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Participation of COX2/mPGES1/PGE2 in mouse and human endometrial stromal decidualization

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Abstract

Background Prostaglandin E2 (PGE2) is vital for embryo implantation and decidualization. Whether COX2/mPGES1/PGE2 pathway is essential for mouse and human decidualization remains unclear.

Results This study showed that *mPGES1* was highly expressed in the mouse uterus's subluminal stromal cells at the implantation site. COX2-specific inhibitor Valdecoxib and mPGES1 selective inhibitor MK886 were used to analyze the roles of mPGES1 and COX2 during mouse and human decidualization. During mouse in vitro decidualization, decidua/trophoblast prolactin-related protein (*Dtprp*) expression was significantly suppressed by Valdecoxib and MK886. Under human in vitro decidualization, *mPGES1* significantly increases, while both *cPGES* and *mPGES2* remain unchanged. PGE2-mediated upregulation of insulin growth factor binding protein 1 (*IGFBP1*) was significantly inhibited by Valdecoxib and MK886.

Conclusions Our findings suggest the involvement of COX2/mPGES1/PGE2 pathway in both mouse and human decidualization.

Keywords PGE2, mPGES1, COX2, Decidualization, Endometrial stromal cell

Background

Embryo implantation is a crucial process in pregnancy. The failure of embryo implantation is a major cause of early pregnancy loss before it is clinically recognized. Synchronization between receptive endometrium and blastocyst competency is consequential for implantation [1]. In the mouse, both PGE2 and prostacyclin I2 (PGI2) are involved in implantation and decidualization [2, 3]. In rats, PGE2 is a crucial mediator of increased vascular permeability at the implantation site [4]. PGE2 has also been shown to be essential during hamster implantation [5]. Analysis of the lipidomic profile in the human endometrial fluid shows that PGE2 and PGF2α concentrations increase significantly during the window of implantation in natural cycles [6]. During mouse embryo implantation, PGE2 is also a key mediator for activating the epithelial

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Na^+ channel; blocking the activation of the epithelial Na^+ channel will lead to embryo implantation failure [7]. Deficiency of lysophosphatidic acid receptor 3 (LPA3) in mice results in significantly reduced litter size and alteration of embryo spacing. Although the exogenous administration of PGE2 or carboprostacyclin (a stable analog of PGI2) into LPA3-deficient female mice can rescue delayed implantation, it does not rescue defects in embryo spacing [8].

PGH2 is generated from the COX2 conversion of arachidonic acid, and it is metabolized to PGE2 by prostaglandin E2 synthases (PGESs) [9]. There are three isoforms of PGESs: microsomal PGES1 (mPGES1, PTGES1), mPGES2 (PTGES2), and cytosolic PGES (cPGES, PTGES3) [10]. mPGES1 is an inducible perinuclear enzyme preferentially coupled with the inducible COX2 to promote PGE2 generation [11, 12] that is strongly expressed at the implantation site in the mouse uterus [2]. In the monkey's endometrium, COX2 and mPGES1 are strongly detected in the mid-luteal phase of the menstrual cycle [13]. In humans, increased expression of *mPGES1* mRNA has been detected in most of the endometriosis samples [14]. Although mPGES1 is a crucial enzyme for producing PGE2, expressed explicitly on the implantation site on day 5 in mice, its role during mouse and human decidualization remains unclear.

MK886 is a specific inhibitor of mPGES1 and has no significant effects on mPGES2 and cPGES [15]. Valdecoxib can selectively inhibit COX2 expression [16]. In this study, MK886 and Valdecoxib were applied to examine the roles of mPGES1 and COX2 during mouse and human in vitro decidualization, respectively. Both mice and human in vitro decidualization were significantly suppressed by MK886 and Valdecoxib.

