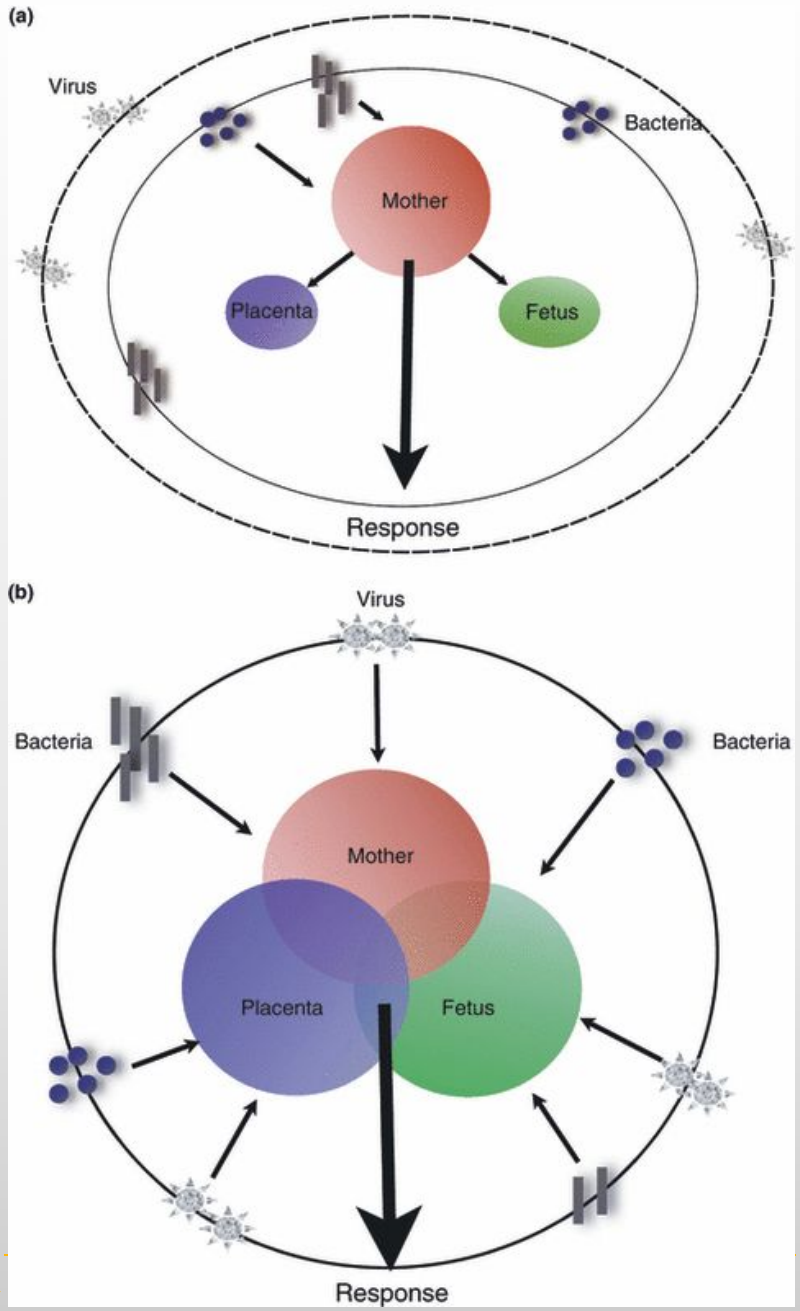
Immunophysiology of reproductive system

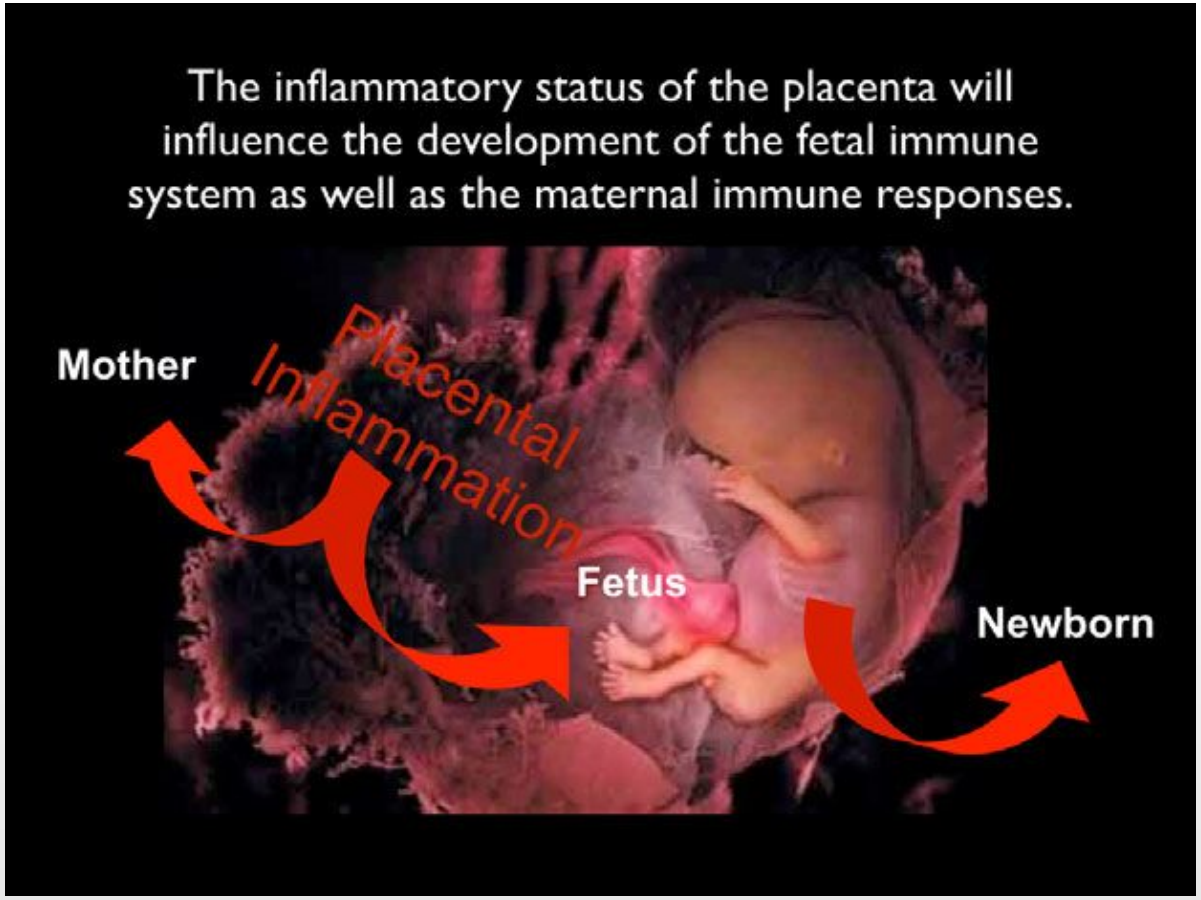
Over 50 years ago, there was the assumption that the **placenta is an allograft expressing paternal proteins** and, therefore, under normal immunological conditions, should be **rejected**. However, as our knowledge of placental biology has significantly increased over the last 50 years, we can appreciate that the **placenta is more than a transplanted organ**. **The placenta is an immune regulatory organ.** The **new integrational model** takes in consideration the fetal–placental immune response and the maternal immune system as integrated. The immunology of pregnancy is the result of the combination of signals and responses originated from the maternal immune system and the fetal–placental immune system. The signals originated in the placenta will modulate