Endometrio ed endometriosi: the same tissue?

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Why does endometriosis develop only in some women?
the endometriotic cell

A) RETROGRADE MENSTRUATION

Endometrial fragments migrate through Fallopian Tubes during menstruation (Sampson, 1927)

B) Blood and linfatic dissemination

In a similar manner to the metastasis of tumor cells.

C) STEM CELLS

Stem cells residing in the basal layer are shed into peritoneal cavity and implant.

D) Metaplasia of coelomic epithelium

Peritoneal mesothelial cells differentiate into endometrium-like tissue under the sex hormones control (mostly estrogen)
**ENDOMETRIOSIS** = a benign disease defined by the presence of *endometrial glands and stroma* outside the uterus; associated with pelvic pain and infertility

eutopic ≠ ectopic
BUT WITHIN THE SAME ECTOPIC LESION WE CAN DISTINGUISH 3 DIFFERENTS TYPE OF DISEASE

a) PERITONEAL IMPLANT
b) OVARIAN ENDOMETRIOMA
c) DIE
IL 33

*IL-1 family*
- Nuclear localisation
- Expressed in uterine endometrial cells, increase with decidualisation
- **Profibrotic** mediation: linked to chronic fibrotic diseases

IL 8

*Chemokine CXC family*
- Induces chemotaxis of neutrophils and expression of adhesion molecules

IL-6

*IL-6 family*
- Promotes B cell differentiation, T cell activation, cytokines secretion.
The endometriotic cell, ectopic endometrium, with peculiar:

- Molecular mechanisms
- Immunobiologic characteristics
- Genetic foundation
• high local estrogens production
• high local prostaglandin production
• resistance to the action of progesterone
Immunobiologic characteristics

Changes in **cellular** and **humoral** immunity

- **activated macrophages** and circulating monocytes secrete growth factors and cytokines
- **NK cells**: over expression of killer-hinibiting receptors

**Proliferative**
- Anti-apoptotic

**Proliferative**
- Angiogenic
- Mediate adhesion

• **increased T cells** in stroma of ectopic endometrium and peritoneal fluid
• **increased cytokines** production (IL-1, IL-8, TNFalpha) and **growth factors** (VEGF)
Uterine Leukocyte Function and Dysfunction: A Hypothesis on the Impact of Endometriosis

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Keywords
Endometriosis, implantation failure, menstruation, NK cells, regulatory T cells

Endometriosis is a chronic inflammatory disease characterized by the growth of endometrial glands and stroma outside of the uterus. The disease affects approximately 10–15% of women of reproductive age and presents with clinical symptoms of pelvic pain and infertility. Changes in the leukocyte populations within the ectopic tissue and eutopic endometrium have been reported, and data suggest these alterations contribute to the pathology and symptoms of the disease. In this review, we discussed differences when comparing uterine NK cells and regulatory T cells within the eutopic endometrium between patients with endometriosis and healthy patients, and how these differences relate to implantation failure and/or decreased clearance of menstrual tissue in patients with the disease. The data demonstrate a critical need to examine endometrium and menstrual tissue in patients with endometriosis excluded from studies examining unknown causes of infertility and heavy menstrual bleeding. The information gathered from excluded patients will further enhance our understanding of how the immune system contributes to the pathophysiology of endometriosis and help to identify biomarkers for patients at higher risk for developing endometriosis-associated infertility.
Fig. 1 Models for development of ectopic lesions and their effect on eutopic endometrium. Inherited factors may lead to development of a regulatory environment in the eutopic endometrium (endogenous model) or a regulatory environment in the peritoneal cavity (exogenous model). Both result in survival of shed endometrial tissue and development of ectopic lesions. Cells and soluble factors from the lesions may then traffic to the eutopic endometrium and promote an environment that leads to implantation failure and continues development of the disease.
Endometriosis is six to sever times more prevalent among first-degree relatives of affected women.

Cluster within families
More common in mono and dizygotic twins
Similar age of onset in non-twins sisters

Predisposition inherited as a complex genetic trait
Epigenetic changes

Different gene expression in endometriotic tissue.

