility and matrix invasion in BC cells, and its silencing in doxorubicin-resistant cells decreases cell proliferation and increases apoptosis (Fig. 1) (33). However, estrogen promoted HOTAIR through its membrane receptor GPR30 by the suppression of miR-148a (34). This highlights that the mutual modulation mechanism between ERα and HOTAIR is very complex and implies the simultaneous activation of other molecular networks.

Similar to HOTAIR, metastasis-associated lung adenocarcinoma transcript-1 (MALAT1) is regulated by estrogen and it associates with EREs along with the polycomb repressive complex 1 (PRC1) (35). MALAT1 binding to chromatin and other components can be reduced in presence of estrogen, indicating it has an inhibitory role in regulating estrogen target genes. Zhao *et al* (36) demonstrated that high-concentration E2 treatment largely decreased MALAT-1 RNA level. Silencing of MALAT1 showed similar effects on the proliferation, migration and invasion of BC cells. These data highlighted that E2 treatment affects BC cells proliferation, migration and invasion in an ERα-independent, via a dose-dependent way by decreasing the MALAT1 RNA level (Fig. 1) (36). Previously, a meta-analysis study revealed that high MALAT1 expression is associated with poor relapse-free survival (37) and its aberrant expression can be related to Oncotype DX 21-gene test, to predict the recurrence score, in patients with ER^+ tumors and early BC (38). These data strongly indicated the role of MALAT-1 as an important prognostic marker in patients with BC.

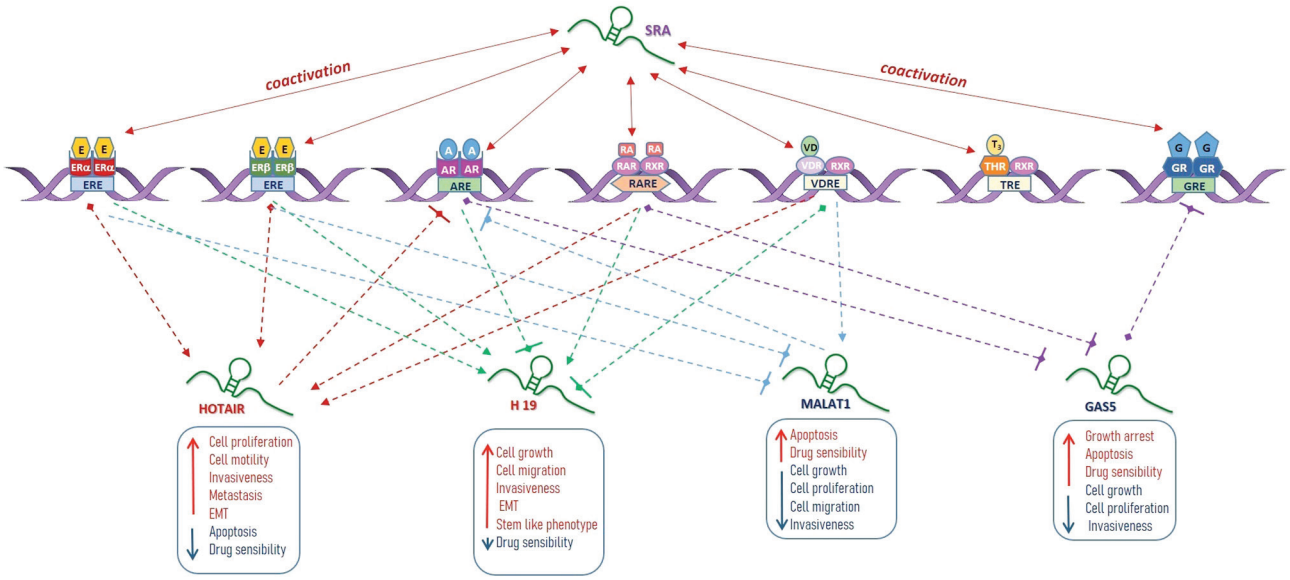

Figure 1. Schematic representation of the reciprocal functional interactions between nuclear receptors and the best-characterized lncRNAs in tumor cells. The lncRNAs steroid receptor RNA activator represents a coactivator for all NRs, which is able to act as a scaffold for the assembly of other coregulators to modulate NR-dependent transcription, in human cancer. The lncRNAs HOTAIR and H1 mostly behave as oncogenes in cancer cells. HOTAIR is able to interact with most of the NRs. It contains in its promoter multiple estrogen response elements and can be transcriptionally induced by estradiol. HOTAIR crosstalk with ERα and ERβ promotes cell proliferation, migration, invasion, metastasis and EMT and reduces apoptosis and drug sensibility in breast and prostate cancer cells. HOTAIR crosstalk with AR leads to a formation of a suppressive complex that decreased AR transcription and promotes cell invasion in prostate cancer cells. HOTAIR crosstalk with RAR can induce myeloid cell differentiation in acute myeloid leukemia cell lines. HOTAIR crosstalk with VDR promotes cell growth and proliferation in keratinocyte carcinoma cells. Similarly, the lncRNA H19 is able to interact with most NRs. Its crosstalk with ERα can modulate cell growth, proliferation, invasion, EMT features, as well as drug resistance through Notch and c-Met activation in breast and prostate cancer cells. Lastly, H19 can be regulated not only by estrogens but also by hypoxia. H19 crosstalk with ERβ can promote stem-like features, especially in papillary thyroid cancer cells, while its crosstalk with RAR can modulate telomerase activity in promyelocytic leukemia cells. However, H19 expression is negatively regulated by androgen/AR signaling in prostate cancer cells, and by VDR signaling in colon cancer cells. Unlike HOTAIR and H19, lncRNAs MALAT1 and GAS5 can be considered tumor suppressor genes. MALAT1 crosstalk with ERα and ERβ leads to a reduction of its expression which translates into effects on cell growth, proliferation and invasion feature, especially in breast cancer cells. On the contrary, androgen/AR signaling is able to induce MALAT1 expression promoting apoptosis in breast cancer cells by miRNA-320b. Moreover, VDR silencing is able to increase MALAT1 expression, thus inducing PI3K/Akt signaling and promoting growth and proliferation in epidermal keratinocytes. GAS5 crosstalk with AR and RAR can modulate cell proliferation in prostate and glioblastoma cancer cells. GAS5 is also capable to interact with GR inhibiting its transcription and consequently promoting growth arrest and apoptosis in breast cancer cells. lncRNA, long non-coding RNA; NR, nuclear receptor; HOTAIR, HOX antisense intergenic RNA; ER, estrogen receptor; EMT, epithelial-mesenchymal transition; AR, androgen receptor; RAR, retinoic acid receptor; VDR, vitamin D receptor; MALAT1, metastasis-associated lung adenocarcinoma transcript-1.

Myocardial infarction-associated transcript (MIAT) is overexpressed in ER$^+$ BC tissues especially in aggressive ductal BC (39). In these cells, MIAT expression is induced by E2 through ERα activation. Silencing MIAT inhibited cell cycle progression and induced apoptosis, whereas its upregulation increased cell proliferation in MCF-7 cells (39). Moreover, Luan *et al* (40) underlined that MIAT promotes BC progression and functions as competing endogenous RNA to regulate dual specificity phosphatase 7 (DUSP7) gene expression by sponging miR155-5p in BC. Diethylstilbestrol led to a dose- and time-dependent upregulation of MIAT in MCF-7 cells that were dependent on ERα. MIAT silencing and pharmacological inhibition decreased cell proliferation by perturbing G1 to S phase cell cycle transition (41). The functional studies could suggest the targeting of MIAT for the optimization of therapeutic strategies in Erα$^+$ patients with BC.

The lncRNA LINC00472 promoter has an ERα binding site and can be upregulated by ERα. When overexpressed, it can interact with the NF-kB transcription factor modulating the downstream pathway (42). *LINC00472* overexpression can perturb tumor growth and reverse the aggressive phenotype of breast tumor cells *in vitro*. A meta-analysis, performed on clinical studies, described overexpression of *LINC00472* in ER$^+$ tumors, associated with improved outcomes of patients, and its low/absent expression in ER$^-$ tumors (42).

Even LINC01016 can be to be directly regulated by ERα, having an ERα binding site on its promoter, and thereby its expression is rapidly induced by estrogen treatment. Silencing of LINC00160 results in reduced proliferation (43). ER$^+$ breast tumors exhibit high expression levels of LINC01016 and patients with higher LINC01016 expression are related to poor overall survival (43). Understanding the molecular mechanisms and molecular pathways involved in the crosstalk between these lncRNAs and Erα could therefore suggest new potential prognostic-predictive markers in patients characterized by ERα$^+$. However, all these data should be confirmed on a large series of patients.

The lncRNA Down syndrome cell adhesion molecule antisense RNA 1-AS1 (DSCAM-AS1) is an estrogen-responsive lncRNA differentially expressed between benign and malignant BC cells (44) and it can distinguish features between luminal subtypes of BC (45). Its overexpression in patients with BC was associated with poor overall survival (46,47). DSCAM-AS1 can induce G1/S transition of cell cycle and represents a poor prognostic factor in luminal patients with BC treated with hormone therapy (48). *In vitro* studies

highlighted that DSCAM-AS1 interacts with nuclear ribonucleoprotein (hnRNPL) in BC cells, promoting tumor progression and inducing tamoxifen resistance (49). More recently, Yadav *et al* (50) demonstrated that progesterone also can induce expression of DSCAM-AS1 and its silencing mimics the effect of progesterone in impeding cell migration and invasion in PR^+ BC cells. Additionally, DSCAM-AS1 sponges miR-130a that regulates the expression of ESR1 by binding to its 3'-untranslated region (UTR), thereby mediating the effect of progesterone in BC cells (50). These data underlined once again that the reciprocal modulation mechanisms are very complex and that they can also involve other mediators such as progesterone.

Numerous other lncRNAs can be deregulated under the effect of estrogen and therefore by the modulation of Erα: i) Eosinophil granule ontogeny transcript (EGOT) dysregulation is associated with tumor size, lymph node metastasis progression and worse survival in patients with BC. Estrogen can reduce the expression of EGOT in a dose-dependent manner, thereby modulating autophagy in BC cells (51). ii) Two lncRNAs, lncRNA152 and lncRNA67, exhibited significant overexpression in ER^+ breast tumors in comparison to non-cancerous breast tissue; moreover, after estrogen treatment, it can regulate cell proliferation and mitogenic division in ER^+ cell lines (52). iii) A recent study, analyzing lncRNAs that are either dysregulated in response to estrogen treatment in BC cells, identified ~90 upregulated lncRNAs and 160 downregulated lncRNAs by E2 stimulus. In ER^+ patients with BC, lncRNA LINC00160 demonstrated a strong correlation with the survival rate and its neighboring E2-responsive coding gene RUNX1 (53).

Numerous other lncRNAs estrogen signaling-dependent are associated with endocrine therapy resistance in BC. BC cells can develop different mechanisms to promote intrinsic and acquired resistance to endocrine therapy; between these, the ligand-independent transactivation of the ERα is one of the main mechanisms responsible for acquired resistance, in which numerous lncRNAs play an essential role. In particular, it is known that aberrant ERα signaling is strongly involved in tamoxifen resistance and several lncRNAs could modulate and promote this process (54). H19 lncRNA level was higher in ER-positive BC tissues than in ER-negative tumors suggesting that it is an estrogen-inducible gene and plays a key role in estrogen-induced cell proliferation (55). Treatment of BC cells with tamoxifen or fulvestrant increases H19 expression while its silencing leads to drug resistance. H19 expression can be modulated by Notch and c-MET inhibition can reverse resistance to tamoxifen and fulvestrant in an H19-dependent manner in these cells (56). Moreover, altered ERα expression can also modify H19 levels thereby modulating the apoptosis response, through pro-apoptotic gene *BCL2 interacting killer* (*BIK*), to chemotherapy in BC cells (57).

lncRNA in non-homologous end joining (NHEJ) pathway 1 (LINP1) expression is upregulated in tamoxifen-resistant BC cells and its knockdown resulted in increased tamoxifen-induced apoptosis. LINP1 transcription is suppressed in the presence of estrogen, and tamoxifen treatment restores its expression (56).

