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Future Directions to Explore to Develop Ideal Anti-Cancer Progesterone Receptor Modulators

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ABSTRACT

Progesterone receptor (PR) modulators, e.g. mifepristone, have provided impressive palliative benefits and increase in overall survival in patients with a variety of end-stage cancers that are devoid of the classical nuclear nPR. The fact that the presence of the nPR is usually protective and affords a better prognosis for patients with cancers e.g., breast, ovarian, and endometrial, suggests that the mediocre response to PR modulator in cancers positive for the nPR may have been related to blocking the benefits of the nPR. The target for PR modulators is likely to be the immunosuppressive protein known as the progesterone induced blocking factor (PIBF) made by membrane (m)PRs. Another immunomodulatory protein requiring mPRs is known as the progesterone membrane receptor component-1 (PGRMC-1) protein. PGRMC-1 may stimulate PIBF by directing local P production by cancer cells. However, PGRMC-1 by itself, without its positive effect on increasing PIBF, may also increase cancer aggressiveness. The most common PR modulator used for treatment has been mifepristone. Interestingly, in high dosages mifepristone down regulates PGRMC-1 but in the 200-300mg dosage used in humans, which is a low dose, it actually may upregulate PGRMC-1. Thus, for the pharmaceutical industry, if they want to develop PR modulators more effective than mifepristone, they should try to develop PR modulators that will reduce both PIBF and PGRMC-1 in the dosages used. Alternatively, they could develop a monoclonal antibody against PGRMC-1 and use that concomitantly with mifepristone or develop a monoclonal antibody against PIBF, which then would not increase PGRMC-1 or use both types of monoclonal antibody drugs at the same time. Alternatively, they could find other chemicals that inhibit PGRMC-1, e.g., Ag-205 or also develops a pure PR antagonist that does not block the glucocorticoid receptor which may allow the use of higher dosages of the PR antagonist.

Keywords

Advanced cancer, Nuclear and membrane progesterone receptor, Progesterone receptor modulators, Progesterone induced blocking factor, Progesterone membrane receptor component-1.

Introduction

Nuclear progesterone receptor (nPR) presence in some cancers

Molecular biology of the nPR

Progesterone receptors are ligand-activated transcription factors [1]. There are three isoforms: PR-A, PR-B, and PR-C. PR-A is actually a truncated version of PR-B missing the first 164 amino acids from the N-terminal end of PR-B [2]. PR-B is actually the parent full length receptor, PR-C, which is also a truncated version of PR-B, it is truncated further down-stream from Protein A [2]. These three isoforms are made from the same gene but with different translational start sites [1,2]. The classical nPR is a member of the steroid hormone subfamily of nPRS [2].

Cancers associated with nPRs and their effect on prognosis

Cancers that are known to be positive for the classical nPR include breast, ovarian, endometrial, and prostate [3]. The presence of the nPR seems to be associated with a better prognosis in patients diagnosed with cancer [4-6]. Confirmation of a protective role of the nPR in limiting cancer progression is evidenced by the observation that when cancers positive for the nPR metastasize, re-biopsy will generally show a loss of the nPR [3-6].

Progesterone receptor modulators

Progesterone (P) is essential for the maintenance of a normal pregnancy. Thus, endeavors were made by the pharmaceutical industry to develop PR antagonists that could block the critical role of P in the pregnancy state leading to termination of the pregnancy [7].

As research and development for PR antagonists proceeded it became clear that none of them were pure antagonists because some molecular effects of P were indeed suppressed but other functions were not impeded, and some biological actions were actually enhanced. Thus, the proper term would be a PR modulator [8].

There were three different types of PR modulators developed. Type I modulators promote DNA binding and inhibit phosphorylation [9]. Type II modulators promote DNA binding and promote PR phosphorylation [9]. Type III modulators also promote DNA binding, similar to types I and II, but also recruit co-repressors, and more strongly promote PR phosphorylation than type II modulators [9]. Examples of type 1, type II and type III modulators are onapristone, mifepristone, and lonaprisan respectively [9]. The first PR modulator approval for pharmaceutical use was mifepristone, but it was approved for therapeutic abortion [10].

