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Mini-Review

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Physiological and pathological roles of locally expressed kisspeptin and KISS1R in the endometrium

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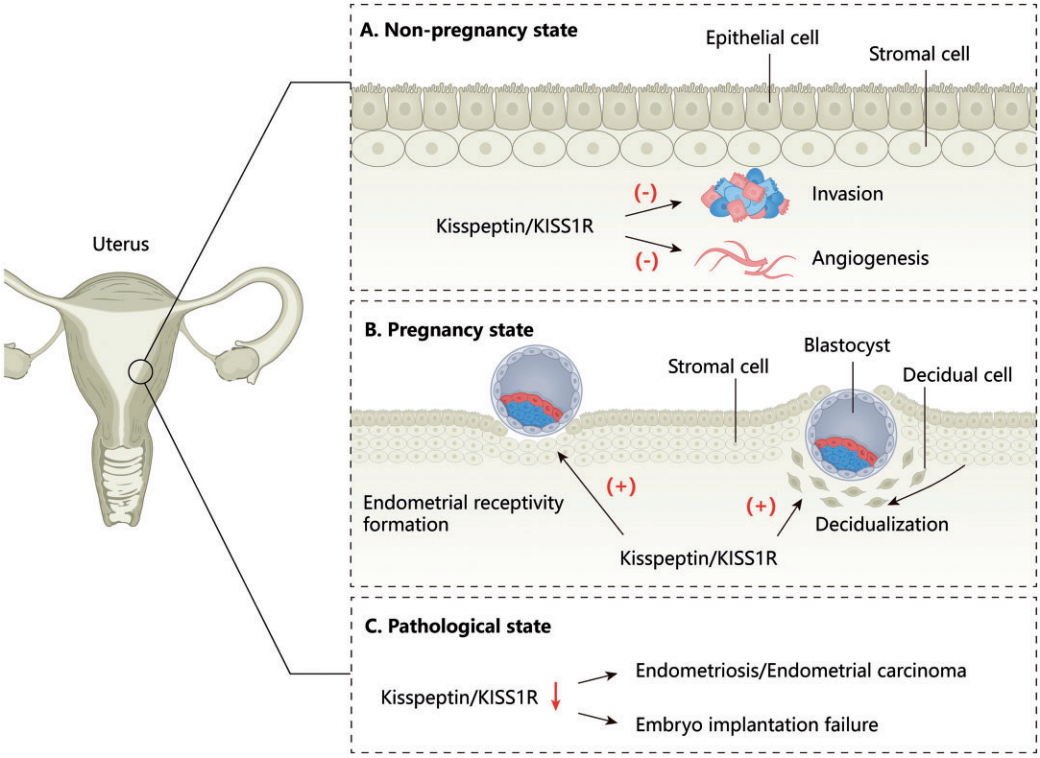
ABSTRACT

Kisspeptins, encoded by the *KISS1* gene, are a family of polypeptides that bind the kisspeptin receptor (KISS1R) to perform biological functions. Produced mainly in the hypothalamus, these neuropeptides regulate the pulsatile secretion of GnRH and trigger the hypothalamus–pituitary–gonadal axis. Other peripheral organs also express kisspeptin, which inhibits metastasis. Kisspeptin and KISS1R are reportedly present in the endometrium and may play roles in limiting the migration and invasion of trophoblasts into the endometrium during pregnancy (decidua) to maintain endometrial homeostasis. A deficiency of kisspeptin and KISS1R in the endometrium can lead to pathological conditions such as endometriosis and endometrial carcinoma. Kisspeptin and KISS1R in the endometrium can also promote endometrial receptivity and decidualization. Overall, kisspeptin and KISS1R are important for maintaining the normal physiological functions of the endometrium. By summarizing the roles of kisspeptin and KISS1R in the endometrium, our review explores the regulatory roles in the peripheral reproductive system of this peptide family that plays broad and profound roles in many physiological processes.

Keywords: kisspeptin / KISS1R / metastasis / angiogenesis / endometrial receptivity / decidualization

GRAPHICAL ABSTRACT



The roles of kisspeptin and KISS1R in physiological and pathological states of the endometrium. KISS1R: kisspeptin receptor.

