REVIEW

Physiological and pathological implications of retinoid action in the endometrium

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Abstract

Retinol (vitamin A) and its derivatives, collectively known as retinoids, are required for maintaining vision, immunity, barrier function, reproduction, embryogenesis and cell proliferation and differentiation. Despite the fact that most events in the endometrium are predominantly regulated by steroid hormones (estrogens and progesterone), accumulating evidence shows that retinoid signaling is also involved in the development and maintenance of the endometrium, stromal decidualization and blastocyst implantation. Moreover, aberrant retinoid metabolism seems to be a critical factor in the development of endometriosis, a common gynecological disease, which affects up to 10% of reproductive age women and is characterized by the ectopic localization of endometrial-like tissue in the pelvic cavity. This review summarizes recent advances in research on the mechanisms and molecular actions of retinoids in normal endometrial development and physiological function. The potential roles of abnormal retinoid signaling in endometriosis are also discussed. The objectives are to identify limitations in current knowledge regarding the molecular actions of retinoids in endometrial biology and to stimulate new investigations toward the development potential therapeutics to ameliorate or prevent endometriosis symptoms.

Key Words
- retinoids
- endometrial stroma
- implantation
- endometriosis

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Introduction

In many species, such as human, nonhuman primates and rodents, the endometrium consists of epithelial glands supported by a connective tissue stroma that undergoes cycles of proliferation and secretory activity. The uterine mucosa proliferates under the influence of estrogen. However, after ovulation, luteal progesterone changes the proliferative pattern to a secretory pattern that includes decidualization of endometrial stromal cells, which provides the nutritive and immune-privileged matrix for embryo implantation (Gellersen & Brosens 2014) and prevents the malignant transformation of endometrial epithelium under unopposed estrogenic action (Cheng *et al.* 2008). Though progesterone is critical for the initiation and maintenance of decidualization in the estrogen-primed endometrium, other factors, including prostaglandins, prolactin, growth factors and extracellular matrix proteins, are important.

Retinoic acid (RA), the physiological active metabolite of vitamin A (retinol), controls multiple biological processes, including differentiation, apoptosis and cell survival, via its nuclear receptors RARs or nonclassical RA receptor peroxisome proliferator-activated

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receptor β/δ (PPARβ/δ). The pathway of RA is also considered to be involved in the proliferation of epithelia and the transformation of endometrial stromal cells into specialized decidual cells. Numerous studies have demonstrated that the distribution of RA (Zheng *et al*. 2000), as well as the expression of RA receptors (Fukunaka *et al*. 2001, Ozaki *et al*. 2017), cellular retinol and RA-binding proteins (CRBP1, CRABP1 and CRABP2; Zheng & Ong 1998, Zheng *et al*. 2000), RA-synthesizing enzymes ALDH1A1 and ALDH1A2 (Napoli 1999, Duester 2000), and the RA-catabolizing enzyme CYP26A1 (Vermot *et al*. 2000) are highly and differentially regulated in the differentiating endometrium during the ovarian cycle and during the phase of blastocyst implantation (Vermot *et al*. 2000, Zheng 2000, Ozaki *et al*. 2017). The expression of these same genes can be modulated by ovarian steroid hormones (i.e., estradiol and progesterone) treatment (Vermot *et al*. 2000, Li & Ong 2003, Rühl *et al*. 2006, Fritzsche *et al*. 2007). The retinoid pathway is known to play vital roles in endometrial development and differentiation (Tanmahasamut & Sidell 2005, Wu *et al*. 2013, Nakajima *et al*. 2016), as well as endometrial neovascularization (Sidell *et al*. 2010) and blastocyst implantation (Han *et al*. 2010, Xia *et al*. 2010, Ma *et al*. 2012).

In addition, accumulating evidence shows that an aberrant RA metabolism can be a critical factor in the development of endometriosis (Pavone *et al*. 2011, Wieser *et al*. 2012, Pierzchalski *et al*. 2014, Yamagata *et al*. 2015), a common gynecological disease that affects up to 10% of reproductive-age women. This disease is characterized by the ectopic localization of endometrial-like tissues in the pelvic cavity, and its pathogenesis involves uncontrollable cell proliferation and is associated with local invasion and distant metastasis. Among the numerous aspects of endometrial behavior regulated by RA are matrix metalloproteinase secretion, gap junctional intracellular communication and the production of various cytokines involved in stromal cell growth, adhesion and differentiation (Wu *et al*. 2013). Interleukin 6 (IL-6), monocyte chemotactic protein 1 (MCP-1), tumor necrosis factor α (TNF-α), vascular endothelial growth factor (VEGF) and connexin43 are all aberrantly expressed in endometriotic lesions (Sawatsri *et al*. 2000, Sharpe-Timms 2001, Nozaki *et al*. 2006, Sidell *et al*. 2010, Wu *et al*. 2013). Thus, many seemingly discordant features of endometriosis, including decreased cell death, increased growth and migration, inflammation and enhanced invasive properties of intraperitoneally seeded endometrial cells, might be accounted for by the dysregulation of RA signaling. This contention was recently supported in a mouse model of endometriosis where treatment with RA suppressed IL-6 and the establishment, growth and vascularity of peritoneal implants, promoted macrophage differentiation (Wieser *et al*. 2012).

RA plays fundamental roles in the normal maintenance of endometrial physiology (Zheng *et al*. 2000, Sidell *et al*. 2002, Ding *et al*. 2003, Kuroda *et al*. 2013), and aberrant RA metabolism might be a predisposing factor for the development of endometriosis (Pavone *et al*. 2011, Wieser *et al*. 2012, Pierzchalski *et al*. 2014, Yamagata *et al*. 2015). However, a comprehensive and systematic analysis and understanding of RA pathway in endometrial physiology and pathology remain lacking. In this review, the latest advances with regard to understanding the retinoid pathway are first discussed, followed by an assessment of the functional roles of this signaling network in endometrial development and physiological function. This review also summarizes evidence that supports fundamental defects in retinoid metabolism and action among women with endometriosis. The objectives are to identify limitations in our current knowledge regarding molecular retinoid actions in endometrial biology and to propose future investigations to develop therapeutic or preventative agents for clinical endometriosis management.

Retinoid metabolism and signaling

Retinol (vitamin A) is a lipid-soluble vitamin that cannot be synthesized *de novo* by animals and is obtained from the diet as either preformed retinoids or carotenoids within the intestine. In the enterocytes, proretinoid carotenoids, such as β-carotene, can be either cleaved and converted to retinoids or incorporated intact and unmodified along with dietary fat and cholesterol into chylomicrons. Dietary retinoids that are newly absorbed by the enterocytes are esterified to retinyl ester and packaged with dietary fat and cholesterol into chylomicrons, which are later secreted into the lymphatic system. Approximately 66%–75% of newly acquired retinoids are absorbed and stored in the liver as lipid droplet retinyl esters (Harrison 2005). The remainder is absorbed by extrahepatic tissues (Quadro 2004). In cases of dietary vitamin A deficiency, the stored retinoid is hydrolyzed and mobilized back to retinol, which can be bound by RBP4 and enter the bloodstream for transport to peripheral tissues. In blood, holo-RBP4 is bound to transthyretin (TTR), a carrier protein for thyroid hormones. In a fasting circulation, retinol-RBP4

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is the preponderant retinoid form comprising >95% of retinoids, whereas, after a retinoid-rich meal, chylomicron retinyl ester concentrations exceed those of retinol-RBP4. In extrahepatic tissues, retinoids are acquired from the circulation in the form of carotenoids and retinyl esters from chylomicrons and retinol from retinol-RBP4-TTR ternary complexes. The uptake of retinol from retinol-RBP4-TTR into cells is mediated by the transmembrane-spanning protein stimulated by retinoic acid 6 (STRA6), which acts as a high-affinity cell surface receptor that binds extracellular holo-RBP, facilitates the dissociation of retinol from its carrier and transports it into cells (Kawaguchi *et al.* 2007, 2015).

Within target cells, carotenoids and retinyl esters can be both converted into retinol, which binds cellular retinol-binding proteins (CRBP1 and CRBP2). Cellular retinol can be stored in the form of retinyl ester catalyzed by lecithin: retinol acyltransferase (LRAT) or converted into transcriptionally active RA metabolites via two enzymatic reactions. First, retinol is converted into retinaldehyde by alcohol dehydrogenases (ADHs) or retinol dehydrogenases (RDHs) (Fig. 1). Aldehyde dehydrogenases (ALDHs) then catalyze the conversion of retinaldehyde into RA (Conaway *et al.* 2013). In the retinal pigment epithelium of the eye, retinol can also be metabolized to 11-cis-retinal, which serves to regenerate the visual pigment rhodopsin.