Results

Expression of mPGES1 in mouse uterus during early pregnancy

The RNA in situ hybridization results demonstrated that *mPGES1* mRNA was highly expressed in the subluminal stromal cells at the implantation site compared to the inter-implantation site in mice (Fig. 1A). Real-time PCR showed that, compared to inter-implantation sites, *mPGES1* mRNA level was upregulated at implantation sites in mice ($P = 0.0181$) (Fig. 1B).

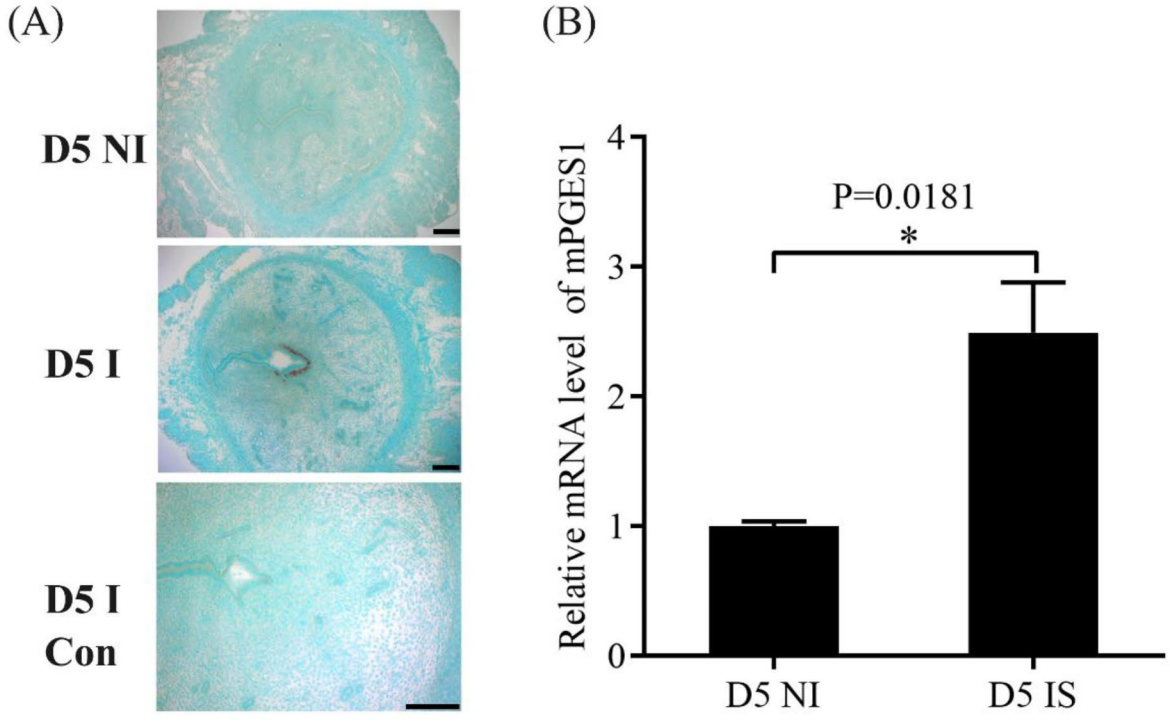

Fig. 1 mPGES1 expression in mouse uterus at implantation site on day 5 of pregnancy. (**A**) In situ hybridization of *mPGES1* mRNA expression; D5 NI, non-implantation site ($n = 3$); D5 I or D5 IS, implantation site ($n = 3$); D5 Con, negative control ($n = 3$). Scale bar = 300 μm. (**B**) Real-time PCR analysis of *mPGES1* mRNA levels in mouse uterus on day 5 of pregnancy ($n = 3$). Data were normalized with *Rpl7*. *$P < 0.05$

Effects of MK886 and Valdecoxib on mouse in vitro decidualization

We explored the role of COX2 and mPGES1 in decidualization through the use of inhibitors. Under in vitro decidualization of induction with progesterone and estradiol-17β, the expression of *Dtprp* was attenuated by MK886 and Valdecoxib in a dose-dependent manner (Fig. 2A and B).