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Introduction

Kisspeptin, a family of peptides with similar structures, functions, and origins, is encoded by *KISS1*, a gene located at 1q32 in human (Lee *et al.*, 1996). Kisspeptin-145, which is unstable and biologically inactive, is the primary product of *KISS1* (West *et al.*, 1998). Kisspeptin-145 is synthesized as prepropeptide and undergoes proteolysis. It is broken down into shorter forms, such as kisspeptin-54, kisspeptin-14, kisspeptin-13, and kisspeptin-10, all of which have a C-terminal region containing an Arg-Phe-NH2 signal motif and the ability to activate the same receptor, KISS1R (Kotani *et al.*, 2001; Gottsch *et al.*, 2009). These proteins are mainly produced in the hypothalamus and are upstream regulators of GnRH, which occupies the central position of the hypothalamus-pituitary-gonadal axis and stimulates the release of FSH and LH. These two hormones then promote the secretion of sex steroids in the gonads to regulate gametogenesis and periodic changes in the endometrium (Oakley *et al.*, 2009; Pinilla *et al.*, 2012; Tng, 2015). Thus the kisspeptin secreted in the hypothalamus plays a crucial but indirect role in endometrial function (Trevisan *et al.*, 2018). Kisspeptin is also secreted by many peripheral organs, including the liver, lungs, gonads, prostate, and placenta (Muir *et al.*, 2001; Ohtaki *et al.*, 2001; Horikoshi *et al.*, 2003). Kisspeptin expressed in the peripheral organs can function as a tumor metastasis suppressor by inhibiting cell invasion and migration (Lee and Welch, 1997). Reduced expression of kisspeptin in peripheral organs has been implicated in the pathogenesis of many types of cancers, including gastric carcinoma, colon cancer, and pancreatic cancer (Shoji *et al.*, 2010; Ji *et al.*, 2013; Zhu *et al.*, 2018). At the same time, kisspeptin also exists in endocrine organs, including adipose tissue and the pancreas, and plays a role in the regulation of energy and glucose metabolism (Hauge-Evans *et al.*, 2006; Li *et al.*, 2009).

The expression of the genes encoding kisspeptin and KISS1R in the endometrium has been reported (Cejudo Roman *et al.*, 2012). Researchers have identified that kisspeptin secreted in the uterus can influence uterine growth and gland development (Leon *et al.*, 2016). Kisspeptin and KISS1R also participate in endometrial homeostasis. Deficiency of kisspeptin and KISS1R in the endometrium can cause disorders related to the abnormal expression of matrix metalloproteinases (MMPs), vascular endothelial growth factor (VEGF), and other molecules; this can lead to altered invasion, migration, and angiogenesis of the endometrium, which may be related to the pathogenesis of diseases associated with abnormal endometrial hyperplasia, such as endometriosis and uterine endometrial carcinoma. Furthermore, kisspeptin and KISS1R deficiency in the endometrium can lead to the failure of endometrial receptivity and abnormal decidualization in the late secretory phase, with negative effects on embryo implantation and pregnancy maintenance (Jiang *et al.*, 2005; Radovick and Babwah, 2019; Abdelkareem *et al.*, 2020).

In this review, we focus on the functions of kisspeptin and KISS1R expressed in the endometrium.

The expression of kisspeptin and KISS1R in the endometrium

Studies have identified that kisspeptin and KISS1R are expressed in the endometrium (Cejudo Roman *et al.*, 2012; Timologou *et al.*, 2016; Abdelkareem *et al.*, 2020). Kisspeptin and KISS1R were found to be weakly expressed in the epithelial glands, and their expression was nearly absent in endometrial stromal cells (ESCs) during the proliferative and early secretory phases in the normal endometrium (Timologou *et al.*, 2016). However, Baba *et al.* (2015) observed that the expression of kisspeptin and KISS1R increases significantly during the late secretory phase and, at this stage, kisspeptin was mainly expressed in the ESCs of the decidualized portion of the endometrial tissues (Baba *et al.*, 2015). They also found that both kisspeptin and KISS1R are nearly absent in the endometrium in the menopausal samples (Baba *et al.*, 2015). Changes in the kisspeptin and KISS1R expression levels and distribution in the endometrium have been reported in mice. Zhang *et al.* (2014) verified that the kisspeptin and KISS1R expression levels in the endometrium of mice were low during the peri-implantation stage and that kisspeptin and KISS1R were mainly located in the luminal and glandular epithelia; however, the ESCs began to decidualize from the fifth day of pregnancy and the kisspeptin and KISS1R expression levels increased significantly, primarily in the decidualizing ESCs (Zhang *et al.*, 2014). Taken together, the presence of kisspeptin and KISS1R in the endometrium may indicate that kisspeptin plays a role in maintaining the normal structure and function of the endometrium. The significantly increased kisspeptin and KISS1R expression levels during the late secretory phase, when the endometrium substantially changes to prepare for embryo implantation and growth, indicate that they may participate in the regulation of embryo implantation and decidualization in the endometrium (Radovick and Babwah, 2019).