Most of the physiologic actions of retinoids are accounted for by the transcriptional regulatory activity of physiological active metabolites, i.e., all-trans-retinoic acid (atRA or RA) and 9-cis retinoic acid (9cRA). The action of RA is mediated by nuclear receptors, RA receptors

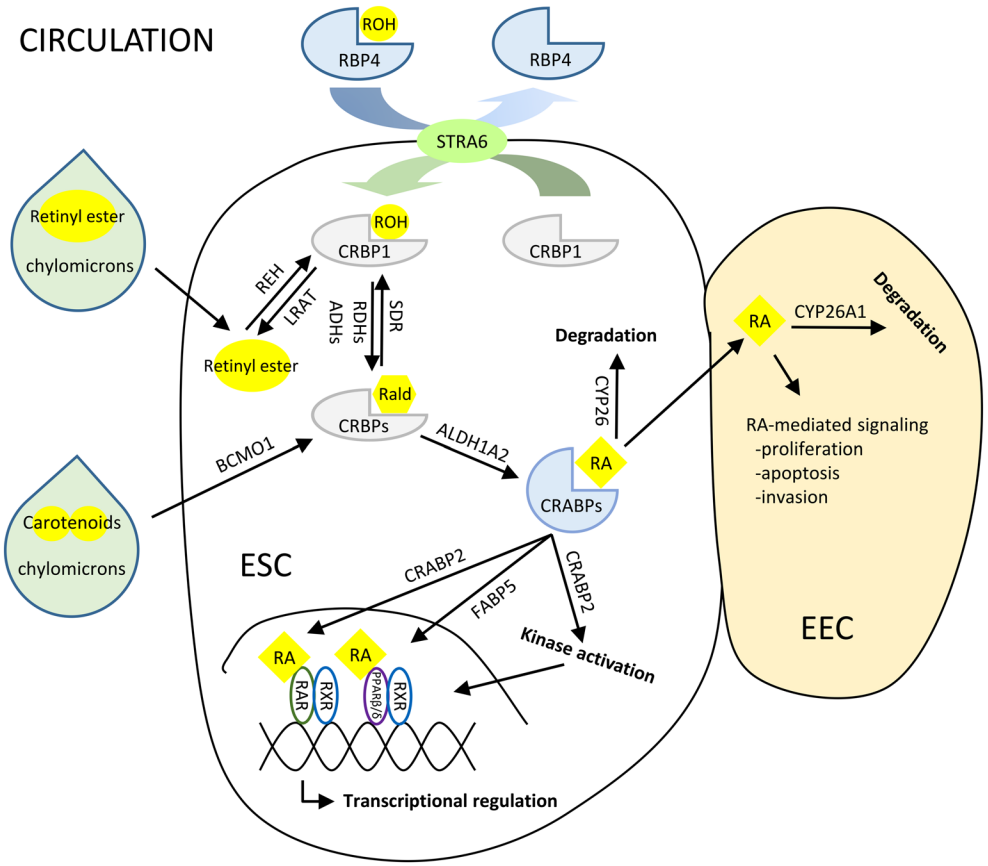

Figure 1
Schematic representation of retinoid uptake, metabolism and signaling in endometrial stromal cells (ESC) and endometrial epithelial cells (EEC). ESC can take up retinoids from the circulation in the forms of retinyl esters in chylomicrons (following a retinoid-rich meal), RBP4-bound retinol (ROH) (during fasting) or albumin-bound RA (very low levels). The transport of retinol from retinol-RBP4 into ESC is mediated by STRA6; however, the cellular processes that mediate retinyl ester and RA uptake are not yet established. Carotenoids in chylomicrons also represent a source of retinoids and can be converted to retinal (Rald) by β-carotene-15, 15′-monooxygenase (BCMO1). Cellular retinol can be oxidized to retinal and RA by dehydrogenases (ADHs, RDHs and ALDHs) or be converted to retinyl ester, a retinoid storage form, catalyzed by LRAT. Retinyl esters can also be hydrolyzed to retinol catalyzed by retinyl ester hydrolase (REH). RA exerts autocrine and paracrine transcriptional regulatory effects through RARs, RXRs and PPARβ/δ or alternatively degraded by CYP26 enzymes in ESC and neighboring EEC. A full colour version of this figure is available at https://doi.org/10.1530/JOE-17-0544.

(RARs): RARα, RARβ and RARγ or peroxisome proliferator-activated receptor β/δ (PPARβ/δ). In conjunction with transcriptional coactivators and corepressors, RARs and PPARs heterodimerize with retinoid X receptors (RXRs: RXRα, RXRβ and RXRγ) and associate with RA response elements (RAREs) or peroxisome proliferator response elements (PPREs) in the regulatory regions of specific target genes to regulate target gene transcription (Chambon 2005, Schug *et al.* 2008, Al Tanoury *et al.* 2013, Rochette-Egly 2014). RA partitioning between the two receptor signaling cascades has opposing effects on cell growth and apoptosis and the alternative pathways are regulated by the ratio of intracellular lipid-binding proteins, cellular RA-binding protein (CRABP2) and fatty acid-binding protein (FABP5; Schug *et al.* 2007). CRABP2 and FABP5 can bind and transport RA to RARs and PPARβ/δ, respectively (Delva *et al.* 1999, Dong *et al.* 1999). Furthermore, besides classical nuclear receptor signaling, RA stimulates rapid nongenomic signaling events through the stimulation of kinase phosphorylation by extra-nuclear RARs, which also can affect gene transcription (Al Tanoury *et al.* 2013, Rochette-Egly 2014). The primary biological ligand for RARs is atRA, whereas 9cRA can bind to RARs and RXRs.

The tissue distribution and levels of RA are regulated through its synthesis by ALDHs (Lin *et al.* 2003) and its catabolism into inactive polar compounds by CYP26 enzymes (Chithalen *et al.* 2002, Conaway *et al.* 2013). CRABPs and FABP5 also participate in the regulation of RA concentration (Dong *et al.* 1999, Noy 2000) and metabolism (Delva *et al.* 1999, Dong *et al.* 1999, Napoli 2016). In RA-sensitive tissues, CRABP1 can protect these vulnerable areas against the toxic effects of excessive amounts of RA (Ruberte *et al.* 1992). Furthermore, many of the components of RA biosynthesis are controlled by atRA via negative feedback. ATRA induces its own catabolism by inducing CYP26 transcription, allowing the degradation of excess atRA. Conversely, atRA can also regulate its biosynthesis by positive feedback, upregulating the expression of several RA biosynthesis components, such as RBP4, CRBP1 and STRA6 (Wu & Ross 2010).

Retinoid action in endometrial development and physiological function

The mammalian uterus develops from fused paramesonephric (Müllerian) ducts during embryonic development. The adult mammalian endometrium is divided into two steroid-responsive compartments, namely, an epithelial compartment consisting of luminal and glandular epithelia and a stromal compartment filled with fibroblasts, microvascular cells, macrophages and perivascular and large granular lymphocytes that infiltrate the stroma during the luteal phase of the menstrual cycle (Punyadeera *et al.* 2003). Luminal epithelium is the first point of contact between the uterus and blastocyst during implantation, while glandular epithelia synthesize and secrete bioactive substances that contribute to uterine receptivity and stromal cell decidualization. The endometrial functional layer undergoes cyclic regeneration regulated by estradiol and progesterone during menstrual or estrous cycles. It initially proliferates under the influence of estrogen. However, after ovulation, in addition to estradiol, the ovary starts to produce progesterone, which changes the proliferative pattern to a secretory one, providing a suitable environment for blastocyst implantation. Following fertilization, the embryo implants into the uterine wall and trophoblast-derived gonadotropins support the pregnancy by maintaining corpus luteum production of progesterone and estradiol. In this case, the endometrial functional layer remains as decidua. If fertilization or implantation fails, the endometrium will be either remodeled (estrous cycle) or shed (menstrual cycle). Numerous factors are involved in the regulation of endometrial development and function and RA plays important roles in these processes.

Hormonal control of endometrial retinoid pathway

Numerous studies revealed that the retinoid pathway and distribution of RA are distinctly and highly regulated in human and rodent endometrial epithelium and stroma (Vermot *et al.* 2000, Rühl *et al.* 2006, Fritzsche *et al.* 2007). The biosynthesis of endogenous RA is catalyzed directly by ALDHs. Among them, ALDH1A1 (also known as RALDH1) and ALDH1A2 (also known as RALDH2) exhibit specific temporal and special expression patterns in human and rodent endometrium during the ovarian cycle and early pregnancy. The abundance of *Aldh1a1* mRNA increases during murine diestrus and proestrus, whereas *Aldh1a2* is highly induced in metestrus (Vermot *et al.* 2000). The tissue localization of ALDH1A1 and ALDH1A2 showed that *ALDH1A1* and *ALDH1A2* are expressed in glandular epithelial and stromal cells, respectively (Vermot *et al.* 2000). The highest *Aldh1a2* expression in mouse stromal cells is observed during the estrogenic phase of the estrous cycle, strongly suggesting that its endogenous expression is estrogen dependent. This speculation was confirmed by subsequent studies in the endometrium of mice, rats and

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Table 1 Upregulated and downregulated genes involved in retinoid metabolism and signaling by estrogen and/or progesterone in the endometrium.