BC anti-estrogen resistance 4 (BCAR4) is inversely associated with the development of resistance to anti-estrogens in BC cells and associated with worse survival and also a higher risk of metastasis in other cancers (58). Recently, a polymorphic variant of the BCAR4 gene associated with BC susceptibility has been identified (59).

The lncRNA DLGAP1 antisense RNA 2 (DLGAP1-AS2) can promote ERα signaling, binding to the AFF3 protein and thereby the inhibition of the degradation of it. It is significantly upregulated in BC and tamoxifen can induce DLGAP1-AS2 expression (60). In the same manner, the lncRNA ERLC1 is involved in ERα signaling in BC tissues. Functionally, ERα induces ERLC1 transcription, which in turn stabilizes the *ESR1* transcript by interaction with miR-129 and FXR1. Its expression became aberrant in tamoxifen-resistant BC cells, and its silencing restored sensitivity to tamoxifen and increased the efficacy of palbociclib or fulvestrant therapy (61).

The lncRNA estrogen inducible lncRNA (ERINA) is aberrantly expressed especially in ER^+ BCs where it was inversely associated with survival and sensitivity to CDK inhibitor. Mechanistically, ERINA interacts with the E2F transcription factor 1 (E2F1), which prevents the binding of E2F1 to the tumor suppressor retinoblastoma protein 1 (RB1), thereby promoting cell-cycle progression. ERINA acts as an ER-responsive gene, and an intronic ER-binding site was identified as an enhancer that mediates the transactivation of ERINA (62). With a similar mechanism of action, Yu *et al* (63) described the lncRNA actin gamma 1 pseudogene 25 (AGPG) as a regulator of E2F1 activity in endocrine resistant BC. AGPG physically interacted with purine rich element binding protein A, thus releasing E2F1 and promoting its signaling activation in $ERα^+$ BC cells.

Horie *et al* (64) revealed that the BC Natural antisense transcript 1 (BNAT1) can induce tamoxifen-resistant in ER^+ BC cells and its silencing significantly reduced the *in vitro* and *in vivo* growth of cancer cells. This mechanism is mediated by binding of BNAT1 binding with ERα and its knockdown reduced ERα expression and its transactivation.

More recently, Chen *et al* (65) indicated that LINC02568 regulates estrogen/ERα-induced gene transcriptional activation *in trans* by stabilizing ERα mRNA through sponging miR-1233-5p in the cytoplasm and by regulating carbonic anhydrase CA12 in *cis* in the nucleus. This crosstalk modulates BC cell growth and tumorigenesis as well as endocrine therapy drug resistance (65).

In conclusion, the ability of numerous lncRNAs related to Erα activity to modulate resistance to therapies makes them important predictive biomarkers, and the evaluation of their aberrant expression could provide an additional tool for the therapeutic stratification of patients with BC.

Prostate cancer. Some lncRNAs are involved in estrogen signaling in prostate cancer. In particular, HOTAIR and MALAT1 can interact with both ERα/ERβ at the chromatin level (35). HOTAIR and MALAT1 silencing determine the abrogation of estrogen sensitivity of the estrogen target gene pS2. Nanni *et al* (66) described that MALAT1 has a role in the transcription repression of hormone receptors target genes such as pS2 and PSA in prostate cancer cells and orthotopic models (35). These observations make HOTAIR and MALAT1 important biomarkers and potential therapeutic targets in prostate cancer.

The nuclear enriched abundant transcript 1 (NEAT1) is a specific transcriptional target of ERα in prostate cancer and it is significantly overexpressed in cancer as compared with benign prostate. In prostate cancer cell lines, ERα overexpression and E2 treatment upregulated NEAT1 transcript levels in a time-dependent manner. NEAT1 acts as a transcriptional activator of different PCa genes and its silencing modified ERα target genes, suggesting that NEAT1 is not only a downstream target but also a mediator of ERα signaling in prostate cancer cells. Moreover, *in vitro* and *in vivo* NEAT1 expression is associated with aggressive phenotype and drug resistance (67). Additionally, NEAT1 lncRNA could therefore represent an important prognostic biomarker and a predictive marker of therapeutic response in patients with prostate cancer.

As previously described, lncRNA H19 is more sensitive to estrogens, a stimulus with a pro-tumoral role in prostate cancer. Bacci *et al* (68) described H19-dependent mechanisms by which estrogen and hypoxia signaling promote the acquisition of an aggressive phenotype in prostate cancer cells. H19 can be independently upregulated by estrogen or hypoxia. Moreover, the same authors revealed that H19/estrogen signaling has a potential impact on the TME by the switch from EMT to a β integrin-mediated invasion (68).

Other tumors. Numerous other lncRNAs are capable of modulating and being modulated by ERα also in other neoplastic pathologies. The lncRNA LINC00312, also known as nasopharyngeal carcinoma-associated gene 7, a novel putative tumor suppressor, is essential for ERα binding and suppression activity in nasopharyngeal carcinoma (NPC). It can promote NPC cell invasion by regulation of ERα and the HRAS/p-c-RAF and JNK2/AP-1/MMP1 signaling pathways (69).

Estrogen signaling has long been implicated in epithelial ovarian cancer progression. The lncRNA ElncRNA1 is transcriptionally regulated by E2 through ERα-EREs and it was described as able to promote epithelial ovarian cancer cell proliferation (70). Moreover, Qiu *et al* (71) reported that E2 significantly dysregulated 115 lncRNAs in ERα-positive SKOV3 ovarian cells compared with E2-untreated controls. Among these, both TC0101441 and TC0101686 were dysregulated by E2 also in other ERα-positive PEO1 ovarian cells and dysregulated in ovarian cancer patients. In particular, high TC0101441 expression was associated with lymph node metastasis, exhibiting a potential involvement in the metastatic progression of ovarian cancer (71).

The lncRNA DSCAM-AS1 overexpression in endometrial cancer (EC) has a significant association with shorter overall survival of patients with EC. In these cells, it is associated with the endometrial tumor promotor prolactin gene and with the expression of ERα together with its target genes trefoil factor 1 and progesterone receptor (PgR). DSCAM-AS1 silencing in EC cell lines reduced cell growth and proliferation by inhibition of NOTCH1, Protein Tyrosine Kinase 2 as well as early growth response factor 1 (EGR1) expression (45).

The lncRNA LINC00899 overexpression is able to inhibit the viability, proliferation, migration and invasion of cervical cancer cells. miR-944 could competitively bind with LINC00899 and its upregulation can inhibit ER expression, thereby promoting the migration and invasion of cervical cells. These data highlight the role of LINC00899/miR-944/ESR1 axis in the regulation of cervical cancer progression (72).

More recently, Cheng *et al* (73) revealed that lncRNA maternally-expressed 3 (MEG3) promoter binds to ERα in liver cancer cells. ERα upregulation repressed the proliferation, migration as well as invasion and promoted apoptosis of HepG2 cells under high glucose conditions. ERα silencing decreased MEG3 expression and in turn enhanced proliferation, migration and invasion. These data highlighted that ERα has a protective role in hepatocellular carcinoma (HCC) being able to inhibit cell progression through positive regulation of lncRNA MEG3 (73).

3. Crosstalk between ERβ and lncRNAs in cancer

ERβ is expressed in different types of tissues and cells, to a higher degree in females as compared with males (74). ERβ has at least five different isoforms, four shorter ERβ isoforms, and a full-length ERβ isoform (75). The five ERβ variants, which result from alternative splicing of the last coding exon, and deletion of coding exons, are named ERβ1-5. They can be detected in multiple normal tissues, especially in BC tissues and cell lines (76).

In the same manner as other superfamily members of hormone NRs, ERβ binds EREs located on target genes promoter regions to modulate their expression levels (75).

MALAT1 and HOTAIR are all, important protagonists in ERβ signaling especially in prostate cancer (35). In normal conditions, MALAT1 acts as a suppressor of gene transcription. After estrogen treatment, ERβ binds to EREs and leads on the one hand the reduction of MALAT1 transcript and on the other hand increases HOTAIR expression. Mechanistically, MALAT1 acts as a suppressor of estrogen-related genes transcription. In turn, HOTAIR is involved in the epigenetic modification associated with transcriptional activation of estrogen-related genes (77).

Although numerous studies have verified that ERβ is an independent prognostic and/or predictive factor in BC, very little information is available regarding the crosstalk between ERβ and lncRNA in BC. ERβ could play a crucial role in BC cell progression, particularly EMT and metastasis (78). This suggests a potential association with HOTAIR as well as ERβ in BC and subsequently downstream molecules, miR-138/204/217 and miR-200c, in BC, although, it remains to be investigated (79).

Crosstalk between HOTAIR and ERβ has instead been abundantly demonstrated in renal cell carcinoma (RCC) cells. Ding *et al* (80) showed that ERβ can increase HOTAIR expression by transcriptional upregulation in multiple RCC cell lines. In RCC tissues, the ERβ expression can be aberrant too (80). Both ERβ activation by 17β-estradiol treatment and its knockdown are able to modulate HOTAIR expression. Crosstalk between ERβ and HOTAIR, by miR-138, miR-200c, miR-204, as well as miR-217, can modulate different oncogenes, such as Cyclin D2, VEGFA and VIM, to induce RCC proliferation as well as invasion (80).

More recently, He *et al* (81) demonstrated that the anti-angiogenic drug sunitinib, widely used for RCC therapy, can induce the expression of lncRNA-ECVSR to influence the RNA stability of ERβ. This leads to an alteration of vasculogenic mimicry formation in RCC cells (81).

The crosstalk between SRA and ERβ signaling has been reported as involved in the pathogenesis from ovarian endometriosis to ovarian clear cell carcinoma (OCCC). A preliminary study revealed that SRA interacts preferentially with ERβ rather than with Erα (82). Lin *et al* (83) described that SRA expression level gradually enhanced from endometriosis (EM) to EM-associated ovarian clear cell carcinoma (EAOCCC) to OCCC, showing an inverse relationship with ERβ expression. During malignant transformation from EM to OCCC, SRAP, as a co-suppressor, may play a role in hypermethylation of the promoter of ERβ and silence the latter. Consequentially, overexpression of SRA accompanied by ERβ reduction may be a crucial step in the EAOCCC development (83). Therefore, interfering with the crosstalk mechanisms between SRA and ERβ and the molecular pathways involved could represent a new potential strategy to prevent the progression of ovarian cancer.

In papillary thyroid carcinoma, H19 and ERβ crosstalk are able to promote stem-like phenotype in cancer cells. E2 significantly promotes H19 transcription via Erβ (84). Both exhibit an aberrant expression in papillary thyroid cancer stem cells (PTCSCs). Knockdown of ERβ decreases tumor growth, diminishes $ALDH^+$ cell populations and suppresses the sphere formation capability of PTC cells. In the same way, silencing of H19 inhibits E2-induced sphere formation ability. In papillary thyroid cancer, H19 can act as competitive endogenous RNA that sequesters miRNA-3126-5p to reciprocally release ERβ expression. Additionally, H19 appears highly expressed in PTC tissue specimens, which is associated with poor overall survival (84). Thus, as ERβ plays a critical role in regulating PTCSC maintenance, targeting ERβ could provide a novel therapeutic avenue for patients with advanced PTC.

