Prolactin: The Bright and the Dark Side

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Prolactin is a phylogenetically old signaling molecule whose gene can be traced to lampreys more than 500 million years ago (1). This fact poses the question of a primitive function for prolactin, which would explain its retention during premammalian evolution. With the origin of mammals, prolactin became linked inextricably to the development of the mammary gland and lactation.

Notwithstanding the variety of actions attributed to prolactin, a common thread is its association with a nurturing function in the postmating phase of reproductive cycles, including behavioral changes (broodiness, suppression of aggression) and metabolic functions (freshwater adaptation, migrations, or seasonal gonadal suppression). Across many species, prolactin exerts similar adaptive roles in homeostasis. For example, in fish and amphibians, it is involved in electrolyte balance across epithelial barriers, in pigeons it controls the secretion of nutrients and electrolytes from an epithelial gland (the crop milk), and in mammals it controls the secretion of milk from the mammary gland. In parallel, prolactin has been implicated in parental behavior ranging from nest fanning in fish, incubation and brooding behavior in birds, to maternal behavior in mammals.

Discovered nearly 90 years ago, prolactin's name addresses its main function, the promotion of lactation. However, this name falls short in uncovering or suggesting prolactin's true potential in physiology. The comprehensive process of pregnancy and lactation points to its multifaceted functions in which it tends to adapt to complex and demanding processes in the mother, requiring multiple diverse systems and organs to undergo a successful transition for successful child delivery and fostering.

During pregnancy and lactation, prolactin participates in the development of the mammary gland and lactation, maternal behavior, increased neurogenesis, insulin resistance and transfer of glucose to the fetus, expansion of β cells, increased appetite, leptin resistance, fat deposition (pregnancy) and mobilization (lactation), bone and calcium homeostasis, anovulation, reduced stress responses, oxytocin secretion, and facilitation of prolactin secretion (2). Nevertheless, except for its effects on fertility and milk production, it must be borne in mind that prolactin often acts as a physiological modulator rather than a master director. Understanding these actions provides a clue for the widespread distribution of prolactin receptors (PRLRs) in the organism. Thus, PRLRs are expressed in numerous organs and cell types, including bone, adipose tissue, gut, reproductive tract, skin, immune system, pituitary, and brain (3, 4), and hence when prolactin is elevated there is potential for a wide variety of systems to be influenced.

Functions of prolactin that are considered adaptive in the lactating and pregnant female might be maladaptive should high prolactin occur in an untimely manner. Therefore, understanding the role of prolactin becomes relevant in explaining many symptoms and manifestations that occur in prolactin overproduction, such as during pharmacological psychiatric treatments or in patients with prolactinomas. In this respect, several scientific reports suggest that PRLR expression and/or signaling is increased in many disease states, and that systemic or local prolactin levels correlate with organ pathogenesis.

Such is the case of the effect of prolactin on food intake and adipose tissue accretion. During pregnancy the normal homeostatic mechanisms regulating appetite are modified to generate a state of positive energy balance and increased food intake to supply the growing fetus with its energy requirements and to increase fat storage to be used during lactation; additionally, prolactin plays a key role in increasing food intake and adiposity during

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Abbreviations: hPRL, human prolactin; PRLR, prolactin receptor.

pregnancy (5, 6). On the dark side, patients with pharmacological or tumoral hyperprolactinemia are prone to excessive weight gain, and normalization of prolactin levels with dopamine agonists correlates in some cases with weight loss (7). Furthermore, transgenic mice with chronic hyperprolactinemia have a marked increase in food intake and adipose tissue deposition (8), and metabolic organs with PRLRs, such as liver and adipose tissue, modify glycogenic and lipogenic pathways accordingly (9).

On the bright side, the proliferating action of prolactin on numerous cell types is functional to the needs of pregnancy and lactation. For example, prolactin induces proliferation of mammary epithelial cells to ensure lactation, acts on pancreatic β cells to prevent gestational diabetes, on adipocytes to store energy, and on endometrial or hepatic cells as needed. However, this proliferating effect induced by prolactin may also be detrimental in untimely hyperprolactinemia.

Many studies have addressed the role of prolactin in promoting cancer using cellular and molecular studies, transgenic rodent models, and epidemiological studies (10, 11). Even so, the role of prolactin and PRLRs in the initiation and/or progression of tumors remains an active area of debate.

In breast cancer, associations between plasma prolactin levels and increased risk of postmenopausal estrogen and progesterone receptor–positive *in situ* invasive breast carcinomas (12), as well as increased tumor size, higher disease stage, node involvement, poorer prognosis, and higher recurrence and mortality risk (13), have been described. Importantly, human prolactin (hPRL) has been implicated in chemotherapeutic resistance in breast cancer (14, 15). Nevertheless, the role of prolactin in breast cancer has been questioned (10, 16). Other studies reveal that prolactin induces mammary cell differentiation and prevents epithelial mesenchymal transition. Therefore, it has been proposed that prolactin may participate in breast tumor initiation, whereas in established breast cancer, it may contribute to reduce aggressiveness and dissemination (17).

In ovarian cancer, prolactin is one of a combination of four analytes that discriminate between disease-free and epithelial ovarian cancer patients (18). Furthermore, prolactin could act as an important survival factor for cervical cancer (19).

