MOLECULAR REPRODUCTION AND DEVELOPMENT 66:218–224 (2003)

# Peroxisome Proliferator-Activated Receptor Delta Expression and Regulation in Mouse Uterus During Embryo Implantation and Decidualization

NAI-ZHENG DING, CHUN-BO TENG, HONG MA, HUA NI, XING-HONG MA, LI-BIN XU, AND ZENG-MING YANG*

*College of Life Sciences, Northeast Agricultural University, Harbin, China*

**ABSTRACT** The aim of this study was to examine the expression and regulation of peroxisome proliferator-activated receptor (PPAR) *PPARδ* gene in mouse uterus during early pregnancy by in situ hybridization and immunohistochemistry. PPARδ expression under pseudopregnancy, delayed implantation, hormonal treatment, and artificial decidualization was also investigated. There was a very low level of PPARδ expression on days 1–4 of pregnancy. On day 5 when embryo implanted, PPARδ expression was exclusively observed in the subluminal stroma surrounding the implanting blastocyst. No corresponding signals were seen in the uterus on day 5 of pregnancy. There was no detectable PPARδ signal under delayed implantation. Once delayed implantation was terminated by estrogen treatment and embryo implanted, a strong level of PPARδ expression was induced in the subluminal stroma surrounding the implanting blastocyst. Estrogen treatment induced a moderate level of PPARδ expression in the glandular epithelium, while progesterone treatment had no effects in the ovariectomized mice. A strong level of PPARδ expression was seen in the decidua on days 6–8 of pregnancy. PPARδ expression was also induced under artificial decidualization. These data suggest that PPARδ expression at implantation sites require the presence of an active blastocyst and may play an essential role for blastocyst implantation. *Mol. Reprod. Dev. 66: 218–224, 2003.* © 2003 Wiley-Liss, Inc.

**Key Words:** mouse; uterus; implantation; PPARδ; pregnancy

## INTRODUCTION

Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear hormone receptors belonging to the steroid receptor superfamily. There are three PPAR isoforms, PPARα, PPARδ (also known as PPARβ), and PPARγ in the mouse (Guan and Breyer, 2001). PPARs must heterodimerize with retinoid X receptors (RXRs) and bind to PPAR response elements (PPREs) present in the promoter region of target gene during transcriptional regulation (Desvergne and Wahli, 1999).

PPARγ has been shown to be essential for the development of adipose tissue, glucose homeostasis, and inhibition of a number of proinflammatory gene expression (Desvergne and Wahli, 1999). PPARγ (−/−) conceptuses exhibit placental defects in trophoblast differentiation and vascular processes (Barak et al., 1999). PPARα is a transcription factor dedicated to stimulate lipid metabolism by the induction of peroxisomal β-oxidation and fatty acid ω-hydroxylation (Schoonjans et al., 1996). Mice lacking functional PPARα are incapable of responding to peroxisome proliferators and fail to induce expression of a variety of genes required for the metabolism of fatty acids, including acyl-CoA oxidase (Lee et al., 1995).

PPARδ is highly expressed in brain, colon, and skin, and may be involved in the bone formation, lipid metabolism, and epidermal maturation (Matsuura et al., 1999; Mano et al., 2000). In the mouse uterus, PPARδ is also highly expressed at the implantation site (Lim et al., 1999). In the COX-2 deficient mice, there were failures in implantation and decidualization (Lim et al., 1997). L-165,041, PPARδ-selective agonist, is able to restore implantation in COX-2 deficient mice. Furthermore, the co-administration of L-165,041 with 9-cis-RA, a RXR agonist, greatly improved implantation rate in COX-2$^{-}$ recipients (Lim et al., 1999). Nevertheless, implantation can proceed in the complete absence of either maternal or embryonic PPARδ although PPARδ deficiency in mice results in placental defects and frequent mid-gestation lethality (Barak et al., 2002).

Although PPARδ expression in mouse uterus during early pregnancy was briefly examined (Lim et al., 1999), the regulation of PPARδ expression under delayed implantation, pseudopregnancy, and steroid treatment is still unknown. The aim of the present study was to determine the expression and regulation of *PPARδ* gene

Grant sponsor: Chinese National Natural Science Foundation; Grant numbers: 39825120, 30170110, 30270163; Grant sponsor: Special Fund for Major State Basic Research Project; Grant number: G1999055903; Grant sponsor: CICCR Program, subproject of the CONRAD Program, Eastern Virginia Medical School, Virginia, USA; Grant number: CIG-01-64.

*Correspondence to: Zeng-Ming Yang, College of Life Sciences, Northeast Agricultural University, Harbin 150030, China.
E-mail: zmyang@mail.neau.edu.cn

Received 18 October 2002; Accepted 18 February 2003
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI 10.1002/mrd.10348

during pregnancy, pseudopregnancy, delayed implantation, steroid treatment, and artificial decidualization in mouse uterus by in situ hybridization and immunohistochemistry.