4. Crosstalk between ARs and lncRNAs in cancer

AR is a member of the steroid-hormone family involved in the regulation of normal growth and development of different organs (85). AR transcription is modulated by circulating androgens and it is both cell-type and age-dependent (86). To perform its function AR needs ligand-dependent binding and interaction with co-activators as well as chaperone proteins (87). The AR inactive form, without a ligand, is located in the cytoplasm, bound to heat shock proteins (hsp90). Upon exposure to androgen [testosterone or dihydrotestosterone (DHT)], it results in a conformational change, dissociation of chaperone proteins and exposure of the nuclear localization signal which allows it to move into the nucleus to bind to the genomic androgen response elements (85). As a result, transcription of AR target genes, mainly involved in the regulation of cell growth, proliferation and survival, is activated (85).

Prostate cancer. Androgen as well as ARs play a crucial role in the initiation and progression of prostate cancer (88). Numerous lncRNAs associated with prostate cancer play oncogenic roles by modulating AR-mediated activity through different mechanisms (89).

Two lncRNAs, prostate-specific transcript 1 (PCGEM1), and prostate cancer associated ncRNA 1 have been described to directly interact with AR under ligand-stimulated conditions, but the data regarding the two lncRNAs are contradictory (90,91), questioning their real involvement in prostate cancer progression and their ability to interact and modulate the AR signaling pathway.

HOTAIR is involved in cancer progression especially in androgen-sensitive to castration-resistant prostate cancer (CRPC) cells (92). HOTAIR can modulate androgen-independent AR activation and AR-mediated gene transcription. It interacts with AR thereby inhibiting its ubiquitination and degradation (92). Moreover, HOTAIR forms a repressive complex with polycomb proteins and decreases AR transcription which results in increased cell invasion and MMP9 expression (93). These data evidence HOTAIR as a novel target gene playing a critical role in invasiveness of prostate cancer cells.

Ozgur *et al* (94) revealed that cellular H19 expression strongly decreased after DHT stimulation in hormone-sensitive prostate cancer cells, and AR inhibition by enzalutamide restored the DHT effect as well as increased H19 expression. The present study provided evidence of the involvement of H19 lncRNA in androgen/receptor pathway-dependent prostate cancer development (94).

Prostate cancer gene 3 (PCA3) lncRNA is overexpressed in prostate cancer tissues compared with adjacent non-neoplastic tissues and it can be involved in AR signaling, since its silencing promotes cell growth and viability (95,96). Moreover, PCA3 knockdown modified the expression of PSA and PCGEM1, AR-inducible genes, as well as sensitized PCa cells to enzalutamide (97). PCA3 silencing also highlights its role in EMT, leading to the overactivation of epithelial markers E-cadherin, claudin-3 and cytokeratin-18 and the dysregulation of vimentin (96). Due to its aberrant oncogenic activity, PCA3 could represent a potential therapeutic target in patients with prostate cancer.

Growth arrest-specific 5 (GAS5) lncRNA plays a crucial role in prostate cancer carcinogenesis and its knockdown in prostate cancer cells leads to the inhibition of tumor progression (98). The interaction between GAS5 and AR could perturb cell proliferation of CRPC. GAS5 silencing in CRPC would upregulate the AR axis, while the high activation of AR could further inhibit the transcription of GAS5 (98). GAS5 can interact with both GR and AR regulating GR/AR-mediated transcriptional activity (99).

The lncRNA BCAR4 is overexpressed in prostate cancer tissues and strongly associated with metastatic progression as well as poor prognosis (100). In AR^+ PCa cells, upregulation of BCAR4 increases cell growth as well as migration and induce resistance to androgen (101). On the contrary, in AR^- prostate cancer cells BCAR4 silencing decreased cell growth (101). Therefore, as well as in BC, BCAR4 represents a potential prognostic and predictive biomarker in patients with prostate cancer.

Instead, some lncRNAs behave like tumor suppressor genes. For example, downregulated RNA in androgen independent cells (DRAIC) lncRNA can inhibit the migration of prostate cancer cells. AR activity induction leads to DRAIC transcription reduction and promotes prostate cancer progression (102). Moreover, DRAIC downregulation increased cell invasion and soft agar colony formation by NF-κB activation (103).

Another tumor suppressor lncRNA, prostate cancer associated transcript 29 (PCAT29) suppresses androgen signaling in

prostate cancer. PCAT29 silencing promoted prostate cancer growth and migration while its overexpression reduced these processes. PCAT29 downregulation results were associated with recurrence in patients with prostate cancer (104). Several other lncRNAs are involved in reciprocal modulation with AR and in the progression of prostate cancer.

AR-regulated lncRNA 1 lncRNA plays a crucial role in AR-dependent prostate cancer development as well as CRPC. It is able to interact with AR mRNA transcript and stabilizes it for protein translation (105).

The androgen-dependent lncRNA suppressor of cytokine signaling 2 antisense (SOCS2-AS1) promotes androgen-dependent prostate cancer growth and migration (87). In CRPC cells increased AR signaling has been strongly associated with SOCS2-AS1 upregulation compared with androgen-dependent LNCaP cells. Moreover, SOCS2-AS1 can modulate the AR target TNF Superfamily Member 10 gene (106).

The prostate cancer upregulated lncRNA 1 is overexpressed in prostate cancer cells and its silencing inhibited AR and NKX3-1 expression, whereas AR silencing decreased PlncRNA-1 expression (107).

TMPO antisense RNA 1 (TMPO-AS1) lncRNA is overexpressed in prostate cancer cell lines and tissues associated with a worse prognosis of patients with prostate cancer. AR can directly regulate the TMPO-AS1 levels in the cytoplasm promoting growth, progression, cell migration and inhibition of apoptosis in prostate cancer cells (108).

The AR-regulated lncRNAs, namely CRPC-lncs, are highly expressed in CRPC tissues. Their silencing reduces the expression of AR and AR variants which as a consequence inhibit CRPC tumor growth (109).

MALAT1 is increased in prostate cancer cells after androgen stimulation, as well as its receptor. MALAT1 knockdown inhibited the DHT administration-induced increase in the cell cycle, induced AR expression in these cells and blocked the tumorigenesis of prostate cancer cells in nude mice. Moreover, MALAT1 can bind miR-320b, negatively regulating its expression, and AR is a target of miR-320b. Consequently, changes induced by MALAT1 silencing can be abolished by miR-320b inhibition or AR overexpression (110).

Recently, a large number of lncRNAs have been associated with AR activity and AR inhibitors sensibility: i) LINC00675, overexpressed in androgen-insensitive prostate cancer cell lines and CRPC, patients can directly modulate AR interaction with mouse double minute-2 (MDM2) and block the ubiquitination of AR by binding to it (111), ii) prostate cancer associated transcript 7 (112) and prostate cancer lncRNA at chromosome 16 (113) lncRNAs are directly related with AR signaling and overexpressed in prostate cancer tissues and AR-dependent cell lines. Their silencing suppressed AR signaling, tumor growth and proliferation. iii) Growth hormone secretagogue receptor (GHSR) opposite strand (GHSROS) lncRNA is overexpressed in prostate cancer cell lines and modulates the expression of protein phosphatase 2 regulatory subunit b gamma gene. The loss of GHSROS may drive AR pathway-independent prostate tumor progression (114). iv) FAM83H-AS1 is upregulated in prostate adenocarcinoma and its silencing in prostate cancer cells modulated cell proliferation, cell cycle and migration. AR signaling is involved in upregulating FAM83H-AS1 expression in prostate cancer cells (115). v) Poly(RC) binding protein 1 antisense RNA 1 is involved in CRPC enzalutamide resistance by enhancing the deubiquitination of AR/AR-V7 (116). vi) Negative expression of AR Regulating LncRNA (NXTAR) bound upstream of the AR promoter inhibiting AR/AR-V7 expression, which in turn upregulates NXTAR levels, and compromising enzalutamide-resistant prostate cancer (117). vii) AC016745.3 overexpression inhibits the proliferation and migration of prostate cancer cells and suppresses the expression of AR target genes by binding non-POU domain containing octamer binding protein (118). viii) RP11-1023L17.1 expression can be directly suppressed by the AR as well as promotes proliferation, migration, cell cycle progression and inhibition of apoptosis. RP11-1023L17.1 can suppress F-Box Protein 32 expression, thereby enhancing c-Myc protein stability (119).

BC. AR is overexpressed in normal breast epithelium as well as in a large proportion of BC tissues and cell models. AR is co-localized with ER together with PgR in epithelial breast cells, indicating a combined role in the modulation of mammary epithelial cell proliferation, and is silent in myoepithelium as well as stromal cells (120,121). However, in a normal breast, androgens are involved in inhibiting breast development, whereas, in BC cell lines, androgens and AR signaling can promote breast cell proliferation and growth (122).

A strong relation between AR signaling and lncRNA has been highlighted in BC in particular in triple-negative BC (TNBC). One of the TNBC subtypes called luminal AR (LAR) was characterized by AR expression (123). A strong association between the lncRNA HOTAIR and AR expression was demonstrated in TNBC patient samples (124). HOTAIR overexpression appeared associated with lymph node metastases and with AR expression indicating a role of HOTAIR in TNBC progression by modulation of the AR signaling pathway (124).

Yang *et al* (125) studied three TNBC cell lines, treated with DHT, to investigate the role of AR-related lncRNAs. They highlighted the downregulation of AR negatively regulated lncRNA (ARNILA), and its role as a negative prognostic marker in patients with TNBC. *In vitro* and *in vivo* studies revealed that ARNILA can induce invasion as well as metastatic progression (125). Moreover, it can promote EMT by upregulating SOX4 expression (125).

SRA1-mediated AR signaling pathway regulation may be also involved in BC development, especially in TNBC. Leygue (126) reported that silencing of SRA1 could reduce the invasiveness and motility of TNBC cells (126).

Currently, Huang *et al* (127) conducted a study to determine the role of the AR signaling pathways (ARSP)-related lncRNAs in the incidence and progression of BC and their relationship with the TME. A total of 340 ARSP-related lncRNAs were detected, of these 203 were upregulated and 137 were downregulated (127). The understanding of the molecular mechanisms beneath the crosstalk between AR and lncRNAs in BC could provide new tools for the prognostic stratification of patients including the development of new therapeutic strategies.

Additional tumors. The effects of lncRNAs on AR signaling have also been assessed in other types of cancers.

In bladder cancer, combined overexpression of X inactive specific transcript (XIST) and AR have been associated with

the advanced TNM stage. XIST knockdown leads to a decrease in proliferation, invasion and migratory potential through modulation of AR signaling. Moreover, XIST suppresses the expression of miR-124 which target 3'-UTR of AR through direct interaction (128).

Nevertheless, in bladder cancer, another lncRNA, LINC00460, appeared aberrantly overexpressed and its silencing decreased the proliferation of bladder cancer cells through modulation of AR expression. Moreover, LINC00460 overexpression has been associated with poor prognosis for patients with bladder cancer (129).

In esophageal squamous cell carcinoma progression, Wu *et al* (130) discovered a micro peptide (YY1BM) encoded by Y-linked lncRNA LINC00278, able to block YY1 binding to AR to activate the expression of *eEF2K*. Recently, He *et al* (131) showed that AR-mediated transcription activation is responsible for the overexpression of LINC01503, which promoted NPC cell proliferation, migration and invasion *in vitro*, and facilitated tumor growth as well as metastasis *in vivo*.

