Noncoding RNAs and the control of hormonal signaling via nuclear receptor regulation

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Abstract

Despite its identification over 100 years ago, new discoveries continue to add to the complexity of the regulation of the endocrine system. Today the nuclear receptors (NRs) that play such a pivotal role in the extensive communication networks of hormones and gene expression remain an area of intense research. By orchestrating core processes, from metabolism to organismal development, the gene expression programs they control are dependent on their cellular context, their own levels, and those of numerous co-regulatory proteins. A previously unknown component of these networks, noncoding RNAs (ncRNAs) are now recognized as potent regulators of NR signaling, influencing receptor and co-factor levels and functions while being reciprocally regulated by the NRs themselves. This review explores the regulation enacted by microRNAs and long ncRNAs on NR function, using representative examples to show the varied roles of ncRNAs, in turn producing significant effects on the NR functional network in health and disease.

Key Words

- ▶ noncoding RNA
- ▶ microRNA
- ▶ miRNA
- ▶ lncRNA
- ▶ eRNA
- ▶ nuclear receptors

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Introduction

Advances in high-throughput sequencing techniques have revealed eukaryotic genomes to be extensively transcribed, generating an array of novel non-protein-coding RNA classes that greatly outnumber protein-coding mRNAs (Carninci *et al.* 2005, Birney *et al.* 2007, Kapranov *et al.* 2007, Bernstein *et al.* 2012, Djebali *et al.* 2012). Noncoding RNAs (ncRNAs) encompass numerous functional classes including tRNA, rRNA, small nuclear RNA, and small nucleolar RNA, widely recognized to play pivotal roles in cell function (reviewed in Matera *et al.* (2007)). More recently, new and potent classes of regulatory RNAs have been discovered. These classes are composed of small RNAs, most prominently the microRNAs (miRNAs), as well as the long ncRNAs (lncRNAs) defined as being over 200 nucleotides (nt) but ranging to

above 10 000-nt. In succession, these discoveries have created new fields in cell biological research, exploring the ability of ncRNAs to regulate the expression of biologically significant genes. It soon became clear that they have the capacity to modulate most important biological processes (Hirose *et al.* 2014), which in turn makes these ncRNAs a focus of interest within health and disease research (Batista & Chang 2013).

miRNAs make up a populous class of small ncRNAs, with more than 2000 human miRNA genes annotated to date in the miRNA database, miRBase (<http://www.mirbase.org>). Most miRNAs are transcribed as long miRNA primary transcripts (pri-miRNAs) by RNA polymerase II (Pol II) (Lee *et al.* 2004), which then undergo a canonical biogenic process characterized by two

sequential enzymatic cleavage steps. The first occurs in the nucleus by the nuclear RNase III enzyme Drosha and the second in the cytoplasm by a second RNase III enzyme, Dicer. This maturation process generates the final mature molecules which are loaded onto the miRNA-induced silencing complex, composed of Argonaute (Ago) proteins (reviewed in Krol *et al.* (2010)). Mature miRNAs are approximately 22-nt single-stranded RNA molecules that mediate post-transcriptional regulation of gene expression either by inhibiting translation or by promoting destabilization of target mRNAs through deadenylation (Fabian *et al.* 2010, Krol *et al.* 2010). In mammals, miRNAs regulate post-transcriptional gene expression by partial complementary binding to their targets, but with full complementary pairing within a limited region of six to eight nt in length at the 5' end of the miRNA, named the 'seed' region (Lewis *et al.* 2005, Bartel 2009). The perfect complementarity between the miRNA seed region and target mRNAs is considered to be the major determinant of miRNA target specificity and regulation. However, many studies have also reported noncanonical modulation of targets, which can occur with mismatches within the seed region or the central region of the miRNA (Bartel 2009, Shin *et al.* 2010, Helwak *et al.* 2013).

