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The role of prolactin and growth hormone in breast cancer

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This review will focus on the role for prolactin (PRL) and growth hormone (GH) in mammary tumor formation. Much attention has previously been focused on circulating levels of GH/PRL in relation to mammary tumor formation. We will review data demonstrating that these ligands also could be produced locally in different organs, including the mammary gland and mammary tumors, and suggest that this local production may be of importance for pathological conditions. We will also discuss mechanisms for crosstalk between steroids and GH/PRL. A crosstalk between GH- and PRL response is possible at multiple levels. In the human, GH can activate both the prolactin receptor (PRLR) and the growth hormone receptor (GHR). We have demonstrated that activation of the PRLR, but not the GHR, is inducing mammary tumors in transgenic mice. Furthermore, the elevated levels of insulin-like growth factor 1 (IGF-I) seen in the GHR activating transgenic mice is not sufficient for tumor induction. The induced tumors express functionally active prolactin that could be of importance for the tumor formation. Paracrine/aurocrine stimulation by PRL may be more important than PRL transported via the circulation. In women, the role for stimulation of the PRLR and/or the GHR in mammary tumor formation has not been proven, although experiments from primates suggest that the PRLR could be of importance. *Oncogene* (2000) **19,** 1072–1076.

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Introduction

The pituitary controls secretion of many hormones known to be important for normal development of the mammary gland (e.g. sex-steroids, prolactin [PRL], growth hormone [GH], cortisol; Topper and Freeman, 1980; Silberstein *et al*., 1994; Humphreys *et al*., 1997; Kleinberg *et al*., 1990; Feldman *et al*., 1993; Ruan *et al*., 1995). This review will focus on the role for PRL and GH in mammary tumor formation. Much attention has previously been focused on circulating levels of GH/PRL in relation to mammary tumor formation. We will review data demonstrating that these ligands also could be produced locally in different organs, including the mammary gland and mammary tumors, and suggest that this local production may be of importance for pathological conditions. We will also discuss mechanisms for crosstalk between steroids and GH/PRL.

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Prolactin is classically considered to be a pituitary hormone mainly involved in milk protein production and it has important functions for development of the mammary gland (Ormandy *et al*., 1997). PRL belongs to the same gene family as GH and placental lactogenes (PLs). The PRL receptor (PRLR; Boutin *et al*., 1988) and the GH receptor (GHR; Leung *et al*., 1987; Godowski *et al*., 1989) are members of the cytokine receptor superfamily. Ligand binding induces homodimerization of two receptor molecules followed by activation of tyrosine kinases in the Janus family, phosphorylating members of the STAT family and proteins involved in the MAP kinase signaling pathway.

A crosstalk between GH- and PRL response is possible at multiple levels. As described signaling pathways are also largely similar, as is some responsive genes. This gives multiple levels possible where crosstalk could occur but also raises the question on how specific responses for GH and PRL could be achieved.

Pituitary hormones

A potential role, other than regulation of steroid secretion, for pituitary hormones in breast cancer in experimental animals and humans have been studied for a long period of time. In treatment of advanced breast cancer in human it was demonstrated that hypohysectomi had beneficial effects in combination with estrogen removal, compared to estrogen removal alone (VanGilder and Goldenberg, 1975). This surgical approach indicates that the pituitary secretes some hormone (e.g. GH or PRL) having ovary independent stimulatory effects on mammary tumor growth.

Humans

To address the question if circulating levels of GH or PRL is important for development of mammary cancer, patients with tumors secreting GH (arcomegaly) or PRL (prolactinomas) can be studied. The support is not strong for that circulating levels of GH should be the most important factor for mammary tumors and the role for PRL is even less clear. In acromegaly a general overrepresentation of malignant disorders have been observed and some studies report the tumors to be localized to specific organs, e.g. breast and colon (Nabarro, 1987; Ituarte *et al*., 1984).

In contrast to the findings in acromegaly, there is no clear correlation reported between women suffering from prolactinomas and breast cancer. However, breast cancer is a common disease and elevated PRL levels can be more widespread than usually believed. The most common hormone producing pituitary tumor in women is prolactinomas secreting PRL. At autopsy

micro prolactinomas is a rather common finding, indicating that PRL producing pituitary tumors is an underestimated condition in an aged population (Burrow *et al*., 1981). Therefore an association between prolactinomas/elevated PRL levels and breast cancer have been difficult to study.

