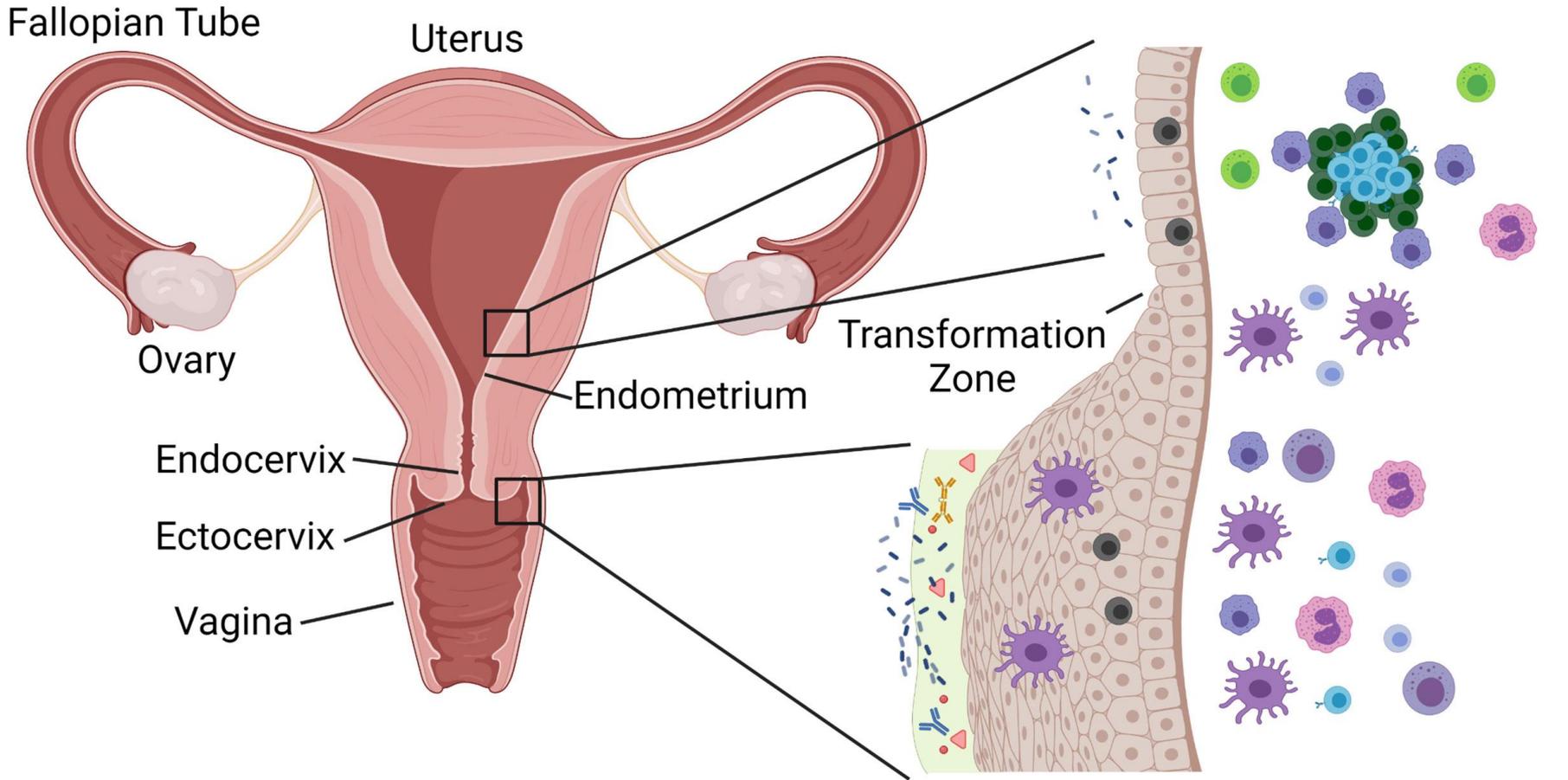


Tolerância materno-fetal

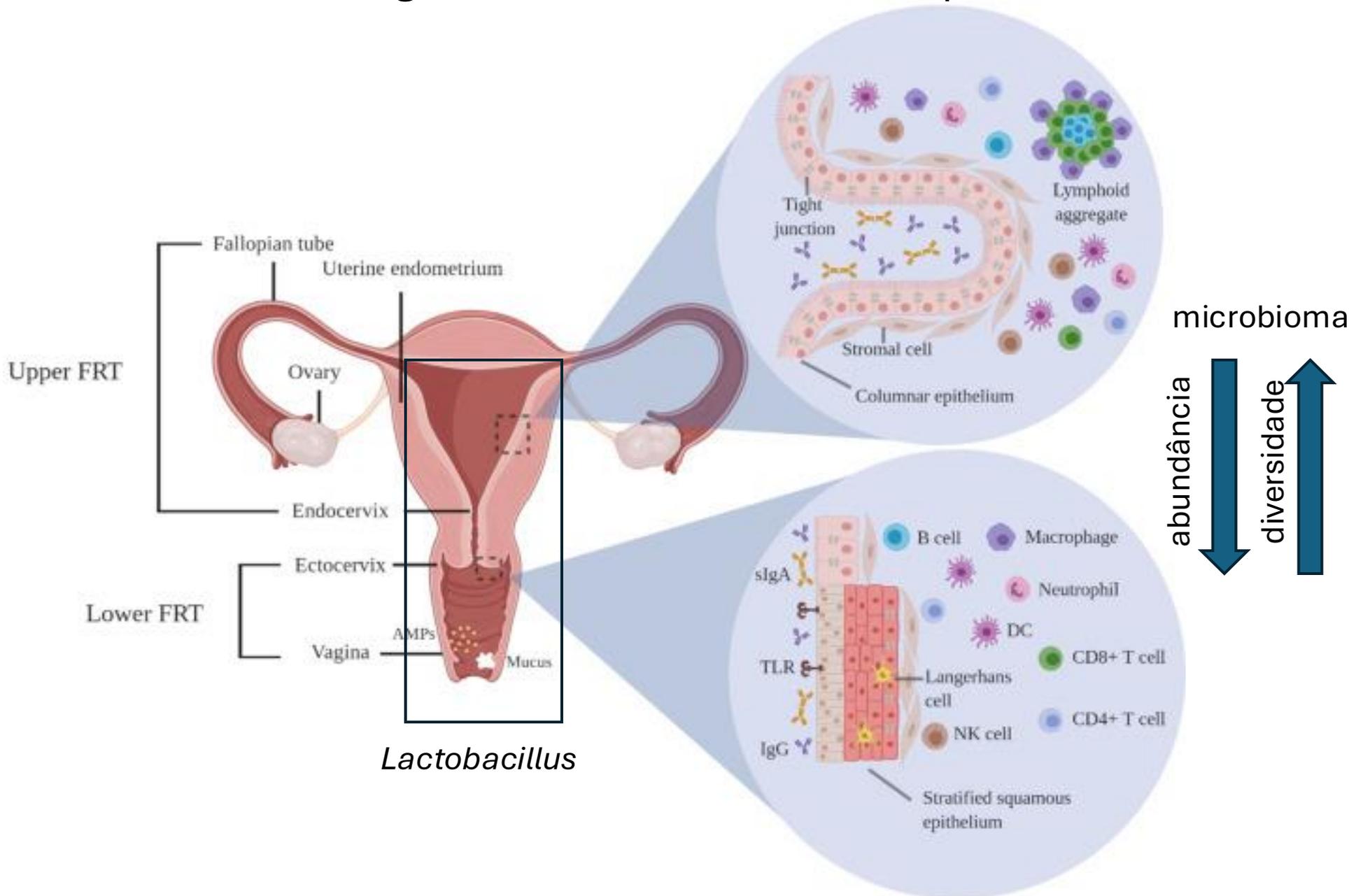
BMI102

Trato genital feminino inferior e superior



- IgA
 IgG
 DC
 Macrophage
 CD4⁺ T Cell
- B Cell
 NK Cell
 uNK Cell
 Neutrophil
 CD8⁺ T Cell
- γδ T Cell
 AMPs
 Mucus
 H⁺

