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Research Article

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The Role of Membrane Progesterone Receptor Associated Proteins in Gynecological and Reproductive Disorders, and Cancers: An Editor's Historical Perspective

Part 1: Molecular Aspects

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ABSTRACT

How can a fetus with half of the antigens from a paternal source not be immunologically rejected? There is evidence that not only does the state of pregnancy fail to preclude invasion of cellular immune cells into uterine tissue, but, in fact, by progesterone (P) blocking the biogenic comma after dopamine, and a lower case t for this: it should read dopamine. This allows a greater infiltration of leukocytes. This invasion seems to be needed to aid in the creation of thin-walled spiral arteries for nutrient exchange between mother and fetus. Related to the speed of the development of these spiral arteries, it is not likely that the main mechanism involves neovascularization, since this is a slow genomic process which would operate by activation of nuclear progesterone receptors (nPRs). Instead, remodeling of the already pre-existing thick-walled uterine arteries by autoimmune mechanisms is more likely. Could the fetal placental unit somehow preclude these cellular immune cells from invading the fetal placental unit? These cells do, in fact infiltrate the fetal placental microenvironment composed of 70% natural killer cells, 20% macrophages, and 10% cytotoxic T-cells. Evidence does exist that one of the main ways of preventing immune rejection of the fetus is by P activating rapid acting membrane (m) PRs to produce immunomodulatory proteins e.g., the progesterone induced blocking factor (PIBF) and the progesterone receptor membrane component-1 protein (PGRMC-1). PIBF, for example, eventually suppresses natural killer cell cytotoxicity by stabilizing perforin granules and granzymes. Understanding these mechanisms has led to a scientifically based treatment regimen to achieve a successful pregnancy.

Keywords: Membrane Progesterone Receptor, Dopamine, Immunomodulatory Proteins, Fetal Placental Semi-Allograft Preterm Delivery, Progesterone Induced Blocking Factor

Introduction

The goal of this perspective is to provide evidence that a normal pregnancy requires stimulation of membrane progesterone receptors (mPRs) to help to produce certain immunomodulatory proteins to help the fetal semi-allograft to escape immune surveillance. Two of these immunomodulatory proteins are the progesterone induced blocking factor (PIBF) And the progesterone receptor membrane component-1 protein (PGRMC-1). Evidence will be provided showing that malignant tumors also utilize mPRs and their associated immunomodulatory proteins to also escape immune surveillance considering the presence of foreign onco-fetal antigens. Because of an increase in thymic helper (TH)-1 cytokine dominance in women with pelvic pain and endometriosis, one may need to increase the immunomodulatory proteins to supranormal levels to neutralize excessive inflammation in women with endometriosis and thus prevent immune rejection of the fetal semi-allograft.

This perspective is to introduce the concept that infertility and/or miscarriage may be related to the relative need to produce a greater amount of these mPR immunomodulatory proteins in cases where there is a greater than normal presence of cellular immune cells. These immune cells are normally needed for uterine artery remodeling to create thin-walled spiral arteries from the thick-walled uterine arteries found during the proliferative phase. Evidence will be provided that the presence of pelvic pain with or without the documented presence of endometriosis is indicative of excessive inflammation making an even

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greater need for raising the level of these immunosuppressive proteins especially in the fetal placental micro-environment. Since evidence suggests that malignant tumors utilize these same mPR induced immunomodulatory proteins to escape immune surveillance, theoretically, instead of enhancing these proteins, as needed for patients with infertility or history of miscarriage, if one suppresses PIBF and other mPR induced immunomodulatory proteins, one could cause cancer regression and improve length and quality of survival. The importance of the cancer studies related to this perspective is based on some of the shared characteristic of malignant tumors and endometriosis (e.g., proliferation of a mass of cells with spread outside the organ of origin) is to provide food for thought as to one potential mechanism as to how endometriosis may proliferate. Just as important, the studies on mPR induced immunomodulatory proteins may show the potential mechanism of how the endometriosis lesions can proliferate outside the uterus which would not normally be an immunologically privileged site. This concept could apply also to uterine fibroids.

Thus, in summary, this perspective will present data supporting the concept that mPR induced immunomodulatory proteins play a significant role in allowing both the fetal semi-allograft and malignant tumor to escape immune surveillance. For pregnancy one wants to enhance PIBF secretion and for cancer to reduce it. Improving PIBF secretion may be especially important to improve fecundity in women with pelvic pain and endometriosis.

A Personal Historical Perspective

The initial scientific interest of the lead author was cancer immunology. His early research involved trying to increase the immunogenicity of relative weak oncofetal tumor antigens followed by autologous inoculation with the killed tumor cells into the host. Though this technique did demonstrate increased longevity in mice bred for a high frequency of spontaneous cancers, the lead author sought a treatment that would better suit a larger human population and that would also be less time consuming [1-4].

