Evidence that progesterone receptor antagonists may help in the treatment of a variety of cancers by locally suppressing natural killer cell activity

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Summary

Purpose: To propose a novel concept that progesterone receptor antagonists, e.g., mifepristone, may prove effective in treating a variety of cancers – even those not shown to be hormonally dependent or possessing progesterone receptors. *Methods:* Multiple human leukemia cell lines were evaluated for mRNA expression of an immunomodulatory protein called the progesterone-induced blocking factor (PIBF) that suppresses natural killer (NK) cell activity during normal pregnancy. Furthermore, we evaluated the effects of progesterone (P) and mifepristone in PIBF protein expression. Finally, the effect of mifepristone treatment of mice with advanced leukemia was evaluated. *Results:* All tumor cell lines evaluated were found to express mRNA for PIBF and some were found to even express the PIBF protein. The addition of P to the media increased the expression of PIBF and mifepristone down-regulated its expression. Treatment of mice with spontaneous leukemia when they already had extensive disease seemed to increase the length and quality of their life. *Conclusions:* These data and other experience with mice with lung cancer and some anecdotal human cancer experience suggest that various cancers may utilize similar mechanisms used by the fetus to escape NK cell surveillance. Mifepristone and other progesterone receptor antagonists may deserve a clinical trial in human cancer even where there is no knowledge of the presence of progesterone receptors.

Key words: Progesterone receptor antagonist; Cancer immunology; Natural killer cells.

Effect of progesterone and progesterone receptors on immune tolerance to the fetus in normal pregnancy

There are data supporting the concept that one of the mechanisms involved in escape from immune surveillance, especially by natural killer (NK) cells in normal pregnancy, is through the hormone progesterone (P) [1].

A 34 kDa protein has been identified in pregnant women which can block NK cell mediated lysis of K562 tumor cells [2]. Because the expression of this protein by CD8+ T-lymphocytes (specifically gamma/delta T cells) needs P exposure for its expression, it was named the progesterone-induced blocking factor (PIBF) [3]. There is evidence that PIBF may induce a shift from TH1 to TH2 cytokines [4, 5].

Progesterone receptors have not been demonstrated in normal T lymphocytes, yet these receptors have been found at a lower density than in other P receptor tissues in normal pregnant women [6-8]. Liver transplants and blood transfusions have been shown to induce P receptors on these gamma/delta T cells even in male patients [9]. Further evidence that an allogeneic stimulus can induce P receptors in gamma/delta T cells leading to PIBF expression when there is exposure to progesterone was shown by injection of paternal lymphocytes prior to ovulation with subsequent demonstration of increased PIBF secretion in mid to late luteal phase in women exposed to embryo transfer [10]. The P receptor on these gamma/delta T cells have a much lower affinity for P than other tissues known to be targets for P, e.g., the endometrium [8].

These data have led to the following hypothesis as to at least one way the fetus escapes immune rejection by NK cells: the fetal semi-allograft induces P receptors in gamma/delta T cells following trophoblast invasion. The interaction with a high concentration of P causes the expression of PIBF by these gamma/delta T cells with induced P receptors. PIBF is only made at the maternal fetal interface because that is where there is an adequate high concentration of P. Progesterone receptors are made throughout the body in gamma/delta T cells but the P level is insufficient to cause PIBF expression by gamma/delta T cells not at the maternal-fetal interface. PIBF inhibits NK cell cytologic activity at least partially by inhibiting the release of perforin from the storage granules of NK cells [11]. PIBF also inhibits TH1 cytokines and favors TH2 cytokines thus inhibiting cellular immune response and promoting humoral response. The suppression of the cellular immune system is limited to the maternal-fetal interface and this constitutes selective immune tolerance.

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Support for this hypothesis was provided by finding in two studies much less PIBF expression in women who eventually lost their pregnancies vs healthy pregnant women [12, 13]. These women had not been treated with any extra progesterone. However, no such difference in PIBF expression was found in aborters vs non-aborters in patients aggressively treated with P [14] so that the serum P was maintained at ≥ 40 ng/ml.

Thus these data are consistent with the hypothesis that many miscarriages are related to immune rejection related to insufficient P secretion leading to insufficient PIBF expression. With aggressive P therapy many of these miscarriages may be avoided and presumably the ones that still occur would be predominantly of a genetic origin, especially accidental aneuploidy.