## MATERIALS AND METHODS

### Animals and Treatments

Mature mice (Kongmin White outbred strain) were caged in a controlled environment with a 14 hr light: 10 hr dark cycle. All animal procedures were approved by the Institutional Animal Care and Use Committee of Northeast Agricultural University. Adult females were mated with fertile or vasectomized males of the same strain to induce pregnancy or pseudopregnancy, respectively (day 1 = day of vaginal plug). Pregnancy on days 1–4 was confirmed by recovering embryos from the reproductive tracts. The implantation sites on days 5–6 were identified by intravenous injection of 0.1 ml of 1% Chicago blue (Sigma Chemical Co., St. Louis, MO) in 0.85% sodium chloride.

To induce delayed implantation, the pregnant mice were ovariectomized at 08:30–09:00 hr on day 4 of pregnancy. Progesterone (1 mg/mouse) was injected to maintain delayed implantation from days 5 to 7. Estradiol-17β (25 ng/mouse) was given to progesterone-primed delayed-implantation mice to terminate delayed implantation. The mice were sacrificed to collect uteri 24 hr after estrogen treatment. The implantation sites were identified by intravenous injection of Chicago blue solution. Delayed implantation was confirmed by flushing the blastocysts from the uterus.

Artificial decidualization was induced by intraluminally infusing 25 μl sesame oil into one uterine horn on day 4 of pseudopregnancy, while the contralateral uninjected horn served as a control. The uteri were collected on day 8 of pseudopregnancy. Decidualization was confirmed by weighing uterine horn and histological examination of uterine sections (Lim et al., 1997).

Hormonal treatments were initiated 2 weeks after mature female mice were ovariectomized. The ovariectomized mice were treated with an injection of estradiol-17β (100 ng/mouse, Sigma), progesterone (1 mg/mouse, Sigma), or a combination of the same doses of progesterone and estradiol-17β for 24 hr. All steroids were dissolved in sesame oil and injected s.c. Controls received the vehicle only (0.1 ml/mouse).

### Immunohistochemistry

Mouse uteri were immediately cut into small pieces, fixed in Bouin's solution, dehydrated, and embedded in paraffin. Sections (7 μm) were cut, deparaffinized, and rehydrated. Nonspecific binding was blocked in 10% normal horse serum in PBS for 1 hr. The sections were incubated with goat anti-human PPARδ (1:300, Santa Cruz Biotechnology, Inc., Santa Cruz, CA) in 10% horse serum overnight at 4°C. After washing in PBS three times for 5 min each, the sections were incubated with biotinylated rabbit anti-goat IgG followed by an avidin–alkaline phosphatase complex and Vector Red according to the manufacturer's protocol (Vectastain ABC-AP kit, Vector Laboratories, Burlingame, CA). Vector Red was visualized as a red color. Endogenous alkaline phosphatase activity was inhibited by supplementing 1 mM levamisole (Sigma) into Vector Red substrate solution. In some sections, goat anti-human PPARδ was replaced with normal goat IgG as a negative control. The sections were counterstained with hematoxylin and mounted. The degree of staining was assessed subjectively by blinded examination of the slides by two investigators and expressed as basal (+/−), low (+), moderate (++), or strong (+++) level.

### In Situ Hybridization

Total RNAs from the rat uterus on day 7 of pregnancy were reverse-transcribed and amplified with forward primer 5′-GAGGAGAAAGAGGAAGTGG and reverse primer 5′-CCACCAGCTTCCTCTTCTC designed according to rat PPARδ (295–724 bp, Genbank Accession number U40064). The amplification of PPARδ cDNA was done for 30 cycles at 94°C for 30 sec, 60°C for 30 sec, and 72°C for 45 sec. The amplified fragment (430 bp) of PPARδ was recovered from the agarose gel and cloned into pGEM-T plasmid (pGEM-T Vector System 1, Promega, Madison, WI). The orientation of PPARδ fragment in pGEM-T plasmid was determined by a combination of the primers for T7, SP6, and PPARδ. The cloned PPARδ fragment was further verified by sequencing and matched with the corresponding region of rat PPARδ sequence. These plasmids were linearized with appropriate enzymes for labeling. Digoxigenin (DIG)-labeled antisense or sense cRNA probes were transcribed in vitro using a DIG RNA labeling kit (T7 for sense and SP6 for antisense; Boehringer Mannheim, Mannheim, Germany).