Membrane progesterone receptors (mPRs)

In contrast to nPRs, mPRs belong to the P and adipoQ receptor (PAQR) family [11]. The five mPR members vary in length from 330 to 377 amino acids [11]. Whereas activation of nPRs is a slow process, mPRs are normally responsible for rapid signaling [8]. They are widely distributed in several organs including, but not limited to, brain, lung, kidney, colon, reproductive tissue, and the immune system [12,13]. Nevertheless, activation of the nPR can lead to rapid signaling action in seconds or minutes by activating mPRs by cross-talk [8,13]. This rapid action activation is very important in subsequent rapid activation of cytoplasmic or membrane associated protein kinases and downstream signaling cascades [14]. In turn, these kinases modify regulatory sites on both the mPR and nPR and their coregulators thereby integrating rapid nongenomic actions of the mPR and slow genomic actions of the nPR [15,16].

PR modulators for treating cancer

PR modulators for treating human cancers positive for the nPR

At first anti-cancer drugs were aimed at inhibiting rapidly growing cancer cells with the hope that these drugs could kill the cancers cells with less damage to the normal cells because normal cells grow at a slower rate. These drugs are still the backbone of chemotherapy, but the cancer eventually develops resistance, and these drugs are generally associated with significant side effects.

The hope for better anti-cancer drugs is to find a critical molecule needed for cancer to proliferate but not critical to human health. Thus, with the demonstration of the presence of estrogen receptors (ER), and with the lack of critical need for the ER for human normal life, ER modulators e.g., tamoxifen, have been used extensively in treating hormone receptors (HR) positive breast cancer hoping that the ER is essential for breast cancer growth. The ER is involved in the development of the PR, thus with success with ER modulators it was logical to try PR modulators for cancer therapy. The caveat, however, was the possibility that suppressing the nPR activity may negate the beneficial effect of the nPR, and either show no benefit or even enhance the spread of cancer. Mifepristone was the PR modulator used in most of the clinical trials. Unfortunately, the results with mifepristone (type II PR modulator) were disappointing for breast cancer trials [17,18]. The type I PR modulator onapristone provided slightly better results in a metastatic breast cancer study where 56% showed a partial response and 27% had stable disease [19]. It is not clear if onapristone may be a better drug than mifepristone, or could it be because the study used metastatic breast cancer patients with the possibility that with advanced cancer possibly the nPR was either lost or markedly reduced. However, because of liver enzyme elevation, the drug never made it to the pharmaceutical market. Recently the rights to onapristone have been purchased by a small start-up company and its efficacy for nPR positive breast cancer is being re-evaluated.

The dosages of mifepristone were generally between 200-400 mg daily. Again, disappointing results were found for recurrent cisplatin and paclitaxel resistant ovarian epithelial cancer. One study showed a response in one study in 25% of the patients but, a subsequent study was not able to corroborate these luke-warm results nor was any benefit found for peritoneal or fallopian tube malignancies with only one of 22 showing partial remission and 15 of 22 showing cancer progression [20,21].

Mifepristone failed to show any benefit either for advanced or recurrent endometrial adenocarcinoma or low-grade sarcoma where cancer progression was found in 75% of the patients after eight weeks of treatment (22). Furthermore, not one woman had a complete remission, or for that matter, even a partial remission [22]. Thus, the oncologic community and pharmaceutical companies lost interest in PR modulators for treating cancer.

The use of PR modulators for cancers devoid of the classical nPR.

