Review

Molecular mechanisms in normal pregnancy and rheumatic diseases

M. Vázquez-Del Mercado, B.T. Martín-Márquez, M.H. Petri, E.A. Martínez-García, J.F. Muñoz-Valle

Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, CUCS, Universidad de Guadalajara, Mexico.

Mónica Vázquez-Del Mercado, MD, PhD; Beatriz T. Martín-Márquez; Marcelo H. Petri ; Erika A. Martínez-García; José F. Muñoz-Valle.

Please address correspondence and reprints requests to: *Mónica Vázquez-Del Mercado, MD, PhD, Head, Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, CUCS, Universidad de Guadalajara, Mexico. E-mail: dravme@hotmail.com*

Received on May 15, 2006; accepted in revised form on October 19, 2006.

Clin Exp Rheumatol 2006; 24: 707-712.

Key words: Pregnancy, rheumatic diseases, immune system.

ABSTRACT

Pregnancy is a phenomenon that is not totally understood, based on the complex molecular interactions between the mother and the embrio. Once the fecundation is completed the fetus starts to fight for survival. The first challenge is the implantation process and the second one is the interaction with the maternal immune system.

This review discusses how the fetus avoids the immune system rejection, and the mechanisms that the maternal immune system adapts in order to be fit for a successful pregnancy.

Also, we focus in this paper on the effects of pregnancy in rheumatic diseases, because the myriad clinical outcomes of the disease itself and the obstetric complications dependent of the disease implicated, as for example in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), spondyloarthropaties and antiphospholipid syndrome (APS).

Introduction

Pregnancy is a phenomenon that is not totally understood, based on the complex molecular interactions between the mother and the fetus itself. In this review we discuss the normal immune response, how the embryo protects him/herself from the maternal immune system in a normal pregnancy and the mechanisms triggered by the presence of the fetal allograft. Finally we describe the molecular knowledge around pregnancy on the presence of autoimmune rheumatic diseases. During the last two decades, an increase interest around the immunological and molecular millieu of the maternal-fetal unit result in interesting publications giving us the insight to this scenario.

The normal immune response

T_H1/T_H2 Subset

T cells may be classified as T_H1/T_H2 subsets: The T_H1 subset produce interleukin-2 (IL-2), interferon γ (IFN-γ) and tumor necrosis factor-α (TNFα) and is related to cellular immunity. The T_H2 subset produce interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6) and interleukin-10 (IL-10) which are responsible for humoral immunity (1) (Table I). Another subset is known as T_H3 and it is involved in T regulation (2).

Naturally Foxp3 $CD4^+$ $CD25^+$ Treg cells

Naturally Foxp3 $CD4^+$ $CD25^+$ cells are postulated as T regulatory cells (T_{reg} cells), characterized phenotypically by high expression of IL-2 receptor α (IL-2Rα/$CD25^+$) originally described by Asano and Sakaguchi (3, 4). T_{reg} cells represent 5 to 10 % of the $CD4^+$ peripheral blood cells (5, 6) (Table I). Studies on *BALB/c* mice showed that $CD4^+CD25^+$ cells appear on the periphery after the 3rd day of life. Neonatal thymectomy on the 3rd day induces organ-specific autoimmune diseases such as ooforitis, gastritis and thyroiditis as a consequence of the absence of the IL-2Rα ($CD25^-$), resulting in T cells with autoreactive phenotype (3).

Recently it has been pointed out the important role of the transcriptional factor Foxp3, a forkhead transcription factor that is an apparently exclusive marker of T cells capable of regulatory function (7, 8). T_{reg} cells are responsible for the maintenance of tolerance based on anergy to T cell receptor (TCR) stimulation.

T_{reg} cells seem to express through the Foxp3 function accessory molecules: cytotoxic T lymphocyte antigen-4,

Table I. Functions of different cell subsets in normal immune response and pregnancy alone or associated with rheumatic disease.