The function of kisspeptin and KISS1R expressed in the endometrium to limit abnormal endometrial hyperplasia

Physiologically, the endometrium periodically proliferates and sheds under the influence of estrogen and progesterone, achieving homeostasis (MacLean and Hayashi, 2022). When the intrinsic properties of the endometrium change, this homeostasis is disrupted and the endometrium exhibits abnormal proliferation with estrogen dependence and progesterone resistance, which is associated with the pathogenesis of endometriosis and endometrial carcinoma (Di Cristofano and Ellenson, 2007; Tsamantioti and Mahdy, 2023). However, the presence of kisspeptin and KISS1R in the endometrium inhibits abnormal endometrial hyperplasia. Studies have shown that an ectopic or eutopic endometrium in patients with endometriosis has lower kisspeptin expression levels compared with endometrium from unaffected women (Abdelkareem *et al.*, 2020). Moreover, KISS1R expression in high-grade endometrial cancer is downregulated through DNA methylation, indicating that the functions of kisspeptin decline in association with the development of endometrial cancer (Kang *et al.*, 2011; Baba *et al.*, 2015). The inhibition of abnormal hyperplasia by kisspeptin may be attributable to limitations on the migration and invasion of endometrial cells and to suppression of angiogenesis, which are two important processes in the pathogenesis of diseases associated with abnormal endometrial hyperplasia (Yan *et al.*, 2001; Leon *et al.*, 2016; Li *et al.*, 2021) (Fig. 1).

The function of kisspeptin and KISS1R in the endometrium to limit the migration and invasion of endometrial cells

Under normal situations, the invasion and migration of endometrial cells are suppressed to maintain homeostasis of the endometrium. However, in some diseases associated with abnormal endometrial hyperplasia, the invasion and migration of endometrial cells are unusually enhanced, perhaps due to the decreased expression of kisspeptin and KISS1R (Abdelkareem *et al.*, 2020). Kisspeptin can suppress metastasis in many types of cancers, in either an autocrine or paracrine fashion, by downregulating a