Uteri were cut into 4–6 mm pieces and flash frozen in liquid nitrogen. Frozen sections (10 μm) were mounted on 3-aminopropyltriethoxy-silane (Sigma)-coated slides and fixed in 4% paraformaldehyde solution in PBS. The sections were washed in PBS twice, treated in 1% Triton X-100 for 20 min and washed again in PBS three times. Following the prehybridization in the solution of 50% formamide and 5× SSC (1× SSC is 0.15 M sodium chloride, 0.015 M sodium citrate) at room temperature for 15 min, the sections were hybridized in the hybridization buffer (5× SSC, 50% formamide, 0.02% BSA, 250 μg/ml yeast tRNA, 10% dextran sulfate, 1 μg/ml denatured DIG-labeled antisense or sense RNA probe for rat PPARδ) at 55°C for 16 hr. After hybridization, the sections were washed in 50% formamide/5× SSC at 55°C for 15 min, 50% formamide/2× SSC at 55°C for 30 min, 50% formamide/0.2× SSC at 55°C twice for 30 min each, and 0.2× SSC at room temperature for 5 min. After nonspecific binding was blocked in 1% block mix (reagent blocking) (Boehringer Mannheim) for 1 hr, the sections were incubated in sheep anti-DIG antibody conjugated with alkaline phosphatase (1:5,000; Boehringer Mannheim) in 1% block mix (reagent blocking) overnight at 4°C. The signal was visualized with 0.4 mM 5-bromo-4-chloro-3-indolyl phosphate and 0.4 mM nitroblue tetrazolium in the buffer containing 100 mM

Tris-HCl, pH 9.5, 100 mM NaCl, and 50 mM $MgCl_2$. Endogenous alkaline phosphatase activity was inhibited with 2 mM levamisole (Sigma). All of the sections were counter-stained with 1% methyl green in 0.12 M glacial acetic acid and 0.08 M sodium acetate for 30 min.

## RESULTS

### PPARδ mRNA in Mouse Uterus During Early Pregnancy

There was no detectable PPARδ mRNA signal in mouse uteri from days 1 to 4 of pregnancy (Fig. 1A,B). On day 5 of pregnancy, a strong level of PPARδ mRNA signal was seen in the subluminal stroma immediately surrounding the implanting blastocyst, while not in the luminal epithelium (Fig. 1C). Once the DIG-labeled PPARδ antisense cRNA was replaced with DIG-labeled PPARδ sense cRNA, there was no corresponding signal in the uretus on day 5 of pregnancy (Fig. 1D). From days 6 to 8 of pregnancy, a strong level of PPARδ mRNA signals were mainly localized in the primary deciduas (Fig. 1F–H).

