The Role of Progesterone in Feto-Maternal Immunological Cross Talk

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Significance of the Study

- Reproduction is one of the most important biological processes, so much so that when a pathway is disrupted there are alternative mechanisms to compensate for the loss of function. Because of this complexity, it is not easy to cover all aspects and mechanisms that allow the fetus to survive in the potentially hostile immunological environment. Therefore, this review focuses on the role of progesterone in feto-maternal immunological interactions and attempts to highlight the recent, as well as the most important, findings of the past decades.

Keywords

Pregnancy · Progesterone · Progesterone-induced blocking factor

Abstract

This review aims to provide a brief historical overview of the feto-maternal immunological relationship, which profoundly influences the outcome of pregnancy. The initial question posed in the 1950s by Medawar [Symp Soc Exp Biol. 1953;7: 320–338] was based on the assumption that the maternal immune system recognizes the fetus as an allograft. Indeed, based on the association between HLA-matching and spontaneous miscarriage, it became obvious that immunological recognition of pregnancy is required for a successful gestation. The restricted expression of polymorphic HLA antigens on the trophoblast, together with the presence of nonpoly-

morphic MHC products, excludes recognition by both T and NK cells of trophoblast-presented antigens; however, $\gamma\delta$ T cells, which constitute the majority of decidual T cells, are likely candidates. Indeed, a high number of activated, progesterone receptor-expressing $\gamma\delta$ T cells are present in the peripheral blood of healthy pregnant women and, in the presence of progesterone, these cells secrete an immunomodulatory protein called progesterone-induced blocking factor (PIBF). As early as in the peri-implantation period, the embryo communicates with the maternal immune system via PIBF containing extracellular vesicles. PIBF contributes to the dominance of Th2-type reactivity which characterizes normal pregnancy by inducing increased production of Th2 cytokines. The high expression of this molecule in the decidua might be one of the reasons for the low cytotoxic activity of decidual NK cells.

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Immunological Recognition of Pregnancy

The concept of pregnancy as an “immunological paradox” was first presented by Peter Medawar [1] in 1953, and ever since then scientists have been attempting to answer the question of why the semiallogeneic fetus is not rejected by its mother. A plausible and simple explanation would be that fetal antigens are hidden or masked, and therefore the maternal immune system does not recognize the presence of the fetus. This concept, however, has been disproved by the demonstration of anti-placental and anti-paternal antibodies in the sera of multiparous women [2], suggesting that pregnancy is recognized by the maternal immune system and the immune reaction does not harm the fetus.

In the 1980s it became evident that maternal recognition of fetal antigens and consequent activation of the maternal immune system are not just harmless but they also required for a normal pregnancy outcome. In abortion-prone murine strain combinations, pregnancy can be rescued by nonspecific immunostimulation of the pregnant female [3] or by immunization of the mother with paternal strain spleen cells [4]. In humans, HLA matching between the parents has been shown to be associated with spontaneous abortion [5]. To further study the relationship between HLA matching and pregnancy outcomes, Ober [6], conducted prospective, population-based studies on Hutterites, who constitute a highly inbred population in which parents often match for HLA [7]. These studies revealed that a high rate of similarity between maternal and paternal HLA types might be a risk factor for pregnancy failure [6].

The above data suggest that recognition of fetal antigens is crucial for the maternal immune system to initiate a series of events that will eventually create a favorable immunological environment for the embryo and the developing fetus.

Expression of HLA Antigens on the Trophoblast

This raises the question of how fetally derived antigens are presented and what immune cell types recognize these antigens.

Early studies showed that the trophoblast is resistant to killing by both NK cells and T cell; however, in the presence of IL-2 the cells became cytotoxic, suggesting that the inability to lyse the target cells is not due to an inherent defect in the killing machinery but rather a failure of lymphocytes to recognize trophoblast-presented anti-

gens [8, 9]. The chorionic villous trophoblast, the principal form of trophoblast in maternal contact, is devoid of HLA antigens [10–12]. On the other hand, extra-villous cytotrophoblast cells do react with antibodies to HLA class I framework antigens [13]. Later, however, it became evident that the extra-villous trophoblast cells that react with these antibodies fail to react with anti-HLA-A or anti-HLA-B antibodies, suggesting that the expression of polymorphic MHC antigens by trophoblast cells may be restricted to HLA-C [14].

