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Endometrial Receptivity in Eutopic Endometrium of Women with Endometriosis It is affected, let me show you why

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Abstract

The endometrium maintains complex controls on proliferation and apoptosis as part of repetitive menstrual cycles that prepare the endometrium for the window of implantation and pregnancy. The reliance on inflammatory mechanisms for both implantation and menstruation, creates the opportunity in the setting of endometriosis for the establishment of chronic inflammation that is disruptive to endometrial receptivity, causing both infertility and abnormal bleeding. Clinically, there can be little doubt that the endometrium of women with endometriosis is less receptive to embryo implantation, and strong evidence exists to suggests that endometrial changes are associated with decreased cycle fecundity as a result of this disease. Here we provide unifying concepts regarding those changes and how they are coordinated to promote progesterone resistance and estrogen dominance through aberrant cell signaling pathways and reduced expression of key homeostatic proteins in eutopic endometrium of women with endometriosis.

Keywords

Endometriosis; endometrium; progesterone resistance; infertility; implantation; endometrial receptivity

Introduction

The endometrium maintains complex autocrine, paracrine and endocrine signaling involving sex steroids, cytokines and chemokines and intracellular signaling, culminating in receptivity to embryo implantation (1). In lieu of a successful pregnancy, the endometrium undergoes complex inflammatory changes that, in a non-scarring fashion, sloughs the lining

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so that it can be replaced following menstruation (2). While acute inflammation is required for both implantation and menstruation (3), chronic inflammation is disruptive and a major cause of infertility and menstrual bleeding disorders (4-6). Endometriosis affects millions of women, and a major cause of infertility and pelvic pain (7). Women with endometriosis are twice as likely to have infertility (8, 9) and pregnancy loss (10, 11). Changes in endometrial receptivity due to endometriosis has been well studied and several key studies support our argument that endometriosis affects the endometrium and reduces fertility. How these changes affect fertility is equally important, as a thorough understanding of the physiological mechanism will provide opportunities for both diagnosis and therapy for this common condition.

Endometriosis and Infertility – What is the Evidence?

In endometriosis, inflammation is centrally associated with the pathophysiology of this disorder, contributing to progesterone resistance and estrogen dominance (12). Endometriosis is a systemic and reversible inflammatory condition that alters endometrial function (13, 14). Clinical and animal studies support this association between endometriosis and infertility, including: 1) early prospective studies that show endometriosis patients are infertile (15, 16); 2) a recent large retrospective study demonstrating increased risk of infertility was associated with endometriosis (8), 3) reduced success rates in women with endometriosis in the setting of intrauterine insemination (IUI) has been repeatedly demonstrated (17-19), and 4) IUI results, in general, that find decreased fecundity comparing endometriosis to other diagnoses (20). Finally, 5) there is a high prevalence of endometriosis in women who have otherwise unexplained infertility (21).

Treatment of endometriosis has been shown to be beneficial for future fertility and improved pregnancy outcomes (22, 23). Studies from In Vitro Fertilization (IVF) cycles have documented a decreased pregnancy rate (24, 25), which can be improved with gonadotropin releasing hormone agonist (GnRHa) suppression (26), surgery (27) or aromatase inhibitor therapy (28). While early studies on donor oocytes has suggested the primary defect associated with endometriosis may reside in the ovary and oocyte quality (29), larger and more recent studies have documented that defective implantation is also likely involved (30). Prapas and co-workers studied the result of 240 cycles, placing sibling oocytes from the same donor into women with or without endometriosis. Adjusted odds ratio (95% CI) showed reduced implantation (0.78 (0.67-0.91)), clinical pregnancy rate (0.22 (0.08-0.57)), ongoing pregnancy (0.11 (0.03-0.35)), and live birth rate (0.19 (0.09-0.38)) for women with endometriosis (30).

Animal studies support clinical data suggesting that endometriosis leads to implantation defects, again implicating the endometrium. Induction of endometriosis in animals demonstrates similar phenotypes to human disease (31-34). The failure to implant embryos associated with endometriosis was transferrable in the peritoneal fluid (PF) in rabbits (35), as well as in mice who received human endometriotic PF (36). Induction of endometriosis in the baboon has been shown to be associated with gradual but profound alterations in the endometrium over time (37), suggesting that inflammation and the immune system may be involved in these changes.