the way the maternal immune system will behave in the presence of potential dangerous signals. The immune system of the mother **should not be thought of as suppressed**, but rather modulated and streamlined to focus on pathogen recognition, communication, trafficking and repair. This suggests that the mother's immune system is still able to mount an attack, but only when **absolutely necessary**. Such modulated mechanisms allow the mother to maintain a well-balanced immune system.



Integrational view of the immune system during pregnancy.

a) The old model conceives the maternal immune system as the major player in response to the fetus and microorganisms. Fetal responses (fetus and placenta) are considered limited.

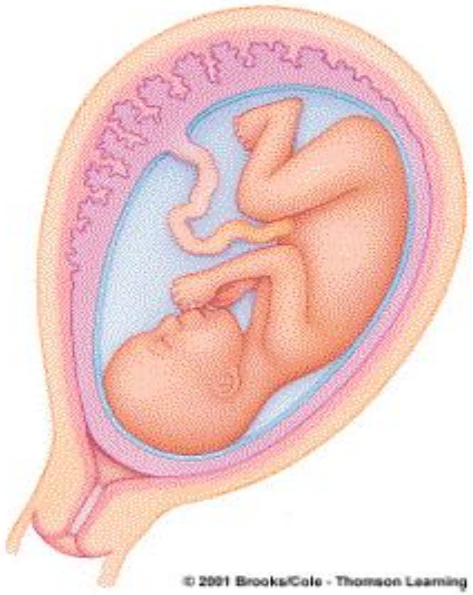
b) b) New integrational model where the fetal–placental immune response and the maternal immune system are integrated.