In addition to HLA-C, the trophoblast also expresses the nonpolymorphic HLA antigens HLA-G and HLA-E. While HLA-A, HLA-B, HLA-C, HLA-E, and HLA-G are present in individual trophoblast populations at the transcriptional level, only HLA-C, HLA-G, and HLA-E are translated to proteins [15, 16]. HLA-E serves as the ligand of the CD94/NKG2A/B inhibitory receptor present on the majority of decidual NK cells [17–20], which partly explains the failure of NK cells to lyse the trophoblast. On the other hand, the absence of polymorphic HLA antigens limits the recognition, by maternal T cells, of trophoblast-presented antigens. Because cytotoxic T cells need to recognize both their target antigen and self HLA in order to be effective [21, 22], the cellular immune response to chorionic villous trophoblast antigens would be blocked through the lack of maternal HLA on this tissue [23]. $\gamma\delta$ T cells constitute a major population among decidual lymphocytes. Seventy percent of decidual T cells express $\gamma\delta$ TCR, and the majority of these cells are activated [24–26]. Because $\gamma\delta$ T cells are able to recognize antigens without MHC restriction [27], they are also plausible candidates for recognition of the fetal antigens presented by the trophoblast. The number of $\gamma\delta$ T cells is significantly increased in the peripheral blood of healthy pregnant women, and almost all of these cells express progesterone receptors (PR), suggesting prior activation [28, 29]. Based on these findings, it is likely that $\gamma\delta$ cells play a role in the recognition of fetal antigens.

Progesterone-Dependent Immunomodulation

The biological activities of progesterone are mediated by genomic pathways via nuclear PR or by nongenomic pathways via membrane receptors.

The link between progesterone and the immune system is partly established by lymphocyte PR, which have been demonstrated in peripheral blood $\gamma\delta$ T cells [28, 29] and in peripheral blood NK cells [30] of pregnant women, with the latter expressing both PR A and B isoforms. The

percentage of circulating PR-expressing lymphocytes increases throughout gestation, and it is significantly lower in women with recurrent miscarriages than in healthy pregnant women of corresponding gestational ages [31, 32], suggesting a relationship between lymphocyte PR expression and the outcome of pregnancy. The regulation of lymphocyte PR is activation dependent. Exposure of human nonpregnancy lymphocytes to in vitro mitogenic or alloantigenic stimuli increases lymphocyte PR expression [33]. The high percentage of circulating PR-expressing lymphocytes found in liver-transplanted patients suggests that in vivo allogeneic stimulation has a similar effect [34]. The latter finding allows the conclusion that PR expression in lymphocytes might not be a consequence of pregnancy-associated hormonal changes but is rather due to chronic stimulation by fetal antigens, and it suggests that efficient recognition of fetal antigens is a requirement for the establishment of progesterone-dependent immune regulatory mechanisms.

Progesterone-Induced Blocking Factor Mediates the Immunological Effects of Progesterone

In the presence of progesterone, PR-positive pregnancy lymphocytes produce a protein called progesterone-induced blocking factor (PIBF), which mediates some of the immunological effects of progesterone [35].

PIBF1 cDNA encodes a protein of 757 amino acid residues with a predicted molecular mass of 89 kDa, which shows no significant amino acid sequence homology with any known protein [36]. Though PIBF was originally described as a molecule secreted by pregnancy lymphocytes, it later became obvious that it is produced by many other cell types and that the full-length PIBF and the shorter secreted forms produced by alternative splicing have very different functions.

The full-length PIBF is associated with the nucleus [37–39] and plays a role in cell cycle regulation. This form has been implicated in regulation of the invasiveness of both the trophoblast and malignant tumors [40–42]. The shorter forms are located in the cytoplasm and, after being secreted, they act as cytokines.

Cytokine-Like Effects of PIBF

Effects of PIBF on Cytokine Production

Pregnancy is characterized by a Th2-biased cytokine balance [43, 44]. The Th1/Th2 ratio is lower in the pe-

ripheral blood of healthy pregnant women than in that of nonpregnant individuals or in women with pathological pregnancies [45]. Administration of Th1 cytokines to pregnant mice results in pregnancy loss [46]. In general, increased production of Th2 cytokines is a characteristic of uneventful pregnancies and favors a normal outcome [45].

