Estrogen and Immune cell

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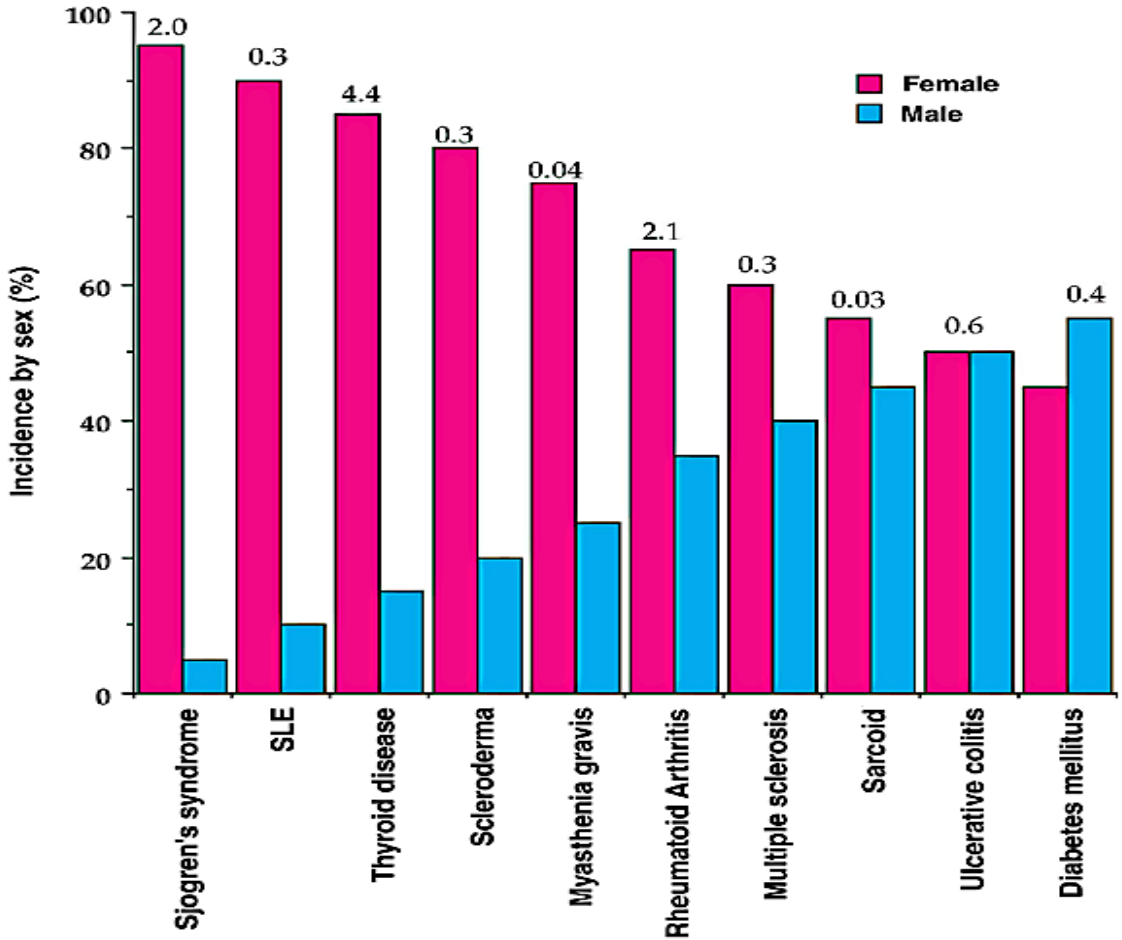
Contents

- Gender Difference in Immunity
- Steroid Hormone / Receptor
- Estrogen on Immune cell

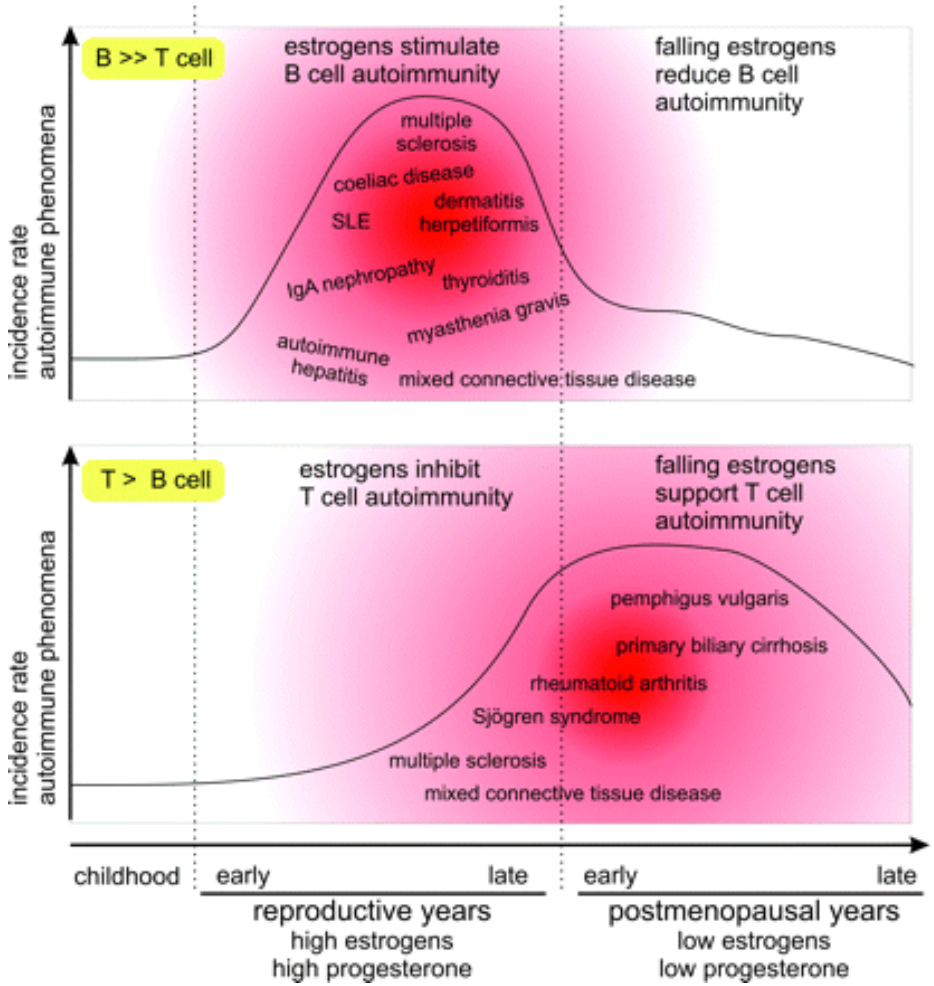
  B cell / T cell / Monocyte / pbNK cell

Gender difference in Autoimmune Disease



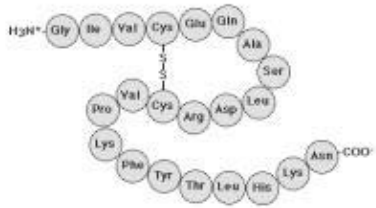
Nature Immunology ***2****, 777 - 780 (2001)*

Autoimmune Disease in Women



Hormones (1)

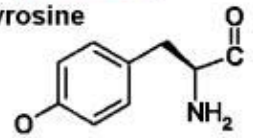
Peptides



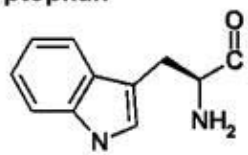
- **MOST** hormones are of this variety

Amines

Tyrosine



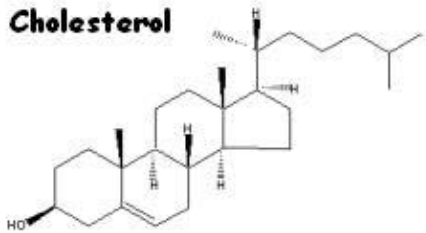
Tryptophan



- Thyroid
  - Triiodothyronine (T3)
  - Thyroxine (T4)
- Adrenal medulla
  - Epinephrine
- Pineal gland
  - Melatonin

Steroids

Cholesterol



- Adrenal cortex
  - Aldosterone
  - Cortisol
- Gonads
  - Testosterone
  - Estrogen
  - Progesterone
  - others...

Regardless of their structure, all hormones act through RECEPTORS

Hormones (2)