Similarity between cancer and the fetal-placement unit

The similarity between the fetal semi-allograft and cancer includes rapid proliferation of cells, invasion of normal tissue and evasion of immune surveillance. Though paternal antigens in the fetus are far more immunogenic than the foreign antigens found in cancer cells, it seemed possible that cancer cells may utilize similar mechanisms as the fetus to escape immune surveillance. Indeed, an immunomodulatory protein was found essential to the fetal-placental unit to escape from immune surveillance known as the progesterone induced blocking factor (PIBF) [23-27]. PIBF complementary DNA encodes a protein composed of 757 amino acids with a predicted molecular mass of 89-90 k Da [28]. The 48 k Da terminal part is biologically active. The PIBF gene is located on chromosome 13 [28]. The mRNA transcribed from the PIBF1

gene contains 18 exons and codes for an 89-90 k Da parent protein [28]. The full length 90 k Da PIBF protein plays a role in cell cycle regulation which regulates invasiveness not only of the trophoblast of the fetal placental unit, but also malignant tumors [29-31].

The parent form of PIBF is converted to shorter cytoplasmic splice variants that have immunosuppressive activity [32,33]. The parent nuclear form of PIBF that is associated with tissue invasion and the cytoplasmic immunosuppressive splice variants are not only present in rapid proliferating cells of the fetal placental unit, but also rapid proliferating malignant tumor cells [34].

Thus, PIBF had the potential to be the sought after mechanism of how cancer could "borrow" a mechanism used for survival of the species by allowing escape of the fetal placental unit from immune rejection, to help preclude the body from also destroying much less immunogenic cancer cells [35]. Obviously, it would seem likely, and it was confirmed, that the interaction of P with the PR would up-regulate production of both the parent PIBF needed for tissue invasion and the secretion of the smaller splice variant isoforms needed to thwart immunosurveillance [36].

The absence of the classical nPR in most tissues, and the presence of both mPRs and PIBF in most tissues makes it likely that PIBF is a product of mPRs. For protection against immune rejection of a highly immunogenic fetal semi-allograft, a much higher level of PIBF may need to be attained thus requiring a high level of P-PR interaction to activate local production of PIBF by embryonic cells. However, a much smaller amount of P secretion may be all that is required to make sufficient PIBF to inhibit immune surveillance of cancer cells. Alternatively, cancer cells could secrete a molecule other than P that activates the PR receptors. Interestingly, there is evidence that PIBF itself can activate mRNA in peripheral CD 4 +T lymphocytes [37]. Thus, there is the possibility that PR modulators could be an effective treatment for various cancers that are devoid of the classical nPR, in contrast to the unimpressive results seen when used to treat cancer positive for the classical nPR. To help support this hypothesis, cancer cell line studies were performed where mifepristone was added to the media for various human leukemia cell lines not known to be associated with the classical nPR. Both mRNA for PIBF and the PIBF protein itself were both down regulated with the addition of mifepristone [38]. This study provided the key evidence to support the hypothesis that successful immunotherapy of various cancers can be achieved by inhibiting an immunomodulating protein (PIBF) that is also needed for the fetus to escape immune surveillance [39]. Mifepristone has been found to inhibit the growth of endometrial cancer cell lines, human gastric adeno carcinoma, non-small cell lung cancer, and ovarian cancer cell lines [40-42].

Placebo controlled studies evaluating the efficacy of mifepristone therapy for various murine spontaneous cancers devoid of the nPR.

Drugs that suppress cancer proliferation in cell line studies have significance but more impressive and convincing would be the demonstration that the drug e.g., mifepristone could suppress cancer proliferation in the intact animal in placebo-controlled studies. Mifepristone was found to increase both length of life and quality of life as determined by body conditioning scores in spontaneous murine cancers not known to be associated with nPRs. Significant beneficial effects were observed in mice with spontaneous lymphocytic leukemia, lung cancer, prostate, and testicular cancer [43-45].