Genes	E_2	P_4	E_2+ P_4	Cell type	Species	References
ALDH1A1	↓[a]	–		Epithelium	Mouse	Vermot *et al.* (2000), Rühl *et al.* (2006)
ALDH1A2	↑[b]	–	↑	Stroma	Human, mouse, rat	Vermot *et al.* (2000), Deng *et al.* (2003), Li *et al.* (2004), Rühl *et al.* (2006)
CYP26A1	–[c]	↑	↑	Epithelium	Mouse	Fritzsche *et al.* (2007)
CRABP2	↑	[d]		Epithelium	Mouse, rat	Wardlaw *et al.* (1997), Li & Ong (2003)
RARα	↑			Epithelium	Rat	Boehm *et al.* (1997)
RARγ	↑			Epithelium	Rat	Boehm *et al.* (1997)
RXRα	↑			Epithelium	Rat	Boehm *et al.* (1997)

[a]Downregulation; [b]upregulation; [c]no effect; [d](blank) remains to be established.
E_2, estradiol; P_4, progesterone.

humans (Deng *et al.* 2003, Li *et al.* 2004, Rühl *et al.* 2006). Using ovariectomized mouse models, Rühl *et al.* (2006) demonstrated that *ALDH1A2* expression is rapidly (within 1–4 h) induced in stromal cells by estradiol but not by progesterone. By contrast, estradiol, but not progesterone, treatment decreases (within 4–24 h) *ALDH1A1* expression levels in glandular epithelium (Rühl *et al.* 2006). In a study by Deng *et al.* (2003), *ALDH1A2* expression was induced within human endometrium by estrogen replacement therapy. Thus, estradiol stimulates *ALDH1A2* expression in endometrial stroma but suppresses *ALDH1A1* expression in the endometrial glandular epithelium. By contrast, progesterone neither induces nor reduces the expression levels of the two genes (Table 1). The selective effects of estradiol are due to the differential expression of estrogen nuclear receptor isotypes ERα and ERβ (Katzenellenbogen & Korach 1997). In rat uteri, ERα is principally expressed in luminal and glandular epithelia, whereas ERβ is predominantly expressed in the stroma (Mowa & Iwanaga 2000*a*,*b*). As *ALDH1A2* expression might be selectively regulated via ERβ, further study should focus on using ERα/ERβ-selective ligands to dissect these estrogen-regulated pathways in the regulation of *ALDH* expression. Meanwhile, a potential estrogen response element was observed in the promoter of the mouse *Aldh1a2* gene (Wang *et al.* 2001). However, whether it plays a functional role remains unknown.

In addition to RA-synthesizing enzymes, RA levels are also regulated by RA-catabolizing enzymes, particularly the CYP26 family. These enzymes catalyze the conversion of RA into less-active polar metabolites (Conaway *et al.* 2013). CYP26A1, one of the most important members of the CYP26 family, is expressed in female reproductive tract (Vermot *et al.* 2000). In endometrial tissue obtained from premenopausal women, the *CYP26A1* mRNA levels were approximately 20 times higher during the late secretory phase than in the proliferative phase (Deng *et al.* 2003). In mouse endometrium, although *CYP26A1* expression is undetectable during the normal ovarian cycle, it is strongly induced in luminal and glandular epithelia, 4 h after progesterone administration (Fritzsche *et al.* 2007) or 24 h after human chorionic gonadotrophin (hCG) administration (Vermot *et al.* 2000). Also, in mouse endometrial epithelium, *Cyp26a1* expression is strongly induced between 3.5 and 4.5 gestational days, i.e., when the developing blastocysts implant into the endometrium. Endometrial *Cyp26a1* expression can be mainly regulated by progesterone because not only *Cyp26a1* mRNA levels are strongly increased in uterine luminal and glandular epithelial cells by the administration of progesterone or the combination of progesterone and estradiol but also the simultaneous administration of an antiprogestin inhibits the gene expression (Fritzsche *et al.* 2007) (Table 1). This regulation of *Cyp26a1* expression by progesterone may occur through direct activation of the progesterone receptor. RU486 (also known as mifepristone) is a synthetic steroid that exerts antiprogesterone action by competing with progesterone for receptor binding (Chan *et al.* 2003). Treatment with either RU486 or the combination of RU486 and progesterone showed an inhibition of *Cyp26a1* expression (Fritzsche *et al.* 2007). The mouse *Cyp26a1* promoter and its regulatory regions were partially characterized by Loudig and coworkers (2000, 2005). Their study showed the presence of two RA response elements on the *Cyp26a1* promoter, but no consensus binding sites for progesterone receptors. Thus, further studies are necessary to identify the possible regulatory elements responsible for the progesterone control of *Cyp26a1* expression.

Several binding proteins involved in the retinoid pathway are also distinctive in rodent and human endometria during the ovarian cycle (Loughney *et al.* 1995, Wardlaw *et al.* 1997). *Crbp1* expression peaked during diestrus, whereas *Crabp2* expression peaked

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sharply during estrus (proliferative phase). In addition, *Crabp2* expression has been shown to be induced directly by estradiol administration in the uteri of ovariectomized rats (Li & Ong 2003) (Table 1). Immunohistochemical studies showed that CRABP2 is localized to the luminal epithelium, whereas CRBP1 in the stroma (Wardlaw *et al.* 1997). CRABP2 expression is associated with local RA levels (Bucco *et al.* 1997, Zheng *et al.* 2000). From these data, it can be concluded that the endometrial stroma upregulates ALDH1A2 and therefore RA production upon estrogen stimulation. RA then diffuses into the adjacent epithelium, where it is catabolized by CYP26A1 induced by progesterone during the late secretory phase or implantation.

Numerous studies demonstrated the expression of RARs and RXRs in human endometrial epithelial and stromal cells (Prentice *et al.* 1992, Loughney *et al.* 1995, Kumarendran *et al.* 1996, Fukunaka *et al.* 2001). Using Northern blot, Kumarendran *et al.* (1996) demonstrated that *RARβ* mRNA expression is 1.7-fold higher in epithelial samples from the proliferative phase than from the secretory phase. Meanwhile, no significant difference was observed between the expression levels of *RARα*, *RARγ* and *RXRα* mRNA in epithelial tissues in the proliferative phase and those in the secretory phases. Similarly, the expression of *RARα*, *RARβ*, *RARγ* and *RXRα* mRNA in human endometrial stroma did not change in the proliferative and secretory phases of the menstrual cycle (Kumarendran *et al.* 1996). Meanwhile, using immunohistochemistry and Western blot analysis, Fukunaka *et al.* (2001) investigated changes in expression and subcellular localization of RARs and RXRs in human endometrial epithelium during the menstrual cycle. Their results indicated that, in the nuclei of endometrial epithelia, RARs and RXRs are expressed strongly in the proliferative phase and reduced during the secretory phase, correlated with serum estradiol concentration and ER expression (Fukunaka *et al.* 2001). Although RXRs decrease during the secretory phase, they are still expressed in the nuclei in the late secretory phase; by contrast, RARs are infrequently detected in the midsecretory and late secretory phases (Fukunaka *et al.* 2001). In stromal cells, the intensity of staining is strong in the proliferative phase but decreases in the secretory phase. Meanwhile, immunoreactivity to RXRs is strong throughout the cycle, similar to that in the nuclei of the epithelial cells (Fukunaka *et al.* 2001). In addition, ERα shows more intense staining in the endometrium of the proliferative phase, and PR shows positive staining in the endometrium of the mid-proliferative and early secretory phases (Fukunaka *et al.* 2001). The expression of retinoid receptors is associated with serum estradiol concentration and ER expression. Consistently, data from Boehm *et al.* (1997) showed that RARα, RARγ and RXRα expression levels are increased by estrogen in rat endometrial epithelium (Table 1). Thus, the expression of RARs is strongly affected by serum estrogen via ER in the endometrium. However, whether progesterone or PR expression inhibits the expression of retinoid receptors in endometrium remains to be determined.

Therefore, the endometrial retinoid pathway is mainly under the influence of ovarian steroid hormones, and RA and its receptors have regulatory effects on the endometrium during the ovarian cycle (Fig. 2).

