Развитие иммунологической толерантности к плоду во время беременности. Роль мужского фактора и Treg клеток

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SOME IMMUNOLOGICAL AND ENDOCRINOLOGICAL PROBLEMS RAISED BY THE EVOLUTION OF VIVIPARITY IN VERTEBRATES

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I. INTRODUCTION

Viviparity of one kind or another is to be found among members of all classes of vertebrates except birds, and among all mammals except monotremes. The pattern of its occurrence in elasmobranchs, and particularly in reptiles—among members of distantly related genera, and in some but not other species of a single genus—leaves one in no doubt that it has evolved independently in many separate lines of descent. For this reason the zoologist has been inclined to take viviparity for granted; there is an undercurrent of thought which suggests that a problem which has been solved independently on so many occasions cannot entail any very radical transformation of the vertebrate mode of life.

III. THE IMMUNOLOGICAL PROBLEM OF PREGNANCY

The immunological problem of pregnancy may be formulated thus: how does the pregnant mother contrive to nourish within itself, for many weeks or months, a foetus that is an antigenically foreign body? The question derives its significance from the fact that the mother does not always contrive to do so; it *is* sometimes immunized against the antigens of its foetus, with the consequence that the foetus, or its successors in later pregnancies, is either destroyed or born with affections that are the more or less immediate outcome of cellular damage. The proof that this is sometimes the case, in the work of Levine and Stetson, Wiener, Race and their many colleagues and successors, is one of the triumphs of modern clinical biology.

The principal cause of haemolytic disease in the newborn is immunization of the mother by the foetal red-cell antigen D of the *Rhesus* series.

Every well-authenticated example of an immunization of the mother by its foetus has implicated the red-cell antigens; none has implicated the ordinary tissue antigens that are responsible for the rapid and violent reactions provoked by grafting tissues such as skin from one individual to another. This does not mean that the participation of tissue antigens can be lightly dismissed. All the methods by which foetal death may be shown to be the consequence of iso-immunization* by red cells depend upon the identification and labelling of red-cell antigens by their specific reactions with antibodies. Unfortunately, antibodies to homoplastic grafts of ordinary tissues have not yet been identified, though there is strong circumstantial evidence for supposing them to be formed.† Antibodies being unknown, the antigenic labelling of individuals is for all practical purposes impossible. One cannot therefore compare the sizes of families born of antigenically compatible and incompatible matings, nor look for a relative shortage of offspring of the incompatible type. Yet it would be most unwise to overlook the possibility that immunization by foetal tissue antigens may be a cause of foetal maceration or resorption, particularly in the early stages of pregnancy. Only a tiny fraction of the early foetal deaths that could conceivably be due to antigenic incompatibility has been shown to be so caused; by far the greater proportion are still etiologically uncertifiable. It would be as well, therefore, to keep an open mind.

its male partner has been prematurely canonized by endocrinologists eager for evidence of hormonal secretion by foetal glands. There are reasons for thinking this interpretation insufficient (Moore, 1947, 1950), and it may well turn out that 'true' freemartinism, as it occurs in cattle, depends upon the residence of genetically male cells within the female. But all these facts are most instructive in a cautionary way. If antigenic diversity had the effect of *preventing* the vascular fusion and cellular exchanges between embryos that might otherwise lead to sexual abnormalities in polytocous mammals, then it would clearly be most advantageous. But antigenic diversity does not have this effect. On the contrary, cellular interchange in foetal life (the only natural occasion on which it could occur) makes the individual anomalously tolerant to genetically foreign cells—as neat a *reductio ad absurdum* of the hypothesis as one could hope to find.

We may now return to the question posed in the first paragraph. The reasons why the foetus does not habitually provoke an immunological reaction from its mother may be classified under three headings: (*a*) the anatomical separation of foetus from mother; (*b*) the antigenic immaturity of the foetus; and (*c*) the immunological indolence or inertness of the mother. There can be little doubt that the first of these is by far the most important.