Trato genital feminino inferior e superior

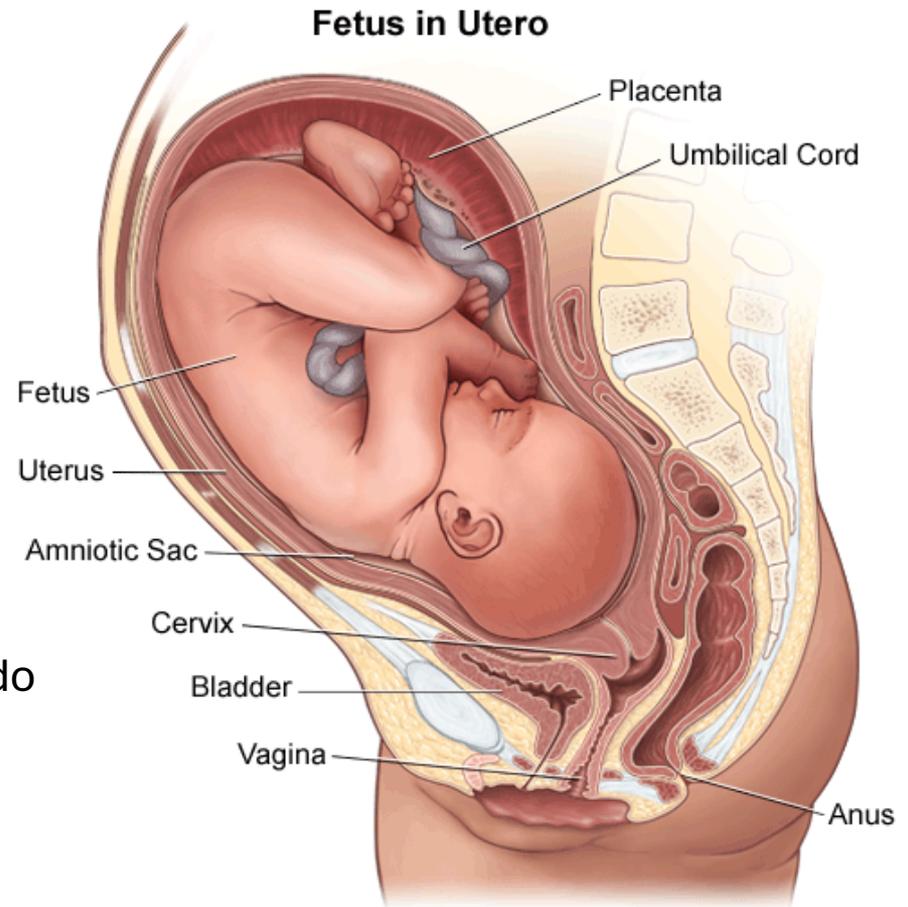


Feto representa um tecido semi alogênico

Expressão de moléculas HLA paternas e outros aloantígenos

Mecanismos de tolerância são essenciais para manutenção do feto

O útero gravídico é um tecido imunoprivilegiado

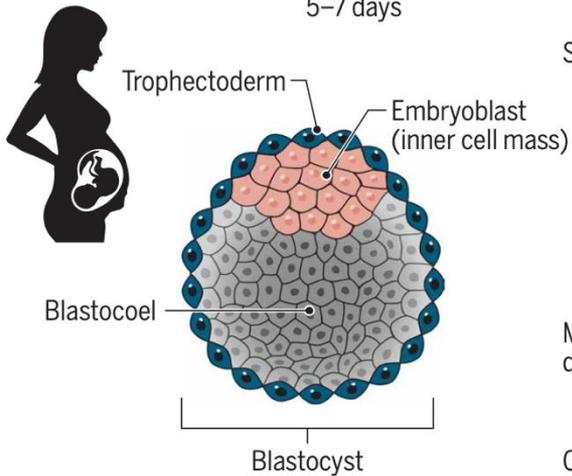


Anatomia da interação materno-fetal

Human

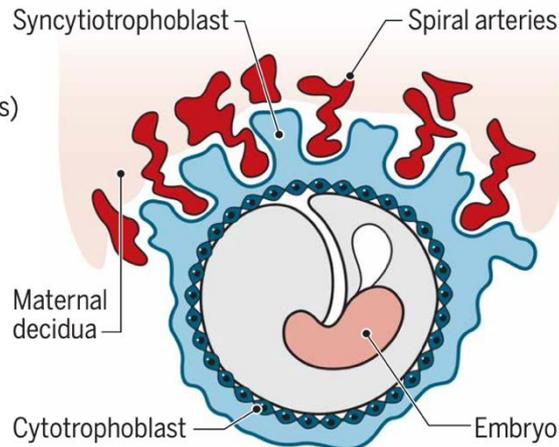
Pre-placentation

5-7 days

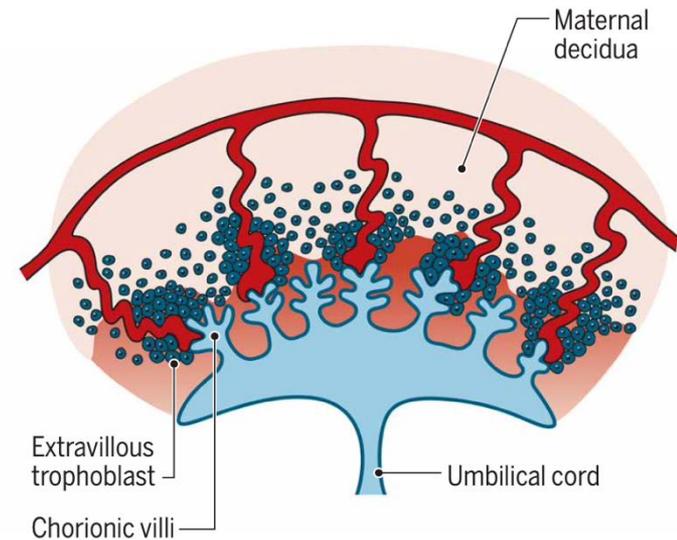


Post-placentation

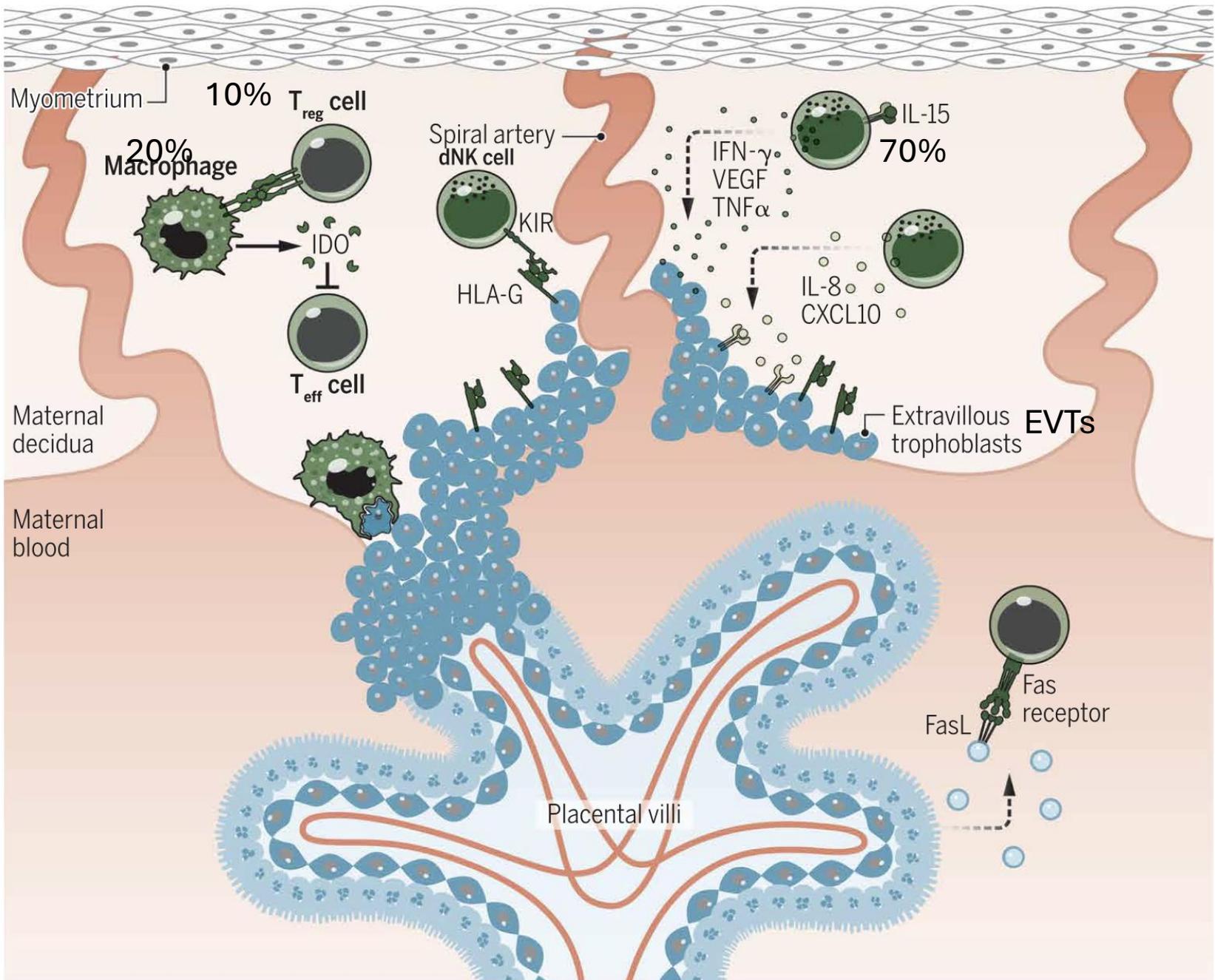
Early 1st trimester



2nd-3rd trimester



Alteração da estrutura
Redução de EVT's e preenchimento do
espaço intraviloidades com sangue materno



Células NK uterinas - uNK

Chegam a ser 70% das células da mãe presentes na descídua durante a implantação

Diferentes de células NK circulantes: expressam KIRs, CD56, mas não CD16

Sua diferenciação em uNK parece depender de hipóxia (1o trimestre) e TGF β
As células CD56++ são resistentes a estresse oxidativo que ocorre na placenta
(EVTs forma um tipo de tampão que causa hipóxia local)

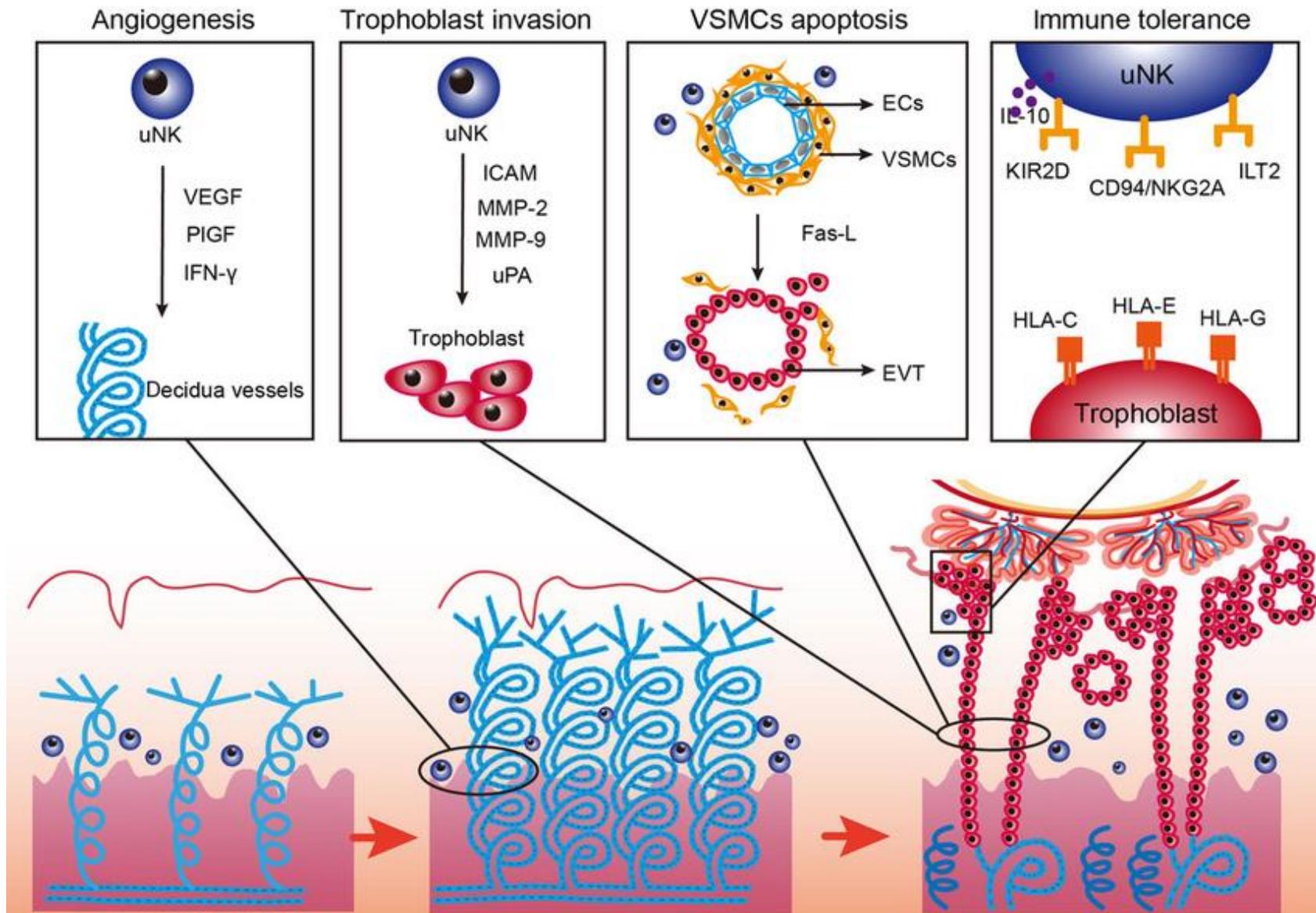
Secretam IL-10 e IFN γ —| Th17

Secretam fatores angiogênicos

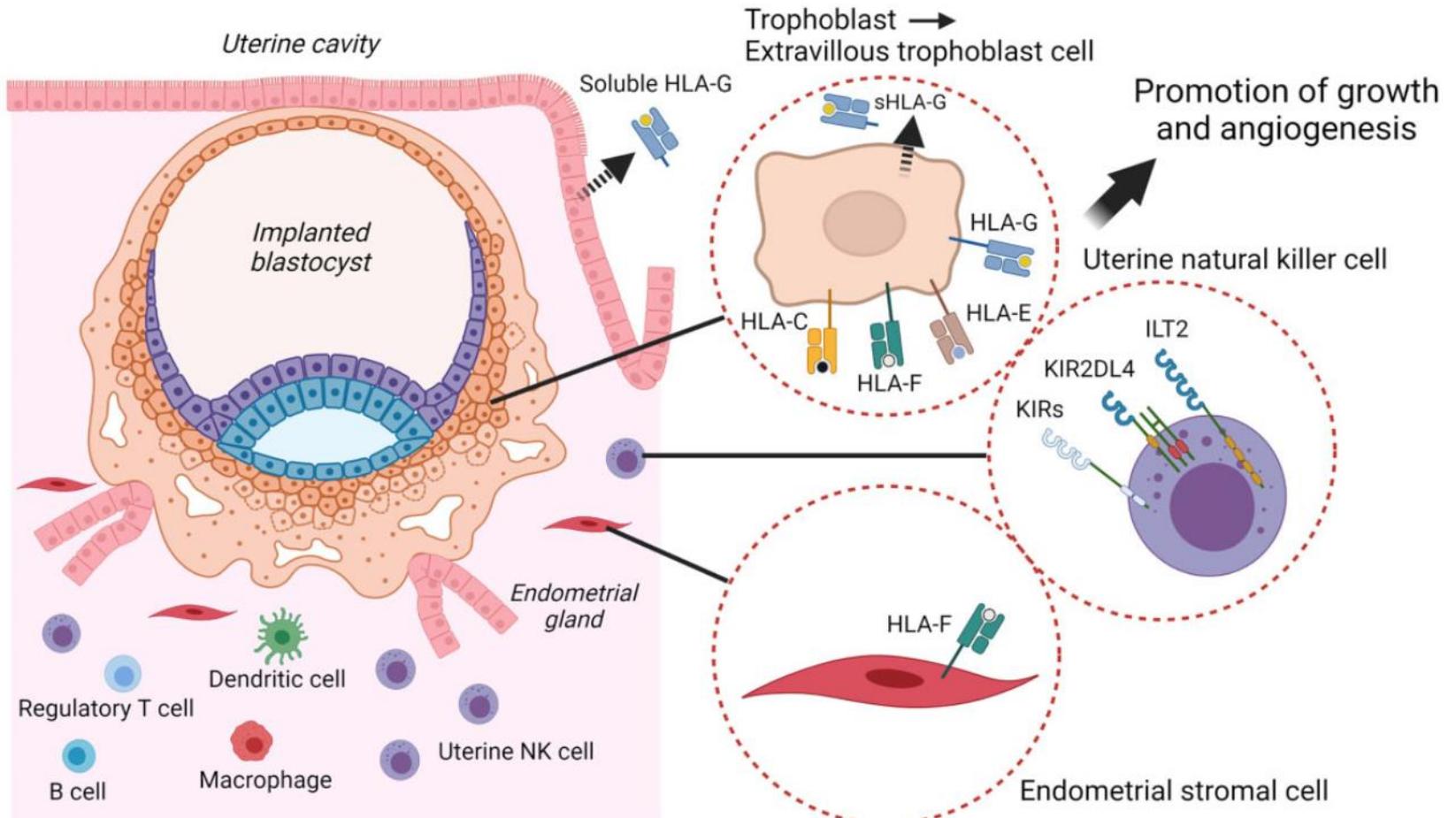
Secretam moléculas adesivas e fatores angiogênicos para facilitar invasão de trofoblastos

