El sistema immunitari i l’embaràs

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WHY?
Structure of the human placenta

How is then possible the tolerance to an haploidentic invading embryo?
What is special about maternal immunity?

- **TOLERANCE**: Haploidentic fetus expressing paternal antigens
- **IMMUNITY**: Pathogens
General concepts

- Not a state of general immunosuppression but rather of **local** and **systemic** immune modulation
- Increased susceptibility to some pathogens: influenza, measles, hepatitis E, HSV
- Immune related causes of infertility
- Women with problems in the immune system have greater probabilities of a bad pregnancy outcome
Maternal immunity is a special state, needing to tolerate the conceptus and defend from pathogens.

WHY?
Tolerance mechanisms of the placenta
NK cells in pregnancy

- Protect both the mother and the conceptus
- High frequency of uterine NK cells in decidual leukocytes with CD56$^{\text{bright}}$ phenotype
- Pregnancy establishment function
- Expression of inhibitory receptors
- Decidua’s blood vessel remodeling function

Ander et al, Sci Immunol, 2019
Esteve-Sole et al, IJMS, 2018
T cells in pregnancy

- Increase in Treg by hormonal changes and alloantigenic exposure
  - Treg cells are regulated also during menstrual cycle
  - Decrease in Treg cell markers associated with idiopathic infertility
- Reduced Th1/Th2 ratio controversial
  - but increased accumulation of paternal-antigens specific Th1 cells is associated with decreased Treg and abortion (murine model)
- Increased gamma-delta T cells, with inhibitory functions

Ander et al, Sci Immunol, 2019
Esteve-Sole et al, IJMS, 2018
Myeloid derived cells in pregnancy

- Increased proportion of M2 macrophages
  - Tissue healing and homeostasis functions
  - Hormone levels regulation
  - Pathogen clearance in the endometrium.
- Monocytes dual role: both in implantation and in pregnancy termination
- Dendritic cells are in a more immature phenotype with regulatory functions
- Mast cells with a different phenotype compared to peripheral counterparts, favor implantations and tissue remodeling.
MATERNAL SIDE

Treg (PDL1, CTLA-4)

uNK (KIR)

Decidua (Treg, uNK cells, FasL)

Extravillous trophoblast (HLA-G, HLA-E, HLA-C, FasL, IDO, PDL1)

Column cytotrophoblast (PDL1)

Chorionic Villi comprises of

Syncytiotrophoblast (IDO, PDL1)

Villous cytotrophoblast: (Complement regulatory proteins; DAF and MCP)

Blood vessels, stroma

FETAL SIDE

Guleria et al, JI, 2007
Defense mechanisms of the placenta
Maternal immunity is a special state, needing to tolerate the conceptus and defend from pathogens.

Both adaptive and innate populations are modulated locally and systemically in the mother during pregnancy.

WHY?
Pregnancy hormones and the immune system

• Dose dependent effects of pregnancy hormones, and combination differential effects

• Depending on concentration and estrogen receptor, estrogens can promote anti-inflammatory states (e.g., inhibiting NK cell cytotoxicity) or inflammatory responses (e.g., increased production of IL-12 and TNF-α by monocytes)

• Progesterone decreases plasmacytoid dendritic cells production of IFN-α

• hCG has clear regulating functions in dendritic, Treg and NK cells, and in extravillous trophoblasts and endothelial cells by different mechanisms

Ostensen 2011
Giefing-Kroll et al, 2015
Bansal et al, 2012
IS THIS EVERYTHING??
B cells in pregnancy

• Understudied with respect to other subsets

• Both protective and harmful:
  – Paternal-specific asymmetric antibodies increased by progesterone and hGC
  – Auto-antibody production (such as anti-phospholipid antibodies)
  – Association of auto-antibody production and pre-eclampsia

• B cells are present in the in amniotic fluid during initial phases of pregnancy
Breg cells

Cancer
Autoimmunity / rheumatic disease
Immune-related treatments
PID
Allergy
Infection
Transplantation
Pregnancy and neonatal period
Breg cells as a mechanism of tolerance

Blair et al, Immunity, 2010

CD19^+CD24^{hi}CD38^{hi}

Breg cells as a new mechanism of tolerance in pregnancy

Jensen et al, Biol of Repr, 2013
Rolle et al, AJRI, 2013
pregnant women sera + Non-pregnant women B cells → IL-10
Maternal immunity is a special state, needing to tolerate the conceptus and defend from pathogens.

Both adaptive and innate populations are modulated locally and systemically in the mother during pregnancy.

WHY?

The immune system is modulated by pregnancy hormones, including Breg cells.
How pregnancy influences rheumatic pathology?

Ostensen et al, 2015
How pregnancy influences rheumatic pathology?

**Table 1** Interaction of pregnancy and some CTDs or vasculitis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Effect of pregnancy on disease</th>
<th>Risk of maternal complications</th>
<th>Risk for fetus/neonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>Improvement in 48–75% of cases</td>
<td>Oestrogens (physiological)</td>
<td>Very rare</td>
</tr>
<tr>
<td>SLE</td>
<td>Flare in 50% of cases</td>
<td>Oestrogens (pharmacological - high)</td>
<td>Fetal loss, intrauterine growth restriction, low birthweight, neonatal lupus</td>
</tr>
<tr>
<td>APS</td>
<td>Aggravation</td>
<td></td>
<td>Fetal loss, intrauterine growth restriction, low birthweight</td>
</tr>
<tr>
<td>SSc</td>
<td>No major effect in disease</td>
<td></td>
<td>Reduced birthweight in premature infants</td>
</tr>
<tr>
<td>Takayasu arteritis</td>
<td>Unchanged, 20% improvement</td>
<td></td>
<td>Only at severe maternal disease, otherwise 85% good neonatal outcome</td>
</tr>
<tr>
<td>ANCA-positive vasculitis</td>
<td>Data insufficient to discern a particular effect</td>
<td></td>
<td>Fetal loss, intrauterine growth restriction, low birthweight</td>
</tr>
</tbody>
</table>

HELLP: haemolysis, elevated liver enzymes low platelet.

Ostensen et al, 2011
Ostensen et al, 2015
Maternal immunity is a special state, needing to tolerate the conceptus and defend from pathogens. Both adaptive and innate populations are modulated locally and systemically in the mother during pregnancy. Pregnancy can modify disease course in rheumatic diseases and disease activity is associated with pregnancy outcome. The immune system is modulated by pregnancy hormones, including Breg cells.
Limitations in the study of the IS during pregnancy

- Difficult to study local changes in immunity
- To study changes in the first days after conception
- Murine model has many structural differences that make it difficult to extrapolate results to humans
- In pathology: difficulty to have big cohorts of homogeneous patients
Maternal immunity is a special state, needing to tolerate the conceptus and defend from pathogens. Both adaptive and innate populations are modulated locally and systemically in the mother during pregnancy. Pregnancy can modify disease course in rheumatic diseases, and disease activity is associated with pregnancy outcome. The immune system is modulated by pregnancy hormones, including Breg cells.
Who made this project possible?

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Time for questions!

Thank you!