The lncRNAs are an emerging class of key regulatory ncRNAs that have already been implicated in a range of cellular processes (Wapinski & Chang 2011, Rinn & Chang 2012). Similar to mRNAs, lncRNAs are mostly transcribed by RNA Pol II, undergo 5'-capping, and usually 3'-polyadenylation and splicing, although diverse unspliced and non-3'-polyadenylated lncRNAs have been described. Unlike mRNAs, lncRNAs have very little or no potential to encode proteins, and although the extent of their coding capacity remains under investigation, results from ribosome profiling experiments indicate that most occupancy of ribosomes by lncRNAs mirrors that of 5'-UTRs and fails to produce functional peptides (Guttman *et al.* 2013). Nevertheless, three groups independently identified peptides encoded by such molecules with specific cellular functions (Magny *et al.* 2013, Bazzini *et al.* 2014, Pauli *et al.* 2014). Some lncRNAs are located between protein-coding genes and termed long intergenic RNAs (lincRNAs), while many others can be transcribed from within the coding genes or in an antisense orientation to mRNAs. The lncRNAs regulate gene expression through an expanding number of defined mechanisms. The relative flexibility of RNA molecules may enable them to function as modular scaffolds, with different sections of a lncRNA binding various protein, DNA, and RNA

substrates, to carry out specific functions in combination (Guttman & Rinn 2012, Mercer & Mattick 2013).

Nuclear receptors (NRs) are ligand-activated transcription factors that regulate gene expression by binding to regulatory regions in the genomic DNA. NRs are critically involved in an array of physiological processes including growth, differentiation, homeostasis, development, and metabolism (Mangelsdorf *et al.* 1995). Conversely, dysregulated NR signaling participates in a range of pathological processes, with NRs implicated in diseases such as diabetes, hormone resistance syndromes, and cancer. Forty-eight NRs have been identified in humans (Xiao *et al.* 2013). Upon ligand binding, these receptors interact with specific DNA sequences in the promoter and enhancer regions of their target genes. The transcription of regulated genes is modulated by co-binding of an array of co-factors as well as RNA polymerases and several components of the transcription initiation machinery (Acevedo & Kraus 2004, Cheung & Kraus 2010, Hah *et al.* 2011). Based on ligand properties, the NR superfamily can be broadly divided into three classes: hormone, metabolic, and orphan NRs (Gadaleta & Magnani 2014). The hormone receptor subfamily includes the estrogen receptors ($ER\alpha$ (ESR1) and $ER\beta$ (ESR2)), androgen receptor (AR), progesterone receptor (PR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR) (Mangelsdorf *et al.* 1995). In terms of structural organization, NRs share a modular structure composed of four domains: an N-terminal activation domain, a DNA-binding domain (DBD), a small hinge region, and a C-terminal ligand-binding domain (LBD) (Helsen & Claessens 2014). Hormone NRs bind to DNA primarily as homodimers. The DBD consists of two zinc finger domains in which a zinc atom is coordinated by four cysteine residues (Helsen *et al.* 2012). The first zinc finger contains a conserved motif known as the 'P-box' that coordinates base-specific interactions within the DNA major groove. The second zinc finger contains another conserved motif, the 'D-box', which forms the dimerization interface (Zechel *et al.* 1994). Hormone NRs have long been known to bind to DNA elements that are arranged as inverted repeats of hexameric motifs separated by three nucleotide spacers. For AR, PR, GR, and MR, the consensus hexamer is 5'-AGAACA-3'. For ERs, the consensus is 5'-AGGTCA-3' (Carroll *et al.* 2006). In addition, AR and PR can also bind to direct repeats of the 5'-AGAACA-3' motifs (Denayer *et al.* 2010, Kerkhofs *et al.* 2012). Recently, chromatin immunoprecipitation coupled with massively parallel DNA sequencing (ChIP-seq) has allowed detailed mapping of NR-binding sites across the whole genome

and has revealed a strong preference for hormone NRs to bind regions of the genome that are distal from transcription start sites of coding genes (> 10 kb) (Carroll *et al.* 2005, Wang *et al.* 2007). These studies have also shown enrichment for binding motifs of other transcription factors, indicating that NRs can bind to DNA indirectly through interaction with other transcription factors (Heldring *et al.* 2011, Sahu *et al.* 2011). Furthermore, it has been shown that multiple NRs can bind to the same genomic locus, indicating an important crosstalk between different NR signaling pathways through co-operative or antagonistic interactions (Ross-Innes *et al.* 2010, Lai *et al.* 2013).