Expression and role of PGES during human in vitro decidualization

Our results showed that when human endometrial stromal cells were induced for in vitro decidualization, *mPGES1* was significantly stimulated; however, the levels of *cPGES* and *mPGES2* were unaffected (Fig. 3A-C). The expression of *IGFBP1* was significantly increased after in vitro decidualization of human endometrial stromal cells (Fig. 3D and E). When human stromal cells were treated with MK886 after in vitro decidualization, the *IGFBP1* level was reduced (Fig. 3D). Furthermore, *IGFBP1* expression was decreased by Valdecoxib under in vitro decidualization (Fig. 3E).

Effects of MK886 and Valdecoxib on PGE2-induced in vitro decidualization in human endometrial stromal cells

Treating human endometrial stromal cells with PGE2 upregulated *IGFBP1* expression (Fig. 4A). PGE2-induced *IGFBP1* expression was abrogated by MK886 (Fig. 4A) and Valdecoxib (Fig. 4B). Moreover, MK886 and Valdecoxib reduced IGFBP1 and were rescued by PGE2 (Fig. 4C and D).

Discussion

In this study, our in situ hybridization assay showed the localization of *mPGES1* was increased in the mouse implantation site. This result was similar to a previous study [2]. mPGES1 is also strongly detected at implantation sites in rat and hamster uteri [5, 17]. It has been shown that the coculture of human endometrial stromal cells with first-trimester trophoblast explants causes an increase in mPGES1 [18]. Although PGES expression in human endometrium is unknown, our data suggests that *mPGES1* is the predominant PGES expressed during human in vitro decidualization. In vitro decidualization in mice and humans is inhibited by MK886, a specific inhibitor for mPGES1. These data suggest that mPGES1 should play a key role during mammalian decidualization.

mPGES1 is the terminal synthase for synthesizing PGE2 from COX2-derived PGH2 [10]. PGE2 and PGF2α are two major markers highly represented in endometrial fluid at the receptive phase during the human menstrual cycle [6]. PGE2 is also used to rescue the abnormalities of embryo implantation in LPA3-deficient mice [8]. During embryo implantation, PGE2 mediates the trypsin activation of the epithelial Na^+ channel [7]. PGE2 stimulates chemokines to enhance embryo development and adhesion to the maternal decidua [19]. Conversely, PGE2 insufficiency causes failure in implantation and decidualization [20]. Furthermore, intrauterine administration of PGE2 can induce decidualization in rats [21]. In our study, PGE2 also significantly stimulated the expression of *IGFBP1* in human endometrial stromal cells, which was abolished by MK886. Therefore, PGE2 was involved in human endometrial stromal cell decidualization.