Induzem apoptose de células de músculo liso vascular

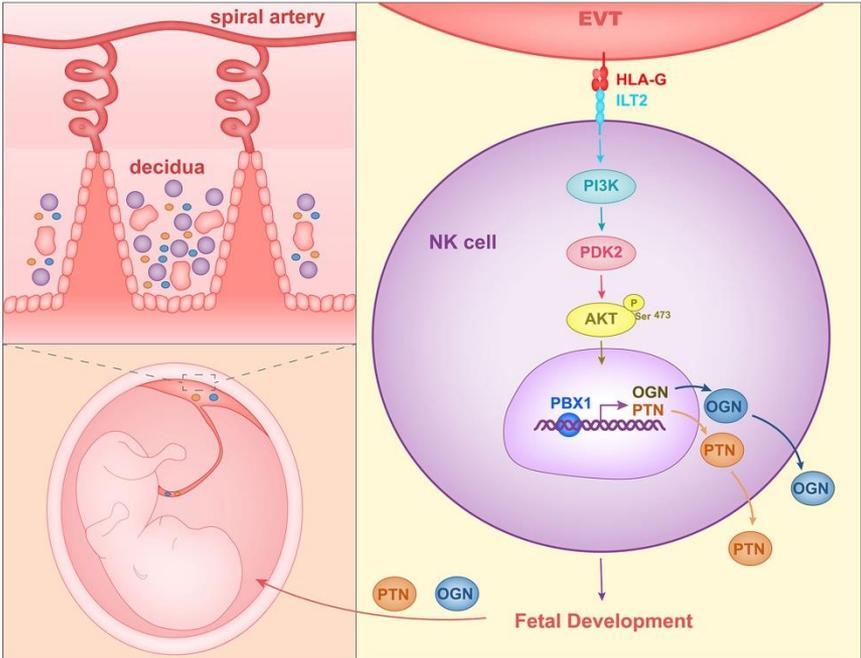
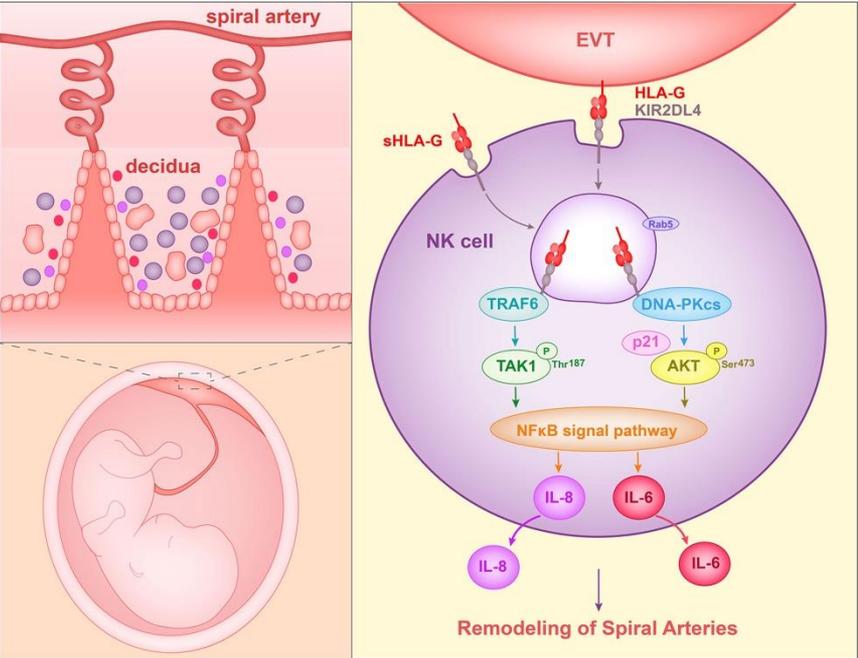
Células NK uterinas - uNK



Expressão de moléculas HLA-I convencionais e não convencionais

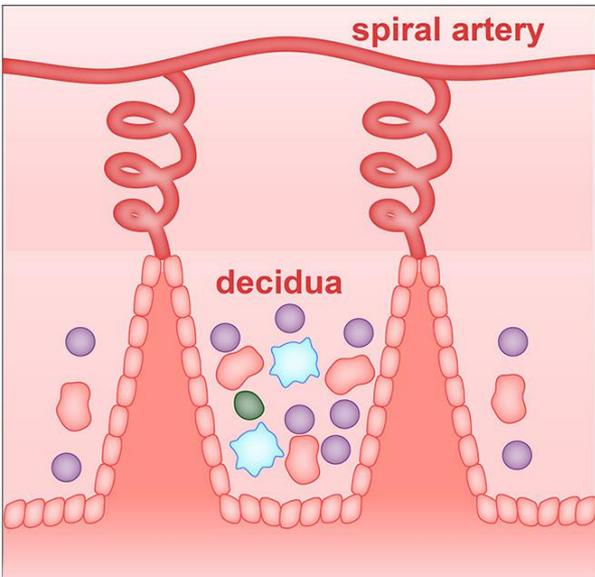


HLA-G – tolerância, implantação e desenvolvimento do feto

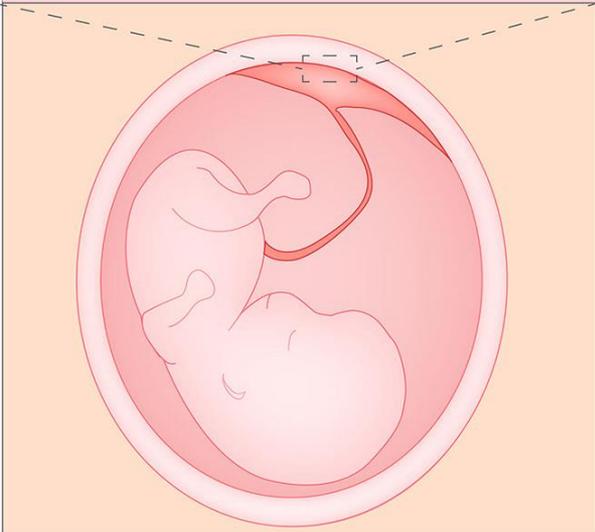
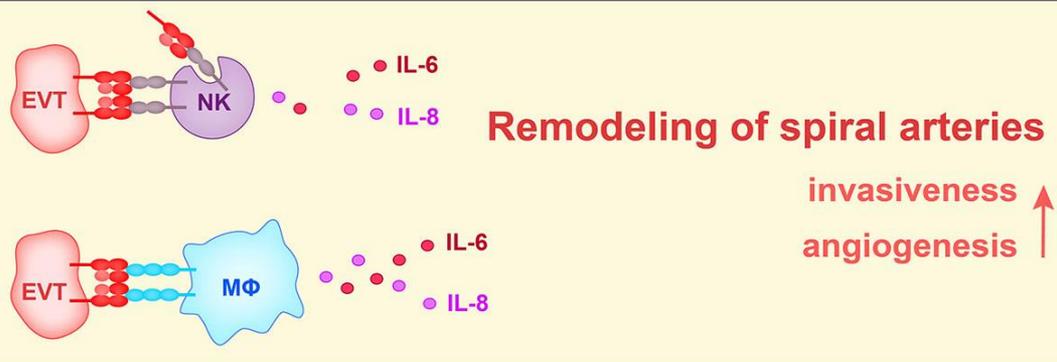


Pleiotrofina
osteoglicina

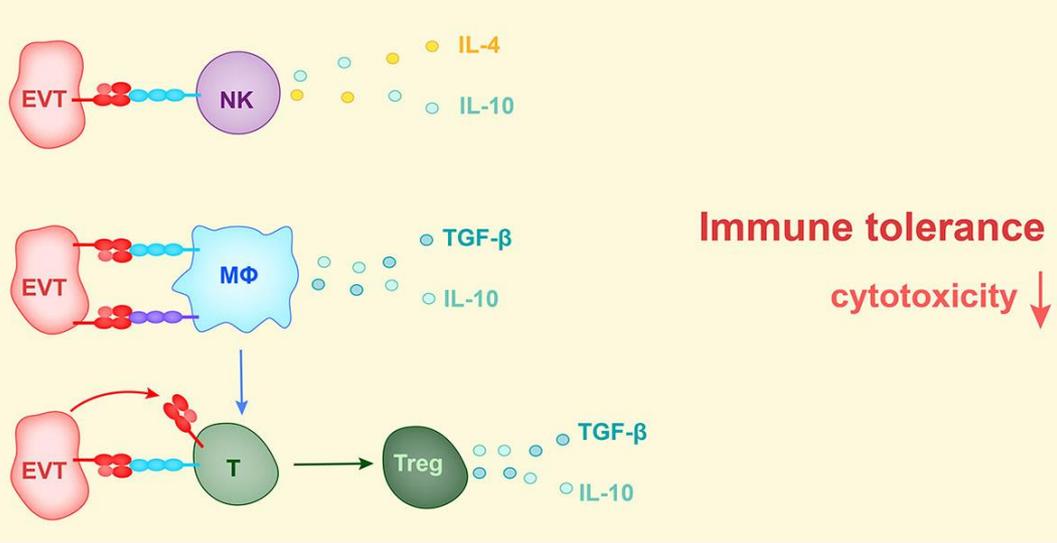
HLA-G – tolerância, implantação e desenvolvimento do feto



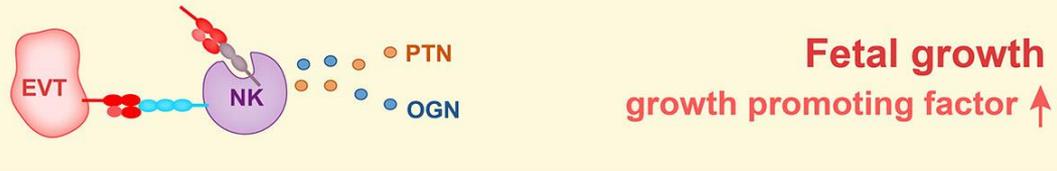
HLA-G 
 KIR2DL4 
 ILT2 



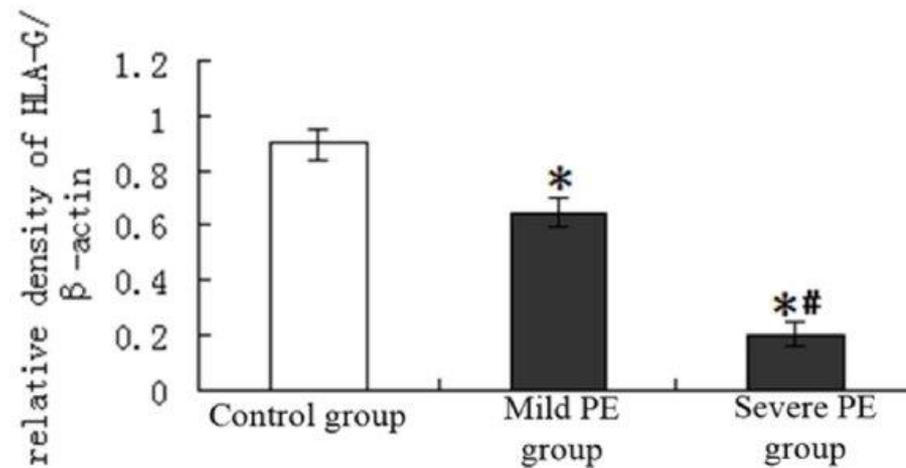
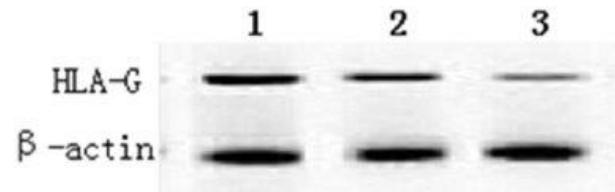
HLA-G 
 ILT2 
 ILT4 



