Review Article

Long non-coding RNAs in placental development and disease

Trishita Basak, Rupasri Ain

Division of Cell Biology and Physiology, CSIR-Indian Institute of Chemical Biology, Kolkata 700032, West Bengal, India

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Correspondence to: Dr. Rupasri Ain. Division of Cell Biology and Physiology, CSIR-Indian Institute of Chemical Biology, 4, Raja S.C. Mullick Road, Jadavpur, Kolkata 700032, West Bengal, India. Email: rupasri@iicb.res.in.

Abstract: To reconceptualize epitranscriptomics, long non-coding RNAs (lncRNAs) are emerging as future frontiers in the paradigm shift of stereotyped biological science. Long non-coding RNAs (lncRNA) represent a class of endogenous RNA molecules with length greater than 200 nucleotides but not exceeding 100 kilobases that do not encode proteins, yet transcribed by RNA Polymerase II and are poly-adenylated. Unlike protein-coding genes, they exhibit poor interspecies conservation. However, lack of sequence conservation does not imply the lack of function. Indeed, this dearth in evolutionary conservation challenges the functional investigation of lncRNAs. Previously characterized as products of pervasive transcription, recent advances in lncRNA research proposes them as imperative mediators of gene regulation at the transcription and post-transcriptional level. Ever-increasing amount of RNA sequencing data is expanding the lncRNA inventory to fundamentally dissect the architecture of eukaryotic complexity. Over the last two decades a flurry of studies identified quite a few placental lncRNAs. However, given the complexity of placental development, many questions have been raised regarding their biological function. Nonetheless, identification of lncRNAs of placental origin in the maternal circulation throughout pregnancy raised the prospect of lncRNAs being evaluated as prognostic biomarker of trophoblast associated disorders leading to adverse pregnancy outcome. In this review, we summarize key findings on the recent advances in lncRNA research during the development of the feto-maternal organ placenta and dys-regulations of lncRNA functionalities as prime determinants of placenta associated pregnancy complications.

Keywords: Long non-coding RNAs (lncRNAs); placenta; trophoblast; intra-uterine growth restriction (IUGR); pre-eclampsia; gestational diabetes mellitus (GDM)

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Introduction

The central dogma of conventional biological science revolves around the production of futuristic proteins as solitary trans-actors of genomic information. However, completion of human genome sequencing as well as high-throughput sequencing of transcriptome revealed that nearly 98% of the genome generates non-coding transcripts. Thousands of such non-coding RNAs have been reported in drosophila (1,2), C. elegans (3), zebrafish (4), mouse (5,6) and humans (7,8). Of these, long non-coding RNAs (lncRNA) contribute to the largest proportion of the mammalian non-coding transcriptome and play diverse regulatory roles that include gene expression (9,10), differentiation (11-13), development (14,15) as well as pathogenesis of several diseases (8,16) including various types of cancers (17).

In Eutherian mammals, proper fetal growth and development within mother's body is dependent on the ability of the fetus to maintain a balance between the adequate supply of nutrients and simultaneous disposal of waste materials to the maternal circulation. The

organ facilitating this bi-directional exchange process is the placenta (18,19). Placental morphogenesis involves differentiation of the multi-potent trophoblast stem cells into various trophoblast lineages as well as extensive angiogenesis (20-25). Trophoblast cells assume various specialized functions of the placenta throughout gestation. Inadequate development of trophoblast cells results in adverse pregnancy outcome affecting both the fetus and the mother. These include various placenta associated disorders, such as, intra-uterine growth restriction, pre-eclampsia, whose etiologies are not sufficiently understood (26-29).

Placenta harbors a unique epigenome (30-33) exclusive from other somatic tissues of the body. It is therefore likely that long non-coding RNAs would play significant role in trophoblast development leading to a functional placenta. This review is an integrated summary on the prevailing lncRNA research central to the development of the placenta optimized to provide their significance to perinatal medicine.

Long non-coding RNAs

Characteristics of lncRNAs

LncRNAs share many features of protein-coding RNAs, including 5'-capping, splicing, poly-adenylation as well as epigenetic marks in the promoter such as increased H3K4me3 and RNA Pol-II binding site. Interestingly, some lncRNAs possess H3K4me1 marks indicating transcription from active enhancer sites (34). Non-polyadenylated lncRNAs are found predominantly in the nucleus. Absence of lncRNA homolog across species indicates lack of sequence conservation. However, sequence conservation in promoter regions of lncRNAs is similar to protein-coding transcripts (34,35). Folding of lncRNAs are rather complex and they form secondary and tertiary structures to serve their functions (36). Owing to their vast numbers, many of newly discovered lncRNAs are poorly characterized with respect to their functions.

Classification of lncRNAs

There are many reviews (37-39) on classification of lncRNAs as classification eases hypothesis-driven research on function of newly discovered lncRNAs. LncRNAs are primarily classified based on (I) genomic locations, (II) functions.

Depending on the genomic locations with respect to the protein-coding genes, lncRNAs can be categorized into the following biotypes:

(I) Long intergenic non-coding RNA (lincRNA): This group of lncRNAs does not intersect with the coding region of any gene. Indeed, they are encoded in between reported protein-coding genes.
(II) Divergent lncRNA, also called pancRNA (promoter associated non-coding RNA): They are transcribed from the opposite strand of the same promoter region of protein coding gene.
(III) Convergent lncRNA: They are transcribed from opposite strands in reverse direction facing each other.
(IV) Intronic lncRNA: They are transcribed from introns.
(V) Overlapping sense lncRNA: They are encoded from sequence overlapping with the sense strand of other gene.
(VI) Overlapping anti-sense lncRNA: They are encoded from sequence overlapping with the anti-sense strand of other gene.
(VII) Enhancer lncRNA: They are transcribed from enhancer regions of other genes and may be expressed as either uni or bi-directional transcripts.

Functions of lncRNAs

Experimentally determined functions of lncRNAs include modification of the chromatin, regulation of transcription and RNA processing, regulation of imprinting and formation of ribo-nucleoprotein complex. There are many elegant reviews that detail functional classification of lncRNAs (40-42). We will briefly describe the functional classification here. Depending on the molecular function lncRNAs can be categorized into the following archetypes (*Figure 1*):

(I) As signals: Due to their cell type-specific as well as unique spatiotemporal expression pattern, lncRNAs may integrate developmental cues and also respond to various biological stimuli and thus function as molecular signals in a variety of developmentally regulated processes. Examples of such lncRNAs include (I) linc-p21 (43) and PANDA (44), which are induced by DNA damage; (II) ROR lncRNA induced by Oct-4 depletion (45) in human iPS cells, (III) plant lncRNA, COLDAIR and COOLAIR are induced by cold and can silence the flowering locus C transcription and promotes Polycomb occupancy

