REVIEW

Non-coding RNAs: long non-coding RNAs and microRNAs in endocrine-related cancers

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Abstract

The human genome is 'pervasively transcribed' leading to a complex array of non-coding RNAs (ncRNAs) that far outnumber coding mRNAs. ncRNAs have regulatory roles in transcription and post-transcriptional processes as well numerous cellular functions that remain to be fully described. Best characterized of the 'expanding universe' of ncRNAs are the ~22 nucleotide microRNAs (miRNAs) that base-pair to target mRNA's 3′ untranslated region within the RNA-induced silencing complex (RISC) and block translation and may stimulate mRNA transcript degradation. Long non-coding RNAs (lncRNAs) are classified as >200 nucleotides in length, but range up to several kb and are heterogeneous in genomic origin and function. lncRNAs fold into structures that interact with DNA, RNA and proteins to regulate chromatin dynamics, protein complex assembly, transcription, telomere biology and splicing. Some lncRNAs act as sponges for miRNAs and decoys for proteins. Nuclear-encoded lncRNAs can be taken up by mitochondria and lncRNAs are transcribed from mtDNA. Both miRNAs and lncRNAs are dysregulated in endocrine cancers. This review provides an overview on the current understanding of the regulation and function of selected lncRNAs and miRNAs, and their interaction, in endocrine-related cancers: breast, prostate, endometrial and thyroid.

Key Words

- miRNA
- lncRNA
- ncRNA
- transcription
- translation

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Introduction

Cancer is a disease of the genome in which tumors have a constellation of genomic and epigenetic alterations that drive their clinical behavior and patient prognosis (Macconaill & Garraway 2010). The Central Dogma proposed by Francis Crick in 1958 envisioned that information flowed from DNA to mRNA, which is translated into functional proteins with the assistance of tRNA and rRNA (reviewed in Morris & Mattick 2014, Jarroux *et al*. 2017). With time, additional classes of RNA that have important regulatory roles in cellular biology were discovered: short nuclear and small nucleolar RNAs (snRNAs and snoRNAs), followed by microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). The Encyclopedia of DNA Elements (ENCODE) Consortium was started in 2003 as an international collaboration funded by the National Human Genome Institute (NHGRI). Analysis of the human genome revealed that while ~85% is transcribed, only ~1% is protein-coding mRNA (ENCODE Project Consortium 2012, Djebali *et al*. 2012, Dykes & Emanueli 2017). The GENCODE consortium (https://www.gencodegenes.org/) is a subproject of ENCODE that produces high-quality reference gene annotation and experimental validation. The current GENECODE, version 27 of the human genome includes 58,288 genes; 200,401 total transcripts; 19,826 protein-coding genes; 15,778 lncRNAs; 14,694 pseudogenes; 7569 small non-coding

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RNA (ncRNA) genes and 1881 miRNAs. Most (85%) small ncRNAs are snRNAs, snoRNAs, miRNAs and tRNAs (Djebali *et al*. 2012). In addition to GENECODE, the FANTOM (Functional Annotation of Mammalian Genomes) project is creating a comprehensive catalog of transcripts encoded in human, mouse, rat, dog, Rhesus monkey and chicken genomes (http://fantom.gsc.riken.jp) (Kawaji *et al*. 2017). Analysis of data from FANTOM5 identified 27,919 human lncRNA genes with high-confidence 5′ ends and provided evidence that 69% (19,175) are functional (Hon *et al*. 2017). The history of the discovery of regulatory RNAs, notably the ncRNAs, has been reviewed (Morris & Mattick 2014).

The advent of next-generation sequencing (NGS) by RNA sequencing (RNA-seq), also called 'whole transcriptome shotgun sequencing' and 'deep RNA-seq', has allowed characterization of the cellular transcriptomes, i.e., the entire spectrum of RNAs produced in a cell type (Wolf 2013), resulting in a glut of data that can be mined by investigators. One database of transcriptomes of potential interest for readers of this review is the NURSA website (www.nursa.org). The transcriptome includes mRNA, rRNA and tRNA; and the ncRNAs: miRNAs, enhancer RNAs (eRNAs), endogenous small-interfering RNAs (siRNAs), Piwi-interacting RNAs (piRNAs), circular RNAs (circRNAs) and lncRNAs (Marrone *et al*. 2014). Table 1 highlights features of these ncRNAs and their roles in cellular processes. The function of piRNAs and snoRNAs in endocrine-related cancers was reviewed (Venkatesh *et al*. 2015). miRNAs are best characterized for their gene silencing of target mRNA by complementary base-paring with the 3′UTR within the RNA-induced silencing complex (RISC) to repress translation and/or cause mRNA degradation (Muluhngwi & Klinge 2015). Like miRNAs, siRNAs and piRNAs bind argonaute (AGO) family members and base-pair with target RNA to cause RNA degradation and/or translation repression (Watanabe & Lin 2014). Studies have shown that RNA polymerase (pol) II-mediated transcriptional activity at gene enhancers is 'pervasive' and bidirectional, generally producing transcripts in both directions including short eRNAs that play roles in enhancer–promoter interactions (reviewed in Lam *et al*. 2014). Enhancers are relatively insensitive to position and distance of their target genes and about half are intragenic, which can result in inhibition or attenuation of nascent transcript elongation (Cinghu *et al*. 2017). circRNAs are usually formed by noncannonical splice reactions and reside in the cytoplasm where one circRNA, CDR1AS, regulates miR-7 stability and transport in neurons (Piwecka *et al*. 2017).

Both miRNAs and lncRNAs are epigenetic regulators of human cancers (Liz & Esteller 2016). Moreover, these RNAs are chemically modified, e.g., by post-transcriptional methylation on N6 of adenosine (m^6A), which alters their activities, providing an additional layer of regulation termed 'epitranscriptomics' (Li *et al*. 2016*c*). Many more papers have been published on miRNAs than lncRNAs in endocrine cancers (Fig. 1). This review provides a brief overview of the identity, regulation and roles of miRNAs and lncRNAs in selected endocrine-related cancers. Because of the scope of published literature on these topics, this review is not a comprehensive analysis of lncRNAs and miRNAs in breast, prostate, endometrial and thyroid cancers. The reader is provided with citations to recent reviews and primary literature for further information.

lncRNAs: classification and functional activities

lncRNAs are defined as ncRNAs of >200 nucleotides that are transcribed by RNA pol II from regulatory regions including promoter upstream elements and technically include eRNAs (Andersson *et al*. 2014). However, eRNAs differ from lncRNAs by being shorter (<2 kbp), without being spliced and are not polyadenylated (Kim *et al*. 2015). By total cellular RNA mass, lncRNA constitutes only 0.03–0.2% while mRNA constitute 3–7% (Dykes & Emanueli 2017). lncRNAs are classified based on their genomic organization: (1) intergenic lncRNAs (lincRNAs) are transcribed between two protein-coding genes; (2) intronic lncRNAs are transcribed from introns of protein-coding genes; (3) overlapping lncRNAs, as the name implies, constitute transcripts that overlap known protein-coding genes; and (4) antisense (as) lncRNAs are transcribed in a direction opposite that of the protein-coding gene (Peng *et al*. 2017*b*) (Fig. 2). Pseudogenes that arise from DNA duplication of coding genes followed by inactivating mutations that render the pseudogene non-coding are transcribed as lncRNAs and sequester some of the miRNAs that interact with conserved miRNA response elements (MREs) in the functional gene (Dykes & Emanueli 2017). However, given the low levels of lncRNA, the functional role of lncRNAs as 'miRNA sponges' by base-pairing and thus blocking miRNA-MRE binding to target mRNA-3′UTRs, is debated. It seems likely that more highly expressed lncRNAs (with higher FKPM (Fragments Per Kilobase Million reads in RNA-seq)) would be more likely to act as competing endogenous RNA (ceRNA) to sequester miRNAs (Dykes & Emanueli 2017). Additional classifications of lncRNAs are by (1) length,

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Table 1 Summary of ncRNAs in humans, excluding rRNA and tRNA, with their size, cellular location, aspects of biogenesis, function, citations for reviews for roles in various endocrine-related cancers and websites.

ncRNA	Description, size, location, function and example of findings in endocrine cancers	Websites
miRNA	~21 nt ssRNA • Nucleus and cytoplasm • Transcribed as pri-RNAs, processed from pre-miRs bearing one or more inverted repeats or hairpins • Form complimentary base-pairs with the 3′ untranslated region of target mRNAs within RISC block translation and/or stimulate mRNA transcript degradation • Expressed in a tissue-specific manner • Most are considered highly stable • IsomiRs are sequence variants of the canonical miRNA currently in the miRBase generated from a single miRNA locus by template and non-template variants • miRNAs in endocrine cancers have been reviewed: thyroid, adrenal, pancreatic, and pituitary cancers (Lima *et al*. 2017); endocrine-resistant breast (Muluhngwi & Klinge 2015); prostrate, ovarian, and breast (Smith *et al*. 2017)	miRBase http://www.mirbase.org miRTarBase: experimentally validated miRNA-target Interactions http://miRTarBase.mbc.nctu.edu.tw miRAD: intragenic miRNA database http://bmi.ana.med.uni-muenchen.de/miriad/ MAGIA http://gencomp.bio.unipd.it/magia/start/ TargetScanHuman search for predicated miRNA targets http://www.targetscan.org/vert_71/ IsomiRage http://cru.genomics.iit.it/Isomirage/
circRNAs	Circular RNAs: 4 types: exonic circRNAs (ecircRNA), circular RNAs from introns, exon–intron circRNAs (EIciRNA) and intergenic circRNAs (Meng *et al*. 2017) • Cytoplasm • Generally formed by alternative splicing of pre-mRNA in which an upstream splice acceptor is joined to a downstream splice donor in a process known as 'backsplicing' (Barrett & Salzman 2016) • Expressed in thousands of human genes • Stable: half-life >48 h • Expressed in a cell-type and tissue-specific manner • Act as miRNA sponges, interact with RNA-binding proteins, can be positive regulators of their parental genes • Can be translated (Yang *et al*. 2017*c*) • circRNAs were identified in human papillary thyroid cancer (Peng *et al*. 2017*a*) and in human breast tumors (Liang *et al*. 2017)	CIRCexplorer (Yang *et al*. 2017*c*) https://omictools.com/circexplorer-tool CIRI https://omictools.com/ciri-tool CircRNA_finder https://omictools.com/circrna-finder-tool MapSplice 2 for mapping RNA-seq data to ref genome for splice junction discovery http://www.netlab.uky.edu/p/bioinfo/MapSplice2 CirclncRNAnet (RRIC:SCR_015794) https://dknet.org/scicrunch/Resources/record/nlx_144509-1/2d26f6b1-5909-5066-a261-a05ca13e12d9/search?mc_cid=23e8e71213&mc_eid=ed4995675c
eRNAs	Enhancer RNAs are produced from enhancers (Lam *et al*. 2014) • Nuclear, 5′methyl-capped, +/– polyadenylation • 800–2000 bp • Low stability and abundance • Usually function in *cis* to increase transcription by facilitating DNA looping between the enhancer and promoter • May facilitate histone modifications and chromatin remodeling (Li *et al*. 2016*b*) • CGA, the common α-subunit of LH, FSH, and TSH is regulated by an eRNA (Nagarajan *et al*. 2015)	
piRNA	PIWI-interacting RNAs • 24–32 nt ss RNAs • Derived from piRNA clusters • Nuclear and cytoplasmic • Bind PIWI subfamily of Argonaut proteins • Involved in gene silencing (Luteijn & Ketting 2013) • Protect genome against instability by repressing transposon activity via transcriptional gene silencing • Expression mostly restricted to germ cells The transposable element (TE) landscape in postnatal human testis is matched by a relevant piRNA repertoire to silence TEs in spermatogenesis (Gainetdinov *et al*. 2017)	

