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The role of microRNAs in the regulation of critical genes and signalling pathways that determine endometrial receptivity

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Review Article

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Summary

Endometrial receptivity is the ability of the endometrium to accept embryos. Thus, endometrial receptivity dysfunction is an important factor leading to embryo implantation failure. A good endometrial receptivity provides a suitable environment for embryo implantation, improving the embryo implantation rate. The "implantation window" stage, or the receptive stage of the endometrium, is regulated by various hormones, genes, proteins and cytokines, among which microRNAs (miRNAs) and their target genes have a regulatory effect on endometrial receptivity. This review outlines the relationship between endometrial receptivity and pregnancy, the mRNAs and related signalling pathways that regulate endometrial receptivity, and the regulatory role of miRNA in endometrial receptivity, providing a deeper understanding of the regulatory mechanisms of miRNA on endometrial receptivity in humans and animals and reference for the endometrial receptivity-related research.

Introduction

Endometrial receptivity is the ability of the endometrium to allow normal embryo implantation. It is the intricate process undertaken by the endometrial tissue to prepare for blastocyst implantation and pregnancy initiation. A good endometrial receptivity provides opportunities for embryo attachment, invasion and development, culminating in a new individual and species continuation (Neykova *et al.*, 2022; Lessey and Young, 2019). Embryo implantation occurs during the implantation window, a mid-secretory phase of the menstrual cycle. Many molecular pathways involving hormones, adhesion molecules, cytokines and growth factors synchronize the implantation window during this phase. Thus, a loss of synchronisation or failure to achieve endometrial receptivity can lead to a miscarriage or infertility (Governini *et al.*, 2021; Blanco-Breindel *et al.*, 2023).

Mammals successfully implant embryos only when the endometrium is in a receptive state, during which the endometrial epithelial cells (EECs) are reshaped to accept embryo implantation. Generally, embryo implantation requires a two-way communication between the blastocyst and the receptive endometrium, with poor quality blastocysts or defective endometrial receptivity leading to an implantation failure (Makrigiannakis *et al.*, 2021; Paulson and Comizzoli, 2021; Bui *et al.*, 2022). During the early implantation stage, the EECs undergo epithelial-mesenchymal transition (EMT) to prepare for subsequent embryo implantation. Subsequently, the endometrial stromal cells (ESCs) undergo decidualization to create a favourable developmental environment for the embryo. Based on this, the EMT and decidualization are crucial for maintaining a good endometrial receptivity. A good endometrial receptivity is the biological basis for embryo implantation and normal development (Crha *et al.*, 2019; Cai *et al.*, 2022). Therefore, improving endometrial receptivity is a key factor in increasing pregnancy rates.

This article provides an overview of mRNA and its related signalling pathways that regulate endometrial receptivity, as well as the regulatory role of miRNA in endometrial receptivity. It provides an important reference for a deeper understanding of the molecular regulatory mechanisms of miRNA on human and animal endometrial receptivity.

mRNAs regulating endometrial receptivity

Homeobox (HOX)

HOX is important in cell proliferation and differentiation and is the main regulatory factor for cell identity and fate during embryonic development (Steens and Klein, 2022; Smith *et al.*, 2019). For example, *HOXA10* can bind to the E-cadherin promoter region and directly regulate its expression, thereby improving endometrial receptivity, which subsequently increases embryo

adhesion and implantation (Zhang *et al.*, 2017). Besides, the mechanism of metformin treatment, which enhances endometrial receptivity, is associated with the upregulation of the *HOXA10* gene (Cheng *et al.*, 2022). Notably, *HOXA9*, *HOXA11* and *HOXD10* are involved and highly expressed during endometrial receptivity. The embryo implantation rate decreases when the *HOXA9*, *HOXA11* and *HOXA10* genes are silenced in the mouse uterus (Kara *et al.*, 2019; Xu *et al.*, 2014). In addition, the expression levels of *HOXA10* and *HOXA11* are significantly reduced in women with endometriosis compared to the non-endometriotic controls, which potentially significantly affects endometrial remodelling and the expression of endometrial receptivity markers (Jana *et al.*, 2013). Therefore, a high expression of *HOX* genes, including *HOXA10*, *HOXA9*, *HOXA11* and *HOXD10*, can serve as markers for achieving endometrial receptivity.