Many factors contribute to the regulation of NRs ultimately enhancing/repressing transcription of target genes; these include the recruitment of co-regulatory proteins, post-translational modifications and interactions with other transcription factors. ncRNAs represent an additional layer of complexity in the network that governs NR-dependent gene expression. By turning our attention to the effects of miRNAs and later lncRNAs on NR function in the specific case of hormonal signaling, we highlight recent advances in our understanding of these processes and discuss the capacity of ncRNAs to act at multiple regulatory levels to fine-tune NR function.

miRNAs and NRs

The interplay between miRNAs and NRs is complex and is represented by a network of feedback and feed-forward regulatory loops. NRs can regulate the expression and/or biogenesis of miRNAs, and, conversely miRNAs regulate NR signaling by targeting NRs and/or co-regulatory proteins (Cochrane *et al.* 2011). In the following sections, we discuss the main features of this crosstalk.

miRNAs and ER α

Many studies in recent years have shown that estrogens, through the action of ER α , can modulate the levels of pri-miRNA transcription (Fig. 1A). This regulation can occur through at least two main mechanisms: ER α can directly bind to the regulatory regions of miRNAs or estrogen can regulate the expression of transcription factors that control the expression of miRNAs (reviewed in Cochrane *et al.* (2011)). By generating and analyzing a miRNA expression microarray for ER α -positive MCF-7 breast cancer cells treated with 17 β -estradiol (E₂), we have previously shown that the expression of the human mir-17-92 cluster and its paralogous clusters, along with

Figure 1

Schematic representation of the crosstalk regulation between ncRNAs and NRs. (A) NRs can regulate the transcription of miRNA genes (the figure depicts a unique transcript containing several miRNAs). (B) miRNAs can bind to the 3'-UTR of NR transcripts and post-transcriptionally regulate them. (C) lncRNAs can modulate NR activity through different mechanisms: lncRNAs can bind to NRs and other proteins, acting as scaffolds (e.g., SRA), (i) they can bind to NRs and prevent them from binding to DNA, thereby acting as decoys (e.g., GAS5) (Carninci *et al.* 2005) (ii) or they can be transcribed from NR enhancers and participate in chromosomal looping (iii). (D) NRs can regulate transcription of lncRNA genes.

the expression of miRNAs encoded by these clusters, are induced by E₂ treatment. In addition, we showed that the regulation occurs indirectly through binding of the E₂-induced transcription factor c-MYC to the promoter of the cluster (Castellano *et al.* 2009). Similarly, Bhat-Nakshatri *et al.* (2009) have reported that E₂ induces the expression of the Let7 family of miRNAs as well as other miRNAs including miR-21, whose expression is regulated by direct binding of ER α to its promoter region. In a later study, we showed that ER α , through the direct transcriptional down-regulation of miR-515-5p, regulates cell proliferation, at least in part, by targeting the sphingosine kinase 1 (SK1) oncogene (Pinho *et al.* 2013). In addition to regulating the expression of miRNAs at the level of transcription, ER α can regulate miRNA processing. Indeed, several proteins involved in miRNA biogenesis, including Dicer and the

component of RISC complex Ago2, are induced by E_2 and their levels differ in ER α -positive and -negative breast cancers (Adams *et al.* 2009, Bhat-Nakshatri *et al.* 2009, Cheng *et al.* 2009).

Conversely, miRNAs can directly target the 3'-UTR of the ER α transcript itself and/or the 3'-UTRs of co-regulatory proteins (Fig. 1B). In some cases, the crosstalk between miRNAs and ER α is in the form of a negative feedback loop. For example, miR-18a, miR-19b, and miR-20b encoded by the E_2 -induced mir-17-92 cluster and/or paralogues directly target the ER α 3'-UTR, causing downregulation of ER α expression at the protein level (Castellano *et al.* 2009). Furthermore, miR-20b targets and downregulates the ER α co-activator AIB1, demonstrating the capacity of such miRNA clusters to fine-tune at multiple points in the same pathway (Castellano *et al.* 2009). In addition to our work, results from several other studies have indicated that miRNAs can directly target the ER α transcript, including miR-206, the first to be identified (Adams *et al.* 2007), and miR-221/222 (Zhao *et al.* 2008). More recently, Leivonen *et al.* (2009) used a protein lysate microarray technology to systematically identify miRNAs that target the ER α 3'-UTR, providing a comprehensive picture of previously characterized, as well as novel ER α -targeting miRNAs.