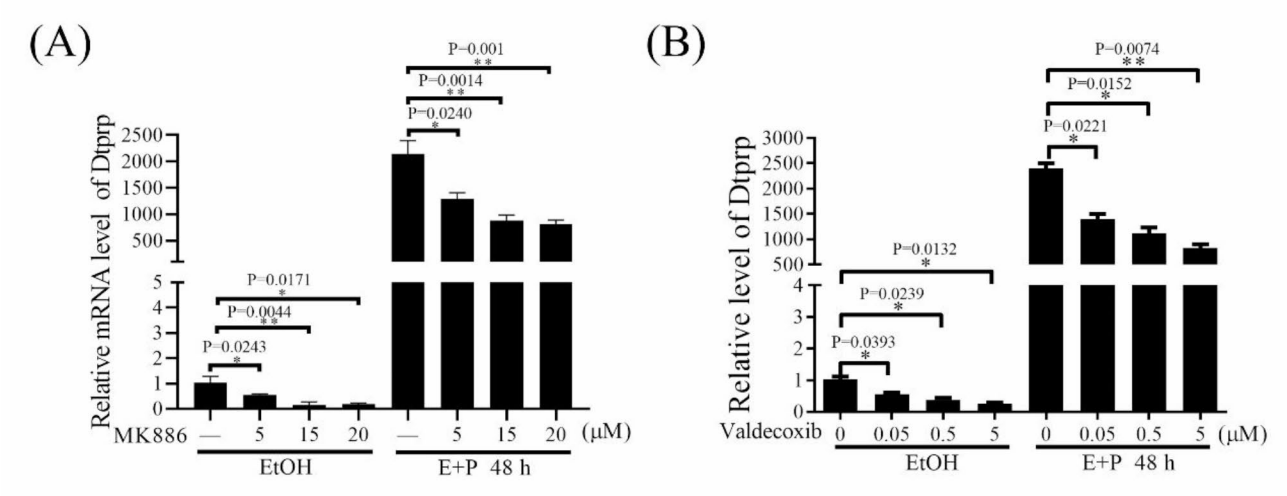

Fig. 2 Effects of MK886 and Valdecoxib on mouse in vitro decidualization. (**A**) Effects of MK886 on mouse in vitro decidualization. (**B**) Effects of Valdecoxib on mouse in vitro decidualization. Mouse endometrial stromal cells were co-treated with estradiol-17β and progesterone (E + P) to induce in vitro decidualization. *Dtprp* level, a marker of mouse in vitro decidualization, was significantly inhibited by MK886 and Valdecoxib($n = 3$). Data were normalized with *Rpl7*. *$P < 0.05$