(*a*) *The anatomical separation of foetus from mother.* Maternal and foetal blood circulations are separated by a barrier which, to whatsoever degree it may be attenuated in primates and rodents, is normally impermeable to cells. This vascular isolation or state of quarantine should normally prevent the immunization of the mother by foetal cells; but, should immunization

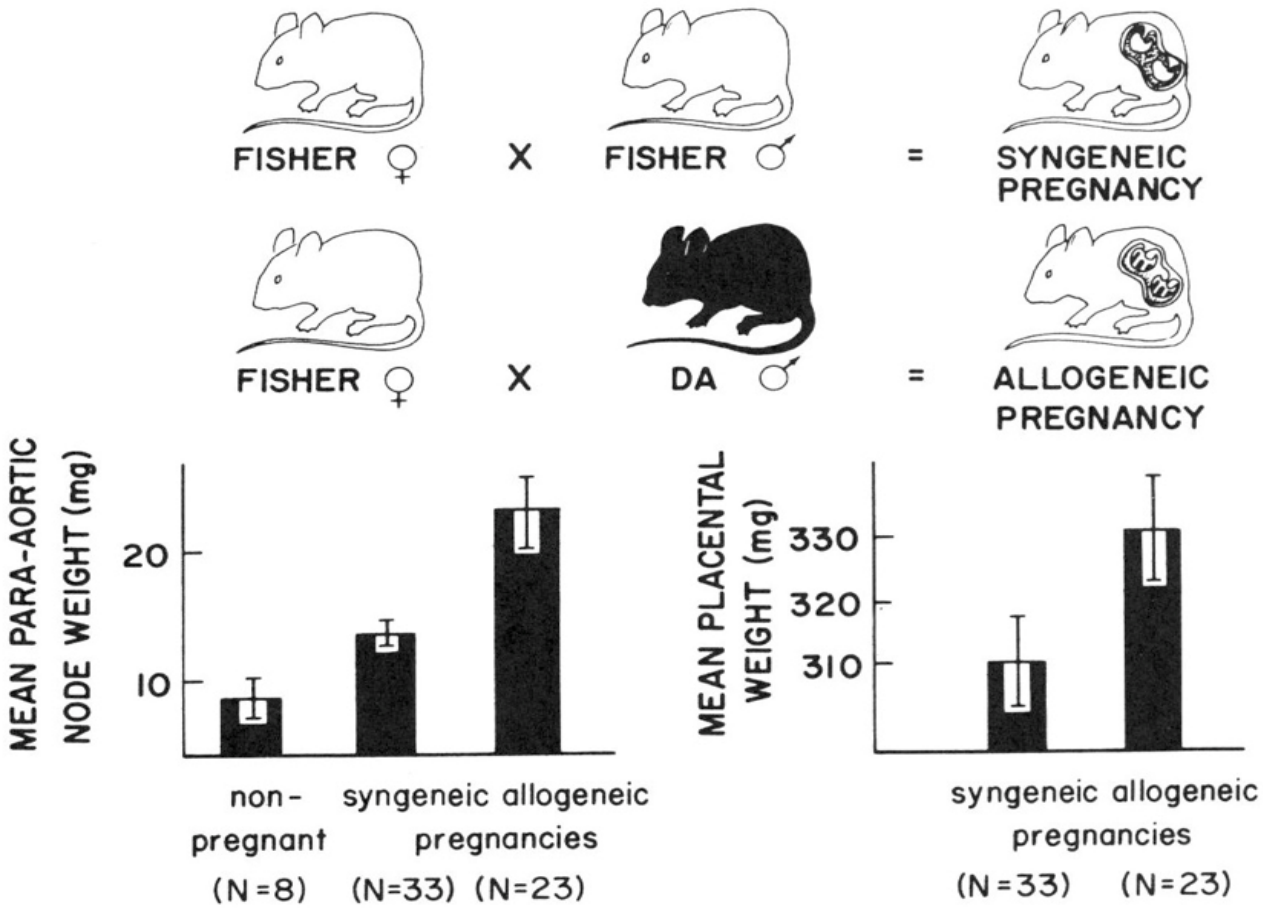
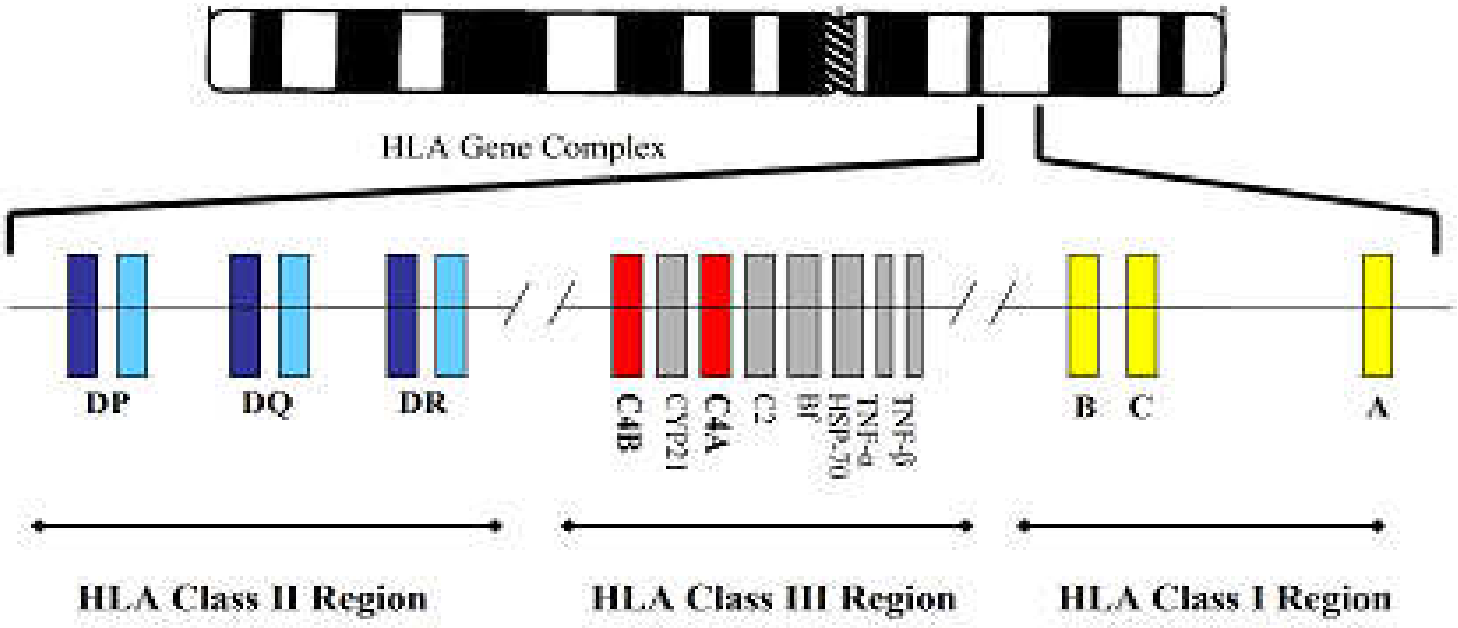