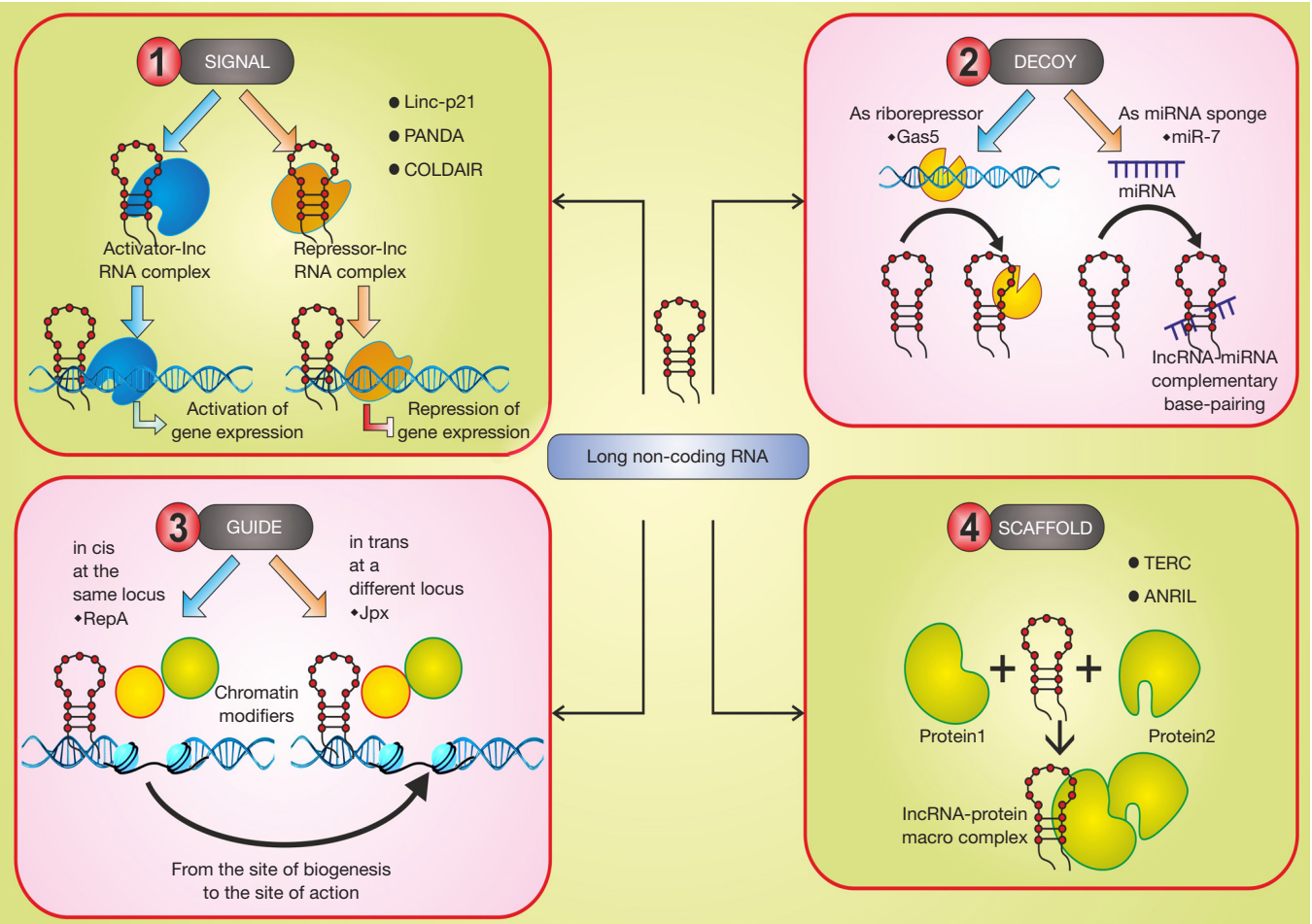

Figure 1 Functional classification of lncRNAs. [1] LncRNAs can interact with potential regulator(s) of gene expression to either form a lncRNA-activator or lncRNA repressor complex thereby either potentiating or restricting gene expression. [2] LncRNAs can function decoy by acting either as a ribo-repressor or as a miRNA sponge to trap miRNAs thereby preventing its function. [3] As guide lncRNAs can modulate epigenetic changes in the genome either at the site of production (in *cis*) or at a different site with respect to the site of biogenesis (in *trans*). [4] LncRNAs can function as scaffolds by forming macromolecular complexes with proteins.

in Arabidopsis (46).

(II) As decoys: They act as "molecular sink" by binding to and titrating target proteins such as RNA-binding proteins (RBPs), transcription factors, or chromatin modifiers or a RNA, in particular miRNAs. Examples include (I) Gas5 lncRNA that impart glucocorticoid resistance (47); (II) Cyrano lncRNA act as a miR-7 sponge in embryonic stem cells controlling self-renewal (48).

(III) As guide: They bind to and direct ribonucleoprotein complexes either in cis- or trans- to specific target locations to regulate gene expression. One example of lncRNA acting as cis-guide is lncRNA RepA-mediated PRC2 recruitment and H3K27 trimethylation of the Xist promoter leading to transcriptional induction of Xist (49). One example of lncRNA acting as trans-guide include Jpx lncRNA that trans-activates Xist although the precise mechanism remains elusive (50).

(IV) As scaffolds: They serve as molecular podium on which protein or RNA moieties can be assembled at the same type and space into a macromolecular complex. One example of scaffold is lncRNA is TERC, which is known to assemble telomerase (51).

It is imperative that a single lncRNA might possess multiple functions as described above based on availability

as well as cellular context.

Discovery of lncRNAs

Low abundance, tissue specificity and lack of sequence conservation make lncRNA discovery difficult. Yet, there are a number of cutting edge methodologies that are being used leading to discovery of lncRNAs. These include (I) cDNA library and tiling arrays, (II) high throughput sequencing serial analysis of gene expression (SAGE), (III) RNA sequencing (RNA-seq), (IV) Cap analysis of gene expression (CAGE), (V) Global run-on sequencing (Gro-seq), (VI) 5'-bromo-uridine immunoprecipitation chase-deep sequencing analysis (bric-seq).

cDNA library and tiling arrays

Identification of lncRNAs were done initially by generation and sequencing of cDNA libraries. The Functional Annotation of the Mammalian Genome (FANTOM) consortium led by RIKEN Omics Science Center has provided the largest collection of about 60770 full-length cDNA sequences for several species (52-54) along with a large number of lncRNAs (52-55).

Another classical method to identify lncRNAs is using tiling arrays. In this method, microarray slides, carrying tiled oligonucleotides that can be designed to cover non-repetitive sequences of specific chromosomes or, potentially, the entire genome, are used to hybridize cDNAs. Tiling arrays used to hybridize polyadenylated transcripts from primary human fibroblasts led to discovery of many lncRNAs including HOTAIR. Emergence of next generation sequencing (NGS) technologies made tiling arrays obsolete due to various drawbacks of using microarrays.

High throughput sequencing serial analysis of gene expression (SAGE)

High-throughput analysis of transcriptome was first done through SAGE. It involves generation of SAGE tags (short cDNA sequence) containing restriction enzyme recognition site at the 3' end of transcripts. SAGE tags are concatenated, cloned and sequenced to identify transcripts. LncRNAs in human cancerous tissues were identified across all 22 autosomes and the sex chromosomes using this method (56). SAGE has been replaced by NGS technologies currently as it profiles a larger number of transcripts in greater depth.

RNA sequencing (RNA-seq)

RNA-seq is the most widespread method used for novel lncRNA discovery. Construction of cDNA sequencing library by using random primers on rRNA-depleted transcripts allows sequencing of both poly(A) + and poly(A) – transcripts. Huge number and variety of lncRNAs in mouse ES cells, neuronal precursor cells, lung fibroblasts, and human tissue/cells have been discovered in using RNAseq (57-59). RNA capture sequencing that combines tiling arrays with RNA-seq led to discovery of many lncRNAs in fibroblasts (60).

Cap analysis of gene expression (CAGE)

CAGE allows simultaneous mapping and quantification of 5'-capped RNAs and is an effective tool for the identification of transcriptionally active promoter regions and Pol II-driven transcription start sites (TSS).

Single cell transcriptional profiling can be done using nanoCAGE. Using CAGE, genome wide comparison of transcripts have been done on human and mouse induced pluripotent stem (iPS) cells, embryonic stem (ES) cells, and differentiated cells (61). About 8,000 novel transcripts were thus identified in mice and 4,000 in humans. These were unannotated lncRNAs that overlap with regulatory regions and associate with retrotransposon elements.

Global run-on sequencing (Gro-seq)

GRO-seq method is based on nuclear run-on assay in the presence of Br-UTP labeled nucleotides followed by capture of Br-UTPtagged transcripts with the antibody anti-Br-UTP and subsequently deep sequencing. This method sequences nascent RNAs and thus provides a genome-wide location, orientation, and density of Pol II-engaged transcripts at a high resolution. Using Gro-seq in human ES cells, antisense lncRNA that arise by divergent transcription were discovered (62). GRO-seq analyses have revealed that only a small fraction of lncRNAs produced by divergent transcription is stable as divergent lncRNA transcripts are generally subjected to exosome-mediated degradation (63).

5'-bromo-uridine immunoprecipitation chase-deep sequencing analysis (bric-seq)

In BRIC-seq endogenous transcripts are labeled by adding 5'-bromo-uridine (BrU) to cell culture media. From isolated total RNAs, BrURNAs are recovered using immuno-purification, which is followed by RT-qPCR or deep sequencing. Fifteen new lncRNAs has been discovered by BRIC-seq on HeLa cells (64). Three of these lncRNAs are involved in cell proliferation and have been named short-

lived noncoding transcripts (SLiTs).

Web resource for lncRNA research

So far, many web-based resources for lncRNAs have been reported. *Table 1* summarizes online resources of lncRNAs.

Placenta

Development of placenta

Placenta is an extra-embryonic transient endocrine organ that develops during pregnancy in Eutherian mammals. It originates by differentiation and morphogenesis from a single layer of trophectoderm that lines the outer layer of blastocyst. Although mouse and human placenta have similarities in terms of function, there exist striking differences in trophoblast cell subtypes in the placenta (*Figure 2*).

In humans, implantation occurs 7–8 days following fertilization. As implantation is initiated maternal uterine endometrial stromal cells (fibroblast-like) differentiate into the decidua by action of hormone progesterone as well as embryonic stimuli. The entire maternal decidua is divided into three regions: decidua basalis, decidua capsularis and decidua parietals (decidua vera). Implantation takes place at the decidua basalis and the basal plate is formed in this region. This can be subdivided into a zona compacta and a zona spongiosa (where the detachment of the placenta takes place following birth). Decidua capsularis lies like a capsule around the chorion. Decidua parietalis is located on the opposite uterus wall.