PIBF alters the Th1/Th2 balance. Mitogen-activated murine spleen cells produce 8–10 times more IL-10, IL-4, and IL-5 in the presence of PIBF than in its absence [47]. Raghupathy et al. [48] reported that progesterone-treated human pregnancy lymphocytes produce PIBF, followed by a decreased production of Th1 cytokines and an increased production of Th2 cytokines. Furthermore, production of the type 2 cytokines IL-4, IL-6, and IL-10 by mitogen-stimulated lymphocytes from women with recurrent miscarriages or preterm delivery as well as IL-4 and IL-10 production by lymphocytes from healthy pregnant women are also significantly increased upon exposure to PIBF [49].

The PIBF receptor is a GPI-anchored protein, which forms a heterodimer with the α chain of the IL-4 receptor [50]. PIBF binding to its receptor induces nuclear translocation of phosphorylated STAT6 dimers. These data suggest the existence of a novel type of IL-4R composed of the IL-4R α chain and the GPI-anchored PIBF receptor. Furthermore, the fact that PIBF signals via the α chain of the IL-4 receptor explains the induction, by PIBF, of Th2-dominant cytokine production.

PIBF Regulates NK Activity during Pregnancy

In vivo data support the effect of PIBF on NK activity. The adoptive transfer of spleen cells with a high NK activity to pregnant mice increases fetal loss [51], and this is counteracted by treatment with PIBF [52]. On the other hand, the increased resorption rates observed in PIBF-depleted mice are corrected by treating the mice with anti-NK antibodies [53], suggesting that PIBF contributes to the success of murine gestation by controlling NK activity.

The secreted forms of PIBF modulate both peripheral and decidual NK activity. Decidual NK cells constitute 60–70% of all decidual lymphocytes in the first trimester of human pregnancy [54] and are both phenotypically and functionally different from peripheral NK cells. Most decidual NK cells are CD16⁺CD56^{bright}, and they show a low cytolytic activity even though they contain cytotoxic granules [55] and selectively overexpress genes of perforin and granzymes A and B [54].

During normal gestation, decidual NK cells contribute to the creation of a favorable environment for implanta-

tion, placentation, and embryonic development [56], but at the same time they are fully armed to fight intrauterine infections if needed [57]. Under certain conditions, e.g., when exposed to hCMV-infected autologous decidual cells [58] or during spontaneous abortion in mice [59], they degranulate, but during normal pregnancy these cells are not cytotoxic despite the abundant presence of cytotoxic molecules in their cytoplasmic granules [60, 61].

The cytotoxic mechanisms exerted by NK cells can potentially damage the trophoblast. In humans, recurrent miscarriages are associated with an increased number of endometrial NK cells [62]. Gulan et al. [63] demonstrated a decreased perforin content of decidual lymphocytes from failed pregnancies as compared to those from normal pregnancy deciduae, suggesting that an increased rate of degranulation might have had taken place in the former case. Lachapelle et al. [64] showed that while the number of endometrial NK cells did not change in recurrent aborters the ratio of the CD16⁺CD56^{bright} uNK cell subset and the CD16⁺CD56^{dim} subset was reduced. In patients who miscarried chromosomally normal embryos the percentage of CD16⁺CD56^{bright} uNK cells decreased compared to those who miscarried chromosomally abnormal embryos or those of normal pregnancy [65]. These data suggest that a part of human recurrent miscarriages with an unknown etiology might be explained by a deficiency in CD16⁺CD56^{bright} uNK cells, although the precise mechanism is unknown. The reason for the decreased cytotoxic potential of decidual NK cells is only partly explained by the presence on the trophoblast of HLA-E molecules, which act as a ligand for the NKG2A inhibitory receptor. It is still not clear why these cells do not release perforin in the decidua.

Although decidual NK cells do not express nuclear PR, they appear to be affected by PIBF. PIBF blocks regulation of perforin expression in decidual lymphocytes cultured with decidual adherent cells; furthermore, anti-PIBF antibodies reverse progesterone-mediated reduction in cytolytic activity of decidual lymphocytes [66]. In the mouse decidua there is an abundance of PIBF⁺ and DBA⁺ decidual NK cells. These cells are absent from the deciduae of alymphoid mice, but they present in the decidua of those reconstituted with bone marrow from male BALB/c mice. Perforin is colocalized with PIBF in cytoplasmic granules in 54% of PIBF⁺ decidual NK cells on day 12.5 of pregnancy, whereas in anti-progesterone-treated mice all of the PIBF⁺ cells are perforin positive on the same gestational day [67]. Faust et al. [68] showed that PIBF inhibits the cytotoxicity of peripheral NK cells via a block

of degranulation without interfering with target conjugation.