Fig. 2-7. Illustrating the fact that the F_1 hybrid fetuses resulting from matings between Fischer female rats and DA strain males have heavier or larger placentas than syngeneic Fischer fetuses. Comparison of the weights of the para-aortic lymph nodes draining the uteri of virgin, female Fischer rats with those of weight- and age-matched Fischer rats bearing Fischer (syngeneic) and (Fischer $\times$ DA)F_1 hybrid (allogeneic) fetuses, respectively, of 18 days' gestation, reveals slight stimulation by syngeneic pregnancies, probably due to fetal tissue-specific antigens (possibly associated with the trophoblast) and a much stronger stimulation by genetically alien fetuses due to their tissue alloantigens. This and other evidence implicates maternal reactivity against the tissue alloantigens of the conceptus as a determinant of the growth rate of the feto-placental unit.

Chromosome 6



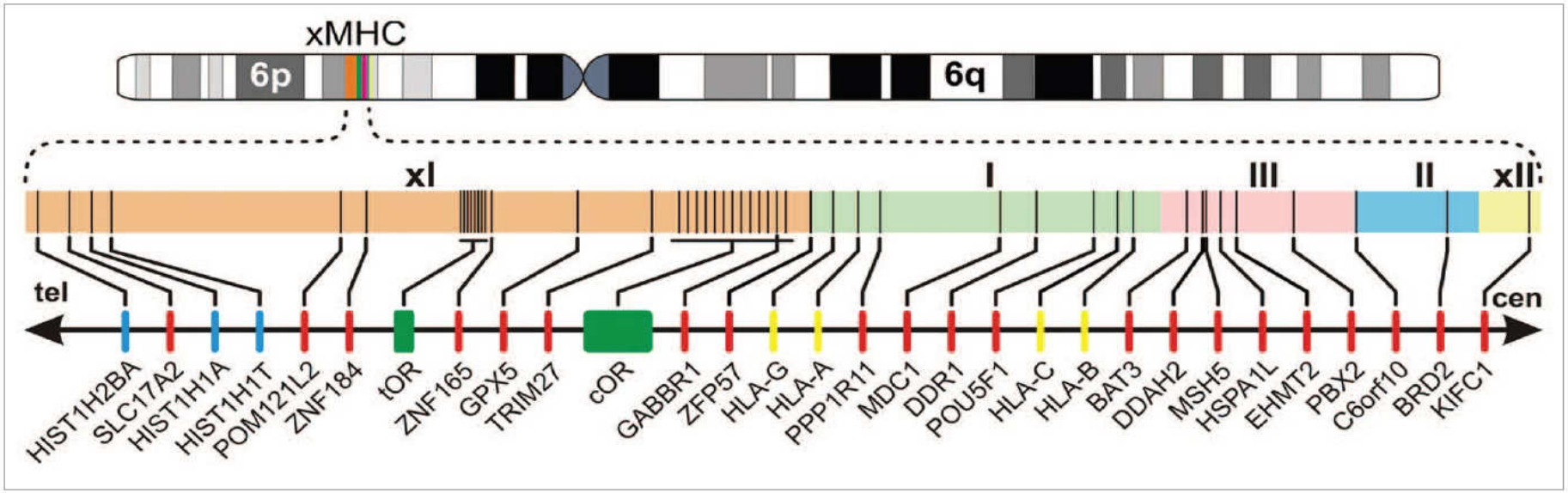


Figure 2. The human extended MHC. Human chromosome 6 is shown with the short (6p) and the long arm (6q). A schematic map of the xMHC is depicted below, with the extended class I (xI, ~3,900 kb), class I (I~1,900 kb), class III (III~700 kb), class II (II~900 kb) and the extended class II (xII, ~200 kb) regions indicated by different colors. Nearly all genes mentioned in the main text are shown, with their approximate locations within a given sub-region indicated by vertical lines. Histones are shown in blue, the two odorant clusters with a total of 34 genes in green, selected HLA class I genes in yellow and all other genes in red. The directions towards telomere (tel) and centromere (cen) are also given. In the mouse, all genes telomeric of (and including) *TRIM27* in the xclass I region are not linked to the MHC, but form a syntenic group of loci on chromosome 13.

Межгеномный конфликт и интрагеномный конфликт

- Естественный отбор работает одновременно в противоположных направлениях
- Это приводит к значительной коадаптации обеих сторон конфликта
- Конфликт между индивидами внутри вида или с особями другого вида приводит к развитию сложных систем поведения и структур
- Внутригеномный конфликт приводит к развитию не менее сложных структур внутри одного организма
- Репродуктивный процесс – сложный набор сочетаний межгеномного и внутригеномного конфликта на всех этапах
- Внутригеномный конфликт имеет место как в организме самца, так и в организме самки, играет важную роль во взаимодействии организмов матери и плода

Триада!!!

- Психологи любят говорить о «диаде» (плод и беременная)
- Но даже с этой точки зрения имеется триада (плацента, плод и мать)
- С точки зрения интрагеномного конфликта – всегда триада
- Три гаплотипа:
  - ↕ гаплотип отца, полученный со сперматозоидом;
  - ↕ гаплотип матери, полученный плодом с яйцеклеткой;
  - ↕ еще один гаплотип: половина генотипа матери, не попавшая к плоду (мать передает плоду только половину своих генов)
- Есть еще один участник конфликта: половина гаплотипа отца, не попавшая к плоду со сперматозоидом (отец передает каждому ребенку только половину своего гаплотипа)

Внутригеномный конфликт

- Половина генов могут «желать» (=действовать так, как если бы они желали), чтобы 100% сперматозоидов были нормальными, а половина – желать, чтобы только половина из них была нормальной
- Половина генов женщины может желать, чтобы выносить все беременности, а половина – желать, чтобы была выношена только половина беременностей
- Некоторые гены «хотят», чтобы плод рос медленно, другие – чтобы он рос быстро, третьи, чтобы была средняя скорость роста
- Одни гены хотят, чтобы плод был мальчиком, другие – чтобы девочкой

Геномный импринтинг как проявление внутригеномного конфликта

- Матригены будут подавлять рост плода
- Патригены будут поддерживать и стимулировать рост плода
- HLA-гаплотипы будут влиять на выбор партнера и судьбу потомства

↕ Выбор:

- До копуляции
- Во время копуляции
- После копуляции

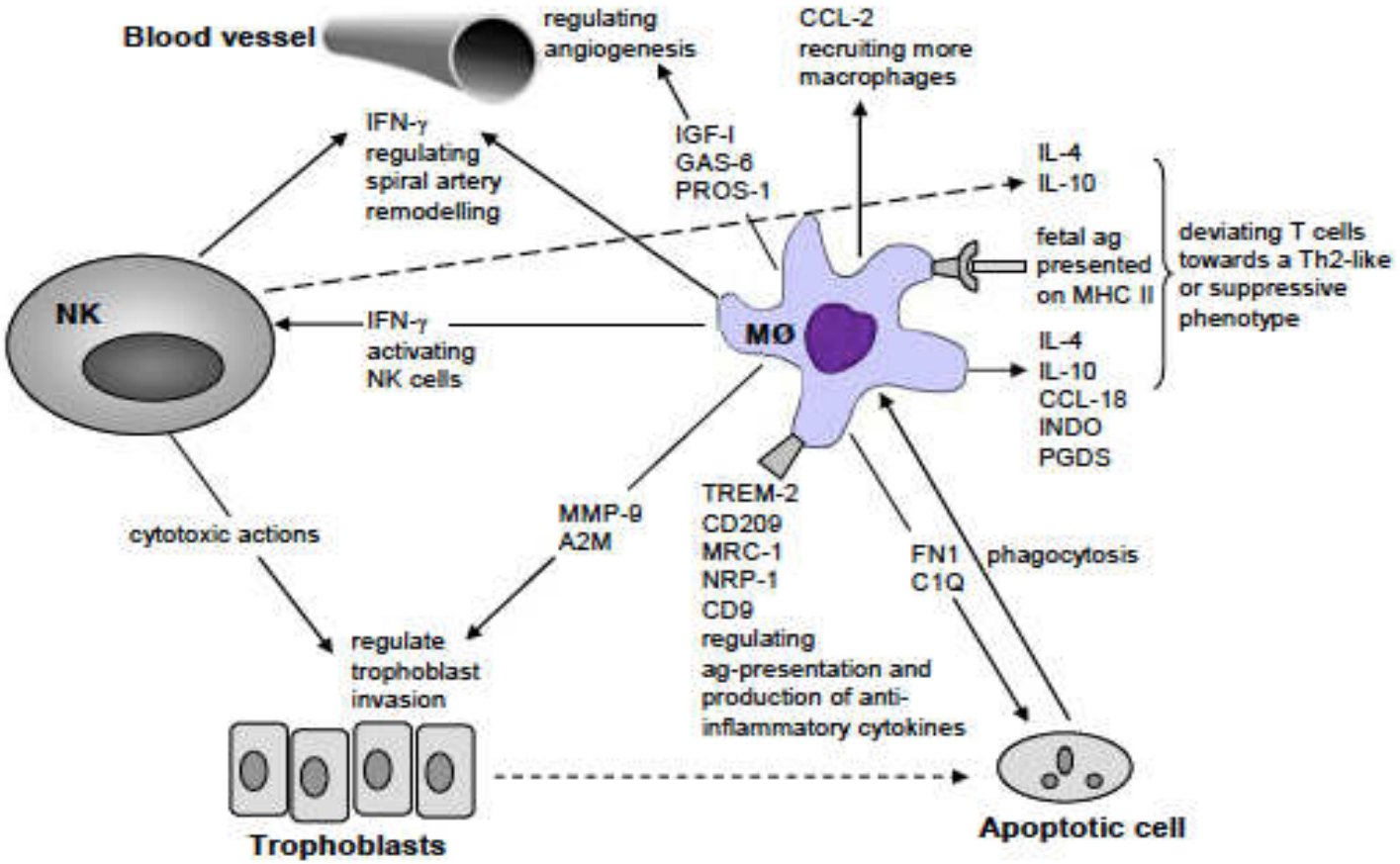
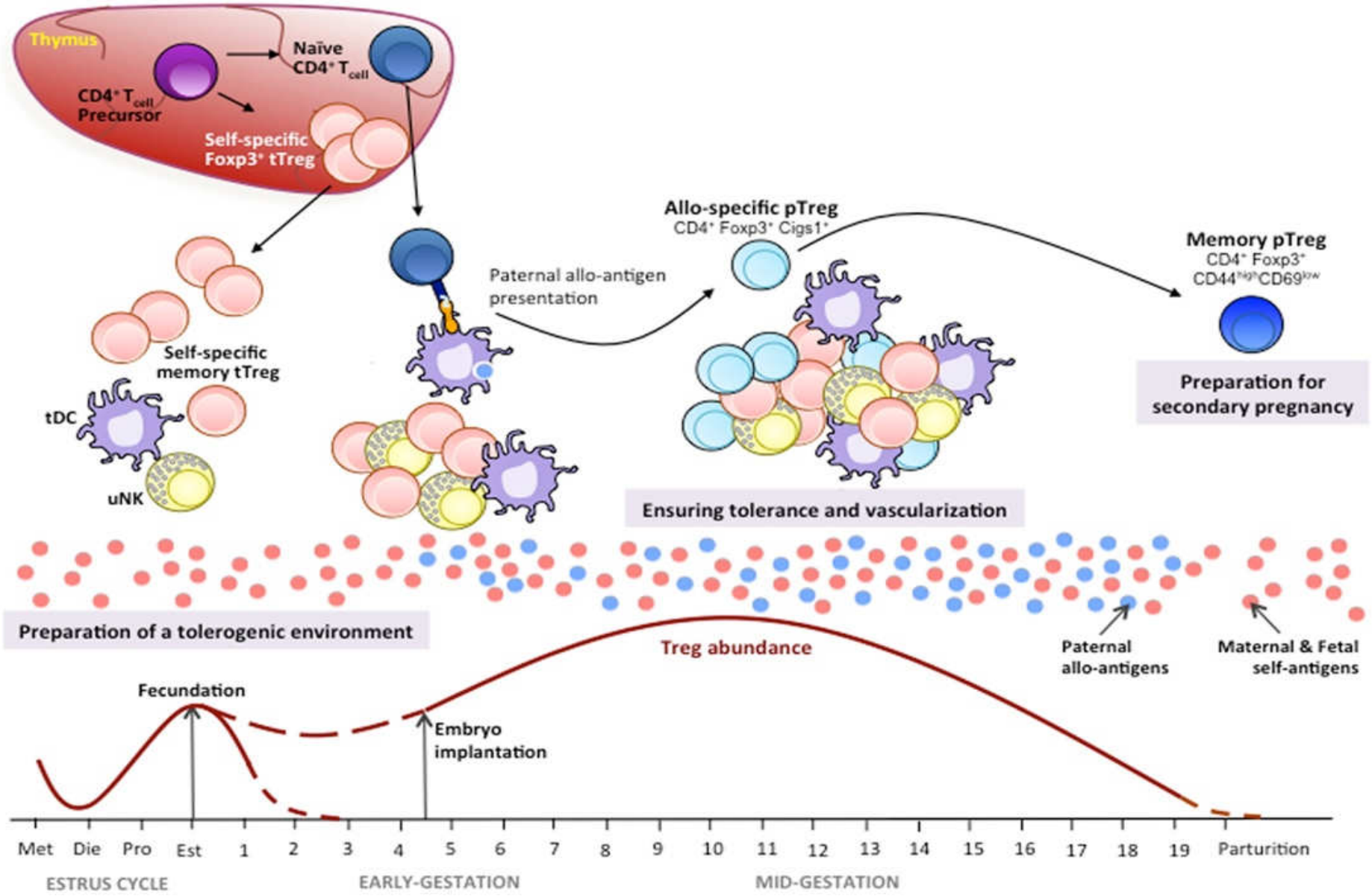