Function / Characteristic	Naturally Foxp3 $CD4^+$ $CD25^+$ cells	Peripheral Natural Killer Cells	Uterine Natural Killer Cells	T_H1/T_H2 Subsets	Dendritic Cells (APC)
Normal Immune Response	Peripheral Tolerance	Innate immunity $CD56^{dim}CD16^+$ Cellular toxicity	↓ count, except in secretory phase	T_H1-cellular immunity T_H2-humoral immunity	Antigen Presenting
Normal Pregnancy	Favor the tolerance mediated by CTLA-4 and APC_{reg}	Unknown	$CD56^{bright}$ $CD16^-$ pre-ovulatory and post-ovulatory phases	Mainly T_H2 response ?	Tolerance to the semiallograft mediated by IDO secretion
Pregnancy in Rheumatic Diseases	Unknown	Unknown	Unknown	Not clear yet References (32, 50, 51)	Unknown

(CTLA-4), glucocorticoid induced by tumor necrosis factor family related receptor (GITR), CD5 surface marker expressed by mature T cells and $CD45RB^{low}$, a tyrosine phosphatase expressed on hematopoietic cells (4, 5). In relation to the effector mechanism of T_{reg} cells, the *in vitro* evidence demonstrates that they mediate their effects through: 1) soluble mediators like IL-10 and transforming growth factor β (TGF-β); 2) cell to cell contact between antigen presenting cell (APC) and T_{reg} cells that might result in activation of T cell receptor (TCR) along with CTLA-4 enhancing T_{reg} cells suppressor activity (5) (Fig. 1).

Natural killer (NK)

The NK cells were identified because of its ability to lyse tumour cells without previous immunization (9). There are two different kinds of NK cells on the peripheral blood, both express CD56 and might or might not express CD16 on the surface. Ninety percent express low levels of CD56 ($CD56^{dim}CD16^+$) and the other 10 % express high levels of CD56 ($CD56^{bright}$ CD16-). The $CD56^{dim}CD16^+$ present cytolytic granules and are more cytotoxic compared to the $CD56^{bright}$ CD16- (10) (Table I).

The function of these NK cells is controlled by the expression of specific receptors for human leukocyte antigen (HLA) class I, mainly the killer immunoglobulin-like receptor (KIR) family, the immunoglobulin like transcript (ILT), CD94/NKG2 and natural cytotoxicity receptors (NCRs). These last ones are specific for NK cells (11). According to the cytokine profile, $CD56^{bright}$ CD16- secretes significantly more IFN-γ through the stimulus of interleukin-12 (IL-12) and interleulin-18 (IL-18) compared to $CD56^{dim}$-$CD16^+$. Other cytokines expressed are granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-10 (12).

Uterine NK (uNK)

In contrast to peripheral blood, uNK cells ($CD56^{bright}$ $CD16^-$) represent the main subset of NK cells in the uterus (10) (Table I). They are characterized by their low cytotoxicity although they are high proliferative (13). uNK cells show small and agranular cytoplasm in the proliferative pre-ovulatory phase; while in the post-ovulatory secretory phase, they become enlarge and with a lot of granules (14) (Table I). uNK cells secrete cytokines that are not produce by peripheral NK cells, such as angiogenic growth factors and leukemia inhibitory factor (14).

Dendritic cells (DCs)

The DCs are a heterogeneous cell population with the main function of APC to naïve T cells. (Table I) DCs might help in the regulation of the immune response through the use of surface molecules and/or cytokines that induce T helper cell (T_H) differentiation (15).

The DCs have 2 origins: myeloid or lymphoid. The blood-derived DCs referred as myeloid DC express CD11b, the integrin CD205 and might express CD4 but does not express CD8α. The lymphoid DCs lacks CD11b surface marker but expresses CD8 α and CD205 (16). Myeloid DCs, could induce T_H1 cells by production of IL-12, but after the burst of IL-12, the DCs are no longer shifted to T_H1 but to T_H2 response (17-19). Lymphoid DCs favour a T_H2 response when culture with interleukin-3 (IL-3).

The immune response in normal pregnancy

Tolerance to the fetal allograft

The menstrual cycle has a post-ovulatory or secretory phase characterized by the activity of cytokines such as IL-10 and IL-4 found on endometrial biopsies (20) which is a supportive response to avoid rejection of the oocyte fecunded by the spermatocyte.

Hormonal modifications during pregnancy are regulated by the feto-maternal unit. Progesterone is the fundamental hormone during the first part of gestation and is found in concentrations 4-6 times higher versus non-pregnant women. Progesterone induces the production of progesterone-induced blocking factor (PIBF) which stimulates IL-4 and IL-10 (T_H2) secretion and inhibits IFN-γ production (T_H1) (21, 22). In early pregnancy the chorionic gonadotrophic hormone (hCG) mantains the pregnancy by the inhibition of the apoptosis of the *corpus luteum*. This release of the hCG induce progesterone production and helps the differentiation toward T_H2 response.