HLA-G 
 KIR2DL4 
 ILT2 



Número reduzido de uNK ou baixa expressão de HLA-G tem correlação com risco de pre eclâmpsia

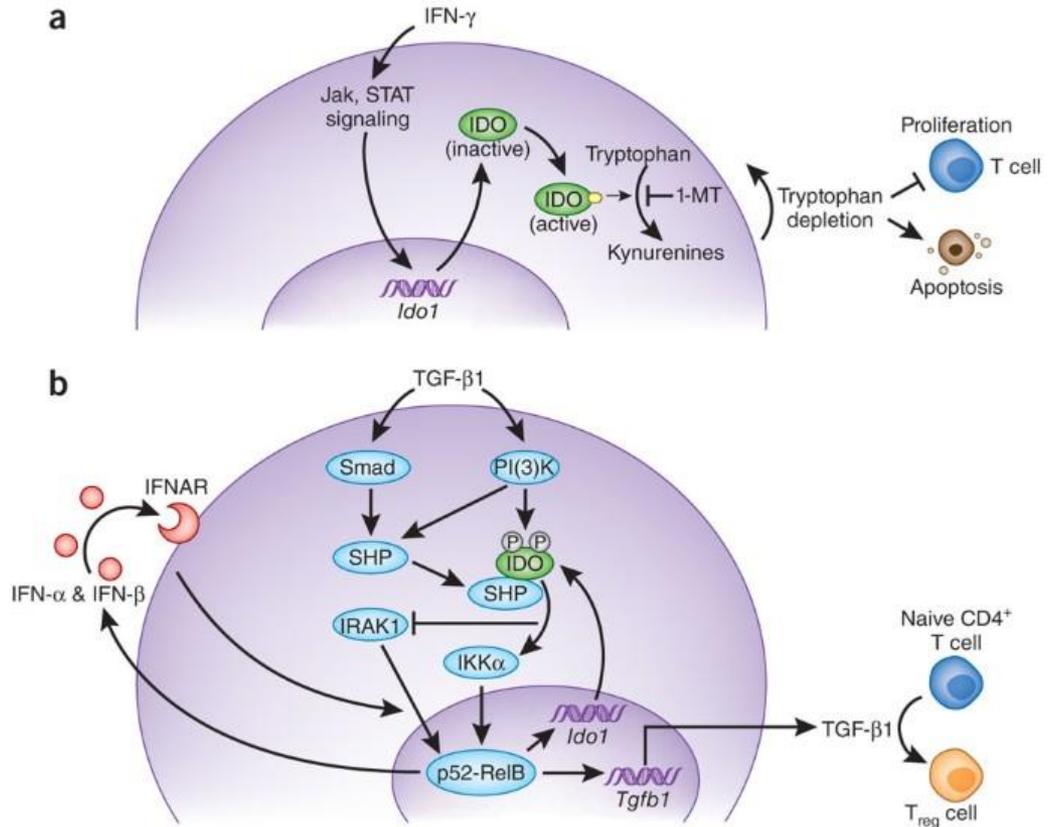


Macrófagos

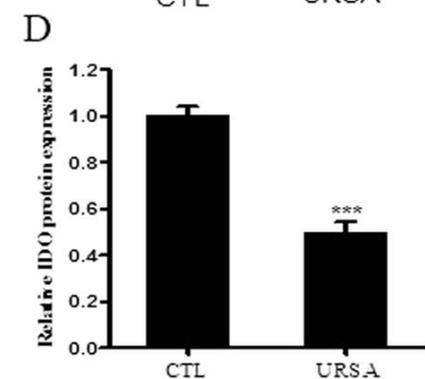
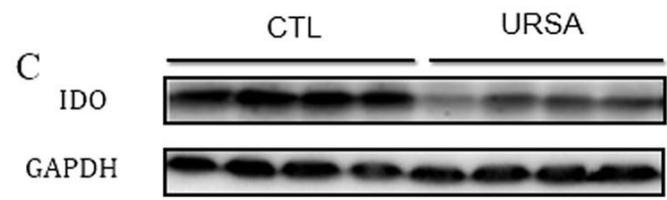
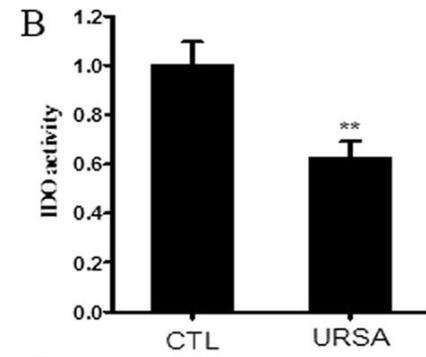
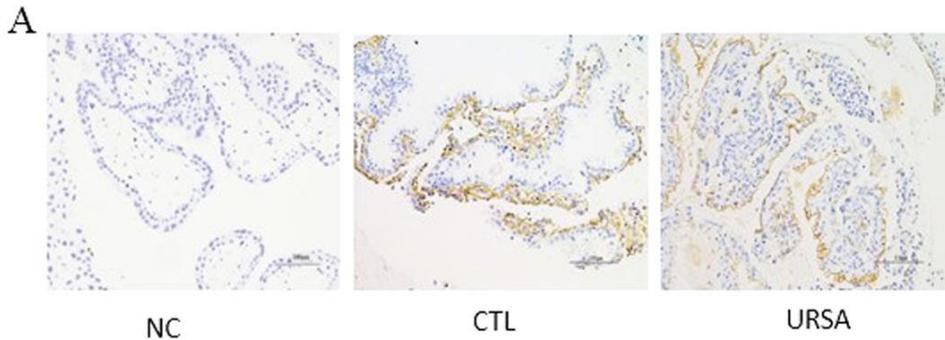
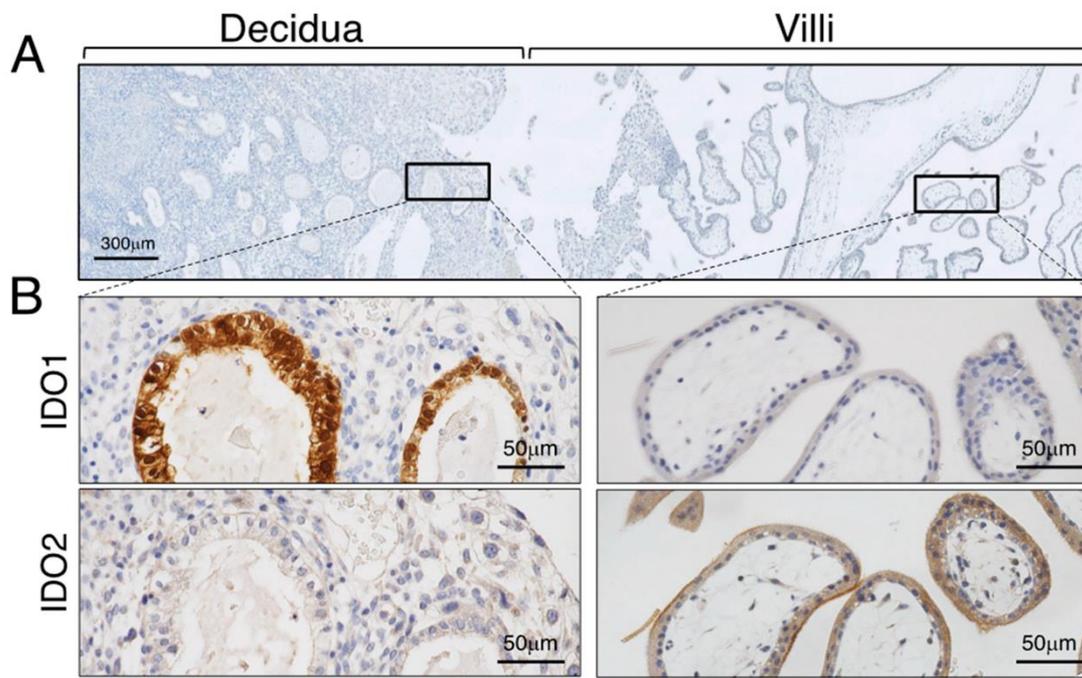
Principais apresentadoras de antígenos

Também participam de remodelamento da descídua (arteríolas espirais)

Apresentam fenótipo tolerogênico – CD163+CD206+DC-SIGN+IDO+, expressam IL-10, CCL2 e CCL18, MMP9 e VEGF



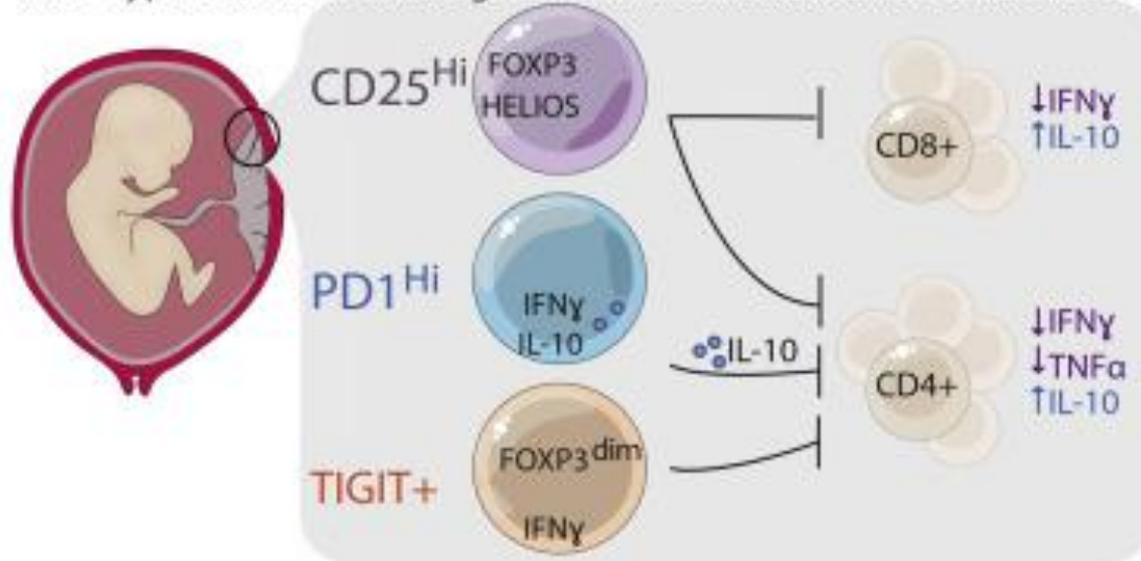
IDO é essencial para a manutenção da gravidez



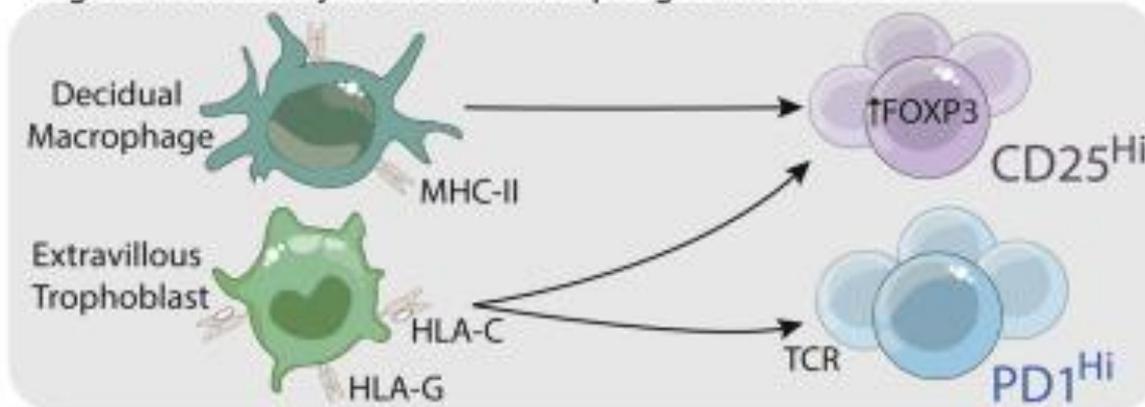
Unexplained recurrent spontaneous abortion