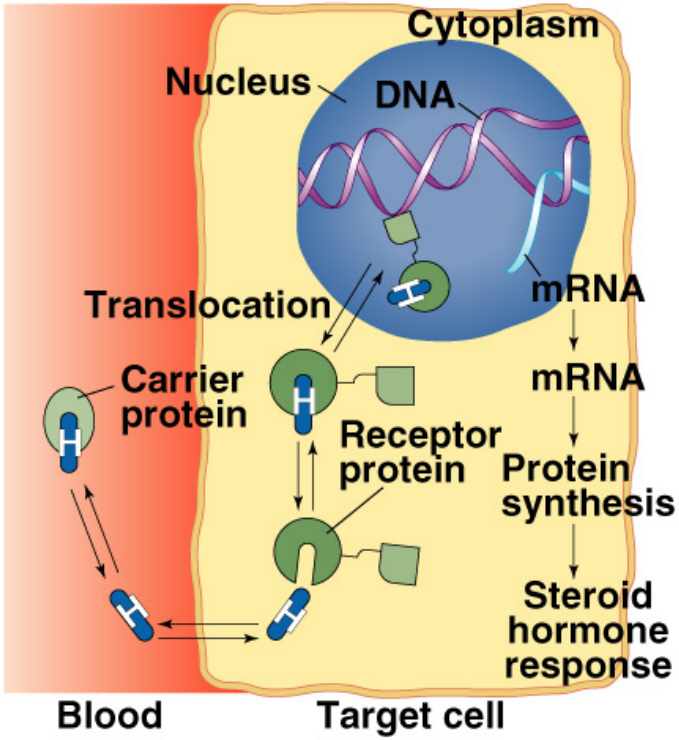
- Lipid-soluble Hormones

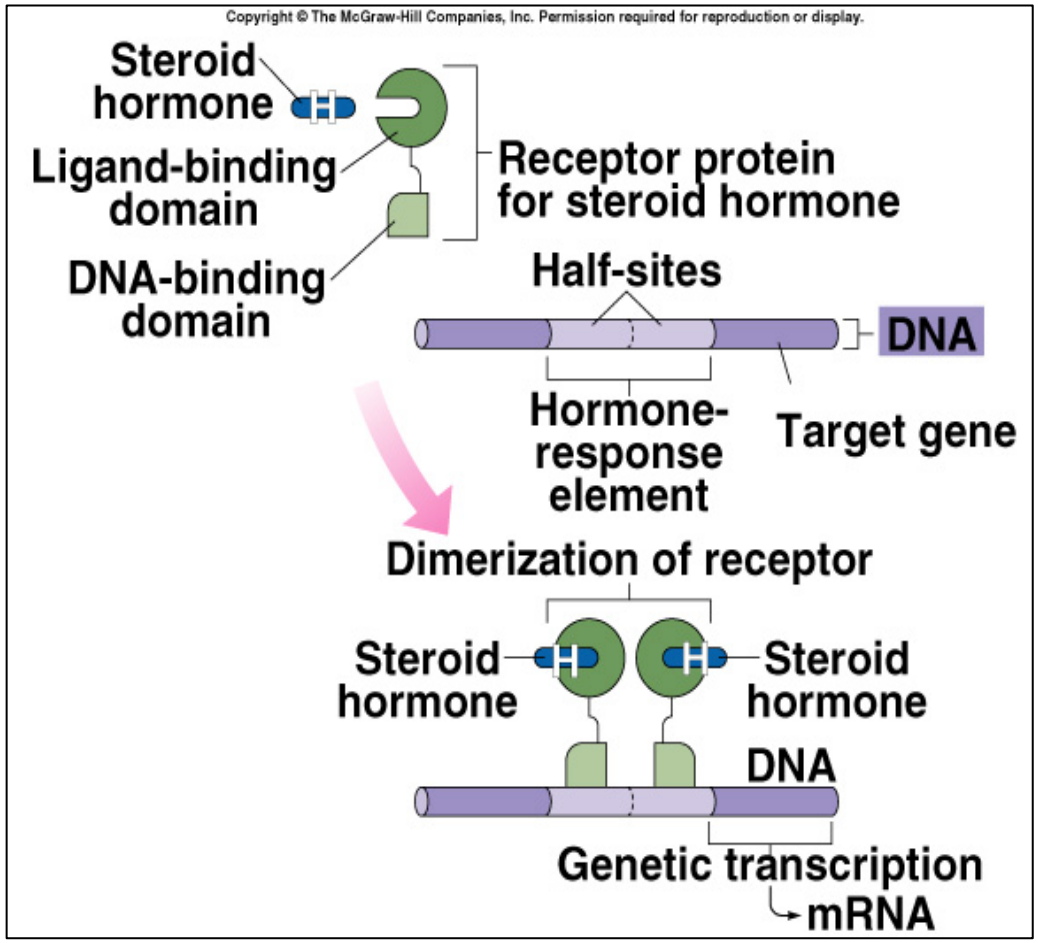
  Steroids, Thyroid hormones

- Water-soluble Hormones

  Amine, peptide and protein hormones

Mechanisms of Steroid Hormone (1)



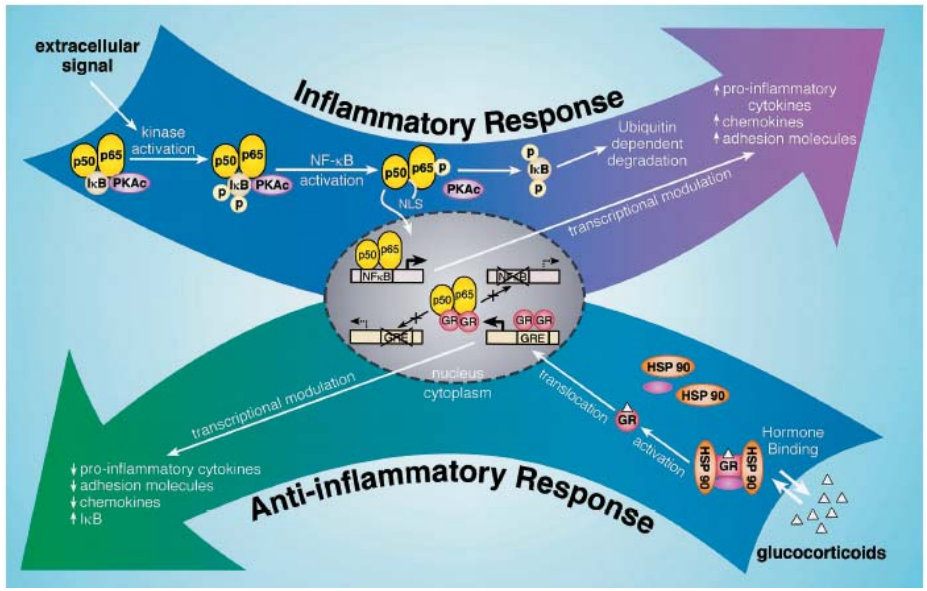


Mechanisms of Steroid Hormone (2)

Nuclear factor-kB (NF-kB)

- Inducible transcription factor *McKay and Cidlowski, (1999)*

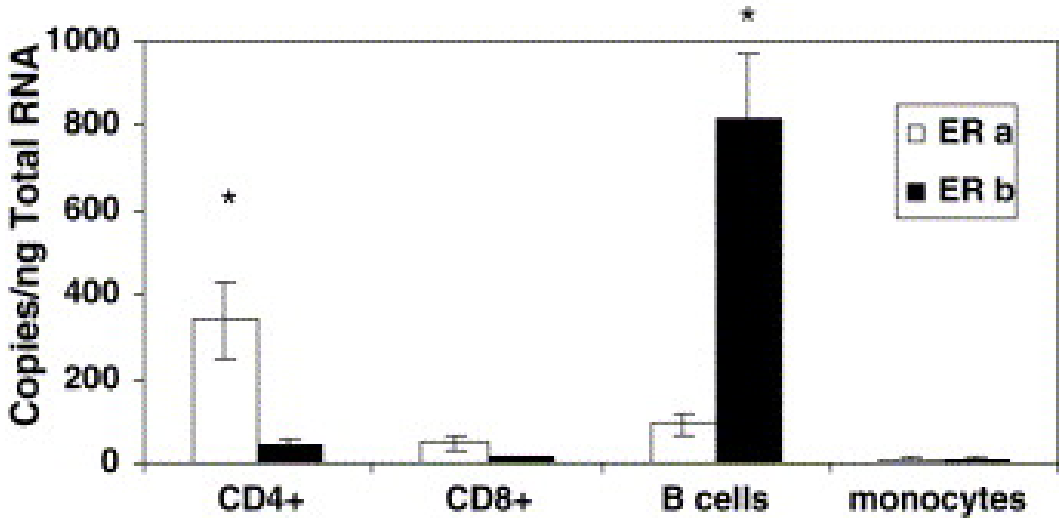
; positively regulates the expression of proimmune and pro-inflammatory genes



✓ **Steroid/receptor complex** *McKay and Cidlowski,(1999)*

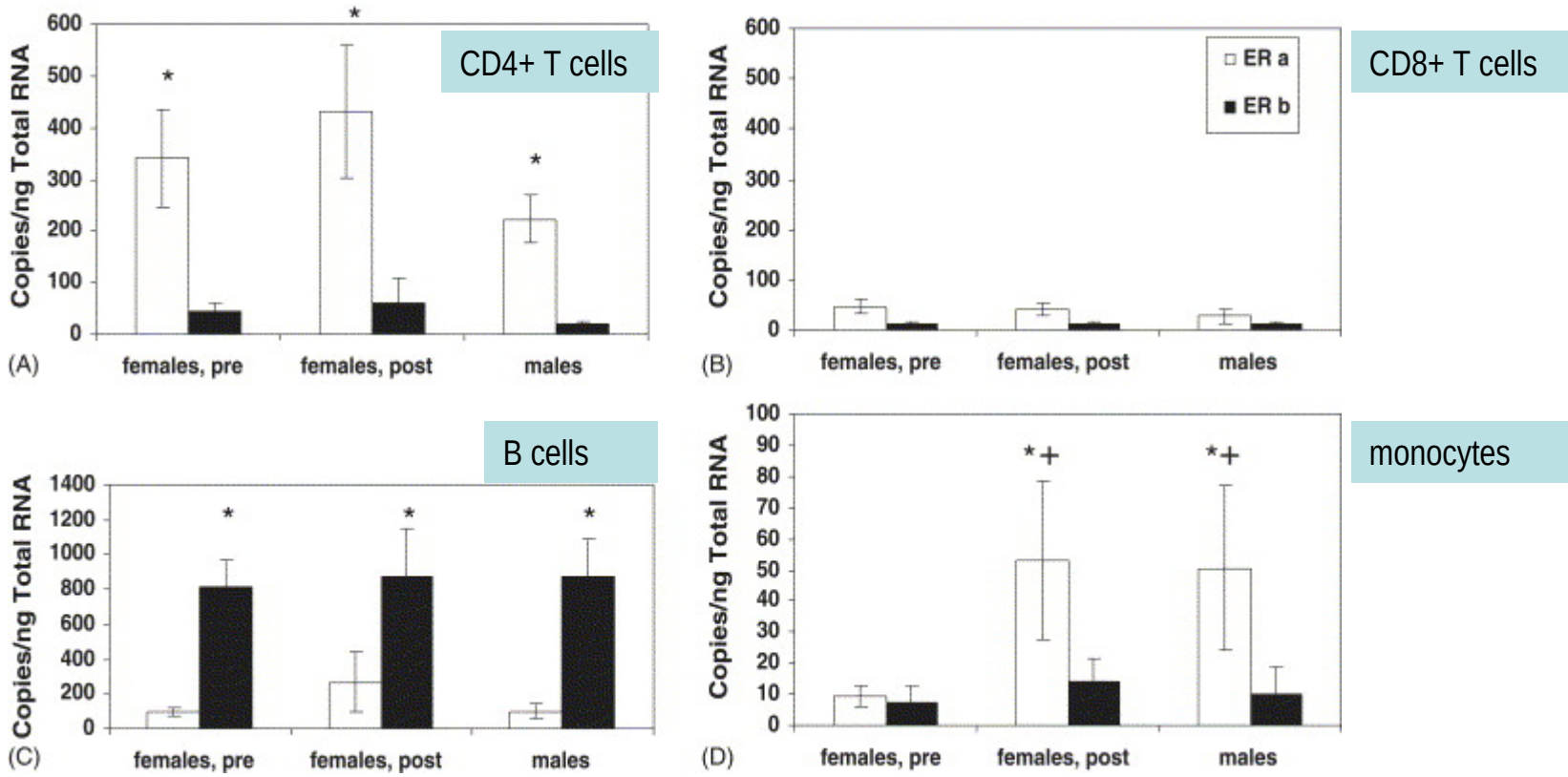
interact with NF-kB and inhibits its transactivational activity

Estrogen receptor (ER) expression (1)



Immunol Lett. (2005) 97:107-13.