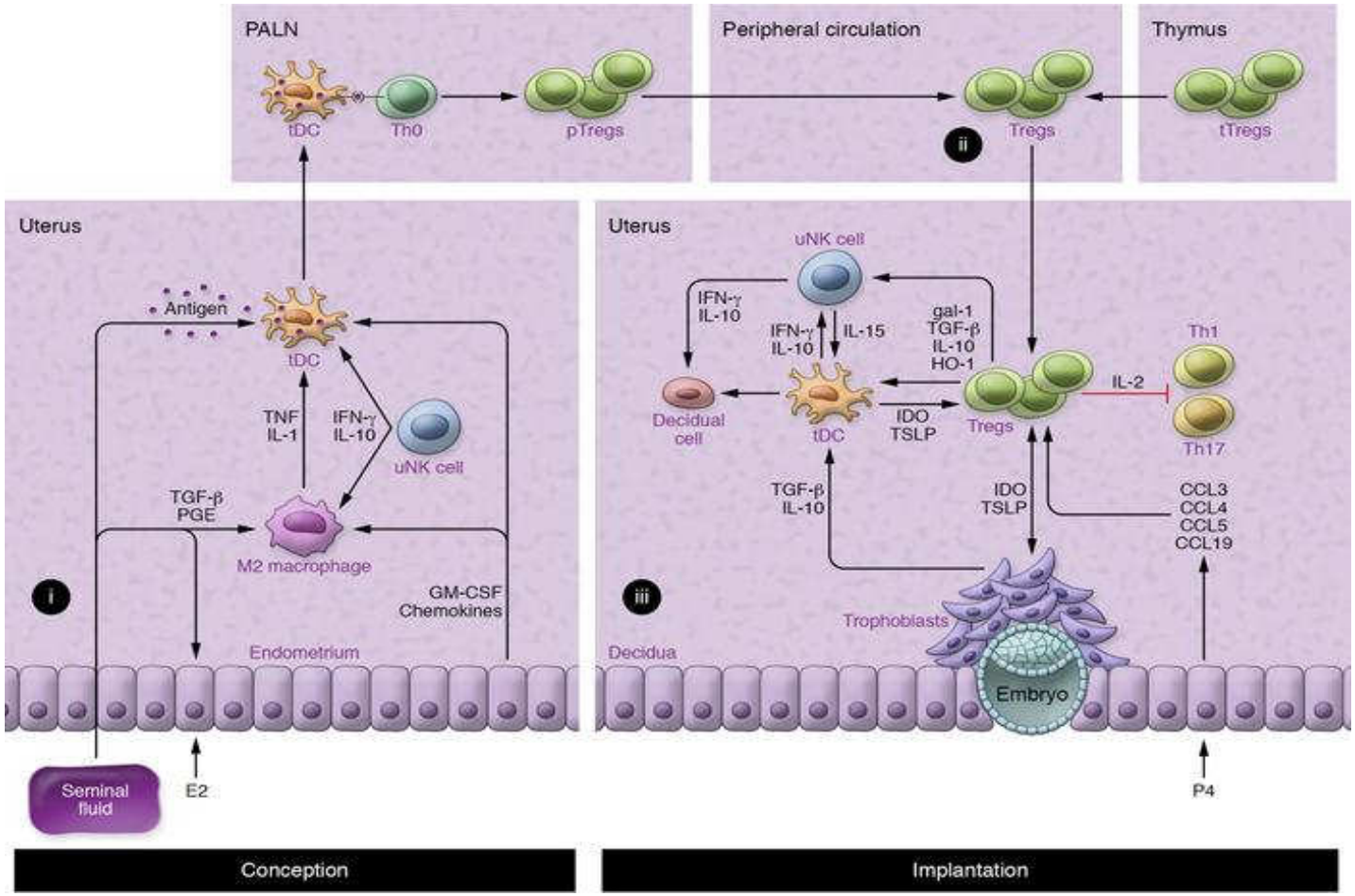
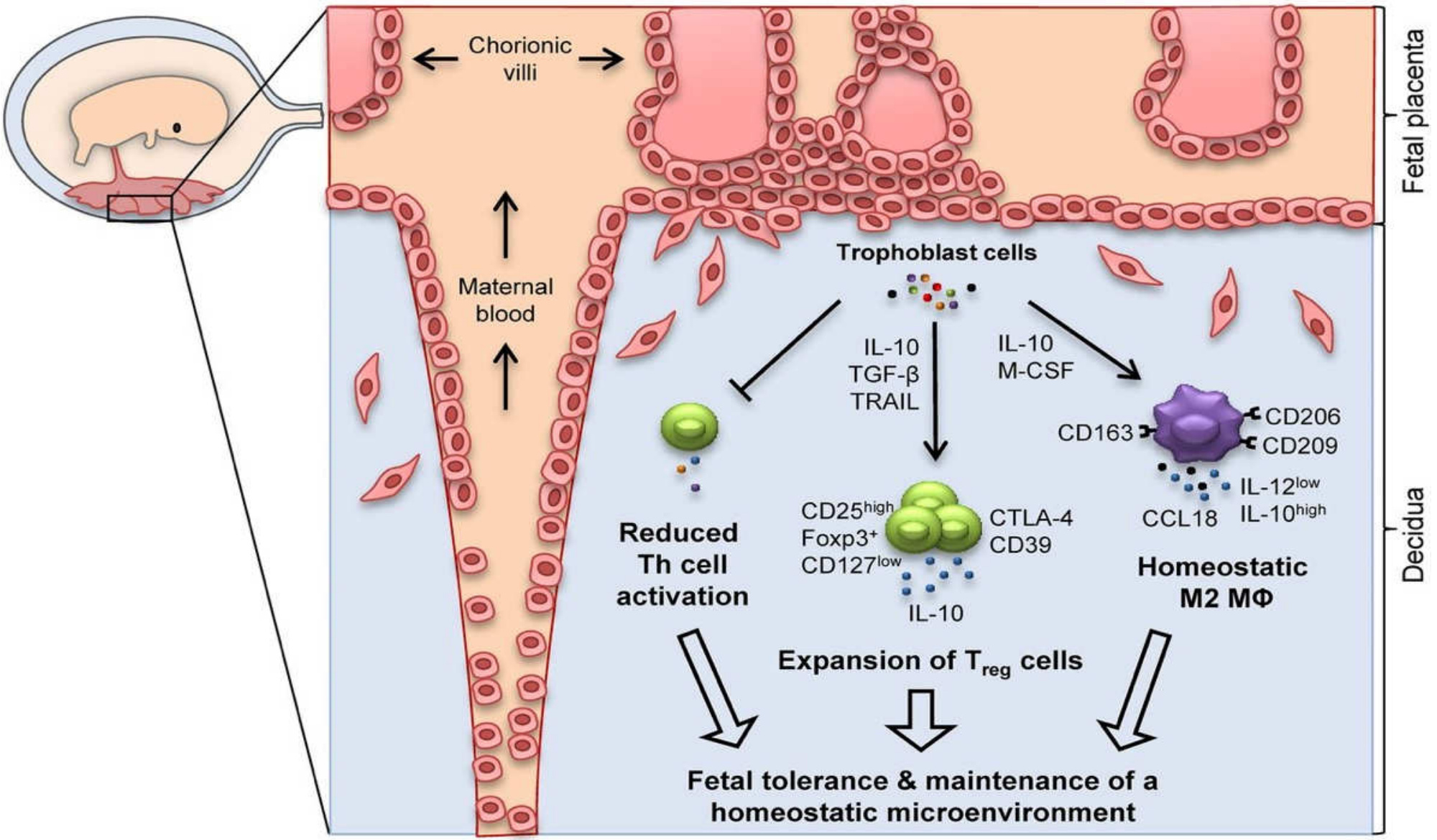


