

Prolactin and cancer: Has the orphan finally found a home?

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ABSTRACT

Prolactin has, for long, been associated with galactorrhea and infertility in women while its role in men is largely unknown. Recently, expression of prolactin in various other tissues like the breast, prostate, decidua, and the brain has been recognized. This has led to evaluation of paracrine and autocrine actions of prolactin at these tissues and a possible role in development of various cancers. Increased expression of PRL receptors has also been implicated in carcinogenesis. Breast cancer has the strongest association with increased prolactin and prolactin receptor levels. Prostate cancer also has reported significant association, while the role of prolactin in colorectal, gynecological, laryngeal, and hepatocellular cancers is more tenuous. Prolactin/prolactin receptor pathway has also been implicated in development of resistance to chemotherapy. Thus, the effects of this pathway in carcinogenesis seem widespread. At the same time, they also offer an exciting new approach to hormonal manipulation of cancers, especially the treatment-resistant cancers.

Key words: Prolactin, cancer, carcinogenesis

INTRODUCTION

Prolactin (PRL), the peptide hormone secreted by the anterior pituitary gland, has, for long, remained restricted to the field of lactation and infertility. While a few studies recently have dealt with the use of prolactin in differentiating true and pseudo- seizures, the multiple effects of this hormone have largely remained unknown. The connection between prolactin and cancer has been suspected for many years, but never conclusively proven. The similarity of prolactin with growth hormone and its actions through the growth-promoting JAK/STAT pathway suggest its tumor-promoting effects. Recent research has underlined the role of PRL and PRL receptor (PRLR) most importantly in breast and prostate cancers, but also in a variety of other

cancers. This review article has been designed to present an overview of the recent understanding regarding role of PRL in cancer and new modalities of cancer therapy based on the PRL pathway.

Breast cancer

Breast cancer is one of the commonest cancers in women, with over one million cases reported worldwide, making up 25% of all cancers in women. In spite of the availability of advanced treatments like surgery, chemotherapy, and radiotherapy, the disease continues to take its toll, with a high incidence of treatment failure due to tumor resistance, both intrinsic and acquired. This has prompted the search for factors causing it and also the means to counteract it, and prolactin is one such candidate. The concept of prolactin as a factor in mammary cancer is not new. It was initially suggested over three decades ago, based on data obtained from murine models. For a long time, this animal data could not be extrapolated to humans due to variety of reasons: (i) most of these studies involved only a few subjects, (ii) a concept of local production of prolactin in breast tissue did not exist, (iii) most of the studies, which used bromocriptine to reduce serum prolactin levels, did not lead to successful treatment, and (iv) most of these

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studies did not reach specific conclusions about the relation between prolactin and breast cancer. However, the high incidence of treatment failure and a number of recent epidemiological studies have again shifted the focus back on to prolactin. These recent studies have brought to fore, a few critical concepts regarding the role of prolactin (PRL) in breast cancer. (i) Even high-normal circulating levels of PRL increase breast cancer risk. (ii) Locally produced prolactin acts as an autocrine/paracrine factor in breast cancer evolution. (iii) A causal relationship between prolactin receptor expression and breast cancer has also been recognized.^[1]

The exact mechanism by which high-normal circulating levels of PRL leads to increased breast cancer risk is not exactly known. PRL may promote breast cancer via the JAK2/STAT5 signaling pathway and may also increase the survival of breast cancer cells by stimulating generation of new cancer cells and decreasing cell death. PRL could also increase cell motility and promote cancer spread. PRL has also been implicated in causing resistance to cytotoxic drugs like cisplatin and drugs like paclitaxel, which act on cellular microtubules.

Circulating prolactin produced by the pituitary is not the only prolactin available to tissues. Many organs like the mammary gland, prostate, brain, deciduas, and skin also express PRL. This extra-pituitary prolactin probably is involved in development of breast tissue, dermatological bio-regulation, and perception of pain. While extra-pituitary secretion has also been reported in animal models, it is assumed to be much more common in humans and is dopamine and POU1F1-independent. A specific regulator of local PRL production has still not been identified, even though insulin, progesterone, and transforming growth factor – β have been proposed as regulators. In the breast, PRL is produced in both the stromal and epithelial compartments. Further, while very little prolactin is produced locally, it is very important for tumor formation due to local availability.