Estrogen receptor (ER) expression (2)



Immunol Lett. (2005) 97:107-13.

Estrogen receptors (ERs) (2)

Preponderance of ER subtype

✓ **Preponderance of one ER subtype over the other might change estrogen effects (7, 8).**

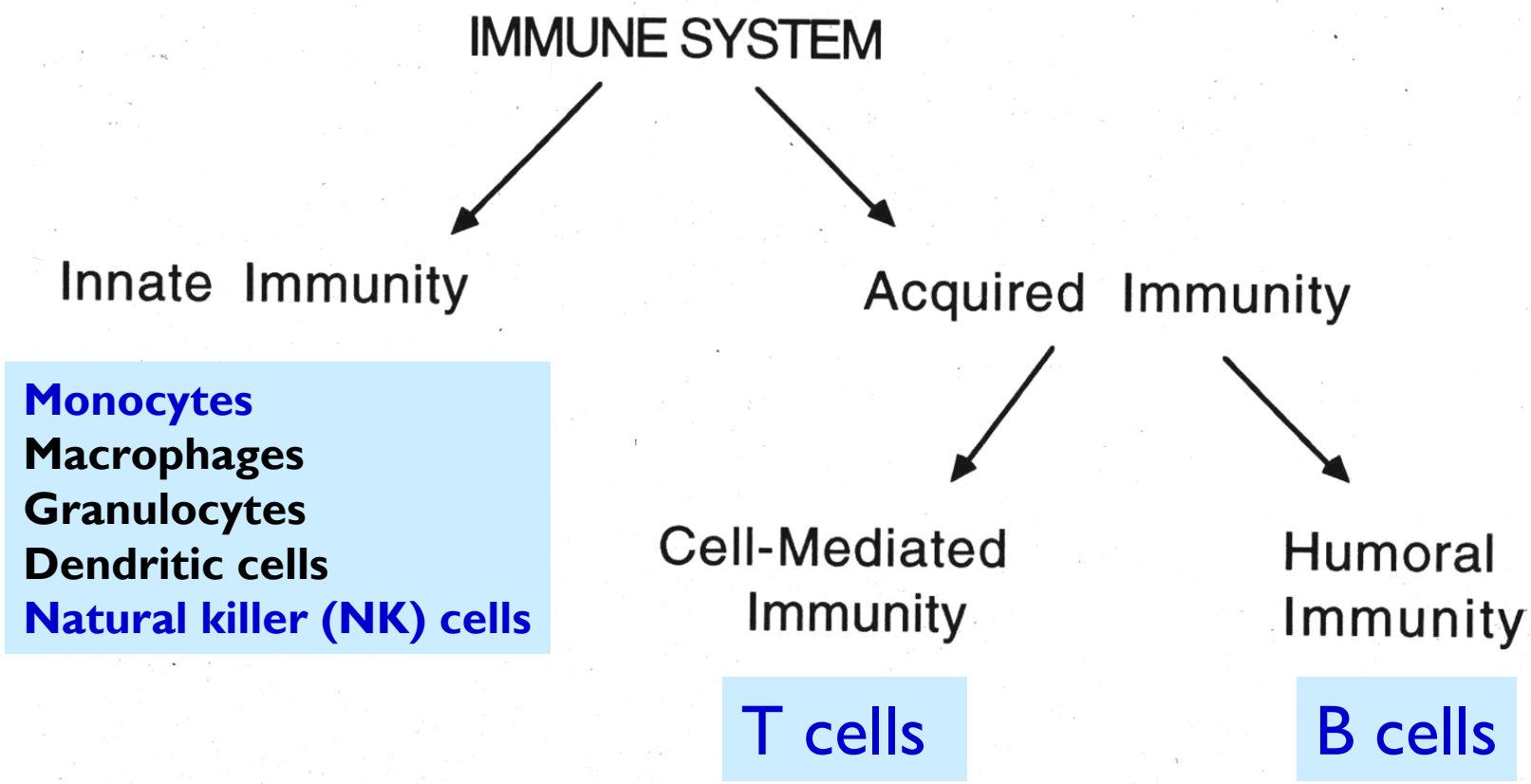
- **RA**

  in synovial tissue of macrophage-like and fibroblast-like synoviocytes, higher density of ERß+ cells than of ERα+ cells (13). (12).

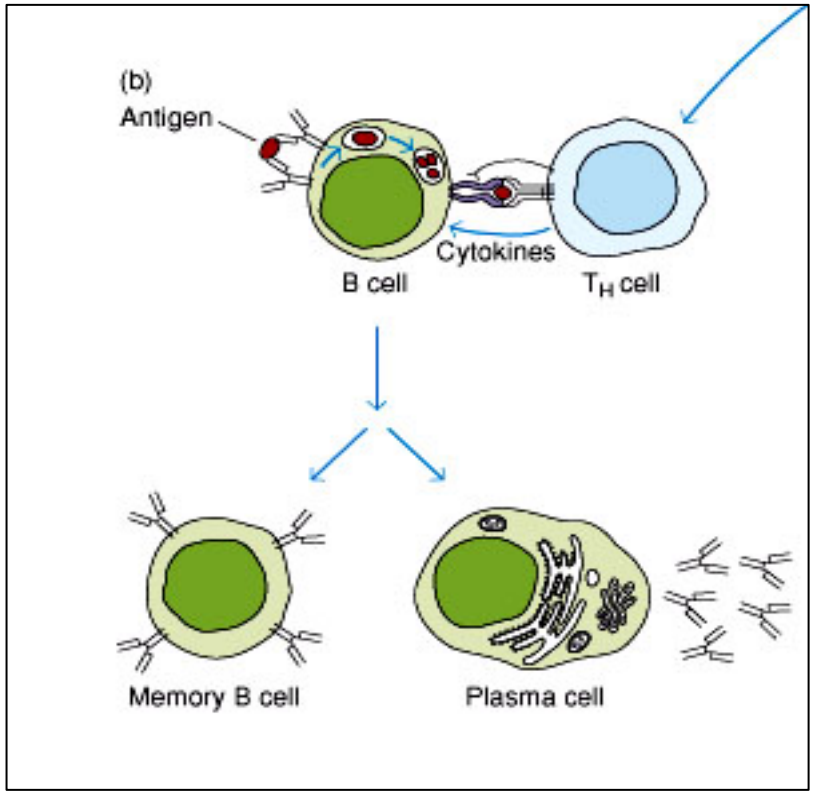
- **SLE**

  the amount of ER-α was lower in T cells than controls, but the quantity of ER-ß was similar, which indicates a relative increase of ER-ß in relation to ER in SLE patients (14).

Immune system



B cell



B cell (1)

B lymphocytes numbers

- *Within the menstrual cycle*
  No differences in B lymphocyte count

- *OCC use*
  Not affect B cell count

- *After menopause*
  Similar to or decreased from the numbers in fertile women

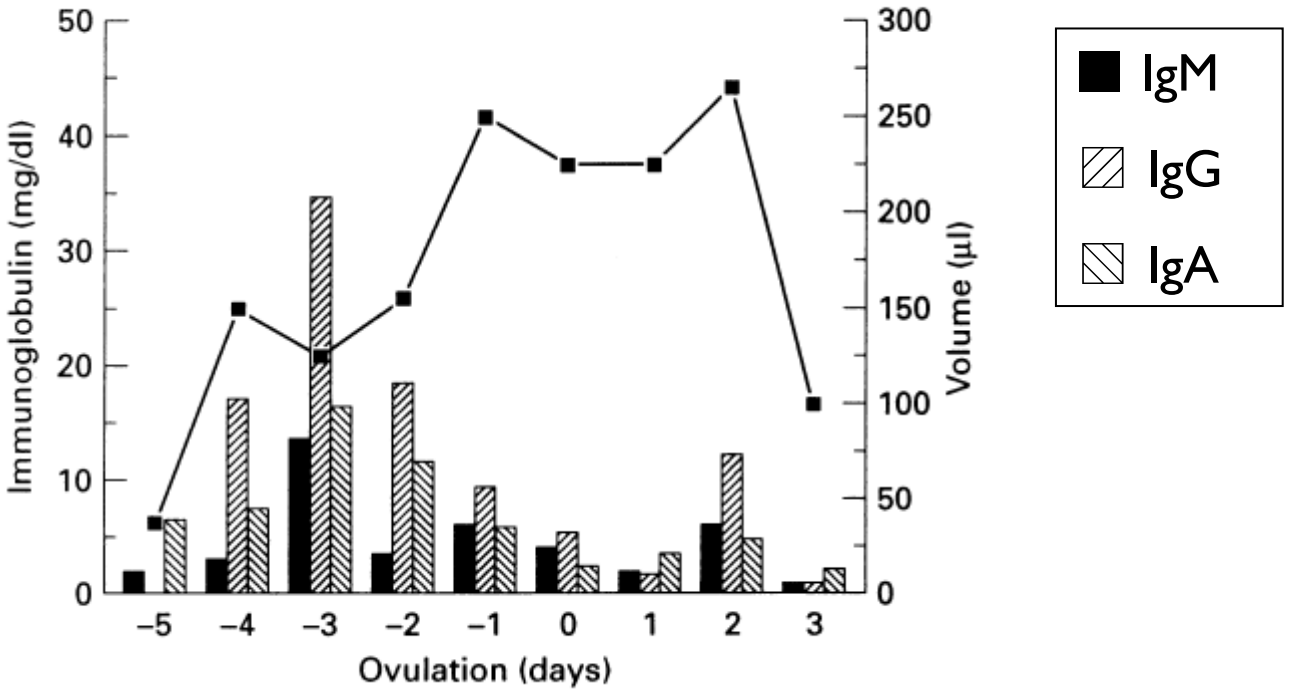
B cell (2)

B lymphocytes function

- E2 can stimulate antibody production by B cells
- E2 at high concentrations leads to a suppression of B-lymphocyte lineage precursors

Immunoglobulins of human uterine cervical secretions

Uterine cervical secretions



Clin Exp Immunol. (1996) 104(3):538-42.