Interleukin (IL)

ILs are lymphokines excreted by the white blood cell and other immune cell (Khan *et al.*, 2023). Among them, *IL-1* is positively correlated with endometrial receptivity in patients with polycystic ovary syndrome (PCOS); thus, it is a therapeutic target for PCOS to improve endometrial receptivity (Zhao *et al.*, 2019). In addition, the production of *IL-1β* promotes oocyte maturation, fertilisation, and endometrial receptivity, thereby promoting embryo implantation (Rehman *et al.*, 2015). Specifically, *IL-1β* is highly expressed in the mid-luteal phase of implantation and positively correlated with endometrial thickness, serum estradiol and progesterone levels, implying that *IL-1β* improves endometrial receptivity, which promotes embryonic development (Wang *et al.*, 2018). Additionally, *IL-10* promotes the attachment of BeWo spheroids to Ishikawa cells and increases *HOXA10* expression through phosphorylation of signal transducer and activator of transcription 3 (STAT3), thereby promoting endometrial receptivity (Wang *et al.*, 2018). *IL-33* promotes endometrial receptivity by increasing *HOXA10* expression through the phosphorylation of STAT3. Decreased intracellular *IL-33* impairs endometrial receptivity in women with adenomyosis (He *et al.*, 2022). In summary, the positive correlation between *IL* members, such as *IL-1*, *IL-1β*, *IL-10* and *IL-33*, and endometrial receptivity suggests that *IL* promotes endometrial receptivity and embryo implantation.

Leukaemia inhibitory factor (LIF)

LIF is a cytokine in the *IL-6* family, which regulates the adhesion characteristics of EECs, enhances endometrial receptivity, and promotes embryo implantation and pregnancy (Camargo-Diaz *et al.*, 2017). Based on in vitro and in vivo studies on the effect of the Cnidium officinale Makino (CoM) roots on endometrial receptivity using embryo implantation models, CoM enhances the adhesion of JAr cells to Ishikawa cells by activating the expression of *LIF* and integrin, thereby enhancing endometrial receptivity (Chung *et al.*, 2019). Hajipour et al. (2021) also revealed that the upregulation of *LIF* is one of the mechanisms by which sildenafil citrate enhances endometrial receptivity. In addition, various bioactive substances such as paeoniflorin increase the adhesion of JAr cells derived from the trophoblastic ectoderm to Ishikawa cells in the endometrium by activating *LIF* expression, which enhances endometrial receptivity (Eun-Yeong *et al.*, 2019; Park *et al.*, 2021; Choi *et al.*, 2017). Therefore, activating *LIF* expression enhances the adhesion between JAr cells and Ishikawa cells, promoting endometrial receptivity.

Vascular endothelial growth factor (VEGF)

Vascular endothelial growth factor (*VEGF*), or vascular permeability factor, is a highly specific endothelial cell mitogen and the most important factor regulating angiogenesis (Dvorak, 2000). *VEGF* stimulates embryo implantation by promoting embryonic development, improving endometrial receptivity, and enhancing the interaction between developing embryos and the endometrium (Guo *et al.*, 2021; Zarei *et al.*, 2019). For example, Bu Shen Zhu Yun Decoction activates the mitogen-activated protein kinase (MAPK) signalling pathway by upregulating *VEGF* and *VEGF* receptor-2, thereby improving endometrial receptivity and embryo implantation rate (Li *et al.*, 2019). In addition, Tiaojing Zhu Yun Formula improves endometrium receptivity and facilitates embryo implantation of controlled ovarian hyperstimulation (COH) rats by upregulating *VEGF* and enhancing the phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt) signalling pathway (You *et al.*, 2022a). Endometrial macrophages modulate uterine receptivity by regulating the expression of *VEGFA*, thereby affecting embryo implantation (Wang *et al.*, 2016). In summary, the upregulation of *VEGF* improves endometrial receptivity and promotes embryo implantation and development.

Other mRNAs that regulate endometrial receptivity

Other mRNAs are also closely related to endometrial receptivity in various species such as mouse, rat, human and goat (Table 1). Their expression trends are also clear; thus, they can serve as potential biomarkers of endometrial receptivity.

miRNA-mediated regulation of the key signalling pathways in endometrial receptivity

MicroRNAs (miRNAs) are a class of non-coding single-stranded ribonucleic acid (RNA) molecules, typically 20-24 nt in length encoded by endogenous genes. MiRNA-encoding genes are transcribed by RNA polymerase II to generate primary transcripts, which are then processed into small RNAs of approximately 21 nucleotides by RNase III endonucleases DROSHA and DICER. All miRNAs are loaded into Argonaute protein in RNA-induced silencing complex and act as post-transcriptional regulators by binding to the 3'-untranslated region of mRNA (Stavast and Erkeland, 2019; Michlewski and Caceres, 2019). MiRNAs play an important regulatory role in endometrial receptivity and the formation of related factors during embryo implantation (Liang *et al.*, 2017; Shekibi *et al.*, 2022; Goharitaban *et al.*, 2022). Notably, miRNAs regulate endometrial receptivity-related key genes to promote or suppress endometrial receptivity by activating or inhibiting signalling pathways, such as PI3K/Akt, extracellular signal-regulated kinase/mechanistic target of rapamycin (ERK/mTOR), NF-κB, Wnt/β-Catenint and LIF/STAT3 signalling pathways.

