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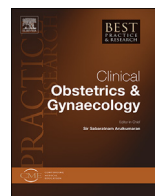
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Progestogens and immunology

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ABSTRACT

Fifty percent of fetal antigens are of paternal origin. These are recognized by the maternal immune system, thereby resulting in lymphocyte activation and the induction of progesterone receptors (PRs) in immune cells. Upon binding of progesterone to PRs on lymphocytes, a downstream mediator called progesterone-induced blocking factor (PIBF) is produced. The full-length PIBF is a 90 kDa protein; however, because of alternative splicing, several smaller isoforms are also produced. While the 90 kDa molecule plays a role in cell cycle regulation, the small isoforms are localized in the cytoplasm, and after secretion, they bind to their receptors on other cells and act in a cytokine-like manner. The communication between the embryo and the maternal immune system is established through PIBF-containing extracellular vesicles. PIBF induces an increased production of Th2 cytokines and inhibits degranulation of NK cells, and by regulating the maternal immune response, it contributes to successful implantation and maintenance of pregnancy.

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Introduction

Progesterone is essential for both the initiation and the maintenance of pregnancy in most mammals, partly, because of its effects on the immune system. The immuno-modulating effects of progesterone have been known for long [1,2], but an article published in the nineties by Siteri et al. [3] first called progesterone "nature's immunosuppressant." They showed that in vitro treatment with 10 μg/ml progesterone significantly altered the function of peripheral human lymphocytes. Although the progesterone concentrations used by Siteri et al. [3] might be comparable to those at the fetomaternal interface (3—10 μg/mg of placental tissue), these concentrations are at least 100 times more than the highest levels in the peripheral blood of 3rd-trimester pregnant women [4]. Later, it became evident that although physiological progesterone concentrations fail to alter the function of peripheral lymphocytes of nonpregnant individuals, the same concentrations significantly reduce NK activity of pregnancy lymphocytes [5]. The high progesterone sensitivity of pregnancy lymphocytes strongly suggested a receptor-mediated action of progesterone in pregnancy lymphocytes.

Progesterone receptors

The presence of nuclear progesterone receptors (PRs) in immune cells has been a matter of controversy [6—8]. Most studies showed absence of nuclear PRs in lymphocytes from nonpregnant women [6—8] while PBMCs [8,9] as well as peripheral blood γδ T cells [10] and NK cells [11] from pregnant women (the latter expressing both PR A and B isoforms) have been shown to contain nPRs. Studies in pregnant mice have reported nuclear PR expression on T cells at both RNA and protein levels [12]. The biological activities of progesterone are also mediated by nongenomic pathways through membrane receptors, e.g., G-protein-coupled membrane progestin receptors (mPRs) [13—15].

Nuclear PRs can be induced by in vitro mitogenic or alloantigenic stimulation of nonpregnancy lymphocytes [16]. A high percentage of PR-positive lymphocytes have been detected in the peripheral blood of liver transplant or transfused patients [17], suggesting that lymphocyte activation resulting from permanent alloantigeneic stimulation by fetal antigens might account for the induction of PRs in lymphocytes. Further evidence comes from a study, where effective immunotherapy with paternal lymphocytes for unexplained recurrent spontaneous abortion increased the expression of PRs on maternal lymphocytes [18], and the increase of PR expression correlated with the success or failure of gestation.

Progesterone-induced blocking factor (PIBF)

The immunological effects of progesterone are mediated by the progesterone-induced blocking factor (PIBF) [19]. PIBF is produced by PR-positive pregnancy lymphocytes and by several pregnancy-related tissues and malignant tumors [20,21]. PIBF is a progesterone target gene localized on chromosome 13 in humans and chromosome 14 in mice. Transcription of the human PIBF1 gene produces 3 unspliced pre-mRNA forms, the longest of which contains 18 exons. The predicted protein contains 756 amino acids and its molecular weight is 90 kDa [22]. Alternative splicing produces PIBF isoforms with different functions. The full-length (90 kDa) PIBF is associated with the nucleus and is involved in cell cycle regulation. Smaller isoforms are localized in the nucleus and act as cytokines [21].

