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Long non-coding RNAs in endometrial physiology and pathophysiology

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Abstract

The endometrium is an essential component of the female uterus which provides the environment for pregnancy establishment and maintenance. Abnormalities of the endometrium not only lead to difficulties in establishing and maintaining pregnancy but also play a causative role in diseases of endometrial origin including endometriosis and endometrial cancer. Non-coding RNAs are proposed to play a role in regulating the genome in both normal endometrial physiology and pathophysiology. In this review, we first provide a general overview of non-coding RNAs and reproductive physiology of the endometrium. We then discuss the role on non-coding RNAs in normal endometrial physiology and pathophysiology of endometrial infertility. We then conclude with non-coding RNAs in the pathophysiology of endometriosis and endometrial cancer.

Non-coding RNAs

The genome contains all the genetic information needed to develop and maintain a living organism. The transcriptome however represents the functional component of the genome. The GENCODE project has been proposed to annotate all the functional elements of the human genome. So far, 60,660 total human genes were identified, 19,962 of which are protein-coding genes, 17,958 are long non-coding RNA genes, and 7,569 are small non-coding RNA genes (Release 36, December 2020 available online: https://www.gencodegenes.org/human/stats.html). The old understanding of the genome mainly focused on the protein-coding genes since proteins play a major role in cellular functions. However, as researchers examine the functions of non-coding RNAs (ncRNAs), they have reached a new understanding of the substantial roles of ncRNAs. Perhaps that could explain the relatively larger proportion of ncRNA genes compared to protein-coding genes of the human genome.

Non-coding RNAs can be classified bases on their functions into housekeeping RNAs and regulatory RNAs. Housekeeping RNAs are the most abundant among other types as they play an essential role in splicing and translation machineries such as ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA) and small nucleolar RNA (snoRNA) (Uchida and Adams, 2019). On the other hand, regulatory RNAs are less abundant but they play an integral role in regulating gene expression (Ferlita et al., 2018). Regulatory ncRNAs have been of great interest to the scientific community owing to their implications in human pathologies. Because ncRNAs can be detected in all biological fluids, they have been employed as non-invasive diagnostic and prognostic biomarkers for a wide array of human diseases (Ferlita et al., 2018). The advent of ncRNAs in biomedical research led to the advancement of RNA-targeted therapies (Crooke et al., 2018). The main classification of regulatory ncRNAs is based on their size specifically to distinguish between small ncRNAs from long ncRNAs. Small ncRNAs are smaller than 200 nucleotides (nt) whereas long ncRNAs are 200nt or longer transcripts (Uchida and Adams, 2019). Among the best investigated small ncRNAs are microRNAs (miRNAs) and piwi-interacting RNAs (piRNAs). miRNAs range in size between 18 to 25nt long and they function mainly by suppressing mRNA translation by binding to the 3’ untranslated regions (3’ UTR) of the target transcript (Ferlita et al., 2018). On the other hand, piRNAs are well-known for silencing non-coding transposable elements by means of epigenetic mechanisms such as DNA and histone methylation (Ozata et al., 2019, Nandi et al., 2016). Long ncRNAs (lncRNAs) can be classified based on their genomic location into intergenic and intragenic lncRNAs. Intragenic lncRNAs can be exonic or intronic lncRNAs, and exonic can be sense or antisense lncRNAs (Ferlita et al., 2018). One of the remarkable features of lncRNAs is their ability to regulate gene expression through diverse mechanisms. Thus, lncRNAs can be further classified based on their mechanism of action into *cis*-acting and *trans*-acting lncRNAs. lncRNAs that act in *cis* regulate the chromatin structure and gene expression of neighboring genes through three proposed mechanisms: the recruitment of regulatory factors to the target gene locus, the transcription per se of the lncRNA independent of the transcript, and the functional DNA elements within the lncRNA promoter region independent of the transcript. On the other hand, lncRNAs that act in *trans* regulate the chromatin structure and gene expression of distant genes as well as post-transcriptional and post-translational regulation of target RNAs and proteins. Examples of lncRNAs that regulate the expression of their target genes include enhancer RNAs (eRNAs), dosage compensation lncRNAs, imprinted lncRNAs and competing endogenous RNAs (ceRNAs) (Quinn and Chang, 2016, Kopp and Mendell, 2018).

Estrogen and progesterone in endometrial physiology

The female menstrual cycle is orchestrated by several hormones that are tightly regulated through the hypothalamic-pituitary-gonadal axis. However, the ovarian hormones estrogen (E2) and progesterone (P4) are the main players that directly act on the endometrium. The menstrual cycle can be divided into three main phases: the proliferative phase, the secretory phase and the menstrual phase. The human endometrium is composed of two layers: the basal layer and the functional layer. Only the functional layer is shed during menses while the basal layer stays intact throughout the lifetime of the reproductive cycle. Main