*i.e. ERK, FAS and FAS ligando, SF-1*

Promote the survival, attachment and proliferation of the endometriotic cell
Epigenetics refers to heritable changes in DNA and chromatin that impact gene expression without changes in DNA sequence. There are 2 basic epigenetic regulatory mechanisms: DNA methylation and histone modifications. DNA methylation is the best understood and most extensively studied epigenetic mechanism and refers to the covalent modification of post-replicative DNA, when a methyl group is added to the cytosine ring to form methyl cytosine. DNA methylation serves a critical role in the regulation of gene expression in development, differentiation, and complex diseases, cancer being the most prominent example.
A Gata2-Dependent Transcription Network Regulates Uterine Progesterone Responsiveness and Endometrial Function

Graphical Abstract

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In Brief
Rubel et al. find that in the uterus, Gata2 regulates the expression of progesterone receptor and its ability to modulate transcription of genes required for receptivity and support of embryo implantation. Gata2 is critical for the uterus to maintain epithelial integrity and prevent stratification in response to an estrogen challenge.

Highlights
- Gata2 regulates the ability of the uterus to support embryo implantation
- Gata2 regulates uterine expression and action of the progesterone receptor
- Gata2 regulates uterine epithelial differentiation
- A Gata2 expression signature is present in the human endometrium

Accession Numbers
GSE40661

Rubel et al., 2016, Cell Reports 17, 1414-1425
October 25, 2016
http://dx.doi.org/10.1016/j.celrep.2016.09.093
Genome-Wide DNA Methylation Analysis Predicts an Epigenetic Switch for GATA Factor Expression in Endometriosis

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In most placental mammals, the differentiation (decidualization) of the endometrial stroma into the decidual cells of pregnancy is induced by the implanting blastocyst; however, primates that menstruate initiate decidualization through an evolutionarily unique mechanism: the post-ovulatory rise in maternal progesterone. Consequently, decidualization is triggered in women with every ovulatory cycle independent of pregnancy.

DNA methylation serves as a critical regulator of gene expression, and global differences in DNA methylation affect multiple aspects of development and disease. Endometriotic cells express variable levels of the DNA methyltransferase enzymes (DNMTs), which introduce and maintain DNA methylation on the C5 position of cytosine in CpG dinucleotides. Abnormal DNA methylation in endometriosis affects the expression of several genes, including homeobox A10 (HOXA10), estrogen receptor beta (ESR2), steroidogenic factor 1 (NR5A1), and aromatase (CYP19A1), which alter steroid signaling and responsiveness, and are critically involved in development and decidualization.
By comparing healthy and diseased cells treated with or without hormones to mimic part of the menstrual cycle, we uncovered many differentially methylated genes with defective expression in endometriosis that also regulate the hormone-dependent aspects of menstruation. In addition to expanding our understanding of how methylation affects endometriosis many fold, this also led us to propose an epigenetic switch that permits GATA6 expression in endometriosis instead of GATA2, and this switch promotes the aberrant expression of many of the genes seen in endometriosis. Our work provides novel unifying insight into the cause and development of endometriosis.
Aberrant endometrial DNA methylome of homeobox A10 and catechol-O-methyltransferase in endometriosis

Fei Ji¹ · Xinhua Yang² · Yan He¹ · Hui Wang³ · Aixingzi Aili² · Yan Ding¹

Fig. 1 Simplified schematic of the potential roles of HOXA10 and COMT in the pathogenesis of endometriosis. HOXA10 acts downstream of activated estrogen receptor (ER); in endometriosis, it is hyper-methylated and this action is decreased. COMT degrades 2-hydroxyestradiol (2-OHE2) the product of 2-hydroxylation of estradiol (E2) and thus decreases the level of available E2 for ER binding and translocation to the nucleus.
Aberrant Methylation of the E-Cadherin Gene Promoter Region in Endometrium and Ovarian Endometriotic Cysts of Patients with Ovarian Endometriosis