The expression of PIBF seems to be crucial for normal progression of pregnancy. Compared to normal mouse fetuses, resorbed mouse fetuses show lower expression of the N terminal exons together with significantly reduced production of the full-length protein [23]. Reduced production of the full-length PIBF protein results in disturbed cell cycle regulation and dysregulated trophoblast invasion, while the absence of PIBF isoforms containing exon 2—4 coded sequences might lead to the loss of local immunosuppression. While the 90 kDa PIBF protein is highly expressed in malignant

tumors [24–30] and regulates trophoblast and tumor cell invasion [31–35], the smaller isoforms act on arachidonic acid metabolism and the immune response. The small isoforms inhibit arachidonic acid release by direct action on the phopholipase A2 enzyme and the subsequent decrease in prostaglandin and/or leukotriene synthesis, contributing to uterine quiescence [19].

The most extensively studied immunological effects of progesterone and its downstream mediator, PIBF, are those exerted on NK activity and on cytokine balance.

PIBF and NK activity

There are differences between peripheral and decidual NK cell populations. Approximately 90% of human peripheral NK cells express a low density of CD56 (CD56^{dim}) molecules and high levels of the FCgRIII (CD16) molecules; the majority of decidual NK cells express a high density of the CD56 molecule (CD56^{bright}) and no CD16. Peripheral CD56^{dim} NK cells are cytotoxic, whereas CD 56^{bright} CD16^{neg} granulated decidual NK cells constitute the dominant lymphocyte population in the early decidua [36]. Despite their high perforin content [37,38], these cells are not cytotoxic but secrete angiogenic factors and cytokines [39,40], and one of their functions might be the control of placentation. Murine decidual DBA + NK cells express PIBF in their cytoplasmic granules in co-localization with perforin [41].

Although Henderson et al. [42] failed to demonstrate PRs in human decidual LGL and T lymphocytes, PRs were detected on decidual stromal cells. Therefore, it is conceivable that PIBF produced by other nonlymphoid cells is internalized by decidual NK cells. Our team found PIBF to inhibit perforin liberation from activated peripheral NK cells [43]. Considering the PIBF positivity of decidual NK cells, it cannot be ruled out that the same mechanism might contribute to the low lytic activity of decidual NK cells.

PIBF and cytokine production

The optimal immunological milieu for the developing fetus is established by the concerted action of the neuroendocrine and immune systems. During pregnancy, the cytokine balance in peripheral blood is shifted toward a Th2 response [44,45]. However, it would be an over-simplification to consider the entire course of pregnancy as a Th2 phenomenon. Certain phases of gestation, for example, implantation or labor, are accompanied by a mild inflammation. The Th1/Th2 ratio is lower in the peripheral blood of healthy pregnant women than in that of nonpregnant individuals or in women with pathological pregnancies [46]. Administration of Th1 cytokines to pregnant mice results in pregnancy loss [47].

Both progesterone [48] and PIBF [49] alter the cytokine balance in favor of a Th2 response. In the uterus, progesterone induces the differentiation of naïve T cells upon antigen recognition into Th2 memory cells [50]. Lymphocytes from pregnant women respond to progesterone treatment with decreased production of Th1 cytokines and an increased production of Th2 cytokines [51]. Lymphocytes from women with recurrent miscarriage or preterm delivery tend to produce elevated levels of Th2 cytokines in the presence of PIBF [52]. These data indicate that progesterone and PIBF alter the cytokine balance and contribute to decreased cell-mediated responses during pregnancy.

Role of progesterone-dependent immunomodulation in the establishment and maintenance of pregnancy

A recent longitudinal study in progesterone-treated pregnant women showed that the immune system of pregnant women is activated and exerts increased antigen-specific cytotoxic T cell responses. Simultaneously, pregnancy promotes a tolerant immune environment (increased IL-10 production and increased frequency of regulatory-T cells) that gradually reverses before the onset of labor. Progesterone suppresses antigen-specific CD4 and CD8 T cell inflammatory cytokine (IFN-γ) and granzyme B release. Thus, exogenous progesterone reduces pro-inflammatory and cytotoxic T cell responses by

effectively modulating immune cell-mediated interactions and regulating differentiated memory cell subset sensitivity to antigen stimulation [53].