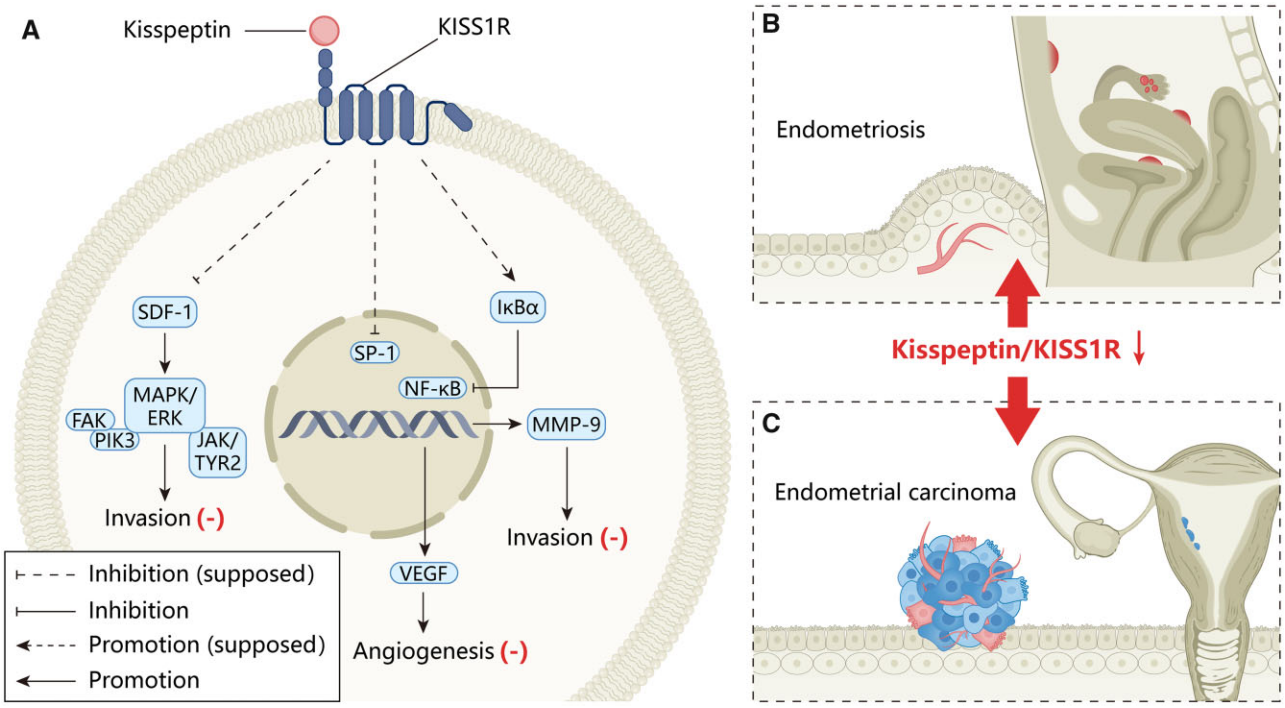

Figure 1. The functions of kisspeptin and KISS1R in limiting invasion and angiogenesis in the endometrium. Kisspeptin expressed in the endometrium binds to the kisspeptin receptor (KISS1R) to trigger downstream molecular signaling pathways, which have physiological functions in the endometrium such as inhibiting invasion and angiogenesis. (**A**) Kisspeptin may inhibit the expression of SDF-1, which activates multiple signaling pathways associated with cell adhesion and migration, such as the FAK, PIK3, MAPK/ERK, and JAK/TYR2 pathways, to suppress cell invasion and migration. Kisspeptin and KISS1R may also inhibit the nuclear translocation of NF-κB by increasing IκBα levels in the cytosol. As NF-κB binds to the promoter of *MMP-9* and increases its expression level, kisspeptin can reduce MMP-9 expression levels and suppress the invasion and migration of endometrial cells. Furthermore, kisspeptin and KISS1R may inhibit the binding of SP-1 to the *VEGF* promoter to reduce VEGF expression levels and suppress angiogenesis. However, more experimental evidence is needed to identify the specific signaling pathways in which kisspeptin is involved. The downregulation of kisspeptin and KISS1R in the endometrium is associated with the pathogenesis of abnormal endometrial hyperplasia, such as endometriosis (**B**) and endometrial carcinoma (**C**), both of which involve the migration and invasion of endometrial cells and angiogenesis. SDF-1, stromal-derived factor 1; FAK, focal adhesion kinase; PIK3, phosphatidylinositol-3-kinase; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; JAK/TYR2, Janus kinase/tyrosine kinase 2; IκBα, NF-Kappa B inhibitor alpha; NF-κB, nuclear factor kappa-B proteins; MMP-9, matrix metalloproteinase 9; SP-1, specificity protein 1; VEGF, vascular endothelial growth factor.