Decreases bone marrow cellularity (1)

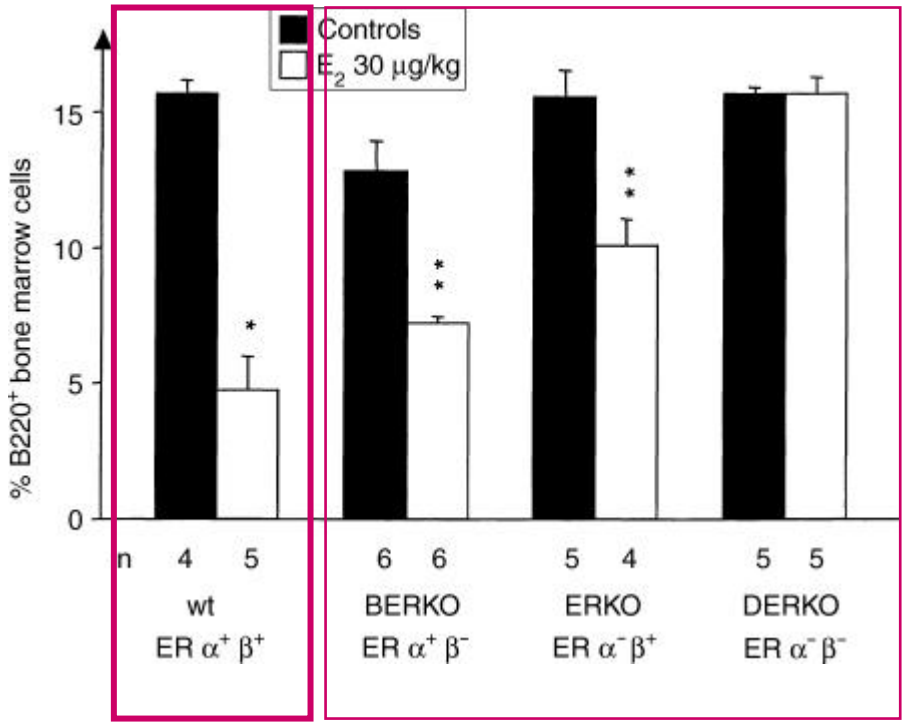
B lymphopoietic cell cellularity

serum [E2] levels , 60 pg/ml

Flow cytometry

*$P < 0{\cdot}05$

Castrated male mice



Immunology (2003)108:346–351

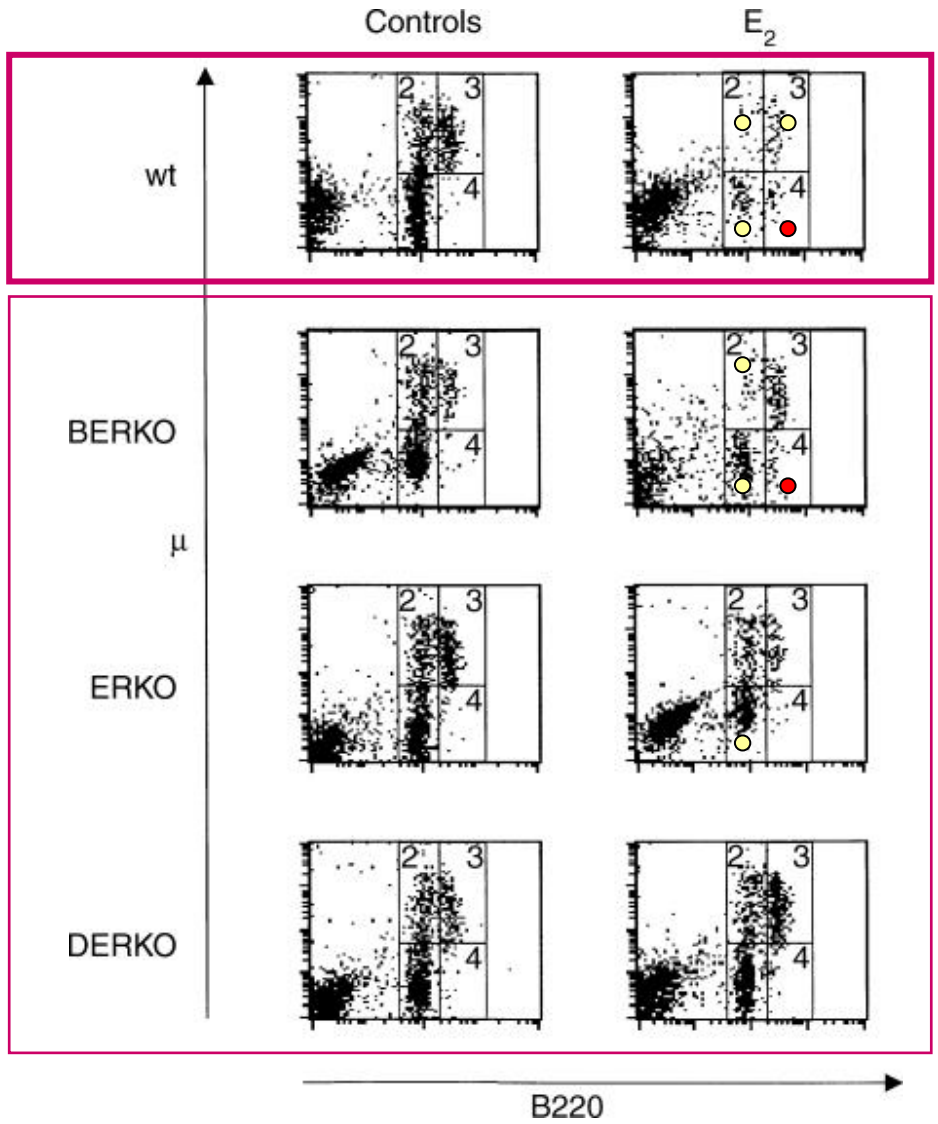
Suppresses B lymphopoiesis (2)

B lymphopoiesis

- 3 stages in B lymphopoiesis :

(1) pro-B cells (B220low m),
(2) pre-B cells (B220low mþ),
(3) B cells (B220high mþ)

Fraction
1, pro-B cells
2, pre-B cells
3, B cells
4, Immunoglobulin producing B cells



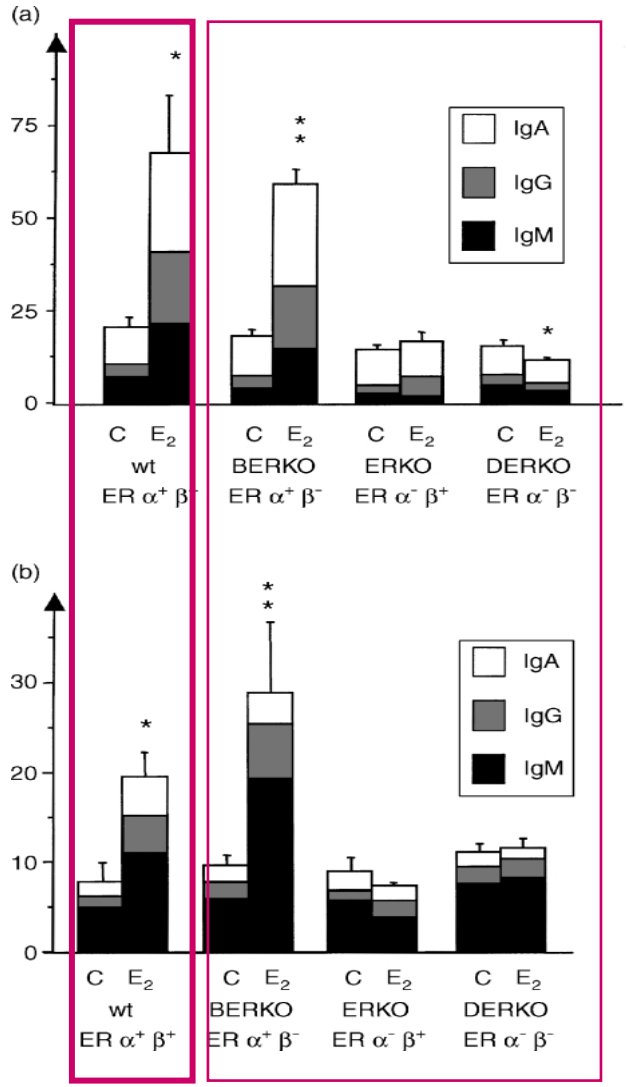
Immunology (2003)108:346–351

Increase immunoglobulin production (3)