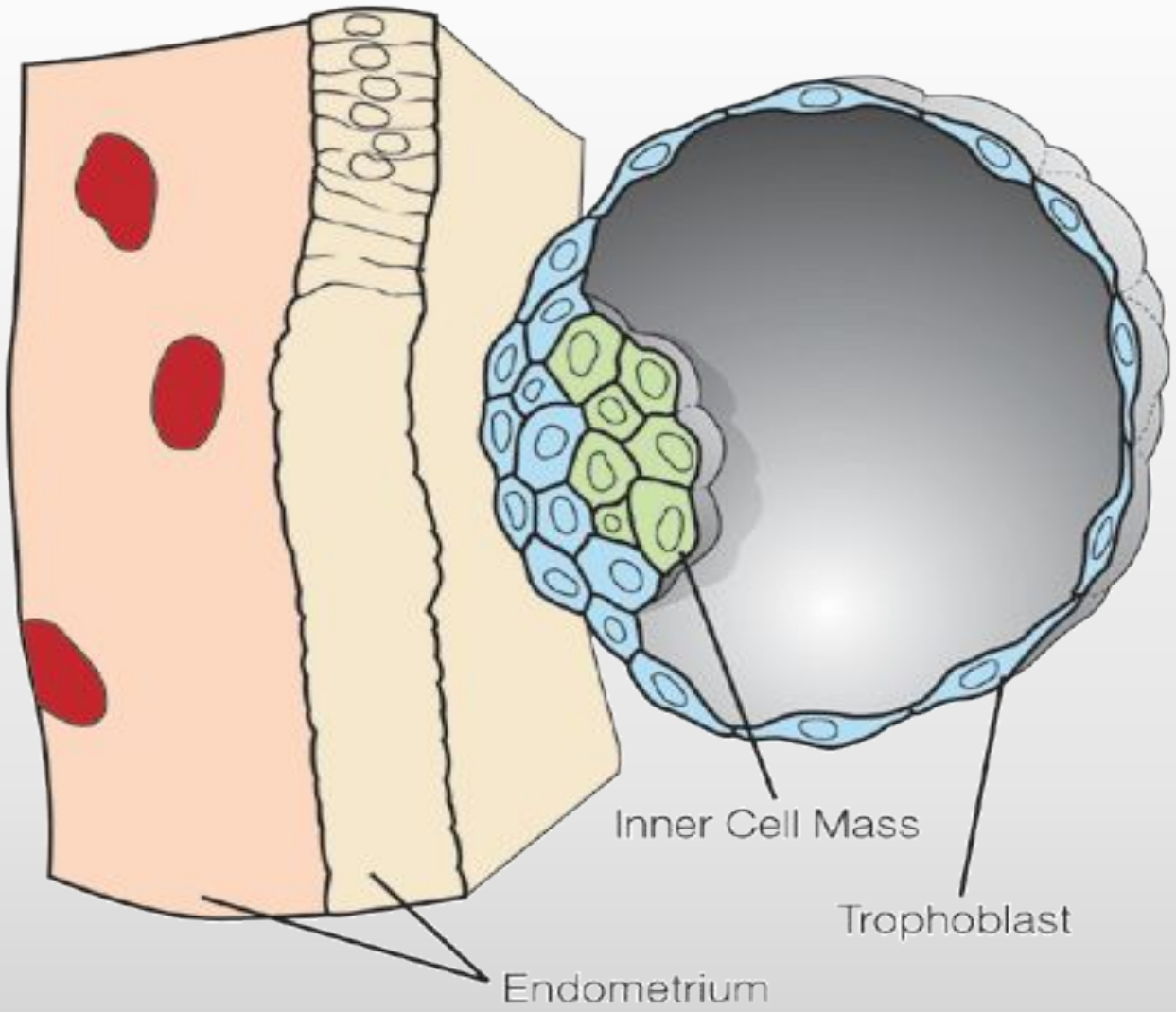


Role of the placenta as a **modulator of fetal and maternal responses**. Inflammation at the placenta has a **bidirectional effect**. Activates the maternal immune system as well as the fetus by creating an inflammatory environment. The inflammatory response may also influence the development of the fetal immune system with important consequences during postnatal age.

