Corticosteroid and Retinoid Metabolism Signalling Pathways During Decidualisation of Human Endometrial Stromal Cells

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In humans, the incidence of embryo wastage and pregnancy loss is extraordinarily high; therefore, pregnancy loss commonly occurs in reproductive women. Furthermore, some women suffer from recurrent pregnancy loss (RPL). In over 50% of RPL cases, no specific cause is identified even after detailed examinations. Impaired decidualisation of uterine endometrium with aberrantly high uterine natural killer (uNK) cell density is associated with unexplained RPL. Glucocorticoid includes active cortisol and inert cortisone, which are mutually catalysed by 11 β -hydroxysteroid dehydrogenase (11 β HSD). 11 β HSD isoform type 1 activates cortisone to cortisol, which binds glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). During decidual transformation in human endometrial stromal cells (HESCs), 11 β HSD1, but not type 2, is particularly induced by progesterone, leading to the local production of active cortisol and regulation of GR and MR gene networks. 11 β HSD1/GR signalling is a significant pathway for the regulation of uNK cells and inflammatory reaction upon decidualisation of HESCs, whereas the MR gene network includes retinoid metabolism. Retinol (vitamin A), which is hydrolysed from retinyl ester, is transformed to retinaldehyde (Rald) and generates retinoic acid (RA) following two-step oxidation. RA binds to CRABP2 and activates retinoic acid receptor (RAR), leading to cell apoptosis and senescence, whereas RA-dependent activation of PPAR β / δ is mediated through FABP5, leading to cell differentiation. The decidualisation of HESCs decreases the expression of CRABP2 and FABP5 and down- and upregulates RAR and PPAR β / δ , respectively. In addition, decidualisation is associated with the upregulation of retinoid metabolism-related genes, including retinol-binding protein 4 (RBP4), cytochrome P450 26A1 (CYP26A1), RDH12 and DHRS3, suggesting that decidualisation suppresses RA signalling by decreasing key cytoplasmic-binding proteins and upregulating retinoid metabolism. Taken together, corticosteroid signalling via 11 β HSD1 induction regulates GR-specific gene networks including inflammation and angiogenesis at the implantation site. Furthermore, retinoid metabolism signalling is controlled via 11 β HSD1/MR signalling, leading to an optimal balance of cell differentiation and apoptosis, such as decidualisation of HESCs. Recently, for the treatment of unexplained RPL, the GR and MR gene networks are targeted via corticosteroid signalling, leading to modulation of uNK cells as well as retinoid metabolism signalling.

Key words: endometrium, decidualisation, 11 β -hydroxysteroid dehydrogenase type 1 (11 β HSD1), retinoid, recurrent pregnancy loss (RPL)

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Abbreviations: 8-bromo-cAMP, 8-bromoadenosine-cAMP; 11 β HSD, 11 β -hydroxysteroid dehydrogen-

ase; GR, Glucocorticoid receptor; HESC, human endometrial stromal cell; IGFBP1, insulin-like growth factor-binding protein-1; MR, Mineralocorticoid receptor; P4, progesterone; PR, progesterone

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receptor; PRL, prolactin; RPL, recurrent pregnancy loss; uNK, uterine natural killer.

Introduction

Successful pregnancy is initiated with a mutual crosstalk between endometrial receptivity and embryo competency. In humans, the incidence of pre-implantation embryo wastage, pre-clinical pregnancy loss, and miscarriage is extraordinarily high. The incidence rate of embryo wastage is estimated to be 30% before implantation (implantation failure), 30% until 6 weeks of pregnancy (biochemical pregnancy loss), and 10%–15% primarily before 12 weeks of gestation (clinical pregnancy loss)¹⁾ (Figure-1). Chromosomal abnormalities in human embryos account for the high incidence of early embryo and pregnancy loss^{2) 3)}. Of women who have experienced pregnancy, 38% have a history of spontaneous abortion; therefore, pregnancy loss is common in reproductive women⁴⁾. Furthermore, some women suffer from repeated pregnancy losses. The European Society for Human Reproduction and Embryology