Ig M, G and A producing cell

Bone marrow

Spleen



Immunology (2003)108:346–351

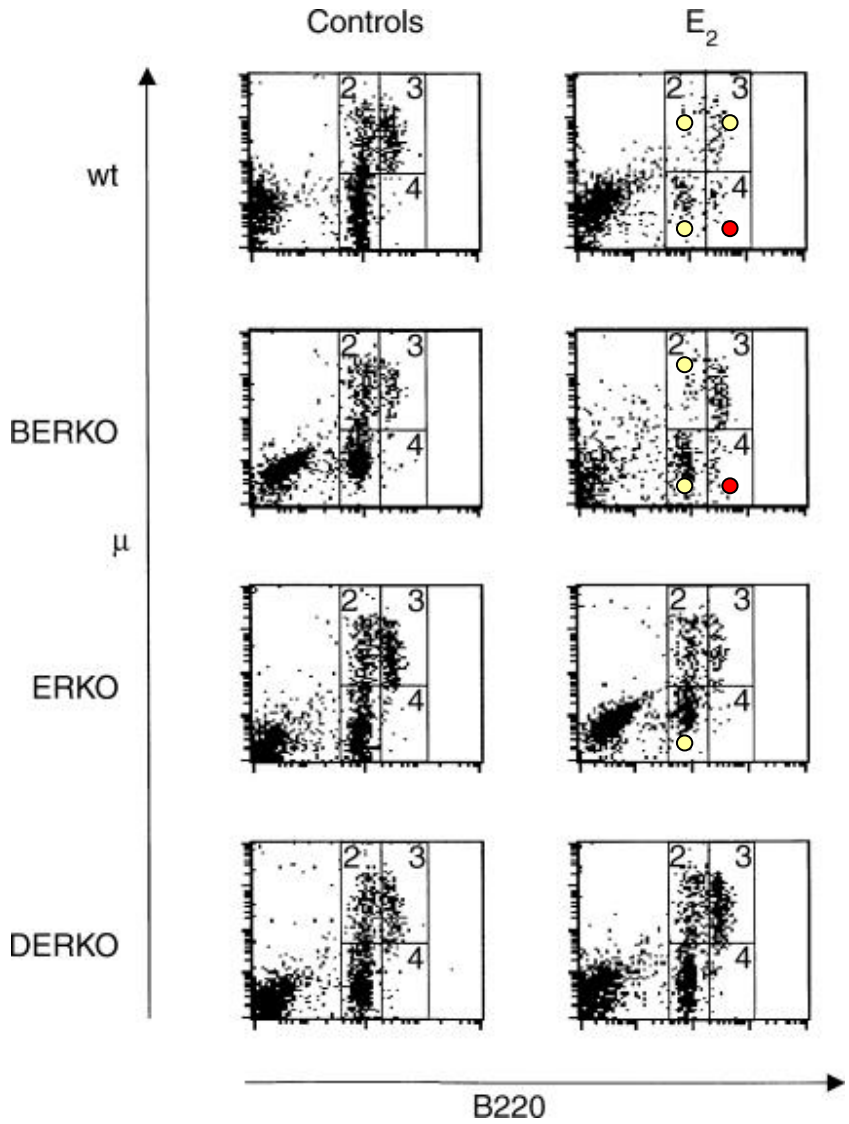
Increasing effect on immunoglobulin (3)

- 3 stages in B lymphopoiesis :

(1) pro-B cells (B220low m),

(2) pre-B cells (B220low mþ),

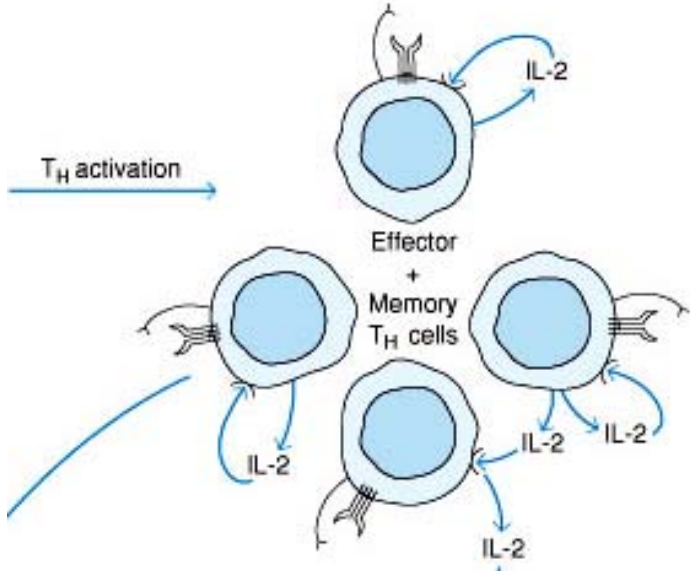
(3) B cells (B220high mþ)

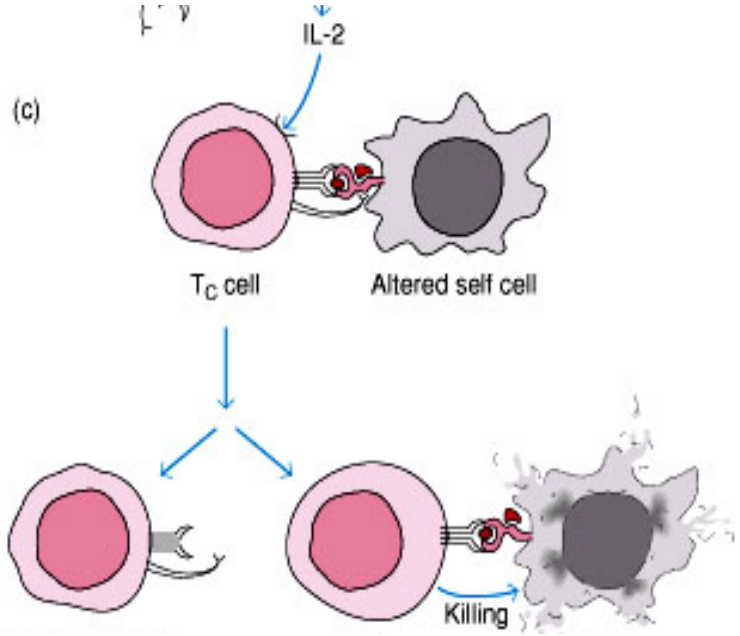


Fraction
1, pro-B cells
2, pre-B cells
3, B cells
4, Immunoglobulin producing B cells

Immunology (2003)108:346–351

T cell


IL-2
T_H activation
Effector
+
Memory
T_H cells
IL-2
IL-2
IL-2
IL-2


IL-2
(c)
T_C cell
Altered self cell
Killing

T cell (1)

T lymphocytes numbers

- *During menstrual cycle*
  No changes in total circulating numbers of lymphocytes and percentage of lymphocyte subtypes

- *OCC preparations*
  Not affect absolute numbers or percentages of lymphocytes

- *Post-menopausal women*
  Reduction of the number of total lymphocytes in comparison to fertile women

T cell (2)

T lymphocytes function

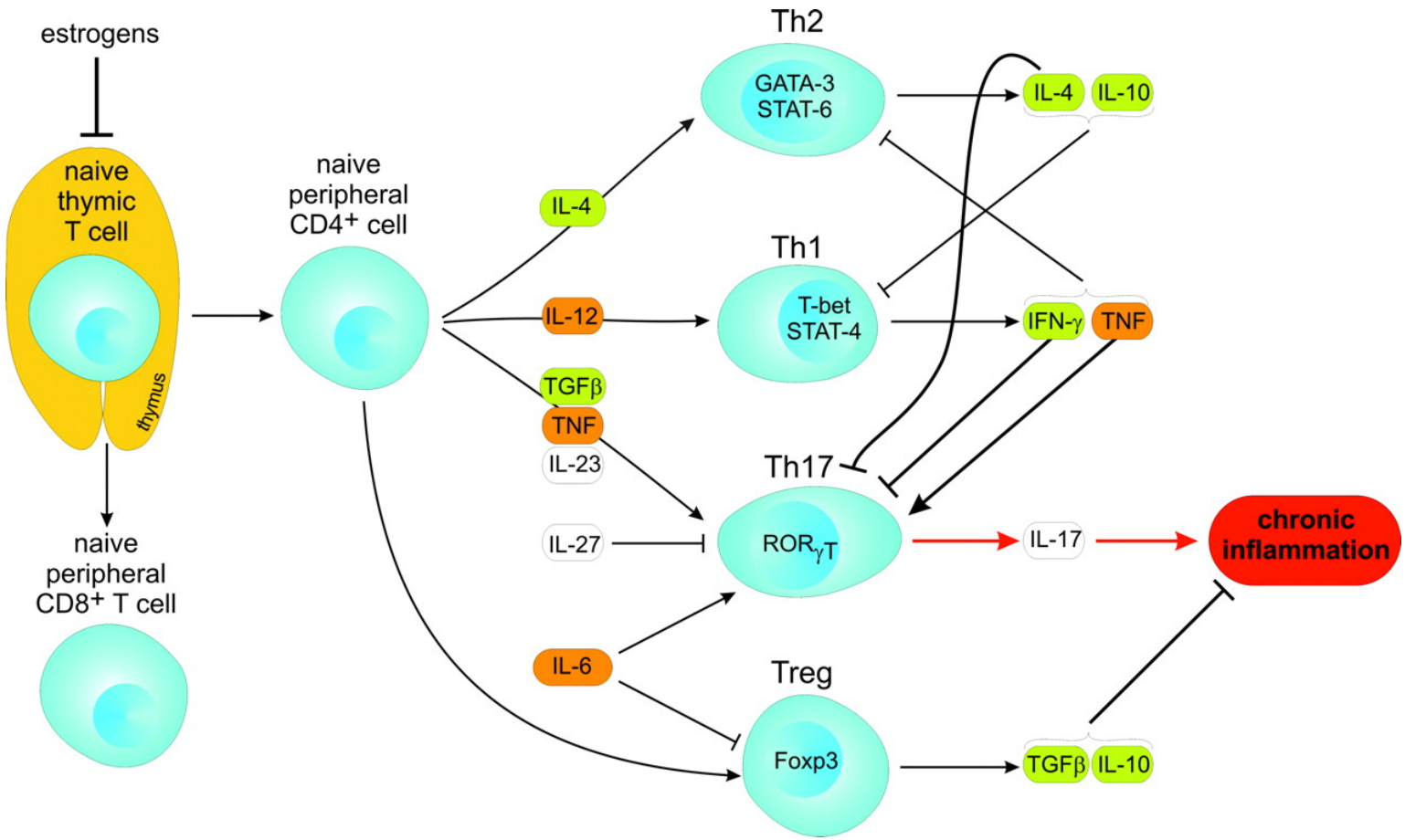
- In vitro, direct effect of estrogens on cytokine secretion
  have shown that 17-estradiol (E2) can modulate both pro- and anti-inflammatory cytokine synthesis by CD4 T cells depending on the dose of hormone [10].