In human and experimental prostate cancer, local expression of prolactin and/or STAT5 activation is increased (10, 20), although some observations do not argue for a role of endocrine prolactin in prostate tumorigenesis. Additionally, there is genetic evidence for amplification of PRLRs and *STAT5* loci in some prostate cancer specimens, and epidemiologically, the presence of prolactin and phosphorylated STAT5 in human prostate tumors correlates with high tumor grade and aggressive disease course (21).

Lastly, in humans, PRLR expression was observed throughout the cancerous progression of the colonic and gastric mucosa, from adenomas to colonic liver metastasis and gastrointestinal cancer cell lines at various stages of growth and differentiation (11). In hepatocellular carcinoma, hPRL expression was upregulated and positively correlated with tumor size and grade, as well as poorer survival (7).

In this context, the work by Ding *et al.* (22) in the present issue shows convincing arguments for a role of autocrine prolactin in the progression of endometrial cancer and provides insight into some underlying mechanisms. Endometrial cancer is the most common gynecologic malignancy in the United States, with increasing yearly rates. Even though most women present with early stage disease, advanced or recurrent disease carries a grave prognosis. Furthermore, chemotherapeutic regimens are not curative, and late-stage endometrial cancer patients tend to develop therapeutic resistance or experience recurrence of the disease. Therefore, novel therapies and molecular targets are warranted for the treatment of this disease.

Ding *et al.* (22) show that forced expression of hPRL in endometrial carcinoma cells promotes cell proliferation, anchorage-independent cell growth, migration, and invasion *in vitro* and *in viv*o. Moreover, silencing hPRL reverts most effects. The authors further demonstrate that hPRL overexpression reduces sensitivity of endometrial carcinoma cells toward doxorubicin and paclitaxel through a proposed mechanism mediated by CD24.

The results by Ding *et al.* (22) uncover a new dark side of prolactin action. Even though some data had pointed to a participation of prolactin in endometrial cancer, this work tackles the problem from different methodological avenues to reach sound conclusions. Of note is that human PRLRs are insensitive to most non-hPRLs, including mouse prolactins, and many heterologous *in vivo* models fail to provide the tumor with the physiological level of endocrine prolactin production. Besides, extrapituitary prolactin production is rarely detected in immortalized human cell lines. The authors circumvent these aspects by forcing hPRL gene expression in endometrial cell lines.

Several data, but not all, had previously suggested a participation of prolactin in endometrial cancer. Expression of both prolactin and its receptor were increased in endometrial cancer samples, arguing for the involvement of an autocrine loop in addition to endocrine overstimulation (23). Nevertheless, using a cutting-edge matrix assembly to monitor the Stat5 activation induced

by prolactin in 40 tissues, the endometrium was not activated (24). Alternatively, prolactin was the strongest discriminative biomarker for endometrial cancer, providing 98.3% sensitivity and 98% specificity when a panel of 64 serum biomarkers was analyzed in sera of patients with endometrial cancer (stages I to III) age-matched healthy women, utilizing a multiplex bead-based immunoassay (25).

Therefore, increased levels of serum prolactin may play a role in growth and progression of endometrial as well as other cancers. The work by Ding *et al.* (22) emphasizes the participation of extrapituitary autocrine prolactin in stimulating endometrial cell proliferation. The prolactin gene in humans and other primates contains an alternative promoter 5.8 kbp upstream of the pituitary transcription start site. This promoter drives the expression of prolactin in a variety of tissues such as breast, prostate, hair follicles, hematopoietic lineages, adipose tissue, and ovary, among others (6, 10, 11, 20, 26). The role of autocrine prolactin has been highlighted in the development of breast, prostate, ovarian, and tongue cancer and in acute myeloid leukemia (10, 11, 20).

Data on the role of prolactin in different cancers have encouraged various laboratories to develop compounds targeting the PRLR, and both PRLR antagonists and PRLR neutralizing antibodies have been developed (11). Positive experimental results show autophagy-mediated programmed cell death by blockade of PRLR signaling in epithelial ovarian cancer using G129R-hPRL (27), as well as inhibition of prostate tumors that had been induced by overexpression of prolactin by coexpression of Δ1–9-G129R-hPRL (a competitive PRLR antagonist) (28). Clinical trials in patients with breast and prostate cancer are underway. Nonetheless, a first report has provided negative results in terms of antitumor activity from a phase I trial of LFA102 (a humanized monoclonal antibody that binds to and inhibits PRLRs) in breast and prostate cancer (29). New trials are warranted.

When targeting PRLRs, one particular tissue should be considered, the pituitary. Antagonizing prolactin may interfere with the antiproliferative and proapoptotic effect of prolactin on lactotropes, as well as with the negative prolactin feedback loop at the hypothalamic level, which may lead to further elevation of circulating prolactin levels. Such was the case in phase I trial of LFA102 in which serum prolactin levels were increased.

In view of the results by Ding *et al.* (22) and in context with the existing literature of prolactin and cancer, patients with endometrial cancer in advanced stages or with chemoresistance could benefit from anti-PRLR strategies used in combination with actual therapies.

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