Mifepristone is a progesterone receptor antagonist that is used to abort normal pregnancies. It has been hypothesized that some cancers may also use PIBF to escape immune surveillance by NK cells [15]. The possibility exists that mifepristone or other progesterone receptor antagonists could be used to abrogate immune tolerance against some cancers.

Expression of mRNA for PIBF and PIBF protein expression by human leukemia cell lines

Data was presented at the 2005 American Association for Cancer Research meeting that all leukemia cell lines tested expressed PIBF mRNA [16]. In fact there appeared to be more mRNA expressed for PIBF protein than any other mRNA for other proteins made by these leukemia cells [16]. Cell lines examined included T cell lines: SRIK-NKL, MOT, HUT 102, HUT 78, HTLV-1+ transformed CD8+ cell line, SRID-TL, JURKAT, SRIA-TL, SRIP-TL, CEM; myeloid cell lines: THP-1, U937, K562, HL60, SRIS-EOSL, ML-1 HEL; B cell lines: T-PLL, R-CLL, 729 pHneo, SRIH-B (ATL), U266, 8226; epithelial cell lines: MDE, KATO-3, CaCo2, MeWo, MCF-7; fibroblasts: BG9; and G-CSF mobilized CD34+ normal cells, as well as PBMC from a normal male donor [16].

PIBF protein in normal pregnancy is expressed by gamma/delta T white blood cells. Thus, the possibility exists that the mRNA for PIBF is not produced for inhibiting NK cell destruction of the tumor cells but is merely there because of the fact that the genes for its production exist in these white blood cells fortuitously by restoration of repressed genes by these white blood cell cancers.

However, there are data to support the possibility that PIBF mRNA and protein expression may really be needed for escape from immune surveillance. Although mRNA expression was found in ten PIBF T cell leukemia lines, it was also found in seven myeloid leukemia cell lines and six B cell leukemia lines.

Furthermore PIBF protein expression was tested in ten cell lines and it was detected in four. The possibility exists that the presence of PIBF has some other function. Even if it has immunological protective effects, it may be produced in some other manner than through a progesterone mechanism. However, the effect of progesterone and mifepristone on PIBF mRNA in three cell lines (*U937, T-PLL, and SRIK-NKL) was clearly upgraded in U937 and T-PLL [16]. Similarly, PIBF protein expression was increased at 24 hours incubation with P in all three cell lines. Treating with mifepristone resulted in reduced production of PIBF mRNA by U937 and T-PLL leukemia cell lines. Also PIBF protein was decreased by treating with mifepristone in U937, T-PLL, and SRIK-NKL leukemia cell lines [16].

Thus these data suggest that some cancers, especially of the lymphoid system, can express PIBF protein, and progesterone and progesterone receptor antagonists could modulate its expression. The next question that arises is whether solid tumors express PIBF similar to lymphoid cancer. Unfortunately we only had access to leukemia/lymphoma cell lines. We hope to test solid human tumor cell lines in the future for PIBF mRNA and protein expression.

Murine intact animal models with anti-cancer effects of progesterone receptor antagonist on survival and quality of life

Data was presented at the 2005 American Society of Cancer Research on the effect of mifepristone on spontaneous lymphocytic leukemia in AKR/J mice [17]. Treatment was not initiated until the mice were six months old when the cancer was well advanced [17]. There were 61 mice gavaged with 0.3 mg mifepristone in 0.3 ml olive oil vs 33 control mice only gavaged with olive oil. Treatment was started at two-week intervals then decreased to one-week intervals after ten weeks. Quality of life was determined by the body conditioning score (BCS) and was determined not by the researchers but independently by the vivariun staff who was blinded as to treatment. Any mouse with a BCS of two or less or who was unable to move or eat independently was euthanized.

The death rate (natural or euthanization) within the first two weeks of gavaging was 11.4% (7/61) in the mifepristone-treated mice vs 45.4% (15/33) for the olive oil controls [17]. The death rate within 30 days of the first gavage was 85.3% (52/61) for mifepristone-treated mice vs 100% (33/33) for olive oil controls [17]. The mice treated with mifepristone were much more active than the olive oil controls and had a slower decline in the BCS [17].

The possibility exists that an even better outcome could have been achieved if the mice had been treated with a higher dosage of mifeprostone or more frequently, or if treatment had started earlier. These studies are ongoing.