Retinoid action in endometrial differentiation and development

Fate determination of endometrium in Müllerian duct

During development, the Müllerian ducts persist in females and differentiate into morphologically and functionally distinct oviducts, uterus and vagina. The oviductal epithelia are composed of ciliated cells and secretory cells (Yamanouchi *et al.* 2010); the uterine epithelia consist of simple columnar luminal and glandular epithelia (Kurita *et al.* 2000) and the vaginal epithelium

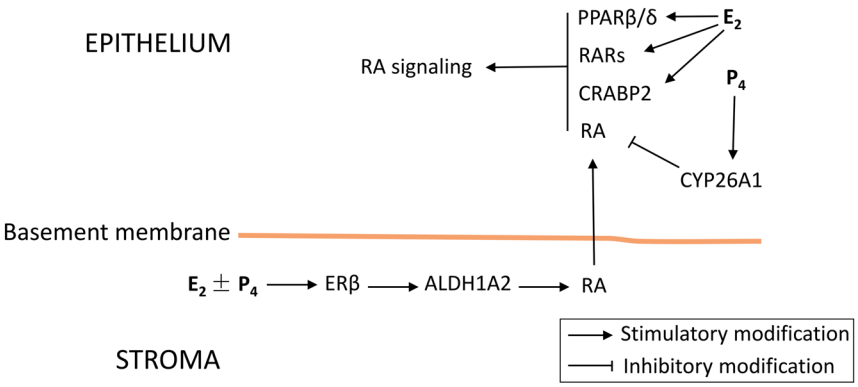

Figure 2
Hormonal control of the retinoid pathway in the endometrium. Estradiol (E_2) or E_2 + progesterone (P_4) can stimulate the expression of ALDH1A2, which can promote RA production, in stromal cells. RA produced by ESC can diffuse to EEC, where E_2 can promote the expression of RARs, PPARβ/δ and CRABP2. Thus, E_2 can increase RA signaling in the endometrium. However, P_4 can inhibit RA signaling through inducing CYP26A1 expression in EEC. A full colour version of this figure is available at https://doi.org/10.1530/JOE-17-0544.

develops into stratified cuboidal epithelium (Nakajima *et al.* 2011*a*). Nakajima *et al.* (2011*a*) performed tissue recombination experiments with epithelium and stroma to investigate the mechanisms underlying differentiation of the Müllerian ducts. The data showed that stromal factors determine the fate, differentiation and growth of Müllerian duct epithelia into the oviducts, uteri and vaginas of mice. DNA microarray analysis showed that the expression of several genes involved in retinoid metabolism is greater in the uteri than in the vaginas of neonatal mice (Suzuki *et al.* 2006, 2007). When pregnant rats are fed with a vitamin A-deficient diet, their fetuses exhibit incomplete Müllerian development (Wilson & Warkany 1948). Furthermore, Müllerian ducts of RAR or RXR KO mice are absent at embryonic day 12.5 (E12.5) (Mendelsohn *et al.* 1994, Kastner *et al.* 1997). These data suggest that retinoid signaling through RAR is essential for Müllerian duct development.

The important role of the retinoid pathway in fetal uterine stroma development was identified in the mouse. In fetal mice, *Rdh10* and *Aldh1a2* are expressed in the stroma of proximal Müllerian ducts, with expression levels decreasing toward the caudal ends (Nakajima *et al.* 2016). RDH10 is the primary enzyme responsible for catalyzing the conversion of retinol to retinaldehyde, the first step of RA synthesis, in embryonic mice (Farjo *et al.* 2011). Uterine *Cyp26a1* expression is essential for blastocyst implantation in pregnant mice (Han *et al.* 2010). However, *Cyp26a1* expression levels are low in Müllerian ducts, suggesting RA is not degraded there and more RA accumulates. Thus, RA levels might be increased in proximal Müllerian ducts. This hypothesis was confirmed in a reporter mouse expressing lacZ regulated by a strong RARE in the promoter. The data demonstrated that the highest endogenous RA levels are in the proximal Müllerian duct stroma, and the levels gradually decrease from the proximal to caudal regions (Nakajima *et al.* 2016). Thus, RA is produced and acts in the stroma of proximal and middle Müllerian ducts. *Rdh10* and *Aldh1a2* expression are significantly higher in the uteri of postnatal mice than those in their vaginas from postnatal day 2 (P2) to P90 (Nakajima *et al.* 2016). Moreover, mice fed from birth with vitamin A-deficient diets for 10 or 14 weeks exhibit squamous metaplasia in their uterine epithelia (Darwiche *et al.* 1993, Jetten *et al.* 1996). These data suggest a critical role of RA signaling in maintaining uterine epithelium.

In organ-cultured Müllerian ducts of RARE-lacZ mice at E14.5 and E17.5, retinal or RA treatment stimulated RA signaling in the stroma and induced uterine epithelial differentiation, which was defined as a layer of columnar epithelial cells negative for oviductal and vaginal epithelial markers. By contrast, inhibition of RAR signaling with the pan-RAR antagonist AGN193109 (AGN; Nakajima *et al.* 2016) induces vaginal epithelial differentiation. Nakajima *et al.* (2016) cultured Müllerian duct explants at E14.5 or E17.5 with RA or RAR antagonists and grafted these under the renal capsules of host mice. At day 30 post grafting, control E14.5 Müllerian ducts developed oviductal and uterine epithelia, while AGN treatment irreversibly induced vaginal epithelia. Meanwhile, grafted E17.5 middle Müllerian ducts had only uterine epithelia, and AGN treatment irreversibly induced vaginal epithelia. In grafted E17.5 caudal Müllerian ducts, vaginal epithelia were observed, and RA treatment permanently induced uterine epithelia but did not induce oviductal epithelia. These data indicate that RA in stroma at developing stages induces uterine epithelia in Müllerian ducts, whereas the inhibition of RAR signaling induces vaginal epithelia. The fate of oviductal stroma is determined at E14.5 (Nakajima *et al.* 2016). In female mouse embryos, activin A induced by inhibin βA is essential for the differentiation of vaginal epithelia (Nakajima *et al.* 2011*b*), whereas RA inhibits inhibin βA expression in the urogenital sinus (Bryant *et al.* 2014). *Hoxa10* is expressed at the boundary between future uterine and oviductal stroma in the Müllerian ducts at E16.5 (Ma *et al.* 1998) and is connected with the determination of the borderline between oviduct and uterus (Benson *et al.* 1996). RA stimulates *Hoxa10* and *Hoxa11* expression in Müllerian ducts; however, AGN abolishes these. Although the *Hoxa10* promoter contains a RARE (Delacroix *et al.* 2010), RAR cannot bind to the predicted RARE in the Müllerian duct (Nakajima *et al.* 2016). Thus, RA seems to induce *Hoxa10* expression via indirect RAR signaling, and other factors might mediate the action of RA on the determination of the border between the uterine and vaginal stroma. These data support a model in which RA-RAR signaling can play a crucial role in the determination of the fate of epithelia and stroma in the female reproductive tract (Fig. 3).

Endometrial gland development

Uterine glands are essential for pregnancy on account of secreting or transporting bioactive substances that regulate uterine receptivity and blastocyst implantation. Uterine gland development or adenogenesis is a postnatal event in rodents, domestic animals and humans (Hu *et al.* 2004). At birth, murine uteri lack uterine glands and consist of simple luminal epithelium supported by undifferentiated mesenchyme. Between P0 and P9, glandular epithelial

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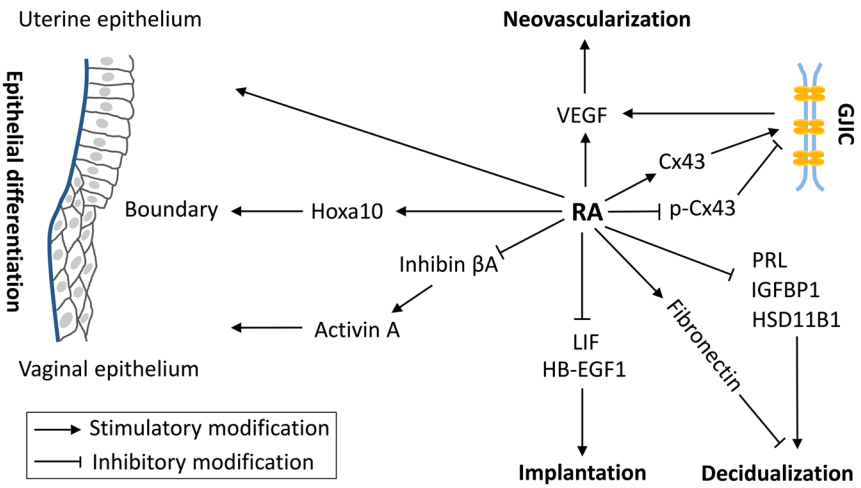