(ESHRE) defines recurrent pregnancy loss (RPL) as ≥ 3 pregnancy losses⁵⁾. The incidence rates of two and three consecutive accidental pregnancy losses is estimated to be 4.2% and 0.9%, respectively⁴⁾. Ogasawara *et al.* reported that an increase in the number of pregnancy losses resulted in the decrease in the likelihood of abnormal embryonic karyotypes and an increase in the frequency of subsequent pregnancy loss⁶⁾. It is highly probable that couples with a history of multiple pregnancy losses have parental, not foetal, risk factors for pregnancy loss⁷⁾. A Japanese RPL research group at the Health, Labour and Welfare Ministry of Japan investigated the frequency of risk factors for RPL and demonstrated rates of approximately 25% for thrombophilia, including antiphospholipid antibody syndrome, 7.8% for organic factors such as uterine malformation, and 6.8% for thyroid disorder (<http://fuiku.jp/study/>). However, in over 50% of RPL cases, no specific cause is identified even after detailed examinations⁸⁾. Candidate risk factors for unexplained RPL include impaired intrauterine circumstances and impaired decidualisation of uterine endometrium⁷⁾. This

Figure-1 Embryo wastage iceberg

In humans, the incidence of embryo wastage and pregnancy loss is extraordinarily high. The incidence rate of embryo wastage is estimated to be 30% before implantation, 30% until 6 weeks of pregnancy (biochemical pregnancy loss), and 10%–15% primarily before 12 weeks of gestation (clinical pregnancy loss).

review aimed to demonstrate the importance of corticosteroid and retinoid signalling pathways in the decidualisation of human endometrium for implantation and maintenance of early pregnancy.

Decidualisation and recurrent reproductive failure

Recent studies reported that decidualised human endometrial stromal cells (HESCs) serve as biosensors of embryo quality at implantation⁹⁻¹². Human developmentally inappropriate embryos may suppress the secretion of implantation regulators, including inflammatory cytokines from decidualising HESCs⁹. However, the endometrium of women with a history of unexplained RPL has high migratory activity to an embryo, regardless of its quality; therefore, it disables the ability to avoid a low-quality embryo¹⁰. In addition, several publications have reported a relationship between recurrent reproductive failure and aberrantly high uterine natural killer (uNK) cell (CD56^{bright} and CD16^{dim}) density in mid-luteal endometrial cells¹³⁻¹⁷. uNK cells, an important part of the innate immune system, are the most abundant immune

cells in pre-implantation endometrium and early pregnancy decidua¹⁸. Further, uNK cells are believed to have a regulatory function in inflammation and angiogenesis via interleukin (IL)-11 and IL-15 secretion^{15) 19)-21)}. Disordered inflammatory regulators, IL33/ST2 in IL1 superfamily are associated with specific reproductive disorders²². From a genetic viewpoint, NLRP2 and NLRP7 genes, which regulate the production of IL1 β , are also reportedly associated with unexplained RPL²³. Therefore, there are obvious evidences suggesting an intimate interaction between RPL and inappropriate inflammation, which leads to abnormal angiogenesis, in mid-luteal endometrial stromal cells during peri-implantation and decidualisation.

Corticosteroid signalling upon decidualisation of HESCs

Glucocorticoids indicate the effects of potent anti-inflammation and immunosuppression. Endogenous glucocorticoids ensure significant functions in embryo implantation, placentation, and foetal growth during the course of early pregnancy.

Figure-2 Cortisol-cortisone interconversion

Glucocorticoid includes active cortisol and inert cortisone, which are mutually catalysed by 11 β -hydroxysteroid dehydrogenase (11 β HSD). NADPH-dependent 11 β HSD isoform type 1 activates cortisone to cortisol, which binds glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). In contrast, 11 β HSD type 2 inactivates cortisol. During decidual transformation in endometrial stromal cells, 11 β HSD1, but not type 2, is highly induced by progesterone, leading to the local production of active cortisol. Red arrow: upregulation of the gene upon decidualisation. Blue arrow: downregulation of the gene.

Glucocorticoid treatment reportedly prevents RPL on the basis of its ability to inhibit excess uNK cells and angiogenesis during the peri-implantation window^{14) 24)}. Glucocorticoid includes active cortisol and inert cortisone, which are catalysed mutually by 11 β -hydroxysteroid dehydrogenase (11 β HSD). The NADPH-dependent 11 β HSD isoform type 1 activates cortisone to cortisol, which binds glucocorticoid receptor (GR); however, cortisol has a high affinity for mineralocorticoid receptor (MR)²⁵⁾. By contrast, 11 β HSD type 2 inactivates cortisol (Figure-2). In human endometrium, both 11 β HSD isoforms as well as GR and MR are expressed. During decidual transformation from endometrial stromal cells, 11 β HSD1, but not type 2, is extremely induced; this induction is driven sensitively by progesterone (P4), leading to the local production of active cortisol²⁶⁾. Predominant cortisol-binding receptors alter GR in undifferentiated cells to MR in decidualising HESCs²⁶⁾. Implantation is one of the inflammatory responses. The balance of corticosteroid signalling plays a significant role in the control of inflammation and maintenance of early pregnancy in decidualising endometrium.