series of invasion and migration effector molecules such as MMPs, which can promote the degradation of the surrounding extracellular matrix (Gao *et al.*, 2007; Lee and Kim, 2009; Chen *et al.*, 2016). Locally expressed kisspeptin in the endometrium can also function in a manner akin to inhibitors of metastasis, suppressing the expression of invasion and migration effector molecules to maintain endometrial homeostasis (Abdelkareem *et al.*, 2020). Endometriosis, as one of the most common benign gynecological diseases, is characterized by the presence of functional endometrial glands and stroma outside the uterine cavity, and its pathogenesis is associated with enhanced invasion and migration abilities of the endometrium (Králíčková *et al.*, 2014). Substantial evidence indicates that in patients with endometriosis, ectopic or eutopic endometrium has a lower kisspeptin expression (Makri *et al.*, 2012; Abdelkareem *et al.*, 2020). Kisspeptin can downregulate the expression of MMPs by increasing the IκBα levels in cytosol to inhibit the nuclear translocation of nuclear factor kappa-B (NF-kB) proteins, such that these proteins cannot bind the promoter of MMP-9 to regulate its expression (Ji *et al.*, 2013). Therefore, kisspeptin can suppress the invasion of endometrial cells (Yan *et al.*, 2001), and decreased levels of local kisspeptin allow the migration of endometrial cells through the fallopian tubes to the peritoneal cavity more easily, leading to ectopic implantation and hyperplasia (Abdelkareem *et al.*, 2020). Besides endometriosis, endometrial carcinoma, a type of uterine cancer arising from the endometrium, that is also associated with abnormal endometrial hyperplasia, also presents with the characteristics of low kisspeptin and KISS1R expression levels in the endometrium (Kang *et al.*, 2011; Baba *et al.*, 2015; Faizan and Muppidi, 2023). The invasion of cancer cells may also be related to the reduced expression of kisspeptin and KISS1R in the endometrium (Schmidt *et al.*, 2014; Haque *et al.*, 2020). Some studies have argued that kisspeptin may prevent endometrial cancer cell invasion and metastasis by inhibiting the expression of stromal-derived factor 1 (SDF-1), which is a type of cysteine, and is also known as C-X-C motif chemokine 12 (CXCL12) (Schmidt *et al.*, 2014). SDF-1 activates multiple signaling pathways, including focal adhesion kinase (FAK), phosphatidylinositol-3-kinase (PI3K), mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), and Janus kinase (JAK)/tyrosine kinase (TYR) 2 pathways, which are involved in endometrial cell adhesion and migration (Haque *et al.*, 2020).

The function of kisspeptin and KISS1R in suppressing angiogenesis in the endometrium

Angiogenesis is the formation of new blood vessels from the existing vasculature (Adair and Montani, 2010). Blood vessels are essential for the exchange diffusion of nutrients and metabolites in all tissues. Therefore, angiogenesis occurs throughout life, both in health and disease (Adair and Montani, 2010). In particular, the angiogenesis of spiral arteries is important for the restoration and hyperplasia of the endometrium during a normal

menstrual cycle. However, in diseases associated with abnormal endometrial hyperplasia, e.g. endometriosis, the abnormal hyperplasia in ectopic endometrium increases the demand for nutrients and oxygen, and thus enhances angiogenesis in these ectopic tissues (Rudzitis-Auth et al., 2022). Angiogenesis is always strictly regulated to maintain homeostasis. VEGF is a key effector molecule and a positive regulator of angiogenesis, which induces the formation of new blood vessels by increasing vascular permeability, mediating the migration of vascular endothelial cells, and promoting cell proliferation (Apte et al., 2019). Angiogenesis is significantly upregulated in the ectopic endometrium of patients with endometriosis (Li et al., 2021). Moreover, studies on human prostate cancer have reported that kisspeptin can suppress VEGF expression by inhibiting the binding of specificity protein 1 to the VEGF promoter, and blocking the activation of the c-Src/FAK and Rac/Cdc42 signaling pathways in human umbilical vein endothelial cells, thereby leading to the inhibition of angiogenesis (Cho et al., 2009). Kisspeptin can also inhibit VEGF expression in human embryonic trophoblast cells and limit placental angiogenesis, helping to maintain a normal pregnancy (Ramaesh et al., 2010; Matjila et al., 2013). In light of the similarities among endometriosis, placental implantation, and tumorigenesis, all of which highly depend on progressive angiogenesis, a deficiency of kisspeptin in the endometrium may promote angiogenesis by increasing VEGF expression, leading to abnormal hyperplasia (Guo et al., 2021; Koninckx et al., 2021). However, this hypothesis should be further verified.