(Continued)

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Table 1 Continued.

ncRNA	Description, size, location, function and example of findings in endocrine cancers	Websites
Endo-siRNA	Endogenous small-interfering RNAs • 20–23 nt • Cytoplasmic • Processed from dsRNAs by DICER • Have a 3′ 2-nt overhang • Form an effector complex with AGO1 or AGO2 (Piatek Monica & Werner 2014) • Detected in mammalian embryonic stem cells, oocytes and spermatocytes (Hilz *et al*. 2016)	
lncRNAs	Long non-coding RNAs • >200 nt • Can be several kb in length • Transcribed by RNA pol II • 5′-Methyl capped • Some are polyadenylated • Expressed in a cell-specific manner • Interact with DNA, RNA, and proteins • Stability generally lower than mRNAs with intronic or promoter-associated lncRNAs less stable than intergenic or antisense lncRNAs (Jarroux *et al*. 2017) • Located in nucleus, cytoplasm, and mitochondria • Regulate gene expression, chromatin modification and dynamics, protein complex assembly, splicing, and translation • Regulate development and differentiation including embryonic development (Bouckenheimer *et al*. 2016) • X chromosome silencing by *XIST*: a 16 kb lncRNA (Cerase *et al*. 2015)	HUGO Gene Nomenclature Committee lncRNAs https://www.genenames.org/cgi-bin/genefamilies/set/788 NONCODE v. 5.0 ncRNA http://www.noncode.org/ lncRNASNP2 is a database of functional SNPs and mutations in human and mouse lncRNAs http://bioinfo.life.hust.edu.cn/lncRNASNP2 Websites reviewed in (Fritah *et al*. 2014) LNCipedia 4.1 https://lncipedia.org/ (146,742 human annotated lncRNAs) DIANA-LncBase v.2 includes miRNA:lncRNA interactions (Paraskevopoulou *et al*. 2016) NONCODE v5.0 http://www.noncode.org/index.php
	Predicting miRNA/target duplex (Rehmsmeier *et al*. 2004) has been used to examine miRNA/lncRNA interaction (Zhou *et al*. 2017)	http://bibiserv.techfak.uni-bielefeld.de/rnahybrid/

e.g. very long lincRNA (vlincRNA); (2) being encoded within specific DNA regulator elements and loci, e.g., in telomeres (*TERRA*), centromeres, rDNA loci (*PAPAS*) or 3′UTR-associated RNAs (uaRNA); (3) biogenesis pathway; (4) subcellular localization or origin, e.g., nuclear, cytoplasmic or mitochondrial; (5) function, e.g., scaffold lncRNA (*HOTAIR*) and (6) association with specific biological processes (Jarroux *et al*. 2017).

lncRNAs show chromatin marks that are typical of transcribed coding genes: H3K4me3 for transcription initiation and H3K36me3 for elongation (Rinn & Chang 2012) and are regulated by transcription factors binding to their promoters. lncRNAs are alternatively spliced, thus generating isoforms. lncRNAs associated with enhancer regions can act in *cis*, leading to increased transcription of neighboring genes, including other lncRNAs (Ørom Ulf & Shiekhattar 2013). Some lncRNAs directly bind target mRNAs which can either target the mRNA for degradation or stabilize the transcript. A class of lncRNAs called 'activating ncRNA-as' specifically activate neighboring coding genes by binding to specific DNA sequences while associating with the Mediator-cohesin complex to loop enhancer/promoter regions (Dykes & Emanueli 2017). Despite their length, which can be several kb, lncRNAs do not have a functional protein-encoding capacity, i.e., those that contain small open reading frames (ORFs) do not form a template for translation (Hu *et al*. 2012).

As indicated in the Introduction, the number of human lncRNAs varies between databases. For example, the NONCODE v5 database includes 96,308 lncRNA genes (Xiyuan *et al*. 2017) compared with 15,778 in GENECODE and 27,919 in FANTOM (Hon *et al*. 2017). lncRNAs are expressed in a tissue-specific manner and are usually 5′-end capped and some are 3′-end polyadenylated (Li *et al*. 2016*a*). Some lncRNAs, e.g., *MALAT1* and *NEAT1*, have a triple-helical structure at the 3′end that protects them from degradation. The landscape of isoforms of lncRNAs adds to the complexity of understanding lncRNA function (Ziegler & Kretz 2017). In addition, the presence of lncRNA modifications and lncRNA editing has been reported and associated with structural and functional changes, which further increases the variety of

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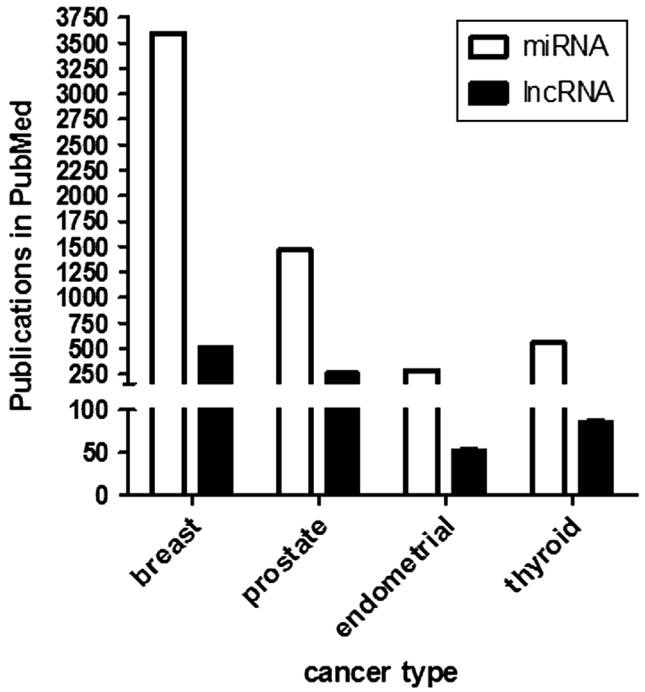

Figure 1
PubMed referenced papers on miRNAs and lncRNAs for endocrine cancers. Values were determined on November 28, 2017.

lncRNAs (reviewed in Ziegler & Kretz 2017). For example, m^{6}A modification is required for *XIST1*-mediated gene silencing (Patil *et al*. 2016). Accumulating evidence implicates roles for dysregulated lncRNAs in cancer (Huarte 2015), autoimmune and inflammatory diseases (Chen *et al*. 2017), including type 1 (Mirza *et al*. 2017) and type 2 diabetes (Motterle *et al*. 2016, Leti & DiStefano 2017) and other diseases.

lncRNA function depends on cellular location (Fig. 3). lncRNAs fold in various conformations that allows interaction with RNA, DNA and proteins to regulate nuclear, cytoplasmic (Delas & Hannon 2017) and mitochondrial function (De Paepe *et al*. 2017). lncRNAs regulate processes including gene transcription, chromatin dynamics, chromatin looping, histone modifications, telomere biology, protein complex assembly, RNA splicing and translation (Mercer & Mattick 2013). Within the nucleus, specific lncRNAs, including *AIRN*, *ANRIL*, *HOTAIR* and *XIST* interact with specific transcription factors, enzymes involved in DNA methylation (DNMT1), chromatin modification (HDAC1, EZH2 (a lysine N-methyltransferase)) and polycomb repressive complex 2 (PRC2) (Nakagawa & Kageyama 2014). lncRNAs are involved in assembly of active e.g., *NEAT1*, or repressed, e.g., *XIST*, nuclear chromatin domains in a cell-dependent manner (Rinn & Guttman 2014). *NEAT1* is an architectural RNA that interacts with >60 RNA-binding proteins and transcription factors in paraspeckles (Yamazaki & Hirose 2015). *NEAT1* is also acts as a 'sponge' for miR-214 and mIR-101, thus upregulating targets of these miRNAs, i.e., HMGA1 and EZH2, respectively (Qian *et al*. 2017, Wang *et al*. 2017*a*,*c*). Thus, many biological processes are regulated by lncRNAs including cell differentiation, proliferation and survival.