Schmidt *et al* (132) demonstrated that in melanoma cells lncRNA SRA-like ncRNA (SLNCR) binds to AR and complexes with different transcription factors to mediate invasion or proliferation. More recently, they revealed that AR and EGR1, a transcription factor mainly involved in the processes of tissue injury, immune responses and cancer, bind to the lncRNA SLNCR and increase melanoma proliferation by p21 (133). The same authors later proved that point mutations or oligonucleotides that abrogate AR binding to *SLNCR* block melanoma invasion, suggesting that targeting lncRNA-protein complexes holds therapeutic promise (134).

Zhai *et al* (135) reported that suppressing AR in RCC (SARCC) lncRNA establishes a physical interaction with AR acting as a tumor suppressor in RCC cells. SARCC expression appears downregulated in RCC tissues and metastatic samples compared with non-neoplastic adjacent tissues. In addition, its dysregulation is strongly associated with the prognosis of patients with RCC. *In vitro*, low expression of SARCC associated with cell invasion, migration, proliferation and drug resistance to sunitinib. Mechanistically, SARCC/AR crosstalk inhibited miR-143-3p expression by modulating K-RAS, MMP-13, AKT and P-ERK expression (135). HOTAIR is also capable of interacting with AR in RCC cells, enhancing the expression of VEGFA and platelet derived growth factor receptor alpha (PDGFA) with the promotion of tumor angiogenesis, and inducing tumor stemness phenotype (136).

Recently, You *et al* (137) showed that AR can increase TWIST1 associated lncRNA regulated via AR expression through binding to the AREs promoting vasculogenesis and metastasis in clear cell RCC via altering TWIST1.

The lncRNA prostate androgen-regulated transcript 1 (PART1) interacts with AR promoting promyelocytic leukemia zinc finger (PLZF) expression, followed by recruitment of EZH2, to mediate epigenetic PDGFB silencing and downstream PI3K/Akt inhibition, and modulating gastric cancer progression (138).

Finally, Qin *et al* (139) described the upregulation of LINC00667 in HCC tissues and cell lines associated with an unfavourable prognosis of patients with HCC. LINC00667 acts as a molecular sponge in the miR-130s-3p/AR signaling pathway thereby promoting HCC tumor progression (139).

5. Crosstalk between other NRs and lncRNAs in cancer

RAR. All-trans retinoic acid (RA) is the main active metabolite of vitamin A (140). RA signaling is involved in different biological processes, including embryonic development along with organogenesis, cell growth, proliferation, cell differentiation, together with metabolism regulation (141). RA translocates in the nucleus by binding to an intracytoplasmic transporter, cellular RA binding protein type II. Retinoids bind to two different NRs, RARs (RAR-α and RAR-β) and retinoid X receptors (RXRs). RARs function as heterodimers with RXRs. In turn, RXRs can be involved in the formation of heterodimers with other different NRs, such as vitamin D_3, thyroid hormone and PPARs (142).

RAR/RXR and RXR/RXR are localized in the nucleus bound to retinoid hormone response elements (RAREs) in the promoter regions of retinoid-responsive genes thereby inducing the transcription of numerous target genes (143).

There are few examples in the literature regarding crosstalk of RAR signaling and lncRNAs in cancer. In acute promyelocytic leukemia (APL) RA/RARs signaling can induce the expression of the lncRNA HOXA-AS2 antisense, which suppresses the TRAIL pathway and reduces expression of caspases (144). Similarly, RA/RARs signaling induces H19 expression in APL cells and its upregulation perturbs telomerase activity, mediated by hTERC-hTR interaction, during tumor evolution (145). Conversely, the lncRNA RA early transcript 1K pseudogene (RAET1K) can reduce RA/RARs signaling. In lung cancer RAET1K interferes with the protective role of RA, modulating miR-135a-5p, which in turn inhibits Cyclin E1 (CCNE1) expression, a cyclin required for G1-S transition. RA promotes the expression of this miRNA, by blocking lung cancer cells in the G1 phase and thereby tumor cells proliferation and progression. RAET1K silencing can repress CCNE1 expression and inhibit cell cycle progression from the G1 to the S phase (146).

A recent study also highlighted crosstalk between HOTAIR and RA/RARs signaling in acute myeloid leukemia. Different acute myeloid leukemia cell lines (HL-60, NB4, U937 and THP-1) have induced myeloid differentiation by all-trans RA (ATRA). All four cell lines exhibited a higher expression level of HOTAIR after the ATRA treatment suggesting its role in the regulation of RA/RARs pathway and consequently in myeloid cell differentiation (147). The lncRNA RNA HOTAIR myeloid 1 (HOTAIRM1) can mediate ATRA-induced differentiation of ALK cells (148). Upregulation of HOTAIRM1 expression is able to enhance ATRA-induced PML-RARA degradation by affecting autophagic flux and thereby controlling myeloid cell differentiation in APL cells (149). lncRNA NEAT1 is also involved in APL cell differentiation induced by ATRA. C/EBPα binds and transactivates NEAT1 whereas PML/RARα suppresses this process suggesting that PML/RARα could contribute to the pathogenesis of APL by suppressing C/EBPα targets (150).

In glioblastoma multiforme cells ATRA treatment dysregulated different lncRNAs' expression. In particular, ATRA

dose-dependently decreased the expression of GAS5 within the microenvironment of the U87MG cell line (151).

RAET1K is necessary for retinoid-induced differentiation in different cells by binding RXRs. RAET1K is upregulated in tumor tissues and is associated with a poor prognosis in patients with lung adenocarcinoma. Aberrant RAET1K expression upregulated cyclin E1 by targeting miR-135, thereby promoting tumor progression (146).

Currently, Wang *et al* (152) asserted that lncHOXA10 is significantly upregulated in gastric cancer tissues and cell lines, and can promote proliferation, migration as well as invasion of cells. lncHOXA10 can suppress RAR-β expression, involved in the modulation of apoptosis, while ATRA can rescue the expression of RAR-β, inhibiting lncHOXA10 in gastric cancer cells (152). RAR-β is also modulated by lncRNA HAND2-AS1 in human bladder cancer. HAND2-AS1 inhibits cell proliferation and promotes apoptosis in bladder cancer cells by sponging miR-146. The last of these can promote cell proliferation by targeting RAR-β and, in turn, HAND2-AS1 can suppress cell proliferation via releasing RAR-β from miR-146 (153). More recently, Fu *et al* (154) described that another lncRNA, lymphocytic leukemia 2 (DLEU2), can modulate RAR-β in colorectal cancer cells. DLEU2 induced promoter methylation of RAR-β to downregulate its expression, and its upregulation induced the MAPK signaling pathway promoting colorectal cancer progression (154).

VDR. VDR is a transcription factor that besides interacting with hormonally active vitamin D3, regulates the expression of more than 900 genes involved in numerous different cellular processes. Both vitamin D/VDR signaling and lncRNAs affect numerous genomic and non-genomic processes, the dysregulation of which can be associated with a wide range of diseases including cancer. The principal evidence is associated with skin cancers. Several studies confirmed the protective effect of VDR in cancer initiation and progression (155), especially in keratinocyte carcinoma (156). Jiang and Bikle (157) profiled 90 well-annotated mouse lncRNAs from cultured mouse keratinocytes after deleting VDR. They detected that H19, HOTTIP, mHOTAIR, Malat1, SRA and Nespas were significantly increased, whereas H19 as, Kcnq1ot1 and lincRNA-p21 were decreased (157). Subsequently, other VDR-associated lncRNAs in BC (158) as well as in lung cancer (159) have been identified. VDR, MALAT1 and LINC00511 were significantly upregulated in tumor cells in BC compared with non-cancerous tissues. In addition, VDR and another lncRNA *SNHG16* were associated in both tumor and non-tumor breast tissues (158). In lung cancer, the coordinate expression of VDR and the lncRNAs MALAT1, SNHG16, SNHG6, LINC00346 and LINC00511 has also been validated in lung cancer tissues (159).

In oral squamous cell carcinoma (OSCC) Jin *et al* (160) evaluated crosstalk between vitamin D/VDR signaling and lncRNAs selecting 46 pairs of tumor tissue and adjacent non-tumor tissue as well as two OSCC cell lines. In the latter, they observed 1045 lncRNAs differentially expressed after the $1,25(OH)_2D$ treatment. In particular lung cancer-associated transcript 1 (LUCAT1) expression was reduced by the $1,25(OH)_2D$ treatment *in vitro* and it appeared strongly overexpressed in the OSCC tumor tissues. LUCAT1 silencing in the OSCC cell lines reduced cell growth in association with a reduction in ERK1/2 phosphorylation (160).

The oncogenic lncRNA colon cancer-associated transcript 2 (CCAT2) has been described as overexpressed in ovarian cancer. Wang *et al* (161) described that $1,25(OH)_2D$ inhibited CCAT2 expression leading to decreased binding of transcription factor 4 (TCF4) to the MYC promoter in ovarian cancer cell lines. This produced inhibition of proliferation, migration and invasive features of ovarian cells (161). In addition, the lncRNA TOPORS-AS1, overexpressed in ovarian cancer cells and involved in suppression of cell proliferation, migration and invasion, is upregulated by VDR. Crosstalk is essential to interrupt the Wnt/β-catenin signaling thereby defining an improved prognosis in patients with ovarian cancer (162).

Finally, the relation between the lncRNA H19 and VDR has been described in colon cancer. VDR can inhibit H19 expression through the regulation of the c-Myc/Mad-1 network. In turn, H19 upregulation blocked VDR expression by upregulating miRNA 675-5p (163).

Gonadotropin receptor. Human GR (h-GR) belongs to the nuclear hormone receptor superfamily and is encoded by nuclear receptor subfamily 3C1 gene on chromosome 5q31.3 (164). In the absence of ligands, the GR is sequestered in the cytoplasm by chaperone proteins. Glucocorticoids, such as cortisol, prednisolone and dexamethasone bind to GR leading to both its dimerization and translocation into the nucleus, where it performs its activity as a transcription regulator (164). DNA-bound GR recruits coregulator complexes forming transcription regulatory complexes that can function in both activation and suppression of transcription. Some lncRNAs have been described as regular and can be regulated by glucocorticoid/GR signaling.

GAS5 lncRNA is able to directly interact with the DNA binding domain of GR acting as a molecular decoy by competing with the glucocorticoid-response element for GR binding, thereby inhibiting GR transcription (165). GAS5 is also able to accumulate in cells that have been starved of growth factors by suppressing GR activity, and GAS5 sensitizes cells to apoptosis (165). In the same way, overexpression of GAS5 leads to growth arrest and apoptosis in human breast cell lines (165).

THRs. Thyroid hormone action is predominantly mediated by THRs, which are encoded by the THRA and THRB genes (166). THRs act as ligand-activated nuclear transcription factors to regulate different physiologic processes through direct gene regulation and with ncRNAs relation (167,168).

Current evidence indicates a crosstalk between the thyroid hormone/THR pathway and lncRNAs in liver cancer. Brain cytoplasmic RNA 1 (BCYRN1/BC200) is abnormally overexpressed in several tumor types, with a significant overexpression in HCC tissues. Using the Disease-Related Human lncRNA Profiler to identify lncRNAs regulated by thyroid hormone/THR signaling in liver cells, BC200 was identified as a lncRNA downregulated by the thyroid hormone (169).

In HCC cells, the taurine upregulated gene 1 (TUG1) is overexpressed and can induce cell proliferation, invasion, metastatic progression as well as apoptosis by distal-less

homeobox 2 (DLX2) activation (170). Alpha-fetoprotein (AFP) is increased in the majority of patients with HCC and TUG1 is involved in THR/AFP signaling. Thyroid hormones suppress TUG1 expression, leading to the downregulation of AFP (171).