Regulation of gene expression by miRNA via the PI3K/Akt signalling pathway

The PI3K/Akt signalling pathway plays a crucial role in cell functions such as proliferation, adhesion, invasion, migration, metabolism and survival through phosphorylation or dephosphorylation. It also plays a role in angiogenesis, endometrial receptivity and successful embryo implantation (Shen *et al.*, 2023). In addition, acupuncture and moxibustion improve endometrial angiogenesis by activating the PI3K/Akt signalling pathway, and

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Table 1. Other mRNAs regulating endometrial receptivity

Gene name	Species	The role of mRNA	Change in expression	References
GRIM-19	mouse	Regulating endometrial receptivity and embryo implantation by regulating adhesion, cell apoptosis, and immune tolerance	down	(Yang *et al.*, 2017)
TLR2/6	mouse	Inhibiting endometrial receptivity by reducing the in vitro adhesion between trophoblast spheres and endometrial cells	down	(Sanchez-Lopez *et al.*, 2014)
MUC-1	mouse	*MUC1* expression is negatively correlated with fertility	down	(Shokrzadeh *et al.*, 2019)
αVβ3 and αVβ5	mouse	Promoting the process of embryo endometrial adhesion	up	(Choi *et al.*, 2017)
MMP9	rat	Promoting endometrial invasion and lesions to suppress endometrial receptivity	down	(Cheng *et al.*, 2022)
ILK	human	By activating Wnt/β-Catenin signalling improves the formation of endometrial receptivity	up	(Chen *et al.*, 2020)
HB-EGF	mouse/human	Positive correlation with endometrial thickness	up	(Shokrzadeh *et al.*, 2018; Sutaji *et al.*, 2023)
OPN	mouse/rat	Promoting blastocyst formation and embryo implantation	up	(Liu *et al.*, 2013; Zarrin *et al.*, 2020)
COX-2	mouse	Expression is negatively correlated with endometrial receptivity	down	(Yu *et al.*, 2021)
ITGβ3	human	Participate in cell adhesion and cell surface-mediated signalling, and play an important role in regulating endometrial receptivity	up	(Luo *et al.*, 2021)
EMX2	human	High expression in the endometrium often leads to abnormal development of the endometrium	down	(Luo *et al.*, 2021)
FOXA2	human	Potential regulatory genes affecting uterine receptivity, blastocyst implantation, and stromal cell decidualization	up	(Kelleher *et al.*, 2019)
PODXL (PCX)	human	*PODXL (PCX)* is a key negative regulator of human endometrial epithelial receptivity for embryo implantation	down	(Paule *et al.*, 2021)
PGR	mouse	Control epithelial and stromal progesterone reactivity and epithelial cell differentiation to provide normal uterine receptivity and subsequent embryo attachment	up	(Gebril *et al.*, 2020)
BCL2L15	goat	*BCL2L15* is the key regulator of endometrial receptivity in goats, regulating the endometrial receptivity via the STAT1 pathway	up	(Yang *et al.*, 2020)
HIF-1α	human	*HIF-1α* is positively associated with endometrial receptivity by regulating PKM_2	up	(Liang *et al.*, 2023)
IGF1R	mouse	Promote embryo attachment	up	(Kang *et al.*, 2015)

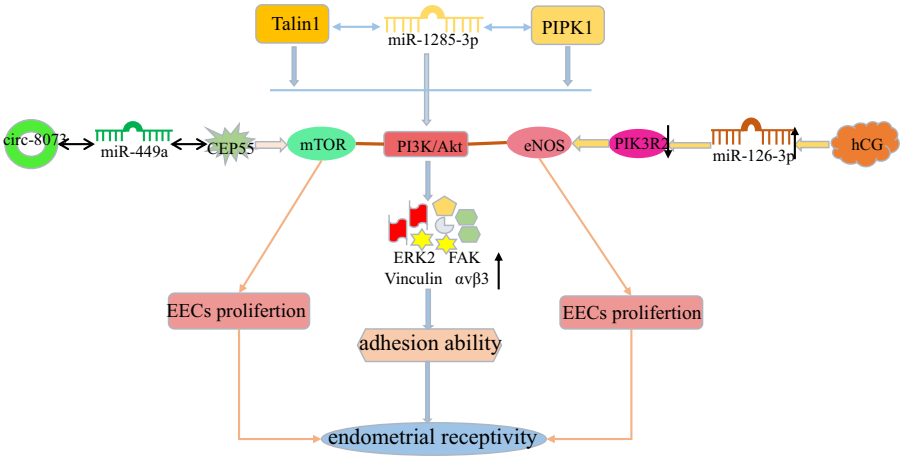

Figure 1. The mechanism of miRNA in regulating endometrial receptivity via the PI3K/AkT signalling pathway. Some miRNAs promote the activation of the PI3K/Akt signalling pathway by regulating the expression of target mRNA, thereby altering the expression of key genes involved in endometrial receptivity, consequently improving endometrial receptivity. The figure is made by WPS, which is a Chinese office software.