Functional roles of lncRNAs in the cytoplasm including acting as a scaffold. For example, the RNA stem-loop structure of *LINC01139* (also called LINK-A) provides a scaffold for HBEGF (heparin-binding epidermal growth factor (EGF)-like growth factor)-triggered, EGF receptor (EGFR):GPNMB (glycoprotein NMB) heterodimer-mediated recruitment of PTK6 (protein tyrosine kinase 6, also called BRK) and LRRK2 (leucine-rich repeat kinase-2) for phosphorylation and stabilization of HIF-1α in MDA-MB-231 triple-negative breast cancer (TNBC) cells (Lin *et al*. 2016). *LINC01139* also binds phosphatidylinositol-3,4,5-trisphosphate (PIP3) and

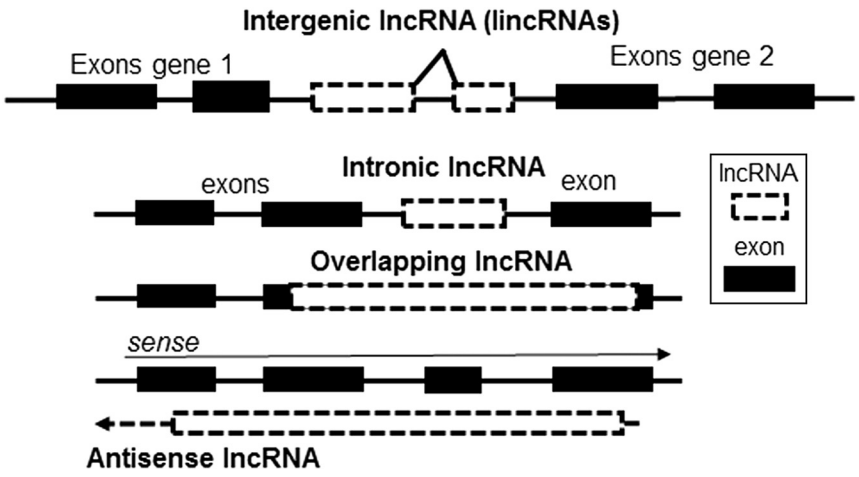

Figure 2
Classification of lncRNAs based on their location and transcription in relation to protein-coding genes. Gene structure is diagramed 5′–3′, left to right, for RNA pol II transcription.

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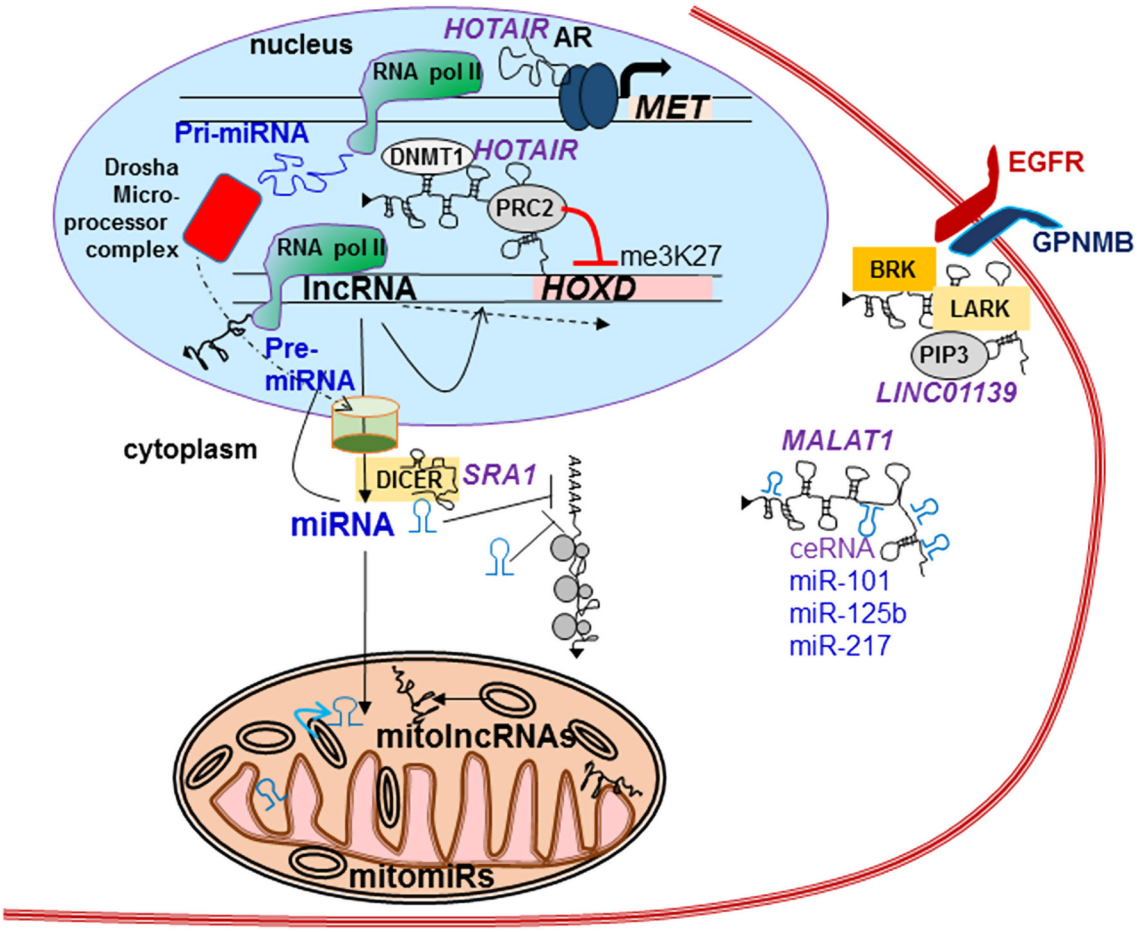

Figure 3
Examples of interactions of lncRNAs and miRNAs in endocrine-related cancers. Not all these interactions may be expected in one cell type. lncRNAs can act in cis on an adjacent gene to regulate its transcription and translation. An example is *HOTAIR*'s interaction with AR (Zhang *et al*. 2015*a*). Nuclear miRNAs can be transported into mitochondria through unknown mechanisms and miRNAs are produced from the mtDNA genome (ds DNA plasmids shown), both are called 'mitomiRs'. lncRNAs are transcribed from mtRNA and are called mitolncRNAs. Pri-miRNAs are process to pre-miRNAs by the Drosha microprocessor complex and exported by Exportin/RAN GTPase to the cytoplasm where they are cleaved into mature miRNAs by DICER which interacts with the lncRNA *SRA1* (Redfern *et al*. 2013). LINC01139 acts as a scaffold for PIP3, BRK, LRK2 and GPNMB, which leads to HIF-1α phosphorylation (Lin *et al*. 2017). *MALAT1* acts as a ceRNA and 'sponges' miRNAs including miR-101, miR-125b and mIR-217 (Table 2 and Supplementary Table 1).

promotes AKT recruitment and phosphorylation (Lin *et al*. 2017). Several lncRNAs modulate mRNA stability (reviewed in Rashid *et al*. 2016). lncRNAs also associate with ribonucleoprotein complexes to regulate translation. For example, *ZFAS1* associates with the 40S ribosome in the cytoplasm of MDA-MB-468 breast cancer (BCa) cells and is downregulated in breast tumors compared with normal breast tissue (Hansji *et al*. 2016).

Examples of lncRNAs dysregulated in endocrine-related cancers

Although many lncRNAs have been identified using bioinformatic approaches, relatively few have been functionally characterized and little is known about the mechanism(s) of action of even the best characterized lncRNAs. This review is not comprehensive with respect to lncRNAs in endocrine-related cancers, but summarizes representative lncRNAs that are best characterized (Table 2 and described below). Examples of recent reviews of lncRNAs include roles in: female reproductive cancers (Ong *et al*. 2017), BCa (Malih *et al*. 2015, Venkatesh *et al*. 2015, Miano *et al*. 2016, Niknafs *et al*. 2016, Warburton & Boone 2017), prostate cancer (PCa) (Alahari *et al*. 2016, Zhang *et al*. 2016*a*,*c*, Yang *et al*. 2017*b*) and thyroid cancer (Murugan *et al*. 2017).

One of the first characterized lncRNAs, *HOTAIR* (HOX Transcript Antisense RNA) is a 2.2 kb lncRNA

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found only in mammals and its structure is conserved, despite changed sequences, especially in its protein-binding segments, implying evolutionary importance (Jarroux *et al*. 2017). *HOTAIR* is transcribed from the HOXC locus from a position intergenic and antisense to the flanking HOXC11 and HOXC12 genes. *HOTAIR* facilitates the HOXD gene cluster for transcriptional repression by recruiting PRC2 (Rinn *et al*. 2007). Analysis of data in the Cancer Genome Atlas (TCGA) revealed that increased *HOTAIR* expression correlates with metastasis and poor prognosis in breast and prostate cancers (Weidle *et al*. 2017). *HOTAIR* is both nuclear and cytoplasmic and considered an onco-lncRNA because of its ability to promote papillary thyroid cancer (PTC) cell proliferation and silencing its expression inhibited cell growth (Zhu *et al*. 2016). HOTAIR is a scaffold for the PRC2 and LSD1 complexes affecting H3K27 methylation and H3K4 demethylation for epigenetic gene silencing promoting cancer metastasis (Wu *et al*. 2014). *HOTAIR* decreases oxidative phosphorylation (OXPHOS) complex III subunit VII (UQCRQ) protein expression, thus reducing OXPHOS efficiency and suggesting that *HOTAIR* is important for mitochondrial function in HeLa cells (Zheng *et al*. 2015).