6. Conclusions

NRs function as a transcriptional signaling network that mediates gene regulatory actions to maintain cellular homeostasis in response to hormonal and environmental factors. The dysregulation of NR signaling is known to contribute to the evolution of hormone-dependent tumors, such as breast and prostate cancer, which are also therapeutic targets. However, NRs signaling affects cancer also because the therapeutic response associated with their target drugs is often altered by changes in the expression and function of a large number of coregulators. They could modulate receptor sensitivity, and modify their protein-protein interaction, thus altering transcription, as well as regulation of chromatin accessibility. Coregulators include coactivators that generally associate with agonist-bound NRs to stimulate gene expression and corepressors that are usually bound to unliganded or antagonist-bound NRs to suppress gene expression. lncRNAs are emerging as new genetic/epigenetic coregulators of NRs. In the last 20 years, lncRNAs have been extensively studied due to their potential role in cancer development and progression. However, the functional characterization of lncRNAs remains complex, interacting with different molecules involved in the regulation of key processes during cell development and diseases. lncRNAs can modulate NRs activity, and in turn, they can be regulated by NRs. Therefore, understanding the mechanisms by which such coregulators interact and modulate NR activity and vice versa could offer new opportunities to develop improved prognostic in addition to diagnostic approaches, along with new therapeutic targets.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Italian Ministry of Health (Ricerca Corrente IRCCS; grant. no. 2778553; year 2023).

Availability of data and materials

Not applicable.

Authors' contributions

MCa, AB and GF were responsible for the conception and design of the present review. MCe and PM collected and assembled the data. MCa, MB and MT contributed to the drafting and revision of the review. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schütz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P and Evans RM: The nuclear receptor superfamily: the second decade. Cell 83: 835-839, 1995.
2. Cheung E and Kraus WL: Genomic analyses of hormone signaling and gene regulation. Annu Rev Physiol 72: 191-218, 2010.
3. Gadaleta RM and Magnani L: Nuclear receptors and chromatin: an inducible couple. J Mol Endocrinol 52: R137-R149, 2014.
4. Lonard DM, Lanz RB and O'Malley BW: Nuclear receptor coregulators and human disease. Endocr Rev 28: 575-587, 2007.
5. Fatica A and Bozzoni I: Long non-coding RNAs: New players in cell differentiation and development. Nat Rev Genet 15: 7-21, 2014.
6. Statello L, Guo CJ, Chen LL and Huarte M: Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol 22: 96-118, 2021.
7. Fang Yand Fullwood MJ: Roles, functions, and mechanisms of long Non-coding RNAs in Cancer. Genomics Proteomics Bioinformatics 14: 42-54, 2016.
8. Foulds CE, Panigrahi AK, Coarfa C, Lanz RB and O'Malley BW: Long Noncoding RNAs as targets and regulators of nuclear receptors. Curr Top Microbiol Immunol 394: 143-176, 2016.
9. Wu J, Nagy LE, Liangpunsakul S and Wang L: Non-coding RNA crosstalk with nuclear receptors in liver disease. Biochim Biophys Acta Mol Basis Dis 1867: 166083, 2021.
10. Lanz RB, McKenna NJ, Onate SA, Albrecht U, Wong J, Tsai SY, Tsai MJ and O'Malley BW: A steroid receptor coactivator, SRA, functions as an RNA and is present in an SRC-1 complex. Cell 97: 17-27, 1999.
11. Emberley E, Huang GJ, Hamedani MK, Czosnek A, Ali D, Grolla A, Lu B, Watson PH, Murphy LC and Leygue E: Identification of new human coding steroid receptor RNA activator isoforms. Biochem Biophys Res Commun 301: 509-515, 2003.
12. Sheng L, Ye L, Zhang D, Cawthorn WP and Xu B: New Insights Into the Long Non-coding RNA SRA: Physiological functions and mechanisms of action. Front Med (Lausanne) 5: 244, 2018.
13. Szwarc MM, Kommagani R, Lessey BA and Lydon JP: The p160/steroid receptor coactivator family: potent arbiters of uterine physiology and dysfunction. Biol Reprod 91: 122, 2014.
14. Tenga A, Beard JA, Takwi A, Wang YM and Chen T: Regulation of Nuclear Receptor Nur77 by miR-124. PLoS One 11: e0148433, 2016.
15. Zhang CJ, Liu C, Wang YX, Zhu N, Hu ZY, Liao DF and Qin L: Long non-coding RNA-SRA promotes neointimal hyperplasia and vascular smooth muscle cells proliferation via MEK-ERK-CREB pathway. Vascul Pharmacol 116: 16-23, 2019.
16. Ho JC, Lee CH and Hong CH: Targeting steroid receptor RNA activator (SRA), a long non-coding RNA, enhances melanogenesis through activation of TRP1 and inhibition of p38 phosphorylation. PLoS One 15: e0237577, 2020.
17. Tello-Flores VA, Beltrán-Anaya FO, Ramírez-Vargas MA, Esteban-Casales BE, Navarro-Tito N, Alarcón-Romero LDC, Luciano-Villa CA, Ramírez M, Del Moral-Hernández Ó and Flores-Alfaro E: Role of Long Non-Coding RNAs and the molecular mechanisms involved in insulin resistance. Int J Mol Sci 22: 7256, 2021.
18. Eoh KJ, Paek J, Kim SW, Kim HJ, Lee HY, Lee SK and Kim YT: Long non-coding RNA, steroid receptor RNA activator (SRA), induces tumor proliferation and invasion through the NOTCH pathway in cervical cancer cell lines. Oncol Rep 38: 3481-3488, 2017.
19. Park SA, Kim LK, Kim YT, Heo TH and Kim HJ: Long non-coding RNA steroid receptor activator promotes the progression of endometrial cancer via Wnt/β-catenin signaling pathway. Int J Biol Sci 6: 99-115, 2020.

20. Hong CH, Ho JC and Lee CH: Steroid Receptor RNA Activator, a Long Noncoding RNA, Activates p38, facilitates epithelial-mesenchymal transformation, and mediates experimental melanoma metastasis. J Invest Dermatol 140: 1355-1363. e1, 2020.
21. Mahdevar M, Vatandoost J, Seyed Forootan F, Kiani-Esfahani A, Esmaeili M, Peymani M, Tavakkoli H, Osmay Gure A, Nasr Esfahani MH and Ghaedi K: Steroid receptor RNA activator gene footprint in the progression and drug resistance of colorectal cancer through oxidative phosphorylation pathway. Life Sci 285: 119950, 2021.
22. Lanz RB, Chua SS, Barron N, Söder BM, DeMayo F and O'Malley BW: Steroid receptor RNA activator stimulates proliferation as well as apoptosis in vivo. Mol Cell Biol 23: 7163-7176, 2003.
23. Kurisu T, Tanaka T, Ishii J, Matsumura K, Sugimura K, Nakatani T and Kawashima H: Expression and function of human steroid receptor RNA activator in prostate cancer cells: Role of endogenous hSRA protein in androgen receptor-mediated transcription. Prostate Cancer Prostatic Dis 9: 173-178, 2006.
24. Kim LK, Park SA, Yang Y, Kim YT, Heo TH and Kim HJ: LncRNA SRA mediates cell migration, invasion, and progression of ovarian cancer via NOTCH signaling and epithelial-mesenchymal transition. Biosci Rep 41: BSR20210565, 2021.
25. Nilsson S, Mäkelä S, Treuter E, Tujague M, Thomsen J, Andersson G, Enmark E, Pettersson K, Warner M and Gustafsson JA: Mechanisms of estrogen action. Physiol Rev 81: 1535-1565, 2001.
26. Eyster KM: The estrogen receptors: An overview from different perspectives. Methods Mol Biol 1366: 1-10, 2016.
27. Moggs JG and Orphanides G: Estrogen receptors: Orchestrators of pleiotropic cellular responses. EMBO Rep 2: 775-781, 2001.
28. Carroll JS, Meyer CA, Song J, Li W, Geistlinger TR, Eeckhoute J, Brodsky AS, Keeton EK, Fertuck KC, Hall GF, *et al*: Genome-wide analysis of estrogen receptor binding sites. Nat Genet 38, 1289-1297, 2006.
29. Stein RA, Chang CY, Kazmin DA, Way J, Schroeder T, Wergin M, Dewhirst MW and McDonnell DP: Estrogen-related receptor alpha is critical for the growth of estrogen receptor-negative breast cancer. Cancer Res 68: 8805-8812, 2008.
30. Bhan A, Hussain I, Ansari KI, Kasiri S, Bashyal Aand Mandal SS: Antisense transcript long noncoding RNA (lncRNA) HOTAIR is transcriptionally induced by estradiol. J Mol Biol 425: 3707-3722, 2013.
31. Sørensen KP, Thomassen M, Tan Q, Bak M, Cold S, Burton M, Larsen MJ and KruseTA: Long non-coding RNA HOTAIR is an independent prognostic marker of metastasis in estrogen receptor-positive primary breast cancer. Breast Cancer Res Treat 142: 529-536, 2013.
32. Cantile M, Di Bonito M, Cerrone M, Collina F, De Laurentiis M and Botti G: Long Non-Coding RNA HOTAIR in breast cancer therapy. Cancers (Basel) 12: 1197, 2020.
33. Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, Tsai MC, Hung T, Argani P, Rinn JL, *et al*: Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature 464: 1071-1076, 2010.
34. Tao S, He H and Chen Q: Estradiol induces HOTAIR levels via GPER-mediated miR-148a inhibition in breast cancer. J Transl Med 13: 131, 2015.
35. Aiello A, Bacci L, Re A, Ripoli C, Pierconti F, Pinto F, Masetti R, Grassi C, Gaetano C, Bassi PF, *et al*: MALAT1 and HOTAIR Long Non-Coding RNAs play opposite role in estrogen-mediated transcriptional regulation in prostate cancer cells. Sci Rep 6: 38414, 2016.
36. Zhao Z, Chen C, Liu Y and Wu C: 17β-Estradiol treatment inhibits breast cell proliferation, migration and invasion by decreas-815 ing MALAT-1 RNA level. Biochem Biophys Res Commun 445: 388-393, 2014.
37. Wang Z, Katsaros D, Biglia N, Shen Y, Fu Y, Loo LWM, Jia W, Obata Y and Yu H: High expression of long non-coding RNA MALAT1 in breast cancer is associated with poor relapse-free survival. Breast Cancer Res Treat 171: 261-271, 2018.
38. Huang Z, Qin Q, Xia L, Lian B, Tan Q, Yu Y and Mo Q: Significance of Oncotype DX 21-gene test and expression of long Non-Coding RNA MALAT1 in early and estrogen receptor-positive breast cancer patients. Cancer Manag Res 13: 587-593, 2021.
39. Alipoor FJ, Asadi MH and Torkzadeh-Mahani M: MIAT lncRNA is overexpressed in breast cancer and its inhibition triggers senescence and G1 arrest in MCF7 cell line. J Cell Biochem 119: 6470-6481, 2018.
40. Luan T, Zhang X, Wang S, Song Y, Zhou S, Lin J, An W, Yuan W, Yang Y, Cai H, *et al*: Long non-coding RNA MIAT promotes breast cancer progression and functions as ceRNA to regulate DUSP7 expression by sponging miR-155-5p. Oncotarget 8: 76153-76164, 2017.
41. Li Y, Jiang B, Wu X, Huang Q, Chen W, Zhu H, Qu X, Xie L, Ma X and Huang G: Long non-coding RNA MIAT is estrogen-responsive and promotes estrogen-induced proliferation in ER-positive breast cancer cells. Biochem Biophys Res Commun 503: 45-50, 2018.
42. Wang Z, Katsaros D, Biglia N, Shen Y, Loo L, Yu X, Lin H, Fu Y, Chu WM, Fei P, *et al*: ERα upregulates the expression of long non-coding RNA LINC00472 which suppresses the phosphorylation of NF-κB in breast cancer. Breast Cancer Res Treat 175: 353-368, 2019.
43. Jonsson P, Coarfa C, Mesmar F, Raz T, Rajapakshe K, Thompson JF, Gunaratne PH and Williams C: Single-Molecule sequencing reveals estrogen-regulated clinically relevant lncRNAs in Breast Cancer. Mol Endocrinol 29: 1634-1645, 2015.
44. Liu D, Rudland PS, Sibson DR and Barraclough R: Identification of mRNAs differentially-expressed between benign and malignant breast tumour cells. Br J Cancer 87: 423-431, 2002.
45. Miano V, Ferrero G, Reineri S, Caizzi L, Annaratone L, Ricci L, Cutrupi S, Castellano I, Cordero F and De Bortoli M: Luminal long non-coding RNAs regulated by estrogen receptor alpha in a ligand-independent manner show functional roles in breast cancer. Oncotarget 7: 3201-3216, 2016.
46. Niknafs YS, Han S, Ma T, Speers C, Zhang C, Wilder-Romans K, Iyer MK, Pitchiaya S, Malik R, Hosono Y, *et al*: The lncRNA landscape of breast cancer reveals a role for DSCAM-AS1 in breast cancer progression. Nat Commun 7: 12791, 2016.
47. Hu C: LncRNA DSCAM-AS1: A pivotal therapeutic target in cancer. Mini Rev Med Chem 23: 530-536, 2023.
48. Sun W, Li AQ, Zhou P, Jiang YZ, Jin X, Liu YR, Guo YJ, Yang WT, Shao ZM and Xu XE: DSCAM-AS1 regulates the G1/S cell cycle transition and is an independent prognostic factor of poor survival in luminal breast cancer patients treated with endocrine therapy. Cancer Med 7: 6137-6146, 2018.
49. Treeck O, Weber F, Fritsch J, Skrzypczak M, Schüler-Toprak S, Buechler C and Ortmann O: DSCAM-AS1 Long Non-Coding RNA exerts oncogenic functions in endometrial adenocarcinoma via activation of a tumor-promoting transcriptome profile. Biomedicines 10: 1727, 2022.
50. Yadav N, Sunder R, Desai S, Dharavath B, Chandrani P, Godbole M and Dutt A: Progesterone modulates the DSCAM-AS1/miR-130a/ESR1 axis to suppress cell invasion and migration in breast cancer. Breast Cancer Res 24: 97, 2022.
51. Xu SP, Zhang JF, Sui SY, Bai NX, Gao S, Zhang GW, Shi QY, You ZL, Zhan C and Pang D: Downregulation of the long noncoding RNA EGOT correlates with malignant status and poor prognosis in breast cancer. Tumour Biol 36: 9807-9812, 2015.
52. Sun M, Gadad SS, Kim DS and Kraus WL: Discovery, Annotation, and functional analysis of long noncoding RNAs controlling cell-cycle gene expression and proliferation in breast cancer cells. Mol Cell 59: 698-711, 2015.
53. Zhang X, Gao S, Li Z, Wang W and Liu G: Identification and analysis of estrogen receptor α promoting tamoxifen resistance-related lncRNAs. Biomed Res Int 20: 9031723, 2020.
54. Basak P, Chatterjee S, Bhat V, Su A, Jin H, Lee-Wing V, Liu Q, Hu P, Murphy LC and Raouf A: Long Non-Coding RNA H19 acts as an estrogen receptor modulator that is required for endocrine therapy resistance in ER+ Breast cancer cells. Cell Physiol Biochem 51: 1518-1532, 2018.
55. Sun H, Wang G, Peng Y, Zeng Y, Zhu QN, Li TL, Cai JQ, Zhou HH and Zhu YS: H19 lncRNA mediates 17β-estradiol-induced cell proliferation in MCF-7 breast cancer cells. Oncol Rep 33: 3045-3052, 2015.
56. Ma T, Liang Y, Li Y, Song X, Zhang N, Li X, Chen B, Zhao W, Wang L and Yang Q: LncRNA LINP1 confers tamoxifen resistance and negatively regulated by ER signaling in breast cancer. Cell Signal 68: 109536, 2020.
57. Si X, Zang R, Zhang E, Liu Y, Shi X, Zhang E, Shao L, Li A, Yang N, Han X, *et al*: LncRNA H19 confers chemoresistance in ERα-positive breast cancer through epigenetic silencing of the pro-apoptotic gene BIK. Oncotarget 7: 81452-81462, 2016.
58. Tu C, Ren X, He J, Zhang C, Chen R, Wang W and Li Z: The Value of LncRNA BCAR4 as a prognostic biomarker on clinical outcomes in human cancers. J Cancer 10: 5992-6002, 2019.