miRNAs and AR

Similarly to the scenario described earlier, androgens through the action of AR can regulate the transcriptional output from miRNA loci. Expression profiling studies in prostate cancer have identified an array of androgen up- and down-regulated miRNAs potentially involved in prostate cancer progression (Porkka *et al.* 2007, Ambros *et al.* 2008, Ozen *et al.* 2008, Waltering *et al.* 2011). Several miRNAs have been experimentally characterized and proven to be directly involved in AR signaling and consequently in prostate cancer. They are regulated by AR and have been shown to act as both oncogenes (oncomirs), including miR-21 (Ribas *et al.* 2009), miR-125b (Shi *et al.* 2007), miR-141 (Waltering *et al.* 2011, Xiao *et al.* 2012), miR-27a (Fletcher *et al.* 2012), and as tumor suppressor genes as in the case of miR-205 (Hulf *et al.* 2013). Interestingly, miR-205 plays an important role in counteracting epithelial-to-mesenchymal transition by targeting ZEB1 and ZEB2, both negative regulators of E-cadherin expression (Gregory *et al.* 2008, Gandellini *et al.* 2009). In addition, it has been shown that circulating levels of miRNAs that are upregulated in prostate cancer, as in the case of miR-141, are increased in prostate cancer

patients compared with healthy controls, indicating a potential use of these ncRNAs as novel biomarkers for this disease (Mitchell *et al.* 2008, Brase *et al.* 2011). Compared with ER α , the 3'-UTR of AR transcript is considerably shorter, and accordingly fewer miRNAs have been predicted to interact with it. A recent study, using a protein lysate microarray combined with 3'-UTR luciferase reporter assays in a panel of prostate cancer cell lines, has identified 13 miRNAs that target and repress the AR transcript (Ostling *et al.* 2011).

miRNAs and other NRs

In addition to estrogens and androgens, other hormones through the action of their cognate NR can regulate miRNA expression, further indicating the important role of miRNAs in NR signaling. Progesterone, through the action of PR, can regulate the expression of numerous miRNAs, including the miR-200 family (Renthall *et al.* 2010), let-7 (Wendler *et al.* 2011), and miR-320 (Xia *et al.* 2010). Glucocorticoids, by activating both GR and MR NRs, have been reported to upregulate miR-15/16 clusters in leukemia cell lines and prostate cancer patients (Rainer *et al.* 2009). In addition, the 3'-UTR of these NRs can be targeted by miRNAs; however, compared with ER α and AR, only few miRNAs have been identified. These include miR-126-3p, which directly interacts with the PR 3'-UTR (Cui *et al.* 2011), and miR-124a, which binds to the GR 3'-UTR (Vreugdenhil *et al.* 2009), and potentially the MR 3'-UTR (Sober *et al.* 2010).

lncRNAs and NRs

It has long been known that lncRNAs can regulate NR transcriptional activity. In 1999, the steroid receptor RNA activator (SRA) was identified as the first lncRNA to bind and co-activate several NRs (Fig. 1Ci; Lanz *et al.* 1999). Subsequently, it was shown that lncRNA growth arrest-specific 5 (GAS5) was able to bind GR and negatively regulate its transcriptional activity by acting as a molecular decoy (Fig. 1Cii; Kino *et al.* 2010). Below we will discuss the key features of both lncRNAs and describe their currently known mechanisms of action.

Using a novel technique called global nuclear run-on and sequencing (GRO-seq) (Core *et al.* 2008), which allows genome-wide detection of nascent RNAs, Hah and colleagues gave the most detailed and comprehensive picture of the effect of estrogen on the global transcriptome of the ER α -positive MCF-7 breast cancer cell line treated with E_2 in a short-time course (10, 40, and 160 min).

The authors showed that E₂ regulates transcription by all three RNA polymerases (Hah *et al.* 2011). In addition to annotated protein coding and non-coding genes, they described an abundance of unannotated non-coding transcripts including divergent, enhancer, antisense, and intergenic transcripts whose expression is regulated by E₂, indicating a role in E₂-dependent transcription (Fig. 1D; Hah *et al.* 2011). Many of these transcripts were enhancer RNAs (eRNAs; Fig. 1Ciii), characterized by histone 3 lysine 4 monomethylation (H3K4me1) and the binding of the co-activator CBP, and whose expression correlates with the expression of nearby mRNAs (Kim *et al.* 2010). Several of the studies discussed below have, in recent years, focused on investigating the role and mode of action of eRNAs at enhancers of NR-regulated genes, although the exact mechanisms by which they promote transcription currently remain unclear.