Células T reguladoras são importantes para bloquear respostas efectoras

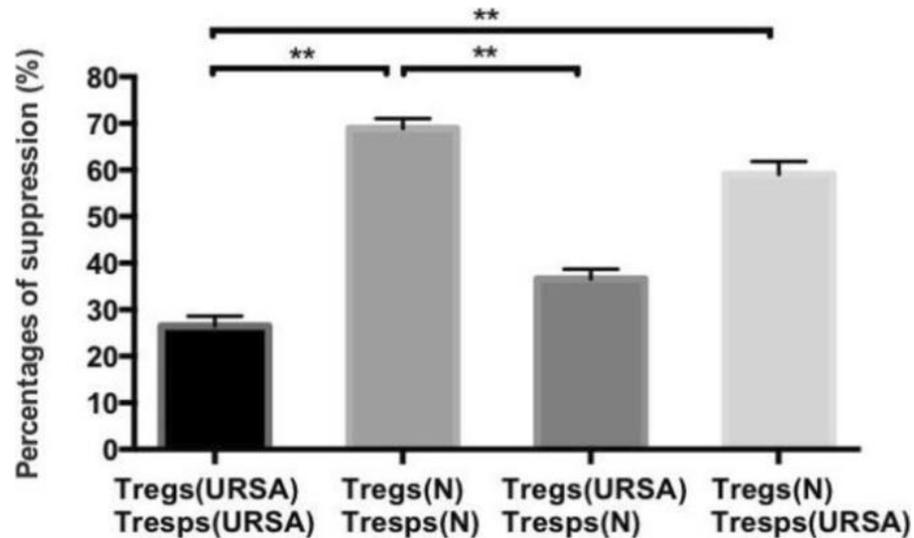
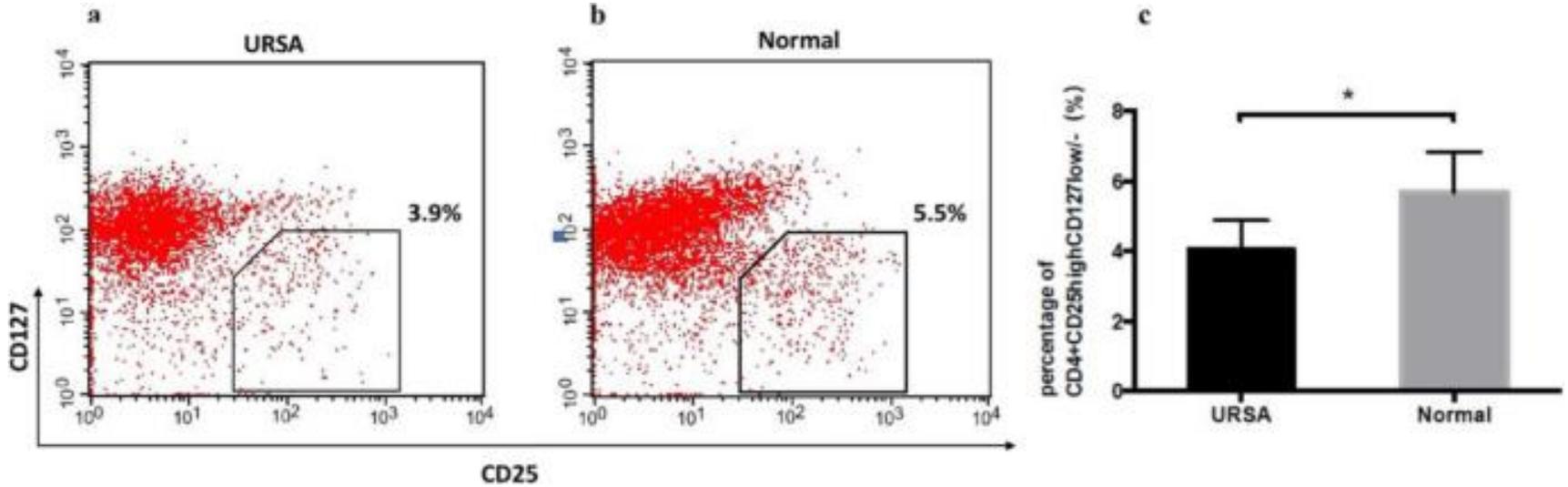
Three types of functional Treg are found at the maternal-fetal interface



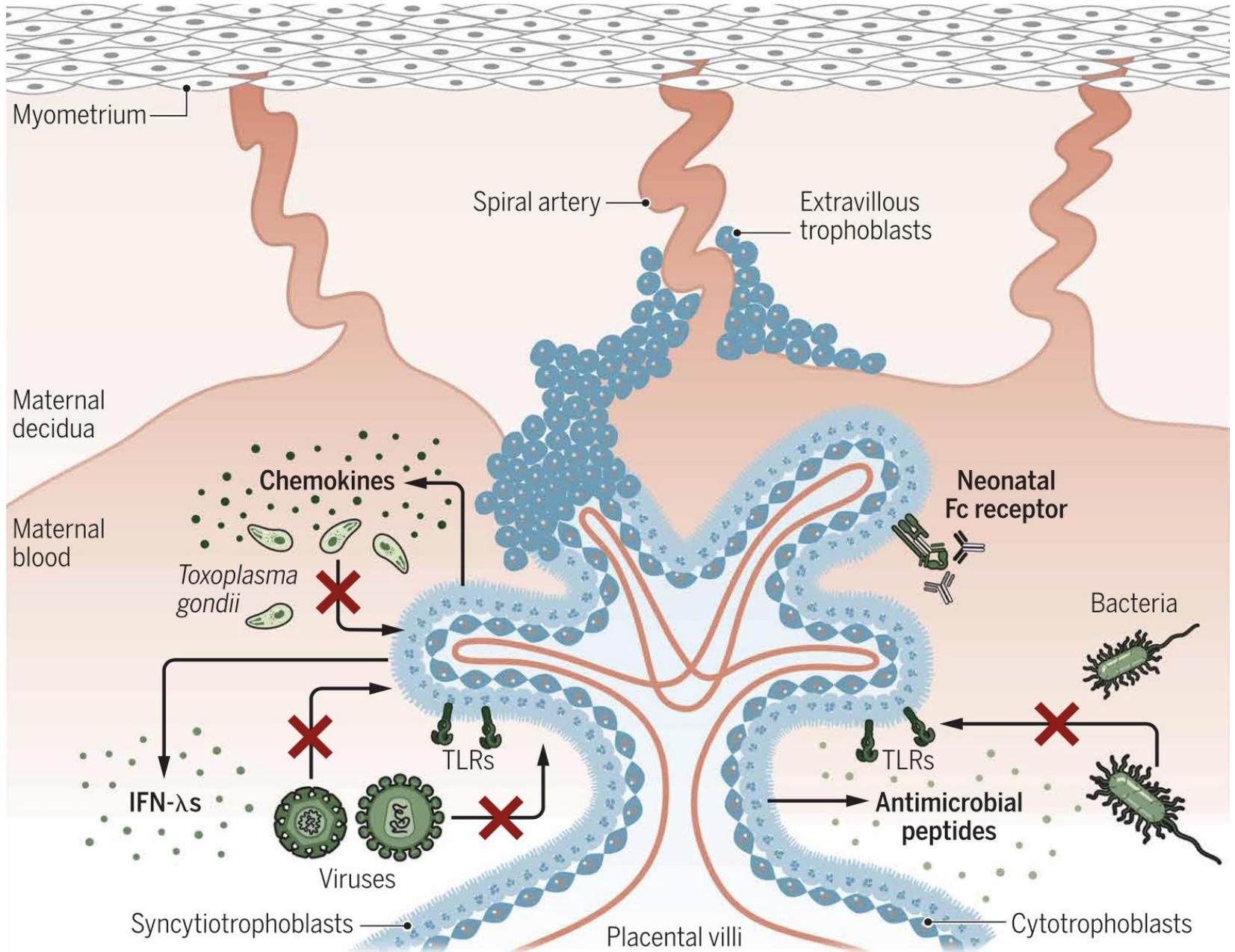
Treg are induced by decidual macrophages and HLA-G⁺ EVT



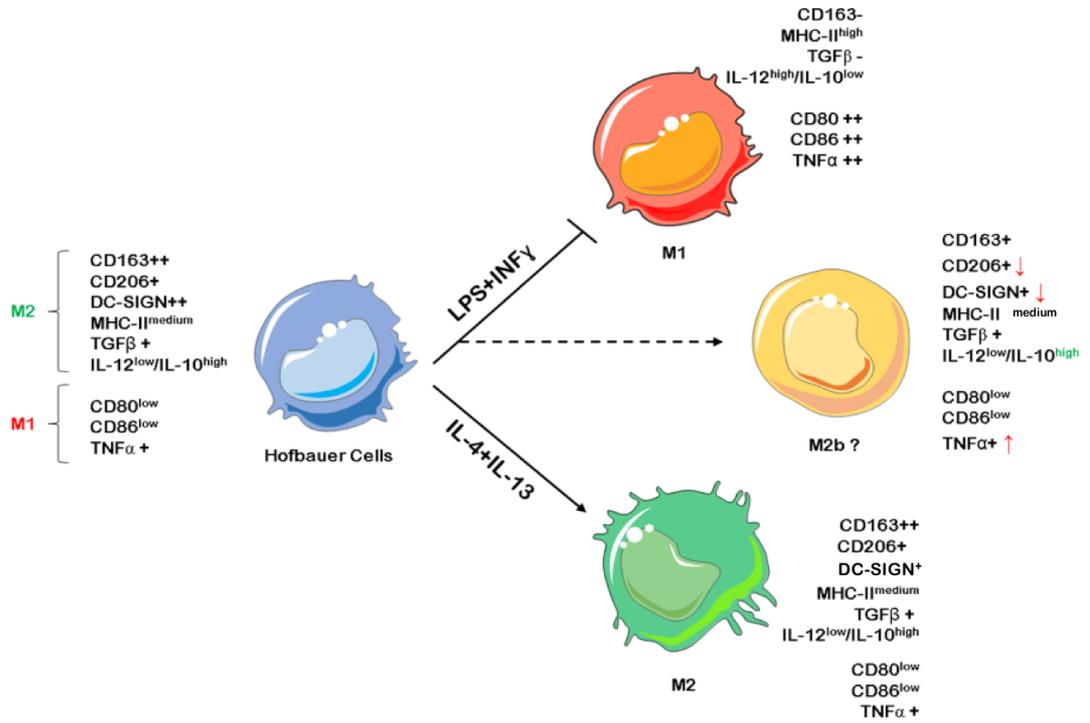
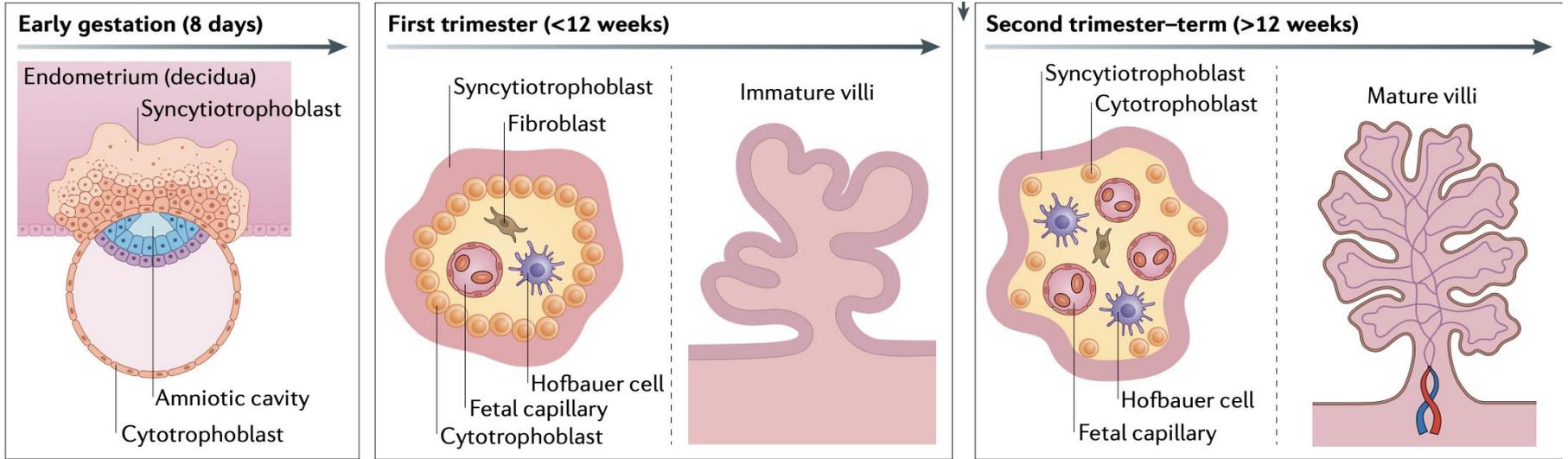
Tregs inibem respostas efetoras



E respostas contra patógenos?