The Placenta

- Interlocking fetal and maternal tissues
- Performs digestive, respiratory, and urinary functions for the fetus
- Materials exchanged across membrane that separates bloodstreams




Inner Cell Mass
Trophoblast
Endometrium

Trophoblasts are specialized cells of the placenta that play an important role in embryo implantation and interaction with the ***Decidualised*** maternal uterus. The core of placental villi is surrounded by two layers of trophoblast; a single layer of mononuclear cytotrophoblast that covers the entire surface of the placenta. It is this syncytiotrophoblast that is in **direct contact with the maternal blood that reaches the placental surface**, and thus facilitates the exchange of nutrients, wastes and gases between the maternal and fetal systems.

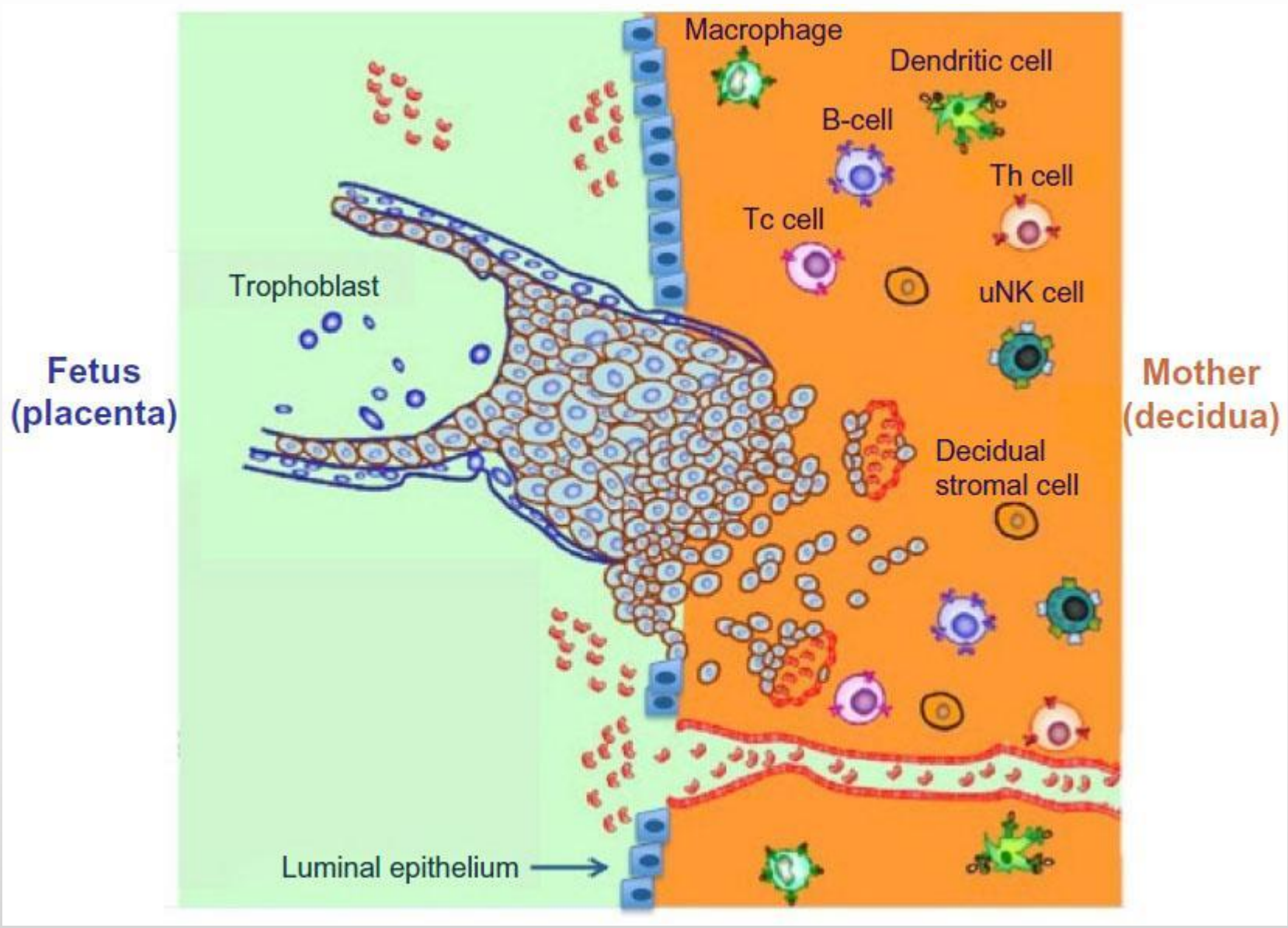
In addition, cytotrophoblast can differentiate into another type of trophoblast called the **extravillous trophoblast** and penetrate into the decidualised uterus. This process is essential not only for physically attaching the placenta to the mother, but also for altering the vasculature in the uterus to allow it to provide an adequate blood supply to the growing fetus as pregnancy progresses. Some of these trophoblast even replace the endothelial cells in the uterine spiral arteries as they remodel these vessels into wide bore conduits that are independent of maternal vasoconstriction. This ensures the fetus receives **a steady supply** of blood, and the placenta is not subjected to fluctuations in oxygen that could cause it damage.