Changes on the immune microenvironment of the endometrium are important for successful implantation and maintenance of pregnancy including uNK cell proliferation (14), reduction of the NK cell cytotoxic activity (23), inhibition

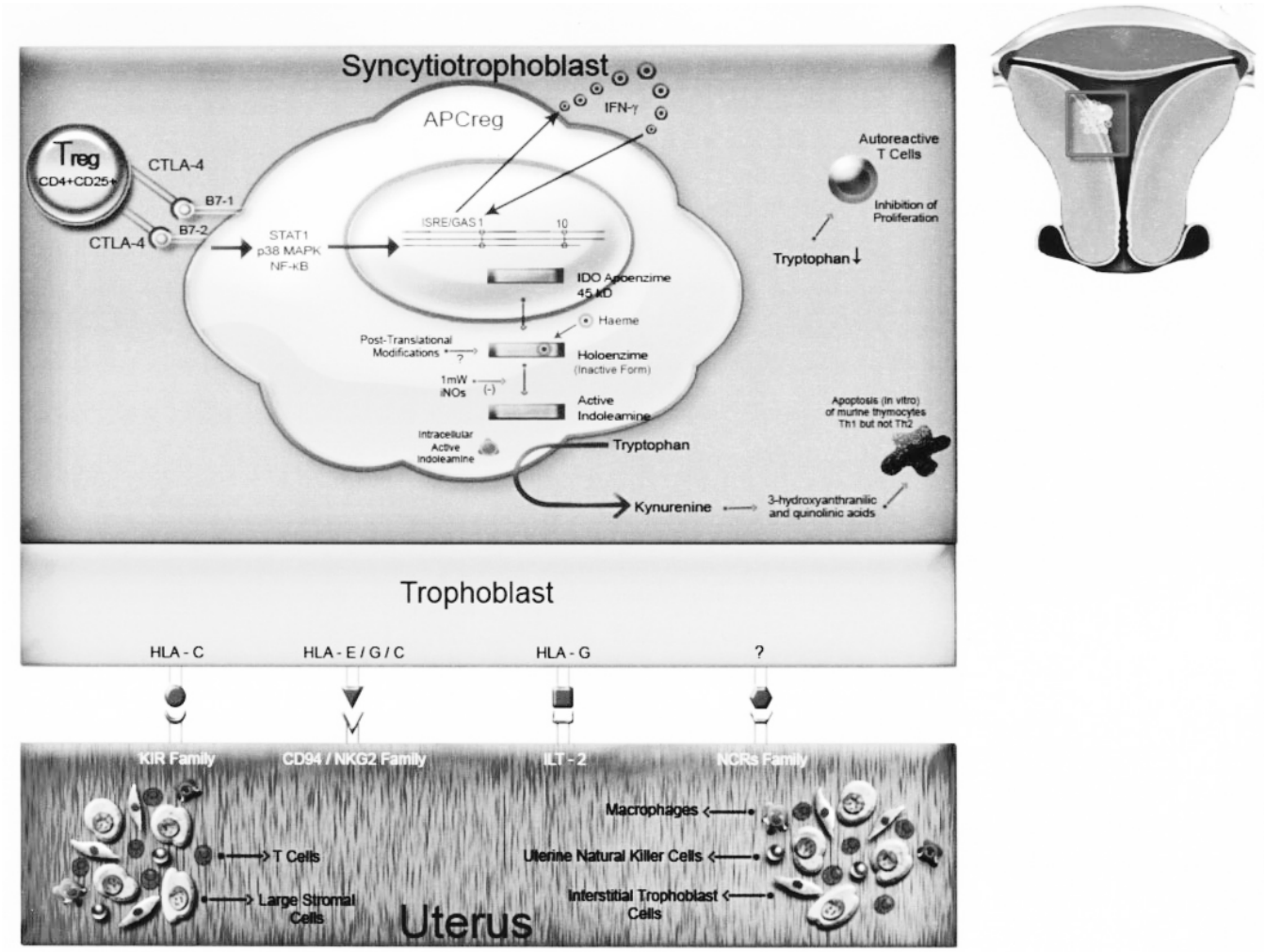

Fig. 1. Molecular mechanism implicated in normal pregnancy.
The figure shows the maternal T_{reg} cells ($CD4^+CD25^+$) express CTLA-4 which acts as a ligand for B7-1 / B7-2 (CD80/CD86) receptor molecules on APC_{reg}. This interaction triggers the signal transduction pathway dependent on STAT-1, p38 MAPK and NFκB to produce IFN-γ. This molecule of IFN-γ acts in a paracrine or autocrine way to activate IDO expression as apoenzyme through the activation of Interferon Stimulatory Response Elements (ISRE) and γ-Activating Sequences (GAS). The addition of the haeme group to the apoenzyme coverts it as a holenzyme (inactive form). Post-translational modifications not known yet, converts the inactive into the active form of IDO, with the consequence degradation of tryptophan to kynurenine in the syncytiotrophoblast. Secondary metabolites from kynurenine, 3-hydroxyanthranilic and quinolinic acids, induce selective apoptosis in murine thymocytes and T_H1 cells. The low disponibility of tryptophan around the syncytiotrophoblast allows cycle arrest of T autoreactive cells. The figure demonstrates on the APCreg cytoplasm, the negative regulation of the active IDO form by the antagonist 1-methyltryptophan (1-MW) to inactive IDO, also mediated by the iNOs enzyme. On the other hand the trophoblast is interacting with the immune maternal uNK $CD56^{bright}CD16^-$, which express activation (CD94/NKG2, NCR family) and inhibitor receptors (ILT-2, KIR family) that recognize their ligands on the surface of the trophoblast: HLA-C, HLA-G and HLA-E molecules. The existence of this interaction suggests that the non-classical HLA molecules protect the fetus for the rejection by maternal uNK cells.

of T cell growth (24-26), deviate of the T_H balance (27-32), hormonal induction, etc.(28, 30) (Fig. 1).

The maximal fecundity is around 30 %. Only 50-60 % of all conceptions advance beyond 20 weeks of gestation. Of the pregnancies lost, 75 % are secondary to a failure of implantation (33). The successful implantation is mediated by hormones like catecholamines and estrogens, cytokines such as TGF-β, IL-10, enzymes like indoleamine 2,3-dioxygenase (IDO), inducible nitric oxide synthetase (iNOs), throphoblast proteinases like cathepsin B and L and cyclooxigenase 1 and 2 (COX-1 and COX-2) (33).

On the other hand, the trophoblast expresses ligands for non-classical HLA molecules (HLA-G, E, C) recognized by the uNK cells receptors (Fig. 1). Through this interaction, the trophoblast, comes in direct contact with maternal lymphocytes in early pregnancy, which means a protective role of the semi allograft (fetus) (14). These uNK cells, a T_H2 based balance (IL-10, IL-4) and the absence of HLA I and II expression by DCs and cytotoxic T cells through IFN-γ secretion (30), allow a successful implantation.

