Reproductive immunology: immunology of pregnancy

Fiona M. Menzies, University of the West of Scotland, UK

A unique problem

Pregnancy presents a complex immunological problem for the mother. Cells and molecules of the maternal immune system interact in such a way as to prevent the rejection of the semiallogenic fetus and support its growth and development. In 1953 Sir Peter Medawar, a pioneer in the field of transplantation biology, presented a lecture in which he asked the following question:

"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 fetus that is an antigenically foreign body?"

To this day, this question remains relevant and, as yet, incompletely answered and is the foundation of the field of **reproductive immunology**. Understanding how the maternal immune system responds to pregnancy is critical for our ability to better diagnose, understand, and treat various pregnancy complications.

Immune cells at the maternal-fetal interface

The placenta is essentially the maternal-fetal interface (Figure 1), serving as an anatomical barrier between baby and mother (with separate circulatory systems). Despite this, the placenta is abundant with immune cells and mediators, including **Uterine Natural Killer cells** (70%), **macrophages** (20%), **T cells** (including CD4+, CD8+, γδ T cells, regulatory T cells) (10%), **dendritic cells** and **B cells** (few). The numbers of these cells and roles that they play differs throughout the various stages of pregnancy.

Protection of the conceptus

Several local and systemic modifications are now suggested to be involved in protection of the developing fetus from attack by the maternal immune system, mainly:

- **Cytokine shift**
  Successful pregnancy is associated with a dominance of Th2-type immunity, and induction of Th1-type responses considered potentially dangerous for the continuation of pregnancy. This paradigm has been expanded to consider Tregs and Th17 cells, with Tregs playing pregnancy-protective roles and Th17 responses being detrimental to pregnancy.
- **Influence of female sex hormones**
  Estrogen and progesterone levels are massively upregulated during pregnancy, and both hormones have been shown to have immunomodulatory functions, impacting immune cell recruitment, expansion and function.
- **Unique HLA expression by trophoblasts**
  Trophoblasts are the main cell type of the placenta, and exhibit unique Major Histocompatibility Complex (MHC) expression compared to mother and baby. MHC class II molecules are not expressed by trophoblasts. HLA-C, E, F, and G (of the MHC class I type) are expressed by trophoblasts and have functions including control of depth of trophoblast invasion and binding to inhibitory NK cell receptors.

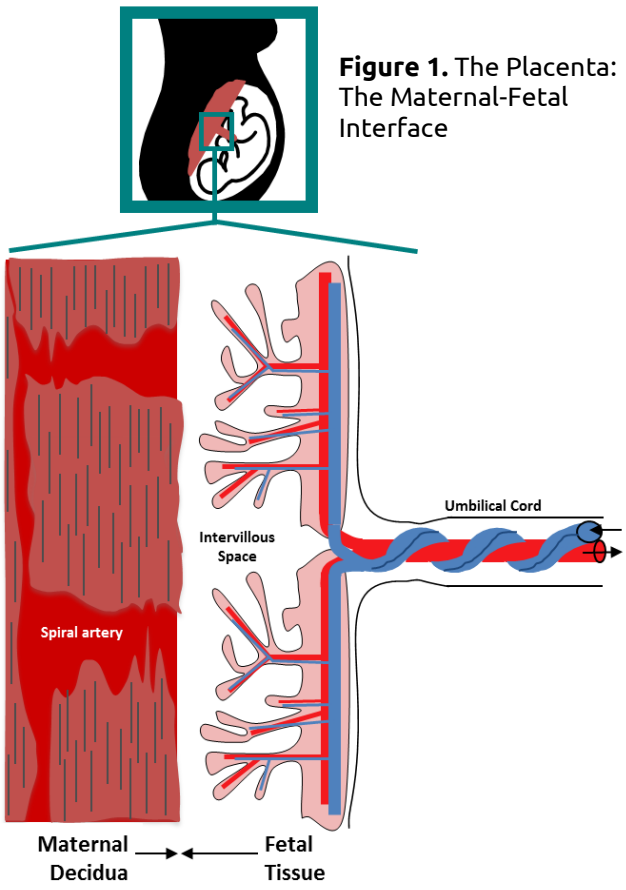

Figure 1. The Placenta: The Maternal-Fetal Interface