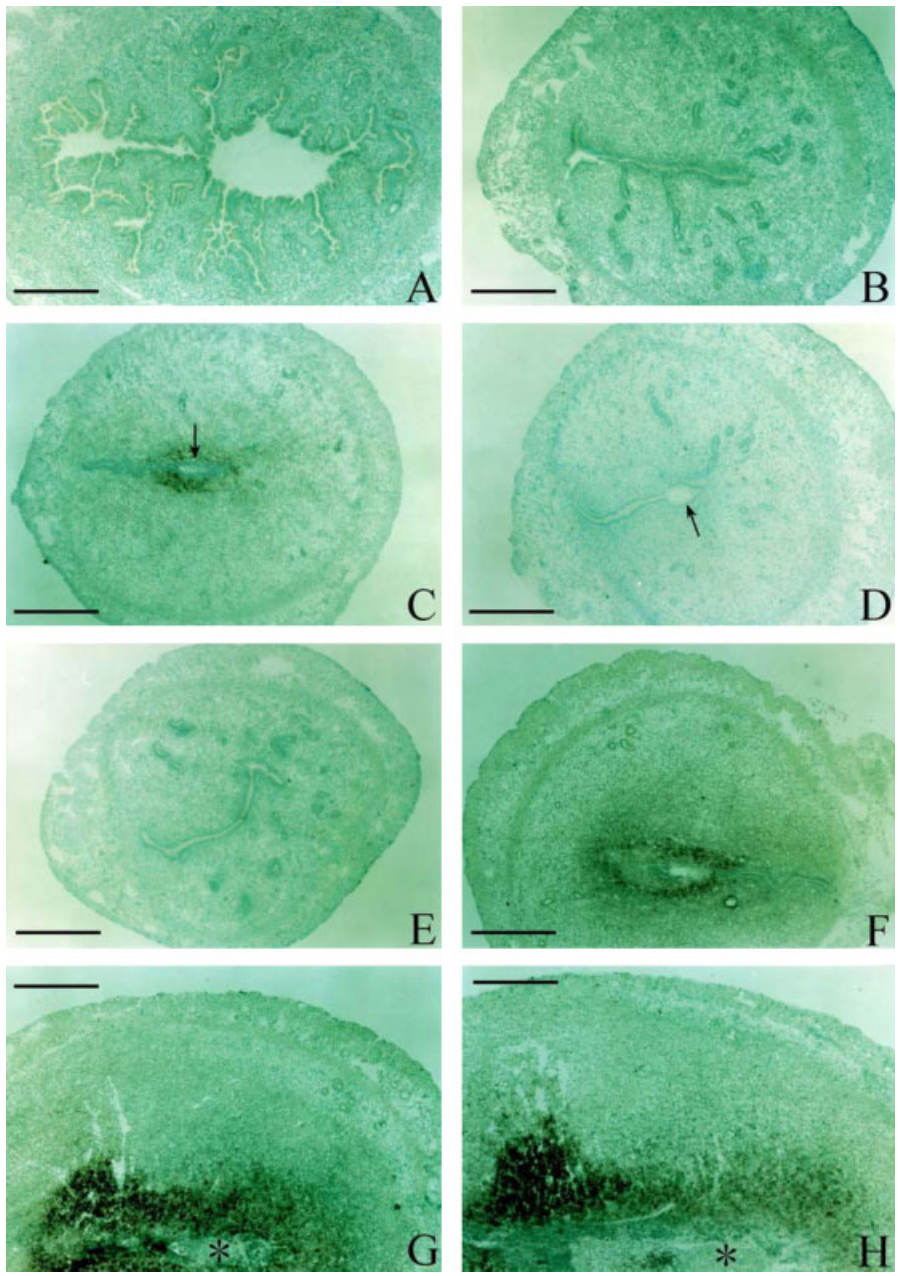


**Fig. 1.** In situ hybridization of PPARδ mRNA in mouse uterus on days 1 (**A**), 4 (**B**), 5 (**C**), 6 (**F**), 7 (**G**), and 8 (**H**) of pregnancy, respectively. PPARδ mRNA signal was not seen in the mouse uterus on day 5 of pregnancy when PPARδ sense cRNA probe was used (**D**). There was no detectable PPARδ mRNA signal in mouse uterus on day 5 of pseudopregnancy (**E**). Arrow, implanting blastocyst; *uterine lumen. Bar = 30 μm.

### Immunohistochemistry of PPARδ Protein During Early Pregnancy

There was a basal level of PPARδ immunostaining in the stroma underlying the luminal epithelium on days 1–3 of pregnancy (Fig. 2A,B). However, there was no detectable PPARδ immunostaining in the whole uterus on day 4 of pregnancy (Fig. 2C). On day 5 of pregnancy, PPARδ immunostaining was strongly localized in the stroma immediately surrounding the implanting blastocyst, while no signal was seen in the luminal epithelium at the opposite side of the lumen (Fig. 2D). On day 6 of pregnancy, PPARδ immunostaining was mainly observed in the primary decidua (Fig. 1F). From days 7 to 8 of pregnancy, PPARδ immunostaining was strongly detected in the decidual zone near the myometrium (Fig. 2G,H).

### PPARδ Expression During Pseudopregnancy

There were no detectable PPARδ mRNA signals in mouse uteri from days 1 to 8 of pseudopregnancy (Fig. 1E). Similarly, PPARδ immunostaining was also not observed in the mouse uteri during days 1–8 of pseudopregnancy (Fig. 2E).