T_H1/T_H2 subset in normal pregnancy

It has been suggested that women and mice during pregnancy show a T_H2 balance as a consequence of suppression of T_H1-type cytokines. Systemic and local expression of T^H2 cytokines in placental tissue might be beneficial for the fetus, specially during the third trimester (28, 31, 32, 34-39) (Table I). In humans, the T_H1/T_H2 paradigm is under discussion.

A previous work of our group, reported increased production of IFN- γ (T_H1) and IL-4 (T_H2) on peripheral blood in normal pregnant women (32). Elevated concentration of the T_H1 cytokines IL-2 and IFN-γ and decreased concentrations of the T_H2-type cytokine IL-4, IL-10, have been reported in spontaneous abortion upon antigen and mitogen-induced activation of maternal peripheral blood mononuclear cells (PBMC) (40).

T_{reg} cells in pregnancy

Maternal T_{reg} cells are essential for the suppression of the immune aggression directed against the fetus (41) T_{reg} cells express CTLA-4, which is a negative regulator that has a structural homology to CD28 (5, 42). The coupling of CTLA-4 to regulatory APC (APC_{reg}) with their accessory molecules CD80 (B7-1) / CD86 (B7-2), triggers the signal transducers and activators of transcription-1 (STAT1), / p38 mitogen-activated protein kinase (p38MAPK)/ nuclear factor κ B (NFκB) pathway, inducing the production of T_H1 cytokines, mainly IFN-γ (24, 42). (Table I). IFN-γ favours the expression of IDO in its form as apoenzyme through the activation of Interferon Stimulatory Response Elements (ISRE) and γ-Activating Sequences (GAS) (43). Once the addition of the haeme group is known as holenzyme (inactive form), secondary to post-translational modifications, it is converted into the active form of IDO, which allows the degradation of tryptophan to kynurenine in the syncytiotrophoblast. Fallarino *et al.* showed that kynurenine metabolite, 3-hydroxyanthranilic and quinolinic acids, induce cycle arrest of autoreactive cells and selective apoptosis in murine thymocytes and T_H1 cells (25, 26, 43-47) (Fig. 1).

uNK and HLA

The uNK cells represent 70 % of the $CD45^+$ leukocytes on the human decidua (10, 48) (Table I). This uNK population is present since the early to the late stages of pregnancy; however, the precise role of this uNK cells is unknown. Some theories related to its putative role are: 1) A possible control on the arterial growth; 2) Trophoblast control invasion through the interaction with non classical HLA I molecules (HLA-C, HLA-G and HLA-E) and their uNK cells receptors: KIR family, ILT group, CD94/NKG2 and NCRs (9, 11, 14, 48) (Fig. 1).