✓ ***With high levels of estrogens***
  inhibiting cell-mediated immune function by promoting Th2 immunity

✓ ***With low levels***
  increase Th1 immunity and susceptibility to cell-mediated autoimmune diseases [11].

- Estrogens have a strong influence on the development and maintenance of thymic function and, thus, on generation of naive CD4+ and CD8+ T cells.

T cell (3)



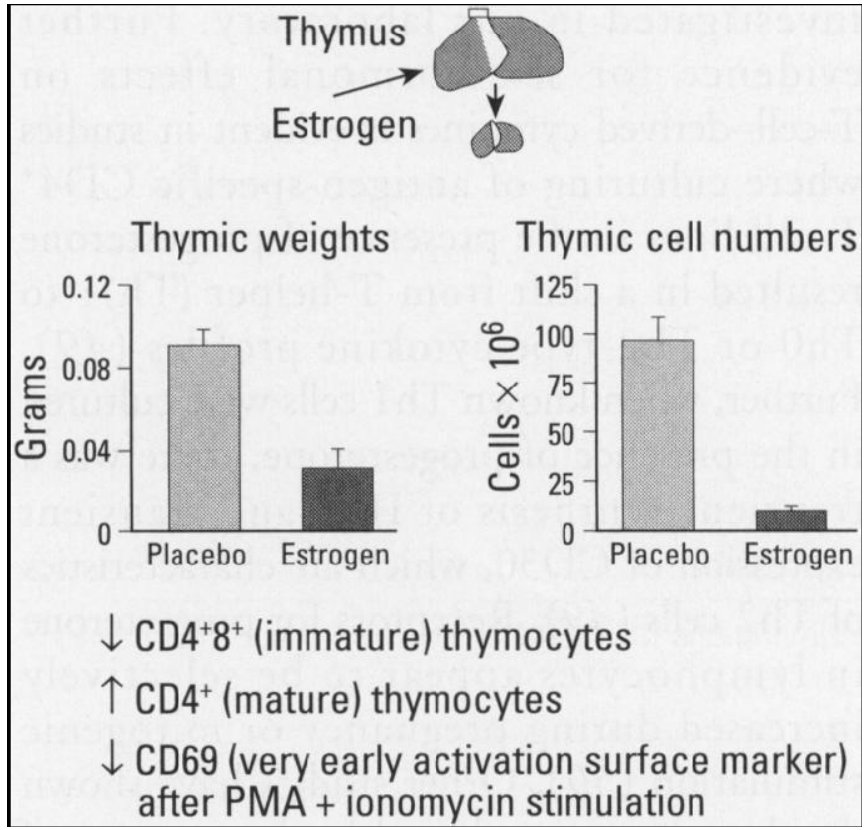
Straub, R. H. Endocr Rev 2007;28:521-574

Effects on Thymus and T Cells

Pubertal orchiectomized normal C57BL/6 mice

due to

- diminished immigration of prothymocytes from the bone marrow or
- hormonal effects on thymic stromal cells (possibly by altering their secretion of crucial cytokines such as IL-1, IL-6, or IL-7, or by inducing apoptosis of these cells).



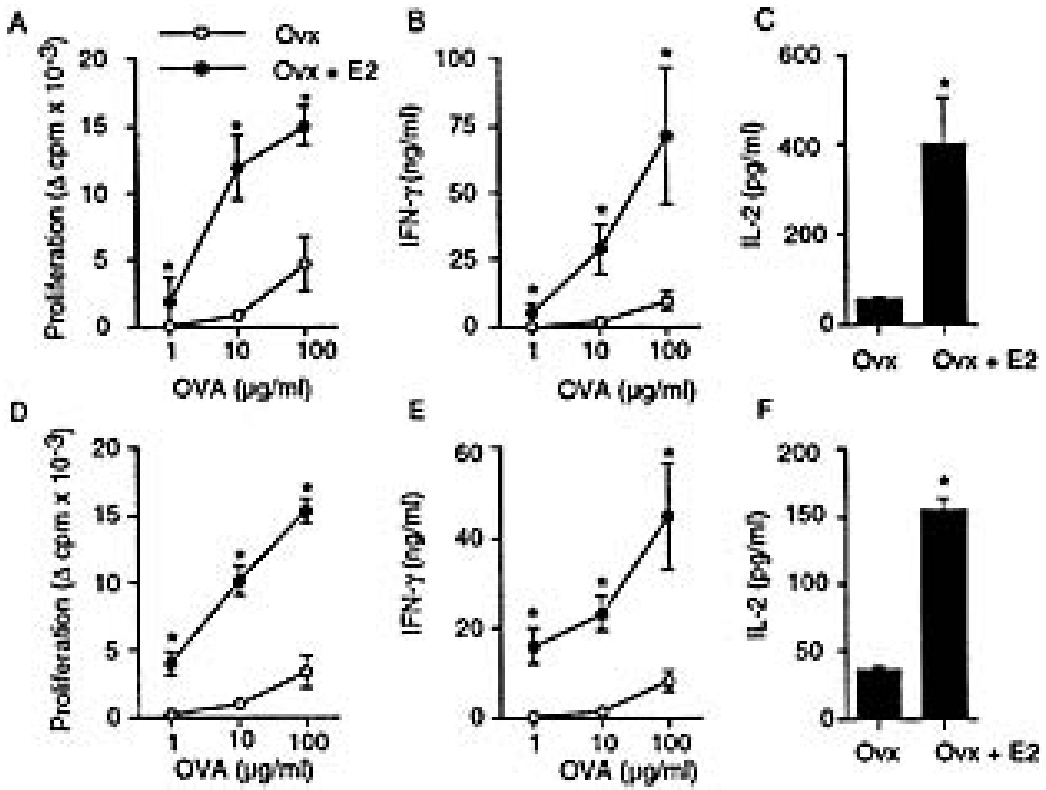
Environ Health Perspect. (1999)107; Suppl 5:681-6

Estradiol enhances primary antigen-specific CD4 T cell responses

With low levels

Immunization with OVA-CFA

with neutral adjuvant OVA-IFA



Eur J Immunol. (2003)33:512-21.

ENDOGENOUS LEVEL OF ESTROGEN UPREGULATES TH1/TH2 RATIO

With high levels

- During pregnancy, the *estrogen level* is also associated with alteration in TH1/TH2 balance,where pregnancy appears to be a "TH2-type phenomenon [44-47].

- The predominance of TH2-type cytokines in pregnancy could be important in avoiding rejection of the semiallogenic fetoplacental unit.

- In line with this concept, levels of IL-4 and IL-10 increase in the peripheral blood during the first weeks of gestation, but later in gestation decrease to levels below normal [48].

*Current Drug Targets - Inflammation & Allergy (*2004) *3:*97-104

During pregnancy (1)

Th1 / Th2 shift

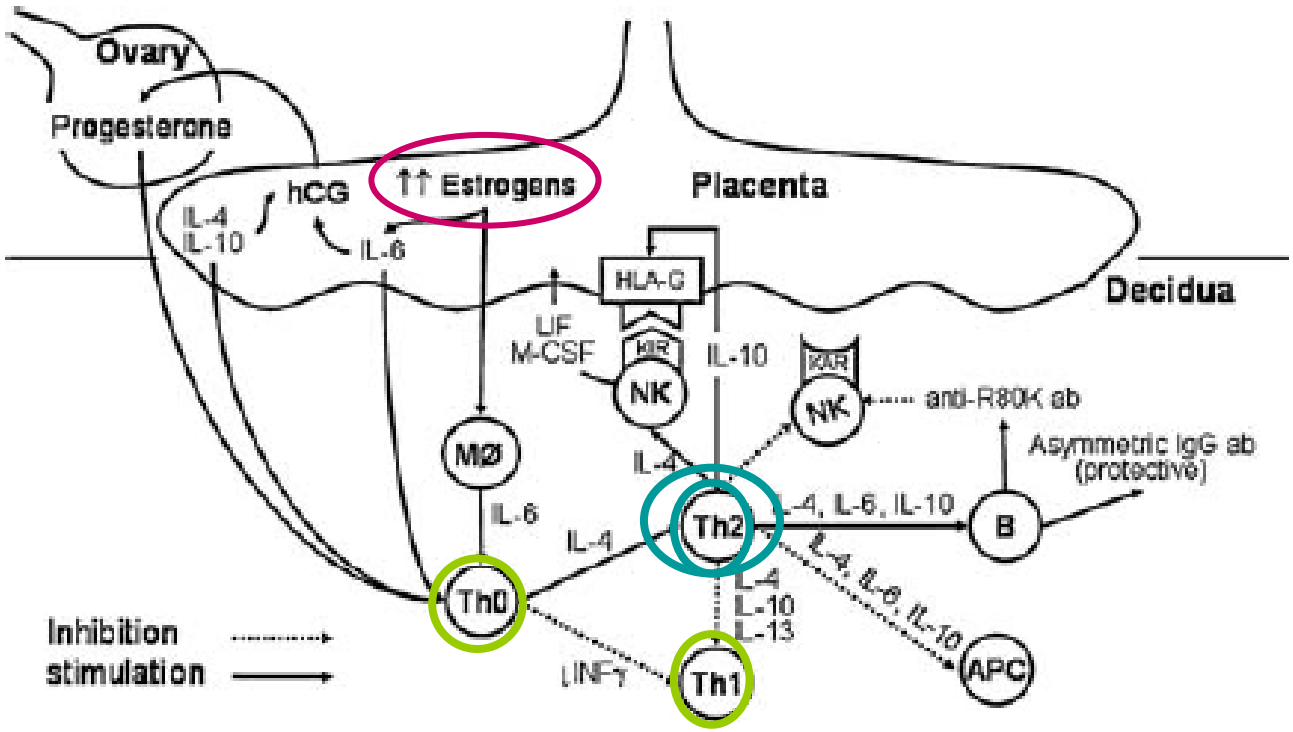
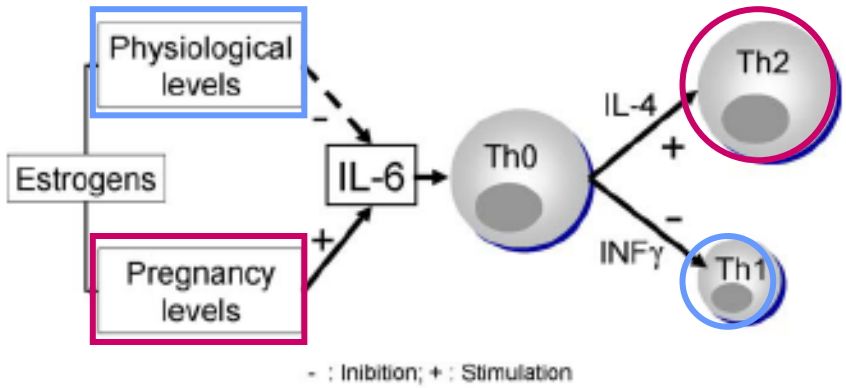