The previous data with leukemia cell lines showing that mifepristone could reduce PIBF protein expression did not prove that in the intact mammal such treatment would have any benefit on disease. Thus the intact mouse model is important since it demonstrated that a progesterone receptor antagonist can inhibit the progression of cancer. Furthermore, since the tumor model is not one known to possess progesterone receptors, and thus be a target for progesterone

or progesterone receptor antagonists, the data supports the immune hypothesis, i.e., that mifepristone abrogates an immune protective mechanism set up by the cancer that causes local production of PIBF which, in turn, inhibits natural killer cells from attacking the tumor.

The AKR/J mouse model does not, however, answer the question as to whether this beneficial effect of treatment with P receptor antagonists has any effect on solid tumors. We are presently conducting studies on the effect of mifepristone therapy on a murine spontaneous lung cancer model and we are noting a similar beneficial effect (data not reported as yet).

Can tumor cells produce progesterone?

The demonstration of PIBF protein expression by human cancer cell lines suggests that this protein could play a role in allowing the tumor to escape immune surveillance especially by NK cells, similar to human pregnancy. However the possibility exists that there may be other ways to produce PIBF.

If the tumor did in fact cause PIBF protein expression through a non-progesterone mechanism, the fact that PIBF protein can by synthesized through recombinant DNA technology, therapy by creating monoclonal antibodies to PIBF might still prove useful.

Nevertheless if the expression of PIBF is found to require or at least be enhanced by P, then the use of progesterone receptor antagonists may prove more effective than monoclonal antibody therapy. Also there are already progesterone receptor antagonists on the market, e.g., mifepristone.

The key in the model for selective immune paralysis of NK cell function in normal pregnancy that paralyzes only those cells in the area of the fetus but not in the rest of the body is the requirement of a large local concentration of P because the P receptor on the gamma/delta T cell is weak. Thus PIBF would only be expressed by those gamma/delta T cells exposed to the high concentration of P at the maternal fetal interface.

There have been many tumor associated antigens (TAA) identified in malignant cells [18-20]. The possibility exists that they can function to cause de novo P receptor induction in gamma delta T cells (similar to the allogeneic stimulus of the embryo/fetus). But where would the high local concentration of P come from that could interact with the newly developed P receptors on the gamma/delta T cells? Interestingly there have been studies suggesting that various cancer cells secrete beta human chorionic gonadotropin (hCG) [21-23]. Beta hCG has a similar biological function to luteinizing hormone (LH) and hCG made by the corpus luteum is responsible for the continued production of P during the first trimester of pregnancy. Thus possibly the cancer cell that can escape NK cell immune surveillance is the one that can make hCG, which in turn leads to P production. The high local concentration of P interaction with de novo P receptors on gamma/delta T cells which have been induced by TAA interaction leads to the expression of PIBF by local gamma/delta T cells. According to the theory the interaction would lead to the local expression of PIBF protein which in turn would inhibit local natural killer cell activity.

Mifepristone in the treatment of human cancer

There are studies on the long-term use of mifepristone and other progesterone receptor antagonists for certain tumors known to possess a progesterone receptor. Benefit has been found in breast cancer [24-27]. Meningiomas have been found to possess P receptors and improvement from long-term treatment from mifepristone has been found in surgically non-resectable meningiomas [28-32]. There has even been one trial with some benefit in women with refractory ovarian cancer [33]. The only other cancer with known P receptors is prostate cancer but clinical trials have yet to be performed.

The assumption has been that only hormonally dependent tumors might respond to progesterone receptor antagonists. Interestingly, so far the only murine animal spontaneous cancer model that has not shown a beneficial effect of mifepristone has been RIII mice with breast carcinoma. The tumors, however, look much different on autopsy with the ones treated by mifepristone looking more vascular. The possibility exists that for this model progesterone is suppressive for growth and perhaps the benefit from increasing NK cell activity is negated by an adverse effect of removing progesterone suppression.