increase endometrial receptivity and implantation sites in PCOS rats (Xing *et al.*, 2022). Liu et al. (2018) also revealed that circ-8073 regulates *CEP55* by sponging miR-449a in dairy goat EECs, promoting the proliferation of the EECs via the PI3K/Akt/mTOR pathway, and regulating endometrial receptivity in dairy goat (Figure 1). In addition, Wang et al. (2023) confirmed that human

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chorionic gonadotropin activates the PI3K/Akt/eNOS pathway via the miR-126-3p/*PIK3R2* axis, promoting EEC proliferation and improving endometrial receptivity (Figure 1). Moreover, Talin1 and phosphatidylinositol 4,5-phosphate kinase (*PIPK1*) competitively bind miR-1285-3p to activate the PI3K/Akt signalling pathway. The activation of the PI3K/AkT signalling pathway further promotes the expression of *ERK2*, *FAK* and Vinculin, αvβ3 molecules crucial in the embryo implantation process, promoting the adhesion ability of EECs to the embryo (Li, 2019) (Figure 1). In summary, miRNA promotes the activation of the PI3K/Akt signalling pathway by regulating the expression of target mRNA, which alters the expression of endometrial receptivity key genes, thereby improving endometrial receptivity.

Regulation of gene expression by miRNA via the ERK/mTOR signalling pathway

Various studies have revealed that the mTOR pathway is important in endometrial receptivity (Qi *et al.*, 2022; Niknafs *et al.*, 2022). For example, dexamethasone disrupts endometrial receptivity by altering the expression of miR-223, miR-200a, LIF, Muc1, SGK1 and ENaC via the ERK1/2-mTOR pathway (Shariati *et al.*, 2019). On the contrary, fluhydrocortisone (Hesam *et al.*, 2019) and calcitonin (Shokrzadeh *et al.*, 2018) improve endometrial receptivity by regulating the expression of endometrial receptivity-related genes (*HB-EGF*, *MSX.1* and miRNA Let-7a) and activating the ERK1/2-mTOR pathway (Figure 2). Additionally, Cui et al. (2020) revealed that miR-184 targets and inhibits the expression of *STC2* via the RAS/RAF/MEK/ERK signalling pathway, thereby promoting the expression of FOXM1 and VEGF and apoptosis of EECs, consequently promoting endometrial receptivity in dairy goats (Figure 2). In summary, miRNA promotes endometrial receptivity by activating the ERK/mTOR signalling pathway to regulate endometrial receptivity-related genes.

Regulation of gene expression by miRNA via the NF-κB signalling pathway

Progesterone and melatonin improve endometrial receptivity in mice and cows, increasing their pregnancy rates, which is closely related to the NF-κB signalling pathway (Feng *et al.*, 2022; Guan *et al.*, 2022; Zheng *et al.*, 2022). Notably, high progesterone levels during early pregnancy in cows induce high expression of miR-20b. MiR-20b blocks the NF-κB signalling pathway by negatively regulating *NCOA3* and inhibits the immune response of bovine EECs, crucial in uterine tissue remodelling, changes in uterine immune microenvironment and placental formation (Yang, 2021) (Figure 3). In addition, miR-182-5p activates the NF-κB signalling pathway by negatively regulating the target gene *NDRG1*, which reduces the E-cadherin expression, inhibits endometrial receptivity and causes embryo implantation failure (Yu *et al.*, 2022) (Figure 3).

The NF-κB signalling pathway is also an important pathway regulating inflammation (Capece *et al.*, 2022). Interestingly, enhancing the endometrium inflammatory process reduces endometrial receptivity (Zhang *et al.*, 2021; Pirtea *et al.*, 2021). Therefore, some of the miRNAs in the NF-κB signalling pathway could be regulating the expression of inflammatory factors, interfering with the embryo implantation process, and reducing the ability of the endometrium to receive embryos. In summary, miRNAs often activate the NF-κB signalling pathway, suppressing endometrial receptivity. Therefore, future studies should explore