After considering the similarity between the fetal semi-allograft and malignant tumors, i.e., rapid proliferation of cells, invasion of normal tissue, and evasion of immune surveillance, the lead author considered the likelihood that the malignant tumor would utilize mechanisms already available for the fetal placental unit to accomplish the delivery of a live baby. Unfortunately, at that time there was little knowledge about the immunology of pregnancy.

The field of reproductive endocrinology and infertility (REI) was just in its incipient stages at that time, so the lead author decided to take a fellowship in REI. Subsequently, after learning the clinical side of REI, which provided to the lead author a sense of what is clinically important, he proceeded to do basic science research in reproductive biology/immunology to hopefully find the mechanism of how the fetal semi-allograft can evade immune surveillance. He hoped that by finding how the fetus escapes immune surveillance that this would lead to also finding that cancer cells use the same mechanism. Hopefully, this information would progress to find unique effective therapies to thwart cancer advancement and to help infertile women or those with recurrent miscarriages or other reproductive abnormalities e.g., pre-term delivery, to have successful outcomes.

The ultimate effect of a hormone requires interaction with a hormone receptor. Subsequently, the hormone and hormone receptor complex migrates to the nucleus. This is followed by transcription and translation of the message leading to the production of enzymes, cytokines, or proteins that initiate the biological effect. In 1989, Baulieu showed that ingesting a progesterone receptor (PR) antagonist called mifepristone can terminate a live pregnancy [5]. Even a very short-term use of one pill of 200mg can kill the fetus [5].

Our interpretation of the mechanism of how short-term blockade of the PR could lead to an abortion must be by removing a block to immune tolerance, leading to immunological rejection of the fetal semi-allograft. Thus, a search was made of the scientific literature to see if there was a product of P interacting with the PR receptor that could be a candidate for an enzyme, cytokine, or protein that may be needed to prevent immune rejection of the fetal semi-allograft. Indeed, such a potential substance was found in a manuscript published by Julia Szekeres-Bartho and her group in 1985 [6]. Initially there was concern that there were no more publications about this substance from 1985 up to the 1989 aforementioned publication of Baulieu. However, in the same year of the publication by Baulieu 2 more publications from Dr. Szekeres-Bartho and her group provided more information about this immunosuppressive substance that it is released from lymphocytes from pregnant women when exposed to P [6-8].

Shortly thereafter Szekeres-Bartho et al showed that this P induced immunosuppressive factor involved a PR (whether it was a nuclear (n) PR or membrane (m) PR was not known) [9]. Later SzekeresBartho et al showed that this factor inhibited NK cells from rejecting the fetus by inhibiting perforin degranulation and granzymes [10-12]. Szekeres-Bartho et al named this factor, which was determined to be a protein, as the progesterone induced blocking factor (PIBF) [12]. Further studies found that PIBF also inhibited T-lymphocyte activity and NK cell function and macrophage killing effects by causing a shift from TH1 cytokine dominance to TH2 cytokine dominance [13].

All the studies by Szekeres-Bartho et al were performed after conception occurred, and suggested PIBF production was needed to maintain normal pregnancies, and that subnormal levels could lead to miscarriage [8]. It was not clear if PIBF was needed for successful implantation. We found that one could detect PIBF shortly after implantation, and that better levels correlated with achieving a pregnancy, and lower levels were associated with failure to conceive [14,15].

Molecular Biology of PIBF

Subsequently, a researcher from Dr. Szekeres-Bartho's laboratories, Dr. Beata Polgar, was able to determine the molecular structure of the parent PIBF protein and determined the portions that are biologically active [16]. Polgar et al found that PIBF complementary DNA encodes a protein composed of 757 amino acids with a predicted molecular mass of 89-

90kDA [16]. The 48kDa N terminal part was biologically active [16]. Furthermore, she found that the PIBF gene was located at chromosome 13 [16]. Polgar et al found that the mRNA transcribed from the PIBF gene contains 18 exons and codons for the parent form of PIBF [16].

The parent form with 757 amino acids has a centrosomal position in the nucleus [17]. It actually may play a role in the integrity of the meiotic spindle [18]. There is evidence that the whole PIBF protein plays a role in cell cycle regulation [17,18]. Invasiveness of both the trophoblast and malignant tumors may be facilitated by the role that the 89-90KDa parent form of PIBF plays in cell cycle regulation [19-21]. Could endometriosis also utilize the 90kDa form of PIBF to facilitate invasion of these endometrial implants? Food for thought and fodder for potential studies.