In women suffering from breast cancer the data regarding serum PRL are rather contradictory. In some studies an association between the serum levels of PRL and mammary tumors is reported, but in other studies no correlation can be found (Zumoff, 1988). Interestingly, increased levels of PRL exist in members of families with a high prevalence of breast cancer, suggesting that serum PRL might be important at least in certain high risk populations (Kwa *et al*., 1974). It has also been demonstrated that hyperprolactinemia is associated with metastatic disease among certain breast cancer patients. Hyperprolactinemia has been suggested to be an indicator of the progression of the disease supported by findings that PRL levels decrease if remission is achieved (Holtkamp *et al*., 1984).

Several investigators have studied the effect of PRL suppression by bromocriptin and L-dopa treatment in breast cancer patients. The data are rather discouraging, showing no effect or only a very limited effect in certain patients (Nagasawa, 1979).

In patients with breast cancer, increased serum levels of GH have been reported (Emerman *et al*., 1985).

Even if circulating levels of GH/PRL is difficult to link to mammary cancer a local production may be of importance, as discussed below. It is clear that mammary tissue has receptors for both GH and PRL. Breast cancers and mammary tumor cell lines express the PRLR (Murphy *et al*., 1984; Bonneterre *et al*., 1987; Reynolds *et al*., 1997). Blocking of the PRLR results in inhibition of growth in cultured tumor cells (Fuh and Wells, 1995). The GHR is also expressed in mammary tumors and tumor cell lines (Decouvelaere *et al*., 1995). The expression of PRLR and GHR is primarily localized to epithelial cells in the mammary gland but some expression is evident also in stromal cells (Mertani *et al*., 1998).

Epidemiological well established risk factors for breast cancer, i.e. early menarche and late menopause, are believed to depend on the life time exposure to estrogen. PRL levels increase at menarche and decrease after menopause as estrogen levels do. Thus, early menarche or late menopause are associated with an increased life time exposure to PRL. Furthermore, it has been demonstrated that after the first full-term pregnancy there is a marked long-lasting decrease in PRL levels, suggesting that this change may relate to the lifetime protection that early pregnancy confers against breast cancer (Musey *et al*., 1987).

Experimental animals

The role for GH and PRL in experimental mammary tumors has been studied using different approaches. The importance for PRL has been investigated in studies using different inbred strains of mice and the frequency of mammary tumors were higher in breeding animals compared with none breeders. However, the effect was not observed in all strains (Medina, 1982). Pituitary grafts secreting increased amount of PRL have been extensively used in mouse and rat. The pituitary grafts have been shown to increase the frequency of mammary tumors in some strains of inbred mice and to substitute for gestation when pregnancy dependent mammary tumors are chemically induced in rodents (Medina, 1982; Matsuzawa, 1986).

One obvious drawback with pituitary transplants is the possibility of prolonged secretion of other hormones than PRL, e.g. GH (Huseby *et al*., 1985; Adler, 1986). This is a major problem if the aim is to compare the role for GH and PRL in mammary tumor formation. The importance for GH has been studied in experiments using mammary tumor transplants in mutant lit/lit mice. This is a mouse strain with extremely low circulating GH and low IGF-I levels because of a mutation in the growth hormone-releasing hormone receptor. The tumor growth is drastically reduced in this model suggesting a function for GH and/or IGF-I in the tumor growth (Yang *et al*., 1996).

One other interesting observation is that GH production can be induced by progestins in the mammary gland in dogs (Selman *et al*., 1994). Treatment of female dogs with progestines causes mammary tumor development in a dose-dependent manner indicating a potential role of GH in the tumor formation. Furthermore, the GH gene is expressed in mammary tumors in dog (Mol *et al*., 1995).

We have used transgenic mice to generate increased levels of GH and PRL to study their specific function in mammary tumor development. The advantage with this approach compared to pituitary grafts is that the transgenic model have elevated levels of a specific hormone. Consequently, the physiological effects observed in the transgenic mice could be attributed to the overexpressed gene, e.g. GH or PRL, in a direct or indirect way. The results of these studies will be discussed below under 'Receptor specificity'.