lncRNAs can bind to NRs and regulate their transcriptional activity

lncRNAs can function as positive or negative regulators of NR-dependent transcription. SRA is a co-activator for several NRs (Lanz *et al.* 1999). It has been shown that multiple stem-loops in the SRA RNA are important for its coactivating function (Lanz *et al.* 2002). Several proteins have been shown to interact with SRA stem-loop structures, including the RNA pseudouridylylase PUS1P and PUS3P (pseudouridylation of SRA leads to enhanced coactivation of NRs (Zhao *et al.* 2004, 2007)), DEAD-box RNA helicases p68 and p72 (Watanabe *et al.* 2001), NR coactivator SRC1 (Lanz *et al.* 1999), as well as NR corepressors SHARP (Shi *et al.* 2001) and SLIRP (Hatchell *et al.* 2006). These findings led to the hypothesis that SRA may act as a 'scaffold' for the assembly of other co-regulatory proteins that direct NR-dependent transcription (Fig. 1Ci). More recently, by using a series of chemical-probing techniques Novikova *et al.* (2012) have determined the secondary structure of the entire SRA transcript. Since for many lncRNA molecules functionality depends on their secondary structure, characterization of this property will give important insights into the links between structure and function.

Connected to its role as a NR coactivator, SRA has been implicated in hormone-driven tumors such as breast and prostate cancers. It has been shown that SRA is overexpressed in breast tumors (Leygue *et al.* 1999, Murphy *et al.* 2000, Lanz *et al.* 2003) and that it affects the growth of breast and prostate cancer cell lines (Agoulunik & Weigel 2009, Cooper *et al.* 2009). *In vivo*, transgenic mice

overexpressing SRA show enhanced epithelial proliferation together with enhanced apoptosis, indicating that SRA could modulate homeostasis in epithelial tumors. However, in this study, the overexpression itself was not sufficient to induce tumorigenesis (Lanz *et al.* 2003).

Interestingly, although SRA1 was originally characterized as a regulatory ncRNA (Lanz *et al.* 1999), several coding isoforms that code for SRA protein (SRAP) have been identified (Emberley *et al.* 2003, Kawashima *et al.* 2003). This is one of a growing number of examples of bifunctional mRNAs that also exert coding-independent function as lncRNAs (Dinger *et al.* 2011).

In contrast to SRA, GAS5 acts as a negative regulator of GR transcription by a different mechanism. GAS5 directly interacts with the GR DBD and acts as a molecular decoy by competing with the glucocorticoid-response element for GR binding, thereby inhibiting GR-mediated transcription (Fig. 1Cii; Kino *et al.* 2010). In addition, Kino *et al.* (2010) showed that GAS5 accumulates in cells that have been starved of growth factors and by repressing GR activity, GAS5 sensitises cells to apoptosis. Since GR shares similar responsive elements with AR, PR, and MR, GAS5 may also regulate these other steroid receptors. Furthermore, it has been shown that overexpression of GAS5 leads to growth arrest and apoptosis in human cell lines, including breast cancer cells, and its expression is significantly downregulated in breast tumors (Mourtada-Maarabouni *et al.* 2009).

Two lncRNAs, PCGEM1 and PRNCR1, overexpressed in aggressive forms of prostate cancer, directly interact with AR under ligand-stimulated conditions and sequentially interact with the receptor via specific post-translational modification of the AR protein (Yang *et al.* 2013). However, these results have been contradicted by results from a later study (Prensner *et al.* 2014), which reported that neither PCGEM1 nor PRNCR1 is associated with castration-resistant prostate cancer, and that neither of them interact with AR, and the authors were also unable to find the post-translational modifications of lncRNA-bound AR identified in the previous study (Prensner *et al.* 2014). Further studies are needed to resolve the discrepancies between these studies.

NRs regulate lncRNAs with enhancer function

The recent discovery that enhancer elements can be transcribed, resulting in the production of a novel class of ncRNA called eRNAs, has added yet more complexity to our understanding of regulated gene expression (Kim *et al.* 2010). Using RNA-seq together with ChIP-seq for RNA Pol II, Kim and colleagues showed that eRNAs are

transcribed bidirectionally by RNA Pol II, and that their levels of expression correlate with those of neighboring mRNAs. This indicates that eRNAs are transcribed at enhancer elements that actively promote mRNA transcription. Initially identified in neurons (Kim *et al.* 2010), expression of eRNAs has subsequently been found in macrophages (De Santa *et al.* 2010), T-cells (Koch *et al.* 2011), and breast and prostate cancer cells (Hah *et al.* 2011, 2013, Wang *et al.* 2011, Li *et al.* 2013), indicating that transcription of eRNAs is a ubiquitous and abundant phenomenon.