Following attachment the polar trophectoderm cells of the blastocyst differentiate into multi-nucleated syncytiotrophoblast cells that invade the decidua basalis. Lacunae, formed within the syntiotrophoblast layer, connect with each other and are filled by maternal blood from eroded decidual blood vessels. These events happen around 9–10th embryonic day. Proliferating cytotrophoblast cells of the chorion penetrate into the cords of the syncytiotrophoblast creating the primary trophoblast villi between the 11th and 13th day (86). After the 16th day the mesenchyme, developed from extra-embryonic mesoderm of the chorion fill the villi, which is now called a secondary villi. At the end of the 3rd week, the mesenchyme of the villi differentiates to form connective tissue and blood vessels. Villi that contain differentiated blood vessels are called tertiary villi. The villi morph into a treelike shape consisting of a mesenchymal core containing fetal circulation and are surrounded by a double trophoblast layer, the outer syncytiotrophoblast, and the inner cytotrophoblast. The intravillous vascular network connects with the umbilical-allantoic vessels establishing the fetal placental circulation. The intra-villous space contains the lacunae, which are already sites of intense maternal circulation. The villi that attaches with the maternal tissue are called anchoring villi. The others remain free in the intervillous spaces and are referred to as floating villi. Around 6 weeks of gestation, some cytotrophoblast cells of the anchoring villi leave the placenta and penetrate through the decidua deep into uterine myometrium. These trophoblast cells are called extra-villous cytotrophoblast or invasive trophoblast cells (87). These invasive trophoblast cells also penetrate into the maternal spiral arteries and in effect remodel the spiral arteries making them flaccid and distended. Invasion of trophoblast cells into the decidua basalis, generate several wedge-shaped areas of decidua tissued called placental septa, which appear in month 4 starting out from the maternal (decidua) plate but do not reach the chorionic plate. These septa divide the fetal part of the placenta into 10–38 convex areas composed of lobes called cotyledons. Each cotyledon is made up of 2 or more anchoring villi and their many branches. Part of decidua basalis that is strongly adhered to the fetal placenta (Chorionic villi) is called maternal placenta and is ~0.5 cm thick. During pregnancy, the maternal blood volume increases by about 50% and the uterine blood flow increases 10 to 12-fold. Increase in flow happens due to spiral artery remodeling by trophoblast cells. Inadequate spiral artery remodeling leads to various placenta associated disorders.

In mice, implantation of the blastocyst is initiated by attachment of the mural trophectoderm to uterine epithelial cells. Following implantation trophectoderm cells differentiate and give rise to primary trophoblast giant cells (TGC) that encapsulate the entire conceptus except for the polar trophectoderm (88). The polar trophectoderm differentiates into ectoplacental cone and the extraembryonic ectoderm that form a cylindrical structure. Trophoblast stem cells (TSC) within the ectoplacental cone differentiate into the distinct regions of the junctional zone. TSCs located at the periphery of the ectoplacental cone differentiate into secondary TGCs that line the boundary of the decidua and placenta. TSCs also differentiate into spongiotrophoblast cells that form a sandwiched layer between the secondary trophoblast giant cells and the labyrinth zone. Glycogen cells of the

Table1 Online resources for lncRNAs

Name of the database	Description	URL	Reference
lncrnadb	Reference database containing a list of potential functionally relevant lncRNAs	http://www.lncrnadb.org/	(65)
NONCODE	It is an integrated database dedicated to non-coding RNAs especially lncRNAs (excluding rRNA and tRNAs) of 17 different species	http://www.noncode.org/	(66)
lncRNASNP2	Database for the mutations and single nucleotide polymorphisms affecting lncRNA structure and function	http://bioinfo.life.hust.edu.cn/lncRNASNP2	(67)
Lnc2Meth	A manually curated database to uncovering the biological relationship between lncRNAs and DNA methylation in disease complications	http://bio-bigdata.hrbmu.edu.cn/Lnc2Meth/	(68)
EVLncRNAs	The currently largest database of experimentally validated repertoire of lncRNAs from 77 different species	http://biophy.dzu.edu.cn/EVLncRNAs/	(69)
DES-ncRNA	A knowledgebase containing data-mined information on human lncRNA research	http://www.cbrc.kaust.edu.sa/des_ncrna/home/index.php	(70)
lncATLAS	A comprehensive database of lncRNA localization based on RNA sequencing datasets	http://lncatlas.crg.eu/	(71)
FARNA	A knowledgebase of inferred functions of non-coding RNA transcripts in humans	http://cbrc.kaust.edu.sa/farna	(72)
lncSNP 2.0	A database of the single nucleotide polymorphisms in human lncRNAs	http://bioinfo.hrbmu.edu.cn/LincSNP	(73)
lncVar	A database associated with the genetic variations associated with lncRNAs in 6 different species	http://bioinfo.ibp.ac.cn/LncVar/	(74)
NPInter v3.0	A database of the experimentally verified interaction between lncRNAs and other molecules	https://www.bioinfo.org/NPInter/	(75)
deepBase v2.0	A database decoding the evolution, expression patterns and functions of lncRNAs across 19 species	http://rna.sysu.edu.cn/deepBase/	(76)
lncReg	A comprehensive database highlighting the regulatory networks associated with lncRNAs	http://bioinformatics.ustc.edu.cn/lncreg/	(77)
LNCipedia	A reference database for annotated human lncRNA sequences	https://lncipedia.org/	(78)
LncRNA2Target	A comprehensive database of differentially expressed genes after lncRNA knockdown or over-expression	https://omictools.com/lncrna2target-tool	(79)
lncRNome	A knowledgebase of human lncRNAs	http://genome.igib.res.in/lncRNome/	(80)
lnCeDB	Database of human lncRNAs functioning as competing endogenous RNAs	http://gyanxet-beta.com/lncedb/	(81)
CPC	A machine-based classifier to predict the protein coding potential of input transcript sequences	http://cpc.cbi.pku.edu.cn/	(82)
COME	A multi-featured database for identification and characterization of novel lncRNAs	https://github.com/lulab/COME	(83)
CPAT	An alignment-free logistic regression-based method which discriminates non-coding transcripts from coding transcripts	http://lilab.research.bcm.edu/cpat/index.php	(84)
PNRD	An integrated database for searching, browsing, predicting and visualizing plant non-coding RNA	http://structuralbiology.cau.edu.cn/PNRD	(85)

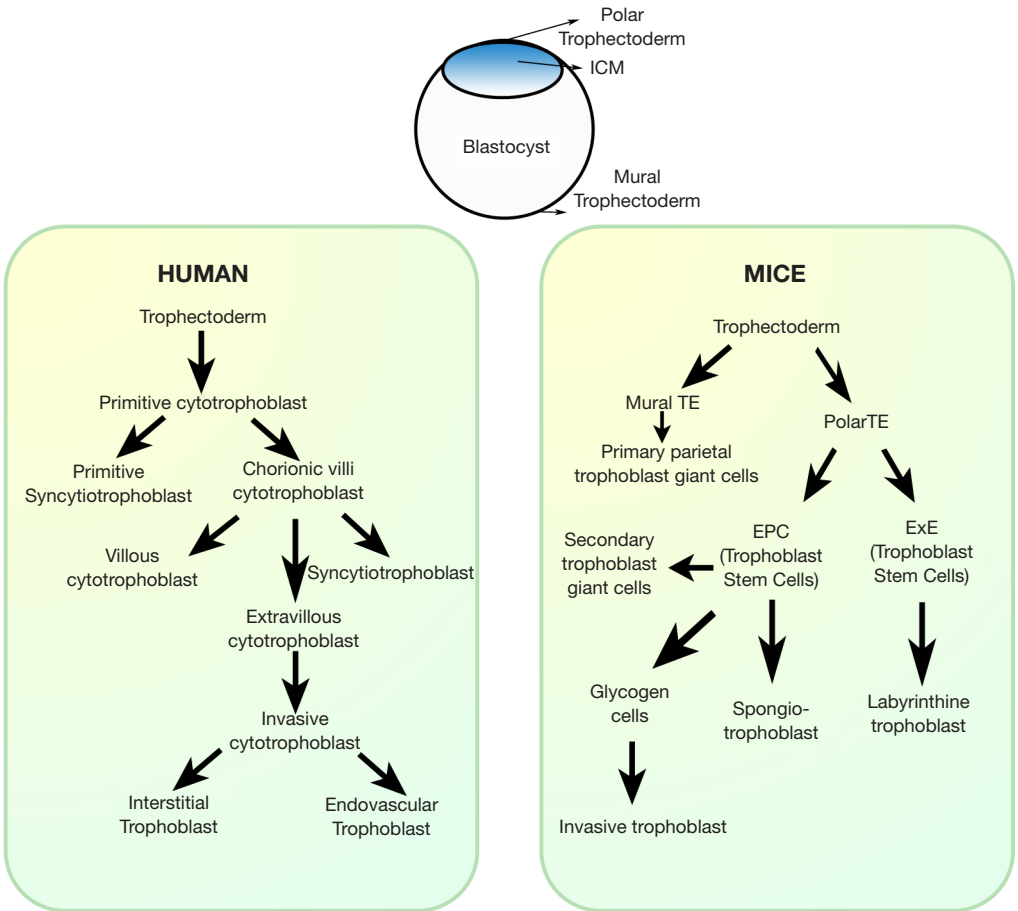

Figure 2 Comparative placentation in human vs. mouse. Flowchart depicting multi-lineage differentiation pathway of human and mouse trophoblast cells during placental development.

junctional zone appear during the last half of pregnancy and are said to be the source of invasive trophoblast cells. Following the chorio-allantoic fusion, TSCs located within the extra-embryonic ectoderm differentiate to labyrinthine trophoblast cells and give rise to the labyrinth zone of the placenta. Two placental zone are evident in mice: junctional zone and labyrinth zone. Labyrinth zone may be compared to fetal placenta in human. Maternal decidua located right above the junctional zone slowly regresses as gestation progresses and part of maternal decidua remains strongly adhered to the placenta till the end of gestation.

Like in humans, a specialized population of trophoblast cells exit the placenta and invade the decidua and arteries. In mice trophoblast invasion is shallow and is limited to decidua, whereas, in rats and hamsters, invasion occurs deep into myometrium resembling that in humans. On time as well as adequate trophoblast invasion is absolutely necessary for healthy progression of pregnancy.

Placenta associated disorders

Pregnancy associated disorders most often arise due to insufficient placental development. Most prevalent of such disorders has been discussed below.

