Immunology and Pregnancy

Colette Kanellopoulos-Langevin
University of Paris Diderot, Paris, France

Since the publication of the seminal article by P. Medawar entitled "Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates",[1] many biologists and clinicians have addressed the paradox of how the maternal immune system maintains tolerance to the semi-allogeneic fetus bearing paternal antigens that are foreign to the mother. After more than 60 years of fundamental and clinical research efforts, much progress has been made in the comprehension of multiple cellular and molecular mechanisms allowing the mammalian fetus to develop safely within the maternal womb. However, the puzzle is still incomplete, information on mechanisms involved require more experiments on animal models, primarily rodents. The production of new therapies for the pathologies of pregnancy remains a challenge for the future.

This special edition of Biomedical Journal entitled "Immunology and Pregnancy" includes four review articles by experts in the field, dealing with different aspects of this fascinating question.

The first review article is written by Dr. D. Vaiman (Paris, France) and is entitled "Genetic Regulation of Recurrent Spontaneous Abortion in Humans".[2] The second review article is written by Drs. S. Tripathi and I. Guleria (Boston, USA) and is entitled "Role of programmed death 1 (PD1)/ programmed death 1 ligand (PDL1) Pathway, and T helper type 17 (Th17) and Treg Cells in Maternal Tolerance to the Fetus".[3] The third review article is from Dr. P. Le Bouteiller (Toulouse, France) and is entitled "HLA-G in Human Early Pregnancy: Control of Uterine Immune Cell Activation and Likely Vascular Remodeling".[4] The fourth review article was contributed by Drs. W. Bracamonte–Baran and W. Burlingham (Madison, USA) and is entitled "Noninherited Maternal Antigens (NIMA), Pregnancy, and Allotolerance".[5]

Dr. Vaiman provides a well-documented, detailed analysis of the major genetic pathways leading to recurrent spontaneous abortions in humans. Numerous potential candidate genes, from the maternal or feto-placental side, are putatively involved in recurrent pregnancy loss. Some genes affect uterine structure or function, embryo ploidy, chromosome structure, immunological dialog between embryo/fetus and mother, maternal autoimmunity, thrombophilia, complement system and its regulation. Animal models are used to decipher the mechanisms at work in the genetic basis of recurrent abortions.

Such an example is provided by Dr. Guleria's studies on mechanisms of the maternal tolerance to the fetus in mouse models, both systemically and at the fetal maternal interface. Their studies have shown that the success of pregnancy results from a finely tuned balance between protective regulatory T (Treg) cells, negative regulators of the maternal immune response and inflammatory Th17. In addition, both Tregs and Th17 cells are regulated by the interaction between costimulatory molecule PD1 and its ligand PDL, a negative costimulatory pathway on T-cells. Thus, maternal tolerance to the fetus is controlled, at least in part, by the cross-talk between the PDL1, Th17, and Tregs.

Dr. Le Bouteiller's studies are focused on HLA-G molecules and their role in the tolerance to the fetus in early human pregnancy. HLA-G-receptor specific interactions on maternal immune cells contribute to limit potentially harmful maternal immune responses by inhibition of decidual NK cell cytotoxicity, T-cell and B-cell proliferation and induction of apoptosis of activated $CD8^+$ T-cells. These HLA-G specific interactions also stimulate placental development through secretion of angiogenic factors by decidual NK cells and macrophages. Thus, HLA-G controls local maternal

DOI: 10.4103/2319-4170.151151

immune response at the maternal-fetal interface and contributes to vascular uterine remodeling in early pregnancy.

Non inherited antigens are parental polymorphic protein epitopes not genetically inherited by the offspring. There are NIMA and noninherited paternal antigens. During a normal pregnancy, the maternal immune system tolerates the inherited paternal antigens expressed by the fetus, and the developing fetal immune system tolerates NIMA. Many studies in mice and humans support the hypothesis that the passage of maternal cells into the fetus and of fetal cells into the mother during fetal and neonatal life (lactation) contributes to a state of stable microchimerism which can result in lifelong tolerance to NIMA. Dr. Burlingham and associates have studied the « NIMA effect » both in humans and experimental mouse models, and have started to decipher the mechanisms involved, particularly the induction of regulatory T-cells. They have proposed a model linking microchimerism and NIMA effect. This has important implications for the physiopathology of pregnancy and the success of allotransplantation.

REFERENCES

1. Medawar PB. Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates. Symp Soc Exp Biol 1953;44:320-38.
2. Vaiman D. Genetic regulation of recurrent spontaneous abortion in humans. Biomed J 2015;38:11-24.
3. Tripathi S, Guleria I. Role of PD1/PDL1 pathway, and Th17 and Treg cells in maternal tolerance to the fetus. Biomed J 2015;38: 25-31.
4. Le Bouteiller P. HLA-G in human early pregnancy: Control of uterine immune cell activation and likely vascular remodeling. Biomed J 2015;38:32-8.
5. Bracamonte-Baran W, Burlingham W. Non-inherited maternal antigens, pregnancy, and allotolerance. Biomed J 2015;38:39-51.