According to Gene Cards (www.genecards.org), *HOTAIR* has binding sites for 70 proteins involved in transcriptional regulation including AGO1, SIN3A, REST, SUZ12, RELA, ROSL1, MAX, MAZ, NR2C2 (orphan NR TR4), TBP, EGR2, ELK4 and SP2. HOTAIR is upregulated by HIF-1α, histone methylase MLL1 and coactivator p300 (Bhan *et al*. 2017). HOTAIR was reported to be induced by E_2 in MCF-7 BCa cells (Bhan *et al*. 2013), but others reported that E_2-ERα directly that repressed *HOTAIR* in MCF-7 cells by binding to a genomic site 14.5 kb upstream of *HOTAIR* (Xue *et al*. 2016*b*). *HOTAIR* is downregulated by miR-141 (Chiyomaru *et al*. 2014) and is directly targeted by miR-34a in PCa cells (Chiyomaru *et al*. 2013). The 3′ domain of *HOTAIR* binds lysine-specific demethylase 1 (LSD1)-CoREST and PRC2 interacts with a 5′ domain. *HOTAIR*–PRC2 interaction represses targets, e.g., HOXD10, PTEN, miR-7 and WIF1, which leads to the activation of the Wnt/β-catenin signaling pathway (Hajjari & Salavaty 2015). *HOTAIR* binds androgen receptor (AR), blocking MDM2 interaction, and preventing AR ubiquitination and protein degradation, thus contributing to castration-resistant prostate cancer (CRPCa) progression (Zhang *et al*. 2015). *HOTAIR* is upregulated in endocrine-resistant BCa cells and its overexpression activates ERα transcriptional

Table 2 Examples of the roles of selected lncRNAs identified in endocrine-related cancers. Name, size, and genome location information is summarized from the sources for lncRNAs in Table 1. Other information is from the references cited.

lncRNA gene	Name, size, location	Interactions	Regulation	Endocrine cancer
PCA3	Prostate cancer-associated 3 23,134 nt 9q21.2 Antisense lincRNA within *PRUNE2*	*PCA3* and *PRUNE2* pre-mRNA are co-expressed and form a double-stranded RNA that recruits adenosine deaminase acting on RNA (ADAR) proteins to form a complex (Zhang *et al*. 2016*a*,*c*)	Increased by androgens in prostate cancer cells (Salameh *et al*. 2015) Suppressed by ERβ (Zhang *et al*. 2016*a*,*c*)	PCa-specific urine biomarker (Laxman *et al*. 2008); levels inversely correlate with the tumor suppressor *PRUNE2* in human PCa specimens (Salameh *et al*. 2015)
GAS5	Growth arrest specific 5 1q25.1 The *GAS5* gene has 12 exons that are alternatively spliced into 2 mature lncRNAs and *GAS5* introns encode 10 snoRNAs (reviewed in Pickard & Williams 2014) Tumor suppressor	Forms hairpin structures and interacts with the DNA binding domain of GR to inhibit GR-GRE binding and GR-induced gene transcription (Kino *et al*. 2010) Represses onco-miR-21 (Zhang *et al*. 2013) Inhibited miR-103 in EC cells (Guo *et al*. 2015) Inhibited activation of the AKT/mTOR pathway in PC3 PCa cells (Xue *et al*. 2016*a*)		Low expression correlated with poor prognosis in thyroid cancer tissues (Guo *et al*. 2017); low expression in breast tumors from trastuzumab-treated patient (Li *et al*. 2016*b*) Lower in PCa tissues than normal prostate (Xue *et al*. 2016*a*)
MEG3	Maternally expressed 3 14q32.2 81,622 nt Tumor suppressor	Binds miR-421 (Zhang *et al*. 2017*c*,*e*) Co-immunoprecipitates with PI3K in HEC-1B EC cells (Sun *et al*. 2017*a*)		Downregulated in breast (Zhang *et al*. 2016*a*,*c*, 2017*c*,*e*), prostate (Zhang *et al*. 2016*a*,*c*), endometrial (Guo *et al*. 2016*b*, Sun *et al*. 2017*a*), and PTC (Murugan *et al*. 2017) tumors

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activity independent of ligand (Xue *et al*. 2016*a*). ERα interacts directly of *HOTAIR* in RNA pulldown assays using nuclear extracts from MCF-7 BCa cells (Xue *et al*. 2017). Overexpression of *HOTAIR* in MCF-7 cells grown under hormone-free (serum-starved) medium conditions increases the number of DNA sites to which ERα binds in chromatin immunoprecipitation assays (ChIP) and increases mRNA expression of some ERα target genes, e.g., *GREB1*, *TFF1*, *PGR* and *CTSD* (Xue *et al*. 2016*b*). The authors concluded that *HOTAIR* increases ligand-independent ERα transcription. This observation is concordant with a report of increased *HOTAIR* immunostaining in tamoxifen-resistant human breast tumors (Xue *et al*. 2016*b*).

In contrast, *HOTAIR* was not among the 20 lncRNAs identified as upregulated and 9 downregulated by 'apo-ERα' (non-ligand-occupied ERα) in a bioinformatic analysis of BCa cell lines and tumor tissues with experimental follow-up in MCF-7 cells (Miano *et al*. 2016). That study identified *DSCAM-AS1* as the most apo-ERα-upregulated lncRNA and its expression was higher in luminal A and B breast tumors compared to normal breast, HER2+ or basal-like tumors. Knockdown of *DSCAM-AS1* stimulated an increase in epithelial-to-mesenchymal (EMT) markers in MCF-7 cells. *DSCAM-AS1* was also upregulated in prostate and lung tumors (Miano *et al*. 2016). A bioinformatics interrogation of 947 breast tumor RNA-seq libraries identified gene sets positively correlated with *DSCAM-AS1* expression as significantly associated with clinical signatures of cancer aggression, tamoxifen resistance, higher grade, stage and metastasis (Niknafs *et al*. 2016).

HOTAIR interacts with ERβ in a complex with eNOS on gene promoters to stimulate transcription in LNCaP PCa cells and a primary prostate tumor-derived cell line (called C27IM) and with ERα/eNOS in MCF-7 cells (Aiello *et al*. 2016). A potential concern with regard to the conclusion of the ChIPping of ERβ is the notorious lack of specificity of ERβ antibodies (Andersson *et al*. 2017, Nelson *et al*. 2017). *HOTAIR* is upregulated in endometrial cancer (EC) (Smolle *et al*. 2015) and contributes to cisplatin resistance by inhibiting autophagy (Sun *et al*. 2017*b*). *HOTAIR* is highly expressed in ovarian cancer (Luo *et al*. 2017); endometrial, ovarian and cervical cancers (Li *et al*. 2017*a*) and thyroid cancers (Zhang *et al*. 2017*c*,*e*), including PTC (Zhu *et al*. 2016).

MALAT1 (metastasis-associated lung adenocarcinoma transcript 1, 8755 nt) is another well-studied lncRNAs with roles in endocrine-related cancers (reviewed in Zhang *et al*. 2017*d*). *MALAT1* is expressed in almost all human tissues and is conserved across 33 mammalian species (Jarroux *et al*. 2017). *MALAT1* lacks a poly A tail, but has a genomically encoded poly A tract and is processed into a 6.7 kb nuclear form and a smaller *MALAT1*-associated small cytoplasmic RNA (mascRNA) (Zhang *et al*. 2017*d*). *MALAT1* is m^{6}A modified on 4 of 7 sites located in hairpins of *MALAT1* within HeLa, HEK-293T and MDA-MB-231 cells (Liu *et al*. 2013). Others reported that m^{6}A on position 2577 of *MALAT1* alter its secondary structure, enhancing its interaction with the m^{6}A reader heterogeneous nuclear ribonucleoprotein C (HNRNPC) (Zhou *et al*. 2016). The DROSHA-DGCR8 microprocessor associates with the 5′ end of *MALAT1*. *MALAT1* acts as a sponge for nuclear miR-9 and cytoplasmic miR-133, miR-200s and miR-205, although the exact mechanisms of how *MALAT1* gets to the cytoplasm are unclear (Zhang *et al*. 2017*d*). In turn, *MALAT1* is post-transcriptionally downregulated by miR-101, miR-125b and miR-217. The crystal structure of *MALAT1* revealed it to be a triple helix RNA that is stable in cells, e.g., $t_{1/2}$ of 7 h in HeLa cells (Brown *et al*. 2014). Functionally, nuclear speckle-associated *MALAT1* is involved in alternative splicing by acting as a scaffold (Tripathi *et al*. 2010). *MALAT1* is considered oncogenic and it upregulates the Wnt/β-catenin pathway (Ong *et al*. 2017). Capture hybridization analysis of RNA targets (CHART) identified *MALAT1* genomic-binding sites to be at actively transcribed loci (reviewed in Zhang *et al*. 2017*d*). However, *Malat1*-knockout (ko) mice showed no obvious phenotype, were viable and fertile and showed correct localization of nuclear speckles (Nakagawa *et al*. 2012). Expression of the lncRNA *Neat1*, which is located 30 kb upstream (5′) to *Malat1*, was lower in *Malat1* ko mice, suggesting a role for *Malat1* as a *cis*-regulator of *Neat1*. RNA-seq studies in adult *Malat1* ko mice revealed upregulation of a small number of adjacent genes, also suggesting *cis* regulation (Zhang *et al*. 2012). One explanation for the lack of concordance between cellular and whole mouse studies is that *Malat1* may only function under stress conditions (reviewed in Zhang *et al*. 2017*d*). Increased *MALAT1* is found in many cancers including breast tumors (Ellis *et al*. 2012), castration-resistant prostate (Ren *et al*. 2013, Wang *et al*. 2014, Sowalsky *et al*. 2015), EEC (Zhao *et al*. 2014), recurrent ovarian cancer (Yang *et al*. 2017*b*) and thyroid tumors (Zhang *et al*. 2017*a*,*b*). Studies suggest that increased *MALAT1* plays a role in metastasis (reviewed in Zhang *et al*. 2017*d*). *MALAT1* mutations are frequent in breast tumors (Arun *et al*. 2016, Nik-Zainal *et al*. 2016). *MALAT1* expression was higher in thyroid cancer tissues and in thyroid cancer cells than normal thyroid (Huang *et al*. 2016*a*). Likewise, *NEAT1* is upregulated in breast (Qian *et al*.