endometrial cell types include epithelial cells that make up the uterine lining and uterine glands, stromal cells which make up the majority of the endometrium, and lastly endothelial cells that make up the vasculature. It is well established that P4 withdrawal initiates the inflammatory response leading to menstruation. Similarly, P4 withdrawal increases matrix metalloproteinases (MMPs) expression in the functional layer which induces the breakdown of the extracellular matrix (ECM) leading to tissue sloughing. Immune cells such as neutrophils and macrophages invade the endometrium following P4 withdrawal to promote tissue destruction and regulate the inflammatory response (Maybin and Critchley, 2012, Maybin and Critchley, 2015). Shortly after the first few days of menses, endometrial repair of the epithelium takes place. During the proliferative phase, all endometrial cell types grow exponentially to regenerate the functional layer after menses. Several growth factors play key role in vascular regeneration and cellular proliferation such are vascular endothelial growth factor (VEGF), stromal-derived growth factor-1 (SDF-1), and insulin-like growth factor-1 (IGF1). However, the ovarian E2 is the predominant hormone during the proliferative phase and the main trigger of cellular proliferation (Maybin and Critchley, 2012, Maybin and Critchley, 2015). E2 acts through the estrogen receptor (ER) which, upon ligand binding, translocate to the nucleus and activates several hundred target genes including the progesterone receptor gene (PGR). Thus, one of the well-recognized functions of E2/ER actions is priming the endometrium for P4 action. The secretory phase begins after ovulation when the corpus luteum produces ample amount of P4 along with E2. P4 acts via the progesterone receptor (PR) and counteracts the E2/ER action. Thus, P4 halts endometrial growth and induces epithelial and stromal cell differentiation to prepare the endometrium for embryo implantation (Ashary et al., 2018). During this phase, the endometrium becomes receptive and the blastocyst can attach to the luminal epithelium during a narrow timeframe known as the window of implantation (Ashary et al., 2018). Specific morphological and functional transformation of the luminal epithelium is critical to initiate this process such as reorganization of the apical epithelium and the development of pinopodes (Aplin and Ruane, 2017). The embryonic trophoblast breaches the luminal epithelium to invade the endometrium. This invasion allows trophoblast to proliferate and come in direct contact with the endometrial stroma. In the mouse, trophoblast invasion induces stromal cell decidualization which transforms stromal cells into highly specialized secretory decidual cells (Aplin and Ruane, 2017). In humans by contrast, decidualization of stromal cells occurs in response to the post-ovulatory rise of P4 independent of the conceptus (Ramathal et al., 2010). However, stromal cell decidualization in both species is essential for proper implantation and placentation. Defective decidualization is associated with pregnancy disorders such as recurrent miscarriages and preeclampsia (Garrido-Gomez et al., 2017, Gellersen and Brosens, 2014). The decidua regulates trophoblast invasion to prevent excessive tissue breakdown mediated by trophoblastic factors such as MMPs (Sharma et al., 2016). Moreover, the decidua provides the initial nourishment for the embryo before the development of the placenta and creates an optimal environment for implantation (Ashary et al., 2018).

Long, non-coding RNAs and the menstrual/reproductive cycle

Epigenetic modifications such as DNA methylation play a significant role in reproductive function. Imprinted genes are expressed unequally from one allele based on parent-of-origin methylation (Paczkowski et al., 2015). *H19* is one of the first identified imprinted genes which was baffling at the time because *H19* can be transcribed but not translated, yet its deletion caused a significant phenotype of overgrowth (Kallen et al., 2013, Brannan et al., 1990, Gabory et al., 2009, Zhang and Tycko, 1992). *H19* yields a lncRNA that is transcribed exclusively from the maternal allele whereas the paternal allele is epigenetically silenced via methylation (Nordin et al., 2014). *H19* belongs to a gene cluster that contains the paternally imprinted gene *IGF2* (Kallen et al., 2013). *H19* gene is predominantly expressed during embryonic development and repressed after birth in most tissues except few organs including the uterus (Adriaenssens et al., 1999). Several studies have shown that steroid hormones regulate the expression of *H19* in various hormone responsive tissues and cell lines (Adriaenssens et al., 1999, Ariel et al., 1997). In the endometrium, *H19* transcripts were detected in the stroma whereas glandular and luminal epithelium were devoid of *H19* expression (Adriaenssens et al., 1999). One of the early studies that investigated the expression pattern of *H19* in human endometrial tissues found fluctuating levels of *H19* throughout the menstrual cycle (Ariel et al., 1997). *H19* expression begins to increase before decidualization and peaks at the end of the secretory phase (Ariel et al., 1997). Discrepancies among studies have been observed and could be owed to variable mice strains, study objectives and protocols. In one study using Swiss 3T3 mice, *H19* expression was predominantly regulated by E2 (Adriaenssens et al., 1999). Thus, *H19* expression gradually increases in response to E2 during the proliferative phase and remains elevated throughout ovulation and early secretory phase then decreases to basal levels during diestrus (Adriaenssens et al., 1999). Conversely, genome-wide analysis of lncRNAs in uterine tissue of Kunming White outbred mice have shown that *H19* expression was significantly upregulated during the window of implantation suggesting a major role of P4 in regulating the expression of *H19* (Wang et al., 2017). The role of *H19* in endometrial function was emphasized by several findings that have shown aberrant *H19* expression is related to reproductive dysfunctions such as unexplained infertility and endometriosis (Korucuoglu et al., 2010, Ghazal et al., 2015). It is well established that *H19* lncRNA acts as a competing endogenous RNA (ceRNA) in several tissues including the endometrium. This mechanism suggests that *H19* lncRNA binds complementary miRNAs to prevent or diminish their actions. One of the well-studied miRNAs that bind *H19* is *let-7* miRNA (Kallen et al., 2013). Therefore, higher *H19* expression can compete for *let-7* binding and inhibit *let-7* from targeting other mRNAs leading to higher expression of *let-7* targets and vice versa. A recent study investigating the role of *H19* in endometriosis found that human endometrial stromal cells (HESCs) express *H19* in response to E2 in vitro and this pathway is essential for HESCs proliferation due to its major role in regulating IGF signaling (Ghazal et al., 2015). One of *let-7* targets is insulin-like growth factor 1 receptor (*IGF1R*) which was found downregulated in women with endometriosis due to significant downregulation of *H19* expression (Ghazal et al., 2015). IGF1R is activated by IGF1 and IGF2 signaling which was shown to play a critical role in endometrial stromal cell proliferation and differentiation (Ghazal et al., 2015). *Igf1* null female mice are infertile due to multiple defects in the

reproductive tract (Baker et al., 1996). These findings indicate that infertility associated with endometriosis could be related to *H19* downregulation.

Another *let-7* target is one of the cell-extracellular matrix adhesion proteins known as integrin beta 3 (*ITGB3*) (He et al., 2019). Several studies have shown that ITGB3 plays a critical role in blastocyst adhesion and invasion (He et al., 2019, Zeng et al., 2017, Liu et al., 2012). The transcript level of *ITGB3* as well as *H19* lncRNA were significantly downregulated in endometrial tissue obtained during the mid-luteal phase (window of implantation) from women with recurrent implantation failure (Zeng et al., 2017). A recent study investigating the role of *H19* in trophoblast adhesion found a direct correlation between *H19* and *ITGB3* RNA and protein expression (He et al., 2019). He D. and colleagues found that *H19* downregulation decreased *ITGB3* expression and impaired trophoblast adhesion and invasion in vitro (He et al., 2019). Similar to early findings, the mechanism involves the upregulation of *let-7* miRNA (He et al., 2019). Additionally, *H19* lncRNA, *ITGB3* transcripts, and ITGB3 protein levels were significantly downregulated in embryonic chorion tissue samples from women with spontaneous abortion (He et al., 2019). These findings suggest that *H19* downregulation impacts several key regulators of endometrial receptivity and embryo implantation.

