International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Immunology in Pregnancy: The Mechanism behind Immune Tolerance

Choudhary V., Singh N., Deshwal V.

Abstract: ***The immune system in humans is a complex system which is capable of discriminating the selfantigen from the non - selfantigens and thereby mounting an appropriate allogenic immune response against the foreign antigens. Pregnancy is not an immunodeficient state. Whereas a successful organ transplant requires constant immunosuppression, a successful pregnancy requires a robust, dynamic and responsive immune system. Women are able to respond to both humoral and cell mediated immunity against the paternal antigen. During pregnancy, the maternal immune response is shifted from Th1 (cell mediated immunity) to Th2 (humoral immunity) response. This change in immune response is known as immunomodulation. Interferon - β is a crucial immune modulator during pregnancy; it protects the fetus against viral infections and contributes to the process of immune regulation at the maternal–fetal interface. During pregnancy, the development of a fetal immunological system also occurs with intricate interaction between the maternal and fetal interface.***

Keywords: Immunology, Immunomodulation , T helper cells

1. Introduction

It is a question of great interest to the immunologist that why a fetus which has received half of its histocompatibility antigens from father is not rejected? Successful pregnancy is itself an immunological paradox. Fetus is one such tissue which is repeatedly grafted and repeatedly tolerated. Pregnancy is associated with suppression of various humoral and cell mediated immunological functions. This allows the accommodation of the foreign semi allogenic fetal graft that contains antigens of both the maternal and the paternal origin. This tolerance is unique involving a complex interaction of maternal microbiome, uterine decidua and the trophoblasts.[1]

One of the immunological adaptation is expression of the major histocompatibility complex molecules on the surface of trophoblasts. All the cells of the body express the MHC class Ia. It is uncommon for two unrelated individuals to share compatible MHC class Ia. Hence the trophoblast cells express a form of MHC that does not vary in between individuals i. e. HLA class Ib (non classic form of HLA) – known as HLA - E, HLA - F, and HLA - G. The Natural killer cells residing in the decidua fails to recognize these non classic form of HLAand this indeed promotes uterine quiescence.2

The second immune adaptation in pregnancy is a shift of immune response from Th1 to Th2. This leads to suppression of secretion of interleukin 2 (IL - 2), Interferon - a, tumor necrosis factor (TNF). This leads to upregulation of secretion of IL - 4, IL - 10, and IL - 13.

Specific type of CD4 T cells serve as a mucosal and barrier immunity. These cells are known as Th - 17 cells and T - reg cells. Th - 17 cells are proinflammatory and express cytokine IL - 17. The T - reg cells express the transcription factor forkhead box protein - 3 (FOXP3) and confer the tolerizing property. There is a shift towards T - reg cells in the first trimester, which peaks during second trimester and falls towards delivery.

Another mechanism which plays role in immunology in pregnancy is the hormonal influence. Hormones can affect the differentiation of Th cells. Serum estradiol levels increase up to 500 - fold during pregnancy. Low estradiol promotes Th1 responses, whereas high estradiol promotes Th2 responses. Elevated progesterone inhibits Th1 responses during pregnancyand can induce Th2 - type cytokines (e. g., IL - 4 and IL - 5) further enhancing the polarization to Th2. Moreover, progesterone may exert anti - inflammatory responses as supported by higher IL - 10 levels in women who received progesterone compared to placebo.[3, 4, 5]

Placenta also has an important role to play in the immunology of pregnancy. The placenta, through cytokines and hormones secreted by trophoblast cells, educate uterine maternal immune cells and determines the immunological environment at the maternal/ fetal interface, as well as at the maternal systemic immune system. The transition from pro to anti - inflammatory status is essential for the success of pregnancy, and it is the result of the communication between the placenta and the maternal immune cells. Embryo - derived hCG is one of the first immune modulatory factors that change the phenotype of the signals present at the uterus.[6, 7, 8, 9]

2. Conclusion

The changes indicate highly dynamic co - operative interactions between the maternal and fetal immune system, rather than a broad maternal immune suppression. The uNK cells have a NK cell - like function, but they are specific for the uterus as they show a different phenotype compared with peripheral NK cells. These receptors bind to the MHC Ia and b (HLA - C, HLA - E and HLA - G) on trophoblast (see also section `MHC Ib expression by trophoblast'), by binding to these MHC I antigens, the inhibitory receptors inhibit the lytic activity of the uNK cells. Type 2 cytokines in general stimulate trophoblast outgrowth and invasion. The importance of this relative dominance of type 2 cytokines over type 1 cytokines may be stressed by the fact that pregnancy loss is associated with less type 2 cytokine production as compared with normal pregnancies. This

immunomodulation explains the remission of autoimmune disorders such as rheumatoid arthritis, multiple sclerosis in pregnancy (cell mediated immune diseases) and meanwhile flaring up of autoimmune diseases such as systemic lupus erythematosus which are regulated by autoantibodies.

References

[1] Aarli, A., Kristoffersen, E. K., Jensen, T. S., Ulvestad, E. and Matre, R. (1997) Suppressive effect on lymphoproliferation in vitro by soluble annexin II released from isolated placental membranes. Am. J. Reprod. Immunol., 38, 313±319.
[2] Clark, D. A., Yu, G., Levy, G. A. and Gorczynski, R. M. (2001) Procoagulants in fetus rejection: the role of the OX - 2 (CD200) tolerance signal. Semin. Immunol., 13, 255±263.
[3] Pazos M, Sperling RS, Moran TM, Kraus TA. The influence of pregnancy on systemic immunity. *Immunol Res* (2012) 54: 254–61. doi: 10.1007/s12026 - 012 - 8303 - 9
[4] Piccinni MP, Giudizi MG, Biagiotti R, Beloni L, Giannarini L, Sampognaro S, et al. Progesterone favors the development of human T helper cells producing Th2 - type cytokines and promotes both IL - 4 production and membrane CD30 expression in established Th1 cell clones. *J Immunol* (1995) 155: 128–33.
[5] Piccinni MP, Scaletti C, Maggi E, Romagnani S. Role of hormone - controlled Th1 - and Th2 - type cytokines in successful pregnancy. *J Neuroimmunol* (2000) 109: 30–3. doi: 10.1016/S0165 - 5728 (00) 00299 - X
[6] Kaislasuo J, Simpson S, Petersen JF, et al. IL - 10 to TNFalpha ratios throughout early first trimester can discriminate healthy pregnancies from pregnancy losses. Am J Reprod Immunol.2019; 83: e13195.
[7] Silasi M, You Y, Simpson S, et al. Human chorionic gonadotropin modulates CXCL10 expression through histone methylation in human decidua. Sci Rep.2020; 10 (1): 5785
[8] Zhang YH, Aldo P, You Y, et al. Trophoblast - secreted soluble - PD - L1 modulates macrophage polarization and function. J Leukoc Biol.2020; 108 (3): 983 - 998.
[9] Mor G, Cardenas I, Abrahams V, Guller S. Inflammation and pregnancy: the role of the immune system at the implantation site. Ann N Y Acad Sci.2011; 1221: 80 - 87.