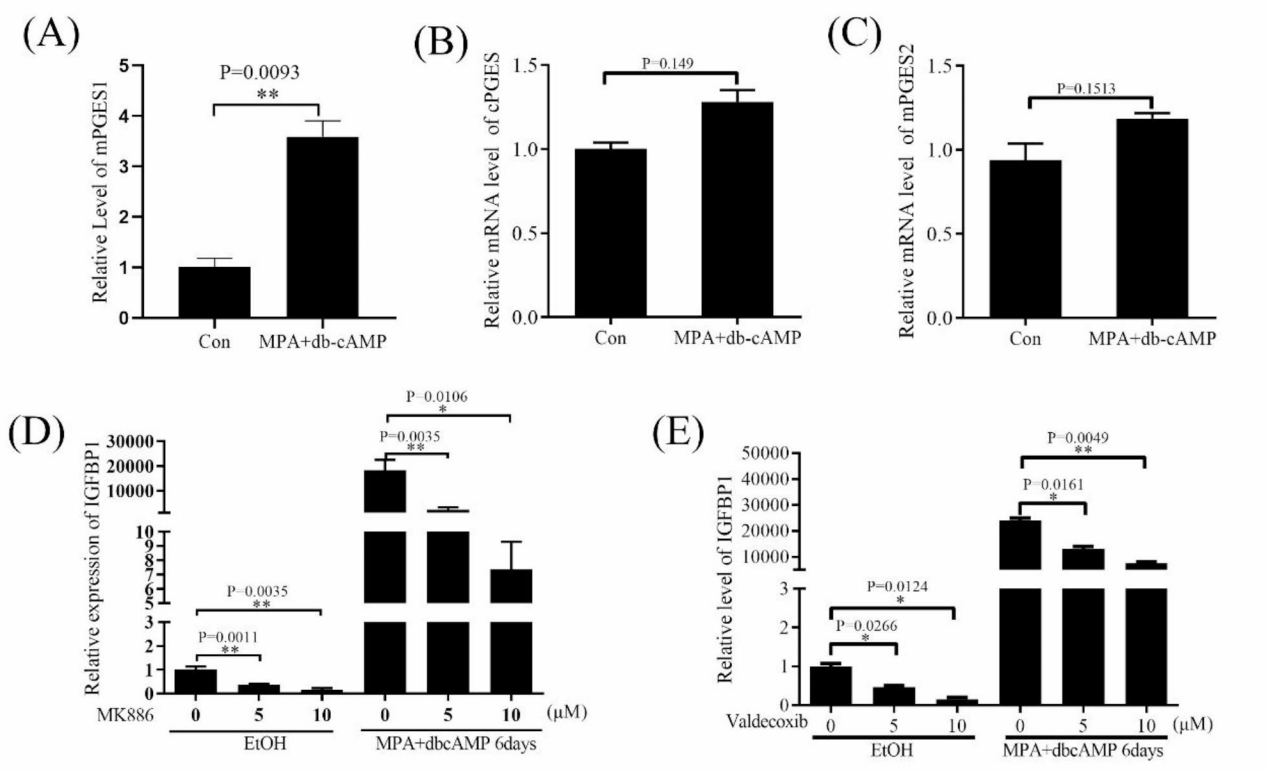

Fig. 3 Expression and function of prostaglandin synthases during human in vitro decidualization. (**A**)*mPGES1* expression. (**B**)*cPGES* expression. (**C**)*mPGES2* expression. (**D**) Effects of MK886 on human in vitro decidualization. (**E**) Effects of Valdecoxib on human in vitro decidualization. Human endometrium stromal cells were induced for in vitro decidualization by MPA and db-cAMP for 6 days. Cells were treated with DMSO as the control. *IGFBP1* expression was significantly inhibited by 5 and 10 μM of MK886 or Valdecoxib, respectively($n=3$). Data were normalized with *RPL7*. *$P<0.05$

As the rate-limiting enzyme in the production of prostaglandins, COX2 plays an essential role during early pregnancy, including fertilization and embryo development [22]. COX2 is strongly expressed at implantation sites in day 5 pregnant mouse uterus [23], which is also co-localized with mPGES1 expression [2]. COX2-deficient females are infertile with abnormalities in ovulation, fertilization, implantation, and decidualization [24]. Our study suggested that the COX2-specific inhibitor Valdecoxib significantly inhibited the mouse and human in vitro decidualization. It is possible that COX2 and mPGES1 are essential for mouse and human decidualization.

Conclusions

This study showed that mPGES-1, the terminal synthase for synthesizing PGE2 from COX2-derived PGH2, is highly expressed in the stroma cells surrounding the embryo on day 5 of pregnancy. Both COX2 and mPGES1 inhibitors blocked the process of in vitro decidualization in the mouse or human endometrial stromal cells. Our results demonstrated that COX2/mPGES1/PGE2 pathway may participate in mouse and human endometrial stromal decidualization.

Methods

Animal treatments

This study was approved by the Institutional Animal Care and Use Committee of Shanxi Agricultural University. Mature mice (CD-1 strain, 6 weeks old) were purchased from Hunan Slack Laboratory Animal Co., LTD and maintained in a temperature (22 ℃) and light (12 h light and 12 h dark) controlled SPF environment. Female mice were mated with fertile CD1 males to induce pregnancy (day 1 = vaginal plug). To identify the implantation sites on day 5 of pregnancy, animals were injected with 100 μL of 1% Chicago sky blue (Sigma-Aldrich, St. Louis, MO, USA) via the tail vein and euthanized by cervical dislocation after 5 min. Samples of implantation site (IS) and non-implantation site (NI) were collected from the uterus on day 5 of pregnancy and stored at -80 ℃ for in situ hybridization ($n=5$ mice) and real-time PCR analysis ($n=5$ mice).

In situ hybridization

In situ hybridization was performed as previously described [2]. Shortly, frozen mice sections of uterine implantation and non-implantation sites (10 μm, cut by Leica CM1860 and stored at -80 ℃), mounted on the