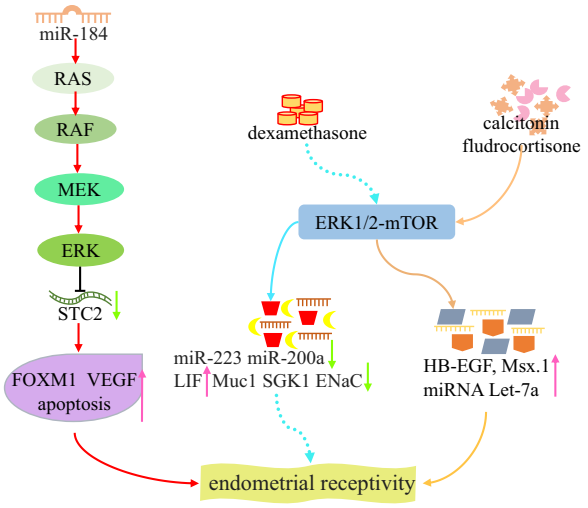

Figure 2. The mechanism of miRNA in regulating endometrial receptivity via the ERK/mTOR signalling pathway. MiR-184 regulates genes associated with endometrial receptivity by activating the ERK/mTOR signalling pathway, thus promoting endometrial receptivity. Some drug treatments regulate the expression of endometrial receptivity-related genes and miRNAs via the ERK/mTOR signalling pathway, consequently altering endometrial receptivity. The figure is made by WPS, which is a Chinese office software.

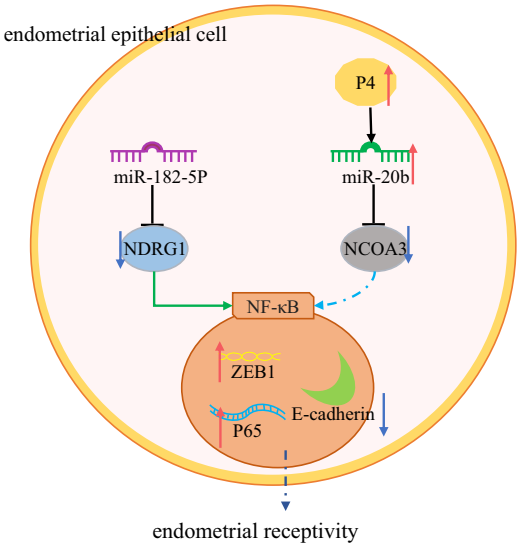

Figure 3. The mechanism of miRNA in regulating endometrial receptivity via the NF-κB signalling pathway. MiRNA typically inhibits target mRNA to activate NF-κB signalling pathway inhibits endometrial receptivity. MiRNA typically inhibits target mRNA to block NF-κB signalling pathway promotes endometrial receptivity. The figure is made by WPS, which is a Chinese office software.

the miRNAs that inhibit the NF-κB signalling pathway to improve endometrial receptivity.

Regulation of gene expression by miRNA via the Wnt/β-catenin signalling pathway

The Wnt/β-catenin signalling pathway is a highly conserved pathway involved in various processes such as cell development, proliferation, differentiation, apoptosis and autophagy. It plays a crucial role in embryonic development and maintaining dynamic homeostasis in the body (Ma *et al.*, 2023; Liu *et al.*, 2023). *Integrin-*

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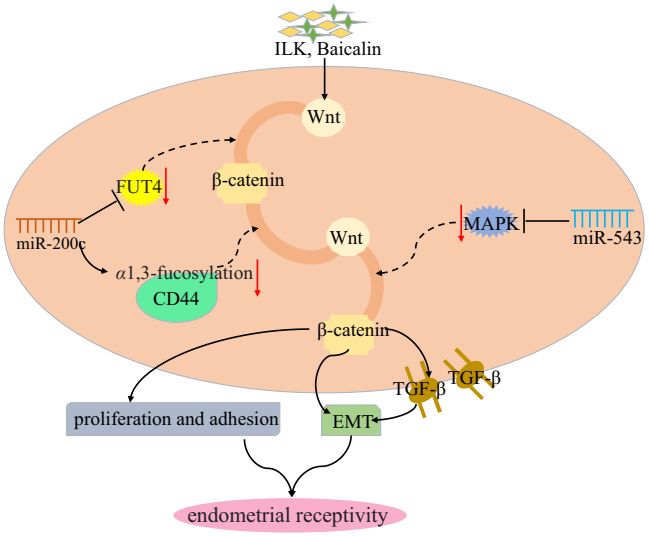

Figure 4. The mechanism of miRNA in regulating endometrial receptivity via the Wnt/β-catenin signalling pathway. MiRNA typically inhibits target mRNA, thereby inactivating the Wnt/β-catenin signalling pathway, leading to the inhibition of endometrial receptivity. The figure is made by WPS, which is a Chinese office software.