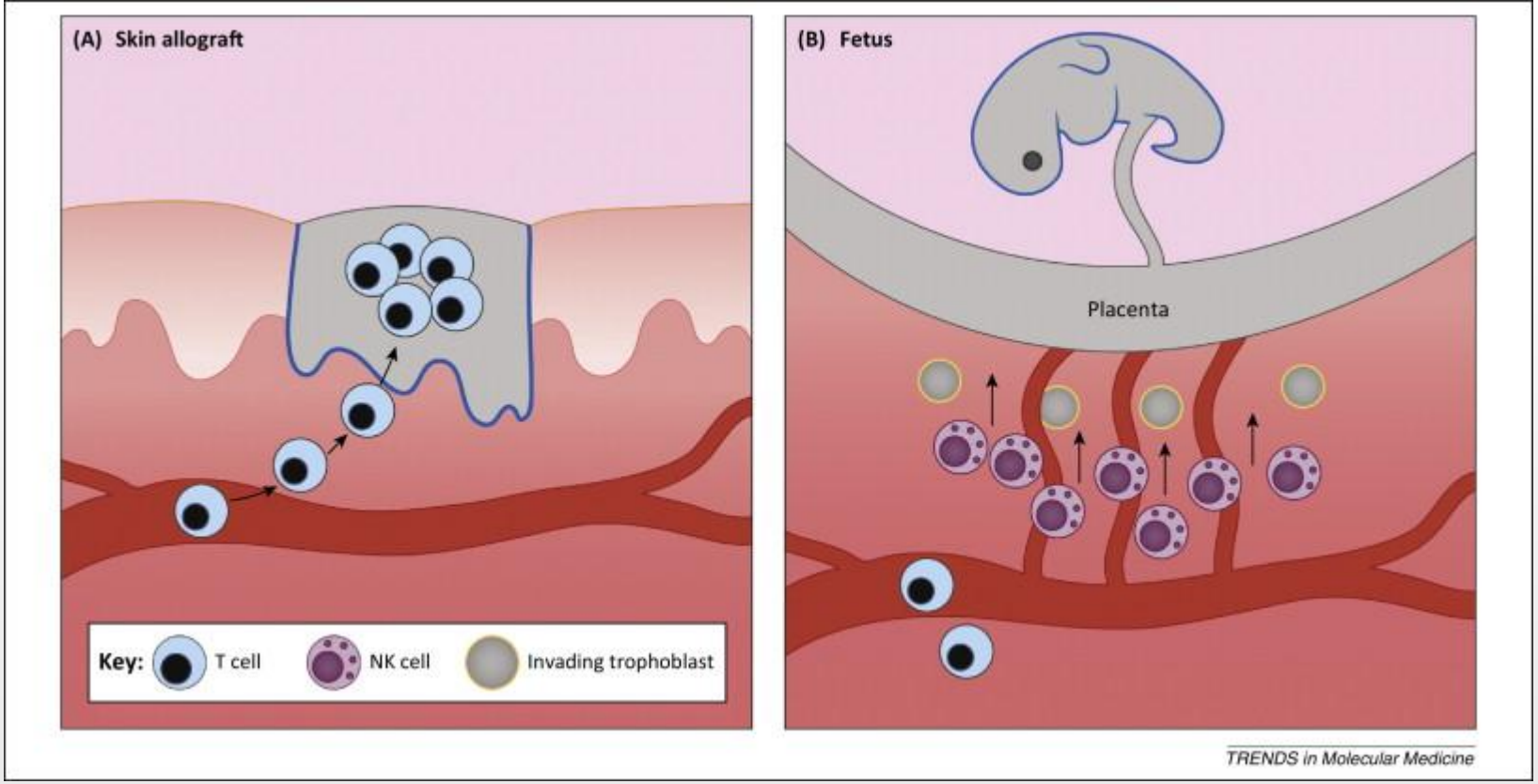
Decidualization *is a process that results in significant changes to cells of the endometrium in preparation for, and during, pregnancy.*