Treating very advanced human cancers negative for the nPR with mifepristone

To appease the large segment of the world's population that are against therapeutic abortion, huge restrictions were placed on the ability to obtain mifepristone for clinical use. In the United States, if you were not a licensed abortionist, one needed to acquire a compassionate use investigative new drug (IND) approval to obtain mifepristone for off-label use for cancer. Based on the aforementioned, cancer cell line and animal studies that showed potential benefit of PR modulator, the United States Food and Drug Administration, after we secured Institutional Review Board (IRB) approval, allowed mifepristone therapy on a case-by-case basis in certain cases of very advanced cancer when there did not appear to be any other standard therapeutic options. The dosage approved was 200 mg per day of daily mifepristone. The FDA did also grant approval for an investigator-initiated study for stage IV non-small cell lung cancer that had progressed despite a minimum of two courses of chemo or immunotherapy. Related to delay in obtaining FDA approval and delay in obtaining the medication for the investigator-initiated study (which required a one-month gap from initiation of 300 mg mifepristone from their last chemo or immunotherapy) some patients died within one week of receiving the medication. Nevertheless, despite the extremely advanced state of their metastatic cancer, including brain metastases, every person treated with mifepristone exhibited some major palliative benefit. Several patients predicted to die within six months, lived over two years, and some over five years or more. Often times those who did die, succumbed not from that cancer, but instead from unrelated medical events seen in an older population e.g., myocardial infraction or pneumonia. In fact, only one patient, with a malignant fibrous histiocytoma, died from progression of the cancer, but still did show significant palliative benefits for a few months [46]. Otherwise, not only did all the other patients demonstrate palliative benefits from mifepristone therapy, but none of them showed tumor progression as long as they remained on the drug. Besides malignant fibrous histiocytoma treatment with mifepristone provided palliative benefits and extension of survival in patients with very advanced thymic epithelial cell carcinoma, transitional cell carcinoma of the renal pelvis, leiomyosarcoma, pancreatic cancer, glioblastoma multiform stage IV, fibroblastic osteogenic sarcoma, NSCLC, SCLC, and colon cancer [46-53].

Experience with this drug has found that complete remission is possible with total regression of all metastatic lesions [54]. However, the majority of the patients only exhibit partial remission. Nevertheless, even without radiographic evidence of any decrease

in tumor size, within a couple weeks the patients report feeling much better with marked reduction in pain, weakness, and dyspnea on exertion. As long as the patient stays on the medication, usually no new metastatic lesions will appear nor will any grow. Over a period of time (sometimes a couple years) there may be observed slow growth, especially of the primary lesion, but this is still consistent with an extension of a good quality of life and prevention of rapid spread is still prevented.

This is in contrast to most other chemo or immunotherapy drugs where once tumor growth is seen, rapid spread usually occurs. Generally, then the drug is stopped with the hope of finding another standard treatment or a clinical trial. In fact, the most common cause of death from rapid progression of cancer in patients who were treated with mifepristone was from heeding the advice of their oncologist to stop mifepristone in favor of another recently approved drug, or a clinical trial in which they met eligibility criteria. This decision by their oncologist was possibly related to lack of experience with mifepristone treatment, nor realizing that some growth while on this drug is still consistent with a significant extension of a high-quality life. Unfortunately, the second most common reason for stopping the medication is the patients can no longer afford it. Because it is off-label use, third party payers do not reimburse the patient for the drug. The very rapid spread of the cancer with stoppage of mifepristone, yet the extremely long survivals seen in those patients who remain treated, who despite being advanced, but not at the moment moribund, suggests that PIBF is required for the tumor to invade healthy tissue and evade immune surveillance. Furthermore, the cancers find it difficult to mutate so resistance to mifepristone is thwarted [55]. Thus, mifepristone treatment does not appear to be a "cure," but a method to convert cancer into a chronic disorder with a good quality of life, as is true for so many non-malignant pathologic disorders where suffering is reduced while on treatment, but symptoms and even death ensues once the treatment is stopped.