Células do feto – Macrófagos Hofbauer



Perfil M2 resistente a estímulos pró inflamatórios

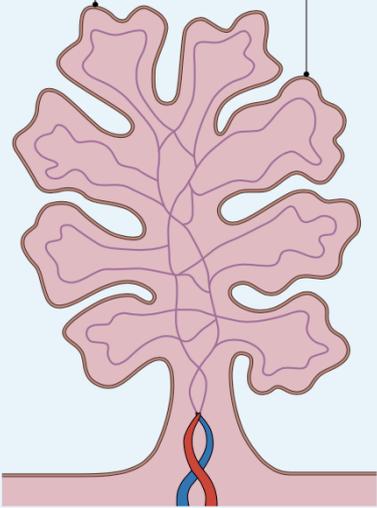
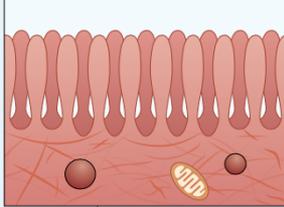
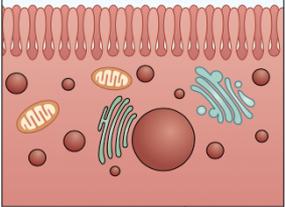
Mecanismos de defesa da placenta

Physical defences

Lack of cell-cell junctions

Dense actin network

Syncytiotrophoblast

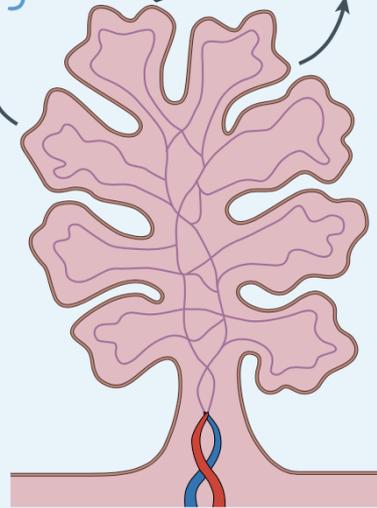
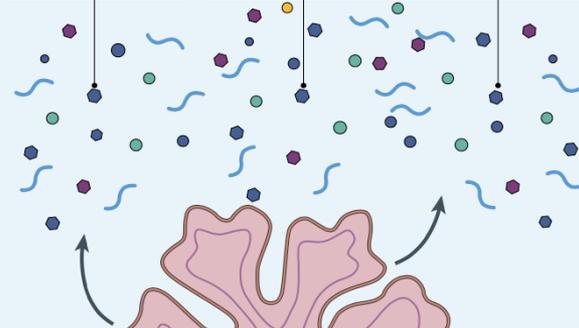
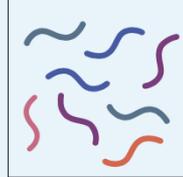
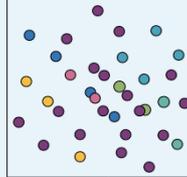
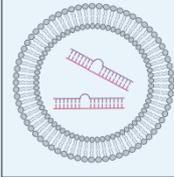


Constitutive release of effectors

Exosomes

Cytokines

Antimicrobial peptides



Innate immune response to infection

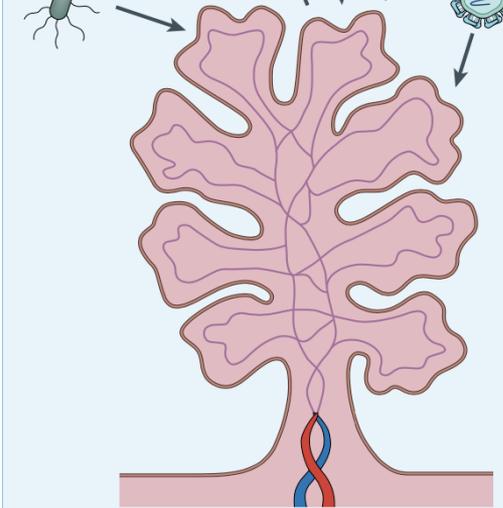
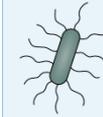
Cytokines (IL-1 β , IFN λ)

Chemokines (CCL22, CCL17)

Toxoplasma gondii

Listeria monocytogenes

Zika virus

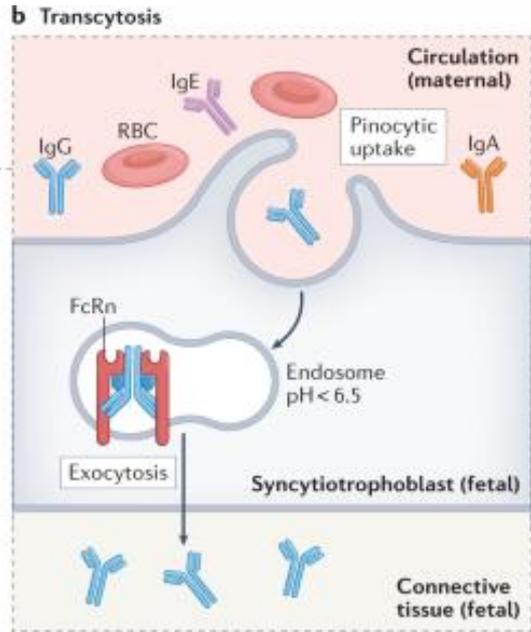
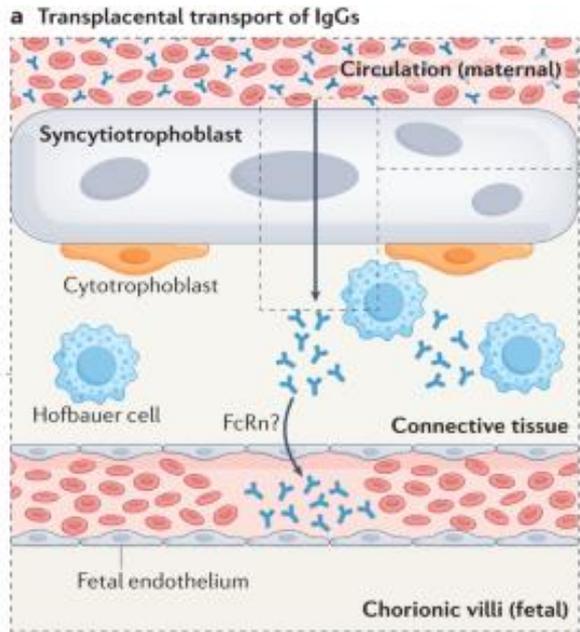


Resistência a infecção por *Lysteria monocytogenes*, dependente do citoesqueleto se actina de SYNs

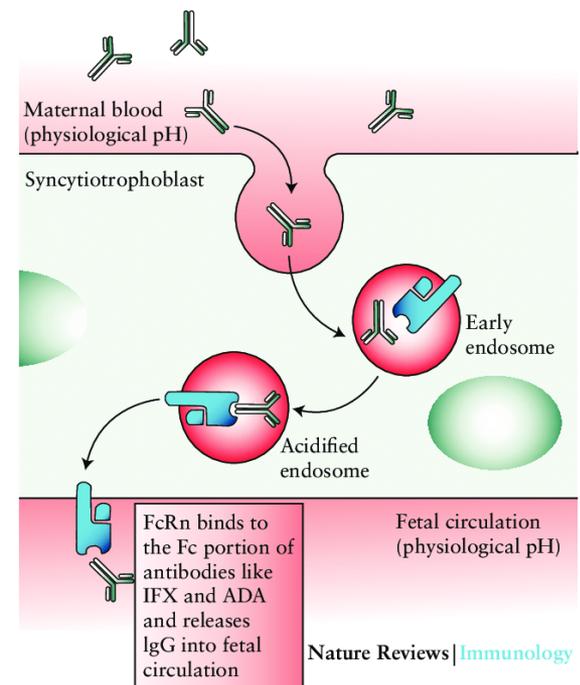
SYNs também dificultam entrada de *Toxoplasma gondii* na placenta

Secreção de IFN tipo III (falta desta citocina leva à susceptibilidade a infecção por ZIKV – injeção de IFN III peguilado restringe infecção vertical por ZIKV

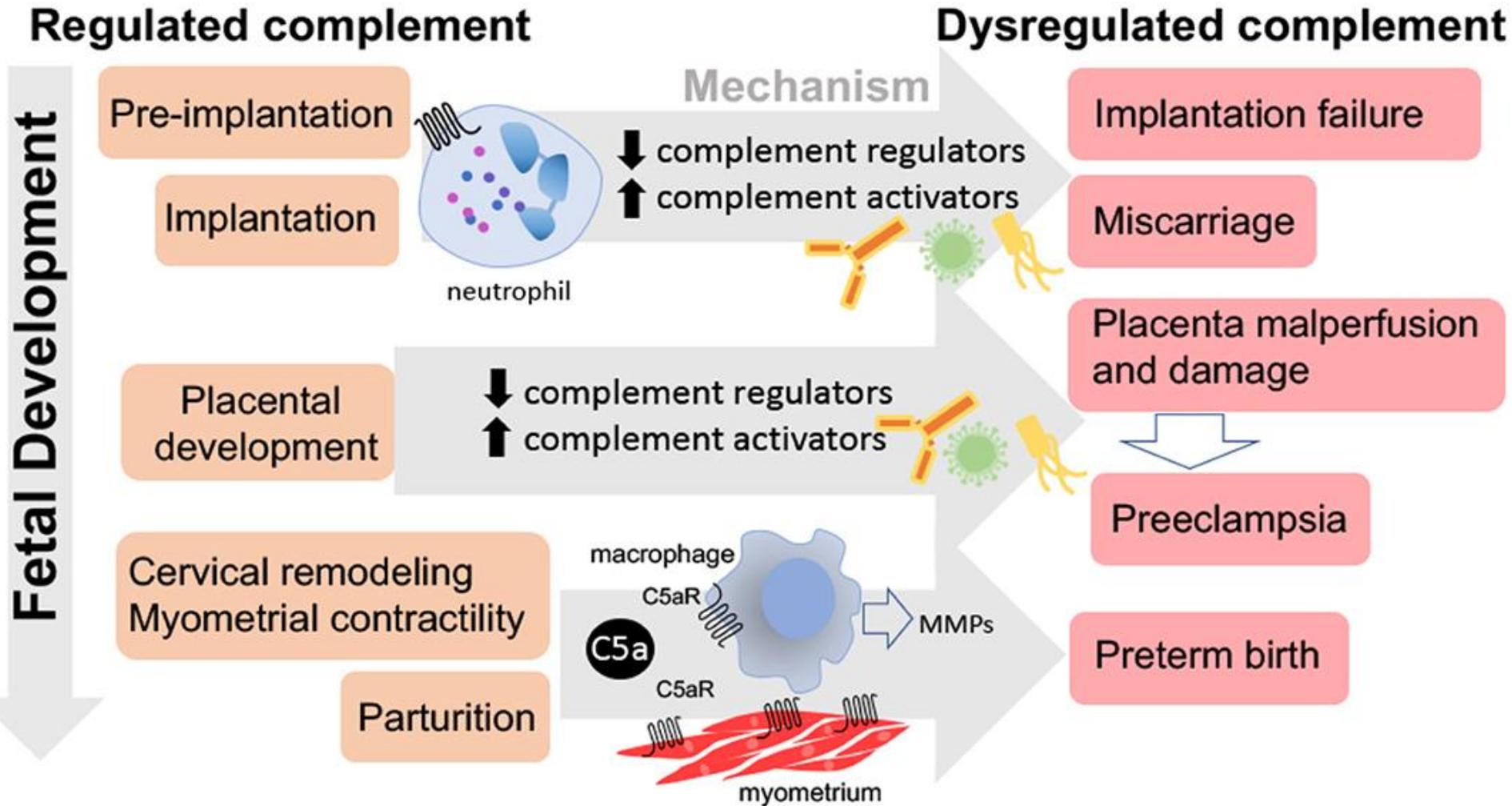
Transporte de IgG pelo receptor FCg neonatal