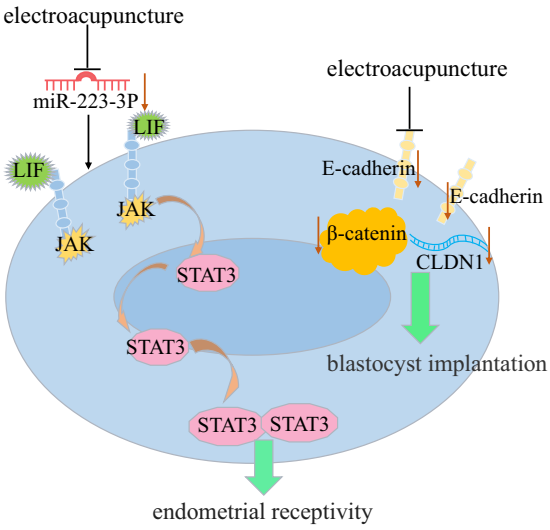

Figure 5. The mechanism of miRNA in regulating endometrial receptivity via the Leukaemia inhibitory factor (LIF)/STAT3 signalling pathway. Electroacupuncture therapy reduces cell adhesion molecules, thereby activating the LIF/STAT3 signalling pathway, which improves endometrial receptivity. Electroacupuncture therapy activates the LIF/STAT3 signalling pathway by inhibiting the expression of miR-223-3p, thereby enhancing endometrial receptivity. The figure is made by WPS, which is a Chinese office software.

linked kinase (ILK) (Chen *et al.*, 2020) and baicalin (Zhang *et al.*, 2015) promote endometrial receptivity and embryo implantation via the Wnt/β-catenin signalling pathway (Figure 4). Zheng et al. (2017) also revealed the miR-200c targeted inhibition of fucosyltransferase IV (FUT4) expression while reducing the glycoprotein CD44 α1,3-fucosylation inactivates the Wnt/β-catenin signalling pathway, leading to endometrial receptivity dysfunction (Figure 4). Besides, miR-543 inhibits *MAPK* expression and inactivates the Wnt/β-catenin pathway, inducing the inhibition of the EMT of ESCs by transforming growth factors β (Wang *et al.*, 2021) (Figure 4). In summary, the Wnt/β-catenin signalling pathway plays an important regulatory role in initiating endometrial receptivity. The miRNAs often activate the Wnt/β-Catenin signalling pathway, promoting endometrial receptivity, or suppress the Wnt/β-catenin signalling pathway, inhibiting endometrial receptivity.

Regulation of gene expression by miRNA via the LIF/STAT3 signalling pathway

The LIF/STAT3 signalling pathway also affects endometrial receptivity (Liang *et al.*, 2018, 2021; Hu *et al.*, 2019). For example, implantation failure in subclinical hypothyroidism rats is related to abnormal LIF/STAT3 signalling (Shan *et al.*, 2019). Generally, COH induces endometrial receptivity dysfunction during the implantation window. However, electroacupuncture therapy reduces cell adhesion molecules such as E-Cadherin, β-catenin and *CLDN1*, which activates the LIF/STAT3 signalling pathway, improves endometrial receptivity, and promotes blastocyst implantation in COH rats (You *et al.*, 2021) (Figure 5). In addition, miR-223-3p expression inhibits the LIF/STAT3 signalling pathway in the rat endometrium. However, electroacupuncture therapy enhances endometrial receptivity by inhibiting miR-223-3p expression in the LIF/STAT3 signalling pathway (You *et al.*, 2022b) (Figure 5). In summary, miRNA promotes endometrial receptivity by regulating the LIF/STAT3 signalling pathway. However, there are few reports on the specific regulatory effects of miRNA on endometrial receptivity. Therefore, the LIF/STAT3 signalling pathway is a potential signalling pathway for miRNA regulation of endometrial receptivity, though more research is needed.

The regulatory role of miRNA in endometrial receptivity

A good endometrial receptivity is a prerequisite for successful embryo implantation. Therefore, scholars are constantly exploring methods to improve endometrial receptivity. Many miRNAs regulate endometrial receptivity in mouse and other animals and can serve as useful diagnostic and therapeutic targets for successful embryo implantation, providing reference for relevant scientific research and clinical application (Table 2).

The regulatory effect of miRNA on endometrial receptivity in mouse

Cullin 3 (CUL3), an E3 ubiquitin ligase, interacts with beclin 1 (BECN1), thereby promoting K48-linked ubiquitination and degradation of BECN1.In mice, miR-23a-3p inhibits target gene *CUL3* expression by negatively regulating β-Catenin ubiquitination to promote endometrial receptivity and embryo implantation (Huang *et al.*, 2020). According to Akbar et al. (2020), inhibiting miR-183-5p also significantly reduces the embryo implantation rate and increases the expression of target gene catenin alpha 2 (*CTNNA2*) in vivo using a mouse pregnancy model, implying that miR-183-5p regulates endometrial receptivity and enhances embryo implantation. Another study revealed that miR-let-7a/g enhances mouse endometrial receptivity by inhibiting the Wnt signalling pathway by negatively regulating oestrogen and progesterone, improving embryo attachment and growth related to implantation (Li *et al.*, 2020).

