

CHAPTER 13

MATERNAL IMMUNE RECOGNITION OF PREGNANCY

Mefkure E. SAHIN, I. Ipek MUDERRIS

Why does not the endometrium reject the fetus?

After performing skin transplants to treat skin burns during World War II, Peter Medawar published a paper in 1953 that explained how skin-graft rejection was an immunological phenomenon (1,2). Since this information was published, the question arose in the field of reproductive immunology of why a fetus is not also rejected as an immunological response. One possible explanation for not rejecting the fetus is that the maternal immune system does not recognize the concealed or masked fetal antigens. Anti-placental and anti-paternal antibodies have been observed in the sera of women who have previously given birth, but this has not proved that maternal immune system not harm the fetus (3).

Where does fetal- maternal interaction occur?

The fetal blastocyst comprises an outer layer (trophectoderm), an inner cell mass (the embryo blast), and a fluid-filled cavity called the blastocoels. All true embryonic stem cells arise from the embryo blast, and these are then capable of forming all cell types within the embryo. The trophectoderm layer develops into the villous placenta, and the extravillous trophoblast cells (EVT) subsequently invade the uterus to form a connection with the maternal blood supply and remains in contact with that blood supply throughout the pregnancy. A “syncytium” is a multinucleated cell formed from several cell fusions and that often forms “syncytial knots” that can travel through the circulation system and to the lung capillaries, where they remain. This arrangement, which includes the placental trophoblast barriers, serves to completely separate the fetal somatic cells from the mother’s immune system (4).

Which immune cells will be active during early implantation?

It is possible for fetal cells may invade the mother’s circulation system. Early in the first-known transplantation procedures, physicians observed that multiparous women had antibodies to allogenic leukocytes (allo-antibodies), which are specific to paternal human leukocyte antigens (HLAs). Women with anti-D antibodies can produce antibodies against fetal allo-antigens, which would not immunosuppressive the fetus (5).

References

1. Medawar P. Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates. *Symp Soc Exp Biol* 1953;7:320–38.)
2. Colucci F, Moffett A, Trowsdale J. Medawar and the immunological paradox of pregnancy: 60 years on. *Eur J Immunol* 2014;44:1883–5.
3. Billington WD: Transfer of antigens and antibodies between mother and fetus; in Coulam CB, Faulk WP, McIntyre J (eds): *Immunological Obstetrics*. New York, Norton, 1992, pp 290–304.
4. Moffett-King A. Natural killer cells and pregnancy. *Nat Rev Immunol* 2002;2: 656–63.
5. Howard H, Martlew V, McFadyen I, Clarke C, Duguid J, Bromilow I, et al. Consequences for fetus and neonate of maternal red cell allo-immunisation. *Arch Dis Child Fetal Neonatal Ed* 1998;78:F62–6.
6. Moffett, A., Chazara, O., & Colucci, F. (2017). Maternal allo-recognition of the fetus. *Fertility and sterility*, 107(6), 1269-1272
7. Moffett A, Colucci F. Uterine NK cells: active regulators at the maternal-fetal interface. *J Clin Invest* 2014;124:1872–9.
8. Tilburgs T, Roelen DL, van der Mast BJ, de Groot-Swings GM, Kleijburg C, Scherjon SA, et al. Evidence for a selective migration of fetus-specific CD4⁺CD25^{bright} regulatory T cells from the peripheral blood to the decidua in human pregnancy. *J Immunol* 2008;180:5737–45.
9. Ljunggren HG, Karre K. In search of the missing self: MHC molecules and NK cell recognition. *ImmunolToday* 1990;11:237–44.
10. King A, Loke YW. On the nature and function of human uterine granular lymphocytes. *Immunol Today* 1991;12:432–5.
11. Moffett A, Shreeve N. First do no harm: uterine natural killer (NK) cells in assisted reproduction. *Hum Reprod* 2015;30:1519–25
12. Trundley A, Moffett A. Human uterine leukocytes and pregnancy. *Tissue Antigens* 2004;63:1–12.
13. Nakimuli A, Chazara O, Hiby SE, Farrell L, Tukwasibwe S, Jayaraman J, et al. A KIR B centromeric region present in Africans but not Europeans protects pregnant women from pre-eclampsia. *Proc Natl Acad Sci U S A* 2015;112:845–50.
14. Hiby SE, Apps R, Sharkey AM, Farrell LE, Gardner L, Mulder A, et al. Maternal activating KIRs protect against human reproductive failure mediated by fetal HLA-C2. *J Clin Invest* 2010;120:4102–10.
15. Szekeres-Bartho J, Barakonyi A, Polgar B, et al: The role of g/d T cells in progesterone-mediated immunomodulation during pregnancy: a review. *Am J Reprod Immunol* 1999; 42: 44–48.
16. Szekeres-Bartho J, Szekeres GY, Debre P, et al: Reactivity of lymphocytes to a progesterone receptor-specific monoclonal antibody. *Cell Immunol* 1990; 125: 273–283.
17. Szekeres-Bartho J, Kilar F, Falkay G, et al: Progesterone- treated lymphocytes of healthy pregnant women release a factor inhibiting cytotoxicity and prostaglandin synthesis. *Am J Reprod Immunol Microbiol* 1985; 9: 15–18.
18. Kim K, Lee K, Rhee K: CEP90 is required for the assembly and centrosomal accumulation of centriolar satellites, which is essential for primary cilia formation. *PLoS One* 2012; 7: e48196.
19. Chaouat G, Menu E, Clark DA, et al: Control of fetal survival in CBA x DBA/2 mice by lymphokine therapy. *J Reprod Fertil* 1990; 89: 447–458.
20. Raghupathy R, Al Mutawa E, Makhseed M, et al: Modulation of cytokine production by hydrocortisone in lymphocytes from women with recurrent abortion. *Br J Obstet Gynaecol* 2005; 112: 1096–1101.
21. Raghupathy R, Al Mutawa E, Al-Azemi M, et al: The progesterone-induced blocking factor (PIBF) modulates cytokine production by lymphocytes from women with recurrent miscarriage and with preterm delivery. *J Reprod Immunol* 2009; 80: 91–99.

22. Koopman LA, Kocow HD, Rybalov B, et al: Human decidual natural killer cells are a unique NK cell subset with immunomodulatory potential. *J Exp Med* 2003; 198: 1201–1212.
23. Redhead ML, Portilho NA, Felker AM, et al: The transcription factor NFIL3 is essential for normal placental and embryonic development but not for uterine natural killer (UNK) cell differentiation in mice. *Biol Reprod* 2016; 94: 101.
24. Polgar B, Nagy E, Miko E, et al: Urinary progesterone- induced blocking factor concentration is related to pregnancy outcome. *Biol Reprod* 2004; 71: 1699–1705.