Medroxyprogesterone Acetate and Metastases: Of Mice and (wo)Men

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The current research strategy for the treatment of cancer is to identify a specific target and develop drugs to block tumor growth or destroy cancer cells. This approach must also produce minimal side effects for the patient. Regrettably, it is unlikely that there is a single answer to cure cancer, but it is hoped that a combination of incremental advances that retard cancer development and progression will, together, create improvements in cancer care.

In the case of breast cancer, there has been a two-pronged attack on the disease, and both approaches, which target the estrogen receptor (ER), have had some measure of success in the clinic (1). Chemoprevention of breast cancer with the antiestrogen tamoxifen can reduce the incidence of tumors by approximately 50% in high-risk women (2). Similarly, preventing the growth of metastases by the appropriate application of adjuvant endocrine therapy following surgery can enhance survivorship substantially (3). However, current strategies of exploiting the ER target have probably reached their zenith, and new targets and approaches for achieving cancer-selective toxicity in ER-negative breast cancer are required.

Unfortunately, the problem of finding and exploiting cancer-specific targets for therapy is not new but one that has confounded our best efforts for a century. Paul Ehrlich is the individual who, in the early years of the 20th century, established the scientific method of screening chemicals to kill infectious disease selectively without harming the patient (4). He successfully developed a chemical therapy (i.e., chemotherapy) to treat syphilis and wanted to use the same principles to treat cancer. The key to Ehrlich’s initial success in antibacterial chemotherapy was to select an appropriate animal model of human disease for testing the chemicals. He used the same logic to address a cure for cancer. At that time, there was sufficient knowledge to maintain transplantable cancer in repeated generations of laboratory mice. He could, therefore, test selective anticancer chemicals for clinical applications. However, his initial hopes were followed by disillusionment. Many of Ehrlich’s results in mice with grafted tumors were conflicting and confusing. In 1915, he admitted defeat and declared “I have wasted 15 years of my life in experimental cancer.” He died in August 1915.

Today, with the explosion of basic cancer research, we are confronted with a wide range of potential targets for cancer therapy, all of which can be evaluated in mouse models. In this issue of the Journal, Palmieri et al. (5) have focused their efforts on blunting the calling card of cancer that kills—metastatic colonization. What is interesting about their observations is the proposition that a new target, the glucocorticoid receptor (GR), may be able to be teased out of ER-negative breast cancer and exploited in the future to aid patients.

The approach used by Palmieri et al. (5) employs a mouse model that is generally accepted to parallel the seeding and subsequent growth of metastatic cells in women. Human ER- and progesterone receptor (PR)–negative breast cancer cells (MDA-MB-231T) were injected intravenously into athymic mice, and the incidence, number, and size of gross pulmonary metastases were measured. The authors report that the synthetic progestin medroxyprogesterone acetate (MPA) reduced colony-forming efficiency in soft agar by 40%–50% and reduced metastatic colonization to 73% and 64% of control levels in two separate experiments using athymic mice.

MPA is a promiscuous steroid that has predominately progesteroidal activity but also has glucocorticoid (6,7) and androgenic (8) activity. It is the glucocorticoid-like actions of MPA that turn on the metastasis suppressor gene Nm23-H1 in MDA-MB-231T breast cancer cells (9). Transfection of the MDA-MB-231T cells with an antisense Nm23-H1 construct caused a reversal of effects of MPA on colony-forming efficiency in soft agar. Regrettably, the same experiment was not performed in vivo, creating doubts about the actual role of Nm23-H1 under “field testing conditions.” Nevertheless, the authors do show an association between elevations of Nm23-H1 in pulmonary colonies in their MPA-treated mice, although it should be remembered that these are tumor cells that form metastases despite expressing increased levels of Nm23-H1.

The central thesis of Palmieri et al. (5) focuses on the possibility that an antinvasive tumor suppressor gene can be reactivated by MPA, thereby reducing the numbers of metastatic lesions that successfully seed. Fewer metastatic lesions would potentially extrapolate to a lower probability of cancer-related death. If the use of MPA were only a reinvention of the Ehrlich approach to screening compounds (which it is not), one would wonder how MPA could possibly be applied appropriately in women. The received wisdom for breast cancer is that metastatic spread has often occurred already by the time of diagnosis of the primary tumor. This is certainly true of all node-positive breast cancers and is also true for about one-third of node-negative breast cancers. Indeed, early metastatic spread is the basis for all current adjuvant treatment strategies, which aim to destroy the micrometastases that are already established around a woman’s body (10).