Using GRO-seq, several groups have shown that eRNA expression is induced by external stimuli, such as hormones, as well as regulated by NRs. Hah and colleagues identified eRNAs at ER α enhancers as a class of noncoding transcripts regulated by E₂ in MCF-7 cells. The vast majority of eRNAs showed upregulation upon E₂ treatment, strongly indicating a positive function in the enhancer activation process (Hah *et al.* 2011). Similarly, GRO-seq was performed for the AR-positive LNCaP prostate cancer cell line treated with the hormone 5 α -dihydrotestosterone (DHT) to activate the AR (Wang *et al.* 2011). Just as E₂ regulates the expression of eRNAs at enhancers of ER α -regulated genes, DHT induces bidirectional transcription of eRNAs at enhancers of AR-regulated genes.

One question many groups have tried to resolve is whether the production and accumulation of eRNAs contribute to enhancer function, or are merely a by-product of enhancer activation. Some have proposed that the act of transcription at enhancer elements may favor an open chromatin environment thereby promoting enhancer function, while others suggest that eRNAs may promote transcription by facilitating chromatin looping, which is an event that promotes a physical interaction between enhancers and target gene promoters (Orom *et al.* 2010, Orom & Shiekhattar 2011, Natoli & Andrau 2012). Hah and colleagues addressed this question within the context of ER α -enhancer transcription. By integrating the previously performed GRO-seq together with a variety of existing genomic data sets from MCF-7 cells, including ChIP-seq, DNase-seq, and ChIA-PET, they determined that eRNAs at ER α -binding sites positively correlate with the features of active enhancers (e.g., RNA Pol II, ER α coregulators, enhancer histone modifications H3K4me1, and H3 lysine 27 acetylation, H3K27ac), as well as enhancers looping to target genes (Hah *et al.* 2013). However, inhibition of eRNAs by the small molecule flavopiridol, a CDK9 inhibitor that blocks RNA Pol II transcription elongation, did not affect the assembly of ER α enhancer complexes and did not affect E₂-induced

enhancer–promoter looping at ER α -bound enhancers, indicating that eRNAs were not required for chromatin looping (Hah *et al.* 2013). However, by performing knockdown of eRNAs using both siRNAs and locked nucleic acid antisense oligonucleotides, Li *et al.* (2013) found strong inhibition of enhancer–promoter interaction and a concomitant decrease in expression of the coding gene regulated by that specific enhancer. Importantly, they demonstrated interaction of several eRNAs with the cohesin complex, which has been previously shown to be implicated in enhancer–promoter looping (Fig. 1Ciii; Kagey *et al.* 2010). The discrepancy between these two studies may be explained by the different techniques used (pharmacological inhibition of enhancer transcription versus eRNA knockdown) or may indicate different mechanisms acting at specific enhancers.

Results from recent studies of Rev-Erb enhancers in macrophages (Lam *et al.* 2013) and AR enhancers in LNCaP cells (Hsieh *et al.* 2014) have supported a functional role for eRNAs in enhancer–promoter looping and target gene activation. Further studies will certainly be required to clarify the role of eRNAs at enhancer sites.

Conclusions

NRs are key mediators of hormonal signals, with the responses they generate dependent on a variety of co-occurring factors and contexts. Dysregulation of these factors can generate pathological gene expression programs, as seen in breast and prostate cancers, as well as various metabolic syndromes. While the mechanisms by which miRNAs repress gene expression through 3'-UTR binding are now quite well understood, the diversity of mechanisms by which lncRNAs produce their effects continues to expand. As discussed in this review, miRNAs and lncRNAs have the capacity to regulate NR levels and activity, thereby affecting NR signaling, chromatin landscape and eventually transcription. Conversely, NRs can stimulate or repress ncRNA transcription (Fig. 1). Despite these recent discoveries, many questions still remain unanswered. In addition to the mechanisms described in this review, lncRNAs have been shown to act as epigenetic regulators by directly recruiting chromatin factors to specific genomic loci (Guttman *et al.* 2009, Mercer & Mattick 2013). Indeed, the lncRNA HOTAIR is over-expressed and required for cell migration and invasion in metastatic ER α -positive breast cancer cells (Gupta *et al.* 2010). Research is now focusing on identifying novel ncRNA players that can modulate NR signaling and unraveling their modes of action in normal cells, as well

as in the disease setting. Given the importance of NRs in hormone-driven cancers, a deeper understanding of the crosstalk between these factors will have important therapeutic implications, including their potential utility as biomarkers or therapeutic targets.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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