In an attempt to characterize the functional roles of lncRNAs in the endometrium, Liang and colleagues explored the role of long intergenic non-coding RNA (lincRNA) *LINC473* in HESCs decidualization (Liang et al., 2016). The specific interest in *LINC473* was due to previously published studies on the molecular link between *LINC473* expression upon cAMP activation which play an integral role in HESCs decidualization (Liang et al., 2016). They found that *LINC473* expression is regulated by cAMP/PKA signaling in HESCs independent of progesterone and estrogen (Liang et al., 2016). *LINC473* promoter region contained a binding site for STAT3 at the transcription start site and STAT3 phosphorylation was required for *LINC473* induction (Liang et al., 2016). STAT3 is a transcription factor and its expression in endometrial stroma increases remarkably during decidualization owing to its essential role during embryo implantation (Lee et al., 2013). *LINC473* expression is required for proper HESCs decidualization as *LINC473* knockdown significantly reduced *PRL* and *IGFPB1* expression in vitro (Liang et al., 2016). Moreover, several key players in endometrial decidualization and receptivity were significantly downregulated upon *LINC473* knockdown such as *PGR, FOXO1, HOXA10, HOXA11* and *WNT4* (Liang et al., 2016). However, *CEBPB* expression, the predominant regulator of decidual marker *PRL*, was not affected by *LINC473* knockdown suggesting a profound regulatory role of *LINC473* in decidualization independent of the cAMP/PKA pathway axis (Liang et al., 2016). This study strongly suggests that *LINC473,* which expression is induced by cAMP/PKA signaling, mediates stromal cell decidualization through the transcriptional regulation of *PRL, IGFBP1, PGR, FOXO1, HOXA10, HOXA11* and *WNT4* but the mechanism of regulation is yet to be elucidated.

Homeobox (Hox) genes play a critical role during early reproductive tract development as well as during embryo implantation (Chau et al., 2002, Gendron et al., 1997). In the human endometrium as well as in mice uterus, *HOXA10* and *HOXA11* expressions significantly increase during the window of implantation (Gendron et al., 1997, Chau et al., 2002). The

disruption of either gene expression in humans or mice was associated with infertility due to implantation failure (Chau et al., 2002, Gendron et al., 1997). Therefore, a growing interest to identify upstream transcriptional regulators for *HOXA10* and *HOXA11* led to the recognition of *HOXA11* antisense lncRNA. The expression pattern of *HOXA11* antisense in the endometrium follows a cyclical pattern with respect to the menstrual cycle (Chau et al., 2002). To the contrary of *HOXA11* expression, *HOXA11* antisense expression peaks during the late proliferative phase of the cycle (Chau et al., 2002). Progesterone treatment had a significant impact on *HOXA11* antisense expression which is consistent with the natural increase in progesterone during the luteal phase of the cycle when *HOXA11* antisense expression is greatly diminished (Chau et al., 2002). This study demonstrated that *HOXA11* antisense has an opposing effect on *HOXA11* expression. However, *Hoxa11* antisense RNA transfection into female mice during the luteal phase when *Hoxa11* expression is highest did not block *Hoxa11* translation or function (Chau et al., 2002). The researchers speculated that *HOXA11* antisense could be competing for transcription in a mechanism known as transcriptional interference to block *HOXA11* transcription during the proliferative phase (Chau et al., 2002). Following P4 rise during the luteal phase, *HOXA11* antisense is suppressed allowing for the increase in *HOXA11* expression which is critical for implantation. Table 1 provides a summary of our current knowledge on the lncRNAs just discussed and their proposed role in the normal endometrium.

Long, non-coding RNAs in uterine disease

Embryo implantation and endometrial receptivity are fundamental for pregnancy establishment, and the impairment of one directly disrupts the other. Implantation failure following in vitro fertilization (IVF) is devastating. It is a costly procedure, yet the success rate is less than 60% (Feng et al., 2018, Xu et al., 2019a). Mounting evidence suggest that the receptive endometrium as well as the implanting blastocyst exhibit a unique transcriptome signature that significantly differ from non-receptive endometria as well as non-implanting blastocysts (Feng et al., 2018, Xu et al., 2019a, Fan et al., 2017, Wang et al., 2017, Wang et al., 2014). A recent study revealed that human blastocysts obtained after IVF can secrete factors that regulate the RNA expression profile of human endometrial epithelial cells (HEEC) (Takamura et al., 2020). HEEC form the lining of the endometrium and their optimal function is essential for blastocyst adhesion (Takamura et al., 2020). The study objective was to assess the impact of the implanting blastocyst on endometrial receptivity, specifically HEEC functions (Takamura et al., 2020). HEEC was incubated with media obtained from implanting and non-implanting embryos. Microarray analysis of HEEC revealed that a significant number of lncRNAs was differentially expressed in HEEC treated with media obtained from non-implanting embryos compared to implanting ones (Takamura et al., 2020). One of the significantly mis-expressed lncRNA is the phosphatase and tensin homolog pseudogene 1 (*PTENP1*) (Takamura et al., 2020). *PTENP1* lncRNA was significantly downregulated in HEEC treated with non-implanting embryos compared to implanting ones. Most notably is the significant reduction of *PTENP1* lncRNA in endometrial tissue obtained from women with unexplained infertility during the late secretory phase compared to fertile women (Takamura et al., 2020). *PTENP1* expression follows a cyclical pattern in human endometrial tissue throughout the menstrual cycle which

peaks during the late secretory phase (Takamura et al., 2020). Interestingly, *PTENP1* was shown to regulate the expression of *PTEN* gene by acting as a ceRNA that sponge miRNAs targeting *PTEN* transcripts leading to increase the bioavailability of *PTEN* (Takamura et al., 2020). Although the role of PTEN in endometrial receptivity is not well understood, similar to *PTENP1, PTEN* expression follows a cyclical pattern in human endometrial tissue throughout the menstrual cycle (Kayisli et al., 2004). The highest expression of *PTEN* was detected during the late secretory phase and early pregnancy (Guzeloglu-Kayisli et al., 2003). These findings indicate that progesterone regulates the expression of *PTEN* in endometrial tissue which was confirmed in vitro (Guzeloglu-Kayisli et al., 2003). Estrogen, on the other hand, increases PTEN phosphorylation which decreases PTEN activity indicating a vital role of E2 during the proliferative phase to suppress PTEN mediated apoptosis (Guzeloglu-Kayisli et al., 2003). PTEN protein suppresses molecular pathways that mediate cell survival such as PI3K/AKT pathway and promotes proapoptotic factors. These findings suggest that PTEN actions mediate apoptosis during the late secretory phase to facilitate the cell death of endometrial epithelial and decidual cells allowing embryo implantation and invasion to take place (Takamura et al., 2020, Guzeloglu-Kayisli et al., 2003, Kayisli et al., 2004).