We have had some anecdotal experience in treating end-stage extensively metastatic non-hormone dependent human tumors with 200 mg mifepristone orally daily. The first case was a middle-aged woman with a rare epithelial cancer, thymic cell cancer. This malignancy does not normally respond to any chemotherapy and it is very aggressive. She was first treated with radiation therapy. Despite the treatment the tumor progressed and spread throughout the lungs. She was started on mifepristone and shortly after therapy was started she reported feeling much more energy and she was able to function very close to her normal self. The lesions did not disappear but the rate of growth seemed to slow considerably. She had taken mifepristone for almost two years but stopped because of advice from another treating physician and her fear of developing uterine cancer from the therapy. She was advised that there might be a 10% risk of endometrial hyperplasia (and so far no cases of endometrial carcinoma) but she stopped therapy [34]. She was advised by the other physician to try another course of radiation therapy and she developed complications from the second course of therapy. She died several months later and no autopsy was performed. To date she has lived the second longest with this aggressive cancer. She died at age 59.

An elderly man had adenocarcinoma of the colon widely metastatic to the liver and lungs. He had been treated with 5 fluorouracil (5-FU) but became progressively weaker and could not eat well. He was placed on mifepristone and within two weeks his energy and appetite returned and he was able to resume significant activities. He was treated for over a year and during this time he stated that he felt well and had no pain. His biggest metastic lesion had grown only 3 mm in six months. He started showing confusion but an MRI of his brain was negative. The confusion was attributed to uremia. There was a progression of his pre-existing renovascular disease; however there had never been any renal metastasis. He was to be discharged from the hospital the next day but he had a myocardial infarction that night and died at the age of 84.

Another woman aged 61 has adenocarcinoma of the colon widely metastatic to the peritoneum, ovaries and liver. She was advised that without treatment she would live only six months but with a 5-prong "multichemotherapy cocktail" she could live one year. Because of a fear of not having a good quality of life with the chemotherapy from the start vs maybe three months untreated she refused chemotherapy but requested mifepristone. She is being treated with 200 mg per day and for the last six months has felt "perfectly normal" and is performing all of her usual activities. The lesions did not regress and with family pressure she began a course of 5-FU and is soon to start bevacizumab. Interestingly, fatigue is one of the most common side-effects of long-term mifepristone reported when treating meningiomas [28, 29, 34] but in these three cases, the treatment resulted in increased energy.

Conclusions and Summary

Though immune tolerance to the fetus in normal pregnancy requires both local suppression of attack by cytotoxic T cells and NK cells, the "achilles heel" for the fetal semi-allograft appears to be the NK cell. Evidence suggests that suppression of NK cell destruction of the fetus requires progesterone and the mechanism may rely on the formation of a 34 kDa protein (PIBF) which is expressed by gamma/delta T cells which have had de novo induction of P receptors by the fetal semi-allograft. The interaction leading to PIBF expression, however, requires exposure to a very high concentration of progesterone. Very small dosages of progesterone receptor antagonists can terminate a pregnancy through immune rejection [35-37].

A model for potential immunotherapy using progesterone receptor antagonists based on the knowledge of immune mechanisms responsible for spontaneous tumors and some anecdotal experience with patients with widely metastatic end-stage disease has been presented lending support to this hypothesis and giving hope that progesterone receptor antagonists may help in the fight against cancer.

Our goal at the present time is to determine the efficacy of mifepristone in other solid murine spontaneous tumor models, e.g., prostate cancer and colon cancer. Variations in the future may include therapy earlier in the disease process, and comparisons of the efficacy of different progesterone receptor antagonists on spontaneous murine cancer.

These data though suggestive do not prove a definite beneficial effect of this therapy, especially in humans. Even if these drugs show efficacy, it does not prove the mechanism is through the one proposed. For example some tumors, e.g., murine hepatoma cells have been found to have an increased levels of glucocorticoid receptors [38]. Mifepristone also has anti-glucocorticoid receptor activity and has even been used to treat Cushing's syndrome [39-41]. Mifepristone has been able to partially suppress corticosteroid induced growth of hepatoma cells possibly by inhibiting the glucocorticoid receptor [38]. However, the authors did not consider that the tumor cells per se may not have P receptors but the mifepristone may have acted by suppressing PIBF if this was being expressed by gamma/delta T cells in the area of the tumors [38]. Thus it would be important to repeat our murine studies with a pure progesterone receptor antagonist that does not have glucocorticoid receptor antagonist properties.

The best way to prove the theory would be to see if gamma/delta T cells expressing PIBF can be demonstrated in controls after reviewing histologic specimens and then to determine if PIBF expression is reduced by progesterone receptor antagonist therapy. Also studies to support the hypothesis should determine if mifepristone increases NK cell activity in the area of the tumor. Hopefully these preliminary data will enable us to attain a grant that would allow these more sophisticated studies to be performed.

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