Intra-uterine growth restriction (IUGR)

IUGR is a pregnancy associated complication where the fetus is retarded from attaining its full gender and race specific genetic growth potential *in utero*. World Health Organization has defined low birth weight as one whose birth weight is less than 2,500 gms irrespective of gestational age. IUGR is said to be present in those babies whose birth weight is below tenth percentile of the average for the gestational age and it affects nearly 3–8%

of worldwide pregnancies (89). Normal fetal growth is characterized by cellular hyperplasia followed by hyperplasia and hypertrophy and lastly by hypertrophy alone. Two third of fetal weight gain occurs beyond 24th week of pregnancy.

Types of IUGR

Pathological growth restricted fetuses can be of two types, (I) symmetrical (~30%) and (II) asymmetrical (~80%). Symmetric IUGR fetuses are affected from very early in the phase of cellular hyperplasia leading to less number of total cells. This form of IUGR is often caused by chromosomal abnormalities or congenital infection. Onset of asymmetrical IUGR generally occurs during phase of cellular hypertrophy. This type of IUGR generally develops due to maternal or placental causes extrinsic to the fetus.

Etiology of IUGR

It could be maternal, fetal placental or unknown. Maternal causes include malnutrition before and during pregnancy, maternal diseases, such as, anemia, hypertension, thrombophilia, heart disease, chronic renal disease, and substance abuse, such as, alcohol, smoking, drugs etc. Fetal causes of IUGR may include (I) chromosomal abnormality, which is associated with 8–12% of IUGR infants; (II) infection etc. Placental cause of IUGR most often could be devastating. It is caused by poor uterine blood flow for long time leading to inadequate substrate transfer. Primary cause of compromised placental blood flow has been attributed to inadequate spiral artery remodeling. Unknown causes of IUGR attribute to ~30% cases.

Complications

In the mother, fetal growth restriction per se does not cause any harm except when there is underlying causes like pre-eclampsia, heart disease, malnutrition, which may be life threatening. In the fetus, complications could be (I) antenatal that include chronic fetal distress, fetal death; (II) intranatal that include hypoxia and acidosis and (III) postnatal. Immediate postnatal complications may include asphyxia, hypoglycemia due to shortage of glycogen reserve in the liver, hypothermia, pulmonary hemorrhage, polycythemia, necrotizing enterocolitis due to reduced intestinal blood flow, Intraventricular hemorrhage. Late postnatal complications may include slow growth, which is found primarily in symmetrical growth retarded babies. It has been observed that IUGR babies are predisposed to develop cardiovascular disease, type2 diabetes and hyperlipidemia in adulthood.

Pre-eclampsia (PE)

PE is a multisystem disorder characterized by development of maternal hypertension and proteinuria after 20th week of gestation in a previously normotensive and non-proteinuric mother. Incidence of PE in varies widely from 2–10% worldwide. Pathophysiology of PE encompasses several organs/tissue that include (I) uteroplacental bed, (II) kidney, (III) blood vessels, (IV) liver.

Uteroplacental bed

There is increased evidence of premature ageing of the placenta with red/white infracts visible on the maternal surface of the placenta. There is syncytial degeneration, marked proliferation of cytotrophoblasts, thickening of basement layer, most importantly; normal endovascular trophoblast invasion is severely impaired, trophoblast invasion is shallow and is limited to decidua-myometrial junction. This results in maternal oxidative and endoplasmic reticulum stress. The blood flow to the placenta is decreased remarkably.

Kidney

Glomerular endotheliosis with swelling of endothelial cells and fibrin like deposits occur in the basement membrane. Interstitial cells in between the capillaries proliferate with associated spasm of the afferent glomerular arterioles. The net effects are reduced renal blood flow, glomerular filtration rate and impaired tubular resorption or secretory functions. Recovery is likely to be complete following delivery.

Blood vessels: There is intense vasospasm. Circulation in the vasa vasorum is impaired leading to damage in vascular walls as well as endothelial integrity.

Liver: Periportal hemorrhagic necrosis of the liver occurs due to thrombosis of the arterioles. However, hepatic insufficiency does not occur because of reserve capacity and regenerative ability of the liver cells.

Mitigation of the disease complications following the delivery of the placenta implicates PE as a placenta-associated pregnancy disorder.

Placenta accreta

In this rare disease placenta is directly anchored to the myometrium without any intervening decidua. The probable cause is defective decidual transformation. The condition is usually associated when the placenta is implanted in lower segment or over the previously injured sites as in Caesarean section. Pathological confirmation includes (I) absence of decidua basalis, (II) absence of Nitabuch's fibrinoid layer and (III) carrying degree of penetration of the villi into the muscle bundle (increta) or upto serosal layer (percreta). Approximately 5–10% of post-

partum hemorrhages are caused by placental accreta.

Gestational diabetes mellitus (GDM)

It is defined as abnormal carbohydrate tolerance with onset of or first detected during pregnancy. During normal pregnancy, early in gestation, maternal estrogen and progesterone increase and promote pancreatic β-cell hyperplasia and increased insulin release. In general, glucose tolerance deteriorates during pregnancy, but only 2–3% develops GDM. As pregnancy progresses, increased levels of human chorionic somatomammotropin (hCS), cortisol, prolactin, progesterone, and estrogen lead to insulin resistance in peripheral tissues, primarily in skeletal muscle. The mechanism of insulin resistance is likely a post-receptor defect, since normal insulin binding by insulin-sensitive cells has been demonstrated. The pancreas releases 1.5–2.5 times more insulin in order to respond to the resultant increase in insulin resistance. Mothers with normal pancreatic function are able to meet these demands, whereas, mothers with borderline pancreatic function have difficulty increasing insulin secretion and consequently produce inadequate levels of insulin leading to GDM. Therefore, GDM manifests as delayed or insufficient insulin secretion in the presence of increasing peripheral resistance in mothers. Children born to GDM mothers are at increased risk of metabolic syndrome. Women with GDM is disposed to increased risk of developing gestational hypertension and preeclampsia with long terms effects on developing metabolic syndrome (90) and cardiovascular disorders (91). Methods for diagnosis of GDM include fasting and screening of random plasma glucose in early pregnancy (92), oral glucose tolerance test (93) or using other serum markers like Pregnancy associated Plasma Protein-A (94), Placenta Growth factor (94) and endoglin (95). Therefore, future studies involving the development of lncRNA biomarkers would potentiate early screening and diagnosis of GDM.

LncRNAs as novel regulators of placental development

Till date there is only one report of genome wide identification of lncRNAs in human term placenta (96). However, there are multiple reports of lncRNAs regulating various functions of placenta during development, primarily focusing on trophoblast cell proliferation (97) and invasion (98). Most of the lncRNAs that were found to regulate trophoblast invasion has been implicated in Preeclampsia and will be discussed in that section of this review.

To identify placental lncRNAs during gestational progress, RNA-seq was performed using human term placenta from male and female fetus (95). A pool of 990 putative and 4,463 known lncRNAs corresponding to 2,899 annotated lncRNA loci was identified. Among them, 1,893 were lincRNAs, 2,012 were antisense lncRNAs, 263 were sense intronic transcripts, and 73 were sense overlapping lncRNAs. Sex-bias comparison revealed differentially expressed lncRNAs HAND2-AS1 and XIST with higher propensities in female libraries as compared to RP1-97J1.2, AC010084.1, and TTTY15 solely restricted to male libraries.

LncRNAs in trophoblast cells

A myriad of lncRNAs still remain to be identified as only a limited number of lncRNAs have been independently analyzed in trophoblast cell types (*Figure 3*). These include (I) the paternally imprinted H19, (II) X-inactive specific transcript (Xist) and its anti-sense transcript Tsix (III) intronic SPRY4-IT1 (IV) Metastasis associated lung adenocarcinoma transcript 1 (MALAT1) (V) Potassium voltage gated channel, member 1, overlapping transcript 1 (Kcnq1ot1) (VI) Maternally expressed gene 3 (MEG3) and (VII) HOX Transcript AntIsense RNA (HOTAIR).

H19

It was the first lncRNA discovered in pre-genomic era when scientists were using differential hybridization of cDNA libraries to clone and analyze spatiotemporal gene expression in various tissues. At that time it was classified as mRNA but H19 was found to be an unusual transcript that did not translate into protein despite having a small open reading frame. H19 showed high sequence conservation across mammals, transcribed by RNA polymerase II, capped, spliced and polyadenylated and localized to the cytoplasm. Transgenic H19 mice were prenatal lethal suggesting its role in embryonic development as well as importance of its dosage. As a non-coding RNA H19 remained to be mysterious until the functional characterization of another lncRNAs, Xist, which was also found to be involved in dosage compensation in mammals. H19 has been investigated by numerous investigators and was found to be a prototype of multi-tasking lncRNA.

In the developing human placenta, H19 is initially expressed from both paternal and maternal alleles.