DCs in normal pregnancy

Decidual macrophages comprise 20 % of placental cells, whereas only a few of T cells are present and B cells are virtually absent (14). Both myeloid and lymphoid DCs express hCG receptors. The hCG up regulates the antigen-presenting activity of myeloid DCs cells culture stimulated with hCG by the expression of CD40 and CD86 that in consequence produce IFN-γ, IL-12 and TNF-γ in a dosed dependent manner (15).

Immature DCs can induce CTLA-4 expression and IL-10 - producing T_{reg} - like cells that inhibit the antigen-driven proliferation of T_H1 through IDO production (15, 42). (Fig.1 and Table I).

Pregnancy and rheumatic diseases

Hormonal status influence in rheumatic diseases

The estrogen administration in lupus murine models such as MRL *lpr* accelerates the renal damage (27). The 17-β estradiol is able to increase B cell activation to produce high titers of anti-DNA double stranded and IL-10 in systemic lupus erythematosus (SLE) patients (27, 49). The lack of protection provided by estrogens to develop rheumatoid arthritis (RA) is lost in relation with the age of presentation of RA in adult women.

Rheumatic diseases and pregnancy

T_H1/T_H2 balance

Studies dealing with cytokine expression during pregnancy and rheumatic diseases are scarce. Ostensen reported in 2005 the cytokine levels of pregnant patients with RA, juvenile idiopathic arthritis (JIA) and ankylosing spondylitis (AS) finding an increase on the plasma levels of the anti-inflammatory cytokines such as receptor antagonist IL-1 (IL-1Ra) and soluble TNF receptor (sTNFR) during the second and third trimesters of pregnancy not related to the underlying disease changes, and low or undetectable levels of IFN-γ and IL-10 [50]. Previous studies including two from our group (32, 51), described elevated concentrations of IL-10 in RA and SLE pregnant patients in a longitudinal follow-up, evaluated by *in vitro* stimulation from PBMC with phytohaemmaglutinin showing depressed cell-mediated immunity (32, 52). Despite the depressed cell-mediated immunity, the PBMC could still increase their IL-10 secretion (32, 50). (Table I)

In addition to a general T_H2 response reflected by high IL-10 levels found in our first paper about RA and SLE patients during pregnancy (32), a significant change in IFN-γ was observed in RA patients but only during the first trimester of pregnancy, compared with a major T_H1 response in healthy pregnant women (27).

In our second paper we analyzed the placental mRNA expression of T_H1 and T_H2 cytokines and the activity of the nuclear factor NFB with a non clear definition of T_H1 or T_H2 response in RA, SLE and healthy pregnant women (51).

Effect of pregnancy in rheumatic diseases

The clinical outcome of autoimmune rheumatic diseases such as RA, SLE, antiphospholipid syndrome (APS), systemic sclerosis and spondyloarthropathies during pregnancy, has long been described (53, 54).

Since 1938, Phillip Hench described an intriguing improvement in pregnant women with inflammatory arthritis (55, 56). Recently, it was informed remission of disease activity in 86 % of pregnancies in RA and persistence of disease activity in 14 % (39). Ostensen *et al.* informed that patients suffering from RA during pregnancy improved the RA clinical activity since the first trimester up to the mid pregnancy in around 75 % of the cases, however RA flares occurred in 77 - 90 % around 6 months postpartum (57, 58).

In SLE, the course of pregnancy has a different outcome based on the clinical activity registered at the moment of conception (59, 60). Clowse *et al.*

reported recently the data obtained from the Hopkins Lupus Cohort between 1987 to 2002, where 21% of SLE pregnant patients experienced a moderate to severe flare (61). Fetal loss in this cohort was reported of 42 % in active SLE whereas 11 % in SLE with low activity (61). In pregnant patients with RA, premature birth or intrauterine growth retardation do not seem to be increase versus normal population (39).