Preeclampsia is a pregnancy complication that yearly impacts 8 million pregnant women worldwide (Garrido-Gomez et al., 2017). Preeclampsia is associated with shallow cytotrophoblast invasion, defective remodeling of spiral arteries leading to abnormal placentation (Garrido-Gomez et al., 2017, Fisher, 2015). Mounting evidence suggests that aberrant decidualization plays a key role in the pathophysiology of preeclampsia (Garrido-Gomez et al., 2017, Lv et al., 2018). Several key regulators of glucose metabolism have been implicated in endometrial decidualization (Tsai et al., 2014). The inhibition of glucose metabolism pathway reduced decidualization significantly indicating an integral role of glucose metabolism in endometrial decidualization (Tsai et al., 2014). A recent study investigating the role of lncRNA hexokinase 2 pseudogene 1 (*HK2P1*) in severe preeclampsia uncovered a novel role of *HK2P1* in decidualization (Lv et al., 2018). The expression of *HK2* and *HK2P1* was significantly reduced in women with severe preeclampsia suggesting a possible role of *HK2* and *HK2P1* downregulation the pathophysiology of preeclampsia (Lv et al., 2018). Hexokinase 2 (HK2) phosphorylates glucose to glucose-6-phosphate which is the first rate-limiting step in glycolysis (Lv et al., 2018). The expression of *HK2* and *HK2P1* is significantly upregulated during in vitro decidualization and the knockdown of either *HK2* or *HK2P1* reduced decidual markers greatly (Lv et al., 2018). Interestingly, the knockdown of *HK2* resulted in *HK2P1* downregulation and vice versa (Lv et al., 2018). *HK2* and *HK2P1* 3’ UTRs share 93.13% homology suggesting a ceRNA type of regulation (Lv et al., 2018). Among putative miRNAs targeting both *HK2* and *HK2P1, miR-6887-3p* was found upregulated in women with severe preeclampsia (Lv et al., 2018). Moreover, the overexpression of *miR-6887-3p* in HESCs reduced *HK2* and *HK2P1* expression (Lv et al., 2018). In vitro studies using luciferase assay revealed that *miR-6887-3p* binds specifically to *HK2* and *HK2P1* 3’UTR region (Lv et al., 2018). The overexpression of *miR-6887-3p* in HESCs inhibited the expression of decidualization markers and glucose utilization (Lv et al., 2018). This study

suggests that *HK2P1* lncRNA promotes the expression of *HK2* post-transcriptionally by acting as a ceRNA that buffers *miR-6887-3p* and prevents *HK2* downregulation.

Endometriosis is a common disease of the endometrium that affects women of reproductive age (Nothnick, 2017). Common symptoms of endometriosis include pain, dysmenorrhea, and infertility in addition to a serious impairment of women's ability to manage daily activities (Nothnick, 2017). Endometriosis is characterized by the development of ectopic lesions of endometrial tissue in the pelvic cavity which can be further classified based on the location of the lesions into peritoneal endometriosis, ovarian endometriosis and deep infiltrating endometriosis (Nothnick, 2017, Donnez et al., 2018, Konrad et al., 2020). The most commonly accepted theory of endometriosis etiology is retrograde menstruation which affects up to 90% of menstruating women but only causes the disease in 15% indicating that several factors contribute to the development of the disease (Nothnick, 2017). Currently, laparoscopy is the main diagnostic procedure available which is invasive and requires general anesthesia in addition to the potential risks associated with a surgical procedure (Nothnick et al., 2015). The demand for developing a safe and easy diagnostic test utilizing biomarkers of endometriosis is unequivocal. In an attempt to identify differentially expressed lncRNAs as diagnostic and prognostic biomarkers for endometriosis, several studies examined the role of lncRNAs in the pathogenesis of endometriosis.

One of the largest and recently published studies investigated the diagnostic and prognostic value of Urothelial carcinoma-associated-1 (*UCA1*) lncRNA in ovarian endometriosis (Huang et al., 2019a). *UCA1* lncRNA was significantly downregulated in ectopic lesions compared to matched eutopic endometrial tissues of women with ovarian endometriosis (Huang et al., 2019a). Similarly, serum levels of *UCA1* was significantly lower in patients with ovarian endometriosis compared to healthy control. In addition, serum level of *UCA1* correlated with the progression of the disease (Huang et al., 2019a). The level of *UCA1* was lower in stage II compared to stage I, and stage IV was the lowest among other groups. Interestingly, the serum levels of *UCA1* lncRNA after laparoscopic treatment significantly increased (Huang et al., 2019a). Moreover, lower *UCA1* serum level was detected in patients with disease recurrence compared to patients who did not experience recurrence after two years follow up (Huang et al., 2019a). These findings suggest that serum *UCA1* lncRNA in ovarian endometriosis can provide a valuable diagnostic and prognostic biomarker that can benefit in early detection and treatment.