The function of kisspeptin and KISS1R in endometrial receptivity and decidualization to prepare for embryo implantation

During each menstrual cycle, the endometrium changes substantially in the late secretory phase to prepare for embryo implantation. These cyclical changes, which include endometrial receptivity and decidualization, are a type of homeostasis (Ng et al., 2020). If the intrinsic properties of the endometrium change and endometrial homeostasis is disrupted, endometrial receptivity and decidualization may be blocked, which may lead to a failure of embryo implantation (Ng et al., 2020). Studies mentioned above have shown that the kisspeptin and KISS1R expression levels in the endometrium vary at different stages of the menstrual cycle and increase considerably in the late secretory phase (Baba et al., 2015). Kisspeptin and KISS1R are mainly expressed in the ESCs in the secretory phase when the ESCs transform into decidual cells (Baba et al., 2015). However, kisspeptin and KISS1R mainly exist in the epithelial glands during the proliferative and early secretory phases (Baba et al., 2015). Therefore, kisspeptin and KISS1R in the endometrium may play crucial roles in endometrial receptivity formation and decidualization to prepare for embryo implantation during every menstrual cycle and to help maintain endometrial homeostasis (Fig. 2).

The function of kisspeptin and KISS1R in endometrial receptivity formation

Endometrial receptivity is the ability of the endometrium to allow embryo implantation during the implantation window period that occurs 5–6 days after normal menstrual ovulation in humans and during Days 4–5 of pregnancy in mice (Lessey and Young, 2019). Endometrial receptivity is important for a normal pregnancy (Lessey and Young, 2019). Studies have shown that on the fourth day of pregnancy in mice, kisspeptin is detected at high levels throughout the endometrium and strongly localized to the subluminal epithelial layer and the outside of the glandular epithelium, whereas KISS1R is mainly expressed in the distal face of the luminal epithelial layer in wild-type mice, indicating that kisspeptin may play a role in establishing endometrial receptivity (Calder et al., 2014). Female *Kiss1*$^{-/-}$ mice subjected to acute replacement of gonadotropins and estradiol treatment showed restored ovulation, mating, and fertilization but not embryo implantation; however, the embryos of hormone-restored mice could be successfully implanted in the endometrium of wild-type mice (Calder et al., 2014). Accordingly, embryo implantation failure may be attributable to kisspeptin deficiency in the maternal endometrium and not in the embryo (Calder et al., 2014). Likewise, another study showed that kisspeptin treatment can increase the adhesion of mouse blastocysts to collagen I (Taylor et al., 2014). During the implantation window, kisspeptin in the endometrium regulates the establishment of endometrium receptivity, perhaps through the expression of leukemia inhibitory factor (LIF) in the uterine glands; LIF is an important cytokine for embryo implantation and initiates embryo–uterine communication, leading to embryo attachment and stromal cell decidualization (Kelleher et al., 2018). Hormone-primed *Kiss1*$^{-/-}$ mice reportedly exhibited noticeably lower levels of LIF in the glandular lumen during day 4 of pregnancy than wild-type hormone-primed control females; after receiving LIF treatment, embryo implantation in the hormone-primed *Kiss1*$^{-/-}$ mice was partly restored (Calder et al., 2014). In conclusion, kisspeptin in the endometrium during the endometrial implantation window may promote endometrial receptivity by upregulating the expression of LIF in the glandular lumen to promote embryo attachment. However, most of the evidence supporting this conclusion is from studies involving mice; thus, the findings of those studies may not be generalizable to the embryo implantation process in humans. Therefore, more clinical studies are warranted to verify the findings in humans.

The function of kisspeptin and KISS1R in decidualization

Decidualization refers to the functional and morphological changes that occur within the endometrium to form the decidual lining in which blastocyst implantation occurs (Ng et al., 2020). The endometrium in humans undergoes decidualization every menstrual cycle; in the absence of a blastocyst, decidualization ends with the shedding of the upper layer of the decidualized endometrium, also known as menstruation (Ng et al., 2020). The main changes observed include the secretory transformation of the uterine glands, an influx of specialized uterine natural killer (NK) cells, and vascular remodeling (Gellersen et al., 2007). Decidualized endometrium plays a vital role in encapsulating the early conceptus and supporting subsequent trophoblast invasion (Gellersen et al., 2010). Decidualization can also lead to the negative selection of nonviable embryos (Salker et al., 2010; Teklenburg et al., 2010), determine the optimal implantation window (Cha et al., 2012), and promote uterine homeostasis (Schatz et al., 2016). Poor decidualization can result in a failure in pregnancy establishment and embryo implantation (Salker et al., 2010; Valdes et al., 2017). Studies have shown that locally expressed kisspeptin may participate in the regulation of decidualization and influence embryo implantation (Baba et al., 2015). Decreased kisspeptin signaling in the decidua is associated with recurrent spontaneous abortion (Wu et al., 2014). Zhang et al. (2014) verified that the Kisspeptin and KISS1R protein expression levels in mice dramatically increased with the progression of uterine decidualization regulated by progesterone and estrogen;