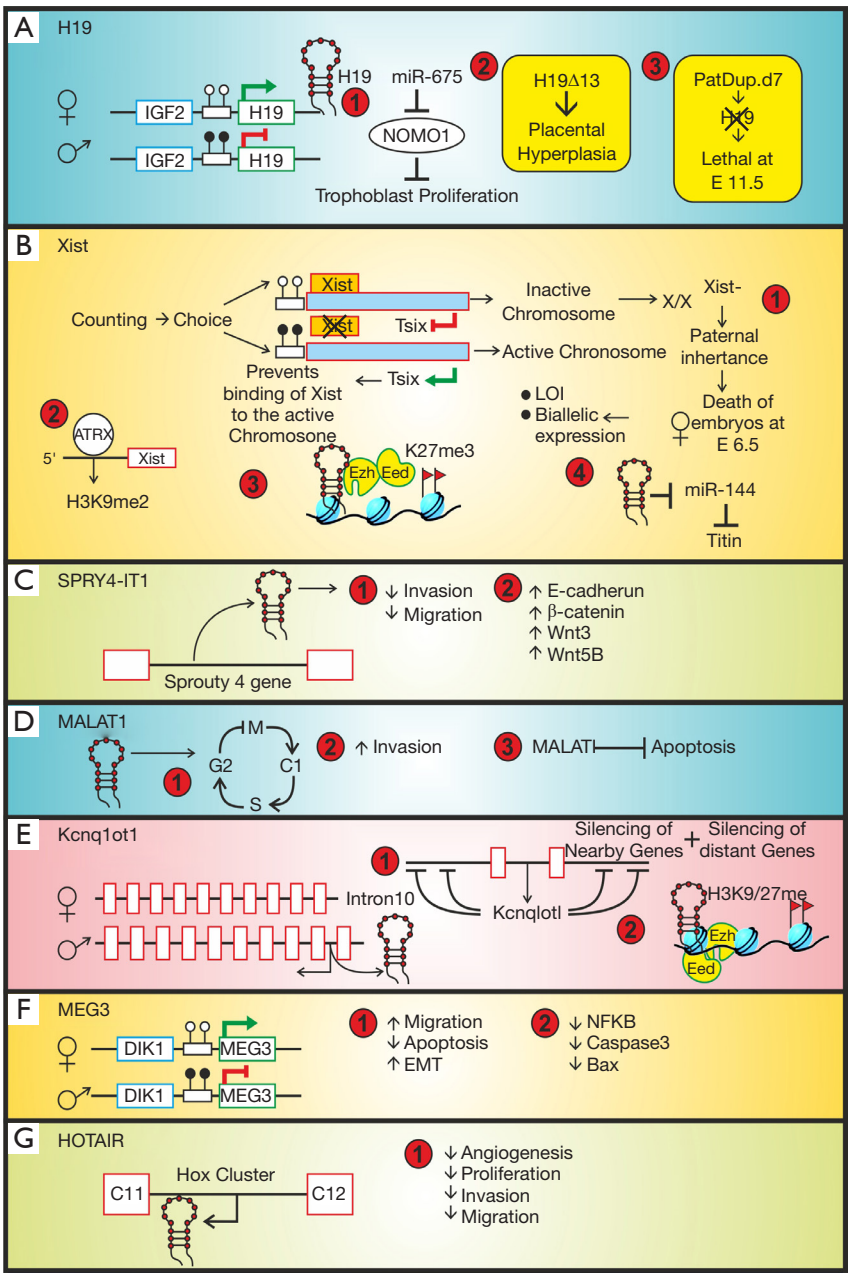

Figure 3 Most studied lncRNAs in trophoblast development. (A) Hypomethylation (unfilled circles) of H19 promoter results in H19 synthesis from the maternal allele which encodes miR-675 to inhibit NOMO-1. Deletion of H19 results in the formation of hyperplastic placenta. Embryos with a PatDup.d7 mutation in chromosome 7 die at embryonic day 11.5 due to lack of H19. (B) Xist is expressed from and binds the inactive X-chromosome. Binding of Xist to active X-chromosome is prevented by Tsix. [1] Paternal inheritance of Xist mutation results in death of female embryos at E6.5, Xist [2] recruits ATRX to its 5' H3K9 hotspot thereby nucleating histone modifiers, [3] interacts with Ezh and Eed to regulate H3K27 trimethylation, [4] inhibits miR-144 and regulates trophoblast cell proliferation and invasion. (C) SPRY4-IT1 negatively regulates trophoblast invasion and migration via down regulation of E-cadherin, β-catenin, Wnt3 and Wnt 5B. (D) MALAT-1 prevents G_2/M transition in trophoblast cells and regulates trophoblast invasion and apoptosis. (E) Kcnq1ot1 synthesized from intron 10 of Kcnq1 gene regulates [1] imprinting of both nearby and distant genes in the placenta and [2] regulates H3K9/27 methylation by recruiting chromatin modifiers like Eed and Ezh. (F) Hypomethylation of Meg3 (unfilled circles) allows its production from the maternal allele. Meg3 increases EMT and migration of trophoblast cells and decreases apoptosis via down regulation of NFkB, caspase 3 and Bax. (G) HOTAIR regulates trophoblast angiogenesis, proliferation, invasion and migration.

Interestingly, functional imprinting restricting H19 to the maternal allele starts around 10 weeks of gestation implies that H19 imprinting is established during the development of the placenta (99,100). H19 was reported to be abundant in the RNA from cultured cytotrophoblast cells isolated from human term placenta (101). Interestingly, bi-allelic expression of H19 was found to be exclusive to the extra-villous cytotrophoblasts while the mesenchymal stromal cells retained the mono-allelic expression pattern throughout placental development (102). Mouse embryos harboring a paternal duplication of chromosome 7 (PatDup.d7) lack H19, die at 11.5 dpc and lack spongiotrophoblast (103). H19Δ13 mouse model of overgrowth harboring a deletion of 13kb encompassing the H19 gene and the H19-IGF2 imprinting control region IC1 resulted in 45% increase in placental weight at E19. Owing to loss of imprinting of the adjacent IGF2 gene on the maternal chromosome, these hyperplastic placentas transported 20–35% less glucose and system A amino acids with a 20% reduction in transporter genes like Slc2a3 and Scl38a4 (18,104).

Cai and Cullen [2007] (105) demonstrated that miR675 is encoded by H19 in human keratinocytes. Gao *et al.* [2012] (106) demonstrated that H19 inhibited human trophoblast cell proliferation via encoding miR-675 that down regulated Nodal Modulator 1 (NOMO1) protein expression. They hypothesized that low expression level of H19 in placenta leading to down regulation of miR-675 that targets NOMO1 and interferes with nodal signaling results in excessive trophoblast cells proliferation and thus marks early-onset severe preeclampsia. Interestingly, forced induction of H19 in mouse ESCs predisposes them to trophoblast lineage commitment and Cdx2 expression even under high Oct3/4 level (107). Functional relevance of H19 lncRNA in trophoblast development is quite evident from the foregoing discussion yet more insights into the mechanism of action remains to be evaluated.

X-inactive specific transcript (Xist) and Tsix

Indispensable function of lncRNA Xist in trophoblast development was first demonstrated by elegant experiments done by Mugford *et al.* [2012] (108). Lack of any apparent open reading frame in the 17kb transcript of Xist along with its nuclear localization affirmed its categorization as lncRNAs (109). Xist regulates the process of X-chromosome inactivation (XCI) in females. Xist is expressed from and coats the inactivated X chromosome (Xi) in cis. Paternally inherited X chromosome is inactivated by imprinting (methylation) in the female embryos' extra-embryonic lineage, which gives rise to trophoblast cells, during mouse embryogenesis. Extra-embryonic ectoderm (ExE) cells failed to express CDX2, a marker for trophoblast progenitor cells, at embryonic day 6.5 in female embryos harboring a paternally derived Xist mutation. These embryos subsequently die due to poor trophoblast development. As expected, spongiotrophoblast progenitors, which originate from the CDX2 positive trophoblast stem (TS) cells located within the developing ectoplacental cone, also failed to be maintained. It was further demonstrated that mutation in Xist leads to complete reversal of imprinted XCI patterns in TS cells derived from X/XXist-embryos. These results highlight the importance of Xist mediated dosage compensation for the maintenance of trophoblast progenitors (108). These results were in line with a previous report by Marahrens *et al.* (110). They showed that transgenic mice with a paternally derived mutation of Xist (X/XXist-) resulted in inheritance dependent female-specific embryonic lethality at E6.5 due to loss of imprinting, biallelic X chromosome expression in the trophoblast and perturbed trophectodermal development. In developing mouse embryo evidence of imprinted XCI is first observed by the two-cell stage (111). "Random XCI" was observed in the epiblast originated from the inner cell mass of the blastocyst. Embryonic lineage reactivates and undergoes a second round of XCI (112), and this time in a "random" way such that paternal and maternal X chromosome have an equal chance of becoming the inactive X (Xi). In contrast, the extra-embryonic cells retain imprinted XCI. It has been demonstrated by Erwin *et al.* [2012] (113) that mutually exclusive binding of Cdx2 and Oct4 to Xist underlies the switch between imprinted and random XCI.

Genetic and biochemical studies initiated identified numerous proteins in Xist interactome (114-117). Accumulating reports hint towards the role of Xist in epigenetic regulation by chromatin modification (118). Interestingly, the 5' region of Xist has been identified as a potential nucleation centre for H3K9 dimethylation which serves as a nucleation center for repressive histone and chromatin modifiers (119). At the molecular level, Xist aids in the formation of facultative heterochromatin on the inactive X chromosome by various mechanisms. Firstly, Xist transiently recruit polycomb group protein Eed, Ezh2 and Suz12 to trophoblast giant cells developed from cultured blastocysts thereby initiating H3-K27 methylation (120,121). In addition, ChIP analysis established a stable association of another protein ATRX with the H3K9

dimethylation hotspot 5' of Xist in an *ex vivo* model of trophoblast stem (TS) cell differentiation (122). As growing research focus on Xist mediated dosage compensation, regulation of trophoblast specific function by Xist is limited. However, a recent report suggests that XIST potentiates titin expression by inhibiting miR-144 to monitor human trophoblast cell proliferation and invasion (123). To complement the functions of Xist, the expression of Tsix is temporarily regulated to authorize felicitous XCI. Indeed, Tsix assists in methylation of the Xist gene promoter on the maternal allele thereby repressing Xist function and activating the maternal X chromosome.