During normal pregnancy, the human decidua contains a high number of immune cells, such as macrophages, natural killer (NK) cells and regulatory T cells (Treg). **70% of decidual leukocytes are NK cells, 20–25% are macrophages and 1.7% are dendritic cells.** From the adaptive immune system, B cells are absent, but T lymphocytes constitute about 3–10% of the decidual immune cells. **During the first trimester, NK cells, dendritic cells and macrophages infiltrate the decidua and accumulate around the invading trophoblast cells.** Deletion of either macrophages, NK cells or dendritic cells (DC) has deleterious effects**.** Elegant studies have shown that **in the absence of NK cells, trophoblast cells are not able to reach the endometrial vascularity leading to termination of the pregnancy. These studies suggest that uNK cells are critical for trophoblast invasion in the uterus. Similarly, depletion of DCs prevented blastocyst implantation and decidual formation. Indeed, this study suggests that uDC are necessary for decidual formation and may affect the angiogenic response by inhibiting blood vessel maturation.**

These data further support the idea that the fetal–maternal immune interaction is more complex than the comparison to *transplant allograft*.

Consequently, the presence of immune cells at the implantation site is not associated with a response to the '**foreign'** fetus but to **facilitate and protect the pregnancy**. Therefore, the immune system at the implantation site is not suppressed, on the contrary it is active, functional and is carefully controlled.


Macrophage
Dendritic cell
B-cell
Th cell
Tc cell
uNK cell
Trophoblast
Fetus
(placenta)
Mother
(decidua)
Decidual
stromal cell
Luminal epithelium



Comparison and contrast between a cellular response to a skin allograft and to a semi-allogeneic fetus and its placenta. (A) **Transplanted skin cells express allogeneic HLA-A and HLA-B molecules** (blue border). A large fraction of CTLs (cytotoxic T cells) are activated by allogeneic MHC class I molecules through the direct allorecognition pathway and extravasate into the tissue, where they destroy the allograft. (B) The invading trophoblast cells **do not express HLA-A and HLA-B molecules**, but instead express HLA-C molecules which interact with KIRs on maternal NK cells in the placental bed of the uterus. Here the interactions between KIRs and fetal HLA-C regulate **vascular remodeling of the uterus**, allocation of nutrients to the feto-placental unit and fetal growth. *The potentially destructive CTLs rarely extravasate, and few allogeneic HLA-C-restricted CTLs are found in the uterus*.

The interaction between the trophoblast HLA molecules and the KIR receptors of the uNK cells of the maternal endometrium **inhibits cytotoxic activity** and modulates cytokine production and growth factors by uNK cells to favor trophoblast growth, endometriuminvasion, and vascular remodeling.

Unlike CTLs, however, and unlike conventional NK cells, uNK (uterine NK cells) cells are not good killers and do not destroy the bearer of allogeneic MHC molecules (the trophoblast) but respond by producing soluble factors that promote placentation. NK receptors are expressed by uNK cells and may also regulate interactions with trophoblasts as well with other uterine leukocytes and stromal cells. uNK cells are a unique subset that populates the uterine mucosa and which, **contrary to their blood counterparts** whose evocative name they share, keep their killer instinct under control and instead help the growing placenta and fetus. uNK cells, by producing growth factors, chemokines, and cytokines , contribute to regulating trophoblast invasion and vascular remodeling in the uterus, a vital process for the placenta to sustain fetal growth.

Cytokines produced by uNK cells at the human fetal-maternal interface include interleukin (IL) 8, interferon-inducible-protein-10 (IP-10), and the most synthesized cytokine by uNK, regulated upon activation normal T-cell expressed and secreted (RANTES), triggers the migration of the invasive trophoblast. Angiogenic factors of uNK include vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), as well as the most abundant, NKG5.