Figure 12. Possible functions of decidual NK cells and macrophages in early human pregnancy, based on the findings in this thesis.


Thymus
Naïve CD4+ Tcell
CD4+ Tcell Precursor
Self-specific Foxp3+ tTreg
Allo-specific pTreg
CD4+ Foxp3+ Cigs1+
Paternal allo-antigen presentation
Memory pTreg
CD4+ Foxp3+ CD44high CD69low
Preparation for secondary pregnancy
Self-specific memory tTreg
tDC
uNK
Ensuring tolerance and vascularization
Preparation of a tolerogenic environment
Paternal allo-antigens
Maternal & Fetal self-antigens
Treg abundance
Fecundation
Embryo implantation
Met Die Pro Est 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 Parturition
ESTRUS CYCLE
EARLY-GESTATION
MID-GESTATION

QuickTime™ Ë a
îÓÚÓ — JPEG ‰ÂÍÓÏÔ¾ÂÒÒÓ¾
Ú¾Â· ÛÂÚÒ½, ˜ÚÓ·Þ ,Ë‰ÂÚ¸ ðÚÛ Í‡¾ÚËÌÍÛ.


PALN
tDC
Th0
pTregs
Peripheral circulation
Tregs
ii
Thymus
tTregs
Uterus
Antigen
tDC
TNF
IL-1
IFN-γ
IL-10
uNK cell
TGF-β
PGE
M2 macrophage
GM-CSF
Chemokines
i
Endometrium
Seminal fluid
E2
Uterus
uNK cell
IFN-γ
IL-10
IFN-γ
IL-10
IL-15
gal-1
TGF-β
IL-10
HO-1
Th1
IL-2
Decidual cell
tDC
IDO
TSLP
Tregs
Th17
TGF-β
IL-10
IDO
TSLP
CCL3
CCL4
CCL5
CCL19
iii
Trophoblasts
Decidua
Embryo
P4
Conception
Implantation


Chorionic villi
Maternal blood
Fetal placenta
Decidua
Trophoblast cells
IL-10
TGF-β
TRAIL
IL-10
M-CSF
CD163
CD206
CD209
IL-12low
IL-10high
CCL18
Reduced Th cell activation
CD25high
Foxp3+
CD127low
CTLA-4
CD39
IL-10
Homeostatic M2 MΦ
Expansion of Treg cells
Fetal tolerance & maintenance of a homeostatic microenvironment

Спасибо!