Most recently, maternally expressed gene 3 (MEG3-210) lncRNA was found significantly downregulated in eutopic endometrial tissue from women with endometriosis compared to control group (Liu et al., 2020). *MEG3* lncRNA is well characterized in the cancer research due to its tumor suppressive potential (Ghafouri-Fard and Taheri, 2019). *MEG3* lncRNA was shown to regulate the expression of p53 and promote p53 transcriptional activity therefore *MEG3* was described as a tumor suppresser lncRNA (Ghafouri-Fard and Taheri, 2019). *MEG3* acts as a chromatin-interacting lncRNA that regulates the expression of target genes through its interaction with the polycomb repressive complex 2 (PRC2) (Ghafouri-Fard and Taheri, 2019). Additionally *MEG3* acts as a ceRNA that can sponge several miRNAs and regulate the expression of their target mRNAs (Ghafouri-Fard and Taheri, 2019). Although Liu and colleagues investigated the role of *MEG3-210* in the pathogenesis of endometriosis,

MEG3-210 lncRNA mechanism of action was not explored (Liu et al., 2020). Rather, *MEG3-210* downregulation was associated with several tumorigenic pathways such as the activation of mitogenic-activated protein kinases (MAPK) leading to increased migration and invasion of endometrial stromal cells in vitro (Liu et al., 2020). Interestingly, they proposed that these mechanisms are mediated by Galectin-1 overexpression which they found interacting with *MEG3-210* but did not investigate Galectin-1 transcriptional regulation (Liu et al., 2020). Galectins are glycan binding proteins that play a multitude of cellular functions due to their ability to modulate their target proteins and the signaling pathways they mediate (Hisrich et al., 2020). Galectins can be secreted into the ECM and therefore can be detected in patients' serum (Johannes et al., 2018). Galectin-1 level was significantly higher in eutopic endometrial tissue as well as in serum samples from women with endometriosis (Liu et al., 2020). Suggesting a possible clinical application of Galectin-1 as a diagnostic marker (Liu et al., 2020). Further studies are needed to elucidate the functional role of *MEG3-210* in the transcriptional regulation of Galectine-1.

Metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) lncRNA was significantly upregulated in ectopic lesions compared to matched eutopic endometrial tissue obtained from women with endometriosis as well as endometrial tissue obtained from women without endometriosis (Liang et al., 2017, Liu et al., 2019a). *MALAT1* acts as ceRNA that can sponge *miR-200c* and decrease its bioavailability (Liang et al., 2017). As a result, *MALAT1* overexpression inhibits *miR-200c* from suppressing its target mRNAs such as Zinc finger E-box-binding homeobox 1 and 2 (*ZEB1/2*) (Liang et al., 2017). ZEB1 and ZEB2 transcription factors were found upregulated in ectopic lesions and were shown to suppress E-cadherin expression directly or indirectly (Konrad et al., 2020). E-cadherin is an epithelial cell marker and a type of cell adhesion proteins that connect epithelial cells together. E-cadherin downregulation was described in epithelial-mesenchymal transition (EMT) pathway which is proposed to mediate endometrial cell migration and invasion leading to the formation of ectopic lesions (Konrad et al., 2020). Several studies reported a significant reduction in E-cadherin expression in ectopic endometrial tissue compared to eutopic endometrium (Konrad et al., 2020, Lin et al., 2019). In vitro studies using HESCs confirmed the role of *MALAT1* and *miR-200c* in regulating ZEB1/2 and E-cadherin expression (Liang et al., 2017). Moreover, *miR-200c* was shown to reduce endometriotic lesions volume in vivo using a rat model of endometriosis whereas *miR-200c* inhibitor had the opposite effect (Liang et al., 2017). These findings demonstrate that *miR-200c* has a therapeutic potential, but further studies are needed to determine the safety and efficacy of *miR-200c* administration to reduce ectopic lesion proliferation and prevent future disease recurrence.

Among the hundreds of markedly upregulated lncRNAs in ectopic lesions compared to matched eutopic and normal endometria, few were investigated. Actin filament associated protein1- antisense RNA1 (*AFAP1-AS1*) and *CCDC144NL-AS1* were shown to play a role in ectopic lesions migration and invasion in vitro (Lin et al., 2019, Zhang et al., 2018a). *AFAP1-AS1* upregulation correlates with EMT markers such as high ZEB1 and low E-cadherin in addition to higher migration and invasion potentials compared to *AFAP1-AS1* downregulation in ectopic endometrial epithelial cells (Lin et al., 2019). In vivo knockdown of *AFAP1-AS1* using xenograft in nude mice as a model of endometriosis resulted in

significant reduction in tumor size (Lin et al., 2019). On the other hand, *CCDC144NL-AS1* knockdown significantly decreased EMT marker vimentin and MMP9 expression in vitro (Zhang et al., 2018a). MMP9 expression was reported to be significantly elevated in the plasma and peritoneal fluid of patients with endometriosis (Liu et al., 2016). However, *AFAP1-AS1* and *CCDC144NL-AS1* studies are preliminary and further studies are required to recognize the clinical applications of these interesting lncRNAs.

Assessment and evaluation of *H19* lncRNA expression and potential role in endometriosis has been inconsistent which could be owing to diverse research protocols, objectives and patients' diagnosis. The study by Ghazal and colleagues compared eutopic endometrial tissue from women with endometriosis to normal endometrial tissues and found *H19* lncRNA significantly downregulated in eutopic endometrium of women with endometriosis (Ghazal et al., 2015). They hypothesized that E2 induces the expression of *H19* lncRNA during the proliferative phase, which by acting as a molecular sponge for *let-7* miRNA increases the level of *IGF1R* transcripts and promotes IGF1 signaling and stromal cell proliferation (Ghazal et al., 2015). Although ectopic lesions samples were collected from the patients in this study, they were not examined for *H19* expression. However, the impact of *H19* downregulation on stromal cell proliferation provides a feasible explanation of the infertility associated with endometriosis. On the contrary, Liu and colleagues reported that *H19* lncRNA is significantly upregulated in ectopic lesions and eutopic endometrial tissues compared to healthy control (Liu et al., 2019b, Xu et al., 2019b). The knockdown of *H19* in ectopic endometrial cells resulted in a significant increase in several miRNAs; *miR-124-3p* was the most significant (Liu et al., 2019b). One of *miR-124-3p* putative targets was integrin beta-3 (*ITGB3*) which was shown to play a critical role in cell adhesion and invasion (He et al., 2019). Therefore, they hypothesized that the upregulation of *H19* in ectopic lesions promotes endometrial cell proliferation and invasion via increasing the bioavailability of *ITGB3* (Liu et al., 2019b). Although the in vitro assessment of *H19/miR-124-p3/ITGB3* provides compelling evidence of their role in cell proliferation and invasion, the expression level of *ITGB3* in ectopic lesions was not assessed. Thus, this study provides a supporting evidence that *H19* lncRNA play a critical role in endometrial cell proliferation despite the differences in mechanism of action. Xu and colleagues recruited infertile women with and without endometriosis to investigate the role of *H19* lncRNA in endometriosis (Xu et al., 2019b). Similar to the previous study, they found that *H19* expression is significantly upregulated in eutopic endometrial tissue compared to endometrial tissue without endometriosis (Xu et al., 2019b). This increased level of *H19* positively correlated with elevated levels of alpha smooth muscle actin (*ACTA2*) expression although heterogeneity between patient samples was apparent (Xu et al., 2019b). They have shown that *H19* lncRNA acts as a ceRNA via *miR-216a-5p* competitive binding leading to increased *ACTA2* transcripts level (Xu et al., 2019b). Moreover, in vitro knockdown of *H19* as well as *ACTA2* significantly reduced endometrial stromal cells invasion and migration. Therefore, they hypothesized that *H19* lncRNA regulates stromal cell invasion and migration by increasing the bioavailability of *ACTA2* expression post-transcriptionally (Xu et al., 2019b). However, the role of *ACTA2* upregulation in relation to infertility was not examined although all patients suffered from infertility. After all, *H19* lncRNA studies were inconclusive but they have shown that *H19* lncRNA plays a critical role in the pathogenesis of endometriosis. A