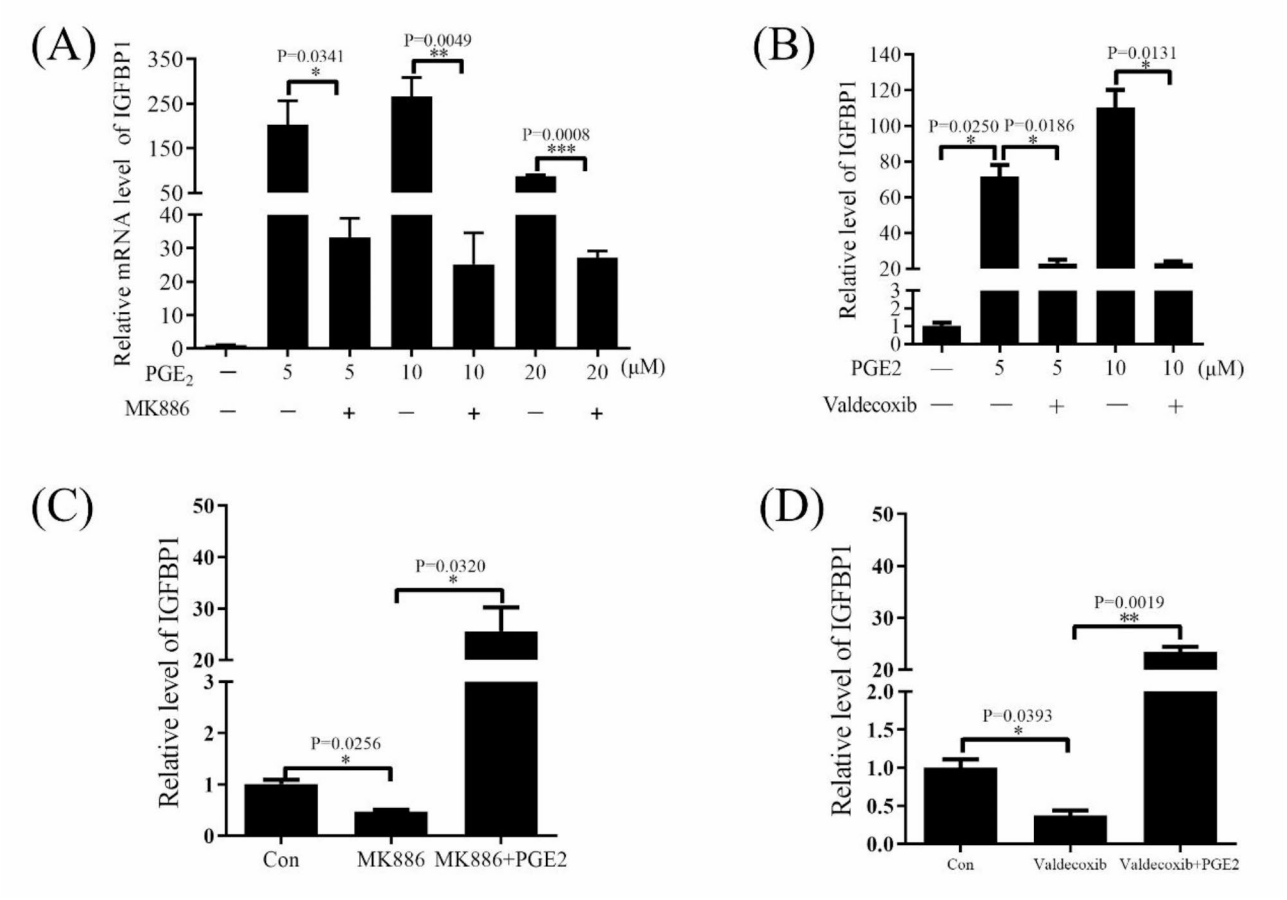

Fig. 4 Effects of MK886 and Valdecoxib on PGE2-induced *IGFBP1* expression in human endometrium stromal cells. (**A**) Effects of MK886 on PGE2-induced *IGFBP1* expression. (**B**) Effects of Valdecoxib on PGE2-induced *IGFBP1* expression. (**C**) Effects of PGE2 on MK886-abolished *IGFBP1* expression. (D) Effects of PGE2 on Valdecoxib-abolished *IGFBP1* expression($n = 3$). Data were normalized with *RPL7*. *$P < 0.05$