Endometrial biomarkers are differentially expressed in the endometrium of women with endometriosis compared to normal women (38, 39) and studies over the years have refined and expanded these approaches to include miRNA arrays, proteomics and selected molecules including BCL6 (Fig 1). Early studies on endometrial proteins that participate in embryo attachment and invasion reported a decrease in expression of key proteins associated endometriosis (5, 40). Endometrial integrins are cell-surface receptors for extracellular matrix proteins that were first described in early 1990 (41, 42). We and others reported on specific key integrins including the αvβ3 integrin with a role in implantation (41, 43, 44) and this integrin was decreased in women with infertility and endometriosis (45) and unexplained infertility (46). L-selectin ligand, another extracellular ligand thought to be an attachment receptor on the endometrium for embryo-derived selectin, is decreased in the endometrium of endometriosis and unexplained infertility (47-49).

The changes in endometrial gene expression associated with defective endometrial receptivity reflect a shift away from normal progesterone action (39) and toward excessive estrogen activity. Such alterations in the balance between estrogen and progesterone likely impact fertility and implantation while also promoting the pathogenesis of endometriosis as a disease (50). Progesterone receptor changes and down-stream effects of progesterone (51, 52) are noted in women with endometriosis (53). Park et al. suggested that the endometrium of women with endometriosis is more proliferative as a result of endometriosis (54) and we demonstrated the endometrium displays an inappropriate elevation in secretory phase estrogen receptors (ESR1) at the time of implantation (55). As ESR1 levels are down-regulated in almost all mammalian species studied at implantation and the primary role of progesterone,(56) this failure to down-regulate ESR1 is a single primary endpoint that may predict implantation failure.

Endometriosis and Inflammation

Why would the endometrium and endometrial receptivity be altered in endometriosis? Inflammation is known to alter endometrial receptivity and has been associated specifically with endometriosis (57, 58). Endometriosis results in systemic and local cytokine expression changes that disrupts normal endometrial function (59-62), and is reversible by surgical removal of endometriosis (63). One of the hallmark changes seen in the endometrium of women with endometriosis is an induction of p450 aromatase expression (64, 65). While usually restricted to certain cell types including the ovary, placenta, and brain (66), over-expression in endometrium changes the dynamic of progesterone to estrogen activity, and favors development and growth of endometriosis (67). Further, inflammation has been shown to influence aromatase and steroid receptor expression (68). Brosens demonstrated that elevated aromatase expression is associated with poor IVF outcomes (69). Estrogen, perhaps locally produced, has been shown to inhibit key molecules in attachment of embryos including the αvβ3 integrin (70). Reduced integrin expression associated with reduced IVF outcomes that can be over-come with aromatase inhibitors given in the cycle of stimulation (28). Thus, this is a one example of a single biomarker that has been shown to predict IVF outcome and be amenable to therapy.

The pro-implantation cytokine, leukemia inhibitory factor (LIF), is essential for normal implantation (71), LIF was shown to peak at the time of implantation in the mouse and in animals with targeted LIF mutations, embryos would float within the uterus, but not implant. Exogenous LIF would result in implantation suggesting a soluble effect of this cytokine. Studies in the human have shown that LIF is present at the time of implantation(72) but its expression is reduced in women with endometriosis (73). Other key molecules that are required for normal endometrial receptivity such as HOXA10 (74), is reduced in endometriosis but restored after surgical resection of disease (75). Reduction in HOXA10 has been reported to be due to epigenetic changes associated with aberrant methylation of the HOXA10 promoter (76).

The inflammatory response seen in endometriosis is unusual and may be related to intrinsic programmatic endometrial responses to progesterone withdrawal (2). During the late phases of the menstrual cycle progesterone levels fall and inflammatory responses ensue in an orchestrated response required for menstruation (2, 77). Since progesterone action is impaired in the setting of endometriosis (78), this may mimic progesterone withdrawal and thereby stimulate a premature inflammatory (premenstrual) response (79). Rel-A (p65) is a subunit of NF-kB that is central to the inflammatory response. Rel-A inhibits progesterone receptor via the PR promoter (80) and therefore further contributes to progesterone resistance. ARID1A, an anti-inflammatory protein that is often mutated in ovarian and breast cancers (81, 82), is down-regulated in endometriosis (83), and appears to be a key regulator of the inflammatory response seen in this disease, by blocking Rel-A action on cytokine expression (82). Inflammatory responses are also exaggerated by the loss of other regulatory proteins including protein-inhibitor of STAT3 (PIAS3), which we recently reported was reduced in the endometrium of women with endometriosis (84).