Figure 3
Schematic representation of retinoid action in endometrial development and physiological function. RA signaling in the Müllerian duct determines the differentiation of epithelium to form the future uterus and vagina involving Hoxa10, inhibin βA and activin A. Besides, RA signaling stimulates endometrial GJIC formation through inducing Cx43 expression and neovascularization through inducing VEGF expression. RA prevents stromal cell decidualization through inhibiting PRL, IGFBP1 and HSD11B1 production and promotes maintenance of fibronectin, an indicator of the undifferentiated stromal phenotype. In addition, RA reduces factors like LIF and HB-EGF1, which are required for endometrial receptivity, and successful implantation during late secretory phase requires lower RA levels in the luminal epithelia. A full colour version of this figure is available at https://doi.org/10.1530/JOE-17-0544.

cells differentiate and bud from luminal epithelia. By P15, the uterine histoarchitecture resembles that of the adult (Spencer *et al.* 2012). Gland morphogenesis also occurs during endometrial regeneration following menses or parturition (Garry *et al.* 2010, Huang *et al.* 2012). Based on data from the available literature, the luminal and glandular epithelia of mouse uteri have common but distinctly expressed genes (Cha *et al.* 2012, Filant & Spencer 2013). The components of the retinoid pathway, including *Aldh1a1*, *Aldh1a3*, *Rdh1* and *Rdh10*, are enriched in the glandular epithelia of neonatal uteri. Through microarray analysis, the glandular epithelium-enriched genes in P10 uteri were found to be associated with branching morphogenesis, growth and RA biosynthesis. *Aldh1a1* is enriched in developing neonatal and adult endometrial glands (Filant & Spencer 2013). Furthermore, the expression levels of *Aldh1a1* and *Aldh1a3* on P10 are much lower in progesterone-induced uterine gland-knockout (PUGKO) mice than in control mice (Filant & Spencer 2013). In addition, retinyl palmitate increases glandular epithelial areas in the uteri of neonatal pigs treated for 14 days starting from birth (Vallet *et al.* 1995). These data suggest that the retinoid pathway is involved in uterine adenogenesis. Further studies are still needed to elucidate the functional role of the retinoid pathway and the mechanisms governing uterine adenogenesis in neonates. The involvement of RA signaling in postnatal mouse endometrial adenogenesis will require conditional postnatal deletion models, such as the PR-Cre system.

Endometrial proliferation

Ovarian estrogen induces the proliferation of epithelial cells and stromal fibroblasts during the pre-ovulatory phase (Punyadeera *et al.* 2003). Studies in rodents suggested that RA plays an important role in modulating the effects of estrogen on the endometrium. As discussed earlier, endometria upregulate *ALDH1A2* upon estrogen stimulation during the proliferative phase (Vermot *et al.* 2000, Deng *et al.* 2003, Rühl *et al.* 2006). Furthermore, the expression levels of RA receptors (Fukunaka *et al.* 2001) and CRABP2 (Loughney *et al.* 1995, Wardlaw *et al.* 1997, Li & Ong 2003), which bind and deliver RA to nuclear RAR, are stimulated by estradiol in the proliferative phase in epithelial and stromal cells. These data suggest that estrogen coordinately upregulates RA production, transport and signaling in the proliferative phase of the ovarian cycle. This coordinated mechanism may play a role in antiproliferative effects that counterbalance estrogen-induced endometrial proliferation. Studies on vitamin A-deficient rats demonstrated that physiologic levels of RA suppress endometrial hyperplasia and metaplasia associated with chronic estrogen administration (Bo & Smith 1966). In addition, pharmacological doses of RA in immature ovariectomized rat suppress estrogen-induced endometrial cell proliferation (Boettger-Tong & Stancel 1995, Loughney & Redfern 1995). This might be a beneficial suppressive effect on estrogen-induced endometrial proliferation. RA can also effectively suppress the estrogen-stimulated proliferation of breast cancer cells and in several endometrial carcinoma lines (Carter *et al.* 1996, Toma *et al.* 1997). Targeting physiological RA accumulation in the endometrium by estradiol is a potential suppressor mechanism to prevent malignant transformation of hyperplastic endometrial cells during the ovarian cycle and gestation. In the case of vitamin A deficiency, uterine epithelium forms regions of

keratinized squamous metaplasia, indicating that RA is needed to maintain simple columnar uterine epithelium (Ponnamperuma *et al.* 1999).

Gap junction intercellular communications

Decidualized stromal cells not only acquire epithelioid structure and function, accumulating glycogen, lipids and subcellular organelles (Lawn *et al.* 1971) but also express interdigitating lamellar processes within clustered microdomains called gap junctions. These gap junctions act as membranous channels for the direct exchange of small molecules (e.g., second messengers) among adjacent cells or between these cells and their extracellular environments (Yamasaki *et al.* 1999). Gap junction intercellular communications (GJIC) are critical to the success of decidualization because their blockade suppresses the proliferation and differentiation of uterine stromal cells (Yu *et al.* 2011, Diao *et al.* 2013, Yu *et al.* 2014*a*, Winterhager & Kidder 2015). Connexin (CX) proteins are the major components of gap junctions, and CX43 (also known as GJA1) is the predominant CX protein in endometrial stromal cells (Jahn *et al.* 1995, Winterhager *et al.* 2009) and undergoes a variety of changes during the ovarian cycle (Mantena *et al.* 2006). The attenuation of *CX43* expression disrupts GJIC between neighboring cells and impedes the differentiation of stromal cells in human and mouse endometrium (Laws *et al.* 2008, Yu *et al.* 2011). Endometrial CX43 may be regulated by hormonal changes, and the progesterone and estrogen levels in serum are reported to determine the expression levels of CX43 in the endometrium (Yu *et al.* 2014*b*, Winterhager & Kidder 2015). RA and other retinoids enhance GJIC and CX43 expression levels in numerous cell types, certain human cancer cell types, mouse fibroblasts and rat liver cells, through transcriptional and translational mechanisms (Stahl & Sies 1998, Carystinos *et al.* 2001). When treated with RA, *CX43* expression in human endometrial stromal cells shows a dose-dependent increase at the mRNA and protein levels (Tanmahasamut & Sidell 2005) (Table 2). Concomitant with the increase in CX43 expression, stromal cells treated with RA exhibit a 2.5-fold enhancement in their GJIC as assessed by dye transfer experiments (Tanmahasamut & Sidell 2005). The ability of endometrial stromal cells to serve as an RA-responsive target is supported by the presence of RA nuclear receptors (i.e., RARs and RXRs) in these cells (Prentice 1992, Comptour *et al.* 2016). In addition to its expression level, the phosphorylation status of CX43 influences GJIC, including gap junction assembly and channel gating (Solan & Lampe 2009). In endometrial tissue, phosphorylation of CX43 mostly impairs GJIC (Tanmahasamut & Sidell 2005, Wu *et al.* 2013). Phosphorylation of CX43 is mediated by two serine/threonine protein kinase families, protein kinase C (PKC) (Oh *et al.* 1991) and MAPK (Warn-Cramer *et al.* 1996). RA induced the CX43 de-phosphorylation at serine 262 in human endometrial stromal cells (Tanmahasamut & Sidell 2005, Wu *et al.* 2013). RA antagonized the effects of 12-O-tetradecanoylphorbol-13-acetate (a PKC activator) and inhibited PKC activity in numerous cell systems (Cope 1986, Verma 1988, Nakagawa *et al.* 2003), although the activation of PKC activity by RA has also been reported (Kambhampati *et al.* 2003). Inhibition of MAPK activity by RA was previously reported (Nakagawa *et al.* 2003). The signaling pathway(s) involved in the CX43-dephosphorylating effects of RA remains to be elucidated, but protein phosphatase 2 has been implicated (Wu *et al.* 2013). Overall, these data support that retinoid signaling can enhance GJIC among endometrial stromal cells (Fig. 3).

Endometrial neovascularization

Increased vascular permeability and angiogenesis are vital to the successful stromal decidualization, embryo

Table 2 Effect of RA on the production of factors in the endometrial cells.

Factors	Regulation	Cell type	Species	References
CX43	↑	Stromal cells	Human	Tanmahasamut & Sidell (2005), Wu *et al.* (2013)
VEGF	↑	Stromal cells	Human, mouse	Matsumoto & Sato (2006), Sidell *et al.* (2010)
PRL	↓	Stromal cells	Human	Brar *et al.* (1996), Ozaki *et al.* (2017)
IGFBP1	↓	Stromal cells	Human	Brar *et al.* (1996), Ozaki *et al.* (2017)
HSD11B1	↓	Stromal cells	Human	Ozaki *et al.* (2017)
Fibronectin	↑	Stromal cells	Human	Brar *et al.* (1996)
LIF	↓	Epithelial cells	Mouse	Ma *et al.* (2012)
HB-EGF1	↓	Epithelial cells	Mouse	Ma *et al.* (2012)
HSD17B2	↑	Epithelial cells	Human	Cheng *et al.* (2008), Yamagata *et al.* (2015), Pavone *et al.* (2017)

↑, Upregulation; ↓, Downregulation.