Regulation of uNK cells via 11 β HSD1/GR signalling in endometrium

Endometrial receptivity and early pregnancy are controlled by pro- and anti-inflammatory gene networks in decidualising stromal cells underlying the luminal epithelium²²⁾. The association between unexplained RPL and elevated uNK cells in mid-luteal endometrium has been previously reported¹³⁾⁻¹⁷⁾. The aberrantly high uNK cell density plays a role in poor induction of 11 β HSD1 and decidual marker genes, such as prolactin (PRL) and insulin-like growth factor-binding protein-1 (IGFBP1), in decidualising HESCs²⁷⁾. Degression of 11 β HSD1 expression in decidualising HESCs may lead to insufficient production of cortisol and impaired regulation of GR and MR gene networks at local implantation sites in women with a history of unexplained RPL²⁶⁾. By silencing 11 β HSD1 with carbenoxolone disodium salt or 11 β HSD1 inhibitor, PF915275 attenuated IGFBP1 expression, suggesting impaired decidualisation of HESCs²⁶⁾. 11 β HSD1 may be a key enzyme as a novel decidual marker in the decidual transformation of endometrium for

pregnancy maintenance. 11 β HSD1 has been sufficiently well-conserved during evolution and is also regulated under a hAT-Charlie family DNA transposon (MER20), which contributes to the evolution of mammalian pregnancy, in endometrial stromal cells²⁸⁾. On the contrary, glucocorticoid treatment can modulate uNK cell count via GR, which has been demonstrated to be a surface nuclear receptor on uNK cells²⁹⁾. Moreover, glucocorticoids also regulate inflammatory cytokines, prostaglandin and NF- κ B signalling via GR. In addition, GR in decidualising HESCs is important in epigenetic programming via Krüppel-associated box domain zinc finger proteins (KRAB-ZFPs), which are transcriptional repressors that are associated with heterochromatin formation, thus enhancing the global level of trimethylation of histone H3 lysine 9 (H3K9me3)²⁶⁾. 11 β HSD1/GR signalling is a significant pathway for the regulation of GR network genes, including uNK cells, and inflammatory reaction upon decidualisation of HESCs.

Importance of retinoid metabolism signalling via 11 β HSD1/MR signalling in decidualising endometrium

Endometrial stromal cells with high uNK cell density impaired 11 β HSD1 and MR expressions, but not GR²⁷⁾. Furthermore, MR is a predominant cortisol-binding receptor in decidualising HESCs; thus, MR and its gene network must have an essential role in implantation and decidualisation²⁶⁾. DHRS3, an MR-dependent enzyme, was detected from the microarray data of decidualising HESCs following siRNA-mediated MR silencing. DHRS3 in alcohol dehydrogenase and NADP(H)-dependent short-chain dehydrogenases/reductases (SDR) oxidises retinaldehyde (Rald) to retinol and promotes lipid droplet formation³⁰⁾. DHRS3 expression was substantially upregulated upon decidualisation, and the appearance of perinuclear lipid droplets in decidualising cells was relatively abundant compared with undifferentiated stromal cells, suggesting that retinoid is stored as retinyl esters in lipid droplets (retinosome) via MR and DHRS3 during decidual transformation of HESCs²⁶⁾. In addition, DHRS3 paralleled lipid droplet accumulation in decidualising HESCs with the treatment of MR

Figure-3 Retinoid metabolism signalling

Retinol (vitamin A), which is hydrolysed from retinyl ester, is transformed to retinaldehyde (Rald) and generates retinoic acid (RA) following two-step oxidation. RA binds to CRABP2 and activates retinoic acid receptor (RAR), leading to apoptosis and senescence. By contrast, RA-dependent activation of PPAR β/δ is mediated through FABP5. Decidualisation of HESCs decreases the expression of CRABP2 and FABP5 and down- and upregulates RAR and PPAR β/δ , respectively. In addition, decidualisation is also associated with upregulation of retinol-binding protein 4 (RBP4), cytochrome P450 26A1 (CYP26A1), RDH12 and DHRS3, suggesting that decidualisation suppresses RA signalling by decreasing key cytoplasmic-binding proteins and upregulating retinoid metabolism. Red arrows: gene upregulation upon decidualisation. Blue arrows: gene downregulation.

agonist (aldosterone) and antagonist (RU26752)²⁶⁾. With regard to adipocyte tissue, lipid droplet accumulation completely failed in MR knockout cells³¹⁾. Moreover, MR downregulation inhibits cell differentiation; thus, MR signalling is significant in MR-dependent adipogenesis³²⁾, indicating the link between MR, cell differentiation, and lipid droplet; however, the details are unknown. A study on endometrial cells suggests that retinoid metabolism signalling via MR modulates cell differentiation and lipid droplet accumulation^{26) 27) 33)}.