Murine Xist is positively regulated by Jpx lncRNA and negatively regulated by the antisense Tsix lnc transcript (124-127). Tsix is essential for preventing the inactivation of the maternally inherited X chromosome in extra-embryonic lineages where imprinted X-chromosome inactivation (XCI) occurs. Tsix expression becomes monoallelic and is associated with Xist repression on the active X chromosome (Xa, maternal) at the onset of X inactivation (124). Tsix expression is lost around day 9.5 and Xist repression on the Xa is maintained by other mechanisms, including DNA methylation (128,129). These observations suggest that Tsix regulates the initiation of Xist silencing, but is dispensable for its maintenance.

Unlike in mice, X-inactivation is not imprinted in human placenta and Tsix is not required for XCI (130,131). Due to ethical reasons, XCI is not studied well in early human development. Trans-differentiation of embryonic stem cells to TS cells and chorionic villi hybrid with mouse cells are generally used models for XCI studies. Data on XCI in human placenta point towards random skewed XCI patterns (132).

SPRY4-IT1

SPRY4-IT1 is a 708bp intronic lncRNA encoded from the Sprouty4 gene localized in chromosome 5q31.3 and expressed abundantly in human placenta (133). Expression of this lncRNA increases in preeclamptic placentas (134). In-vitro studies using immortalized first trimester human extravillous cytotrophoblast cells HTR-8/SVneo uncovered the role of this lncRNA in trophoblast cells. SPRY4-IT1 is inhibitory to EMT-associated events like invasion and migration of trophoblast cells. Indeed, the proliferative capacity, and migratory phenotype of HTR-8/SVneo harboring over-expressed SPRY4-IT1 was suppressed as compared to their respective controls. SPTY4-IT1 also induced E-cadherin and β-catenin expression with a concomitant decline in vimentin levels. A reversal of these effects was observed upon down-regulation of SPRY4-IT1 (134,135). RNA immunoprecipitation experiment identified the cytoplasmic RNA binding protein HuR as a novel SPRY4-IT1 interacting protein which actually modulates β-catenin at the post-transcriptional level. Additionally, knockdown of SPRY4-IT1 in HTR-8/SVneo cells diminished WNT3 and WNT5B transcript by 58% and 39% respectively. Altogether, SPRY4-IT1 modulates the canonical Wnt/ β-catenin pathway to inhibit epithelial to mesenchymal transition in trophoblast cells (135). Therefore, SPRY4-IT1 mediated EMT dysfunction of trophoblast cells might serve as a promising therapeutic option to suppress PE.

Metastasis associated lung adenocarcinoma transcript-1 (MALAT-1)

MALAT-1, the first lncRNA associated with human disease was identified in a subtractive hybridization-based screening of transcripts associated with metastasis and patient survival in stage-I non-small cell lung cancer (136). It is a 6.5 kb polyadenylated and unspliced lncRNA localized to human chromosome 11q13 and mouse chromosome 19qA. In contrast to the traditional cleavage and polyadenylation mechanism, the 3'-end of MALAT-1 lacks the poly (A) structure. MALAT-1 over-expression was found in severe forms of invasive placentation, such as placenta accreta (137) prompted investigation on MALAT-1 in trophoblast development. Using first trimester choriocarcinoma cell line, JEG-3, it was demonstrated that shRNA mediated silencing of MALAT-1 leads to suppression of proliferative ability and arrested them in G_0/G_1 phase of the cell cycle thereby reducing the number of G_2/M phase cells. Reduction in MALAT1 expression also triggered the apoptotic pathway and intensified the percentage of apoptotic cells with elevated levels of cleaved caspase-3, cleaved caspase-9 and PARP-1 in addition to impeded migration and invasion in JEG-3 cells (9). Another study suggested that the invasion capability of BeWo, JAR and JEG-3 cells were significantly suppressed after transient knockdown of MALAT-1 (137).

Potassium voltage gated channel, member 1, overlapping transcript 1 (Kcnq1ot1)

Originally named as LIT1, Kcnq1ot1 was identified in a

screen of differentially expressed transcripts dictating the genomic organization of the imprinting cluster on human chromosome 11p15 (138). The expression of Kcnq1ot1 begins at the two-cell stage in parallel to Xist and the dynamics of inactivation differs between embryonic and extra-embryonic lineages (139-141). It is a 91kb stable, unspliced, antisense lncRNA expressed from the paternal chromosome (142,143). The transcription start site of Kcnq1ot1 is positioned on the imprinting control region (ICR) located in the intron 10 of KCNQ1 gene which houses 8 other protein-coding genes that expressed from the maternal allele (126). Epigenetic silencing by this lncRNA extends over 400kb *in cis* in the mouse embryo. Surprisingly, the silenced region spreads over 780kb in the placenta suggesting a critical role of Kcnq1ot1 in placental development.

Similar to Xist, Kcnq1ot1 defines a distinct nuclear domain *in cis* to epigenetically inactivate genes within the domain boundary. Interestingly, this domain is larger in the placenta as compared to the embryo suggesting a greater number of silenced genes in the placental cluster (143). Although Kcnq1ot1 is transcribed in all tissues, it is only in placenta, where both nearby (Cdkn1c, Kcnq1, Slc22a18, and Phlda2) and distantly placed genes (Cd81, Osbp15, Ascl2, and Tssc4), on either side of the Kcnq1 ICR, are imprinted, whereas embryonic tissues show imprinting of only nearby genes. Interestingly, truncation of the Kcnq1ot1 transcript led to up regulation of all imprinted genes in the domain (144). Kcnq1ot1 RNA, although present at a lower level in placenta, was found to interact with chromatin very strongly in placenta than in other tissues. In placenta, Kcnq1ot1 RNA was found to interact with both PRC2 complex members (Suz12 and Ezh2) and G9a histone methyl transferase (142). In addition, permissible imprinting of the maternally expressed genes by shRNA mediated silencing of Kcnq1ot1 in embryonic and extra-embryonic stem cells specifies that the act of transcription and not post-transcriptional effect of Kcnq1ot1 is critical to early development imprinting maintenance (145).

Maternally expressed gene 3 (MEG3)

Also known as the gene trap locus 2 (Gtl2), Meg3 was identified as a differentially expressed transcript in mouse embryonic development during paternal transmission of lacZ insertion in distal chromosome 12. Despite having multiple ORFs in numerous spliced version, lack of strong Kozak sequence of these ORFs entailed Meg3 gene functions as RNA (146). Later, the human homolog MEG3 was identified as an imprinted gene which is preferentially expressed from the maternal allele (147). Mapped 90kb apart from DLK1 to human chromosome 14q32.3 and mouse distal chromosome 12, MEG3 is the first imprinted gene to be identified at these particular chromosomal loci.

Research initiative undertaken to elucidate Meg3 functionality in placental development is rather limited. The initial clue highlighting Meg3 as a placenta associated lncRNA came from studies exploiting Meg3 knockout mice model carrying a 5.9 kb deletion extending 300 bp of the Meg3 promoter till exon five of the gene. Indeed, transmission of the truncated gene from the maternal chromosome emanated in prenatal death of the pups accompanied by silencing of the maternally expressed genes in 18.5 dpc placenta without affecting the growth of the organ (148). Additionally, *in vitro* data using two different human trophoblast cell lines HTR8/Svneo and JEG-3 suggest that RNA interference-based silencing of endogenous MEG3 impedes migration and enhances apoptosis of trophoblast cells. Also, ectopic over-expression of MEG3 in these cells decreased NFκB, caspase 3 and Bax expression leading to decrease in apoptosis and enhanced their migration (149). In addition, elevated MEG3 also contributes to Smad7 mediated epithelial to mesenchymal transition in HTR8/Svneo by enhancing the expression of mesenchymal bio-markers like N-cadherin, vimentin and slug followed by simultaneous reduction in E-cadherin (150). Epigenetic loss of imprinting at the intergenic MEG3 DMR bestowed "Temple syndrome" in a Caucasian female born to healthy, non-consanguineous parents. Clinical features manifest IUGR, low-birth weight, hypotonia, developmental delay, premature puberty, short stature and truncal obesity (151).

HOTAIR

HOTAIR was identified in a tiling array based characterization of the transcriptional landscape of HOX loci using human adult primary fibroblast (152). HOTAIR is a 2.2 kb lncRNA encoded in the anti-sense direction between HoxC11 and HoxC12 of the HoxC gene cluster on human chromosome 12q13.13. Murine HOTAIR shares about 58% sequence similarity to human HOTAIR (153). Interestingly, the absence of HOTAIR in non-mammalian vertebrates is indicative of its mammalian specific function (154). HOTAIR represents a classical paradigm of *trans*-acting guide lncRNA.