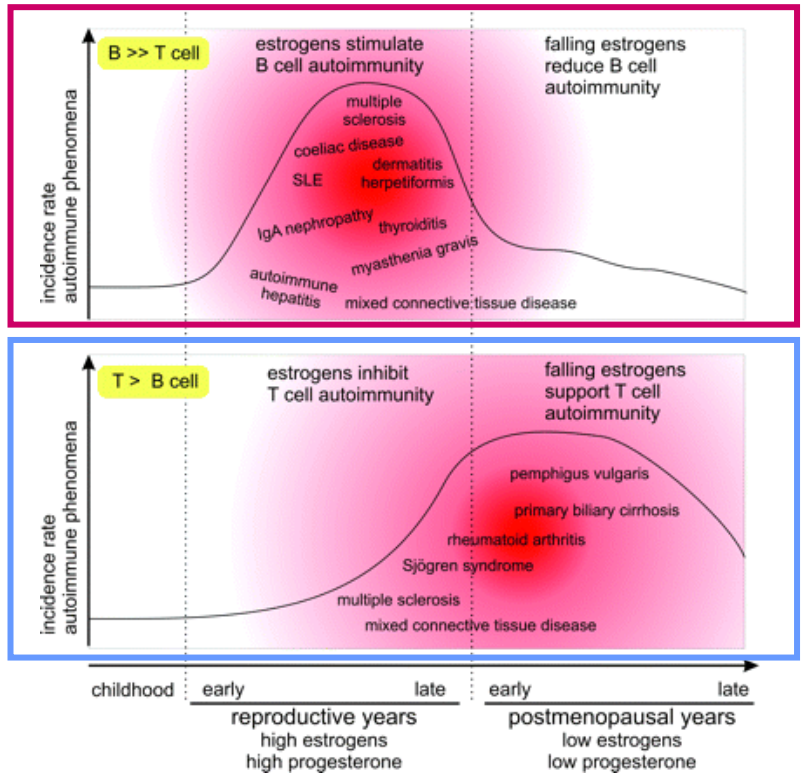
FIGURE 1. Cytokine and endocrine networks at the feto-maternal interface.

Ann N Y Acad Sci. (2006)1069:247-56.

E2 on T cell

✓ Estrogen modulation is dose dependant



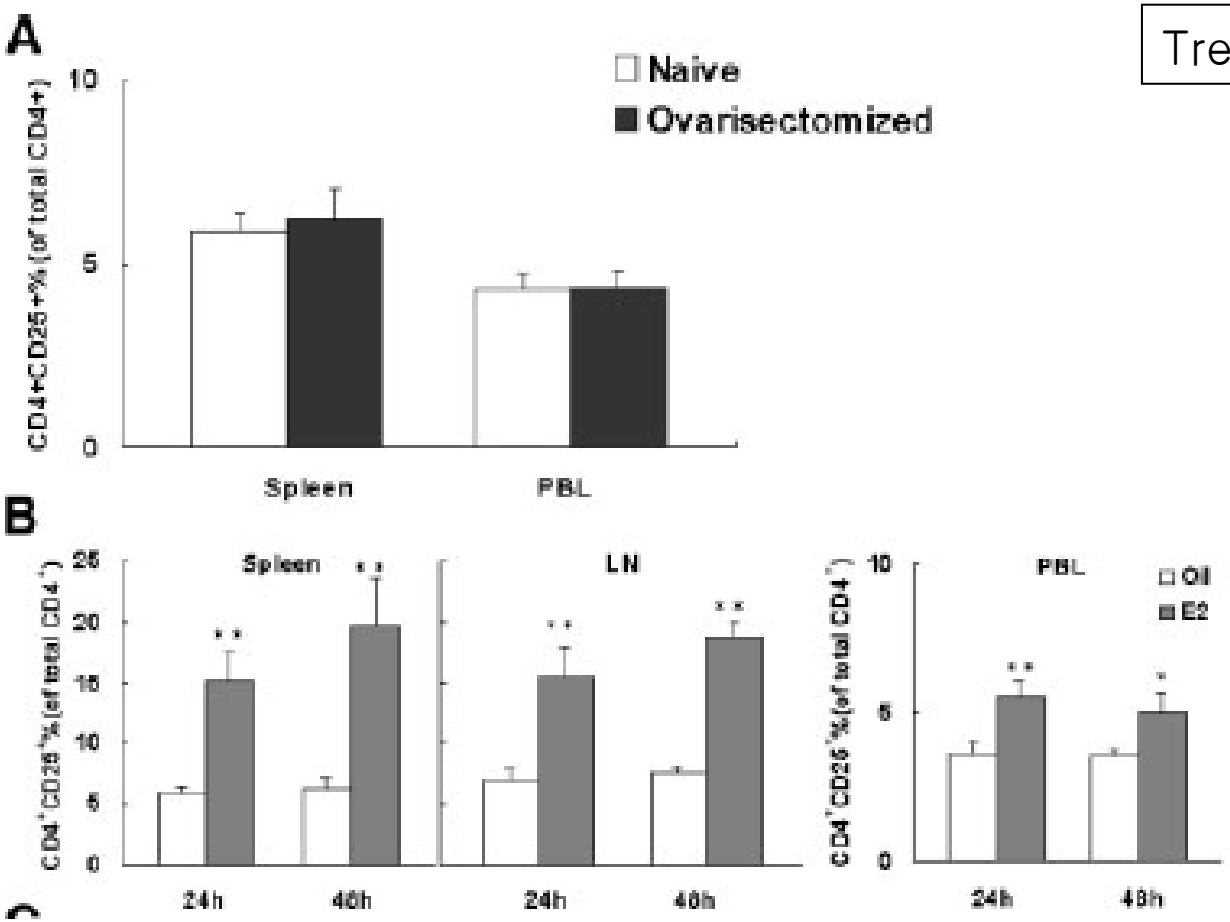


Reproductive Toxicology (2006)22: 234–241

In mice

Induction of Regulatory T Cells by Physiological Level Estrogen (1)