FcR neonatal



Controle da ativação do sistema complemento que também tem papel no controle de patógenos



Patógenos TORCH

Conseguem infectar o feto, apesar de mecanismos de defesa

- T Toxoplasma
- O (other) ZIKV, Listeria, Treponema pallidum, varicella zoster, HIV
- R rubéola
- C citomegalovírus
- H herpes simplex

Table 1 | TORCH pathogens and the hallmarks of their infections

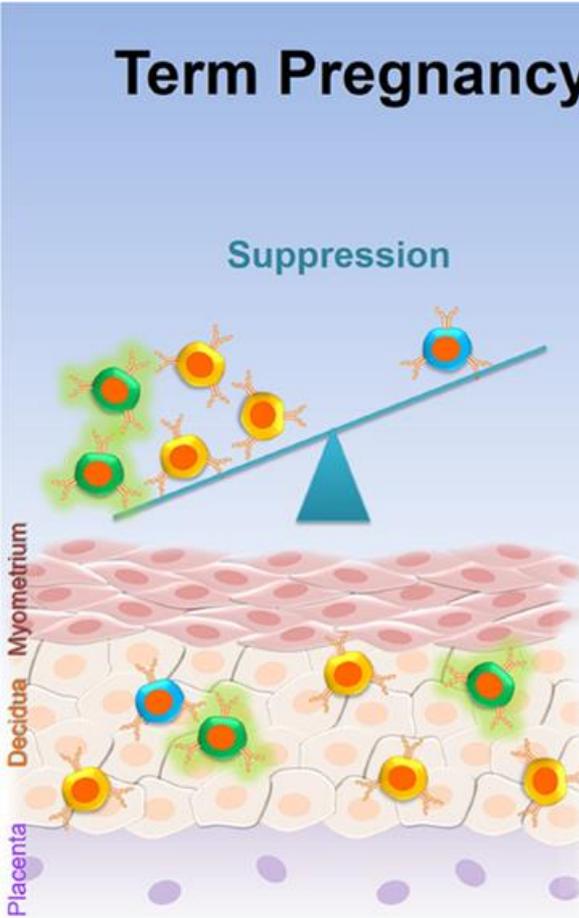
Pathogen	Mode of transmission	Hallmarks of congenital infection
Bacteria		
<i>Listeria monocytogenes</i>	Contaminated food	Stillbirth/pregnancy loss; preterm delivery; neonatal sepsis
<i>Treponema pallidum</i>	Sexual	Stillbirth/pregnancy loss; low birthweight; fetal hepatosplenomegaly; developmental delay; saddle nose deformity; rhinitis; dental deformities; chorioretinitis; anaemia; rash; dilated bowel; skin thickening; periostitis; bone fractures and demineralization
<i>Streptococcus agalactiae</i>	Commensal	Neonatal sepsis
<i>Staphylococcus aureus</i>	Commensal	Neonatal sepsis
<i>Escherichia coli</i>	Commensal	Neonatal sepsis
Viruses		
Cytomegalovirus	Faecal-oral	Chorioretinitis; low birthweight; hearing loss; developmental delay; anaemia/thrombocytopenia; rash; stillbirth/pregnancy loss; ventriculomegaly; microcephaly; intracerebral calcification; echogenic bowel/abdominal calcifications; normal
Herpes simplex virus 1 and 2	Sexual or oral contact	Neonatal meningitis; dermatological lesions; ventriculomegaly; microcephaly; intracerebral calcifications; chorioretinitis; optic atrophy; limb dysplasia
Varicella zoster virus	Respiratory droplets	IUGR; limb abnormalities
Lymphocytic choriomeningitis virus	Fomites (rodent based)	Ventriculomegaly/hydrocephalus; developmental delay; motor and sensory deficits; chorioretinitis; hearing loss
Zika virus	Arbovirus (<i>Aedes</i> species, sexual, blood borne)	Microcephaly; IUGR; hepatosplenomegaly; intrahepatic calcifications; ventriculomegaly; intracerebral calcifications; echogenic bowel; stillbirth/pregnancy loss
West Nile virus	Arbovirus (<i>Culex</i> species)	Chorioretinitis; meningitis/encephalitis; possible lissencephaly
Rift Valley fever virus	Arbovirus (<i>Aedes</i> species, <i>Culex</i> species, <i>Anopheles</i> and <i>Mansonia</i> species, contact with contaminated animal materials)	Stillbirth/pregnancy loss; preterm delivery
Human parvovirus B19	Respiratory droplets	Anaemia; hydrops; stillbirth/pregnancy loss
Parasites		
<i>Plasmodium falciparum</i> <i>Plasmodium vivax</i>	Arthropod vector (<i>Anopheles</i> species)	IUGR; preterm delivery; severe hypoglycaemia
<i>Toxoplasma gondii</i>	Ingestion of contaminated food or oocytes	Ventriculomegaly; hydrocephalus; intracerebral calcifications; choroid plexus cysts; hydrocephalus; ascites; IUGR; hepatosplenomegaly
<i>Trypanosoma cruzi</i>	Arthropod vector (Triatominae subfamily)	IUGR; respiratory failure; hepatosplenomegaly; meningitis; heart failure; hydrops; heart disease; megacolon

Alteração do perfil imunológico durante a gravidez

Term Pregnancy

Suppression

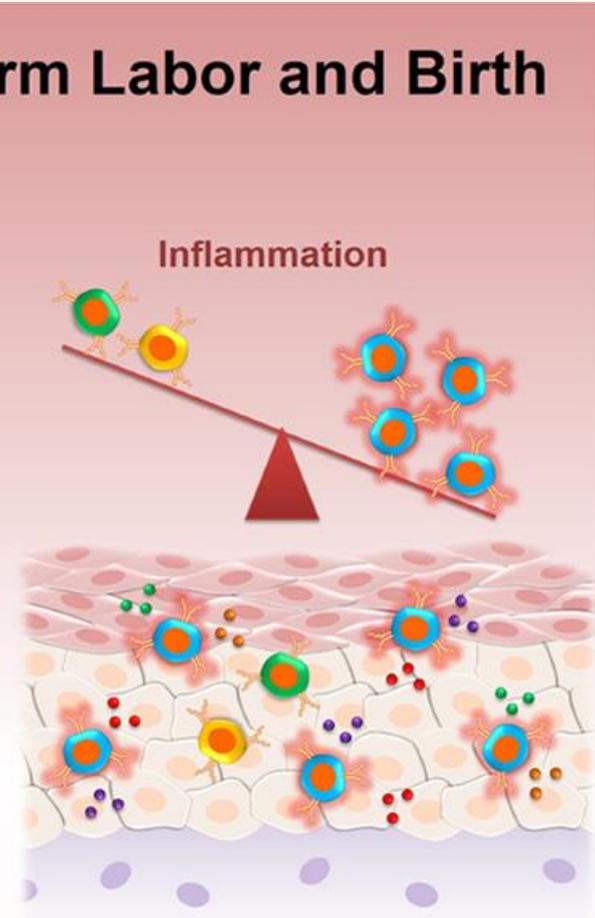
Placenta
Decidua
Myometrium



- Effector T cell
- Exhausted T cell
- Functional regulatory T cell

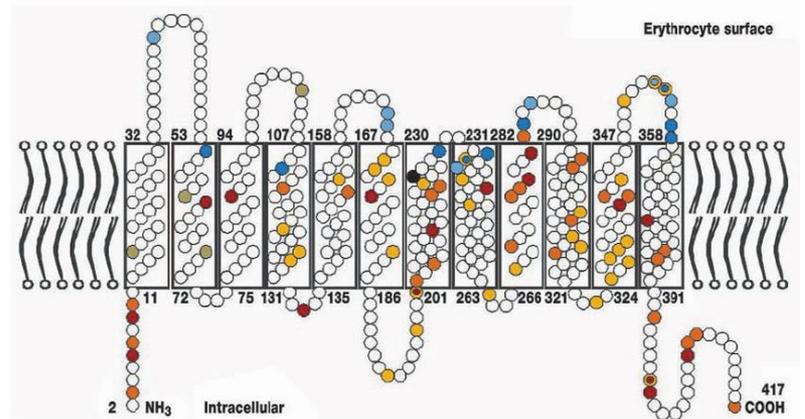
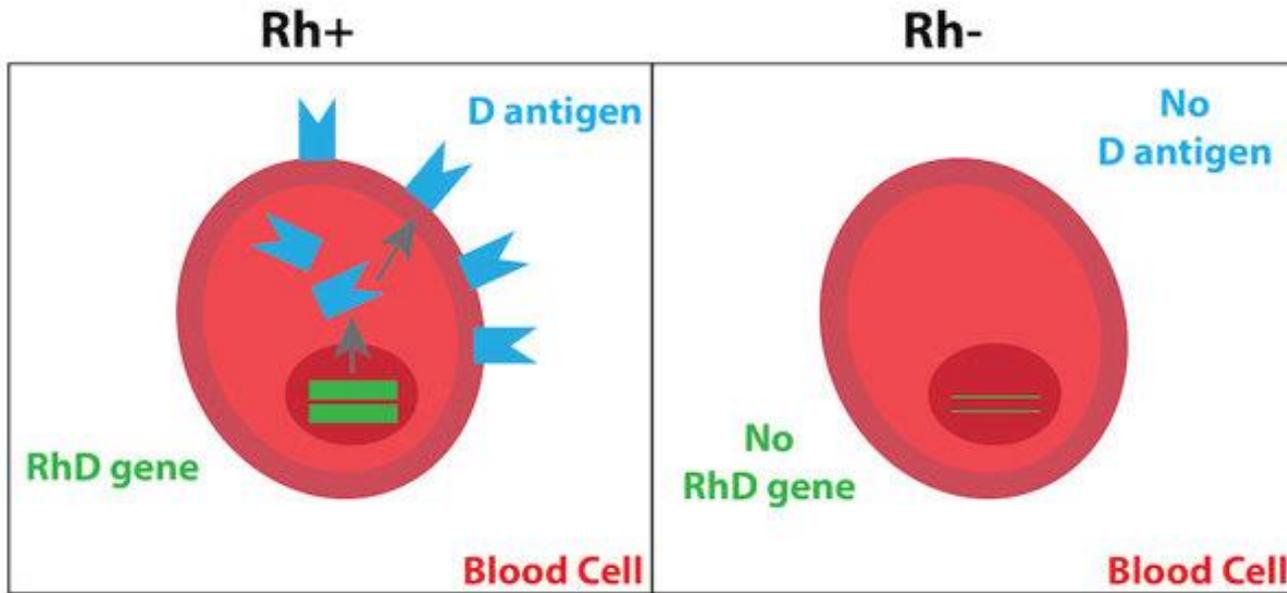
Preterm Labor and Birth

Inflammation



- Granzyme B
- Perforin
- IFN γ
- TNF α
- Activated effector T cell
- Impaired regulatory T cell

Fator Rh



Anemia hemolítica neonatal ou eritroblastose fetal

Rhesus D in pregnancy - haemolytic disease of the newborn



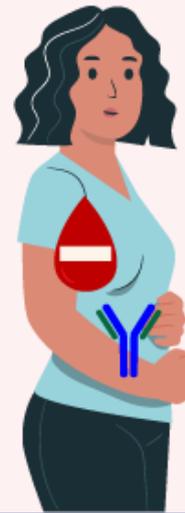
Rh negative mother with a Rh positive baby



During birth (or a sensitising event during pregnancy), the baby's Rh positive blood enters the mother's bloodstream