The Immunosuppressive Role of Shorter Cytoplasmic Splice Variants of the Parent PIBF Protein.

The aforementioned study by Polgar et al also found that PIBF was also expressed by tumor cell lines of human mammary carcinoma cell-line MCF-7 that was positive for the nPR in addition to circulating gamma/delta T cells seen in abundance in the human pregnant state [16]. From the same research laboratory, Dr. Lachmann et al found that although the parent PIBF protein was found in various normal tissues, there was much higher concentrations of the parent form of PIBF in peripheral blood mononuclear cells (PBMCs), placenta, and mammary carcinoma cell lines [17].

Lachmann et al also found that the parent PIBF could be split into splice variants with a lower molecular weight. The most frequently identified splice variant encoding for a 35KDa protein which was abundant in stomach cancer, uterine cancer, peripheral blood mononuclear cells, embryos, testes, and placenta [17]. The presence of this 35KDa splice variant was present in mammary carcinoma whether the tumor was positive or negative for the nuclear estrogen or P receptor [17]. However, still the most abundant form of PIBF was the parent 90kDa protein [17]. The 35KDa isoform contains the N terminal 223 amino acids of the parent form and 75 amino acids from the C-terminal end [17]. Lachmann et al, speculated that the 90KDa form of PIBF is not actually part of the centrosome but rather a microtubule associated protein, and that it could lead to disturbed centrosome duplication leading to unusual segregation of chromosomes which could subsequently lead to tumorigenesis [17]. Indeed, over expression and mutation of the centrosome associated proteins observed in tumors is correlated with centrosome amplification and aneuploidy [22]. Studies by Dr. Szekeres-Barthos's team found that the 90KDa parent form of PIBF was important in not only tumor invasion into normal tissues, but also trophoblast invasion [19,20].

The aforementioned 34-35KDa splice variants are located in the cytoplasm. There is evidence that splice variants are immunosuppressive and cause a shift in TH-1 cellular immune cytokine dominance to TH-2 immunoprotective cytokines [23,24]. The cytoplasmic splice variants bind to the GP1 anchored PIBF receptor which forms a heterocomplex with the alpha chain of the IL-4 receptor [25]. This binding is at least partially responsible for the change of TH1 dominance in the follicular phase of a nonpregnant woman to TH-2 dominance found during a viable pregnancy [24, 25]. The PIBF receptor signals through the JAK/STAT pathway [25]. There is evidence that at least one way that the 34-35 KDa intracytoplasmic splice variant PIBF protein helps the trophoblast to evade immune surveillance by the plentiful decidual natural killer (NK) cells (which represents at least 25% of decidual lymphocytes) is by stabilizing perforin granules and stabilization of granzymes A and B thus suppressing the mechanism of how NK cells attack other cells and tissues [26,27]. Thus, PIBF seems to play a major role in inhibiting immune rejection, so that one may be infertile related to immune rejection so early that a positive pregnancy test does not occur. Alternatively, the death of the fetus may be later leading to 1st trimester miscarriage [11-15].

Further Studies to Learn More about the Role PIBF Plays in Conception and Prevention of Miscarriage.

The initial assay used by Dr. Szekeres-Bartho's team, and our group, was an immunocytochemistry technique because the anti-PIBF antibody was polyclonal related to lack of purification of the PIBF protein. With the purification of the PIBF protein, to learn more about the role of PIBF, our group worked on developing a monoclonal antibody that would allow us to develop a more sensitive technique for detection than the immunocytochemistry technique. We eventually did develop a more sensitive ELISA technique.

Interestingly, although low PIBF levels correlate with miscarriage in untreated women, no differences were found in those completing the 1st trimester vs those with miscarriage in women supplemented with P after ovulation and during the 1st trimester (28). One interpretation of that study is that P supplementation may correct miscarriages from PIBF deficiency so that miscarriage despite P supplementation may be related to other factors, e.g., aneuploidy [28].

One question to answer was, does the corpus luteum of pregnancy have a functional role by the secretion of some hormone or other molecules that increases the efficacy of production of PIBF? The serum PIBF levels 1 week after ovulation in those women who had a positive pregnancy test were no different than women conceiving with donor eggs or by frozen embryo transfer where there was no corpus luteum (because of the corpus luteum formation was impeded by a graduated estradiol (E2) regimen) [29]. Thus, we concluded that a corpus luteum is not essential for PIBF production [29].

There is a need for E2 to help develop nPRs [30]. It was not clear initially as to whether the production of PIBF required activation of the nPR, or possibly just the mPR, or both [31]. The biological activity of P is mediated by slow genomic pathways through nPRs or by non-genomic quicker pathways using mPRs [30-32].