59. Peng R, Cao J, Guo Q, Sun Q, Xu L, Xie X and Song C: Variant in BCAR4 gene correlated with the breast cancer susceptibility and mRNA expression of lncRNA BCAR4 in Chinese Han population. Breast Cancer 28: 424-433, 2021.
60. Liang X, Zhao Y, Fang Z, Shao N, Zhai D, Zhang M, Yu L and Shi Y: DLGAP1-AS2 promotes estrogen receptor signalling and confers tamoxifen resistance in breast cancer. Mol Biol Rep 49: 3939-3947, 2022
61. Yuan H, Yan L, Wu M, Shang Y, Guo Q, Ma X, Zhang X, Zhu Y, Wu Z, Lobie PE and Zhu T: Analysis of the Estrogen Receptor-Associated LncRNA Landscape Identifies a Role for ERLC1 in breast cancer progression. Cancer Res 82: 391-405, 2022.
62. Fang Z, Wang Y, Wang Z, Xu M, Ren S, Yang D, Hong M and Xie W: ERINA Is an Estrogen-Responsive LncRNA That Drives Breast Cancer through the E2F1/RB1 Pathway. Cancer Res 80: 4399-4413, 2020.
63. Yu S, Wang Y, Gong X, Fan Z, Wang Z, Liang Z, Wu R, Cao B, Wang N, Bi C, *et al*: LncRNA AGPG confers endocrine resistance in breast cancer by promoting E2F1 activity. Cancer Res: Jul 28, 2023 (Epub ahead of print).
64. Horie K, Takagi K, Takeiwa T, Mitobe Y, Kawabata H, Suzuki T, Ikeda K and Inoue S: Estrogen-Inducible LncRNA BNAT1 functions as a modulator for estrogen receptor signaling in endocrine-resistant breast cancer cells. Cells 11: 3610, 2022.
65. Chen X, Ding JC, Hu GS, Shu XY, Liu Y, Du J, Wen ZJ, Liu JY, Huang HH, Tang GH and Liu W: Estrogen-Induced LncRNA, LINC02568, promotes estrogen receptor-positive breast cancer development and drug resistance through both In Trans and In Cis Mechanisms. Adv Sci (Weinh) 10: e2206663, 2023.
66. Nanni S, Aiello A, Salis C, Re A, Cencioni C, Bacci L, Pierconti F, Pinto F, Ripoli C, Ostano P, *et al*: Metabolic reprogramming by malat1 depletion in prostate cancer. Cancers (Basel) 13: 15, 2020.
67. Chakravarty D, Sboner A, Nair SS, Giannopoulou E, Li R, Hennig S, Mosquera JM, Pauwels J, Park K, Kossai M, *et al*: The oestrogen receptor alpha-regulated lncRNA NEAT1 is a critical modulator of prostate cancer. Nat Commun 5: 5383, 2014.
68. Bacci L, Aiello A, Ripoli C, Loria R, Pugliese D, Pierconti F, Rotili D, Strigari L, Pinto F, Bassi PF, *et al*: H19-Dependent transcriptional regulation of β3 and β4 Integrins Upon estrogen and hypoxia favors metastatic potential in prostate cancer. Int J Mol Sci 20: 4012, 2019.
69. Huang C, Wu M, Tang Y, Li X, Ouyang J, Xiao L, Li D and Li G: NAG7 promotes human nasopharyngeal carcinoma invasion through inhibition of estrogen receptor alpha and up-regulation of JNK2/AP-1/MMP1 pathways. J Cell Physiol 221: 394-401, 2009.
70. Qiu JJ, Zhang XD, Tang XY, Zheng TT, Zhang Y and Hua KQ: ElncRNA1, a long non-coding RNA that is transcriptionally induced by oestrogen, promotes epithelial ovarian cancer cell proliferation. Int J Oncol 51: 507-514, 2017.
71. Qiu J, Ye L, Ding J, Feng W, Zhang Y, Lv T, Wang J and Hua K: Effects of oestrogen on long noncoding RNA expression in oestrogen receptor alpha-positive ovarian cancer cells. J Steroid Biochem Mol Biol 141: 60-70, 2014.
72. Chen Y, Gu Y, Gu Y and Wu J: Long Noncoding RNA LINC00899/miR-944/ESR1 Axis regulates cervical cancer cell proliferation, migration, and invasion. J Interferon Cytokine Res 41: 220-233, 2021.
73. Cheng T, Bai Y, Huang S, Wang Y, Zhou S, Liu H, Zhang R, Luo X and Yu P: Estrogen receptor 1 inhibits the progression of hepatocellular carcinoma via positively regulating lncRNA maternally expressed gene 3 under high glucose conditions. J Gastrointest Oncol 13: 2485-2496, 2022.
74. Rochira V, Granata AR, Madeo B, Zirilli L, Rossi G and Carani C: Estrogens in males: What have we learned in the last 10 years? Asian J Androl 7: 3-20, 2005.
75. Girault I, Andrieu C, Tozlu S, Spyratos F, Bièche I and Lidereau R: Altered expression pattern of alternatively spliced estrogen receptor beta transcripts in breast carcinoma. Cancer Lett 215: 101-112, 2004.
76. Tong D, Schuster E, Seifert M, Czerwenka K, Leodolte S and Zeillinger R: Expression of estrogen receptor beta isoforms in human breast cancer tissues and cell lines. Breast Cancer Res Treat 71: 249-255, 2002.
77. Nanni S, Bacci L, Aiello A, Re A, Salis C, Grassi C, Pontecorvi A, Gaetano C and Farsetti A: Signaling through estrogen receptors modulates long non-coding RNAs in prostate cancer. Mol Cell Endocrinol 511: 110864, 2020.
78. Piperigkou Z, Bouris P, Onisto M, Franchi M, Kletsas D, Theocharis AD and Karamanos NK: Estrogen receptor beta modulates breast cancer cells functional properties, signaling and expression of matrix molecules. Matrix Biol 56: 4-23, 2016.
79. Mozdarani H, Ezzatizadeh V and Rahbar Parvaneh R: The emerging role of the long non-coding RNA HOTAIR in breast cancer development and treatment. J Transl Med 18: 152, 2020.
80. Ding J, Yeh CR, Sun Y, Lin C, Chou J, Ou Z, Chang C, Qi J and Yeh S: Estrogen receptor β promotes renal cell carcinoma progression via regulating LncRNA HOTAIR-miR-138/200c/204/217 associated CeRNA network. Oncogene 37: 5037-5053, 2018.
81. He M, Yang H, Shi H, Hu Y, Chang C, Liu S and Yeh S: Sunitinib increases the cancer stem cells and vasculogenic mimicry formation via modulating the lncRNA-ECVSR/ERβ/Hif2-α signaling. Cancer Lett 524: 15-28, 2022.
82. Chooniedass-Kothari S, Vincett D, Yan Y, Cooper C, Hamedani MK, Myal Y and Leygue E: The protein encoded by the functional steroid receptor RNA activator is a new modulator of ER alpha transcriptional activity. FEBS Lett 584: 1174-1180, 2010.
83. Lin K, Zhan H, Ma J, Xu K, Wu R, Zhou C and Lin J: Increased steroid receptor RNA activator protein (SRAP) accompanied by decreased estrogen receptor-beta (ER-β) levels during the malignant transformation of endometriosis associated ovarian clear cell carcinoma. Acta Histochem 116: 878-882, 2014.
84. Li M, Chai HF, Peng F, Meng YT, Zhang LZ, Zhang L, Zou H, Liang QL, Li MM, Mao KG, *et al*: Estrogen receptor β upregulated by lncRNA-H19 to promote cancer stem-like properties in papillary thyroid carcinoma. Cell Death Dis 9: 1120, 2018.
85. Davey RA and Grossmann M: Androgen receptor structure, function and biology: From bench to bedside. Clin Biochem Rev 37: 3-15, 2016.
86. Wilson EM: Analysis of interdomain interactions of the androgen receptor. Methods Mol Biol 776: 113-129, 2011.
87. van de Wijngaart DJ, Dubbink HJ, van Royen ME, Trapman J and Jenster G: Androgen receptor coregulators: Recruitment via the coactivator binding groove. Mol Cell Endocrinol 352: 57-69, 2012.
88. Culig Z and Santer FR: Androgen receptor signaling in prostate cancer. Cancer Metastasis Rev 33: 413-427, 2014.
89. Kumar S, Prajapati KS, Singh AK, Kushwaha PP, Shuaib M and Gupta S: Long non-coding RNA regulating androgen receptor signaling in breast and prostate cancer. Cancer Lett 504: 15-22, 2021.
90. Yang L, Lin C, Jin C, Yang JC, Tanasa B, Li W, Merkurjev D, Ohgi KA, Meng D, Zhang J, *et al*: lncRNA-dependent mechanisms of androgen-receptor-regulated gene activation programs. Nature 500: 598-602, 2013.
91. Prensner JR, Sahu A, Iyer MK, Malik R, Chandler B, Asangani IA, Poliakov A, Vergara IA, Alshalalfa M, Jenkins RB, *et al*: The lncRNAs PCGEM1 and PRNCR1 are not implicated in castration resistant prostate cancer. Oncotarget 5: 1434-1438, 2014.
92. Zhang A, Zhao JC, Kim J, Fong KW, Yang YA, Chakravarti D, Mo YY and Yu J: LncRNA HOTAIR enhances the androgen-receptor-mediated transcriptional program and drives castration-resistant prostate cancer. Cell Rep 13: 209-221, 2015.
93. Li L, Dang Q, Xie H, Yang Z, He D, Liang L, Song W, Yeh S and Chang C: Infiltrating mast cells enhance prostate cancer invasion via altering LncRNA-HOTAIR/PRC2-androgen receptor (AR)-MMP9 signals and increased stem/progenitor cell population. Oncotarget 6: 14179-14190, 2015.
94. Ozgur E and Gezer U: Investigation of lncRNA H19 in prostate cancer cells and secreted exosomes upon androgen stimulation or androgen receptor blockage. Bratisl Lek Listy 121: 362-365, 2020.
95. Warrick JI, Tomlins SA, Carskadon SL, Young AM, Siddiqui J, Wei JT, Chinnaiyan AM, Kunju LP and Palanisamy N: Evaluation of tissue PCA3 expression in prostate cancer by RNA in situ hybridization-a correlative study with urine PCA3 and TMPRSS2-ERG. Mod Pathol 27: 609-620, 2014.
96. Lemos AE, Ferreira LB, Batoreu NM, de Freitas PP, Bonamino MH and Gimba ER: PCA3 long noncoding RNA modulates the expression of key cancer-related genes in LNCaP prostate cancer cells. Tumour Biol 37: 11339-11348, 2016.
97. Özgür E, Celik AI, Darendeliler E and Gezer U: PCA3 silencing sensitizes prostate cancer cells to enzalutamide-mediated androgen receptor blockade. Anticancer Res 37: 3631-3637, 2017.
98. Lv S, Pu X, Luo M, Wen H, Xu Z, Wei Q and Dang Q: Long noncoding RNA GAS5 interacts and suppresses androgen receptor activity in prostate cancer cells. Prostate 81: 893-901, 2021.