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2017), endometrial (Wang *et al*. 2017*a*,*c*), ovarian (Chen *et al*. 2016) and thyroid tumors (Li *et al*. 2017*b*) and is the highest lncRNA in prostate cancer and strongly associated with metastasis (Chakravarty *et al*. 2014).

lincRNA-p21 (gene name *TP53COR1*) is a transcript of ~3 kb that is increased by p53 in response to DNA damage and serves as a transcriptional repressor in the p53 pathway by directly interacting with HNRNPK (hnRNP-K), increasing p21 transcription and inhibiting the transcription of pro-survival genes, thus triggering apoptosis (Barsotti & Prives 2010, Dimitrova *et al*. 2014). lincRNA-p21 is increased by hypoxia via HIF-1α and interacts with and stabilizes HIF-1α, resulting in increased glycolysis in HeLa cells (Yang *et al*. 2014). lincRNA-p21 is degraded by let-7 (Yoon *et al*. 2014). lincRNA-p21 is transcribed into two isoforms with Alu inverted repeat elements and colocalizes with the lncRNA *NEAT1* in the nucleus of U2OS, HCT-116 and MCF-7 cells (Chillón & Pyle 2016). lincRNA-p21 represses the translation of specific target genes, including *CTNNB1* (β-catenin), through RISC complex activation. Knockdown of heat-shock factor 1 (HSF1) in MDA-MB-231 cells increased lincRNA-p21 expression and the authors identified miR-320a, b and c as dependent on HSF1 that may target lincRNA-p21 through its 5′ sequence, although this was not demonstrated (Chou *et al*. 2015). lincRNA-21 is downregulated in PCa and acts as a tumor suppressor in PCa cells (Wang *et al*. 2017*a*,*c*). Overexpression of lincRNA-p21 in DU145 and LNCaP PCa cells decreased pyruvate kinase M2 (*PKM2*) expression in a PTEN/AKT/mTOR cascade-dependent manner and transfection with shlincRNAP21 reduced glucose consumption (Wang *et al*. 2017*b*,*d*). There are no reports on lncRNA-21/*TP53COR1* in either endometrial or thyroid cancer.

lncRNAs in breast tumors

A recent review of the function of selected lncRNAs upregulated (19) and downregulated (5) in BCa noted that while thousands of dysregulated lncRNAs have been identified, about most relatively little is known (Warburton & Boone 2017). Bioinformatic reanalysis of RNA-seq data from 658 invasive ductal carcinomas from TCGA and sorted by PAM50 assay transcriptomic data identified 1623 lncRNAs expressed at FPKM (fragments per kilobase of non-overlapped exon per million fragments mapped) >1 in 10% of the tumors that the authors postulated are relevant in BCa (Su *et al*. 2014). lncRNA-based unsupervised hierarchical consensus clustering revealed four subgroups that correlated with mRNA transcriptome PAM50 classification: basal-like, HER2-enriched and luminal A and B. Clustering suggested that *HOTAIR* was higher in HER2-enriched breast tumors. *ACC005152.3*, *RP11-84E24.2* and *HOTAIRM1* were higher in basal-like breast tumors, whereas *RP11-53019.2* and *RP11-473L15.3* were higher in luminal-type tumors. Su and coworkers correlated increases in lncRNAs with increased adjacent gene expression: *HOTAIR* with *HOXC11*; *HOTAIRM1* with *HOXAI*; *RP11-53O19.2* and *RP11-473L15.3* with *MRPS30* and *ACC005152*.3 and *RP11-84E24.2* with *SOX9* (Su *et al*. 2014). *HOTAIRM1 SOX9* is a stem cell factor involved in tamoxifen-resistant BCa (Jeselsohn *et al*. 2017). *HOTAIR* and *BCL2* expression were correlated in breast tumors and *HOTAIR* was shown to act as a ceRNA by base-pairing with miR-206, thus relieving mIR-206's repression of *BCL2* expression (Ding *et al*. 2017). *HOTAIRM1* expression increased in recurrent ovarian cancer (Yang *et al*. 2017*b*), but acts as a tumor suppressor in colorectal cancer (Wan *et al*. 2016).

Another group performed a similar analysis on RNA-seq data in the TCGA using ~1000 breast tumors, an independent RNA-seq dataset of 50 pairs of matched tumors and adjacent normal tissues from BCa patients, and 23 normal breast tissues from healthy women (Zhang *et al*. 2016*b*,*d*). They identified 2171 lincRNAs expressed in at least one sample, often at low levels, and ultimately identified 83 differentially expressed lincRNAs of which 60 were downregulated in breast tumor samples. Among the upregulated lincRNAs, *GATA-AS1* was associated with higher expression of its adjacent protein-coding gene *GATA3* and both were associated with ERα+ breast cancer. GATA3 regulates the transcription of genes involved in maintaining luminal mammary gland differentiation (Kouros-Mehr *et al*. 2006) and acts as a licensing factor for ERα-chromatin binding (Theodorou *et al*. 2013). *GATA-AS1* may be unique in BCa since no reports were found for the other endocrine cancers discussed in this review. One upregulated lincRNA RP5-1198O20 was associated with lower survival rates in BCa patients (Zhang *et al*. 2016*b*,*d*). How RP5-1198O20 contributes to BCa mortality is currently unknown.

ANRIL was identified as the lncRNA with the highest expression in SK-BR3 HER2+ BCa cells vs MCF-10A cells in a lncRNA array qPCR study (Lee *et al*. 2017). *ANRIL* expression was also higher in MCF-7 and T47D cells compared with MCF-10A cells. Some lncRNAs are associated with specific metastasis, e.g., lnc-BM (*OR5BM1P*) for BCa brain metastasis by interacting with JAK2 to activate a STAT3-ICAM1 axis that increases cell adhesion to brain capillaries and extravasation (Wang *et al*. 2017*b*,*d*).

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XIST is best known for X chromosome inactivation (da Rocha & Heard 2017). However, *XIST* interacts on a genome-wide scale with a variety of proteins, including the scaffold attachment factor A (SAF-A), in the non-chromatin nuclear scaffold/matrix (Creamer & Lawrence 2017). *XIST* is downregulated in breast tumors, but its molecular mechanisms as a tumor suppressor are unclear (Huang *et al*. 2016*b*). One idea is that loss of *XIST* induces reactivation of X-linked genes that contribute to BCa progression (Chaligne *et al*. 2015). However, *XIST*'s role as a tumor suppressor may depend on the type of breast tumor. Patients with high *XIST* mRNA and low protein expression of 53BP1 in BRCA1-like breast tumors showed no benefit from high-dose alkylating chemotherapy and lower disease-free and overall survival (Schouten *et al*. 2016). *XIST* expression was also decreased in uterine papillary serous carcinoma accompanied by widespread X chromosome demethylation (Zhang *et al*. 2014). There are no apparent functional studies of *XIST* in EC cells.

New lncRNAs continue to be discovered. A recent example is *ESRP2-AS* that was first identified in a methylated lncRNA screen in a transgenic mouse model of human BCa (C3(1) SV40Tag) and shown to be higher in human breast tumors compared to normal breast tissue (Heilmann *et al*. 2017). Additional lncRNAs identified in BCa are included in Table 2.

lncRNAs in prostate tumors

Most lncRNAs identified in PCa are upregulated, thus acting as oncogenes (reviewed in Zhang *et al*. 2016*a*,*c*). Upregulated lncRNAs include *HOTAIR*, *PCGEM1*, *PRNCR1*, *ANRIL*, *PCAT1*, *MALAT1* and specific for PCa *PCA3*. Downregulated lncRNAs in PCa include *GAS5*, *PTENP1* and *MEG3*. Refer Table 2 for details on *PCA3*, *GAS5* and *MEG3*. MEG3 modulates the activity of TGF-β genes by binding to distal regulatory elements forming an RNA–DNA triplex and interacts with the PRC2 complex (Mondal *et al*. 2015). *PCAT1* is the most highly upregulated lncRNA in PCa (Alahari *et al*. 2016). Mechanistically *PCAT1* post-transcriptionally represses tumor suppressor gene *BRCA2*, thus impairing homologous recombination DNA repair. Overexpression of *PCAT1* in DU145 PCa cells increased proliferation, migration, and invasion and post-transcriptionally upregulated MYC by interacting with miR-3667-3p (Prensner *et al*. 2014). Another study showed interaction between *PCAT1* and miR-145-5p that resulted in upregulation of FSCN1, an actin-binding protein involved in invasion and migration (Xu *et al*. 2017). Overall, *PCAT1* has an oncogenic role in PCa (Alahari *et al*. 2016). Interestingly, a PCa risk SNP (rs7463708) promotes transformation via upregulation of *PCAT1* lncRNA (Guo *et al*. 2016*a*). *PCAT1* is also upregulated in hepatocellular carcinoma (HCC) (Zhang *et al*. 2017*a*,*b*). Additional lncRNAs in PCa are included in Table 2.

lncRNAs in EC

The death rate for cancer of the uterine corpus, which is associated with obesity, is increasing in the U.S. (Siegel *et al*. 2017). EC is classified as type I or II with most patients having well-differentiated endometrioid endometrial carcinomas (EEC, type I) (Takenaka *et al*. 2016). The identity and characteristics of lncRNAs dysregulated in EEC, including *MALAT1*, *HOTAIR*, *SRA*, *H19*, *OVAAL*, *RP11395G12.3*, *LA16313D11.11*, *CASC2*, *ASLNC04080* and *ENST0000050294* were reviewed (Takenaka *et al*. 2016). The roles and functions of selected lncRNAs, i.e., *MALAT1*, *HOTAIR*, *H19*, *MEG2*, *CCA2*, *ANRIL*, *OCAL*, *BC2200* and *CUDR* in cancers of the female reproductive system including endometrial, ovarian and cervical cancers were recently reviewed (Hosseini *et al*. 2017). *H19* is a well-studied imprinted, maternally expressed lncRNA that encodes miR-675 and is overexpressed in breast, HCC, prostate, colorectal, esophageal, bladder and many other cancers but is downregulated in adrenocortical neoplasms (reviewed in Huarte 2015).

lncRNAs in thyroid cancer

The role of lncRNAs in the pathogenesis of thyroid cancer was recently reviewed (Murugan *et al*. 2017). PTC is the most common thyroid malignancy (Siegel *et al*. 2017). A microarray analysis of lncRNAs in 62 PTC tumors identified 3499 lncRNAs (1192 upregulated, 2307 downregulated) that were differentially expressed compared with paired noncancerous tissue (Lan *et al*. 2015). qPCR confirmed the 'direction' of lncRNA expression in PTC: TCONS_l2_00010365, n386477, n340790, lnc-LLPH-2:1 and NR_003225.2 were upregulated and lnc-PSD4-1:14, n335550, lnc-KCMF1-2:1, lnc-PLA2R1-1:1 and ENST00000422494.1 were downregulated (Lan *et al*. 2015). As indicated in Table 2, *MALAT1* is upregulated in thyroid tumors (Zhang *et al*. 2017*a*,*b*). *MALAT1* is also upregulated in SW1736, KAT18 and FTC133 thyroid cancer cells and knockdown of *MALAT1* inhibited cell proliferation and invasion by upregulating the expression of the scaffolding protein IQGAP1 (Huang *et al*. 2016*a*).