Recently, it was demonstrated in monkeys that hGH treatment induced mammary gland hyperplasia in aging animals (Ng *et al*., 1997). In the study female monkeys aged 16–20 years were treated for 7 weeks with either human GH (hGH; 100 μg/kg per day), IGF-I (120 μg/kg per day) or a combination of hGH and IGF-I. The effect on the mammary gland was most prominent in the group receiving both hGH and IGF-I. Interestingly, the group treated with hGH had a greater increase in lobule number and size than the group receiving only IGF-I, indicating that hGH exerted direct effects on the epithelial cells not mediated via IGF-I. The expression of GHR mRNA was localized to adipose tissue and PRLR mRNA was expressed in epithelial cells as analysed by *in situ* hybridization. The monkey data suggest that hGH acts via the PRLR on the epithelial cells, or that a signal is transferred from the GH-responsive stromal cells to the epithelial cells. However, in humans the GHR expression is localized to both epithelial and stromal cells in the mammary gland (Mertani *et al*., 1998).

Receptor specificity

Both GHR (Mertani *et al*., 1998) and PRLR (Jahn *et al*., 1991) are expressed in the mammary gland. The respective activity of GH on the GHR and the PRLR differs related to what species the GH is derived from. Human GH (hGH) activates both the GHR and the

PRLR in primates and non-primates in contrast to non-primate GH that only acts via the GHR (Goffin *et al*., 1996). In contrast to GH, PRL is only mediating its effects via the PRLR. Therefore, in the human, PRLR stimulation is obtained both by PRL and GH.

Our initial observation that metallothionein promoter-hGH (Mt-hGH) transgenic mice developed pregnancy independent, metastatic mammary tumors at a high frequency (Törnell *et al*., 1991, 1992) made us investigate the receptor specificity in the tumor induction. In the study using Mt-hGH transgenic mice we could conclude that hGH can induce mammary tumors in mice and that the effect is not linked to a particular strain of mice. We were not able to determine if the tumor inducing effect of hGH was mediated via the GHR or the PRLR, or if the elevated IGF-I levels seen in the MT-hGH transgenic animals was of importance for the tumor development.

To investigate the receptor specificity in the mammary tumor formation we used mice transgenic for bovine GH (Mt-bGH) to selectively stimulate the GHR and mice transgenic for rat prolactin (Mt-rPRL) to selectively activate the PRLR (Wennbo *et al*., 1997). The bGH transgenic animals had an increased body weight (demonstrating biologically active GH) and displayed high levels of immunoreactive bGH and IGF-I in serum. In contrast to the bGH mice, the rPRL transgenic mice had normal levels of IGF-I in serum and the body weight was not changed from controls. All of the female rPRL transgenic mice developed mammary adenocarcinomas at an age between 11–15 months in contrast to none of the bGH transgenic animals. Consequently, PRLR activation is important for mammary tumor induction in mice in contrast to GHR activation in combination with high levels of IGF-I (Wennbo *et al*., 1997) that fails to induce mammary tumors.

Endocrine/paracrine/autocrine mechanisms?

Recently it was shown that mammary tumors and normal mammary tissue express both PRL and GH, suggesting a possible paracrine function of the hormones in tumor development and growth (Kurtz *et al*., 1993; Clevenger *et al*., 1995; Mol *et al*., 1995). Furthermore, PRL can be secreted by breast cancer cells cultured *in vitro* (Ginsburg and Vonderhaar, 1995). In experimental animals, PRL expression has been demonstrated in the mammary gland from lactating rats and mice (Steinmetz *et al*., 1993; Ginsburg *et al*., 1996), and PRL can act as a local growth factor in chemically induced mammary tumors in rats (Mershon *et al*., 1995).

There is no clear correlation between patients with prolactionomas and breast cancer and also the data on serum PRL levels in patients with breast cancer is conflicting. Inhibiting PRL secretion with bromocriptine treatment has given inconsistent results with only small effects on the tumor growth in some cases (Nagasawa, 1979). Therefore, the data supporting the concept that circulating PRL is of great importance for mammary tumor formation in humans is weak.