summary of our current knowledge on these lncRNAs and their proposed role in endometrial abnormalities associated with embryo implantation failure, preeclampsia and endometriosis is provided in Table 2.

Endometrial cancer (EC) is a common tumor of the female reproductive system. There are several classifications of EC based on the cellular characteristics and molecular features of the tumor biopsy; most commonly known are type I and type II. Type II EC, also known as non-endometrioid endometrial carcinoma (NEEC), occurs exclusively in post-menopausal women which accounts for 20% of all EC cases (Treeck et al., 2020, Smolle et al., 2015). NEEC can be further classified into serous, clear-cell EC and carcinosarcoma (Treeck et al., 2020). Type I EC, also known as endometrioid endometrial carcinoma (EEC), arise from endometrial glands and accounts for 80% of EC cases (Smolle et al., 2015). EEC is characterized by elevated estrogen level, endometrial hyperplasia, and frequent mutation in the tumor suppresser phosphatase and tensin homolog (*PTEN)* gene (Smolle et al., 2015). The expression of *PTEN* transcript is regulated by several mechanisms including upstream regulators, epigenetic modulators, and post-transcriptional regulators such as miRNAs and lncRNAs. Several studies have shown that *PTEN* transcript expression can be regulated by several lncRNAs including the pseudogene *PTENP1,* which shares 95% homology with the *PTEN* gene 3' UTR (Poliseno et al., 2010, Xin et al., 2015). The sense lncRNA acts as a ceRNA that buffers miRNAs targeting *PTEN* and therefore prevents *PTEN* silencing (Tay et al., 2011). Overexpression studies of the *PTENP1* 3' UTR resulted in significant increase in *PTEN* transcripts level (Poliseno et al., 2010). Suggesting a tumor suppressive feature of *PTENP1* pseudogene. Examination of the *PTEN* gene methylation in endometrial samples obtained from women with endometrial hyperplasia and EC revealed that *PTEN* gene is not methylated (Kovalenko et al., 2018). On the other hand, *PTENP1* pseudogene was highly methylated in over 70% of endometrial hyperplasia and 70% of EC biopsies (Kovalenko et al., 2018). These findings suggest that *PTEN* expression could be compromised by unrestrained miRNA activity as a result of *PTENP1* pseudogene silencing. Other lncRNAs that regulate *PTEN* expression and were implicated in EC include Fer-1-like protein 4 (*FER1L4*), *RP11-395G23.3,* and *LA16c-313D11.11* (Qiao and Li, 2016, Xin et al., 2015). *FER1L4* expression was found significantly downregulated in EC tissue compared to adjacent normal endometrial tissue (Qiao and Li, 2016). The overexpression of *FER1L4* lncRNA in vitro promotes the expression of *PTEN* and inhibits the activation of AKT pathway (Qiao and Li, 2016). Similarly, lncRNAs *RP11-395G23.3* and *LA16c-313D11.11* were found downregulated in EC compared to control group (Xin et al., 2015). lncRNAs *RP11-395G23.3* and *LA16c-313D11.11* were confirmed targets of *miR-205-5p* which directly regulates *PTEN* expression (Xin et al., 2015). The expression level of *miR-205-5p* was found significantly upregulated in EC and associated with poor prognosis (Xin et al., 2015). Therefore, the lncRNAs *RP11-395G23.3* and *LA16c-313D11.11* act as ceRNA similar to *PTENP1.*

Mounting evidence suggest that endometrial hyperplasia observed in type I EC is due to unopposed estrogen activity (Kim and Chapman-Davis, 2010). It is well established that progesterone antagonizes estrogen mediated actions and inhibits endometrial cell proliferation. Nuclear enriched abundant transcript 1 (*NEAT1*) lncRNA was shown to be negatively regulated by progesterone in endometrial cancer cell lines (Ishikawa) (Huang et

al., 2019b). Several studies have reported that *NEAT1* is overexpressed in EC tissue samples compared to adjacent tissue (Wang et al., 2019, Li et al., 2016). Elevated *NEAT1* expression in EC promotes cell proliferation, migration, and invasion through various pathways. *NEAT1* lncRNA acts as a ceRNA for several miRNAs. For instance, *miR-146b-5p* was confirmed to target lymphoid enhancing factor 1 (*LEF1*) as well as *NEAT1* expression in EC cell lines (Huang et al., 2019b). *LEF1* encodes for a transcription factor and a component of the Wnt/β-catenin signaling pathway that activates the transcription of oncogenic genes such as *c-MYC* (Huang et al., 2019b). *NEAT1* overexpression was shown to be positively correlated with *LEF1* upregulation and *miR-146b-5p* downregulation indicating that *NEAT1*, by acting as a molecular sponge for *miR-146b-5p*, increases the bioavailability of *LEF1* leading to the activation of Wnt/β-catenin pathway (Huang et al., 2019b). *NEAT1* was also shown to sponge *miR-144-3p* leading to the upregulation of its target transcripts (Wang et al., 2019). *EZH2*, one of *miR-144-3p* targets that was implicated in endometrial cancer, is a histone methyltransferase that modulates the chromatin structure at the promoter region of target genes (Wang et al., 2019). Several recent studies have shown that *EZH2* transcripts and protein levels were significantly upregulated in type I EC tissue samples compared to matched normal endometrial tissue (Krill et al., 2020, Oki et al., 2017).