Related to the new issues concerning abortion, especially in the United States, and especially in certain states of the union, there is a strong contingency of politicians who are pushing to remove mifepristone from the pharmaceutical market to prevent easy use for therapeutic abortions. Thus, it is presently next to impossible to get the United States FDA to grant a compassionate use IND even on a case-by-case basis. Fortunately, though direct shipping from manufacturers to patient is prohibited, purchasing of the drug by the treating physician is still legal with the exception of some states. The physicians can then distribute the drug to the patient at the time of the visit. Interestingly, there are no restrictions on the 300mg dosage of mifepristone which is not approved for pregnancy termination, but rather Cushing's Syndrome (in higher dosage mifepristone blocks the glucocorticoid receptor). The 300 mg dosage has no restrictions on its use. The beneficial effects for advanced cancer have been demonstrated with this dosage also without side effects [50,51]. However, the cost of a tablet of the 200 mg dosage of mifepristone is 42 dollars a pill. The cost of the 300mg dosage is five hundred dollars a pill.

The quick improvement of pain and asthenia observed with mifepristone therapy even before any radiographic regression of metastatic lesions, suggest that products of the mPR (possible PIBF) that allows tumor progression is responsible for the pathological state and morbidity rather than the damaging effect on organ structure and tissue by the tumor itself [55]. Despite very impressive demonstration of efficacy of mifepristone, as least with published care reports and editorials, there does not appear to be great interest among the clinical oncologists in exploring PR modulators for treating advanced cancer at least by the absence of presentation of research in scientific meetings or publications pro or con in journals. The first dramatic case report of marked longevity and palliation was a case of colon cancer was published in 2009 [53]. Thus, perhaps the best group to confirm or refute the efficacy of this treatment may be palliative oncologists.

To date the only case that was granted a compassionate use IND for a cancer that was not end-stage was a male with multi-focal renal cell carcinoma. His oncology group recommended a bilateral nephrectomy. However, the patient did not want to be crippled by dialysis with its tenfold risk of heart attack and stroke. There were no drug options at that time so permission to use mifepristone was granted. He is still alive and doing well 22 years later [56].

A large study of mifepristone given daily at the 200mg dosage for unrespectable meningioma found the drug to be very well tolerated without serious side effects [57]. Related to its safety profile, demonstration of significant anti-cancer effects, and significant clinical benefits even when all other therapies have failed, and even in very advanced cases, ease of administration ie one oral pill per day, and seemingly resistance to tumor mutation leading to drug resistance, and its efficacy in a large variety of cancers, not just one type of cancer, (e.g., osimertinib for NSCLC with the EGFR mutation) and evidence that it crosses the blood-brain barrier, there is reason to believe that that mifepristone may be the best single anti-cancer drug on the present pharmaceutical market, even though it would be an off-label use. Nevertheless, the information accrued by experience with mifepristone in treating cancer could lead to even more efficacious therapies. In fact, the goal of this commentary is to provide some insight as to develop even better treatment options not only for patients with end stage cancer, but even much earlier stages, was the goal of this perspective, and also to suggest strategies as to how and when to use mifepristone or other available PR modulators to maximize cancer therapy. Before suggesting targets to develop more efficacious anti-cancer drugs based on the present knowledge of the role of mPRs in the progression of cancer, a brief discussion of another immunomodulatory problem, the progesterone receptor membrane component-1(PGRMC-1), is prudent.

The progesterone membrane component-1 (PGRMC-1) protein

Molecular aspects The PGRMC-1/Sigma-2 receptor is a 24 kDa multifunctional protein including a cytochrome b 15 binding protein [57,58].

Cancer aggression associated with PGRMC-1 protein

We previously mentioned in this commentary/perspective that it is not known whether the cancer cells secrete P in small amounts to activate mPRs or some other molecule other than P. The PGRMC-1 protein may induce P-signaling [59]. PGRMC-1 regulates cell proliferation and apoptosis through interaction between a cytochrome b3 binding domain and other binding partners, e.g., epidermal growth factor receptor (EGFR), P450 protein, and plasminogen activator inhibitor RNA binding protein-1 [59-63]. Other functions involve steroidogenesis, vesicle trafficking, mitotic spindle regulation, cell cycle regulation, angiogenesis, anchorage-independent growth, promotion of autophagy, invasive growth, and hypoxic biology [64]. There is evidence that PGRMC-1 protein suppresses the P53 and Wnt/Beta-catenin pathways to promote pluripotent- stem cell self-renewal [65]. All these functions of PGRMC-1 increase cancer aggressiveness.