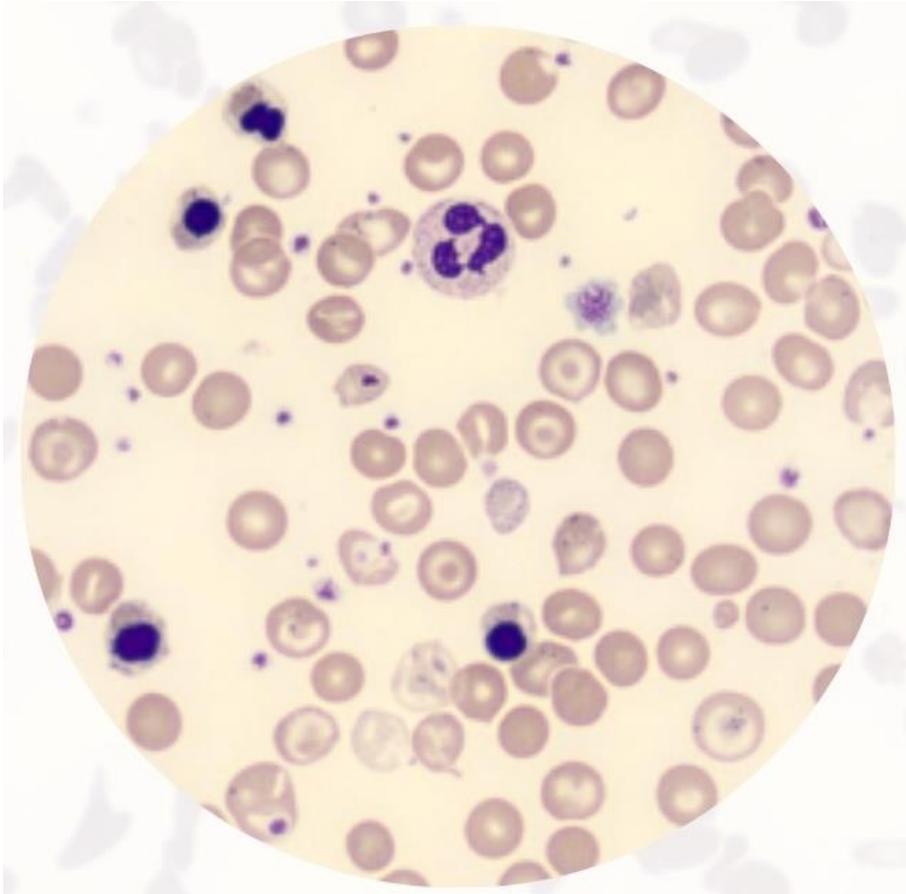
Rh positive blood causes Rh antibodies to be produced



Months later, the Rh antibodies can still be found in the mother's bloodstream



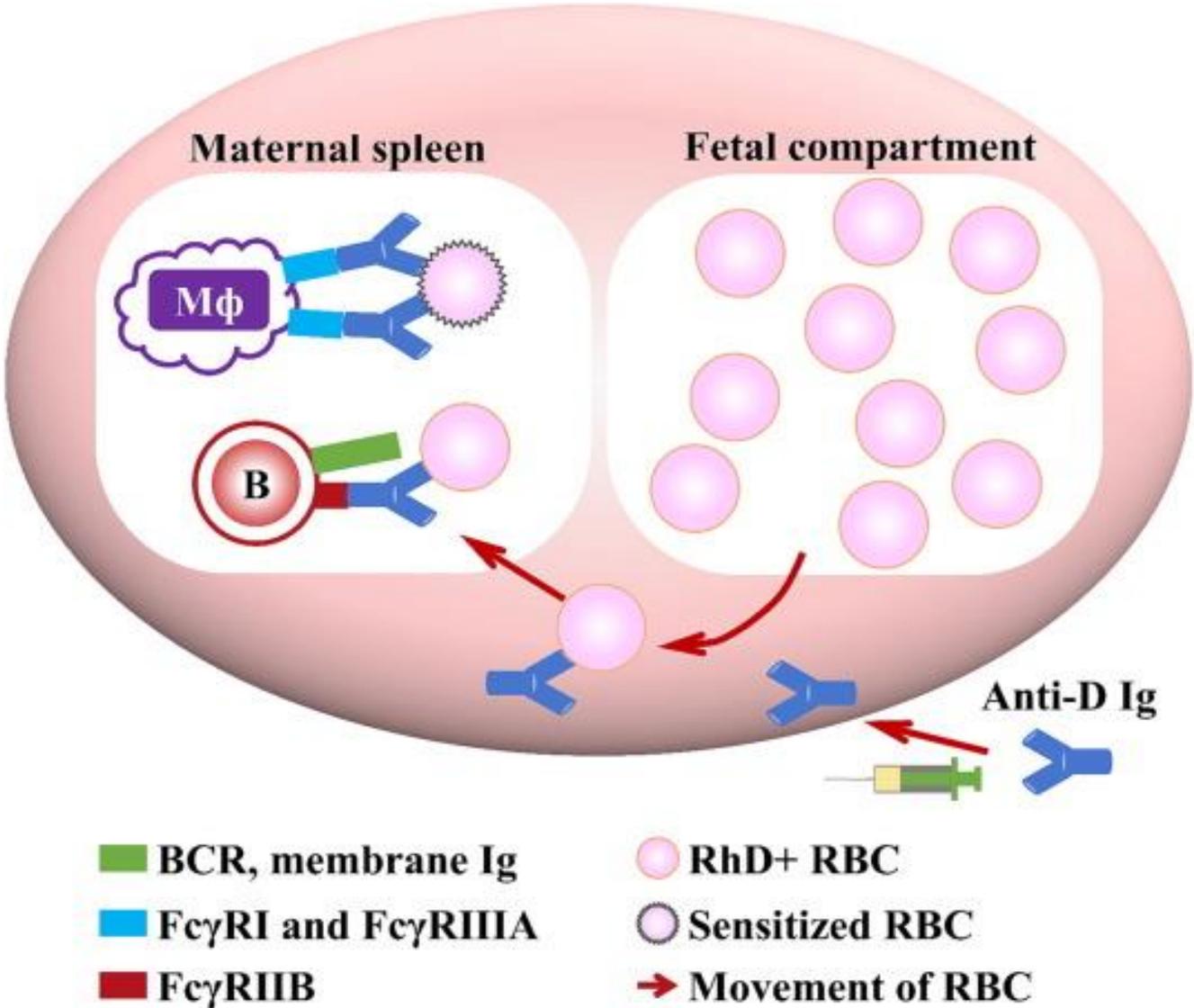
During the mother's next pregnancy, these antibodies will attack the Rh positive baby



Anemia em diferentes graus

Pode ser fatal

RhoGAM – anticorpo contra RhD

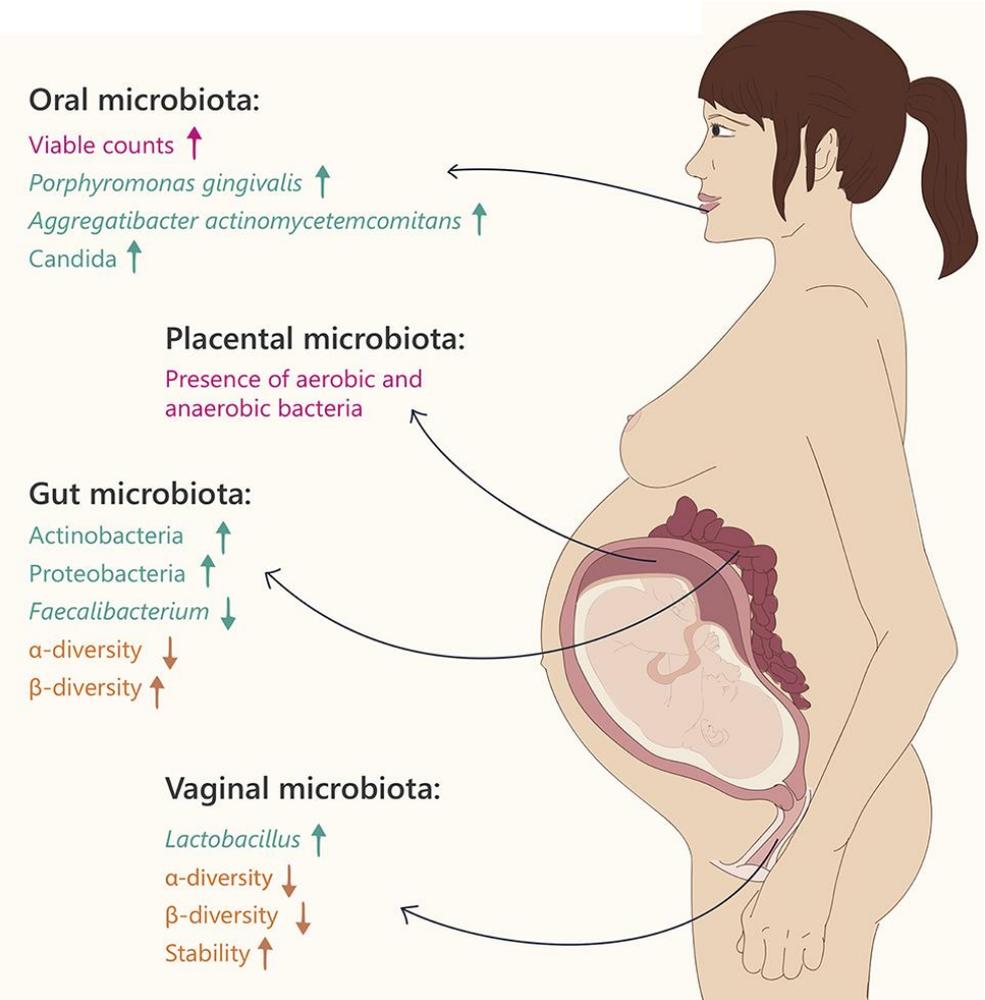


Microbiota e gravidez – a mãe é doadora da microbiota do recém nascido

A microbiota intestinal da mãe é importante no equilíbrio de respostas imunes e inflamatórias - metabólitos

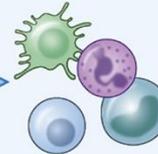
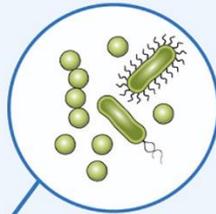
A microbiota genital da mãe contribui para a microbiota intestinal do recém nascido

Cesarianas têm sido associadas com doenças crônicas e autoimunes na criança

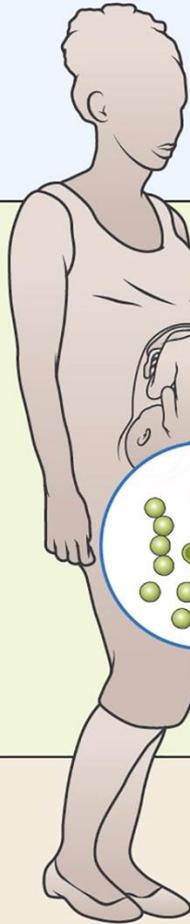


Vaginal delivery

Child
microbiome

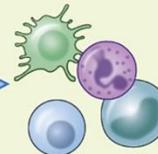
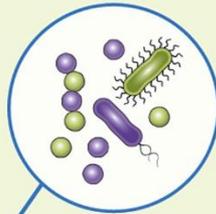


Baseline risk
of immune and
inflammatory
disease



C-section delivery + seeding

Maternal
microbiome

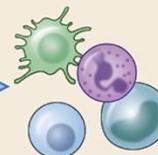
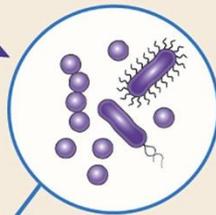


Lower risk of immune
and inflammatory
disease than
C-section delivery



C-section delivery

Environmental
microbes



Higher risk of immune
and inflammatory
disease than
vaginal delivery



Vaginal Delivery



VS.

Cesarean Delivery



Introduced to Vaginal Microbes: Lactobacillus

Introduced to Skin Flora: Staphylococcus

Normal Introduction of Gut Microbes

Abnormal Microbial Introduction

Normal Development of the Immune System
•Production of specific cytokines for proper immune system development

Disrupted Intestinal Microbial Colonization
•Increase risk for Atopic Diseases, Asthma, Allergic Rhinitis, and Celiac Disease
•Association: Delayed Onset of Lactation
•Lack Breast Milk Support for Gut Flora

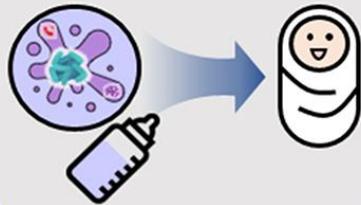
Richardson; 2013

Microbiota transplantation to restore C-section related dysbiosis

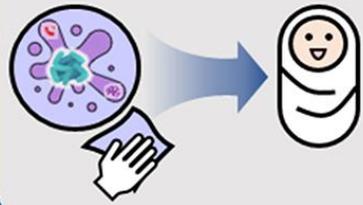
C-section



Ingest maternal vaginal fluids



Swab babies with maternal vaginal fluids



Ingest maternal feces



Infant microbiota restoration ?