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implantation and placentation (Dey *et al.* 2004, Matsumoto & Sato 2006, Wang & Dey 2006, Matsumoto *et al.* 2007). VEGF, originally reported as a vascular permeability factor, is also a potent mitogen for endothelial cells and a key regulatory growth factor for vasculogenesis or angiogenesis (Ferrara *et al.* 1997). In human endometrial stromal cells, RA can combine with transcriptional activators of VEGF to stimulate the expression and secretion of VEGF through a translational mechanism mediated by reactive oxygen species (ROS; Sidell *et al.* 2010) (Table 2). In addition, GJIC plays a key role in endometrial neovascularization. The conditional deletion of *CX43* genes in stromal cells and the consequent disruption of GJIC result in the reduction of VEGF production and striking impairment in the development of new blood vessels within stromal compartments (Laws *et al.* 2008, Yu *et al.* 2011). Notably, *CX43* overexpression promotes VEGF secretion (Yu *et al.* 2016). As discussed earlier, retinoid signaling can enhance GJIC among endometrial stromal cells by stimulating *CX43* expression and dephosphorylation. Thus, retinoid signaling might promote neovascularization by enhancing stromal *CX43* expression and GJIC. Evidence showed that COX-2-derived prostaglandins participate in uterine angiogenesis during implantation and decidualization (Matsumoto *et al.* 2002). In *Cox-2* KO mice, failure of implantation and decidualization are primarily due to defects in VEGF signaling. cPGI (an analog of PGI_2) together with 9cRA improves poor implantation in Cox-2(−/−) mice. Moreover, the administration of cPGI and 9cRA restore the expression of VEGF and angiogenesis (Matsumoto & Sato 2006). In addition, Saito *et al.* (2007) examined RA effects on *in vitro* capillary-like tube formation using human umbilical vein endothelial cells and demonstrated that RA as well as RAR agonist Am80 significantly induced capillary-like tube formation. The RA-induced tube formation was inhibited by RAR antagonist. Meanwhile, the RA-induced tube formation was completely abolished by coincubation with VEGF antibody or with VEGF receptor (VEGFR)-2 antibody, but not VEGFR-1 antibody (Saito *et al.* 2007). These data provide evidence that although ovarian steroid hormones primarily influence uterine vascular permeability and angiogenesis during the preimplantation period, RA-RAR signaling participates by regulating VEGF production (Fig. 3).

Stromal decidualization

Stromal decidualization denotes the transformation of mesenchymal stromal cells into specialized decidual cells, which acquire epithelioid structure and function, accumulating glycogen, lipids and subcellular organelles (Lawn *et al.* 1971) in part through a process of mesenchymal-epithelial transformation (Yu *et al.* 2016). Decidual cells provide the nutritive and immune-privileged matrix that is required for blastocyst implantation and placental formation in mouse and human uteri (Zhang *et al.* 2013, Gellersen & Brosens 2014). Perturbed or inadequate decidualization leads to embryo miscarriage and early pregnancy failure (Kommagani *et al.* 2013). Accompanied by typical morphological changes, differentiating stromal cells express biochemical decidual markers, such as prolactin (PRL), insulin-like growth factor-binding protein-1 (IGFBP1) (Irwin *et al.* 1994, Brar *et al.* 1997) and 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) (Brosens *et al.* 1999, Kuroda *et al.* 2013). Data from Ozaki *et al.* (2017) showed that RARs, as well as CRABP2 and FABP5, which are responsible for binding and delivering RA to nuclear receptors RARs and PPARβ/δ respectively, decreased in decidualizing human endometrial stromal cells despite an increase in PPARβ/δ. Besides, decidualization was also associated with increased expression of CYP25A1 (Table 3). In addition, exposure of differentiating stromal cells to 10 nM RA or retinal prevents the inhibition of the RAR pathway and perturbs expression of PRL, IGFBP1 and 11βHSD1 (Ozaki *et al.* 2017). Brar *et al.* (1996) consistently demonstrated that RA treatment suppressed PRL and IGFBP1 production and promoted maintenance of fibronectin, an indicator of the undifferentiated stromal phenotype (Yu *et al.* 2016) (Table 2). Though PPARβ/δ and RXRs are highly expressed at implantation sites in human and rat endometrium (Fukunaka *et al.* 2001, Ding *et al.* 2003) and endometrial stromal cells can synthesize RA from retinol during decidualization and blastocyst implantation (Ulven *et al.* 2000, Deng *et al.* 2003), no evidence exists that RA, even at low concentrations, promotes stromal decidualization, at least not when assessed by the induction of responsive

Table 3 Upregulated and downregulated genes involved in retinoid metabolism and signaling in decidualizing endometrial stromal cells.

Genes	Upregulation or downregulation	Species	References
RBP4	↑	Human	Ozaki *et al.* (2017), Pavone *et al.* (2017)
CYP26A1	↑	Human	Ozaki *et al.* (2017)
CRABP2	↓	Human	Ozaki *et al.* (2017), Pavone *et al.* (2017)
FABP5	↓	Human	Ozaki *et al.* (2017)
RARα	↓	Human	Ozaki *et al.* (2017)
PPARβ/δ	↑	Human	Ozaki *et al.* (2017)

↑, Upregulation; ↓, Downregulation; E_2, estradiol; P_4, progesterone.

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decidual markers (PRL, IGFBP1 and HSD11B1). At high concentrations, RA decreases cell viability and exhibits toxic effects (Ozaki *et al.* 2017). These data suggested that RA signaling is attenuated upon decidualization, and RA treatment suppresses the decidualization and contributes to the maintenance of stromal cells in an undecidualized state. Furthermore, RA was suggested to prevent the increase in intracellular cAMP accumulation in stromal cells that occurs during the induction of decidualization *in vitro* with progesterone and estradiol (Brar *et al.* 1996). Meanwhile, the activation of the cAMP signal pathway is essential and sufficient to induce PRL production in endometrial stromal cells (Tang *et al.* 1993, Gellersen *et al.* 1994), and inhibition of PRL production by RA cannot be restored by cAMP treatment (Brar *et al.* 1996). The inhibition of intracellular cAMP production by RA is a plausible mechanism by which RA suppresses stromal decidualization. On the other hand, endogenous RA biosynthesis from retinol is increased 1.4-fold in endometrial stromal cells subjected to *in vitro* decidualization compared to control cells (Sidell *et al.* 2010). Thus, more precise dose-response relationships should be established to fully understand the possible differential effects of RA signaling via the opposing CRABP2-RAR vs FABP5-PPARβ pathways.

Retinoid signaling in blastocyst implantation

In humans and rodents, implantation occurs via successive blastocyst apposition, attachment, and adhesion to the receptive luminal epithelium, followed by the penetration and invasion of trophectoderm into the decidualized stroma (Dey *et al.* 2004). Successful implantation requires not only a receptive endometrium but also a preimplantation blastocyst temporally competent to engage in precise crosstalk with the maternal endometrial signals. Recent evidence suggested that two separate uterine signals during blastocyst implantation. One signal primes the trophectoderm for attachment to the luminal epithelium, and the other results in the uptake of amino acids by the blastocyst, the motility of which is initiated for invasion (Gonzalez 2012). Signaling of endometrial receptivity to blastocyst attachment involves the actions of ovarian steroid hormones on the luminal epithelia and paracrine factors expressed by different endometrial cell types (Cha *et al.* 2012, Zhang *et al.* 2013).

Rodent studies demonstrated that the tight regulation of retinoid pathways play crucial roles in maintaining uterine receptivity and blastocyst implantation (Osteen *et al.* 2003, Han *et al.* 2010). In mice, the uterus becomes receptive to blastocyst implantation by the afternoon of gestational day 4 but is refractory by the afternoon of day 5 (Zhang *et al.* 2013). No *Cyp26a1* mRNA was found in preimplantation endometrium, while its expression was specifically induced between 3.5 and 4.5 gestational days, i.e., the implantation period, was localized in luminal epithelia (Vermot *et al.* 2000, Han *et al.* 2010). The specific spatiotemporal expression pattern of *Cyp26a1* in preimplantation endometrium suggests that it is involved in blastocyst attachment and/or invasion to the endometrium but not in the initial preparations of the endometrium. This hypothesis was supported by data in which the number of implantation sites was significantly reduced when *Cyp26a1*-specific antisense oligos or anti-CYP26A1 antibodies were injected into the uterus on day 3 of pregnancy (Han *et al.* 2010). As described previously, the RA pathway is inhibited during the late secretory phase by endogenous expression of *Cyp26a1*. RA can inhibit matrix metalloproteases (Bruner-Tran *et al.* 2002, Osteen *et al.* 2003), thus, CYP26A1-mediated degradation of RA may facilitate blastocyst implantation (Osteen *et al.* 2003).