Poly (ADP-ribose) polymerase 2 (*PARP-2*) is a gene involved in endometrial receptivity for trophoblast implantation. Moreover, miR-149 inhibits endometrial receptivity by downregulating the

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Table 2. The regulatory role of miRNA in endometrial receptivity

miRNA	Species	Target Gene	Improved/Impaired Receptivity
miR-23a-3p	mouse	*CUL3*	Improved
miR-183-5p	mouse	*CTNNA2*	Improved
miR-let-7a/g	mouse	–	Improved
miR-149	mouse	*PARP-2*	Impaired
miR-223-3p	mouse	*LIF*	Impaired
miR-181	mouse	*LIF*	Impaired
miR-494-3p	mouse	*LIF*	Impaired
miR-183	mouse	*HB-EGF* and *LAMC1*	Impaired
miR-205-5p	mouse	*ZEB1*	Improved
miR-145 and miR-199	human	–	Improved
miR-30d	human	*Snai1*	Improved
miR-133b	human	*SGK1*	Improved
miR-1290	human	*LHX6*	Improved
miR-192-5p	human	*ARHGAP19*	Impaired
miR-125b	human	*MMP26*	Impaired
miR-146a-3p	human	*ZNF23*	Impaired
miR-29c	human	*COL4A1*	Impaired
miR-23b-3p	human	*SFRP4*	Improved
miR-543	human	–	Improved
miR-31	human	*FOXP3 and CXCL12*	Improved
miR-124-3p	human	*LIF*, *MUC1* and *BCL2*	Impaired
miR-449a	goat	*LGR4*	Improved
miR-182	dairy goat	*HOXA10*	Improved
miR-26a	dairy goat	*PTEN*	Improved
miR-15b	dairy goat	*LIF*	Improved
miR-34a/c	caprine	*CEP55*	Improved
bta-miR-200b	bovine	*MYB*	Improved
ssc-miR-21-5p	pig	*PDCD4*	Impaired
miR-1246	buffalo	*MUC1* and *β-catenin*	Improved
miR-134-5p	sheep	*CREB1*	Impaired

target gene *PARP-2* and upregulating caspase-8 (Verma *et al.*, 2022; Soni *et al.*, 2021). At the same time, miR-223-3p and miR-181 inhibit endometrial receptivity and embryo implantation in mice by targeting and downregulating the *LIF*, a key regulatory factor for endometrial receptivity (Dong *et al.*, 2016; Chu *et al.*, 2015). On the contrary, electroacupuncture therapy enhances endometrial receptivity by inhibiting the expression of miR-223-3p on the LIF/STAT3 signalling pathway (You *et al.*, 2022b). Yuan et al. (2021) also revealed that miR-494-3p targeting *LIF* regulates endometrial receptivity via the PI3K/Akt/mTOR pathway, and inhibiting miR-494-3p increases the *LIF* and *VEGF* expression levels, thereby increasing endometrial receptivity in mice. Besides, miR-183 inhibits embryo implantation by regulating *HB-EGF* and *LAMC1* in the mouse uterus, suggesting that miR-183 inhibits endometrial receptivity (Cao *et al.*, 2020). Exosomes miR-205-5p upregulate E-cadherin by targeting *ZEB1*, thereby improving endometrial receptivity (Yu *et al.*, 2023).

The regulatory effect of miRNA on endometrial receptivity in human

miR-145 and miR-199 transfection into Ishikawa cells significantly reduces the *podocalyxin (PODXL)* expression, which significantly promotes the endometrial receptivity of the Ishikawa monolayer (Shekibi *et al.*, 2022). Polychlorinated biphenyls induce endometrial receptivity dysfunction by disrupting the interaction between the key gene miR-30d regulating endometrial receptivity and the EMT process. *Snai1* is targeted by miR-30d and induced by polychlorinated biphenyls (Cai *et al.*, 2016). Lack of miR-30d in the mother or embryo results in a significant downregulation of the endometrial receptivity markers, which reduces the implantation rate and damages embryonic growth (Balaguer *et al.*, 2019). In addition, Kong et al. (2016) revealed that miR-133b targets *SGK1* to increase *HOXA10* expression and promote the attachment of BeWo spheres to Ishikawa cells, which induce endometrial receptivity and embryo attachment. Shi et al. (2021) also revealed that miR-1290 is an extracellular vesicle derived from placental trophoblasts, which stimulates the interaction between the endometrium and embryo by targeting *LHX6*, thereby promoting endometrial receptivity.