Local production of PRL has been demonstrated in several PRL-responsive tissues, in both humans and rodents, e.g., mammary gland, uterus, immune system and prostate (Ben-Jonathan *et al*., 1996; Steinmetz *et al*., 1993).

In the rat, PRL is expressed in mammary tumors induced by the carcinogen nitrosomethylurea (NMU) (Mershon *et al*., 1995) and in normal lactating tissue (Steinmetz *et al*., 1993). A tumor cell line derived from NMU tumors also expresses PRL and PRLR. Cell proliferation of the NMU cell line was suppressed by PRL antiserum (Mershon *et al*., 1995).

In humans, PRL is expressed in normal and malignant breast tissue (Clevenger *et al*., 1995), and by *in situ* hybridization PRL expression has been localized to the epithelial cells. In tumor tissue, a heterogenity of the expression among the tumor cells was observed (Clevenger *et al*., 1995). In several human mammary tumor cell lines expressing PRLR, e.g., MCF-7 and T47Dco, secretion of PRL to the cell culture media has been demonstrated (Ginsburg *et al*., 1996). PRLR antagonists can inhibit the growth rate of mammary tumor cell lines e.g., MCF-7 cells (Fuh and Wells, 1995).

The previous observations of local production of PRL in the mammary gland and our observation that transgenic animals with high as well as low serum levels of rPRL developed mammary tumors (Wennbo *et al*., 1997) made us examine the potential function of locally expressed PRL in the rPRL transgenic animals.

All Mt-rPRL transgenic female mice from two different lines, one low expressing line displaying serum rPRL levels in the normal range of mouse PRL, and one high expressing line displaying serum rPRL levels approximately four times higher than endogenous peak levels of PRL, developed pregnancy independent tumors. First we demonstrated that the rPRL transgene was expressed in mammary tumors of both lines of rPRL trangenic mice. Cell lines established from mammary tumors from the transgenic line with low serum levels expressed PRLR mRNA and secreted rPRL to the culture media indicating a possible autocrine mechanism of action. Furthermore, in organ culture experiments the locally produced rPRL was functionally active, inducing differentiation and milk protein production in an auto/paracrine manner (Wennbo *et al*., 1997). During pregnancy and lactation the endogenous mPRL gene is expressed in the mammary gland (Wennbo unpublished).

Human-GH has also been demonstrated to be expressed in mammary tumors (Mol *et al*., 1995; Gebre-Medhin, unpublished) but the evidence for an autocrine mode of action is not as strong as for PRL.

Interaction between the prolactin/growth hormone systems and steroid signaling mechanisms

Multiple systems beside PRL and GH have been suggested to be important for mammary development and tumor formation. Steroid hormones play an important role for normal development and possibly also for tumor formation in the mammary gland. Recently ways for crosstalk between the steroid system and the prolactin pathway have been described.

Many of the effects mediated through the PRLR (Schmitt-Ney *et al*., 1992; Wakao *et al*., 1994; DaSilva *et al*., 1996; Liu *et al*., 1996) and the GHR (Wood *et al*., 1995; Udy *et al*., 1997) are transduced via the

STAT (Signal Transducer and Activator of Transcription) system. The principal STAT's being activated in mammary cells by the PRLR are STAT 5a and b. *In vivo*, STAT5a is of fundamental importance for lobuloalveolar formation during pregnancy and lactation (Liu *et al*., 1997). Activation of the progestin receptor can increase the levels of STAT5 and promote translocation into the nucleus (Richter *et al*., 1998). Furthermore, the progestin receptor (Richter *et al*., 1998) and glucocorticoid receptors (Stocklin *et al*., 1996) can associate to STAT5 to enhance the prolactin response.

Conclusions and future perspectives

Increased activation of the prolactin receptor lead to tumor formation in mice. It is likely the locally produced ligand is of greater importance than hormones supplied via the circulation. To further clarify the question of the role for locally produced ligand versus endocrine activation, systems as tissue-specific gene expression in transgenic animals and tissue specific knockout of specific receptors could be employed. In women, the role for stimulation of the PRLR and/or the GHR in mammary tumor formation has not been proven although experiments from primates suggest that the PRLR could be of importance. A more focused analysis to study local production of GH and/or PRL in relation to mammary tumors in women can be very productive.

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