These inflammatory responses of the endometrium of endometriosis has important downstream effects that impact fertility (85-90) and have been recently reviewed (5, 91). Interleukin-17 is central to many of the changes in endometriosis including the stimulating effect on cyclooxygenase-2 (Cox-2) activity, IL-8 and aromatase expression (92). IL-17 is specifically elevated in the blood and endometrium of women with endometriosis (61). COX-2 (93) and prostaglandins (94, 95) are central to eutopic endometrial changes associated with endometriosis. The shift toward estrogen dominance induces these factors that promote inflammation, angiogenesis, cell proliferation and immunosuppression. IL-17-induced IL-8 has been shown to target the PTEN/AKT signaling pathway which is aberrantly activated in endometriosis (96). IL-17 also induces the inflammatory cytokine IL-6 (61), that is elevated in the endometrium of endometriosis patients (97, 98). IL-17 expression is reduced following treatment of endometriosis (61).

We have reported that endometriosis is associated with sustained activation of STAT3 in eutopic endometrium, that is driven by IL-6 (13) and exacerbated by down-regulation of its primary inhibitor, protein-inhibitor of STAT3 (PIAS3) in women with endometriosis (84). STAT3 phosphorylation stabilizes hypoxia-induced factor 1-alpha (HIF1A)?(13) and stimulates expression of BCL6 expression (99). STAT3 activation appears to contribute to progesterone resistance and is central to inflammatory responses, including stimulation of these downstream effectors leading to the hallmark changes seen in endometriosis:

proliferation, cell-survival and angiogenesis. HIF1A, which normally appears at menstruation is responsible for many down-stream effects including angiogenesis. Inflammation associated with endometriosis has been implicated in epigenetic change (100) as well as aberrant activation of signaling pathways.

Endometriosis and Infertility: Role of Eutopic Endometrium

Endometriosis has been described as a progesterone resistant disease due to the blunted or inadequate response to progesterone of both the eutopic and ectopic endometrial cells and tissue (101-103). This is demonstrated by low expression of PR (104), blunted expression of progesterone target genes (105-107), and an inadequate decidualization response (103, 105, 107). Progesterone resistance associated with endometriosis contributes to increased cell proliferation and survival (54) and elevated estrogen receptors (55). As progesterone plays a role in decreasing inflammation in the endometrium, the insensitivity to progesterone signaling results in a pro-inflammatory condition (108, 109). The consequences of this is far-reaching affecting estrogen driven mechanisms and differentiating capacity of the tissue.

A role for eutopic endometrium in endometriosis-related infertility has also been focused on the defects in decidualization, a change in endometrial morphology that is essential for pregnancy success (110-112). There are multiple pathways by which decidualization defects might arise, and many have been identified as aberrant in endometriosis and defects in decidual responses have been widely reported (103, 113, 114). The decidua is an important component of the maternal/embryo interface that provides nutrients to the embryo, protects the developing embryo from stress pathways and immune rejection, and regulates the invasion of the trophoblast. Thus, aberrant decidualization would lead to unfavorable effects on embryo implantation and pregnancy. Although progesterone is a key hormone involved in initiating and prolonging the decidualization process signaling pathways have been demonstrated to amplify this response, including the PKA pathway (115-119), while the AKT and MAPK pathways have been demonstrated to blunt decidualization. Impaired decidualization has been reported in both eutopic and ectopic tissues in endometriosis (103, 110, 120). Human endometrial stromal cells suppress AKT during decidualization (121) and increased activation of PI3K/AKT impedes decidualization (103). FOX01, required for decidualization, is inactivated by AKT pathway (122) while inhibition of PI3K and AKT increases nuclear FOXO1 and IGFBP1 expression in response to progestin and dibutyryl cAMP treatment (103). PI3K/AKT also activates estrogen receptor alpha (ESR1), increasing its activation (123). In addition, in keeping with clinical observations of decreased estrogen receptor beta (ESR2)(124) AKT has also been shown to down-regulate ESR2(124), with the net effect of enhancing estrogen action. The AKT pathway may also impact progesterone action; AKT can downregulate PR protein expression of PR in breast cancer and endometrial cancer cells, and in stromal cells derived from endometriosis (125-127). AKT has been shown to attenuate PR action in endometrial cancer cells by affecting recruitment of coregulators to PR on chromatin (128). AKT inhibitors increased cellular PR and decreased cell survival and increased apoptosis in endometriosis (127). NOTCH1 is another gene that is critical for decidualization of both mouse and human uterine stromal cells (129). Decreased Notch signaling is associated with endometriosis and contributes to impaired

