Endometriosis
Epigenetics and Stem Cells

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What is the Pathogenesis of Endometriosis?
Theories for the Origin of Endometriosis

- Retrograde menstruation
- Embryonic rests
- Colemic metaplasia
- Immune
- Genetic
- Stem cells
Support of Sampson’s theory

- Dependent distribution
- Common occurrence of retrograde menstruation
- High incidence with outflow tract obstruction
- Tubal patency common
- Risk factors that include frequent menstruation and early menarche.
- Animal models involving peritoneal transplant
Sampson’s Theory does not explain the presence of endometriosis outside of the peritoneal cavity or in men.
The Stem Cell Theory of Endometriosis
Adult Stem Cells

- Adult stem cells are cells that have traveled to tissue niches early in an organism’s development to reside there in a relatively undifferentiated state.

- These adult stem cells, also called progenitor stem cells (PSC) can renew themselves and differentiate into most of the specialized cell types located in the surrounding tissue.
Localization of label-retaining cells (LRCs) in postnatal and prepubertal-labeled mice

Stromal BrdU retaing cells

BrdU Labeled Cells (%) vs Chase Period (wks)
Endometriosis

It is likely that endometriosis that arises via retrograde menstruation is derived from shed progenitor stem cells.
Multipotent Endometrial Stromal Cells

Chondrocytes

Osteocytes

Adipocytes

Myocytes

Wolff 2007; Schwab 2007; Dimitrov 2008
in vitro Differentiation

Control Endometrial Stromal Cells

Nestin

Neurogenic Differentiated

Tyrosine Hydroxylase
ESC Neurotransplantation

- Engraft in mice brains
  - PCR detects human DNA

- Engraft in mice brains
  - Striatum (transplant site)

- Migrate & Differentiate morphologically in vivo
  - Substantia nigra (lesion site)
ESC Neurotransplantation

- Rescues dopamine concentrations

![Graph showing rescued dopamine concentrations in different groups: Unlesioned (no MPTP), Sham (+MPTP), Transplanted (+MPTP). All groups are significantly different (*p<0.05).](image)

*all p<0.05*
Can Bone Marrow Derived Stem Cells Differentiate Into Endometrium?
Patients

- Four bone marrow transplant recipients
- HLA type that allowed determination of the origin of any cell
- Age 28-43
- Rx Chemotherapy and TBI
RT-PCR amplifying HLA A11
Bone Marrow
Stem Cell-Derived Endometrium

Marker of Differentiation

A

Calcitonin

B

HLA

C

Merge
Do Stem Cells Contribute to Endometrium in a murine model?
Identification of bone marrow-derived cells in murine-endometrium

Transplant of Male bone marrow into female mice. Assessment of SRY gene expression and Y chromosome by FISH

Stem cell origin of endometrium in mouse
Stem Cell Origin of Endometrium in a Mouse Model

Stem cells are recruited to the uterus for repair and tissue regeneration.
Can Stem Cells Contribute to Endometriosis?
Methods

- Wild Type and LacZ transgenic mice
- Hysterectomy and ectopic uterine transplant
- Beta-Galactosidase activity and expression
IHC using anti Beta-galactosidase antibody

Wt control

LacZ transgenic

Wt transplanted to LacZ transgenic
IHC using anti Beta-galactosidase
X-GAL staining of Beta-Galactosidase activity

Glandular cell

Stromal Cell
A Novel Origin of Endometriosis

- Stem cells contribute to murine endometriosis
Endometriosis Is Not One Disease!

- Retrograde menstruation leads to peritoneal disease
- Metaplasia leads to endometriomas
- Stem cells lead to lung and brain endometriosis as well as contribute to endometriosis in the peritoneal cavity
Novel Treatments

PATHOGENESIS

Genetic predisposition

Retrograde menstruation and/or stem cell recruitment

Peritoneal invasion

Dysfunctional immune response

Angiogenesis & increased local estrogen

Endometriosis
How does endometriosis lead to infertility?
Infertility Treatment: No Role for Medical Suppression

Surgical Intervention: Fecundity Rate

- **Control group**
  2.4 %

- **Intervention group**
  4.7 %

Why do our treatments fail?

How does endometriosis effect fertility?
HOXA10 in the Human Endometrium

- HOXA10 is expressed in the endometrium where it is necessary for implantation.

- HOXA10 expression varies with menstrual cycle; epithelial expression dramatically rises at the time of implantation.

- Estrogen and Progesterone regulate HOXA10

Taylor et al, J Clin Invest 1998; 101:1379
HOXA10 Expression
human endometrium

Taylor et al, J Clin Invest 1998; 101:1379-1384
HOXA10 Expression

Implantation Window

Animal Models of Endometriosis

Allows determination of cause and effect

- Mouse
- Non-Human Primate
Murine Experimental Endometriosis
Control Endometriosis

**Hoxa10**

Control  |  Endometriosis
---|---

**Hoxa11**

Control  |  Endometriosis
---|---

**Igfbp1**

Control  |  Endometriosis
---|---

**Itgb3**

Control  |  Endometriosis
---|---

Lee and Taylor, BOR 2009
Epigenetic Alterations
The two main components of the epigenetic code

DNA methylation
Methyl marks added to certain DNA bases repress gene activity.

Histone modification
A combination of different molecules can attach to the ‘tails’ of proteins called histones. These alter the activity of the DNA wrapped around them.
Chromatin Modifications

Euchromatin: Gene Activation

Heterochromatin: Gene Silencing
The HOXA10 Gene
Hoxa10 DNA Methylation

Lee and Taylor, Biol Reprod 2009
Hoxa10 DNA Methylation

A

B

C

Methylation level (%)
Baboons with experimentally induced endometriosis
Uterus

Peritoneum

Upper Panel - One Month
Lower Panel - Four Months
Expression of HOXA10 in the eutopic endometrium of baboons with endometriosis

Methylation of the HOXA10 gene

Epigenetic changes in HOXA10 in women with endometriosis

Surgical Intervention: Fecundity Rate

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  2.4%

- Intervention group
  4.7%

Figure 1. Cumulative Probability of a Pregnancy Carried Beyond 20 Weeks in the 36 Weeks after Laparoscopy in Women with Endometriosis, According to Study Group.

Conclusion

- Stem Cells contribute to endometrium and endometriosis

- Endometriosis induces irreversible epigenetic changes in the endometrium
  - Disease may be chronic and not curable
Mobilized stem cells may be capable of replacing endometrial cells that were epigenetically altered by endometriosis.
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