In the group of spondyloarthopathies, the peripheral arthritis and uveitis usually improve, but the spinal disease may worsen in around 25 % of patients during pregnancy (54).

About APS, pre-eclampsia and eclampsia associated to APS contribute to increase the risk of premature (less than 34 weeks) delivery. The risk of arterial and venous thrombosis in pregnant patients with APS, is considerable whether anti-phospholipid antibodies or circulating anticoagulant have been deleted (54).

The little knowledge around molecular mechanisms involved in pregnancy and the need to clarify the relationship between clinical outcome of autoimmune rheumatic diseases and pregnancy evoked us to make this review.

Acknowledgements

We extend our gratitude to Michelle Rivail Da Silva who kindly supervised the figure edition.

References

1. MOSMANN T.R, S SAD: The expanding universe of T-cell subsets*: T_H1, T_H2 and more. Immunol Today* 1996; 17: 138-46.
2. KIDD P: T_H1/T_H2 balance: the hypothesis, its limitations, and implications for health and disease. *Altern Med Rev* 2003; 8: 223-46.
3. ASANO M, M TODA, N SAKAGUCHI, S. SAKAGUCHI: Autoimmune disease as a consequence of developmental abnormality of a T cell subpopulation. *J Exp Med* 1996; 184: 387-96.
4. SAKAGUCHI S: Naturally arising Foxp3-expressing $CD25^+CD4^+$ regulatory T cells in immunological tolerance to self and non-self. *Nat Immunol* 2005; 6: 345-52.
5. WOOD, KJ, SAKAGUCHI S: Regulatory T cells in transplantation tolerance. *Nat Rev Immunol* 2003; 3: 199-210.
6. KUNIYASU Y, TAKAHASHI T, ITOH M, SHIMIZU J, TODA G, SAKAGUCHI S: Naturally anergic and suppressive CD25(+)CD4(+) T cells as a functionally and phenotypically distinct immunoregulatory T cell subpopulation. *Int Immunol* 2000; 12: 1145-55.
7. FONTENOT JD, GAVIN MA, RUDENSKY AY: Foxp3 programs the development and function of $CD4^+CD25^+$ regulatory T cells. *Nat Immunol* 2003; 4: 330-6.
8. FONTENOT JD, RASMUSSEN JP, WILLIAMS LM, DOOLEY JL, FARR AG, RUDENSKY AY: Regulatory T cell lineage specification by the forkhead transcription factor foxp3. *Immunity* 2005; 22: 329-41.
9. MORETTA A, BOTTINO C, MINGARI MC, BIASSONI R, MORETTA L: What is a natural killer cell? *Nat Immunol* 2002; 3: 6-8.
10. TRUNDLEY A, MOFFETT A: Human uterine leukocytes and pregnancy. *Tissue Antigens* 2004; 63: 1-12.
11. BIASSONI R, CANTONI C, PENDE D *et al.*: Human natural killer cell receptors and co-receptors. *Immunol Rev* 2001; 181: 203-14.
12. COOPER MA, FEHNIGER TA, CALIGIURI MA: The biology of human natural killer-cell subsets. *Trends Immunol* 2001; 22: 633-40.
13. SINDRAM-TRUJILLO AP, SCHERJON SA, VAN HULST-VAN MIERT PP *et al.*, Differential distribution of NK cells in decidua basalis compared with decidua parietalis after uncomplicated human term pregnancy. *Hum Immunol* 2003; 64: 921-9.
14. MOFFETT-KING A: Natural killer cells and pregnancy. *Nat Rev Immunol* 2002; 2: 656-63.
15. YOSHIMURA T, INABA M, SUGIURA K *et al.*: Analyses of dendritic cell subsets in pregnancy. *Am J Reprod Immunol* 2003; 50: 137-45.
16. ITANO AA, JENKINS MK: Antigen presentation to naive CD4 T cells in the lymph node. *Nat Immunol* 2003; 4: 733-9.
17. SCHULZ O, EDWARDS AD, SCHITO M *et al.*: CD40 triggering of heterodimeric IL-12 p70 production by dendritic cells *in vivo* requires a microbial priming signal. *Immunity* 2000; 13: 453-62.
18. EBNER S, RATZINGER G, KROSBACHER B *et al.*: Production of IL-12 by human monocyte-derived dendritic cells is optimal when the stimulus is given at the onset of maturation, and is further enhanced by IL-4. *J Immunol* 2001; 166: 633-41.