HOTAIR transcript shows a progressive decrease

throughout human gestation. HOTAIR suppresses placental angiogenesis and was found to play a critical role in suppressing the proliferation, invasion, migration and tube formation capacity of HUVECs by functionally down regulating the expression of vascular endothelial growth factor A (97). A lncRNA PCR array identified HOTAIR as a target of YY1 in primary trophoblast cells obtained from first trimester placenta (155). Another report using the same microarray approach highlights that a zinc-finger mRNA binding protein tristetraprolin decreases the half-life of HOTAIR in villous tissue samples (156). A combination of *ex vivo* trophoblast explants culture with *in vitro* gain and loss of HOTAIR function in HTR8/Svneo cells identified HOTAIR as an inducer of the invasive potential of trophoblast cells by activating the PI3K/AKT signaling pathway with a surge in MMP2 levels (155). However, a contradictory report using the same cell line highlights HOTAIR as an inhibitor of trophoblast invasion (157). Therefore, additional investigations are necessary to reconfirm the role of HOTAIR in trophoblast biology.

Other lncRNAs associated with trophoblast development and placental biology

In addition to the lncRNAs described above, numerous novel lncRNAs, which regulate placental function, has been reported.

X-linked lncRHOFX1 is expressed robustly in the trophectoderm and primitive endoderm cells of human blastocyst-stage embryos. It is also abundantly expressed in trophoblast progenitors differentiated from human pluripotent stem cells *in vitro*. It is the first identified lncRNA which provides an excellent concoction of innate immunity dependent viral suppression to early placentation (158).

High expression of lncRNA TERRA (telomeric repeat containing RNA) has been documented in human term placenta. This lncRNA maintains the length of telomeres in human placenta. Promoter hypomethylation in addition to elevated TERRA expression is associated with alternative lengthening of telomeres (ALT) in the absence of hTERT (159).

A novel lncRNA GPR1AS was identified in human GPR1-ZDBF2 intergenic loci on chromosome 2q33.3. This lncRNA displayed placental specific expression, being encoded from the paternal allele. Transcribed in an antisense orientation from introns 2 of GPR1, GPR1AS is devoid of any ZDBF2 exon in the human genome. GPR1AS is a human ortholog of mouse Zdbf2 linc and the epigenetic regulations between GPR1 and ZDBF2 cluster is well conserved between human and mouse (160).

Another study brought forward two long intergenic lncRNAs LINC00629 and MIR503HG between HPRT1 and PLAC1 loci on chromosome Xq26, a region which houses other genes critical to placental development. MIR503HG was exclusively expressed by the placenta and LINC00629 was also highly expressed by placenta and other reproductive tissues like ovary, testis and cervix. Impaired migration and invasion of human choriocarcinoma JEG-3 cells upon ectopic over expression of LINC00629 and MIR503HG highlights its role in human reproduction (161). Another antisense lncRNA GNG12-AS1 mapped to the DIRAS3 locus is biallelically expressed in the placenta (162).

LncRNAs associated with PE

Numerous research works have been initiated to explore global alteration of lncRNAs during the development of PE. Accumulating evidences hint towards equilibrium between pro-proliferative and anti-proliferative lncRNAs as crucial determinants of PE etiologies thereby making lncRNAs potential candidates in PE pathogenesis. Indeed, modulation of trophoblast function and vasculogenic remodelling of the spiral arteries by lncRNAs is imperative to majority of the PE cases observed. Global dynamicity of lncRNA transcripts in PE placentas have been reported by two independent research groups using microarray analysis. The first study involving 32 early onset PE (EOPE) and age-matched preterm control caesarean pregnancies identified 15,646 up-regulated and 13,178 down-regulated lncRNAs as references for future functional studies (163). Another microarray profile exploiting six PE and five normal placenta revealed differential expression of 738 lncRNAs out of which 259 were up regulated and 479 were down regulated in PE cohorts. Validation of this result in 40 PE and control placenta contributed to the fact that dysregulation of three of these highly expressed lncRNAs (LOC391553, LOC284100, CEACAMP8) attributed to PE (164). Other lncRNAs reported in the context of PE pathophysiology include (I) H19, (II) SPRY4-IT1, (III) MALAT1, (IV) MEG3 and (V) HOTAIR.

H19

Loss of the H19 gene imprinting in the placental tissues

of pre-eclampsia patients (100,165) and positive regulation of trophoblast invasiveness by H19 prompted interest in role of H19 imprinting in the etiology of PE. This LOI studies were further extended using pyrosequencing-based analysis of global DNA methylation followed by methylation sensitive high resolution melting in PE placentas obtained from a cohort of Chinese patients. This technique demonstrated intensified global DNA methylation along with hypermethylation in the promoter region of H19 with elevated DNMT1 levels followed by a concomitant decrease in H19 transcripts in placentas from early-onset PE (EOPE) patients (106). Likewise, placentas isolated from severe PE (sPE) subjects harboured significant methylation at a single CpG site within exon1 of H19. This observation was further reinforced by treatment of JEG-3 cells with 5-aza-2'-deoxycytidine which reverberated in a surge of H19 transcripts followed by perturbed proliferation, migration and invasion (166). Another study involving 193 PE and 201 control subjects correlated H19 rs217727 single polymorphism to the risk of PE susceptibility (167). Interestingly, a recent study suggested the role of endocrine disrupting chemicals in the imprinting of H19. This pyrosequencing based population study involving 179 pregnant women with 11 phthalate and 8 phenol exposures during the first trimester of pregnancy alters H19 methylation levels resulting in hypomethylation of H19 DMR (168).

SPRY4-IT1

A study involving 25 preeclamptic and normal pregnancy patients suggested 2.8-fold increase in SPRY4-IT1 level in PE placentas as compared to normal ones. In HTR-8/SVneo trophoblast cells SPRY4-IT1 knockdown enhanced the cell migration and proliferation, and reduced the response of cells to apoptosis. As expected, reverse effect was observed by ectopic over expression of SPRY4-IT1 (134). Same group reported three years later that SPRY4-IT1 levels were robustly up regulated in PE placentas as compared to controls in a study involving 50 nulliparous PE and normal pregnancy patients (135). Using HTR-8/SVneo trophoblast cells, it was demonstrated that over expression of SPRY4-IT1 suppressed trophoblast cell migration and invasion, whereas reduced expression of SPRY4-IT1 prevented the epithelial mesenchymal transition (EMT) process. RNA immune-precipitation experiment showed that SPRY4-IT1 bound directly to HuR and altered β-catenin expression in HTR-8/SVneo cells. Furthermore, WNT3 and WNT5B expression were changed following transfection of HTR-8/SVneo with SPRY4-IT1 (135).

Metastasis associated lung adenocarcinoma transcript-1 (MALAT-1)

Only one report has been published so far that highlighted the role of MALAT-1 in trophoblast dysfunction associated with the pathophysiology of PE. A significant reduction in MALAT-1 levels was in preeclamptic placentas as compared to healthy subjects. This data along with *in vitro* control of MALAT-1 in JEG-3 cells suggests that mitigated MALAT1 might contribute to shallow trophoblast invasion which is a hallmark of PE (98). Lower endogenous MALAT1 levels were reported in mesenchymal stem cells (MSCs) isolated from the umbilical cords of PE patients as compared to healthy donors suggesting impaired apoptosis, enhanced proliferation, migration and invasion and immunosuppressive properties of MSCs in PE (169).

Maternally expressed gene 3 (MEG3)

Decreased proliferation of extra-villous trophoblast cells contributing to incomplete spiral artery remodelling is paramount to PE. Two different studies report significant MEG3 down regulation in placental samples from PE patients as compared to normotensive healthy donors (149,150). MEG 3 is also suggested as a potential candidate regulating vascular smooth muscle cell (VSMC) loss from the maternal uterine spiral arteries by regulating crucial processes of vascular transformation like VSMC migration and apoptosis (170). Overall, depleted MEG3 might potentiate inappropriate spiral artery remodelling in PE subjects which makes it a prime therapeutic target for early intervention of PE.

Hox Transcription Antisense RNA (HOTAIR)

A single report involving 23 severe PE and normotensive patients elucidate that HOTAIR transcript level is increased significantly in placental subjects from PE patients as compared to normal healthy subjects (157). However, additional studies are necessary to delineate the importance of this lncRNA in the pathophysiology of PE. In contrast to HOTAIR, the extent of HOTTIP (a newly discovered lncRNA mapped to the 5' end of the HoxA cluster on chromosome 7p15.2) is drastically lowered in PE placenta. Reduction of cellular proliferation through G_0/G_1 arrest by

interference of HOTTIP transcript exemplifies synergistic function amidst varied mechanism of two lncRNAs from the same HOX gene but different HOX cluster in the commencement of PE (171).

Other lncRNAs associated with PE

Several novel lncRNAs have been reported to be differentially regulated during the development of PE. Of these, a highly conserved 418bp lncRNA uc.187, 1.7kb RPAIN (transcript variant 12 of RPA interacting protein), CCAT1, DLX-AS1 and lncDC were robustly up regulated in PE placenta (49,172,173). *In vitro* studies suggested that the proliferative potential and invasiveness of HTR8/Sv-neo cells was enhanced upon silencing uc.187 in accordance with the increase in MMP-2/9, Ki-67 and decrease in TIMP-1. Knockdown of uc.187 inhibited apoptosis with a concomitant down regulation of cleaved caspase-3 and up regulation of Bcl-2 (172). In addition to the anti-proliferative role of RPAIN in HTR8/Sv-neo cells, it modulates trophoblast invasion and apoptosis via the adjacent complement protein C1q thereby providing another therapeutic target for PE diagnosis (174). LncRNA DLX-AS1 is an excellent example of non-coding RNA cross-talk via inhibitory interaction with mir-365c in HTR8/Sv-neo cells to modulate GADD45A in PE (173).