99. Zhou Y and Chen B: GAS5-mediated regulation of cell signaling (Review). Mol Med Rep 22: 3049-3056, 2020.
100. Wang B, Xu W, Cai Y, Liu K, Wu J, Guo C and Yuan C: The functional role of oncogenic LncRNA BCAR4 for cancer outcome. Curr Pharm Des 27: 4107-4113, 2021.
101. Cai Z, Wu Y, Li Y, Ren J, Wang L: BCAR4 activates GLI2 signaling in prostate cancer to contribute to castration resistance. Aging (Albany NY) 10: 3702-3712, 2018.
102. Sakurai K, Reon BJ, Anaya J and Dutta A: The lncRNA DRAIC/PCAT29 locus constitutes a tumor-suppressive nexus. Mol Cancer Res 13: 828-838, 2015.
103. Saha S, Kiran M, Kuscu C, Chatrath A, Wotton D, Mayo MW and Dutta A: Long Noncoding RNA DRAIC inhibits prostate cancer progression by interacting with IKK to Inhibit NF-κB Activation. Cancer Res 80: 950-963, 2020.
104. Malik R, Patel L, Prensner JR, Shi Y, Iyer MK, Subramaniyan S, Carley A, Niknafs YS, Sahu A, Han S, *et al*: The lncRNA PCAT29 inhibits oncogenic phenotypes in prostate cancer. Mol Cancer Res 12: 1081-1087, 2014.
105. Zhang Y, Pitchiaya S, Cieślik M, Niknafs YS, Tien JC, Hosono Y, Iyer MK, Yazdani S, Subramaniam S, Shukla SK, *et al*: Analysis of the androgen receptor-regulated lncRNA landscape identifies a role for ARLNC1 in prostate cancer progression. Nat Genet 50: 814-824, 2018.
106. Misawa A, Takayama K, Urano T and Inoue S: Androgen-induced Long Noncoding RNA (lncRNA) SOCS2-AS1 promotes cell growth and inhibits apoptosis in prostate cancer cells. J Biol Chem 291: 17861-17880, 2016.
107. Fang Z, Xu C, Li Y, Cai X, Ren S, Liu H, Wang Y, Wang F, Chen R, Qu M, *et al*: A feed-forward regulatory loop between androgen receptor and PlncRNA-1 promotes prostate cancer progression. Cancer Lett 374: 62-74, 2016.
108. Huang W, Su X, Yan W, Kong Z, Wang D, Huang Y, Zhai Q, Zhang X, Wu H, Li Y, *et al*: Overexpression of AR-regulated lncRNA TMPO-AS1 correlates with tumor progression and poor prognosis in prostate cancer. Prostate 78: 1248-1261, 2018.
109. Takayama KI, Fujimura T, Suzuki Y and Inoue S: Identification of long non-coding RNAs in advanced prostate cancer associated with androgen receptor splicing factors. Commun Biol 3: 393, 2020.
110. Dai X, Liu L, Liang Z, Guo K, Xu S and Wang H: Silencing of lncRNA MALAT1 inhibits cell cycle progression via androgen receptor signaling in prostate cancer cells. Pathol Res Pract 215: 712-721, 2019.
111. Yao M, Shi X, Li Y, Xiao Y, Butler W, Huang Y, Du L, Wu T, Bian X, Shi G, *et al*: LINC00675 activates androgen receptor axis signaling pathway to promote castration-resistant prostate cancer progression. Cell Death Dis 11: 638, 2020.
112. Li Z, Teng J, Jia Z, Zhang G and Ai X: The long non-coding RNA PCAL7 promotes prostate cancer by strengthening androgen receptor signaling. J Clin Lab Anal 35: e23645, 2021.
113. Shi Z, Chen J, Wumaner A, Li M, Liang C and Li M: A novel long non-coding RNA PCLN16 facilitates androgen receptor signaling in prostate cancer. Biochem Biophys Res Commun 537: 78-84, 2021.
114. Thomas PB, Jeffery P, Gahete MD, Whiteside E, Walpole C, Maugham M, Jovanovic L, Gunter J, Williams E, Nelson C, *et al*: The long non-coding RNA GHSROS reprograms prostate cancer cell lines toward a more aggressive phenotype. Peer J 9: e10280, 2021.
115. Liu B, Qian D, Zhou W, Jiang H, Xiang Z and Wu D: A Novel Androgen-Induced lncRNA FAM83H-AS1 Promotes Prostate Cancer Progression via the miR-15a/CCNE2 Axis. Front Oncol 10: 620306, 2021.
116. Zhang B, Zhang M, Shen C, Liu G, Zhang F, Hou J and Yao W: LncRNA PCBP1-AS1-mediated AR/AR-V7 deubiquitination enhances prostate cancer enzalutamide resistance. Cell Death Dis 12: 856, 2021.
117. Ghildiyal R, Sawant M, Renganathan A, Mahajan K, Kim EH, Luo J, Dang HX, Maher CA, Feng FY and Mahajan NP: Loss of Long Noncoding RNA NXTAR in prostate cancer augments androgen receptor expression and enzalutamide resistance. Cancer Res 82: 155-168, 2022.
118. Lu Y, Wan X, Huang W, Zhang L, Luo J, Li D, Huang Y, Li Y and Xu Y: AC016745.3 regulates the transcription of AR target genes by antagonizing NONO. Life (Basel) 11: 1208, 2021.
119. Huang W, Chen Q, Lu Y, Kong Z, Wan X, Huang Y, Qiu M and Li Y: Androgen-Responsive Oncogenic lncRNA RP11-1023L17.1 Enhances c-Myc protein stability in prostate cancer. Int J Mol Sci 23: 12219, 2022.
120. Zhou J, Anderson K, Bievre M, Ng S and Bondy CA: Primate mammary gland insulin-like growth factor system: Cellular localization and regulation by sex steroids. J Investig Med 49: 47-55, 2001.
121. Dimitrakakis C and Bondy C: Androgens and the breast. Breast Cancer Res 11: 212, 2009.
122. Hickey TE, Robinson JL, Carroll JS and Tilley WD: Minireview: The androgen receptor in breast tissues: Growth inhibitor, tumor suppressor, oncogene? Mol Endocrinol 26: 1252-1267, 2012.
123. Burstein MD, Tsimelzon A, Poage GM, Covington KR, Contreras A, Fuqua SA, Savage MI, Osborne CK, Hilsenbeck SG, Chang JC, *et al*: Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. Clin Cancer Res 21: 1688-1698, 2015.
124. Collina F, Aquino G, Brogna M, Cipolletta S, Buonfanti G, De Laurentiis M, Di Bonito M, Cantile M and Botti G: LncRNA HOTAIR up-regulation is strongly related with lymph nodes metastasis and LAR subtype of Triple Negative Breast Cancer. J Cancer 10: 2018-2024, 2019.
125. Yang F, Shen Y, Zhang W, Jin J, Huang D, Fang H, Ji W, Shi Y, Tang L, Chen W, *et al*: An androgen receptor negatively induced long non-coding RNA ARNILA binding to miR-204 promotes the invasion and metastasis of triple-negative breast cancer. Cell Death Differ 25: 2209-2220, 2018.
126. Leygue E: Steroid receptor RNA activator (SRA1): Unusual bifaceted gene products with suspected relevance to breast cancer. Nucl Recept Signal 5: e006, 2007.
127. Huang G, Cao H, Liu G and Chen J: Role of androgen receptor signaling pathway-related lncRNAs in the prognosis and immune infiltration of breast cancer. Sci Rep 12: 20631, 2022.
128. Xiong Y, Wang L, Li Y, Chen M, He W and Qi L: The Long Non-Coding RNA XIST Interacted with MiR-124 to modulate bladder cancer growth, invasion and migration by targeting androgen receptor (AR). Cell Physiol Biochem 43: 405-418, 2017.
129. Wen L, Zhang X, Bian J, Han L, Huang H, He M, Wei M and Wang P: The long non-coding RNA LINC00460 predicts the prognosis and promotes the proliferation and migration of cells in bladder urothelial carcinoma. Oncol Lett 17: 3874-3880, 2019.
130. Wu S, Zhang L, Deng J, Guo B, Li F, Wang Y, Wu R, Zhang S, Lu J and Zhou Y: A novel micropeptide encoded by Y-Linked LINC00278 links cigarette smoking and AR signaling in male esophageal squamous cell carcinoma. Cancer Res 80: 2790-2803, 2020.
131. He SW, Xu C, Li YQ, Li YQ, Zhao Y, Zhang PP, Lei Y, Liang YL, Li JY, Li Q, *et al*: AR-induced long non-coding RNA LINC01503 facilitates proliferation and metastasis via the SFPQ-FOSL1 axis in nasopharyngeal carcinoma. Oncogene 39: 5616-5632, 2020.
132. Schmidt K, Joyce CE, Buquicchio F, Brown A, Ritz J, Distel RJ, Yoon CH and Novina CD: The lncRNA SLNCR1 Mediates Melanoma Invasion through a Conserved SRA1-like Region. Cell Rep 15: 2025-2037, 2016.
133. Schmidt K, Carroll JS, Yee E, Thomas DD, Wert-Lamas L, Neier SC, Sheynkman G, Ritz J and Novina CD: The lncRNA SLNCR recruits the androgen receptor to EGR1-Bound genes in melanoma and inhibits expression of tumor suppressor p21. Cell Rep 27: 2493-2507. e4, 2019.
134. Schmidt K, Weidmann CA, Hilimire TA, Yee E, Hatfield BM, Schneekloth JS Jr, Weeks KM and Novina CD: Targeting the Oncogenic Long Non-coding RNA SLNCR1 by blocking its sequence-specific binding to the androgen receptor. Cell Rep 30: 541-554. e5, 2020.
135. Zhai W, Sun Y, Guo C, Hu G, Wang M, Zheng J, Lin W, Huang Q, Li G, Zheng J and Chang C: LncRNA-SARCC suppresses renal cell carcinoma (RCC) progression via altering the androgen receptor(AR)/miRNA-143-3p signals. Cell Death Differ 24: 1502-1517, 2017.
136. Bai JY, Jin B, Ma JB, Liu TJ, Yang C, Chong Y, Wang X, He D and Guo P: HOTAIR and androgen receptor synergistically increase GLI2 transcription to promote tumor angiogenesis and cancer stemness in renal cell carcinoma. Cancer Lett 498: 70-79, 2021.
137. You B, Sun Y, Luo J, Wang K, Liu Q, Fang R, Liu B, Chou F, Wang R, Meng J, *et al*: Androgen receptor promotes renal cell carcinoma (RCC) vasculogenic mimicry (VM) via altering TWIST1 nonsense-mediated decay through lncRNA-TANAR. Oncogene 40: 1674-1689, 2021.