To rule out the possibility that human chorionic gonadotropins in pregnant patients stimulate and (s) to factor in placental precursor cells e.g., trophoblast cells, we evaluated PIBF levels in menopausal women on estrogen and P replacement and found that serum PIBF levels also increased significantly during the P treatment phase [29, 33]. We subsequently found that PIBF was significantly increased in menopausal women not given E2 and even in males given intramuscular P [33,34]. Thus, since E2 is usually needed to induce nPRs in tissues, and this genomic type

of response, which usually takes longer for its manifestation to occur, coupled with the fact E2 is not needed for P to cause a rapid increase in PIBF, the data suggested to these authors that it is the mPR rather than the nPR when activated that leads to PIBF secretion since PIBF production occurs shortly after P exposure and a genomic nPR driven reaction would take longer [31].

Possible Differences in the mPRs in NK Cells vs mPRs in Fetal/Placental Tissue (Embryonic Cells, Mesenchymal Cells and Trophoblast Cells) in Producing PIBF

As mentioned, one 200mg pill of mifepristone is able to abort a healthy pregnancy where there is a great amount of P being secreted both by the corpus luteum of pregnancy and placental tissue [5]. Thus, if the mechanism for inducing a therapeutic abortion is through immune rejection by blocking the secretion of PIBF by circulating gamma/delta T cells, then one should be able to document that even in the presence of P, mifepristone, a PR antagonist, lowers serum PIBF. However, we found that mifepristone does not lower serum PIBF in the presence of P [35].

One theoretical conclusion from this aforementioned study is that PR antagonists terminate pregnancy in some other way than by suppressing PIBF [35]. However, an alternative hypothesis is that the serum PIBF is mostly contributed by circulating gamma/delta T cells, and the mPRs in the gamma/delta T-cells are not susceptible to blockade by PR antagonists at least in the presence of P. An extension of this hypothesis is that it is in the locally produced PIBF in the fetal-placental microenvironment that is mostly responsible for the fetus to escape immune surveillance, and that PIBF made by fetal placental cells is able to be blocked by PR antagonists even in the presence of P [35].

The locally produced PIBF is produced by rapidly proliferating cells including embryonic, mesenchymal and trophoblast cells, but also rapidly growing cancer cells. To test the hypothesis that PIBF secreted from rapidly proliferating cells can be suppressed by PR antagonists, we evaluated multiple different human leukemia cell lines to see if P can activate the mPR in these cancer cells leading to production of messenger (m) RNA for PIBF and the PIBF protein itself. We also evaluated whether they can be down-regulated by mifepristone. We purposely chose cancer cell lines that do not have the presence of nPRs [36].

We found that supplementation of P to the media markedly increased mRNA for PIBF and the PIBF protein itself [36]. However, adding mifepristone to the media markedly suppressed PIBF production both in culture media not supplemented with P and media supplemented with P [36]. These data thus suggested that there is indeed a difference in the mPRs of gamma/delta T cells vs rapidly proliferating cancer cells (and possibly fetal/placental cells) at least in susceptibility to suppressing PIBF production by mifepristone in the presence of P. Thus, the possibility exists that PIBF in the serum vs the fetal/placental or cancer microenvironment could have somewhat different functions.

Breast cancer cells secrete in culture high levels of PIBF [16,17]. However, we found that the serum PIBF levels are not increased in women with breast cancer whether positive or negative for the nPR, nor in women with gynecologic cancers that may also have nPRs [37,38]. Thus, we infer that the source of PIBF in the serum after ovulation is predominately from progesterone interacting with mPRS of gamma/delta T cells, with probably only a minor negligible contribution to serum levels of PIBF from the rapidly proliferating fetal and placental cells which are locally producing PIBF.

Do any Pregestational Agents other than P Itself Stimulate PIBF

Our group failed to demonstrate any rise of serum PIBF in women treated with medroxyprogesterone acetate, norethindrone, dydrogesterone or 17 hydroxy progesterone [34]. Thus, if the secretion of adequate PIBF is one requirement for successful conception, using pure P rather than a synthetic progestin (which does not increase PIBF levels) would seem to be a more logical therapeutic choice. The P should be started right after egg release from the follicle to minimize the immune insult 6 days later when the fetal-placental unit invades the endometrium (possibly with the help of the parent 90kDa form of PIBF). The prevention of damage from a cellular immune attack causing immediate death or injury leading to future death of the fetus probably requires the rapidly proliferating embryonic, mesenchymal and trophoblast cells to produce the splice variants of PIBF that have immunoprotective effects [13,17,19, 20, 23]. Though synthetic progestins seem to interact with nPRs allowing similar histologic changes in the endometrium similar to P, they do not appear to interact nearly as well as P with the mPR in making immunoprotective proteins.

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