A few studies have also found that breast tumors also express higher levels of the PRL receptor (PRLR) when compared to adjacent healthy tissue.^[2,3] Even low levels of prolactin receptor expression are adequate to mediate actions of PRL in breast cancer cell lines. A family of prolactin receptor (PRLr) isoforms, numbering six, mediates the effects of PRL in human tissue. These six isoforms are variably expressed in normal tissues and malignant tissues. PRLR-triggered signaling cascades have also been implicated in benign breast tumors. A study by Plotnikov *et al.*^[4] found that impaired turnover of the prolactin receptor in breast cancer cells results in

accelerated proliferation and increased invasive growth. Conversely, antagonism of the prolactin receptor resulted in reduction of clonogenic capacity of breast cancer cells and potentiated the action of cytotoxic anti-cancer drugs.^[5] This has very important implications in chemotherapy of breast cancer, especially the resistant types. The local production of prolactin cannot be controlled by conventional dopamine agonists that act at the pituitary level. This failure of bromocriptine (the most commonly used dopamine agonist in cancer studies) to reduce local PRL levels resulted in the failure of this drug in cancer studies. This highlights the need to develop a special category of therapeutic agents targeted at reducing the action of endogenous PRL by blocking the PRL receptor. The human PRLR antagonist G129R-hPRL, which sterically hinders the sequential dimerization and subsequent activation of the PRLR, causes apoptosis of both estrogen receptor-positive and estrogen receptor-negative breast cancer cell lines. In the study by Howell *et al.*,^[5] the 'pure' prolactin receptor antagonist $\Delta 1-9$ significantly augmented the cytotoxic effects of doxorubicin and paclitaxel *in vitro*. This therapy also inhibited the colony-forming efficiency of cell lines and primary cancers. Autocrine prolactin in breast cancer cell lines can also be antagonized by prolactin-neutralizing antibodies.^[6] Most of the studies on antibodies have *been in vitro*, in which these neutralizing antibodies have been shown to inhibit MCF-7 and T47Dco cell growth and to increase cell apoptosis.^[7] Thus, these studies suggest that a judicious combination of cytotoxic agents, PRLR antagonists/neutralizing antibodies could provide a new form of therapy for resistant breast cancers. At the genetic level, construction of a PRLR single nucleotide polymorphism risk profile for affected patients could enable personalized treatment strategies.

Interactions between estrogen and prolactin systems

Recent research has indicated significant interaction between estrogen and prolactin systems. Estrogen stimulates prolactin secretion and can also up-regulate human prolactin receptor gene expression and stimulate growth of tumorigenesis.^[8] Prolactin has been shown to exert some of its effects on mammary tumor cells via the estrogen receptor. Anti-estrogens like tamoxifen have also been found to block the prolactin receptors. This could represent another pathway of cancer therapy, discrete from the anti-estrogenic effects of these drugs. Interestingly, hyperprolactinemia results in hypogonadism, suppresses the ovarian reproductive cycle, and reduces estrogen. Thus, the interactions between prolactin and estrogen pathways are complex, and careful studies are needed to formulate treatment strategies.

PROSTATE CANCER

Prostate cancer is presently the most frequently diagnosed cancer and represents the second most common cause of death from cancer in men. PRL has an important role in the development of prostate gland. In 1955, Grayhack^[9] discovered that when prolactin was inhibited in rats during embryonic development, only 80% of the prostate was developed, which shows that prolactin is important in differentiation and development of the prostate. There is also significant evidence of the existence of prolactin's paracrine and autocrine actions. The mainstay of treatment of prostate cancer includes radical prostatectomy, radiation, and androgen deprivation therapy. However, just like in breast cancer, resistance to hormone therapy has also been noted in prostate cancer. Also, prostate cancer often metastasizes to the bone, which makes treatment even more difficult. Epidemiological studies exploring a correlation between serum PRL levels and prostate cancer incidence or severity have been equivocal. Both malignant and healthy prostates produce PRL. The PRL-positive tissues show a good correlation with activated Stat5 and a high Gleason score. Prostatic fluids from patients with cancer also have higher PRL levels than controls, which also lend support to the existence of prostate-derived PRL. Most of the effects of prolactin on prostate cancer cells are similar to those on breast cancer cells. *In vitro*, prolactin induces proliferation and antagonizes apoptosis in prostate organ culture and in some tumor cell lines. In humans, receptors for prolactin are expressed in the prostate, and this expression is particularly elevated in prostate cancer and carcinoma *in situ*. While hypogonadism caused by hyperprolactinemia could have a role in reduction of prostate cancer, as reported in a study,^[10] the bulk of evidence seems to suggest that up-regulation of PRLR and local production of PRL in prostate could be important in increased risk of prostate cancer and treatment resistance.