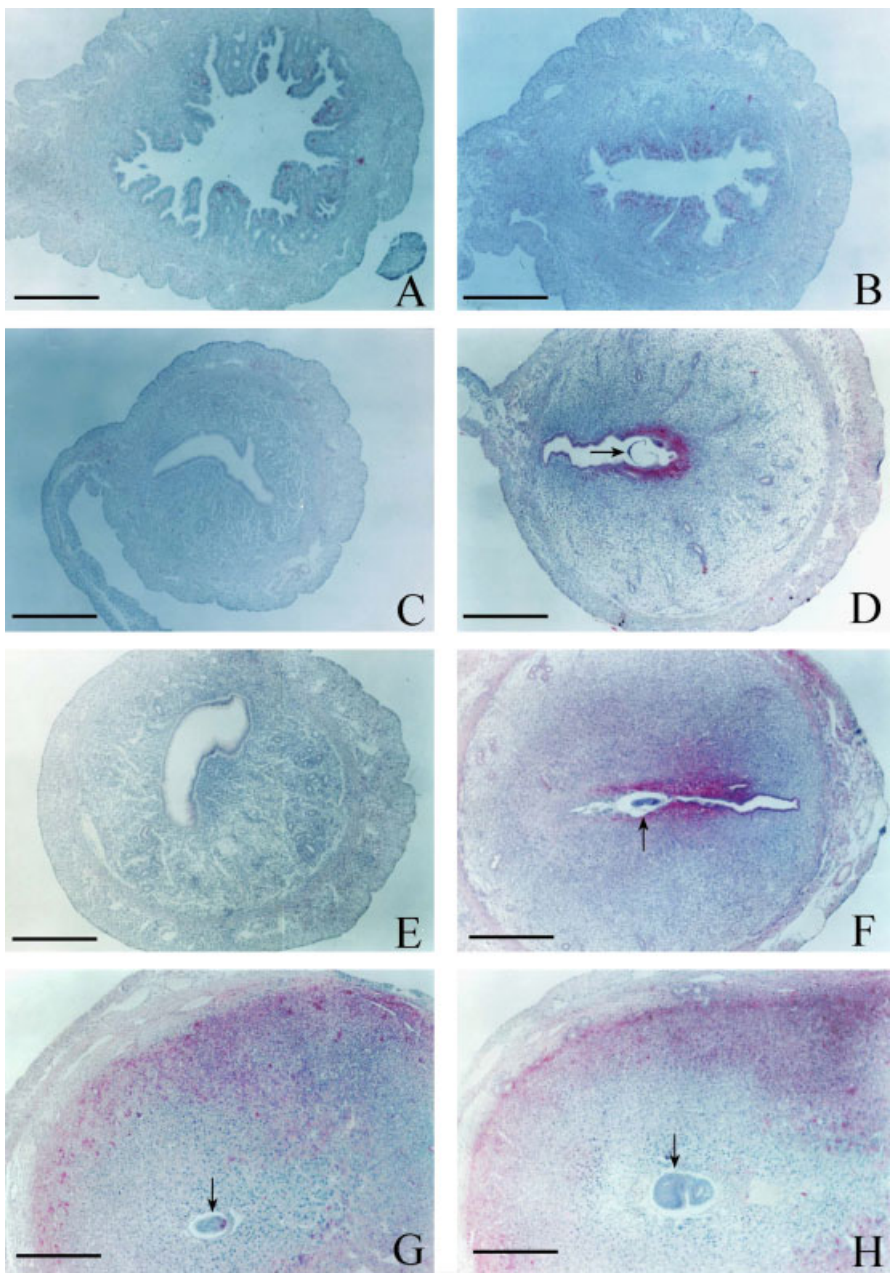


**Fig. 2.** Immunostaining of PPARδ protein in mouse uterus on days 1 (**A**), 2 (**B**), 4 (**C**), 5 (**D**), 6 (**F**), 7 (**G**), and 8 (**H**) of pregnancy, respectively. There was no detectable PPARδ immunostaining on day 5 of pseudopregnancy (**E**). Arrow, implanting embryo. Bar = 30 μm.

### PPARδ Expression During Delayed Implantation

There was no detectable PPARδ mRNA signal in the uterus under delayed implantation (Fig. 3A). After delayed implantation was determinated by estrogen treatment and embryos implanted, PPARδ mRNA signal was strongly observed in the subluminal stroma immediately surrounding the implanting blastocysts (Fig. 3B).

PPARδ immunostaining was not seen in the uterus under delayed implantation (Fig. 3C). However, a strong level of PPARδ immunostaining was observed in the subluminal stromal cells immediately surrounding the implanting blastocysts (Fig. 3D).

### PPARδ Expression During Artificial Decidualization

There was no detectable PPARδ mRNA signal in the control horn (Fig. 3E). However, PPARδ expression was