Retinoids are versatile vitamin A (retinol) derivatives that play roles in the regulation of multiple cellular functions and immune tolerance³⁴⁾. In pregnancy, retinoid synthesis is necessary for embryogenesis and foetal development; however, excessive levels are toxic to the embryo and foetus^{35) 36)}. Retinol, an essential fat-soluble vitamin, is transported to target cells, converted to Rald, and then to all-trans-retinoic acid (RA), which is the most active retinoid metabolite^{34) 37)}. RA regulates two opposing cell fate decisions depending on the activation of specific pathways: differentiation and apoptosis or senescence. RA bound to cellular RA-binding proteins, CRABP2 and FABP5, activates the retinoic acid receptor (RAR), leading to activation of the apoptotic machinery. By contrast,

RA-dependent activation of peroxisome proliferator-activated receptor (PPAR) β/δ promotes cellular differentiation³⁸⁾ (Figure-3).

An *in vitro* endometrial research reported that decidualisation of HESCs decreases the expression of the RA-binding proteins CRABP2 and FABP5 in HESCs and down- and upregulates pro-apoptotic RAR α and PPAR β/δ , associated with cell differentiation, respectively³³⁾. In addition, decidualisation was also related to upregulation of retinol-binding protein 4 (RBP4) and various enzymes involved in the metabolism of RA and its precursor, Rald, such as cytochrome P450 26A1 (CYP26A1), which inactivates RA, and members of the family of SDR, including RDH12 and DHRS3, which are then exported by RBP4 (Figure-3). Treatment of HESCs with RA antagonised the induction of PRL, IGFBP1, and 11 β HSD1 upon decidualisation of HESCs in a dose-dependent manner. Treatment with Rald also attenuated the expression of these decidual genes³³⁾. The treatment of decidualising cultures with RA or Rald selectively upregulated CRABP2 and RAR expression but not FABP5 or PPAR β/δ . Collectively, the data suggest that the decidualisation of HESCs suppresses RA signalling by decreasing key cytoplasmic-binding proteins and by upregulating retinoid metabolism. Yet,

additional RA exposure is toxic for decidualising HESCs and induces a response that may lead to implantation failure or pregnancy loss³³⁾.

GR and MR-specific gene networks as a target for treatment of unexplained RPL

Reprogramming of corticosteroid and retinoid metabolism signalling is important during decidual transformation of HESCs (Figure-4). Moreover, perturbation of decidualisation is associated with pregnancy failure. To treat unexplained RPL, Tang *et al.* reported a randomised controlled trial using prednisolone treatment for patients with RPL with aberrantly high uNK cell counts. The live birth rate with prednisolone was relatively higher, but there was no significant difference between groups (60% with prednisolone vs. 40% with placebo)³⁹⁾. Implantation is an inflammatory process via local secretion of pro-inflammatory cytokines and prostaglandins from decidual endometrium⁴⁰⁾⁻⁴³⁾. Appropriate prednisolone administration may be difficult for

regulation of corticosteroid signalling during implantation. 11 β HSD1 is highly induced in response to P4 treatment in decidualising HESCs²⁶⁾. Therefore, P4 treatment can control uNK cells via 11 β HSD1/GR signalling. In addition, regardless of what uNK cells express GR, but not PR, as a surface nuclear receptor, P4 has an ability to modulate uNK cells directly via GR⁴⁴⁾ ⁴⁵⁾. Remarkably, P4 can bind to MR directly, but this binding upon decidualisation is undetermined⁴⁶⁾. Notably, P4 supplementation for prevention of unexplained RPL has been reported⁴⁵⁾ ⁴⁷⁾. Nevertheless, luteal support with P4 activates corticosteroid signalling and GR and MR gene networks, leading to modulation of uNK cells and retinoid metabolism signalling. New trials of targeted therapy at corticosteroid and retinoid metabolism signalling for unexplained RPL are warranted.

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Figure-4 Regulation of decidualisation of endometrial stromal cells via corticosteroid and retinoid metabolism signalling pathways

Corticosteroid signalling via 11 β HSD1 induction regulates GR-specific gene networks including inflammation and angiogenesis at the implantation site. Furthermore, retinoid signalling is controlled via 11 β HSD1/MR signalling, leading to an optimal balance of cell differentiation and apoptosis, such as decidualisation of endometrial stromal cells.

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Disclosure Statement

The author has nothing to disclose.

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