19. HOCHREIN H, O'KEEFFE M, LUFT T *et al.*: Interleukin (IL)-4 is a major regulatory cytokine governing bioactive IL-12 production by mouse and human dendritic cells. *J Exp Med* 2000; 192: 823-33.
20. LIM KJ, ODUKOYA OA, AJJAN RA, LI TC, WEETMAN AP, COOKE ID: Profile of cytokine mRNA expression in peri-implantation human endometrium. *Mol Hum Reprod* 1998; 4: 77-81.
21. SZEKERES-BARTHO J, WEGMANN TG: A progesterone-dependent immunomodulatory protein alters the T_H1/T_H2 balance. *J Reprod Immunol* 1996; 31: 81-95.
22. DORIA ACM: Immunoendocrine changes in healthy subjects and SLE patients during pregnancy. 2004 [cited 2004; Available from: www.rheuma21st.com/cutting_index.html.
23. BULMER JN, LASH GE: Human uterine natural killer cells: a reappraisal. *Mol Immunol* 2005; 42: 511-21.
24. MUNN DH, SHARMA MD, MELLOR AL: Ligation of B7-1/B7-2 by human $CD4^+$ T cells triggers indoleamine 2,3-dioxygenase activity in dendritic cells. *J Immunol* 2004; 172: 4100-10.
25. MUNN DH, ZHOU M, ATTWOOD JT *et al.*: Prevention of allogeneic fetal rejection by tryptophan catabolism. *Science* 1998; 281: 1191-3.
26. FALLARINO F, GROHMANN U, VACCA C *et al.*: T cell apoptosis by tryptophan catabolism. *Cell Death Differ* 2002; 9: 1069-77.
27. SALEM ML: Estrogen, a double-edged sword: modulation of T_H1- and T_H2-mediated inflammations by differential regulation of T_H1/T_H2 cytokine production. *Curr Drug Targets Inflamm Allergy* 2004; 3: 97-104.
28. WEGMANN TG, LIN H, GUILBERT L, MOSMANN TR: Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? *Immunol Today* 1993; 14: 353-6.
29. CHAOUAT G: Innately moving away from the Th1/Th2 paradigm in pregnancy. *Clin Exp Immunol* 2003; 131: 393-5.
30. SACKS G, SARGENT I, REDMAN C: Innate immunity in pregnancy. *Immunol Today* 2000; 21: 200-1.
31. LUPPI P: How immune mechanisms are affected by pregnancy. *Vaccine* 2003; 21: 3352-7.
32. MUNOZ-VALLE JF, VAZQUEZ-DEL MERCADO M, GARCIA-IGLESIAS T *et al.*: T(H)1/T(H)2 cytokine profile, metalloprotease-9 activity and hormonal status in pregnant rheumatoid arthritis and systemic lupus erythematosus patients. *Clin Exp Immunol* 2003; 131: 377-84.
33. NORWITZ ER, SCHUST DJ, FISHER SJ: Implantation and the survival of early pregnancy. *N Engl J Med* 2001; 345: 1400-8.
34. LIN H, MOSMANN TR, GUILBERT L, TUNTIPOPIPAT S, WEGMANN TG: Synthesis of T helper 2-type cytokines at the maternal-fetal interface. *J Immunol* 1993; 151: 4562-73.
35. DELASSUS S, COUTINHO GC, SAUCIER C, DARCHE S, KOURILSKY P: Differential cytokine expression in maternal blood and placenta during murine gestation. *J Immunol* 1994; 152: 2411-20.
36. CHAOUAT G, ASSAL MELIANI A, MARTAL J *et al.*: IL-10 prevents naturally occurring fetal loss in the CBA x DBA/2 mating combination, and local defect in IL-10 production in this abortion-prone combination is corrected by *in vivo* injection of IFN-tau. *J Immunol* 1995; 154: 4261-8.
37. Krishnan L, Guilbert LJ, Russell AS, Wegmann TG, Mosmann TR, Belosevic M: Pregnancy impairs resistance of C57BL/6 mice to Leishmania major infection and causes decreased antigen-specific IFN-gamma response and increased production of T helper 2 cytokines. *J Immunol* 1996; 156: 644-52.
38. KRISHNAN L, GUILBERT LJ, WEGMANN TG, BELOSEVIC M, MOSMANN TR: T helper 1 response against Leishmania major in pregnant C57BL/6 mice increases implantation failure and fetal resorptions. Correlation with increased IFN-gamma and TNF and reduced IL-10 production by placental cells. J *Immunol* 1996; 156: 653-62.
39. DORIA A, IACCARINO L, ARIENTI S *et al.*: Th2 immune deviation induced by pregnan-