H19 lncRNA was reported in several studies as a hormone responsive lncRNA irrespective of the variable findings (Adriaenssens et al., 1999, Ariel et al., 1997, Ghazal et al., 2015). *H19* was reported as a tumor suppressor and an oncogene in several cancer types (Matouk et al., 2016). Nonetheless, several studies reported that H19 is upregulated in EC tissue samples indicating an oncogenic role of *H19* in EC (Zhao et al., 2017, Zhang et al., 2018b, Zhu et al., 2019). In vitro knockdown of *H19* was shown to decrease the migration and invasion of EC cell lines (Zhao et al., 2017). Another study found that *H19* acts as a ceRNA to increase the bioavailability of *HOXA10* (Zhang et al., 2018b). HOXA10 is a well-known transcription factor that plays a critical role in endometrial receptivity but the role of HOXA10 in EC was not clear (Wang et al., 2018, Li et al., 2015a). Recently, *H19* upregulation in EC was shown to promote hypoxia inducible factor-1α (*HIF-1α*) expression by competing with *miR-20b-5p* which targets *HIF-1α* (Zhu et al., 2019). Hypoxia is a critical cue to induce angiogenesis and tissue repair in regenerating tissues such as the endometrium (Maybin et al., 2018). However, cancer cells exploit this mechanism to promote cell survival and metastasis (Matouk et al., 2016). *H19* overexpression leading to *HIF-1α* upregulation was shown to promote EC cell proliferation, and migration through EMT (Zhu et al., 2019).

Most recently, several lncRNAs were shown to act as oncogenes by promoting the expression of other oncogenes such as *c-MYC* and *c-MET*. Colon cancer associated transcript-1 (*CCAT1)* lncRNA was found significantly upregulated in endometrial tissues of type I EC patients as well as EC cell lines (Treeck et al., 2020). *CCAT1* may act as an oncogene owing to its ability to sponge several tumor suppressor miRNAs such as *let-7* (Deng et al., 2015). *CCAT1* overexpression in hepatocellular carcinoma cells lines was shown to decrease *let-7* expression leading to the upregulation of *let-7* targets such as *c-MYC* and *HMGA2* expression (Deng et al., 2015). Small nucleolar RNA host gene 8 (*SNHG8*) was also upregulated in patients with EC and correlated with poor prognosis (Yang et al., 2018). *SNHG8* acts as a molecular sponge for *miR-152* which was shown to

target *c-MET* (Yang et al., 2018). Mesenchymal-epithelial transition receptor (c-MET), also known as hepatocyte growth factor receptor (HGFR), is a tyrosine kinase receptor which promotes tumorigenesis when activated aberrantly. The overexpression of *c-MET* is correlated with poor prognosis in several cancer types including EC (Li et al., 2015b, Moosavi et al., 2019, Liang and Wang, 2020).

Other lncRNAs promoted EC proliferation and invasion by directly interacting with tumorigenic factors such as EZH2, mTOR, VEGFA. These lncRNA were found significantly upregulated in type I EC as well as several EC cell lines: prostate cancer associated transcript 1 (*PCAT1),* deleted in lymphocytic leukemia 1 (*DLEU1*), and testis developmental related gene 1 (*TDRG1*). Although *PCAT1* expression among EC patients was heterogenous, lower PCAT1 expression correlated with higher survival rate suggesting that *PCAT1* expression can serve as a prognosis biomarker of EC (Zhang et al., 2020). The overexpression of *PCAT1* lncRNA was associated with E-cadherin downregulation and EZH2 upregulation suggesting that *PCAT1* promotes EC invasion via EMT (Zhang et al., 2020). *PCAT1* lncRNA was shown to interact with EZH2 via chromatin immunoprecipitation (ChIP) assay indicating that *PCAT1* may act through chromatin remodeling mediated by EZH2 (Zhang et al., 2020). *DLEU1* lncRNA was shown to interact directly with mTOR leading to the activation of PI3K/AKT mTOR pathway and enhanced tumorigenesis (Du et al., 2018). Downregulation of *DLEU1* in vitro inhibited cell proliferation and migration as well as decreased mTOR expression and downstream effectors (Du et al., 2018). *TDRG1* lncRNA overexpression promoted EC tumorigenicity by directly interacting with the angiogenic factor vascular endothelial growth factor A (VEGFA) (Chen et al., 2018).

Several lncRNAs such as *NEAT1*, antisense lncRNA *AC002454.1*, *LINC01279*, lncRNA *TC0101441*, *MALAT1*, ovarian adenocarcinoma amplified lncRNA (*OVAL*), HOX transcript antisense intergenic RNA (*HOTAIR*), and steroid receptor RNA activator (*SRA*) were not discussed in this review given that there are recent review articles about lncRNAs in endometriosis and endometrial cancer (Smolle et al., 2015, Wang et al., 2020). Table 3 provides a summary of our current knowledge on the lncRNAs just discussed, including their regulation and proposed role in endometrial cancer.

Concluding remarks, future research

Several research efforts carried out genome-wide analysis of differentially expressed lncRNA in tissues obtained from the endometrium from women with endometrial pathologies compared to control group. Hundreds of lncRNAs are differentially expressed but the role of each is not well defined. For instance, RNA sequencing analysis of human endometrial tissue obtained from normally cycling women during the proliferative and secretory phases, specifically the window of implantation, reported 516 differentially expressed lncRNAs (Sigurgeirsson et al., 2017). Nuclear enriched abundant transcript 1 (*NEAT1*) was one of the most differentially expressed lncRNAs (Sigurgeirsson et al., 2017). However, identification of differentially expressed lncRNAs is not enough to understand their functional roles in the menstrual cycle. Further characterization studies are needed to understand the physiological and functional roles of these cycle-specific lncRNAs in the

endometrium. Current research endeavor must focus on identifying biomarkers that can improve the success rate of embryo implantation after IVF procedures as well as the diagnosis and prognosis of endometrial pathologies. It is evident as we further our understanding on the regulation and role of lncRNAs in the endometrium, we will deepen our understanding on normal and abnormal endometrial physiology which will lead to new diagnostic and therapeutics based upon the biology of these regulatory RNAs.