Putting all of these observations together, it cannot be ruled out that PIBF present in the cytoplasmic granules of decidual NK cells contributes to a low decidual NK activity by inhibiting the release of perforin and other cytotoxic molecules.

The Embryo Communicates with the Maternal Immune System via Extracellular Vesicles

Earlier evidence suggests that the embryo signals the maternal immune system. Daya and Clark [69] demonstrated immunosuppressive factors in an embryo culture medium, and Kelemen et al. [70] reported an increased expression of IL-10 mRNA in peripheral lymphocytes incubated with the culture media of fertilized eggs but not in those incubated with follicular fluid. Thus, there is evidence that the embryo releases signals that alter maternal immune functions from the earliest stages of pregnancy; however, the mechanism of signal transport has not been thoroughly investigated.

Extracellular vesicles (EV) are produced by all types of cells, and because they transport different kinds of molecules from one cell to the other they can be considered a means of intercellular communication and as such are candidates for conveying signals from the embryo to the mother.

We have previously demonstrated EV in culture media of in vitro cultured human embryos [71]; thus it seemed plausible that these structures might be involved in communication between the embryo and the endometrium during implantation.

EV originating from various cell types and carrying different molecules can both activate and suppress the function of the immune system by presenting antigens [72, 73], MHC molecules [74–77], cytokines [78–81], or microRNA [82]. Embryo-derived EV are also detectable at the embryo-maternal interface in mouse implantation sites [83]. Immuno-electron microscopy revealed that among others these embryo-derived EV carry PIBF. Mouse embryo-derived EV adhere to the surface of both CD4⁺ and CD8⁺ murine peripheral T lymphocytes, partly via phosphatidylserine binding. Embryo-derived EV induce IL-10 production by murine peripheral CD8⁺ lymphocytes, and this effect is abrogated by pretreatment of the EV with anti-PIBF antibody [83]. These data suggest that the embryo communicates with the maternal immune system via EV, and that PIBF⁺ embryo-derived

EV alter the function of peripheral lymphocytes, thus contributing to the communication between the embryo and the mother in the early stage of pregnancy.

Cytokine-Like Effects of PIBF Contribute to the Maintenance of Pregnancy

PIBF is present in pregnancy serum as well as in the urine of pregnant women, and its concentration is predictive of the outcome of pregnancy.

A study on 500 pregnant women and 80 nonpregnant individuals revealed that during normal human pregnancy the concentration of PIBF in urine samples continuously increases until the 37th gestational week and starts to decrease thereafter, disappearing when labor starts. In women with threatened miscarriage or threatened preterm delivery, urinary PIBF levels remain significantly lower than those of healthy pregnant women of corresponding gestational ages [84]. In the urine of patients with preeclampsia, PIBF concentrations are significantly lower than in normal pregnancy, and they correlate with the number of symptoms presented. The onset of labor is also predictable on the basis of this test; however, the predictive value of PIBF measurement depends on the interval between sampling and the onset of labor. In samples that are taken within 2 days before the start of labor, PIBF concentrations were significantly lower than in those obtained 7–16 days before labor [84]. This was confirmed later by several studies. Hudić et al. [85] was able to predict preterm births based on lower-than-normal pregnancy PIBF values within 5 days before labor, while Beta

et al. [86] showed that in women who have a spontaneous early preterm delivery the maternal serum levels of PIBF are not altered at 11–13 weeks of gestation. In line with this, Check et al. [87] reported that the failure to detect PIBF at 3–5 weeks of seemingly normal pregnancy is associated with a higher rate of miscarriage. The same group demonstrated a difference in the percentage of PIBF+ lymphocytes between pregnant and nonpregnant women [88] and an increased percentage of PIBF+ cells following lymphocyte immunotherapy [89]. Mifepristone treatment for nonsurgical termination of pregnancy resulted in a decreased proportion of PIBF-positive lymphocytes [90].

These data, in line with previous in vivo findings, suggest that PIBF production is a characteristic feature of normal pregnancy and that determination of PIBF concentrations in urine or in the serum of pregnant women might be of use for diagnosis of threatened premature pregnancy termination.

Taken together, these data indicate that recognition of fetal antigens initiates changes in the functioning of the maternal immune system. The progesterone-dependent mediator PIBF plays an important role in this process by inducing Th2-dominant cytokine production and by controlling NK activity, thus creating a favorable environment for the embryo and the developing fetus.

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