Uterine NK progenitor cells: the endometrium of women with and without endometriosis

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Uterine natural killer cells

- Low cytotoxicity
- Regulate immune cell function via cytokine production
- Tissue remodelling: vessel maturation & trophoblast invasion → important in fertility (Moffett, 2002)
- Increase during secretory phase & pregnancy (Proliferate/ Chemotaxis)
Progenitor immune cells in endometrium
Endometriosis

• Endometriotic tissue outside of the uterine cavity
• >25% of women with endometriosis are subfertile
• Eutopic endometrium in women with endometriosis is altered

• Normal: Fertile, tubal ligation
• Endometriosis
Hypothesis 1

uNK cell progenitors are increased in women with endometriosis-associated infertility
uNK cell development

Stage 1: CD34+ CD10+
Stage 2: CD34+ CD117+ CD94-
Stage 3: CD34- CD117+ CD94-
Stage 4: CD34- CD117+/- CD94+
Gating Strategy for uNK cell stages of development

Stage 1
CD34+ CD10+

Stage 2
CD34+ CD117+ CD94-

Stage 3
CD34- CD117+ CD94-

Stage 4
CD34- CD117+/- CD94+
Stages 1+2 uNK cells are significantly higher in women with endometriosis associated infertility.
Summary 1
Stage 1+2 uNK cells are significantly higher in women with endometriosis

Hypothesis 2
Stage 1+2 uNK increase may be due to altered endometrial microenvironment
Protein array of endometrial microenvironment

- Cytokine array (42 different cytokines)
- Eutopic endometrial samples

**Stem Cell Factor**
- Stem cell factor (SCF) significantly reduced in endometriosis
- Self-renewal and maintenance of HSCs *in vivo*
- Required for NK cell development
Stem Cell Factor is reduced in endometrium of women with endometriosis associated infertility.
SCF receptor (CD117) is significantly increased in endometriosis

* gated by FMO
Hypothesis 3: Endometrial SCF production dysfunctional in women with endometriosis

OESTROGEN & PROGESTERONE

GROWTH FACTORS

X
Healthy/fertile

Endometriosis

Conditioned media

Detect SCF levels

Human endometrial cell culture

Oestrogen

Progesterone

Oestrogen/Progesterone

Relative fold change of SCF protein
SCF treatment of CD34+ human endometrial cells

CD34+ cells + SCF → 3 weeks

NORMAL % of CD45+ cells (n=4)

Day 0 + SCF

**NORMAL** (n=4)
Summary

• Stage 1 and 2 uNK cells are significantly increased in endometriosis

• SCF levels are reduced in eutopic endometrium of women with endometriosis

• Endometrial cells from women with endometriosis fail to respond to sex steroid hormone stimulus

• Development of uNK cell progenitors from women with endometriosis is restored by treatment with SCF
Conclusion

• Low levels of endometrial SCF in women with endometriosis prevent maturation of the local uNK cell population

• Suggests a mechanism to explain endometriosis associated infertility

• May open new avenues for treatment such as SCF replacement
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