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Table 1:

The role of lncRNA in endometrial physiology

Condition	lncRNA	Role	References
Normal endometrium	*H19*	• Acts as competing endogenous RNA (ceRNA) for miR *let-7* and regulates several *let-7* targets • Expression in the endometrium is cyclical • Sex steroid hormones regulates *H19* expression though discrepant	Ariel et al., 1997 Adriaenssens et al., 1999 Kallen et al., 2013
	LINC473	• Imperative role in HESC decidualization • Directly regulated by STAT3 transcription factor • *LINC473* Knockdown negatively impacts decidualization and receptivity markers such as *PRL, IGFBP1, PGR, FOXO1,* and *HOXA10;* mechanism is not clear	Liang et al., 2016
	HOXA11 antisense	• Expression is cyclical in human endometrium and peaks during late proliferative phase • Downregulated upon P4 treatment • Could be acting through transcriptional interference to block *HOXA11* transcription	Chau et al., 2002
	PTENP1	• Acts as ceRNA and regulates the expression of *PTEN* • Expression is cyclical in human endometrium and peaks during late secretory phase and early pregnancy	Takamura et al., 2020
	HK2P1	• Acts as ceRNA to regulate the expression of *HK2* • Upregulated during in vitro decidualization	Lv et al., 2018

Table 2:

The role of lncRNA in endometrial disease

Condition	lncRNA	Role	References
Implantation failure	*H19*	• Downregulated during the mid-luteal phase in women with recurrent implantation failure • Downregulated in embryonic chorion tissue from women with spontaneous abortion • Acts as ceRNA for *let-7* to regulate *ITGB3* expression • Knockdown impaired trophoblast adhesion and invasion in vitro	He et al., 2019 Zeng et al., 2017 Kallen et al., 2013
	PTENP1	• Downregulated in women with unexplained fertility • Facilitate apoptosis of endometrial epithelial and decidual cells to allow embryo implantation and invasion through PTEN regulation	Takamura et al., 2020
Preeclampsia	*HK2P1*	• Downregulated in women with severe preeclampsia	Lv et al., 2018
Endometriosis	*UCA1*	• Downregulated in ectopic lesions compared to matched eutopic endometrial tissue of women with ovarian endometriosis. • Downregulated in patients' serum compared to healthy control • Can serve as a diagnostic and prognostic biomarker • Regulation and function in endometriosis are not reported	Huang et al., 2019a
	MEG3-210	• Acts as a chromatin-interacting lncRNA and ceRNA • Interacts with Galectine-1 • Downregulated in eutopic endometrial tissue in women with endometriosis compared to control group; mechanism of action is not clear	Liu et al., 2020 Ghafouri-Fard and Taheri, 2019
	MALAT1	• Acts as ceRNA to regulate the expression of ZEB1 and ZEB2 transcription factors • Upregulated in ectopic lesions compared to matched eutopic endometrial tissue and control group	Liang et al., 2017 Liu et al., 2019a
	AFAP1-AS1	• Upregulated in ectopic lesions compared to matched eutopic and normal endometrium • Promotes migration and invasion of ectopic endometrial epithelial cells via EMT; mechanism not clear	Lin et al., 2019
	CCDC144NL-AS1	• Upregulated in ectopic lesions compared to matched eutopic and normal endometrium • In vitro knockdown significantly decreased vimentin and MMP9; mechanism not clear	Zhang et al., 2018a
	H19	Controversial: • Downregulated in eutopic endometrial tissue of women with endometriosis; *H19* acts as ceRNA and regulates stromal cell proliferation through *IGF1R* (Ghazal et al., 2015). • Upregulated in ectopic lesions and eutopic endometrial tissue compared to healthy control; *H19* acts as ceRNA and regulates cell proliferation and invasion through *ITGB3* (He et al., 2019)	

Condition	lncRNA	Role	References
		• Upregulated in eutopic endometrial tissue obtained from infertile women with endometriosis compared to control infertile women without endometriosis; *H19* acts as ceRNA and regulates stromal cell invasion and migration through *ACTA2* (Xu et al., 2019b).	

Table 3:

The role of lncRNA in endometrial cancer

Condition	lncRNA	Role	References
Endometrial cancer	*PTENP1*	• Highly methylated in 70% of EC biopsies • Acts as ceRNAs to regulate the expression of *PTEN*	Kovalenko et al., 2018
	FER1L4	• Promotes the expression of *PTEN* and inhibits AKT activation, mechanism not clear. • Downregulated in EC tissue compared to adjacent normal endometrial tissue.	Qiao and Li, 2016
	RP11-395G23.3 & LA16c-313D11.11	• Act as ceRNAs to regulate the expression of *PTEN.* • Downregulated in EC and associated with poor prognosis.	Xin et al., 2015
	NEAT1	• Negatively regulated by P4 • Overexpressed in EC tissue compared to adjacent normal tissue • Promotes cell proliferation, migration and invasion • Acts as ceRNA to regulate *LEF1* and *EZH2*	Huang et al., 2019b. Wang et al., 2019 Li et al., 2016
	H19	• Upregulated in EC tissue samples • Acts as ceRNA to regulate *HOXA10* and *HIF-1A* expression • Promotes EC cell proliferation and migration through EMT	Zhao et al., 2017 Zhang et al., 2018b Zhu et al., 2019
	CCAT1	• Upregulated in endometrial tissues of type I EC and EC cell lines • Acts as ceRNA for let-7 leading to the upregulation of *c-Myc* and *HMGA2*	Treeck et al., 2020 Deng et al., 2015
	SNHG8	• Upregulated in patients with EC and correlated with poor prognosis • Acts as ceRNA to regulate the expression of *c-MET (*aka *HGFR)*	Yang et al., 2018
	PCAT1	• Upregulated in endometrial tissues of type I EC and EC cell lines • Promotes EC invasion via EMT • May act through chromatin remodeling via EZH2 interaction	Zhang et al., 2020
	DLEU1	• Upregulated in endometrial tissues of type I EC and EC cell lines • Promotes cell proliferation and migration through mTOR pathway activation • Interacts directly with mTOR	Du et al., 2018
	TDRG1	• Upregulated in endometrial tissues of type I EC and EC cell lines • Promotes tumorigenesis through interacting with VEGF-A	Chen et al., 2018