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Mitochondrial-encoded lncRNAs and lncRNA imported into mitochondria

The human mitochondrial DNA (mtDNA) genome is transcribed as a polycistronic precursor and encodes 13 proteins that function in mt OXPHOS, two rRNAs that are components of the mt ribosome and 22 tRNA (Kim *et al.* 2017*b*). Seven lncRNAs have been identified to be derived from mtDNA (De Paepe *et al.* 2017). These are referred to as mitolncRNAs (Vendramin *et al.* 2017). Several are chimeric lncRNAs containing nucleotides of mtDNA: *LIPCAR*, *SncmtRNA*, *ASncmtRNA-1* and *ASncmtRNA-2*. *LIPCAR* is cardiac specific and levels are elevated in circulation of patients with chronic heart failure (Kumarswamy *et al.* 2014). *ASncmtRNA-1* and *ASncmtRNA-2* are present in mitochondria and nuclei, suggesting a possible role in retrograde signaling (De Paepe *et al.* 2017). *ASncmtRNA-1* and *ASncmtRNA-2* are downregulated in breast and prostate tumors (Burzio *et al.* 2009), suggesting tumor suppressor activity. However, complete knockdown of *ASncmtRNA-1* and *ASncmtRNA-2* stimulated apoptotic cell death by downregulating the translation of survivin, an anti-apoptotic protein, only in cancer cells through an undefined mechanism, although these lncRNAs were shown to interact with DICER (Vidaurre *et al.* 2014). To date, the mechanism of *ASncmtRNA-1* and *ASncmtRNA-2* remains unknown (De Paepe *et al.* 2017, Dong *et al.* 2017). Three lncRNAs: ncND5, lncND6 and lncCyt b were identified as antisense transcripts of the mtND5, mtND6 and mtCYTB mRNAs but little is known about their function (Rackham *et al.* 2011). There is speculation that these three lncRNAs are transported to the nucleus by unknown RNA-binding proteins (Dong *et al.* 2017). Recently, two novel lncRNAs *MDL1* and *MDL1AS* encoded in the D-loop of human mitochondrial DNA were discovered and identical transcripts were identified in mouse and rat genomes (Gao *et al.* 2017).

RMRP (RNA Component Of Mitochondrial RNA-Processing Endoribonuclease) is a nuclear DNA-encoded lncRNA that binds RNA-binding proteins HUR, PNPASE and GRSF1 for transport into mitochondria where *RMRP* is the RNA component of the mitochondrial RNA-processing endoribonuclease (RNase MRP) for mtDNA replication and RNA processing (Dong *et al.* 2017). RMRP acts as a sponge for miR-206 an oncogene in lung cancer (Meng *et al.* 2016). Deep sequencing of 360 primary breast tumors identified mutations in the promoters of lncRNAs *RMRP* and *NEAT1* that increased their expression and noted increased expression of these lncRNAs in breast tumors (Rheinbay *et al.* 2017). However, RMRP's role in BCa remains to be fully elucidated, and no publications were found with respect to *RMRP* in prostate, endometrial, ovarian or thyroid cancer.

SRA1, steroid receptor RNA activator, was first identified as an RNA transcript acting as an RNA coactivator in a complex with SRC-1 (*NCOA1*) to increase progesterone, glucocorticoid, androgen, estrogen, thyroid hormone, retinoic acid and peroxisome proliferator-activated receptor (PR, GR, AR, ERα, TRβ, RARγ, RXRγ and PPARγ) transcriptional activity (Lanz *et al.* 1999). Knockout of *Sra1* in mice showed that the *Sra−/−* mice were resistant to high-fat diet-induced obesity and had lower fat mass (Liu *et al.* 2014). In humans, inactivating *SRA1* mutations were identified in three families with a proband with idiopathic hypogonadotropic hypogonadism (Kotan *et al.* 2016). The *SRA1* gene also encodes a protein steroid receptor coactivator protein (SRAP) (reviewed in Leygue 2007) that interacts with AR and is involved in PCa (Kawashima *et al.* 2003). Notably, *SRA1* and SRAP do not interact (McKay *et al.* 2014). *SRA1*'s identity as a lncRNA was revealed in 2012 (Novikova *et al.* 2012). Additional protein-binding partners of *SRA1* were recently reviewed (Liu *et al.* 2016). *SRA1* interacts with DICER (Redfern *et al.* 2013). By its interaction with SLIRP (SRA stem-loop interacting RNA-binding protein), *SRA1* has a repressive function by recruiting corepressors (reviewed in Liu *et al.* 2016). SLIRP represses NR transactivation in an *SRA1*-dependent manner (Hatchell *et al.* 2006). Interestingly, *Slirp*-knockout mice are sub-fertile, and males have defects in sperm motility and mitochondrial morphology (Colley *et al.* 2013). *SRA1* and SLIRP were identified as a BCL2-interacting RNA and proteins, respectively in mitochondria of H1299 lung adenocarcinoma cells (Trisciuoglio *et al.* 2016). The SMRT/HDAC1 corepressor complex interacts with *SRA1* (Dong *et al.* 2017). *SRA1* is upregulated in steroid hormone-responsive tumors including breast, endometrial and ovarian (reviewed in Liu *et al.* 2016).

lncRNAs in circulation

Circulating nucleic acids, including miRNAs and lncRNAs, are found in cell-free serum, plasma and other bodily fluids and differ between cancer patients, including those with prostate and breast tumors and non-cancer/normal individuals (reviewed in Qi *et al.* 2016). In addition, virtually all cells release membrane-enclosed extracellular vesicles (EV): exosomes (0.04–0.15 µm diameter) and microvesicles (0.2–1 µm diameter); further, apoptotic

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cells release apoptotic bodies (0.5–2 µm diameter) that do not contain miRNAs and lncRNAs (Kim *et al.* 2017*a*). Exosomes, which arise from the endosomal pathway, and microvesicles have been reported to transport mRNAs, ncRNAs, including miRNAs, lncRNAs and circRNAs, as a mechanism of intercellular communication (Kim *et al.* 2017*a*). Cancer exosomes modulate the immune response and the tumor environment locally and at a distance, i.e., metastasis to secondary sites, by horizontal cargo transfer to recipient cells (Ruivo *et al.* 2017). In a recent study, isolated exosomes from tamoxifen-resistant LCC2 BCa cells were shown to contain ~25-fold higher lncRNA *UCA1* compared to parental MCF-7 cells and incubation of MCF-7 cells with exosomes from LCC2 cells resulted in decreased growth inhibition by tamoxifen (Xu *et al.* 2016), although no uptake of *UCA1* or other lncRNAs or miRNAs was examined. There is great interest in EVs as biomarkers and as tools to deliver therapeutic genetic materials and drugs. Interestingly, a recent study reported that EVs isolated from BCa patients with metastatic disease and whose initial tumor had been ERα+/PR+/HER2- contained mtRNA from cancer-associated fibroblasts (CAFs) (Sansone *et al.* 2017). Xenograft transplantation studies in immunocompromised mice demonstrated that transfer of mtDNA from CAFs contributed to resistance to fulvestrant *in vivo*. Whether accompanying miRNAs and lncRNAs play a role in these findings was not evaluated.

lncRNA therapeutics

Antisense oligonucleotides (ASO), liposome-delivered RNAi, vector-expressed shRNAs and decoy RNAs or small molecules that compete for domain–domain interactions between lncRNA and proteins or within the lncRNA are of interest in targeting overexpressed lncRNAs in cancer (Weidle *et al.* 2017). Targeting of lncRNAs using lncRNAs and nanoparticle-coated siRNAs has been successful in preclinical mouse models of BCa (Liu *et al.* 2015, Wang *et al.* 2017*b*,*d*). Approximately 25 RNAi-based therapeutics are under clinical investigation (Weidle *et al.* 2017).

Overview of miRNA biosynthesis in endocrine-related cancers

miRNAs are small (22 nucleotides), evolutionarily conserved, single-stranded, ncRNAs that regulate mRNA translation or stability by base-pairing with miRNA response elements (MREs) in the 3′UTR of the target transcript within the RNA-induced silencing complex (RISC). The chronology of miRNA discovery was recently reviewed (Drusco & Croce 2017). Comparative genomics analysis indicated that >60% of human protein-coding genes have been under selective pressure to maintain pairing to miRNAs with >45,000 miRNA-binding sites within 3′UTRs conserved (Friedman *et al.* 2009). The human genome includes 2,588 mature miRNAs (mirBase release 21) http://www.mirbase.org/ (Kozomara & Griffiths-Jones 2014).

The biogenesis of miRNAs has been reviewed (Ha & Kim 2014, Klinge 2015). In brief, in the canonical pathway of miRNA biogenesis, miRNAs are transcribed as primary-micro-RNAs (pri-miRNAs) by RNA pol II either as independent transcription units or are cotranscribed within introns of pre-mRNAs (~50% of miRNAs) (Saini *et al.* 2007). Most pri-miRNAs are >1 kb, thus meeting the definition of a lncRNA (Dykes & Emanueli 2017). About half of all miRNAs are produced from non-coding transcripts, i.e., host lncRNAs. One example is *DLEU2* that encodes the miR-15a/16.1 cluster and *MIR155HG* that encodes miR-155 (reviewed in Dykes & Emanueli 2017). Pri-miRs are capped and polyadenylated (Cai *et al.* 2004). The microprocessor complex of DROSHA (an RNAse III endonuclease) and DGCR8, plus additional proteins, cleaves hairpin-loop-containing pri-miR into 60–70 nucleotide (nt) precursor (pre)-miRNAs. The efficiency of pri-miRNA processing depends on stem length (36 ± 3 nt) and the appearance of bulges in the structure (Roden *et al.* 2017). DGCR8 acts as an oncogene in prostate cancer whereas DROSHA has oncogenic or tumor suppressor activity depending on the cancer type (reviewed in Hata & Kashima 2016). Alternative pathways of miRNA biogenesis include miRtrons, which are processed by spliceosomes in a DROSHA/DGCR8-independent/DICER-dependent manner and DROSHA/DGCR8-dependent/DICER-independent yielding miR-451 (reviewed in Daugaard & Hansen 2017). The widespread reduction of miRNAs in human tumors has been attributed to dysregulation of the DROSHA/DGCR8 microprocessor complex as a result of the many pathways that regulate microprocessor components, e.g., p72 is sequestered by YAP in the Hippo pathway in a cell-density-dependent manner (Mori *et al.* 2014). RNA-binding proteins also regulate pri-miRNA accessibility (Fernandez *et al.* 2017).