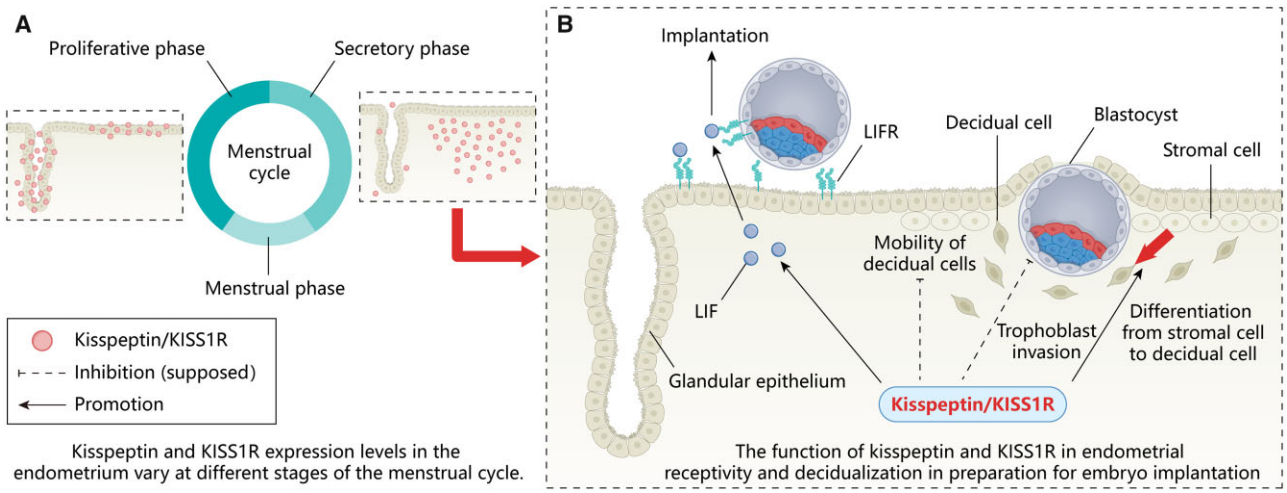

Figure 2. The expression levels of kisspeptin and KISS1R at different stages of the menstrual cycle and their roles in embryo implantation. (**A**) The expression levels of kisspeptin and KISS1R vary in the endometrium at different stages of the menstrual cycle. During the proliferative phase, kisspeptin and KISS1R are expressed in the epithelial glands, and their expression is nearly absent in endometrial stromal cells. However, the expression levels of kisspeptin and KISS1R increase significantly and they are mainly expressed in stromal cells during the secretory phase, when the endometrium undergoes major changes to prepare for embryo implantation. (**B**) Kisspeptin and KISS1R in the endometrium play roles in embryo implantation by promoting the establishment of endometrial receptivity and decidualization. Kisspeptin and KISS1R can regulate the establishment of endometrial receptivity by increasing the expression level of LIF, which can initiate embryo-uterine communication and lead to embryo attachment. For decidualization, kisspeptin and KISS1R can promote the differentiation of stromal cells directly. Furthermore, they may inhibit the mobility of decidual cells and suppress trophoblast invasion, which needs to be studied further. KISS1R, kisspeptin receptor; LIF, leukemia inhibitory factor; LIFR, leukemia inhibitory factor receptor.