The PGRMC-1 protein is upregulated in various malignancies including those known to be associated with the nPR, e.g., breast, and ovary and those not associated with nPR including hepatocellular cancer, lung, cervix and colon [66-70]. Upregulated PGRMC-1 expression correlated with increase in tumor size and metastasis leading to poor overall survival and poor quality of life and decreased tumor-free interval [66-72].

Future strategies for developing anti-cancer medications based on existing knowledge of the role of nPRs and immunomodulatory proteins requiring the mPR, and the interaction with nPRs.

Based on basic science research and clinical studies, the ideal PR modulator would suppress both PIBF and PGRMC-1 proteins. Mifepristone in high dosages seems to adequately suppress PIBF and PGRMC-1 cancer cell studies in cell line studies [72]. However, in lower dosages that would be the equivalent of the mifepristone exposure to cancers in human beings taking 200-300 mg daily mifepristone, the PGRMC-1 protein is up-regulated rather than down-regulated [73]. Hypothetically PGRMC-1 could stimulate local P production by cancer cells leading to an up-regulation of PIBF secretion by these cancer cells leading to invasion of local tissue and metastasis. However, even without its stimulating effect on PIBF, PGRMC-1 by itself may increase local tumor invasion and slow tumor growth. This would explain the observation that frequently mifepristone will inhibit the growth and spread of metastatic lesions but not inhibit slow growth especially of the primary lesion. It should be remembered that mifepristone is not a PR antagonist, but rather a modulator, and it is not unusual for HR modulators to inhibit certain reactions at one concentration, but stimulate the same process at another dosage, or even have the opposite effect in another tissue.

Unfortunately increasing the dosage of mifepristone to reach a level to suppress PGRMC-1 is not feasible because in higher dosages it may cause hypercortisolism and life-threatening hypokalemia. This may occur because in higher dosages mifepristone blocks the glucocorticoid receptor. One has to be careful that even in lower dosages certain drugs e.g., alpelisib can interfere with the metabolism of mifepristone and thus block the glucocorticoid receptor [74]. Thus, research and development could try to manufacture a PR modulator that in low dosages suppresses both PIBF and PGRMC-1. If one cannot develop a PR modulator that will suppress PGRMC-1 in lower concentrations, then an alternative suggestion would be to develop a PR modulator with no anti-glucocorticoid activity to allow a higher dosage of the PR modulator to be given.

Other areas to explore would be suppression of PGRMC-1 with a monoclonal antibody type of anti-cancer drug or, for that matter, one could develop a monoclonal antibody against PIBF which would not block the glucocorticoid receptor. Interestingly, there is a naturally occurring substance that inhibits PGRMC-1 known as AG-205 for which a patent has been filed by RJ Craven [75]. Until that time of developing even better drugs suppressing these mPR immunomodulating proteins, certain strategies could be used with what is available today. One could try another PR modulator. We did demonstrate significant short-term palliative benefit in a patient with very advanced prostate cancer who only wanted to use it to enable his family to come in from various geographical locations to have a pleasant good-bye reunion. Similar to mifepristone, ulipristal provided quick relief of pain and improved energy and mental clarity, but he stopped it when the family left because he could not financially afford to continue. The American Cancer Society advised him that they could not provide any financial support for off-label use of drugs.

The patent for the 300 mg dosage of mifepristone is about to expire so possibly a generic company may start making it without the abortion label stigmata. Perhaps the generic companies or manufacturer of the brand will decrease the price when it to be used on a daily basis, (hopefully for years) in patients with cancer, instead of a single one-time pill to terminate a pregnancy.

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