Moreover, miR-192-5p is an upstream regulatory factor of *ARHGAP19*, which promotes the transition of EECs from non-receptive to receptive states by regulating the remodelling of connexin and membrane-related cytoskeleton (Liang *et al.*, 2021). Another study revealed that miR-192-5p inhibits endometrial receptivity by hindering epithelial transformation during embryo implantation (Liang *et al.*, 2020). Therefore, sustained high levels of miR-192-5p are harmful to embryo implantation. At the same time, miR-125b inhibits EEC migration and invasion by downregulating *MMP26*, which weakens the embryo attachment and subsequent endometrial invasion, leading to decreased endometrial receptivity (Chen *et al.*, 2016). The overexpression of miR-146a-3p also significantly inhibits the expression of *LIF*, integrin3, claudin4 and *DKK1* in EECs, which inhibits endometrial receptivity (Wei *et al.*, 2021). In the endometrium of infertile women, the overexpression of miR-29c and downregulation of *COL4A1* reduces the EECs adhesion ability in vitro, suggesting that miR-29c plays a role in the secretion phase of infertile women, decreasing receptivity and implantation success rate (Griffiths *et al.*, 2019). MiR-23b-3p also regulates the adhesion of human EECs, suggesting that it may be a key regulator of endometrial epithelial adhesion and endometrial receptivity (Barton *et al.*, 2023).

Furthermore, research has also revealed that the downregulation of miR-543 affects embryo implantation, leading to endometriosis-related infertility (Yang *et al.*, 2019). Another study revealed that miR-31 is the best potential biomarker for endometrial receptivity and may function through immunosuppressive mechanisms (Kresowik *et al.*, 2014). MiR-124-3p negatively impacts embryo implantation by suppressing endometrial receptivity formation and embryo development through targeted inhibition of *LIF*, *MUC1* and *BCL2* expression (Yao *et al.*, 2024).

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The regulatory effect of miRNA on endometrial receptivity in livestock

The miR-449a/c expression in the uterine cycle is associated with endometrial development (Naydenov *et al.*, 2022). MiR-449a promotes endometrial receptivity by regulating the apoptosis of goat ESCs and negatively regulating *LGR4* (An *et al.*, 2017). Similarly, miR-182 promotes endometrial receptivity by down-regulating pleiotrophin and regulating apoptosis-related genes and endometrial receptivity marker genes such as *osteopontin (OPN)*, *cyclooxygenase-2* (*COX-2* and *prolactin receptor (PRLR)* in dairy goat EECs (Zhang *et al.*, 2017). miR-26a also regulates the expression of *OPN*, *VEGF*, *COX-2* and *prolactin (PRL)* in endometrial cells, thereby promoting endometrial receptivity (Zhang *et al.*, 2018). At the same time, miR-26a promotes the proliferation of EECs and induces ESC apoptosis via the *PTEN*-PI3K/Akt pathway in dairy goats (Zhang *et al.*, 2018).

Furthermore, miR-15b is competitively bound by lncRNA882 and LIF in EECs, which upregulates *LIF* and induces endometrial receptivity in dairy goats (Zhang *et al.*, 2019). Liu et al. (2020) also revealed that miR-34a and miR-34c are highly expressed in goats and induce apoptosis of EECs by binding to circ-8073 and *CEP55* via the RAS/RAF/MEK/ERK and PI3K/Akt/mTOR pathways, which induce endometrial receptivity in dairy goats. The apoptosis of EECs is an important process for endometrial receptivity induction and embryo implantation. However, bta-miR-200b affects the apoptosis of bovine EECs by targeting *MYB* genes, thereby promoting endometrial receptivity (Lyu *et al.*, 2023). In pigs, knocking down ssc-miR-21-5p inhibits Akt phosphorylation by targeting *PDCD4*, which hinders endometrial receptivity, decreasing the embryo implantation rate (Hua *et al.*, 2020). Besides, in buffalo, miR-1246 secreted by the trophoblast reduces the expression of endometrial receptivity gene (*MUC1* and *β-catenin*), implying that miR-1246 is a potential marker for buffalo endometrial receptivity (Dubey *et al.*, 2023). In the same line, miR-134-5p inhibits the proliferation of sheep ESCs by inhibiting the target gene *CREB1*, thereby inhibiting the establishment of endometrial receptivity (Li *et al.*, 2023).

Conclusions and future perspectives

endometrial receptivity is crucial for successful embryo implantation and pregnancy. endometrial receptivity dysfunction induces EEC attachment failure or poor embryo reception, which decreases the pregnancy rate. Various factors influence endometrial receptivity via multiple signalling pathways, including mRNA and miRNAs, which play a crucial role in endometrial receptivity induction by participating in the signalling pathways, such as the PI3K/Akt signalling pathway. Although the regulatory mechanisms of some miRNAs regulating endometrial receptivity have been studied, the regulatory mechanism of miRNAs on endometrial receptivity is still unclear. Therefore, further research on the molecular regulatory network of miRNA on endometrial receptivity is needed to improve endometrial receptivity and pregnancy rates. In addition, miRNAs should be explored as biomarkers or therapeutic targets for detecting or improving endometrial receptivity in maternal therapy.

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