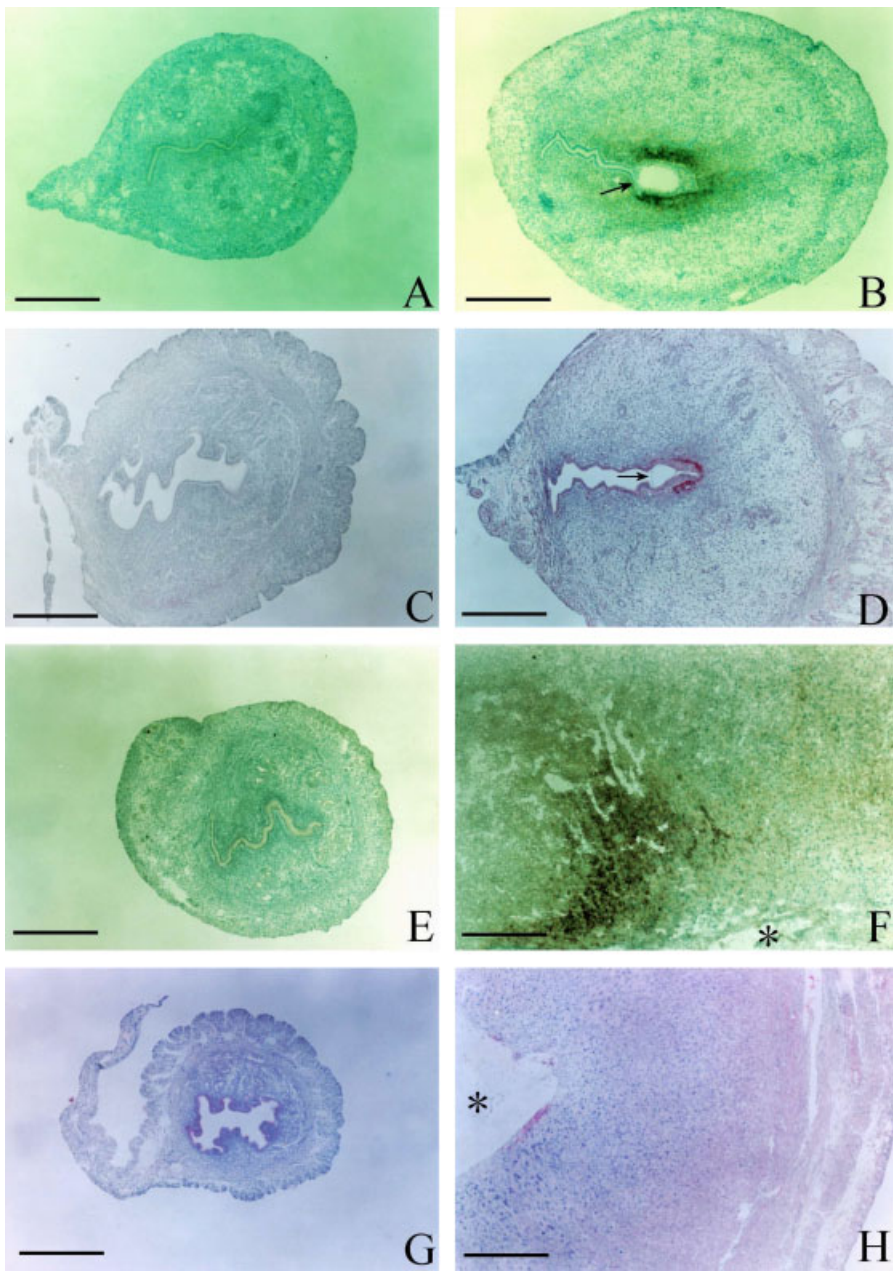


**Fig. 3.** PPARδ expression in mouse uterus. Both PPARδ mRNA (**A**) and protein (**C**) were not detected in the uterus during delayed implantation. After delayed implantation was terminated by estrogen treatment and embryo implanted, both PPARδ mRNA (**B**) and protein (**D**) were strongly shown in the subluminal stromal cells immediately surrounded the implanting blastocyst (arrows). Both PPARδ mRNA (**E**) and protein (**G**) were not detected in the control uterine horn. After decidualization was artificially induced by injecting sesame oil into pseudopregnant uterine horn on day 4, the expression of PPARδ mRNA (**F**) and protein (**H**) expression was seen in the decidualized cells. Arrow, implanting blastocyst; *uterine lumen. Bar = 30 μm.

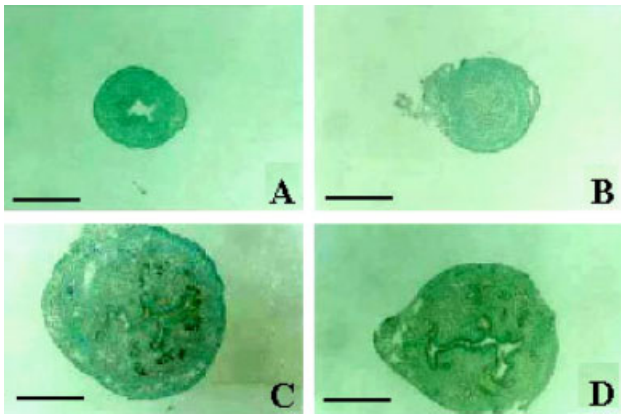


**Fig. 4.** Hormonal regulation of PPARδ mRNA expression in the ovariectomized mice treated with sesame oil (**A**), progesterone (**B**), estrodiol-17β (**C**), and a combination of progesterone and estrogen (**D**). Bar = 30 μm.

stimulated in the decidual cells, especially in a subpopulation of cells in the decidual bed at the mesometrial pole (Fig. 3F).

There was a basal level of PPARδ immunostaining in the luminal epithelium in the control uterus (Fig. 3G). During artificial decidualization, a low level of PPARδ immunostaining was detected in the decidual cells (Fig. 3H).

### Hormonal Regulation of PPARδ Expression

There was no detectable PPARδ mRNA signal in the ovariectomized uterus (Fig. 4A). Although PPARδ mRNA expression was not seen in the progesterone-treated uterus (Fig. 4B), estrogen treatment induced a moderate level of PPARδ signal in the glandular epithelium (Fig. 4C). However, no PPARδ expression was detected in the uterus treated by a combination of estrogen and progesterone (Fig. 4D).

## DISCUSSION

In our study, both PPARδ mRNA and immunostaining was strongly detected in the subluminal stroma immediately surrounding the implanting blastocyst. This expression pattern was similar to a previous report (Lim et al., 1999). However, the localization of both PPARδ mRNA and immunostaining was more condensed and concentrated in our study. Moreover, this kind of expression pattern was not observed in the delayed uterus. Once delayed implantation was terminated by estrogen treatment and embryos implanted, a strong level of PPARδ mRNA and immunostaining was also induced in the subluminal stroma immediately surrounding the implanting blastocyst. Additionally, no similar expression pattern was seen in the uterus on day 5 of pseudopregnancy. Our data suggest that the presence of an active blastocyst is required for PPARδ expression at implantation sites. At implantation sites, COX-2 is highly expressed in the luminal epithelium and subepithelial stromal cells at the anti-mesometrial pole exclusively surrounding the implanting blastocyst (Chakraborty et al., 1996). PGI2 is abundantly produced at implantation sites. Although PGI2 receptor was not detected or low during the peri-implantation, PPARδ is highly expressed at implantation sites (Lim et al., 1999). COX-2-derived $PGI_2$ might mediate embryo implantation via PPARδ (Lim et al., 1999). $PGI_2$-mediated activation of PPARδ was also reported in colorectal cancer (Gupta et al., 2000). Because $PGI_2$ can act as a potent vasoactive agent to participate in vascular permeability changes (Wheeler-Jones et al., 1997; Murohara et al., 1998), the high level of PPARδ expression in the subluminal stroma at implantation sites may be related to the increase of vascular permeability, which is the first discernible sign of implantation at the site of blastocyst apposition (Psychoyos, 1986).