138. Han H, Wang S, Meng J, Lyu G, Ding G, Hu Y, Wang L, Wu L, Yang W, Lv Y, *et al*: Long noncoding RNA PART1 restrains aggressive gastric cancer through the epigenetic silencing of PDGFB via the PLZF-mediated recruitment of EZH2. Oncogene 39: 6513-6528, 2020.
139. Qin Z, Liu X, Li Z, Wang G, Feng Z, Liu Y, Yang H, Tan C, Zhang Z and Li K: LncRNA LINC00667 aggravates the progression of hepatocellular carcinoma by regulating androgen receptor expression as a miRNA-130a-3p sponge. Cell Death Discov 7: 387, 2021.
140. D'Ambrosio DN, Clugston RD and Blaner WS: Vitamin A metabolism: An update. Nutrients 3: 63-103, 2011.
141. Siddikuzzaman, Guruvayoorappan C and Berlin Grace VM: All trans retinoic acid and cancer. Immunopharmacol Immunotoxicol 33: 241-249, 2011.
142. Dawson MI and Xia Z: The retinoid X receptors and their ligands. Biochim Biophys Acta 1821: 21-56, 2012.
143. Ghyselinck NB and Duester G: Retinoic acid signaling pathways. Development 146: dev167502, 2019.
144. Zhao H, Zhang X, Frazão JB, Condino-Neto A and Newburger PE: HOX antisense lincRNA HOXA-AS2 is an apoptosis repressor in all trans retinoic acid treated NB4 promyelocytic leukemia cells. J Cell Biochem 114: 2375-2383, 2013.
145. El Hajj J, Nguyen E, Liu Q, Bouyer C, Adriaenssens E, Hilal G and Ségal-Bendirdjian E: Telomerase regulation by the long non-coding RNA H19 in human acute promyelocytic leukemia cells. Mol Cancer 17: 85, 2018.
146. Zheng C, Li X, Ren Y, Yin Z and Zhou B: Long Noncoding RNA RAET1K Enhances CCNE1 expression and cell cycle arrest of lung adenocarcinoma cell by sponging miRNA-135a-5p. Front Genet 10: 1348, 2020.
147. Hu L, Liu J, Meng Y, Zheng H, Ding C, Wang H, Charwudzi A, Li M, Li J, Zhai Z and Xiong S: Long non-coding RNA HOTAIR regulates myeloid differentiation through the upregulation of p21 via miR-17-5p in acute myeloid leukaemia. RNA Biol 18: 1434-1444, 2021.
148. Wei S, Zhao M, Wang X, Li Y and Wang K: PU.1 controls the expression of long noncoding RNA HOTAIRM1 during granulocytic differentiation. J Hematol Oncol 9: 44, 2016.
149. Chen ZH, Wang WT, Huang W, Fang K, Sun YM, Liu SR, Luo XQ and Chen YQ: The lncRNA HOTAIRM1 regulates the degradation of PML-RARA oncoprotein and myeloid cell differentiation by enhancing the autophagy pathway. Cell Death Differ 24: 212-224, 2017.
150. Tang D, Hu P, Zhu D, Luo Y, Chen M, Zhang G and Wang Y: C/EBPα is indispensable for PML/RARα-mediated suppression of long non-coding RNA NEAT1 in acute promyelocytic leukemia cells. Aging (Albany NY) 13: 13179-13194, 2021.
151. Pokorná M, Hudec M, Juříčková I, Vácha M, Polívková Z, Kútna V, Pala J, Ovsepian SV, Černá M and O'Leary VB: All-Trans retinoic acid fosters the multifarious U87MG cell line as a model of glioblastoma. Brain Sci 11: 812, 2021.
152. Wang C, Zhao D, Wang K, Gao L, He Y, Wu H, Ruan L, Chen W, Zhang D, Xia T, *et al*: All-Trans retinoic acid rescues the tumor suppressive role of RAR-β by Inhibiting LncHOXA10 expression in gastric tumorigenesis. Nutr Cancer 73: 2065-2077, 2021.
153. Shan L, Liu W and Zhan Y: LncRNA HAND2-AS1 exerts anti-oncogenic effects on bladder cancer via restoration of RARB as a sponge of microRNA-146. Cancer Cell Int 21: 361, 2021.
154. Fu L, Shi Z and Chen B: Deleted in lymphocytic leukemia 2 induces retinoic acid receptor beta promoter methylation and mitogen activated kinase-like protein activation to enhance viability and mobility of colorectal cancer cells. Bioengineered 13: 12847-12862, 2022.
155. Bikle DD: Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol 21: 319-329, 2014.
156. Bikle DD, Jiang Y, Nguyen T, Oda Y and Tu CL: Disruption of Vitamin D and Calcium signaling in keratinocytes predisposes to skin cancer. Front Physiol 7: 296, 2016.
157. Jiang YJ and Bikle DD: LncRNA profiling reveals new mechanism for VDR protection against skin cancer formation. J Steroid Biochem Mol Biol 144 Pt A: 87-90, 2014.
158. Kholghi Oskooei V, Geranpayeh L, Omrani MD and Ghafouri-Fard S: Assessment of functional variants and expression of long noncoding RNAs in vitamin D receptor signaling in breast cancer. Cancer Manag Res 10: 3451-3462, 2018.
159. Gheliji T, Oskooei VK, Ashrafi Hafez A, Taheri M and Ghafouri-Fard S: Evaluation of expression of vitamin D receptor related lncRNAs in lung cancer. Noncoding RNA Res 5: 83-87, 2020.
160. Jin T, Guo Y, Huang Z, Zhang Q, Huang Z, Zhang Y and Huang Z: Vitamin D inhibits the proliferation of oral squamous cell carcinoma by suppressing lncRNA LUCAT1 through the MAPK pathway. J Cancer 11: 5971-5981, 2020.
161. Wang L, Zhou S and Guo B: Vitamin D suppresses ovarian cancer growth and invasion by targeting long Non-Coding RNA CCAT2. Int J Mol Sci 21: 2334, 2020.
162. Fu Y, Katsaros D, Biglia N, Wang Z, Pagano I, Tius M, Tiirikainen M, Rosser C, Yang H and Yu H: Vitamin D receptor upregulates lncRNA TOPORS-AS1 which inhibits the Wnt/β-catenin pathway and associates with favorable prognosis of ovarian cancer. Sci Rep 11: 7484, 2021.
163. Chen S, Bu D, Ma Y, Zhu J, Chen G, Sun L, Zuo S, Li T, Pan Y, Wang X, *et al*: H19 overexpression induces resistance to 1,25(OH)2D3 by Targeting VDR Through miR-675-5p in colon cancer cells. Neoplasia 19: 226-236, 2017.
164. Timmermans S, Souffriau J and Libert C: A general introduction to glucocorticoid biology. Front Immunol 10: 1545, 2019.
165. Kino T, Hurt DE, Ichijo T, Nader N and Chrousos GP: Noncoding RNA gas5 is a growth arrest- and starvation-associated repressor of the glucocorticoid receptor. Sci Signal 3: ra8, 2010.
166. Brent GA: Mechanisms of thyroid hormone action. J Clin Invest 122: 3035-3043, 2012.
167. Aranda A: MicroRNAs and thyroid hormone action. Mol Cell Endocrinol 525: 111175, 2021.
168. Huang PS, Chang CC, Wang CS and Lin KH: Functional roles of non-coding RNAs regulated by thyroid hormones in liver cancer. Biomed J 44: 272-284, 2021.
169. Lin YH, Wu MH, Huang YH, Yeh CT, Chi HC, Tsai CY, Chuang WY, Yu CJ, Chung IH, Chen CY and Lin KH: Thyroid hormone negatively regulates tumorigenesis through suppression of BC200. Endocr Relat Cancer 25: 967-979, 2018.
170. Dai Q, Deng J, Zhou J, Wang Z, Yuan XF, Pan S and Zhang HB: Long non-coding RNA TUG1 promotes cell progression in hepatocellular carcinoma via regulating miR-216b-5p/DLX2 axis. Cancer Cell Int 20: 8, 2020.
171. Lin YH, Wu MH, Huang YH, Yeh CT and Lin KH: TUG1 Is a Regulator of AFP and serves as prognostic marker in Non-Hepatitis B Non-Hepatitis C hepatocellular carcinoma. Cells 9: 262, 2020.