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Immune-inflammation gene signatures in endometriosis patients

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• Heat Map Analysis Shows that Ectopic Tissue is Uniquely Different from Matched Eutopic Endometrium and from Control Endometrium

• Genes Involved in Cytokine–Cytokine Receptor Interaction, Cellular Adhesion, Immune Cell Recruitment, and Apoptosis are Significantly Increased in Endometriotic Lesions

• Genes Involved in Natural Killer and T-Cell Cytotoxicity, Cell Signaling, and Regulation of Inflammatory Responses are Decreased in Expression in Endometriotic Lesions
• Genes Involved in Both Classic and Alternate Complement Pathways are Aberrantly Expressed in Ectopic Tissues Compared with Control Endometrium Samples

• Eutopic Endometrium Shows Dysregulated Immune Activation Compared with Control Endometrium

• Eutopic Endometrium of Patients Aberrantly Express Genes Involved in Regulation of Decidualization, Cellular Adhesion, Cytokine–Cytokine Receptor Interaction, and Apoptosis
We show aberrant transcription of genes involved in decidualization of endometrium, which may explain why our endometriosis patients were referred for infertility-related problems. Indeed, our data validate the presence of immune dysregulation often observed in the peritoneal fluid of women with endometriosis, and further emphasize the importance of using immune gene expression profiles as a guide to better define all the facets that contribute to the pathogenesis of endometriosis.
Ridotta apoptosi
Resistenza al P4

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Role of nuclear progesterone receptor isoforms in uterine pathophysiology

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Identification of multiple and distinct defects in prostaglandin biosynthetic pathways in eutopic and ectopic endometrium of women with endometriosis

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### TABLE 1

Eicosanoid biosynthetic and catabolic enzyme RNA expression in eutopic and ectopic endometrium of endometriosis vs. control patients according to menstrual cycle phase, assessed by real-time PCR.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Proliferative phase (n = 45)</th>
<th>Secretory phase (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group (n = 12)</td>
<td>Eutopic (n = 22)</td>
</tr>
<tr>
<td>Cox-1</td>
<td>237.9 ± 78.3</td>
<td>263.6 ± 103.1</td>
</tr>
<tr>
<td>Cox-2</td>
<td>6.8 ± 5.6</td>
<td>15.1 ± 3.9(a)</td>
</tr>
<tr>
<td>mPGES1</td>
<td>7.4 ± 2.3</td>
<td>20.6 ± 13.3</td>
</tr>
<tr>
<td>mPGES2</td>
<td>86.8 ± 5.9</td>
<td>54.6 ± 3.7(b)</td>
</tr>
<tr>
<td>cPGES</td>
<td>68.3 ± 4.8</td>
<td>63.6 ± 4.6</td>
</tr>
<tr>
<td>Akr1B1</td>
<td>217.6 ± 15.6</td>
<td>216.9 ± 25.9</td>
</tr>
<tr>
<td>Akr1C3</td>
<td>127.9 ± 26.5</td>
<td>132.8 ± 21.1</td>
</tr>
<tr>
<td>15-PGDH</td>
<td>18.4 ± 3.2</td>
<td>41.3 ± 11.4</td>
</tr>
</tbody>
</table>

Note: Values (% GAPDH mRNA levels) are means ± SD. \(aP<.05, \(bP<.01, \(cP<.001, \) vs. the control group; \(dP<.05, \(eP<.01, \) \(fP<.001 vs. the eutopic group; \(gP<.05 vs. the proliferative group.