APES (3-Aminopropyl-Triethoxysilane, Sigma-Aldrich)-pretreated glass slides, were fixed with paraformaldehyde in PBS and rinsed with 1% Triton X-100. Sections were then prehybridized at room temperature and hybridized with the mPGES-1 antisense probe overnight at 55℃. Sections were washed with buffers and incubated with alkaline phosphatase-conjugated anti-DIG (Digoxin) antibody (Roche Applied Science) diluted in blocking solution (1:5000) overnight at 4℃. Finally, signals were detected by 5-Bromo-4-Chloro-3-Indolyl Phosphate (Sigma-Aldrich) and nitroblue tetrazolium (Sigma-Aldrich). Besides, levamisole (Sigma-Aldrich) was used as an endogenous alkaline phosphatase inhibitor to reduce background alkaline phosphatase activity.

Isolation and treatment of mouse uterine stromal cells

Mouse endometrial stromal cells were enzymatically isolated from mouse uteri on day 4 of pregnancy [25]. Briefly, uteri were removed soon after the euthanasia, split longitudinally, and digested in 5 mL of Hanks' balanced salt solution (HBSS, Sigma-Aldrich) containing 6 mg/mL dispase (Roche, Indianapolis, IN) and 1% trypsin (Amresco, Solon, OH) for 1 h at 4℃, then 1 h at 22℃ and 10 min at 37℃. Uteri were treated with 0.15 mg/mL collagenase I (Invitrogen, Carlsbad, CA) with HBSS at 37℃ for 30 min after dislodging epithelial fragments. Then, the endometrial stroma was shaken 20 to 30 times. The supernatant was centrifuged for 5 min at a speed of 1200 rpm. Cell pellets were washed once and re-suspended in DMEM/F12 (Sigma-Aldrich) containing 10% fetal bovine serum (FBS, Gibco Life Technologies, Grand Island, NY, USA). Cells were plated onto culture dishes. The medium was changed to remove free-floating cells after an initial culture for 6 h.

Mouse endometrial stromal cells were induced for in vitro decidualization with 1 μM of progesterone (P4, Sigma-Aldrich) and 10 nM of estradiol-17β for 48 h (E2, Sigma-Aldrich) as previously described [26]; a control group was treated with ethanol.

The cell viability assay

To measure cell viability, stromal cells were seeded onto 96-well plates and treated by MK886 (0, 5, 15, 25, and 50 μM) for 2 days or 6 days and incubated with reagents

Table 1 Primers used in this study

Gene	Primer sequences (5′-3′)	Accession number	Size (bp)	Application
Rpl7 (M)	ACCTTTGGGCTTACTCCATTGATA	M29016	129	Real-time PCR
	AGCCAGAAATCACTGCCACT			
Dtprp (M)	AGCCAGAAATCACTGCCACT	NM_010088	119	Real-time PCR
	TGATCCATGCACCCATAAAA			
RPL7 (H)	CTGCTGTGCCAGAAACCCTT	NM_000971	194	Real-time PCR
	TCTTGCCATCCTCGCCAT			
IGFBP1 (H)	CCAAACTGCAACAAGAATG	NM_000596	87	Real-time PCR
	GTAGACGCACCAGCAGAG3			
mPGES1 (M)	CAGATGAGGCTGCGGAAGAAGG	NM_022415.3	305	In situ hybridization
	CAGGAGAACTGGGCCAGGACAT			
mPGES1 (M)	TCCTCGGCTTCGTGTACTCA	NM_022415.3	126	Real-time PCR
	GAAGGCGTGGGTTCAGCTT			
PTGES1 (H)	GGCTTTGGATGTCTTTGCT	NM_004878.3	155	Real-time PCR
	TTCCTTTGAGTGGCTGGTC			
PTGES2 (H)	TCAGCAAGCGACTCAA	NM_001256335.1	113	Real-time PCR
	CATACACCGCCAAATC			
PTGES3 (H)	TTCATTCTCCGTCCTCG	NM_001282601.1	139	Real-time PCR
	TCTTCTCGCTTCCCTCA			

M, mouse; H, human

from Cell Counting Kit-8 (Sigma-Aldrich) for 4 h. Afterward, the spectrometric absorbance was assessed at 450 nm. The viability rate was calculated as the sample's (MK886 5, 15, 20, 50 μM) OD value divided by the control's (MK886 0 μM) average OD value. The cell viability was unaffected until MK886 was over 25μM in mouse uterine stromal cells (Figure S1 A) and human stromal cells (Figure S1 B).