Pharmacological concentrations of RA are embryotoxic at the early postimplantation stage of development (Huang *et al.* 2001). This observation, along with the well-characterized functions played by CXs in embryonic implantation and development, suggests a possible link between known teratogenic effects of RA (Ross *et al.* 2000) and the possibility that RA at such concentrations may reduce the effective trophoblast invasive capacity through increased GJIC because CX43 expression and GJIC are dramatically reduced during the implantation window (Granot *et al.* 2000) potentially facilitating trophectoderm invasion into the endometrial stroma.

Other studies established the importance of endometrial gland secretions, such as leukemia inhibitory factor (LIF), for endometrial receptivity and blastocyst implantation. LIF binds to its receptor LIFR present in luminal epithelia and activates downstream signaling via STAT3 (Niwa *et al.* 1998). Consequently, LIF induces the expression of luminal epithelia-enriched genes, including *HB-EGF1*, *IGFBP3* and *IRG*, which are associated with uterine receptivity (Kimber 2005). *Lif* KO mice are infertile because of the failure of blastocyst attachment to the uterine luminal epithelium. Excess RA (10 μM) can significantly inhibit the expression of the *Lif*, *Hb-egf* and *Csf1* in endometrial epithelial cells isolated on day 4.5 of pregnancy (Ma *et al.* 2012) (Table 2).

These data suggest that successful implantation during late secretory phase requires lower RA levels in the

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luminal epithelia than what occurs in the proliferative phase, and excess RA might negatively affect stromal decidualization, endometrial receptivity and blastocyst implantation. CYP26A1-mediated degradation of RA is a hallmark of the implantation phase.

Collectively, the endometrial retinoid pathway is distinctly regulated by synthesis catalyzed by ALDHs and catabolism catalyzed by CYP26A1 at different phases and in different compartments of the endometrium, which are mainly controlled by estradiol and progesterone. The retinoid pathway plays crucial roles in endometrial epithelial differentiation and proliferation, neovascularization and GJIC and negatively regulates stromal decidualization and blastocyst implantation (Fig. 3).

Retinoid pathway and endometriosis

Endometriosis is a nonmalignant, but potentially metastatic, gynecological condition, which is estrogen dependent and defined by the presence of hormonally responsive, ectopic implants of endometrial mucosa dispersed in extrauterine locations (Giudice & Kao 2004, Kennedy *et al.* 2005). Approximately 10% of all women and up to 30%–50% of symptomatic premenopausal women are affected and commonly suffer pelvic pain and/or infertility (Nnoaham *et al.* 2011, Stilley *et al.* 2012). Classical and neoclassical concepts of endometriosis etiology were reviewed comprehensively elsewhere (Bulun 2009, Taylor 2010, Burney & Giudice 2012, Bulun *et al.* 2015, Taylor *et al.* 2015) and will not be reiterated thoroughly in this review. Although the theories of endometriosis histogenesis remain controversial, recent findings suggest that defective epigenetic landscape possibly associated with deficient differentiation of endometrial tissue stem cells is a central mechanism responsible for the cellular origins of endometriosis (Bulun *et al.* 2015). Meanwhile, retinoid pathway is fundamentally flawed in endometriotic tissues and even systemically in women with endometriosis (Pavone *et al.* 2010, 2011, 2017, Pierzchalski *et al.* 2014, Taylor *et al.* 2015).

Studies from the group of Bulun showed altered expression of several genes involved in retinol uptake, metabolism and action in cells from patients with endometriosis (Pavone *et al.* 2010, 2011, 2017). Endometriotic stromal cells overall had decreased *CRABP2* and *CRBP1* expression and increased *CYP26B1* expression (Table 4), the latter resulting in the elimination of RA from cells. These results are consistent with decreased retinoid uptake, metabolism and action within endometriotic lesions (Pavone *et al.* 2011). *ALDH1A2* expression levels were significantly reduced in endometriotic tissue and stromal cells (Table 4), resulting in reduced RA levels. Pierzchalski *et al.* (2014) directly quantified RA levels and biosynthesis from retinol in endometrial stromal cells, which were derived from corresponding eutopic and ectopic biopsies; retinol uptake and RA production predominantly occur in these stromal cells (Vermot *et al.* 2000, Pavone *et al.* 2011, Yamagata *et al.* 2014) (Fig. 1). The studies confirmed impaired RA biosynthesis in endometriotic implants. A major defect was the reduced expression of CRBP1, a retinol carrier protein serving as the preferred substrate for retinol dehydrogenase enzymes and the rate-limiting factor in RA biosynthesis (Napoli 2012). Moreover, STRA6, which mediates retinol uptake, showed an abnormally low expression and high levels of DNA methylation in endometriotic stromal cells (Pavone *et al.* 2011, Yamagata *et al.* 2015) (Table 4). Thus, reduced *STRA6*, *CRBP1* and *ALDH1A2* expression levels result in a significantly less efficient conversion of retinol to RA in stromal cells. In addition, *RARα* expression levels are strikingly low in tissues and stromal cells of endometriosis (Pavone *et al.* 2011) (Table 4). Transcriptional activation via the RA-CRABP2-RAR pathway can trigger cell cycle arrest (Donato *et al.* 2007) and apoptosis (Altucci *et al.* 2001, Kitareewan *et al.* 2002, Donato *et al.* 2005) and frequently leads to the inhibition of cell proliferation. Thus, reduced RA-CRABP2-RAR signaling can cause endometriotic cells to escape apoptosis and contribute to the survival of ectopic cells (Nasu *et al.* 2009, Pavone *et al.* 2010). These studies suggested that flaws in RA production and degradation might play a role in the pathogenesis of endometriosis.

Table 4 Changes in genes involved in retinoid uptake, metabolism and signaling in endometriosis.

Genes	Changes	Cell type	References
CRBP1	↓	Stromal cells	Pavone *et al.* (2011, 2017)
CRABP2	↓	Stromal cells	Pavone *et al.* (2010, 2011, 2017)
ALDH1A2	↓	Stromal cells	Pavone *et al.* (2011)
STRA6	↓	Stromal cells	Pavone *et al.* (2010, 2011), Yamagata *et al.* (2015)
RARα	↓	Stromal cells	Pavone *et al.* (2011)
RXRα	↓	Stromal cells	Pavone *et al.* (2011)
CYP26B1	↑	Stromal cells	Pavone *et al.* (2011, 2017)

↓, reduced; ↑, increased.

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Estrogen plays a critical role in the establishment and maintenance of endometriosis (Osteen *et al.* 2005, Bulun 2009, Bulun *et al.* 2015). 17β-hydroxysteroid dehydrogenase type 2 (HSD17B2) catalyzes the conversion of estradiol to estrone, a much less biologically potent estrogen, and plays a crucial role in local estradiol inactivation in the endometrium (Cheng *et al.* 2007). HSD17B2 is present in normal endometrial glandular cells but is lacking in the endometrium of women with endometriosis (Stewart 1994, Giudice *et al.* 2002). Pavone *et al.* (2017) incubated epithelial cells with human serum RBP4 for 48 h and found that HSD17B2 expression was significantly increased in a dose-dependent manner. In serum, retinol is bound by RBP4 in the form of retinol-RBP4 complex (holo-RBP4), which then binds to transthyretin (TTR) and forms a ternary complex (D'Ambrosio *et al.* 2011). Binding of holo-RBP4 to TTR prevents the loss of the RBP4 from the circulation by filtration via the renal glomeruli, as apo-RBP4 cannot be bound by TTR and is lost in the urine. Since the human serum RBP4 used in the study of Pavone *et al.* (2017) may contain significant amounts of holo-RBP4, the increased *HSD17B2* expression might be caused by retinol from holo-RBP4. This hypothesis was supported by another study which demonstrated that RA stimulates the assembly of a multimeric complex composed of RARα/RXRα tethered to transcription factors SP1 and SP3 on the *HSD17B2* promoter where it induces HSD17B2. The RA antagonist ANG abolishes RA-induced *HSD17B2* expression in endometrial cells (Cheng *et al.* 2008, Yamagata *et al.* 2015). Thus, RA appears to be one of the critical paracrine factors that stimulate the production of HSD17B2 in neighboring epithelial cells and an important mechanism for local estradiol inactivation in the endometrium (Table 2). As previously mentioned, as the RA pathway is fundamentally flawed in endometriotic tissues (Pavone *et al.* 2010), this provides a plausible explanation for the aberrant *HSD17B2* expression and the high local estradiol concentrations in endometriosis (Fig. 4).