decidualization through the down-regulation of FOXO1 (129). Interestingly, NOTCH1 may be a target of SIRT1 (130).

Studies have demonstrated that the MAPK pathway is also overactive in the eutopic endometrium from women with endometriosis (131). Microarray analysis in eutopic endometrium from endometriosis patients identified members of the MAPK and PI3K signaling pathways to be significantly regulated (132, 133). These genes included RON, SOS, 14-3-3 protein eta, and uPAR in epithelial cells and KSR and PI3K p85 regulatory subunit alpha in stromal cells. A recent GWAS analysis of Stage A endometriosis revealed a total of 14 pathways were enriched, including the Grb2-Sos, Wnt signaling p130Cas, and extracellular signal-regulated kinase (ERK)1/ERK2/MAPK pathways (134). Wu et al, (135) conducted a comprehensive profiling of gene expression differences between the ectopic and eutopic endometrium taken from women with endometriosis adjusted for menstrual phase and the location of the lesions. Regulators of the MAPK signaling pathway including DUSP5, AKT1, HSPB2, PDGFB, PDGFRA, PLA2G5, MAPK6, MAPK7, RAC1, RAF1, RPS6KA3, TGFB3, MKNK1 were altered. Global analysis of genes performed by Burney et al (136) of eutopic endometrium of women with endometriosis, identified genes associated with inactivation of MAPK signaling cascades such as ERBB receptor feedback inhibitor 1 (ERRFI1, also known as MIG-6), and regulators of G protein signaling 1 (RGS1), which is an activator of GTPases that rapidly turns off G-protein coupled receptor signaling pathways, were decreased in endometriosis. Velarde et al (131) showed that increased ERK1/2 activity in the eutopic endometrial stromal cells from women with endometriosis inhibited cAMP-mediated down-regulation of cyclin D1. FOXO1 an important mediator of decidualization of endometrial stromal cells can be phosphorylated and its function modified by ERK and p38 (137) as well as other kinases such as DYRK1a (138), CK1 (139), and SGK (140).

Summary: Clinical Correlates

While clinical studies support the concept of endometrial receptivity defects endometriosis, these observations need to be based on a physiological mechanism. In this review, we hope that the reader can better understand how those changes noted in the eutopic endometrium of women with infertility and endometriosis biologically impact endometrial receptivity. In vitro Fertilization (IVF) is taking on a larger role for the treatment of infertile couples and is a platform on which endometrial receptivity defects are increasingly being tested (141). Many of the defective pathways described here contribute to infertility and have therapeutic and diagnostic implications. Increasingly, it appears that endometriosis has a negative impact on IVF outcomes, and treatment strategies are evolving to address such defects. Endometrial receptivity defects should remain a relevant and vital part of the workup of couples with infertility.

Conclusions

Strong evidence supports the concept that endometrial defects exist in women with endometriosis. The inflammatory nature of this disease, accompanied by excess estrogen action that leads to a constellation of changes in the eutopic endometrium that interferes

with normal embryo implantation. Signaling pathways associated with proliferation and cell survival are activated in endometriosis, while anti-proliferative progesterone pathways are being turned off. Progesterone resistance results in inadequate antagonism of estrogen action, increased inflammation, inadequate differentiation of the stroma and remodeling of the endometrium, all of which can lead to an non-receptive endometrium for embryo implantation. Inflammation appears to be central to these defects. For these reasons, it seems clear that the eutopic endometrium is a primary barrier to implantation in women with active endometriosis.