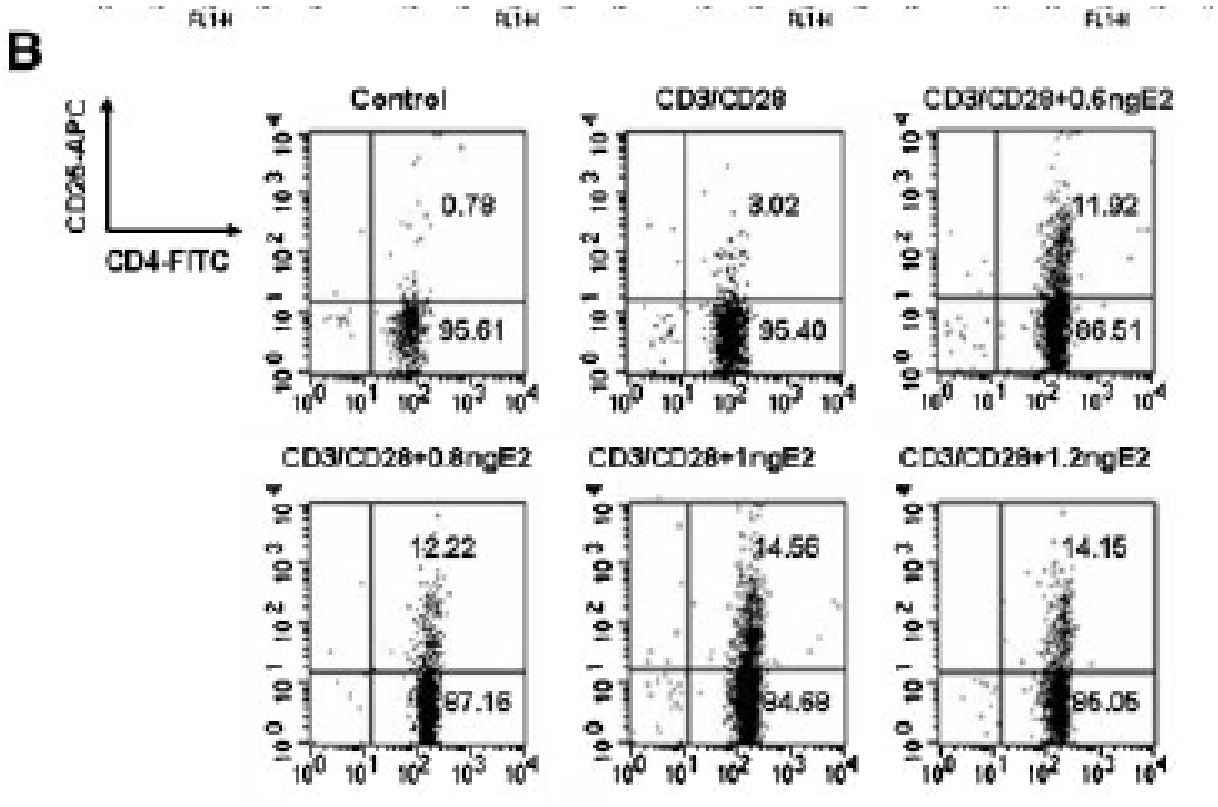
Treg CD4+CD25+



J Cell Physiol.(2008) 214: 456–464

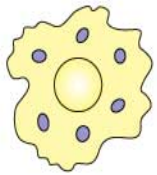
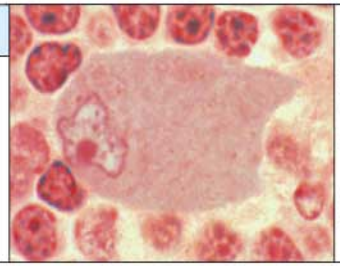
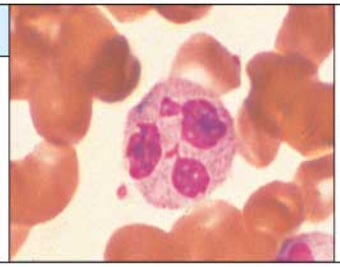
Induction of Regulatory T Cells by Physiological Level Estrogen (2)

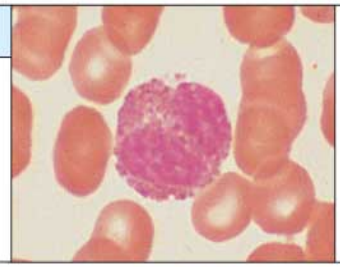
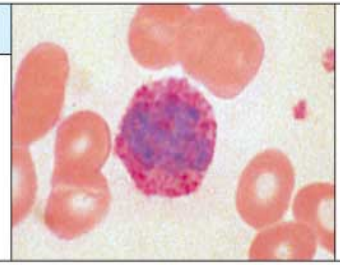
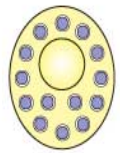
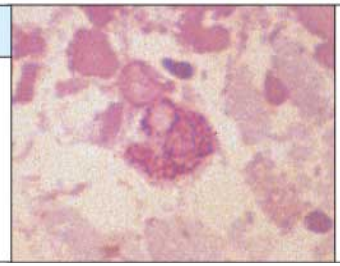
Conversion CD4+CD25-Tcell into CD4+CD25+ Treg



J Cell Physiol.(2008) 214: 456–464

Monocyte/ NK cell

Cell		Activated function
Macrophage 		Phagocytosis and activation of bactericidal mechanisms Antigen presentation
Dendritic cell 		Antigen uptake in peripheral sites Antigen presentation in lymph nodes
Neutrophil 		Phagocytosis and of activation bactericidal mechanisms

Cell		Activated function
Eosinophil 		Killing of antibody-coated parasites
Basophil 		Unknown
Mast cell 		Release of granules containing histamine and other active agents

Monocyte

Monocyte numbers

- *In the luteal phase and during pregnancy*
  Increase in monocyte count as compared with the follicular phase
  : sex hormones induce the release of monocytes from the bone marrow

- *During menopause*
  Increase in blood monocyte number compared to follicular phase
- *Following estrogen replacement therapy*
  monocyte counts decline
  : sex hormones inducing mitotic arrest and apoptosis in monocytes

Monocyte

Monocyte function

- **TNF-** α
  - down-regulation *(Asai et al., 2001)*
  - no effect *(Ralston et al., 1990; Rogers and Eastell, 2001; Bouman et al., 2004a)*

- **IL-1ß**
  - inhibition of IL-1ß production
  - stimulation of IL-1ß mRNA and IL-1ß production

(Polan et al., 1988, 1989; Morishita et al., 1999)

- **IL-12**
  - no effect of 17ß-E2 *(Elenkov et al., 2001)*
  - decreasing effect of 17ß-E2 on IL-12 production *(Matalka, 2003)*

✓ ***In vitro, conflicting results upon monocyte cytokine production with estrogen***

Peripheral blood NK cells

pbNK cell numbers

- *Within the menstrual cycle*

  pb NK cells increase in the late secretory phase compared with the late proliferative phase

  (Flynn et al., 2000; Bouman et al., 2001a; Yovel et al., 2001)

- *During pregnancy*

  Numbers of peripheral NK cells are decreased

  (Watanabe et al., 1997; Kuhnert et al., 1998; Veenstra van Nieuwenhoven et al., 2002).

✓ ***NK cell counts are decreased by estrogen***

Peripheral blood NK cells

pbNK cell funtion, **NK cell activity (NKA)**

- *Post-menopausal women and in males*

  Higher NKA compared to females with a regular menstrual cycle and women on OCC

  (Souza et al., 2001 ; Yovel et al., 2001).

- *Exposure to OCC*

  trend or significant reduction in NKA as compared to non-users

  (Baker et al., 1985; Scanlan et al., 1995; Yovel et al., 2001).

- (In vitro)

  High dose and prolonged exposure to 17ß-E2, suppress NKA

  (Ferguson and McDonald, 1985)

  Low dose and short exposure to 17ß-E2, no significant effect

  (Sulke et al., 1985a,b).

✓ ***Estrogen decreases NK cell numbers and NKA***

Peripheral blood NK cells

***pbNK cell funtion,* Cytokine production**

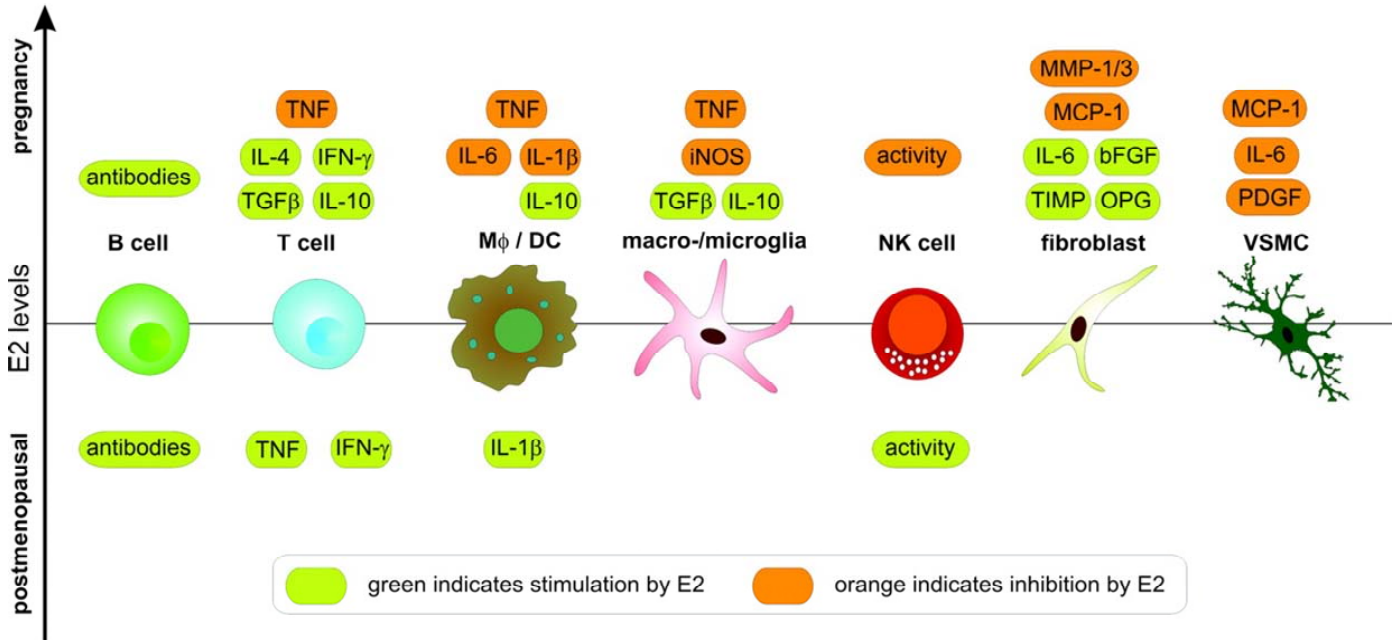
Type I cytokines (IL-2, IFN-δ)

- No effect of the menstrual cycle upon IFN- production of NK cells

  (Bouman et al., 2001a).
- During pregnancy, the stimulated IFN- δ δ production of peripheral NK cells is decreased

✓ *Sex hormones do not affect NK cell cytokine production*

Influence of estrogen in different cell type



Straub, R. H. Endocr Rev 2007;28:521-574

Endocrine Reviews (2007)28(5): 521-574

Summary

- ✓ E2 at periovulatory to pregnancy serum levels is able to stimulate antibody secretion, whereas similar serum levels of E2 lead to a suppression of bone marrow B cell lineage precursors.

- ✓ E2 at periovulatory to pregnancy levels stimulates Th2 cytokine.
- Collectively, E2 at periovulatory to pregnancy levels might be a favorable hormone leading to down-regulation of Th1 cellular immunity.

- ✓ In vitro experiments in which monocytes were incubated with sex hormones revealed conflicting results upon monocyte cytokine production

- ✓ Estrogen decreases NK cell numbers and NKA but, that sex hormones do not affect NK cell cytokine production.

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제일병원
CHEIL GENERAL HOSPITAL
& WOMEN'S HEALTHCARE CENTER

Thank you for your attention !

아이소망센타 / 습관성유산크리닉