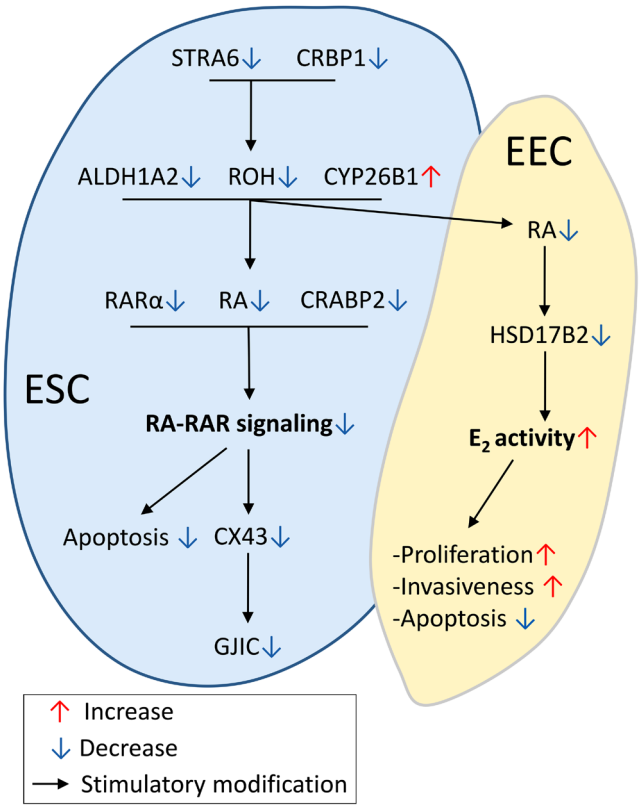

Figure 4
Schematic representation of aberrant retinoid signaling in endometriosis. In stromal cells of endometriosis, reduced STRA6, CRBP1 and ALDH1A2 expression levels result in a significantly less efficient conversion of retinol to RA. Meanwhile, increased CYP26A1 expression promotes RA degradation. Thus, decreased RA levels along with reduced RARα and CRABP2 expression result in a reduced RA-RAR signaling, which results in reduced Cx43 expression and GJIC in stromal cells. Meanwhile, reduced RA levels result in lower HSD17B2 production and high local concentrations of estradiol (E_2) in epithelial cells of endometriosis. The reduced RA signaling and increased local E_2 activity could enhance cell proliferation, invasiveness and impede apoptosis in endometriosis. A full colour version of this figure is available at https://doi.org/10.1530/JOE-17-0544.

As previously mentioned, CX43 is predominantly expressed in endometrial stromal cells (Jahn *et al.* 1995, Winterhager *et al.* 2009) and necessary for GJIC that allow the stroma to serve as an organized tissue. Regidor *et al.* (1997) showed that CX43 levels were reduced in human endometriosis lesions and this finding was confirmed by Yu *et al.* (2014*b*). They reported nearly exclusive CX43 immunostaining in the stromal compartment of normal biopsies, with reduced immunostaining and redistribution to scattered epithelia in the eutopic endometria of women with endometriosis. Moreover, stromal cells isolated from cases of endometriosis exhibited a reduction of ~45% in GJIC, confirmed at the levels of CX43 mRNA and protein expression and also functionally by lower Lucifer Yellow diffusion (Yu *et al.* 2014*b*). As previously mentioned, RA can stimulate CX43 expression and GJIC in stromal cells (Tanmahasamut & Sidell 2005, Wu *et al.* 2013). Thus, flawed retinoid action might cause decreased *CX43* expression and GJIC, reducing decidualization capacity of stromal cells in endometriosis, which could contribute to the development or progression of endometriosis lesions and to the subfertile uterine phenotype associated with the syndrome.

TGF-β1, a member of transforming growth factor-β (TGF-β) superfamily, has been supposed to play an extensive role in the onset and development of endometriosis, such

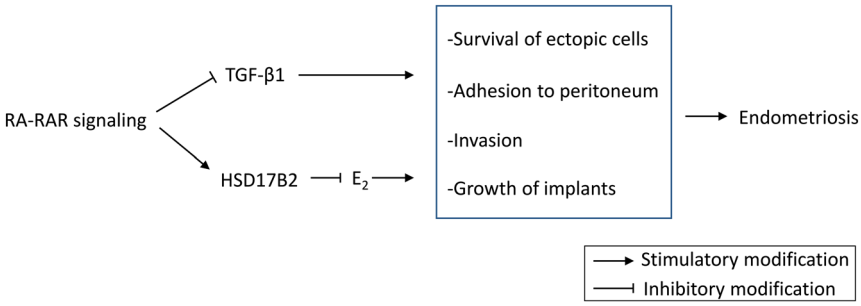

Figure 5
Potential therapeutic mechanism of RA for endometriosis. Activation of the RA-RAR pathway can promote HSD17B2 production, which can stimulate the catabolism of E_2 and inhibit TGF-β1 production. These actions of the RA-RAR pathway imply its potential to suppress the development of endometriosis. A full colour version of this figure is available at https://doi.org/10.1530/JOE-17-0544.

as preventing apoptosis during transit to the peritoneal cavity, promoting adhesion to peritoneum and invasion of endometriosis cells (Omwandho *et al.* 2010). With the exception of one study (Hao *et al.* 2000), two other studies reported that subjects with endometriosis exhibit higher levels of TGF-β1 in peritoneal fluid (Oosterlynck *et al.* 1994, Ku¨pker *et al.* 1998). Interestingly, it was reported that RA could inhibit the TGF-β1 signaling pathway in the endometrial cells and many other cell types (Frenz & Liu 2000, Delgadillo *et al.* 2014, Hu *et al.* 2016). Althoughfurther studies are needed, it can be speculated that RA might suppress the development of endometriosis implants partly through repressing the TGF-β1 signaling pathway (Fig. 5).

These data suggest two possible scenarios to consider the theories of the histogenesis of endometriosis associated with the aberrant retinoid pathway in ectopically growing endometrial cells. On the one hand, defects in RA signaling can result in high local concentrations of estradiol in endometriosis lesions due to deficient oxidation and inactivation of estradiol. On the other hand, reduced RA signaling, along with increased estradiol effects, could enhance cell proliferation and invasiveness and impede apoptosis in endometriosis (Fig. 4). With respect to eutopic endometrial function in endometriosis, impaired RA signaling can be an attributed to dysfunctional stromal differentiation, leading to the reduced capacity for decidualization reported in these cases (Klemmt *et al.* 2006, Aghajanova *et al.* 2009, Lessey *et al.* 2013).

In conclusion, the precisely controlled retinoid signaling may play a critical role in a number of critical endometrial physiological events. In addition, the altered RA pathway may be a leading cause for the histogenesis of endometriosis.

Perspectives for future studies

RBP4, acting as the primary systemic and intercellular transporter of retinol, plays a key role in cellular retinol influx, efflux and exchange (Kawaguchi *et al.* 2015). Pavone *et al.* (2017) observed that RBP4 secretion increases during the decidualization of human endometrial stromal cells. Immunoreactivity for RBP4 is consistently higher near the embryo implantation site compared with non-implantation sites in the baboon endometrium (Fazleabas *et al.* 1994). These data suggest a potential role of RBP4 production and secretion in decidualization and/or implantation, but still require further investigation. Of great interest is that complete deletion of *Aldh* genes in mice results in prenatal lethality, precluding investigation of their roles in postnatal organogenesis. The use of tissue-selective and conditional gene targeting approaches is necessary to better understand the role of these enzymes during the ovarian cycle and gestation. As previously mentioned, excess RA concentration is harmful to decidualization and implantation. Thus, actual retinoid concentrations in the endometrium, as have been performed in some limited studies (Pierzchalski *et al.* 2014), should be measured in future studies.

Accumulating evidence supports that treatment modalities that target the retinoid pathway may have therapeutic utility (Sokalska *et al.* 2013). RA treatment reduced cytokine concentrations and the number and size of lesions (Wieser *et al.* 2012). Thus, RA has the potential to suppress the development of endometriotic implants and agents that target the RA-shuttling system may be useful therapeutic targets in the future, bypassing the toxicity and teratogenicity encountered with RA analogs (Fig. 5). We propose that adjuvant or alternative medical therapies should be developed on the basis of these concepts. Their pharmacological actions and anticipated low side-effect profiles are predicted to be able to provide women with endometriosis with more treatment options for the long-term management of chronic and debilitating gynecologic diseases.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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