Clearly, the immediate clinical application of a compound that prevents the initial colonization of organs with metastatic cells presents a challenge if it is true that metastatic spread has occurred prior to diagnosis. Be that as it may, this is no less of a challenge than previous efforts to test drugs that block enzymes that affect...
the initial breakout of metastatic cells from the primary breast cancer (11). In both cases—i.e., the start and the end of the journey for a metastatic cell—the most logical application of globally antmitastatic drugs would be in chemoprevention. In the case of breast cancer, a growing primary cancer that cannot spread can do no harm. Detection, surgery, and local radiotherapy then become the answer to cancer. Unfortunately, the implementation of these concepts are decades away from appropriate testing in the clinic. Nevertheless, who, 40 years ago, would have bet on a failed postcoital contraceptive (ICI46,474) (12) becoming the first chemopreventive (tamoxifen) for reducing the incidence of breast cancer in high-risk women (2)? Re-invention can prove to be a valuable approach in cancer research and treatment.

Palmieri et al. (5) have chosen to re-visit MPA from its beginnings as a contraceptive administered as a depot injection (13) and as a local contraceptive intrauterine device or intravaginal ring for healthy women (14). MPA was also used in the 1980s, before the ubiquitous use of tamoxifen and, now, aromatase inhibitors for the treatment of breast cancer (15). The progestin therapy was given at huge daily doses of 1000 mg per day, but there were side effects of weight gain related to glucocorticoid activity. Nevertheless, response rates of 45% were attained in patients with ER- and PR-positive disease (16). Today MPA has widespread use as hormone replacement therapy (HRT) in combination with conjugated equine estrogen (0.625 mg + MPA 2.5 mg daily) (17).

There is currently much controversy surrounding the use of HRT for prolonged periods in postmenopausal women (18) because of an increase in the incidence of breast cancer. Low-dose MPA is included in HRT to avoid the side effect of endometrial cancer noted with estrogen replacement alone (19). However, the combination HRT preparation causes an increase in the incidence of breast cancer compared with placebo (20), and there were twice as many lymph node-positive tumors in women taking HRT (45 cases out of 8605 volunteers) than in women taking placebo (21 cases out of 8102 volunteers). Low-dose MPA does not retard metastatic spread. Chlebowski et al. (20) actually noted fewer invasive breast cancers in women taking HRT during the first 3 years but subsequently observed a cumulative increase in invasive breast cancer monitored out to 7 years. There were no differences in the proportions of ER-positive tumors in the HRT and placebo groups. Thus, low-dose MPA does not reduce the numbers of breast cancers nor the numbers that are node positive—i.e., have undergone metastatic spread.

Palmieri et al. (5) went to considerable lengths to recreate the potential use of high-dose MPA as an antitumor agent in patients by ensuring that the serum levels of MPA attained in the athymic mouse are comparable to previously reported therapeu tic levels in patients. The authors demonstrate that the higher the MPA dose, the better the anticolonization action. These data suggest that very high daily doses of MPA would have to be used in any clinical studies of ER-negative breast cancer to explore the GR effect. The authors do show that large daily doses of MPA in their mice caused increased weight gain, but the glucocorticoid actions of MPA did not decrease bone density. It is well established that high-dose MPA causes dramatic weight gain in women and that women using MPA (150 mg, intramuscular injection every 3 months) as a contraceptive (i.e., Depo-Provera) experience decreases in bone density (21). Because Depo-Provera disrupts the menstrual cycle, the bone-thinning action could be the result of lower sex steroid levels, but the glucocorticoid action of MPA cannot be disregarded as a possible explanation. (22).

Because the central thesis of the Palmieri paper (5)—that MPA induced elevation of Nm-23H1 expression and consequent suppression of metastasis—shows promise, it may not be unreasonable to refine their approach and consider other GR-mediated mechanisms that could play a role in antitumor activity in vivo. It is known that the GR can “tether” to other DNA-bound transcription factors to cause antiproliferative effects. In particular, GR can interfere with the expression of the genes for nuclear factor kappa B (NF-κB) and activator protein (AP-1) (23,24). A recent study indicates that interference with NF-κB—mediated pathways is an important target for glucocorticoids when used as antiproliferative agents (25).

With these clues about glucocorticoid action in preventing metastatic colonization and proliferation, the trick is to get the right agent at the right place at the right time. Achieving the right place at the right time may be difficult, because to prevent metastatic colonization from a newly formed primary tumor one must consider chemoprevention. The right agent probably needs to be a selective GR modulator (26,27). The exploitation of tumor selectivity for a steroid receptor would build on prior knowledge with selective ER modulators (28). Overall, the work by Palmieri and coworkers (5) provides tantalizing clues for a new prevention strategy based on work in laboratory mice. However, we know where we are going only if we know where we have been. The challenge for future research will be to refine the therapeutic agent and plan appropriate clinical testing.

References