Pre-miRNAs are exported from the nucleus by Exportin and Ran-GTP or CRM1 to the cytoplasm where they are cleaved by DICER (*DICER1*, an RNAse III enzyme) forming ~21–23 nt transiently double-stranded miRNA duplexes (Kurzynska-Kokorniak *et al.* 2015). DICER, in association with cofactors TRBP and PACT, transfer the mature miRNA to RISC, which contains the catalytic argonaute proteins

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(AGO1, AGO2, AGO3 and AGO4) (Hock & Meister 2008)) that unwind the mIRNA duplexes to form single-stranded miRNAs. The lncRNA *SRA1* binds DICER complex components PACT, TRBP and PKR in various cell lines and also binds NRs, including ERα (Redfern *et al*. 2013). DICER also plays a role in the DNA damage response in which DNA damage results in phosphorylation and binding to double-strand breaks and recruits DNA repair factor MDC1 and 53BP1 (Burger *et al*. 2017). DICER acts as an oncogene in PCa but as a tumor suppressor in breast, endometrial and ovarian cancer (reviewed in Hata & Kashima 2016). DICER is regulated transcriptionally, post-transcriptionally, including by alternative splicing, and by post-translational modifications, e.g. phosphorylation, glycosylation and SUMOylation (Kurzynska-Kokorniak *et al*. 2015). Germline *DICER1* mutations, DICER1 syndrome, were identified as causative in differentiated thyroid cancer and multinodular goiter (de Kock *et al*. 2014, Rutter *et al*. 2016, Khan *et al*. 2017).

In cancer tissues, overexpressed miRNAs that act as oncogenes are referred to as oncomiRs while downregulated miRNAs are called tumor suppressor miRs with their targets, tumor suppressors and oncogenes, respectively dysregulated. However, as we learn more about miRNAs, it is clear that generalization about a particular miRNA being oncogenic or a tumor suppressor depends on cellular context. miRNAs are involved in the post-transcriptional regulation of genes involved in EMT, stemness, cell signaling pathways and regulation of the tumor microenvironment, including the conversion of normal fibroblasts into cancer-associated fibroblasts (CAFs) by transfer of exosomal miRNAs from tumor cells (reviewed in Yang *et al*. 2017*a*). An issue in the field is the lack of congruence of miRNAs identified for a particular cancer type, e.g., thyroid cancer, even within a subtype, in different studies. This may be attributed to the number of tumor samples examined, tumor heterogeneity, whole tumor RNA isolation vs laser-capture microdissected tumor cells, the technique used to identify the miRNA (microarray, quantitate real-time PCR (qPCR), or NGS/RNA-seq.), the gene normalizer and statistical approaches used. Databases of putative and experimentally verified targets of miRNAs are listed in Table 1.

Despite the large datasets available on miRNAs in endocrine cancer, functional studies are needed for each miRNA and its targets. Functional analysis of overexpression and silencing of individual miRNAs is used to validate the role of deregulated miRNAs in cancer cells *in vitro* and animal tumor models, including human tumor cell xenografts and patient-derived xenograft (PDX) *in vivo*. An essential step to validate the identify of an mRNA target of a miRNA is to clone the 3′-UTR of the mRNA target downstream of a luciferase reporter and then transfect that reporter into a cell line, with an appropriate loading control either in the same plasmid or another cotransfected reporter, with overexpression and knockdown of the putative miRNA regulator. The investigator should detect reduced luciferase reporter activity and mutation of the MRE in the 3′UTR is required confirm direct miRNA-mRNA target regulation, i.e., validating that the mRNA is a *bona fide* target of that miRNA. Further validation steps include Western blot to demonstrate decrease target protein expression. Target validation in clinical samples is used to demonstrate disease relevance of the miRNA and its target.

Supplementary Table 1 (see section on supplementary data given at the end of this article) summarizes examples of miRNA dysregulated in BCa, PCa, EC and thyroid cancer with examples of their *bona fide*, validated, mRNA targets. Cellular functions associated with the miRNA are listed in Supplementary Table 1. In addition, I have added lncRNAs that either downregulate a miRNA or act as ceRNAs, i.e., endogenous sponge for binding a miRNA. It will be clear to the reader that many of the miRNA:lncRNA interactions listed are from non-endocrine cancers and are single reports requiring further validation.

miRNAs in BCa

In the 12 years since miRNAs were identified to be dysregulated in BCa (Iorio *et al*. 2005), about 3600 papers have been published in miRNAs in BCa (Fig. 1). There are many recent reviews of the identity, regulation and targets of miRNAs in BCa, e.g., (Egeland *et al*. 2015, Klinge 2015, Muluhngwi & Klinge 2015, van Schooneveld *et al*. 2015, Yahya & Elsayed 2015, Li *et al*. 2017*c*, O'Bryan *et al*. 2017, Smith *et al*. 2017). miRNAs regulate key pathways dysregulated in BCa including apoptosis, cell cycle, cellular energetics, invasion, metabolism and metastasis.

The majority (70%) of primary breast tumors express ERα, and these patients are treated with endocrine therapies including tamoxifen (TAM); the selective estrogen downregulator (SERD), e.g., fulvestrant and aromatase inhibitors (AI), e.g., anastrozole and letrozole (Ring & Dowsett 2004, Clarke *et al*. 2015). Hence, many miRNA studies have examined the correlation of miRNAs with diagnostic markers related to ERα in BCa, estrogen-regulated miRNAs and the potential role of miRNAs in endocrine resistance (Klinge 2015, Muluhngwi & Klinge

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2015). ERα is the target of miRNAs including miR-221, miR-222, miR-873, let-7b and let-7i (reviewed in Muluhngwi & Klinge 2015).

Computational approaches are used to identify putative mRNA and lncRNA targets of miRNAs (Table 2). In addition, specific algorithms to identify possible targets of dysregulated miRNAs in breast tumors and BCa cell lines have been reported (O'Day & Lal 2010, Cava *et al*. 2014, Ru *et al*. 2015, Liang *et al*. 2016, Zhang *et al*. 2016*b*,*d*). More recently, various strategies to directly identify miRNA:RNA targets and RNA modifications by protein:RNA immunoprecipitation and high-throughput RNA-seq have been used to examine protein:RNA interactions in human biology, e.g., HITS-CLIP (high-throughput RNA-seq isolated by crosslinking immunoprecipitation) (Darnell 2010); PAR-CLIP (photoactivatable ribonucleoside-enhanced CLIP) (Farazi *et al*. 2014), iCLIP (crosslinking and immunoprecipitation) (Hong *et al*. 2015), eCLIP (enhanced CLIP) (Van Nostrand *et al*. 2016) and dCLIP (denaturing CLIP) (Rosenberg *et al*. 2017). A downside is that CLIP techniques are technically challenging.

Dysregulation of miRNAs in PCa

Dysregulation of miRNA expression is correlated with aggressive PCa phenotypes including tumor stage, Gleason grade and disease recurrence (Ren *et al*. 2014, Cha *et al*. 2016). Altered miRNA expression is associated with physiological changes in tumorigenesis and disease progression in PCa (reviewed in Chun-Jiao *et al*. 2017, Vanacore *et al*. 2017). Changes in miRNA expression contribute to altered expression of genes involved in pathogenesis of metastatic PCa (Kojima *et al*. 2017). Changes in miRNA expression in PCa have been reviewed and described below.

miRNAs upregulated by AR in PCa include miR-21, miR-27a, miR-32, miR-125b, miR-135a, miR-141 and AR overexpression in PCa downregulates miR-99a (Massillo *et al*. 2017). miR-125b is the most overexpressed miRNA in PCa and downregulates apoptotic genes including *BAK1*. A recent review of 104 studies of miRNAs in PCa tissues identified six miRNA consistently upregulated: miR-34a, miR-106b, miR-183, miR-200a/b and miR-301a; and sixteen miRNAs downregulated: miR-1, miR-23b, miR-27b, miR-34b/c, miR-99b, miR-125b, miR-152, miR-187, miR-199a, miR-204, miR-205, miR-224, miR-452, miR-454 and miR-505 (Chun-Jiao *et al*. 2017). Other oncomiRs overexpressed in PCa are miR-21, miR-32, miR-221, miR-222, miR-181, miR-18a and miR-429 (reviewed in Kanwal *et al*. 2017). 'Andro-miRs': let-7c, miR-31, miR-124, miR-185, miR-205 and miR-488 downregulate AR expression (Massillo *et al*. 2017). Notably, the top four downregulated miRNAs in PCa tissues are miR-187, miR-205, miR-222 and miR-31 (Fuse *et al*. 2012). Additional tumor suppressor miRNAs in PCa and their targets include miR-331-3p that downregulates ERBB2 and AR and is associated with castration-resistant PCa (reviewed in Kanwal *et al*. 2017). miRNAs associated with metastasis include downregulation of miR-1, miR-15, miR-16, miR-23a, miR-29b, miR-126, miR-130, miR-132, miR-141, miR-195, miR-200b, miR-200c, miR-203, miR-205, miR-218, miR-375, miR-377, miR-466, miR-573, miR-675, and miR-802 and upregulation of miR-21, miR-22, miR-25, miR-93, miR-106b, miR-154-3p, miR-379, miR-543 and miR-590-3p (reviewed in Massillo *et al*. 2017). miRNAs upregulated or downregulated in serum, plasma and urine with potential prognostic value in separating men with potentially lethal PCa vs indolent disease were recently reviewed (Massillo *et al*. 2017).