COLORECTAL CANCER

Colorectal cancer is the third highest cause of cancer mortality worldwide. CEA is the most common marker utilized for the detection and follow-up of colorectal cancer. However, a study by Soroush *et al.*^[11] compared serum PRL and CEA level of 47 patients and found that serum PRL and CEA levels were increased in patients with colorectal cancer, but the greater portion of the patients had an increased level of PRL compared with elevated level of CEA. They also found no correlation between the plasma PRL concentration and the stage of the tumor. They concluded that in view of the high cost

of CEA, prolactin could be used as a tumor marker for colorectal cancer. Similar results have been found in a study by Bhatavdekar.^[12] However, evidence about the role of prolactin in colorectal cancer has been mixed, and its role in colorectal cancer remains contentious.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) accounts for more than 6 lakh new cases per year worldwide. Despite several treatment modalities, the long-term survival rate remains unsatisfactory, principally due to high rates of recurrence and metastasis even after treatment. Increased circulating prolactin levels, high p-JAK2 expression, and generation of liver cancer cells through PRLR/JAK2 signaling have all been proposed as mechanisms that could contribute to the development of HCC. A study by Yeh *et al.*^[13] demonstrated significantly higher serum levels of prolactin in people with HCC, and this significant relationship existed irrespective of gender, age, or BMI. These findings have significant implications in the detection and therapy of HCC, if proven. Hence, larger studies, which can prove the role of PRL in activation of JAK2 and exclude the role of other cytokines and growth factors in the JAK2 activation pathway, need to be designed immediately.

GYNECOLOGICAL CANCERS

Elevated levels of serum PRL in ovarian and endometrial cancers have been reported, indicating a potential role for PRL in gynecological cancers. PRL possibly promotes tumorigenesis by activating Ras oncogene, and thus could lead to cells with mutations in tumor suppressor genes turning malignant. A study by Levina *et al.*^[14] found dramatically increased expression of PRL receptor in ovarian and endometrial tumors as well as in endometrial hyperplasia, signifying the importance of PRL signaling in malignant and premalignant conditions. PRL mRNA was expressed in ovarian and endometrial tumors, indicating the presence of an autocrine loop. Serum PRL levels were also significantly elevated in women with a strong family history of ovarian cancer, and this PRL rise could not be attributed to stress.

MALIGNANT LARYNGEAL TUMORS

Laryngeal cancer (LC) is responsible for approximately 159,000 new cases and 90,000 mortalities every year. The mechanisms underlying the proliferation of this form of cancer are not yet fully understood. A recent study by González-Lucano *et al.*^[15] found increased expression of different isoforms of PRLR in LC in comparison with recurrent respiratory papillomatosis. This suggested a

possible role of PRL/PRLR in the development of LC. They concluded that PRLR might be useful as a target for further investigations in laryngeal tissues.

ALL CAUSE MORTALITY

In view of the widespread expression of PRL in various tissues and the emerging role of prolactin in causing multiple cancers, a study was devised by Berinder *et al.*^[10] to assess the overall relative risk of cancer and risk of some specific a priori specified cancer forms in a cohort of 969 women and men with hyperprolactinemia. Their results were different from the majority of prolactin and cancer studies, and they reported a higher incidence of upper gastrointestinal cancer in both males and females and hematopoietic cancer in females. Risk of breast cancer was not increased in women, and there was a reduced risk of prostate cancer in men. An increased overall cancer risk was found in hyperprolactinemia patients.

The last word on the role of PRL in causing cancer and on its receptor conferring resistance to chemotherapeutic agents is yet to be written. The more the number of cancers added to the list, the more is the story getting curiouser and curiouser. Clearly, an association has been demonstrated, but whether that is a cause and effect relationship is yet to be established. The modest PRL elevations could be of local origin. Higher levels that are obtained in prolactinomas usually cause hypogonadism, something that chemotherapies for breast and prostate cancer treatment aim at, and hence this high serum PRL certainly cannot be blamed for causing these cancers.

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