In normal pregnancies, recognition of fetal HLA-C by receptor KIR-BB of uNK triggers the release of TGF-β s by uNK cells. TGF-β - transforming growth factor beta, whose participation in immunoregulation and angiogenesis has been well-established.

Accumulating evidence suggests that tight interactions between placental trophoblasts and Decidual NK dNK cells are critical for trophoblast cell differentiation

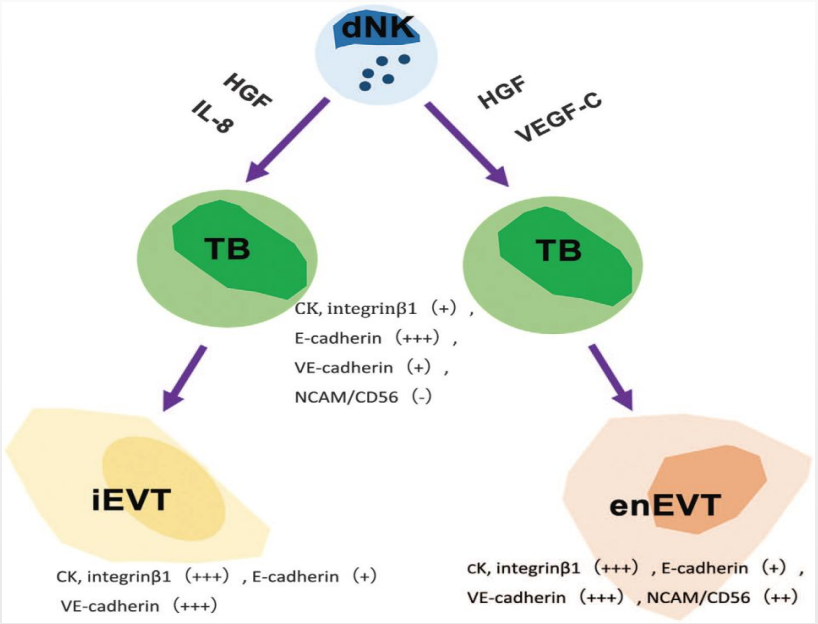


Figure 6. Schematic illustration of the mechanism by which dNK cells promote trophoblastic cells differentiation. The dNK cells can promote trophoblast cells differentiation toward iEVTs through producing IL-8 and HGF, whereas enhance the differentiation of trophoblast cells toward enEVTs by producing VEGF-C and HGF.

Abbrev.: interstitial extravillous trophoblasts (iEVTs), endovascular extravillous trophoblasts (enEVTs)

During gestation, uNK (uterine NK cells) are in intimate contact with placental cells and mediate trophic functions through their involvement in arterial remodeling. They take part in the allocation of nutrients from the mother to the fetoplacental unit. This is thought to be mediated by influencing the depth of trophoblast invasion through cytokines and chemokines, thereby regulating how deeply the fetoplacental unit can tap into the maternal blood supply, but also through the production of angiogenic factors that directly act on vessels.

Mechanisms by which immune cells (focus: uNK cells) regulate key early events in establishment of pregnancy: implantation, angiogenesis, and vascular remodeling.

DCs and macrophages, present in the human endometrium, play a role in decidualization and implantation. After uNK, macrophages are the second most abundant population in the maternofetal interphase in both implantation and early pregnancy development. **Macrophages** congregate around spiral arteries, while the placenta develops and supports vascular remodeling by releasing proangiogenic factors, such as VEGF and MMPs and by removing apoptotic cells. The polarization of decidual macrophages toward M2, found in **normal pregnancie**s, indicates that their immunosuppressive activities are critical for maintaining immunological homeostasis during pregnancy. **Uterine DCs** play a key role in embryo implantation, when they show an immature phenotype. Immature DC's have been associated with the initiation and maintenance of peripheral tolerance and their presence in large numbers in the uterine decidua has been associated with the establishment of healthy pregnancies in women.

Tregs are essential for pregnancy maintenance, and low levels have been found in pregnancy complications. Thus not only women with unexplained recurrent spontaneous abortions, but also patients with preeclampsia display low levels of Tregs in both maternal blood and placenta. The prevalence of Th17 cells and the Th17/Treg ratio increases in peripheral blood in preeclampsia as compared with normal pregnancy.

***Pre-eclampsia** (**PE**) is a **disorder** of pregnancy characterized by the onset of high blood pressure and often a significant amount of protein in urine.*