moreover, kisspeptin and KISS1R were mainly expressed in the ESCs during this stage (Zhang *et al.*, 2014). In an *in vitro* trial, the mRNA expression levels of *Kiss1 and Kiss1r* were found to have increased during stromal cell decidualization, whereas the knockdown of *Kiss1* mRNA decreased the expression of genes that were essential for the proliferation and differentiation, as well as attenuated decidualization, of stromal cells *in vitro* (Zhang *et al.*, 2014). Besides influencing the proliferation and differentiation of decidual cells, kisspeptin signaling can also inhibit metastasis in decidual tissues. Wu *et al.* (2019) demonstrated that kisspeptin and KISS1R inhibit decidual cell mobility, to promote the invasion of embryos into the uterine endometrium (Wu *et al.*, 2019). They also reported that kisspeptin suppresses decidual cell mobility due to downregulation of the Src/FAK pathway, which leads to the reduced expression of MMP-2 and MMP-9 (Wu *et al.*, 2019). Besides inhibiting the mobility of decidual cells directly, kisspeptin and KISS1R present in decidual tissues may also suppress trophoblast invasion, according to a study by Bilban *et al.* (2004). Taken together, kisspeptin and KISS1R in the endometrium play important roles in decidual programming and embryo implantation. However, the detailed mechanisms of how kisspeptin functions during decidualization are far from clear and need to be studied through future research.

Conclusion

In summary, we conclude that kisspeptin and KISS1R expressed in the endometrium play important roles in maintaining endometrial homeostasis by limiting abnormal endometrial hyperplasia and promoting endometrial receptivity and decidualization to prepare for embryo implantation. Low kisspeptin and KISS1R expression levels in the endometrium may be associated with the pathogenesis of endometrial diseases. However, many issues, including the structure, distribution, regulation, and function of these peptides in the endometrium, remain unclear to date. In terms of structure, although the four short peptides belonging to the kisspeptin family can activate their shared receptors with the same affinity and efficiency, not all of these can trigger signaling pathways in endometrial cells or influence the physiological activities mentioned above (Tsoutsouki *et al.*, 2022). Therefore, the main peptides of the kisspeptin family that are involved in endometrial function regulation should be identified. In terms of the distribution of kisspeptin and KISS1R in the endometrium, although Baba *et al.* (2015) demonstrated that the expression levels and distribution of kisspeptin and KISS1R in the endometrium differed across menstrual phases, no other studies have verified these claims. To understand the normal regulatory mechanisms of these peptides in the endometrium, it is essential to identify which type of endometrial cells express kisspeptin and KISS1R during different menstrual phases, as well as the associated changes in the expression levels. In terms of the mechanisms related to the regulation and functions of kisspeptin and KISS1R in the endometrium, the uterus is highly dependent on estrogen-progesterone regulation (MacLean and Hayashi, 2022). Many abnormal conditions of endometrial function, such as embryo implantation failure and endometrial diseases, result from defects in estrogen-progesterone regulation in the endometrium (Yilmaz and Bulun, 2019; Yang *et al.*, 2022). Therefore, kisspeptin and KISS1R are quite likely to be involved in the estrogen-progesterone regulation network given that they play a role in maintaining endometrial homeostasis. Moreover, it is worth further studying how these peptides regulate the endometrium under the influences of estrogen and progesterone under physiological or pathological conditions; it is also worth understanding the relationships of these peptides with estrogen and progesterone. For specific pathological conditions such as endometriosis, endometrial carcinoma, and decidualization failure, the effects of kisspeptin and KISS1R on the pathogenesis and development of these diseases have been observed (Wu *et al.*, 2014; Kang *et al.*, 2011; Abdelkareem *et al.*, 2020). Most studies assessing the effects

of kisspeptin in endometrial diseases have focused on the functions of this peptide family in metastasis inhibition. However, the molecular mechanisms and signaling pathways involved in the inhibition of metastasis by kisspeptin in different types of endometrial diseases are still unclear and warrant further studies. In addition to suppressing metastasis, kisspeptin and KISS1R may participate in the pathogenesis of these endometrial diseases by regulating other physiological activities, including angiogenesis and inflammatory reactions, which have been rarely studied.

In conclusion, large knowledge gaps exist in our understanding of how locally expressed kisspeptin and KISS1R regulate endometrial function. Conducting further studies on these issues will expand our knowledge regarding this important family of peptides that is expressed in many tissues and influences several functions, while deepening our understanding of the regulatory mechanisms in the endometrium.

Data availability

No new data were generated or analyzed in support of this mini-review.

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Authors' roles

All authors participated in the conception, critical revision of important intellectual content, and final approval of the manuscript. The initial draft was written by J.Z.

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Conflict of interest

The authors declare that there is no conflict of interest.

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