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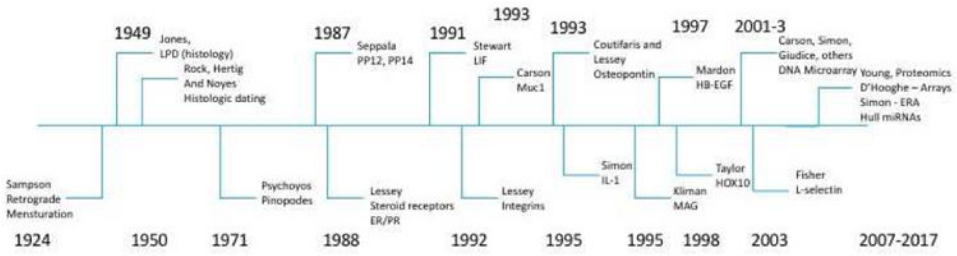

Figure 1.

Timeline for major discoveries in endometriosis and related defects in endometrial receptivity. The history of discovery of endometrial changes associated with endometriosis is shown in this timeline. Pivotal research on endometriosis commenced with the work of Sampson, but the changes in endometrium were noted by representative investigators up to the present day. There are many other important contributions that may not be represented. (144-167)

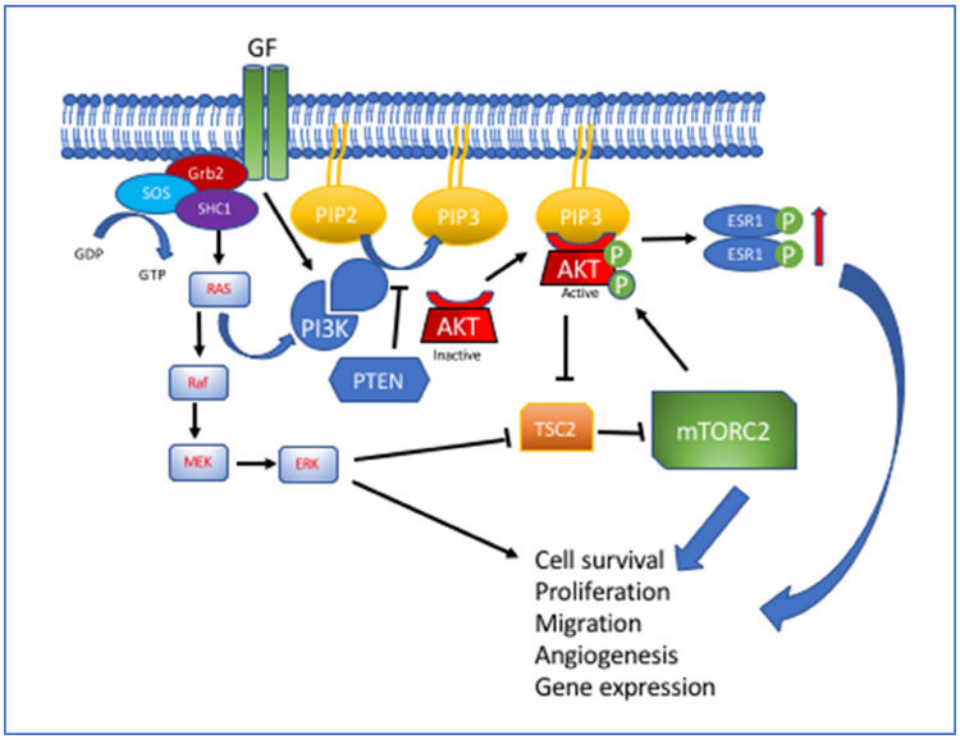

Figure 2.

The PI3K/AKT pathway is triggered when receptor tyrosine kinases are activated by ligand binding (GF) subsequently activating PI3K and adapter proteins (Grb2, SOS and SHC1). PI3K converts intracellular PtdIns-4,5-P2 (PIP2) to PtdIns-3,4,5-P3 (PIP3). In the absence of PTEN, which antagonizes PI3K, PIP3 activates AKT as a primary kinase downstream of PI3K. AKT moves to the plasma membrane, is phosphorylated and activated by mTORC2. PTEN antagonizes PI3K activity by dephosphorylating PIP3, leading to its conversion back to PIP2. Kras also contributes to PI3K activation and triggers generation of ERK pathway.