In contrast to the lncRNAs that are over expressed in PE, the level of lnc-ATB, SNHG5, PGK1P2, HK2P1, EGFR-AS1, TUG1, PVT1, linc00473 and MVIH dropped in PE placenta as compared to healthy pregnant biopsies (175-179). Inhibition of endogenous lnc-ATB, PVT1 and TUG1 in HTR8/Sv-neo cells reduced proliferation, migration, invasion and tube formation (175-177). Whereas TUG1 and PVT1 interacted with the polycomb group protein EZH2 to epigenetically silence RND3 and ANGPTL4 transcription respectively, MVIH synergized with Jun-B to modulate trophoblast proliferation (165,176,177). SNHG5 partly controls the miR-26a-5p/N cadherin axis to perturb trophoblast functions in PE (178). Linc00473 particularly interacted with LSD1 to inhibited TFPI2 and EGFR-AS1 inhibited the JAK/STAT pathway during PE progression (179,180). Enthrallingly, PGK1P2 in conjunction with PGK1 and HK2P1 in conjunction with HK2 is imperative to precarious decidualization by acting as competing endogenous RNA (ceRNA) in PE (181,182).

The existence of multiple susceptible loci harboring placentation related genes in PE etiologies is common for decades. Reports from Finnish PE populations exemplify a lncRNA on chromosome 4q35.1 from intron 3 of STOX2 in the regulation of alternative splicing of the gene. Mutation of this lncRNA prematurely truncates the functional protein to introduce a stop codon thereby deleting the C-terminal domain of the STOX2 protein (183).

LncRNAs associated with IUGR

A limited number of lncRNAs have been studied till date in correlation to IUGR pathophysiology. These include (I) H19, (II) Nuclear paraspeckle assembly transcript 1 (NEAT1), and (III) Kcnq1ot1.

H19

Till date H19 is most extensively studied lncRNA in IUGR pathogenesis. Due to their role in cell proliferation, differentiation and trophoblast development, H19/IGF2 imprinted loci prompted investigations on their expression and function in the context of placental disorders. However, the effect of H19 on trophoblast and cancer cell proliferation is rather controversial. H19 has been reported to promote cell proliferation in various cancer types that include colorectal (184), cervical (185), pancreatic ductal (186) carcinoma and many other types of cancers. In contrast, in human trophoblast cells H19 inhibits cell proliferation (106,187). In line with its effect on trophoblast cell proliferation, H19 promoter hypomethylation has been reported in IUGR placentas from normotensive mothers but not in PE (188,189). Zuckerwise *et al.* [2016] (190) reported contrasting data showing that H19 lncRNA is significantly decreased in placenta from pregnancies with FGR. However, whether these data were from normotensive and hypertensive mothers were not clear from this report. Hypomethylation of the H19 imprinting control region (ICR) in the paternal alleles of the placenta were also reported in ethanol induced mouse model of IUGR (191). In addition, mutation in the telomeric imprinting centre region resulting in biallelic expression of H19 was observed in Silver Russel Syndrome (SRS), a congenital syndrome characterized by severe IUGR (192-194). Nonetheless, the mechanisms by which H19 may impart IUGR phenotype have yet to be elucidated fully.

Nuclear paraspeckle assembly transcript 1 (NEAT1)

NEAT1 was identified using microarray approach to

screen for ubiquitously expressed nuclear enriched polyadenylated RNA transcripts in human fibroblast WI-38 and lymphoblastoid cell-line GM00131 cell lines (195). A single report highlights the importance of NEAT1 in the etiology of IUGR. A PCR-select cDNA subtraction using placental biopsies from 12 IUGR and 12 control singleton pregnancy subjects reported a surge in NEAT1 transcript in IUGR patients. In-situ signal of NEAT1 lncRNA was intensified in the nuclei of villous trophoblast cells from IUGR term placenta as compared to normal placentas. Indeed, NEAT1 co-localized with the DBHS protein PSPC1 and the punctate NEAT1 staining is concomitant to the increased number of paraspeckles in IUGR samples Therefore, an upsurge in NEAT1 level would perhaps promote rapid paraspeckle formation to hyperedit mRNAs in IUGR cases (196).

Potassium voltage gated channel, member 1, overlapping transcript 1 (Kcnq1ot1)

Direct reports suggesting the role of Kcnq1ot1 in IUGR is limiting. However, the Kcnq1 imprinting centre houses two growth inhibitory genes CDKN1C and PHLDA2. Indeed, two novel centromere directed *cis* maternal chromosomal duplication extending 0.88 and 1.13Mb from the middle of Kcnq1 gene respectively display contrasting growth phenotype where 0.88Mb duplication represents the growth retarded phenotype (197).

LncRNAs associated with placental accreta

The only lncRNAs reported to be associated with accrete is Metastasis associated lung adenocarcinoma transcript-1 (MALAT-1). To identify differentially expressed genes, which may impair placentation resulting in placenta previa, increta/percreta (I/P) placental tissues from I/P and non-increta/percreta (non-I/P) sites were concomitantly collected from patients undergoing Cesarean hysterectomy (138). Annealing control primer-polymerase chain reaction (ACP-PCR) followed by cloning and sequencing confirmed over expression of MALAT-1 in I/P samples. Further investigation on the function of MALAT-1 in BeWo, JAR and JEG-3 trophoblast cell lines using siRNA down-regulation led to compromised invasion ability. Thus it was inferred that MALAT-1 directs advanced invasive placentation leading to placenta accreta. However, as discussed earlier that placenta accreta is associated in defective decidualization and in effect decidua basalis is absent in most cases. Therefore, more detailed analysis of origin of placenta accreta and involvement of lncRNAs in pathogenesis remained to be explored.

LncRNAs associated with GDM

Transcriptomic profiling using GeneChip mouse genome microarray in E18 placental samples of GDM mouse model developed by gestational period high-fat diet identified 52 differentially expressed lncRNAs in GDM placentas as compared to control chow fed placentas (198). Hyperglycemic mice model induced by streptozotocin injection however caused H19 hypomethylation resulting in increase H19 transcripts in E10.5 placentas due to adverse uterine environment (199). In GDM patients, the expression level of lncRNA MALAT1 was higher than the controls and correlated with both lncRNA p21 and lncRNA H19 (200). Based on their abundance in GDM, circulating lncRNAs, XLOC_014172 and RP11-230G5.2 have been postulated to act as novel biomarkers in GDM patients as fingerprint for the risk of macrosomia outcome (201).

LncRNAs associated with recurrent miscarriage (RM)

In contrast to infertility, recurrent miscarriage or spontaneous abortion is defined by consecutive loss of pregnancy before 20 completed weeks of gestation. A microarray analysis using chorionic villi tissue samples from 5 RM cases identified 1449 differentially expressed lncRNAs compared to normal pregnancies. Functional analysis of the various pathways regulated by these differentially expressed lncRNAs brought forward ECM-receptor interactions, apoptosis, endocrine and TGF-β signalling as potential deregulated pathways in RM (202). Another attempt exploiting human lncRNA array in decidual samples from sixteen pairs of pregnancies correlated to early spontaneous abortions (SA) and induced abortions (IA) highlighted inflammation and infection pathways as pathophysiological factors underlying SA (203). Interestingly, the level of HOTAIR was reported to be relatively lower in RM trophoblast cells. This together with the *in vitro* data described earlier makes HOTAIR a potential therapeutic target for RM (155) (*Table 2*).

Conclusions

With increasing global scale initiatives to identify non-

Table 2 Differentially regulated lncRNAs in various placental diseases

Disease	Status	Name of the lncRNAs	References
PE	Down regulated	H19, MALAT1, MEG3, LNC-ATB, TUG1, MVIH, EGFR-AS1, PGK1P2, PVT1, SNHG5, Linc00473	(98,106,149,150,165,175,177-182)
	Up regulated	SPRY4-IT1, HOTAIR, Uc.187, RPAIN, DLX6-AS1	(135,157,172-174)
IUGR	Up regulated	H19, NEAT1	(190,196)
Placenta accreta	Up regulated	MALAT1	(137)
GDM	Up regulated	H19, MALAT1	(199,200)

PE, pre-eclampsia; IUGR, intra-uterine growth restriction; GDM, gestational diabetes mellitus; MALAT1, metastasis associated lung adenocarcinoma transcript 1 (MALAT1); NEAT1, nuclear paraspeckle assembly transcript 1; HOTAIR, HOX Transcript Antlsense RNA.

coding components of the genome, new lncRNAs are being identified and this plethora is likely to be amplified in future. The foregoing discussion provided a survey of the present state of knowledge regarding the discovery, functions, and mechanisms of action of the lncRNAs in context of placental development and disease. The increasing rate of pregnancy associated complications demands major insights towards molecular regulation of placental development and origin of its malfunction leading to devastating pregnancy associated disorders. LncRNAs have gained widespread attention in recent years as potentially new regulators of placental development and function and also been proposed as novel entrants in therapeutics. Although many lncRNAs have been systemically identified, present research is limited to a small range of lncRNAs. Therefore, a large number of lncRNAs and specific mechanism of their action as well as the cross-talk between individual lncRNAs still remains to be explored during the morphogenesis of the placenta.

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Footnote

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