Pathogenetic Mechanisms of Deep Infiltrating Endometriosis

Claudia Tosti, MD\textsuperscript{1,2}, Serena Pinzauti, MD\textsuperscript{1,2}, Pietro Santulli, MD, PhD\textsuperscript{2,3}, Charles Chapron, MD\textsuperscript{2,3}, and Felice Petraglia, MD\textsuperscript{1}

Figure 2. Molecular pathways involved in deep infiltrating endometriosis (DIE) pathogenesis.
Figure 1. Signaling mechanisms of deep infiltrating endometriosis (DIE) pathogenesis.
Stem cells and endometriosis

Endometrial Adult/Progenitor Stem Cells: Pathogenetic Theory and New Antiangiogenic Approach for Endometriosis Therapy

G. Pittatore, MD, A. Moggio, BiolSci, C. Benedetto, MD, PhD, B. Bussolati, MD, PhD, and A. Revelli, MD, PhD
Figure 1. Stem cells self-renewal and differentiation. Stem cells are able to indefinitely self-renew or differentiate, giving rise to committed progenitors. At the next step, progenitors evolve into transit-amplifying (TA) cells that rapidly proliferate and differentiate to finally produce differentiated cells of a given cell lineage.
Review: Human uterine stem/progenitor cells: Implications for uterine physiology and pathology

T. Maruyama*, K. Miyazaki, H. Masuda, M. Ono, H. Uchida, Y. Yoshimura
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Maturitas

Review

Stem cells and the reproductive system: Historical perspective and future directions

Cindy M.P. Duke, Hugh S. Taylor*
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Endometrial reconstruction from stem cells

Caroline E. Gargett, Ph.D., a,b and Louie Ye, Ph.D. a,b

a The Ritchie Centre, Monash Institute of Medical Research, and b Department of Obstetrics and Gynaecology, Monash University, Monash Medical Centre, Clayton, Victoria, Australia

Adult stem cells have been identified in the highly regenerative human endometrium on the basis of their functional attributes. They can reconstruct endometrial tissue in vivo suggesting their possible use in treating disorders associated with inadequate endometrium. The identification of specific markers for endometrial mesenchymal stem cells and candidate markers for epithelial progenitor cells enables the potential use of endometrial stem/progenitor cells in reconstructing endometrial tissue in Asherman syndrome and intrauterine adhesions. [Fertil Steril® 2012;98:11–20. ©2012 by American Society for Reproductive Medicine.]
Endometrial Cells Derived From Donor Stem Cells in Bone Marrow Transplant Recipients

Hugh S. Taylor, MD

Context: Regeneration of the endometrium in each menstrual cycle is required for reproduction. Endogenous endometrial stem cells reside in the basalis layer and serve as a source of cells that differentiate to form the endometrium. Bone marrow-derived cells have been shown to take on functions outside the hematopoietic system.

Objective: To investigate the possibility that cells of extraterine origin could repopulate the endometrium.

Design, Setting, and Patients: Endometrium from 4 HLA-mismatched bone marrow transplant recipients (1998-2002) was evaluated for donor HLA expression. Each recipient had a bone marrow donor with an HLA type that enabled determination of the origin of any cell. Endometrial biopsies also were obtained from 4 healthy control women.

Main Outcome Measure: HLA type was determined by immunohistochemistry and by reverse transcription-polymerase chain reaction.

Results: Donor-derived endometrial cells were detected in endometrial biopsy samples from all bone marrow recipients and accounted for 0.2% to 48% of epithelial cells and 0.3% to 92% of stromal cells. None of the controls demonstrated HLA mismatch in endometrial samples.

Conclusion: These findings demonstrate that endometrial cells can originate from donor-derived bone marrow cells and suggest that nonuterine stem cells contribute to the regeneration of endometrial tissue.

Vascular Biology, Atherosclerosis, and Endothelium Biology

Endothelial Progenitor Cells Contribute to the Vascularization of Endometriotic Lesions

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of endometrial tissue outside the uterine cavity, also referred to as endometriotic lesions. Although the pathogenesis of endometriosis is still a matter of discussion, it is widely believed that these lesions originate from shed endometrial fragments that enter the peritoneal cavity through the fallopian tubes by retrograde menstruation. Because they initially lack their own blood supply, rapid
Enhanced expression of the stemness-related factors OCT4, SOX15 and TWIST1 in ectopic endometrium of endometriosis patients