There were multiple failures in implantation and decidualization in the COX-2-deficient mice (Lim et al., 1997). PPARδ selective agonist is able to restore implantation in COX-2 deficient mice. Implantation in these deficient mice could also be considerably improved by treating with carbaprostacyclin (cPGI), a PGI2 agonist and ligand for PPAR (Lim et al., 1999). Nevertheless, implantation can proceed in the complete absence of either maternal or embryonic PPARδ although PPARδ deficiency in mice results in placental defects and frequent mid-gestation lethality (Barak et al., 2002). This suggests that other molecules may compensate the loss of PPARδ. Microsomal prostaglandin E synthase was strongly expressed at implantation site of mouse uterus (Ni et al., 2002). EP2, a subtype of $PGE_2$ receptor, was also highly expressed at implantation site (Lim and Dey, 1997). It is possible that $PGE_2$ may compensate the loss of PPARδ via EP2 and mediate embryo implantation. Additionally, there is a redundancy in the functions of PPARα and PPARδ as transcriptional regulators of fatty acid homeostasis. The high level of PPARδ in skeletal muscle can compensate for deficiency of PPARα (Muoio et al., 2002). PPARδ may be a potent inhibitor of ligand-induced transcriptional activity of PPARα and PPARγ because of the widespread expression of PPARδ and the restricted pattern for PPARα and PPARγ. The relative level of PPARδ expression possibly acts as a gateway receptor to modulate PPARα and PPARγ activity (Shi et al., 2002). Moreover, COX-2 compensation occurs in the absence of COX-1 to provide the critical amount of prostaglandins necessary to maintain fertility in COX-1 deficient mice (Reese et al., 1999). Whether PPARδ deficiency can be compensated by a high level of PPARα expression remains to be determined.

Because both progesterone and estrogen are required for induction of implantation in the mouse (Yoshinaga and Adams, 1966), we then checked hormonal regulation of PPARδ expression. There was no detectable PPARδ expression in the ovariectomized mouse uterus. Progesterone had no effects on the expression, while estrogen only induced modest expression in the uterine glands. Additionally, a high level of PPARδ expression was not seen in the estrous uterus, when estrogen level reached a peak at estrus. The hormonal regulation of

PPARδ expression should be different from the regulation of leukemia inhibitory factor (LIF). LIF expression is required for implantation (Stewart et al., 1992) and under the maternal control. Estrogen significantly induces LIF expression. LIF was also highly expressed in the estrous uterus (Stewart et al., 1992; Yang et al., 1996).

PPARδ is highly expressed in the decidua on days 6–8 of pregnancy. PPARδ expression is also induced in the decidua under artificial decidualization. These results further confirm a previous report on PPARδ localization (Lim et al., 1999). Because COX-2 also shared a similar localization with PPARδ in the decidua (Chakraborty et al., 1996) and PGI2 agonist could restore decidualization in COX-2 deficient mice, COX-2-derived PGI2 may also play a role in decidualization via PPARδ.

In summary, PPARδ expression at implantation sites requires the presence of an active blastocyst and may play an essential role for blastocyst implantation.

## ACKNOWLEDGMENTS

The views expressed by the authors do not necessarily reflect the views of CONRAD or CICCR.

## REFERENCES

Barak Y, Nelson MC, Ong ES, Jones YZ, Ruiz-Lozano P, Chien KR, Koder A, Evans RM. 1999. PPAR gamma is required for placental, cardiac, and adipose tissue development. Mol Cell 4:585–595.

Barak Y, Liao D, He W, Ong ES, Nelson MC, Olefsky JM, Boland R, Evans RM. 2002. Effects of peroxisome proliferator-activated receptor delta on placentation, adiposity, and colorectal cancer. Proc Natl Acad Sci USA 99:303–308.

Chakraborty I, Das SK, Wang J, Dey SK. 1996. Developmental expression of the cyclo-oxygenase-1 and cyclo-oxygenase-2 genes in the peri-implantation mouse uterus and their differential regulation by the blastocyst and ovarian steroids. J Mol Endocrinol 16:107–122.