Earlier evidence suggested that signals emitted by the developing embryo might reach and re-set the function of the maternal immune system [54,55]. Extracellular vesicles (EVs) are produced by numerous cell types, and because of their diverse cargoes, they can be considered as a means of communication between the two sides of the fetomaternal unit [56]. Mouse embryo-derived EVs were shown to adhere to the surface of both $CD4^+$ and $CD8^+$ murine peripheral T lymphocytes, partly, through phosphatidylserine binding. Incubation with embryo-derived EVS increases the number of IL-10 + murine peripheral $CD8^+$ cells, and this effect is counteracted by pretreatment of EVs with anti-PIBF antibody, suggesting that the embryo communicates with the maternal immune system through the EVs [57].

Studies with PR knockout mice have revealed that during pregnancy, immunologically active PIBF is produced by the activation of PRA. Both progesterone and PIBF induce the decidual transformation of endometrial stromal cells. PIBF is present in the mouse endometrium in early pregnancy, with an expression peak during the implantation window [58]. Taken together, these data suggest that PIBF might play a role in implantation. Studies on IVF patients showed that PIBF appears on the lymphocytes of pregnant women early after implantation [59].

During normal pregnancy, the concentration of PIBF in the urine and serum continuously increases until the 37th gestational week, followed by a sharp decrease in preceding labor. In pathological pregnancies, urinary PIBF levels fail to increase. The onset of labor (both in term or in preterm delivery) is predictable on the basis of PIBF levels [60,61]. A recent study showed that the presence of PIBF + decidual B cells protects against preterm labor [62], while a clinical study on women with threatened preterm delivery revealed a relationship between down-regulation of PR expression as well as that of its downstream mediator PIBF and a negative outcome [63]. In the same patients, downregulation of PR and PIBF expression was found to correlate with a Th1-dominant immune response. The authors concluded that differential expression of PR, PIBF, and TNF-α has prognostic value, and hence, it is of clinical significance in predicting preterm labor.

Taken together; these data suggest that a significant part of the immunological pregnancy-protective effect of progesterone is manifested through its downstream mediator − PIBF. Following recognition of fetal antigens, maternal lymphocytes become activated and develop PRs. Progesterone binding to the receptor induces PIBF synthesis, which, by interfering with arachidonic acid metabolism, controlling NK activity, and inducing a Th2 immune response, allows pregnancy to proceed to term.

Summary

Progesterone is essential for both the initiation and the maintenance of pregnancy in most mammals, partly because of its effects on the immune system. The immunological activities of progesterone are mediated by genomic or nongenomic pathways. Nuclear PRs (PRs) are induced following lymphocyte activation. The PIBF is a downstream mediator of progesterone.

The expression of PIBF seems to be crucial for normal progression of pregnancy. The most extensively studied immunological effects of progesterone and its downstream mediator, PIBF, are those exerted on NK activity and on cytokine balance.

Decidual NK cells constitute the dominant lymphocyte population in the early decidua. Despite their high perforin content, these cells are not cytotoxic but secrete angiogenic factors and cytokines. PIBF inhibits perforin liberation from activated peripheral NK cells. Considering the PIBF positivity of decidual NK cells, it cannot be ruled out that the same mechanism might contribute to the low lytic activity of decidual NK cells.

Except for implantation and labor, pregnancy is characterized by a Th2-biased immune response. Both progesterone and PIBF alter the cytokine balance in favor of a Th2 response.

PIBF takes part in implantation, and low serum levels of PIBF predict pregnancy termination. Taken together, these data suggest that the immunological pregnancy-protective effect of progesterone is manifested through its downstream mediator — PIBF, which, by interfering with arachidonic acid metabolism, controlling NK activity, and inducing a Th2 immune response, allows pregnancy to proceed to term.

Practice points

- PIBF could be a potential biomarker for predicting pregnancy termination. However, thus far, no reliable clinical test has been available.
- Because of its immunogenicity, PIBF, in its natural form, cannot be considered as a treatment for preventing premature pregnancy termination in humans.

Research agenda

- Identifying the sites responsible for the immunological effects within the PIBF molecule and synthesizing peptides with the same activity might open new perspectives in the management of specific types of threatened miscarriages and preterm deliveries.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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