Katharina Proestling¹, Peter Birner², Sukirthini Balendran², Nadine Nirtl¹, Erika Marton¹, Gülen Yerlikaya³, Lorenz Kuessel¹, Theresa Reischer¹, Rene Wenzl¹, Berthold Streubel²* and Heinrich Husslein¹
Fig. 3 Expression analyses in 50 control patients, and 110 patients with endometriosis (eutopic and ectopic). IHC was used to analyze the protein expression of OCT4 (a), SOX15 (b), TWIST1 (c) and DCAMKL1 (d). Results are expressed as mean score of the immunohistochemical staining ± SD. Epithelial and stromal expression was analyzed separately. Comparisons with the control group were analysed by t-test, comparisons between EP endometrium and endometriotic tissue were performed using Fisher combination test.
The Role of Stem Cells in the Etiology and Pathophysiology of Endometriosis

Demetra Hufnagel, BS1, Fei Li, MD1, Emine Cosar, MD1, Graciela Krikun, PhD1, and Hugh S. Taylor, MD1

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Abstract

Human endometrium is a dynamic organ that normally undergoes repetitive cyclic regeneration. To enable this rapid regeneration, it is not surprising that the endometrium contains a reservoir of progenitor stem cells. However, this pool of cells that allows the growth of the endometrium also allows for unrestrained growth that can reach beyond the endometrium. In this review, we will address the role of stem cells in endometriosis. Recent characterization of stem cell populations within human endometrium has opened the possibility of understanding their physiologic as well as their pathologic roles. While stem cells are critical to the cyclic regeneration of a healthy endometrium, we have shown that both endometrium-derived and bone marrow-derived stem cells can migrate to ectopic sites and contribute to the development of endometriosis. Furthermore, endometriosis interferes with the normal stem cell trafficking to the uterus that is necessary for endometrial growth and repair. Altered stem cell mobility and engraftment characterize this disease.
Stem Cell Migration between Endometriosis and Endometrium

Although it is clear that BMDSCs migrate to the uterus and endometriosis, stem cells are also capable of tremendous trafficking between locations. Our laboratory has identified the presence of a cell population that migrates from the endometriotic lesion into the uterus; these cells produce factors capable of altering uterine receptivity. .........This is a process by which epithelial cells lose their polarity and are converted to a mesenchymal phenotype. These cells migrate as mesenchymal stem cells. After engraftment in the uterine stroma, these cells, all derived from the endometriosis, displayed activation of the Wnt signaling pathway indicating that they had taken on an epithelial identity; however, these cells were not located in the epithelium. These endometriosis-derived stem cells do not home to the appropriate location in the uterus. The cells were inappropriately localized to the stroma yet secreted signals typical of epithelial cells. Proper establishment of a gradient of signaling molecules between epithelium and stroma is essential for normal endometrial receptivity. The disincorporation of stem cells in the eutopic endometrium disrupts stromal-epithelial signaling and leads to decreased endometrial receptivity in endometriosis patients.
Comprehensive study of angiogenic factors in women with endometriosis compared to women without endometriosis

Gülen Yerlikaya\textsuperscript{a, c, 1}, Sukirthini Balendran\textsuperscript{b, 1}, Katharina Pröstling\textsuperscript{a}, Theresa Reischer\textsuperscript{a}, Peter Birner\textsuperscript{b}, Rene Wenzl\textsuperscript{a}, Lorenz Kuessel\textsuperscript{a}, Berthold Streubel\textsuperscript{b, *}, Heinrich Husslein\textsuperscript{a}

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In summary, we identified new genes (EPHB4 and NRP1) that may contribute to angiogenesis in endometriosis beside known factors (VEGFA, VEGFR2, HIF1A, HGF, and PDGFB). Correlation studies revealed the putative importance of EBHB4 in association with endometriosis. Our analyses support preliminary reports that angiogenic factors seem to be differently expressed in peritoneal implant, ovarian endometriomas and DIE. Our observation that angiogenic factors are differently expressed in the unaffected peritoneum of women with endometriosis compared to women without endometriosis underlines the importance of the peritoneum in the establishment of endometriosis.