Desvergne B, Wahli W. 1999. Peroxisome proliferator-activated receptors: Nuclear control of metabolism. Endocr Rev 20:649–688.

Guan Y, Breyer MD. 2001. Peroxisome proliferator-activated receptors (PPARs): Novel therapeutic targets in renal disease. Kidney Int 60: 14–30.

Gupta RA, Tan J, Krause WF, Geraci MW, Willson TM, Dey SK, DuBois RN. 2000. Prostacyclin-mediated activation of peroxisome proliferator-activated receptor delta in colorectal cancer. Proc Natl Acad Sci USA 97:13275–13280.

Lee SS, Pineau T, Drago J, Lee EJ, Owens JW, Kroetz DL, Fernandez-Salguero PM, Westphal H, Gonzalez FJ. 1995. Targeted disruption of the alpha isoform of the peroxisome proliferator-activated receptor gene in mice results in abolishment of the pleiotropic effects of peroxisome proliferators. Mol Cell Biol 15:3012–3022.

Lim H, Dey SK. 1997. Prostaglandin E2 receptor subtype *EP2* gene expression in the mouse uterus coincides with differentiation of the luminal epithelium for implantation. Endocrinology 138: 4599–4606.

Lim H, Paria BC, Das SK, Dinchuk JE, Langenbach R, Trzaskos JM, Dey SK. 1997. Multiple female reproductive failures in cyclooxygenase 2-deficient mice. Cell 91:197–208.

Lim H, Gupta RA, Ma WG, Paria BC, Moller DE, Morrow JD, DuBois RN, Trzaskos JM, Dey SK. 1999. Cyclo-oxygenase-2-derived prostacyclin mediates embryo implantation in the mouse via PPAR delta. Genes Dev 13:1561–1574.

Mano H, Kimura C, Fujisawa Y, Kameda T, Watanabe-Mano M, Kaneko H, Kaneda T, Hakeda Y, Kumegawa M. 2000. Cloning and function of rabbit peroxisome proliferator-activated receptor delta/beta in mature osteoclasts. J Biol Chem 275:8126–8132.

Matsuura H, Adachi H, Smart RC, Xu X, Arata J, Jetten AM. 1999. Correlation between expression of peroxisome proliferator-activated receptor beta and squamous differentiation in epidermal and tracheobronchial epithelial cells. Mol Cell Endocrinol 147:85–92.

Muoio DM, MacLean PS, Lang DB, Li S, Houmard JA, Way JM, Winegar DA, Corton JC, Dohm GL, Kraus WE. 2002. Fatty acid homeostasis and induction of lipid regulatory genes in skeletal muscles of peroxisome proliferator-activated receptor (PPAR) alpha knock-out mice. Evidence for compensatory regulation by PPAR delta. J Biol Chem 277:26089–26097.

Murohara T, Horowitz J, Silver M, Tsurumi Y, Chen D, Sullivan A, Isner J. 1998. Vascular endothelial growth factor/vascular permeability factor enhances vascular permeability via nitric oxide and prostacyclin. Circulation 97:99–107.

Ni H, Sun T, Ding NZ, Ma XH, Yang ZM. 2002. Differential expression of microsomal PGE synthase at the implantation sites and in the decidual cells in mouse uterus. Biol Reprod 67:351–358.

Psychoyos A. 1986. Uterine receptivity for implantation. Ann NY Acad Sci 476:36–42.

Reese J, Brown N, Paria BC, Morrow J, Dey SK. 1999. COX-2 compensation in the uterus of COX-1 deficient mice during the preimplantation period. Mol Cell Endocrinol 150:23–31.

Schoonjans K, Staels B, Auwerx J. 1996. The peroxisome proliferator activated receptors (PPARS) and their effects on lipid metabolism and adipocyte differentiation. Biochim Biophys Acta 1302:93–109.

Shi Y, Hon M, Evans RM. 2002. The peroxisome proliferator-activated receptor delta, an integrator of transcriptional repression and nuclear receptor signaling. Proc Natl Acad Sci USA 99:2613–2618.

Stewart CL, Raspar P, Brunet LJ, Bhatt H, Gadi I, Kongten F, Abbondanzo SJ. 1992. Blastocyst implantation depends on maternal expression of leukemia inhibitory factor. Nature 359:76–79.

Wheeler-Jones C, Abu-Ghazaleh R, Cospedal R, Houliston RA, Martin J, Zachary I. 1997. Vascular endothelial growth factor stimulates prostacyclin production and activation of cytosolic phospholipase A2 in endothelial cells via p42/p44 mitogen-activated protein kinase. FEBS Letts 420:28–32.

Yang ZM, Chen DB, Le SP, Yasukawa K, Harper MJK. 1996. Differential hormonal regulation of leukemia inhibitory factor (LIF) in rabbit and mouse uterus. Mol Reprod Dev 43:470–476.

Yoshinaga K, Adams CE. 1966. Delayed implantation in the spayed progesterone treated adult mouse. J Reprod Fertil 12:593–595.