Culture and treatment of human endometrial stromal cells

Immortalized human endometrial stromal cell line (ATCC, CRL-4003™) was used in this study. Frozen cells were revived and cultured with DMEM/F12 containing 10% charcoal-treated FBS (cFBS, Biological Industries, Cromwell, Israel) at 37 °C with 5% CO_2. Cells were plated at a density of 3×10^5 per well for each treatment in 12-well plates.

To induce in vitro decidualization, human endometrial stromal cells were treated with 500 μM db-cAMP (Sigma-Aldrich) and 1 μM medroxyprogesterone acetate (MPA, Sigma-Aldrich) for 6 days as previously described [27], the control group was treated with 0.1% (V/V) ethanol with the same time. IGFBP1, a marker of human in vitro decidualization [28], was used in this study.

COX2-specific inhibitor Valdecoxib (0, 5, and 10 μM), mPGES1 selective inhibitor MK886 (0, 5, and 10 μM), or PGE2 (5, 10, and 20 μM) were treated for 6 days with or without in vitro decidualization [29]. Each treatment group contained 3-well cells treated as described above, and at least 3 independent replication experiments were performed.

RNA extraction and real-time PCR

Quantitative real-time PCR (real-time PCR) was performed to analyze the differential expression of each gene. This experiment used the Trizol Kit (Sigma-Aldrich) to extract total RNAs. RNA integrity was checked with agarose gel electrophoresis. Then, the RNAs (500 ng) were reverse transcribed into cDNAs using the PrimeScript reverse transcriptase reagent kit (TaKaRa, Tokyo, Japan). The cDNAs were amplified using the SYBR Premix Ex Taq kit (TaKaRa; DRR041S) on the CFX96 Touch Real-Time PCR Detection System (Bio-Rad, Hercules, CA, USA). The $2^{-\Delta\Delta CT}$ analysis method was used to determine relative fold changes of gene expression compared with *Rpl7* in mice and humans. The sequences of primers used for real-time PCR are listed in Table 1.

Statistical analysis

All results shown are representative of at least three independent experiments for the in vitro study. Data were presented as the mean ± standard deviation and were analyzed using the student's t-test for two groups. A one-way ANOVA test was performed for multiple comparisons. Significance was set at $P < 0.05$.

Abbreviations

Dtprp	Decidua/trophoblast prolactin-related protein
IGFBP1	Insulin growth factor binding protein 1
LPA3	Lysophosphatidic acid receptor 3
PGE2	Prostaglandin E2
PGI2	Prostacyclin I2

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12917-025-04505-5.

Supplementary Material 1

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Author contributions
Peng-Chao Wang: Conceptualization, Methodology, Data curation, Writing-Original draft preparation, Investigation, Writing- Reviewing and Editing; Jie Liu: Data curation, Investigation, Writing- Original draft preparation and editing; Yue-Fang Liu: Writing- Original draft preparation and Editing; Yang Wu: Data curation, Investigation, Writing- Original draft preparation and editing; Zhen-Shan Yang: Writing- Original draft preparation, Writing -review & editing, Supervision; Lin-Li Xue: Conceptualization, Supervision, Writing-review & editing.

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Data availability
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Animal Care and Use Committee of Shanxi Agricultural University. All mouse protocols were approved by the Institutional Animal Care and Use Committee of Shanxi Agricultural University. All methods were carried out in accordance with ARRIVE guidelines. The animals used in this study were derived from commercial sources, and the owners' consent was not required.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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