cy: the two faces of autoimmune rheumatic diseases. *Reprod Toxicol* 2006; 22: 234-41.
40. MARZI M, VIGANO A, TRABATTONI D *et al.*: Characterization of type 1 and type 2 cytokine production profile in physiologic and pathologic human pregnancy. *Clin Exp Immunol* 1996; 106: 127-33.
41. ALUVIHARE VR, KALLIKOURDIS M, BETZ AG: Regulatory T cells mediate maternal tolerance to the fetus. *Nat Immunol* 2004; 5: 266-71.
42. FINGER EB, BLUESTONE JA: When ligand becomes receptor—tolerance via B7 signaling on DCs. *Nat Immunol* 2002; 3: 1056-7.
43. MELLOR AL, MUNN DH: IDO expression by dendritic cells: tolerance and tryptophan catabolism. *Nat Rev Immunol* 2004; 4: 762-74.
44. MELLOR AL, MUNN DH: Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation? *Immunol Today* 1999; 20: 469-73.
45. MUNN DH, SHAFIZADEH E, ATTWOOD JT, BONDAREV I, PASHINE A, MELLOR AL: Inhibition of T cell proliferation by macrophage tryptophan catabolism. *J Exp Med* 1999; 189: 1363-72.
46. LEE GK, PARK HJ, MACLEOD M, CHANDLER P, MUNN DH, MELLOR AL: Tryptophan deprivation sensitizes activated T cells to apoptosis prior to cell division. *Immunology* 2002; 107: 452-60.
47. GROHMANN U, FALLARINO F, PUCCETTI P: Tolerance, DCs and tryptophan: much ado about IDO. *Trends Immunol* 2003; 24: 242-8.
48. PARHAM P: NK cells and trophoblasts: partners in pregnancy. *J Exp Med* 2004; 200: 951-5.
49. MERRILL JT, DINU AR, LAHITA RG: Autoimmunity: The Female Connection. *Medscape Womens Health* 1996; 1: 5.
50. OSTENSEN M, FORGER F, NELSON JL, SCHUHMACHER A, HEBISCH G, VILLIGER PM: Pregnancy in patients with rheumatic disease: anti-inflammatory cytokines increase in pregnancy and decrease post partum. *Ann Rheum Dis* 2005; 64: 839-44.
51. MARTINEZ-BONILLA GE, MUNOZ-VALLE JF, DELGADO-RIZO V *et al.*: Placental cytokine expression and NF-kappaB activity in women with rheumatic diseases. *Scand J Rheumatol* 2006; 35: 160-2.
52. LOCKSHIN MD: *Pregnancy and Rheumatic Diseases. Arthritis and Allied Conditions A Textbook of Rheumatology*, ed. W.W. LIPPINCOT. 2005.
53. PETRI M: *Pregnancy and Rheumatic Disease*. *Rheumatic Disease Clinics of North America*, ed. W.B.S. Company. Vol. 23. 1997, Philadelphia: W.B. Saunders Company.
54. GORDON C: Pregnancy and autoimmune diseases. *Best Pract Res Clin Rheumatol* 2004; 18: 359-79.
55. WILDER RL: Hormones, pregnancy, and autoimmune diseases. *Ann N Y Acad Sci* 1998; 840: 45-50.
56. STRAUB RH, BUTTGEREIT F, CUTOLO M: Benefit of pregnancy in inflammatory arthritis. *Ann Rheum Dis* 2005; 64: 801-3.
57. OSTENSEN M: Sex hormones and pregnancy in rheumatoid arthritis and systemic lupus erythematosus. *Ann N Y Acad Sci* 1999; 876: 131-43; discussion 144.
58. OSTENSEN M VILLIGER PM: Immunology of pregnancy-pregnancy as a remission inducing agent in rheumatoid arthritis. *Transpl Immunol* 2002; 9: 155-60.
59. MOK CC, WONG RW: Pregnancy in systemic lupus erythematosus. *Postgrad Med J* 2001; 77: 157-65.
60. MORONI G, PONTICELLI C: The risk of pregnancy in patients with lupus nephritis. *J Nephrol* 2003; 16: 161-7.
61. CLOWSE ME, MAGDER LS, WITTER F, PETRI M: The impact of increased lupus activity on obstetric outcomes. *Arthritis Rheum* 2005; 52: 514-21.