Dysregulation of miRNAs in EC

EC is the most frequently diagnosed gynecological cancer (Siegel *et al*. 2017). Among the miRNAs differentially expressed in EC vs normal endometrial tissue are the increased expression of miR-10b, miR-21, miR-31, miR-182, miR-183, miR-205, miR-222, miR-223, miR-410, miR-429, miR-449a, miR-994, and miR-1228; and downregulation of let-7, miR-34b-5p, miR-34c-3p, miR-34c-5p, miR-99b, miR-101, miR-130a, miR-143, miR-145, miR-184, miR-193b, miR-204, miR-340, miR-372, miR-429, miR-449a, miR-490 and miR-495 (reviewed in Srivastava *et al*. 2017). In serum samples from women with EC, increased levels of miR-186, miR-222 and miR-223 were identified compared with controls (Montagnana *et al*. 2017). Targets of upregulated miRs in EC include the tumor suppressor PTEN that is downregulated by overexpressed miR-21, miR-130a, miR-205, miR-222 and miR-429 (Srivastava *et al*. 2017). Although much studied, there are currently no miRNA signatures in use for early detection and screening of gynecological cancers (Srivastava *et al*. 2017).

miRNAs in thyroid cancer

The identity and targets of miRNAs dysregulated in PTC and follicular thyroid carcinoma (FTC) have been recently

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reviewed (Pallante *et al*. 2013, Saiselet *et al*. 2016, Yoo *et al*. 2016, Celano *et al*. 2017, Lima *et al*. 2017, Pishkari *et al*. 2018). miRNAs upregulated in PTC include miR-21, miR-31, miR-99-3p, miR-128a, miR-128b, miR-139, miR-141, miR-146a, miR-146b-3p, miR-146b-5p, miR-155, miR-181a, miR-181b, miR-187, miR-191, miR-200a, miR-200b, miR-200c, miR-220, miR-221, miR-222, miR-222-5p, miR-224, miR-375, miR-551b (Pallante *et al*. 2013). Downregulated miRNAs in PTC include: let-7f, miR-1, miR-26a-1, miR-30, miR-30c, miR-138, miR-199, miR-219, miR-292, miR-300 and miR-345 (Pallante *et al*. 2013). With RNA-seq, the arm of each miRNA and isomiRNAs can be detected. Thus, RNA-seq has higher resolution and detected increased miR-21-3p, miR-21-5p, miR-31-3p, miR-31-5p, miR-34a-5p, miR-146-3p, miR-146-5p, miR-182-5p, miR-183-5p, miR-221-3p, miR-221-5p, miR-222-3p and miR-551b-3p in PTC (Saiselet *et al*. 2016). RNA-seq identified miRNAs upregulated in FTC include miR-96-5p, miR-182-5p, miR-221-3p, miR-183-5p and miR-222-3p, whereas miR-31-5p, miR-199a-5p and miR-199b-5p showed consistent downregulation in three independent studies (reviewed in Saiselet *et al*. 2016).

miRNAs in mitochondria

Mitochondrial function is critical for metabolic homeostasis. NGS has identified several miRNAs imported into mitochondria including miR-34, miR-181c-5p and miR-146a-5p (Kim *et al*. 2017*b*). The identity and roles of miRNAs in mitochondrial biology were recently reviewed (Vendramin *et al*. 2017). The term 'mitomiRs' refers to miRNAs functioning in mitochondria, whether nuclear- or mtDNA-encoded (Duarte *et al*. 2015). mitomiRs are 17–25 nt vs the canonical 22 nt for most miRNAs. The exact function and identity of mitomiRs remains unknown and caution is advised since cytoplasmic contamination of mitochondrial extracts is problematic (Vendramin *et al*. 2017). Many ncRNAs appear to be involved in rapid cell stress responses and may be involved in anterograde and retrograde signaling between the nucleus and mitochondria to regulate energy homeostasis and apoptosis. For example, miRNAs appear to provide anterograde regulation of mitochondrial function, apoptosis and cancer cell metabolism (Duarte *et al*. 2015, Cha *et al*. 2017). However, although mitochondrial dysfunction is a hallmark of cancer, the role of ncRNAs in the mitochondrial unfolded protein response (UPRmt) in cancer (reviewed in Kenny & Germain 2017) remains to be examined.

miRNAs in circulation

Screening of free and exosomal-associated miRNAs by high-throughput sequencing platforms has identified changes in breast, ovarian and prostate cancers (Smith *et al*. 2017) and in thyroid cancer (Saiselet *et al*. 2016). The release of exosomes containing miRNAs (as well as other ncRNAs, protein and lipids) and endocytic uptake of the exosomes in recipient cells results in altered regulation of gene translation and has implicated miRNAs as hormones (reviewed in Bayraktar *et al*. 2017). In addition, circulating miRNAs can be transported between cells by microvesicles, apoptotic bodies, lipoproteins (HDL) and ribonucleoproteins, e.g., nucleophosmin 1 and AGO2. Exosomes derived from patients with CRPCa have increased expression of miR-1290 and miR-375 and correlate with decreased overall survival (reviewed in Kanwal *et al*. 2017). CAFs stimulate cancer progression by secreting chemokines, cytokines and growth factors that create the extracellular matrix (ECM) and CAFs secrete EVs containing a different spectrum of miRNAs compared to normal fibroblasts (Bayraktar *et al*. 2017). Among the miRNAs secreted by CAFs that regulate cancer cells are miR-21, miR-143 and miR-378 in BCa (Donnarumma *et al*. 2017); miR-210, miR-409-3p/5p (Yang *et al*. 2017*a*) and miR-409 (Josson *et al*. 2014) in PCa cells; and miR-21 in ovarian cancer (Au Yeung *et al*. 2016). Tumor-associated macrophages (TAMs) are also donors of miRNAs in cancer (reviewed in Bayraktar *et al*. 2017). Increased TAMs is associated with poor survival in advanced thyroid cancer (Ryder *et al*. 2008).

The mandate from NIH in the Precision Medicine Initiate is to have data-driven care for patients. A current goal of clinical trials is to determine if miRNA signatures obtained in fine needle aspiration biopsies and blood (serum or plasma) or urine will provide early diagnosis and track with therapeutic responses in cancer patients. However, the miRNA expression profile identified in blood samples depends on the processing of the sample, the miRNA extraction method, contamination, including by lysis of blood cells, and which normalizers are used (Saiselet *et al*. 2016). In addition to the ongoing efforts to standardize exosome and miRNA purification from biological fluids, factors that impact variability in miRNAs detected in circulation include diet, physical activity and circadian rhythms (reviewed in Smith *et al*. 2017). Most of the clinical trials involving mRNAs are observational, i.e., examining circulating in PCa, ovarian and breast cancers to monitor therapeutic responses to chemotherapy or other treatment strategies (reviewed in Smith *et al*. 2017).

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miRNA therapeutics

Despite the large body of literature supporting miRNAs as biomarkers for diagnosis, prognosis and follow-up in patients with malignancies, the application of miRNA therapeutics into the clinical practice has a number of technical obstacles to overcome include clearance and optimization of bioavailability (reviewed in Chen *et al.* 2015). Nanoformulations of miRNAs, miRNA mimics, miRNA sponges, anti-miR oligonucleotides (AMOs) and small-molecule inhibitors are being tested in animal models. miRNA mimics to replace the expression of downregulated miRNAs by synthetic oligonucleotides that are combined with hydrogels, liposomes, minicells, nanoparticles, synthetic polymers or viral carriers for better delivery are under investigation (Drusco & Croce 2017). Recently, a folate-miR-34a-5p conjugate was shown to be taken by MDA-MB-231 cells, which have high folate receptor levels and to inhibit MDA-MB-231 xenograft tumor growth in mice (Orellana *et al.* 2017). 'AntagomiRs' serve to inhibit oncomiR function, e.g., a miR-10b antagomiR to mice did not inhibit primary mammary tumor growth, but inhibited lung metastasis (Ma *et al.* 2010) and intraperitoneal injection of a miR-92a-LNA inhibitor inhibited human EC cell xenograft growth in mice with no evidence of overt toxicity or metastatic spread (Torres *et al.* 2016). However, many challenges remain for therapeutics with or against miRNAs, notably the contradictory nature of miRNAs.

Conclusions

lncRNAs and miRNAs dysregulated in endocrine cancers, and they serve as biomarkers and potential therapeutic targets and agents in various cancers and other diseases, e.g., cardiovascular disease and type II diabetes. These and other ncRNAs are interconnected and have complex molecular roles in regulating protein-coding and non-coding nuclear gene transcription: RNA stability, epigenetic processes, chromatin accessibility, translation, gene expression in mitochondria, anterograde and retrograde signaling and intracellular and intercellular signaling. The study of lncRNAs is less mature than that of miRNAs. For example, new lncRNAs continue to be discovered, relatively few studies on any specific lncRNA have been published, and each lncRNA may have multiple isoforms that can be post-transcriptionally modified, adding complexity to evaluating their cellular and physiologic function. lncRNA structures are functionally important, but only a few lncRNAs' structures are known. Identification of cell-specific lncRNA-interacting proteins and other RNAs and their subcellular distribution is needed. Both miRNAs and lncRNAs are being actively evaluated as tumor biopsy, plasma, serum, blood and urine biomarkers in the diagnosis and management of endocrine-related cancers as well as therapeutic targets. In addition, lncRNAs and miRNAs may serve as therapeutic agents. Many challenges remain in elucidating the biogenesis and function of ncRNAs in endocrine-related cancers. Our understanding of the functional roles of miRNAs and lncRNAs and their molecular targets is expanding rapidly. However, individual miRNAs and lncRNAs, and their combinations, may have different sets of targets and activities depending on the cell type, microenvironment, microbiome and hormonal milieu; thus, further investigation is required to fully elucidate miRNA and lncRNA function in endocrine-related cancers.

Supplementary data

This is linked to the online version of the paper at https://doi.org/10.1530/ERC-17-0548.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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