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Mini Review

Prolactin and its Activated Mutant Receptor - A Mini-Review

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Abstract

Prolactin(PRL) is a lactogenic hormone that is mainly produced by the anterior pituitary gland. In addition to circulating PRL, several human tissues express PRL like epithelial and stromal breast tissue, prostate, anterior pituitary, decidua and some immune cells. The biological function of PRL include development of mammary gland cells and lactation. Each of these functions requires expression of the PRL receptor(PRLR), which its downstream signalling involved JAK2/STAT5, Ras/Raf/MAPK and PI3K/akt pathway. Isolated prolactin deficiency has up to now been reported in 9 patients in literature. In various animal models, there is tracing to be found activated PRL/PRLR oncogenic signalling in the role of mammary tumorigenesis. These findings link to PRLR I146L in multiple fibroadenomas and a major local growth promoter via autocrine/paracrine in human breast cancer and even in familial hyperprolactinemia. The data provide targeting activated PRL/PRLR as an additional insight in breast cancer.

Keywords: *Oncogenic Activation of PRLR; Breast Cancer; Target Therapy*

Introduction

Prolactin(PRL)is an anterior pituitary hormone that, along with GHs, forms a family of hormones that probably resulted from the duplication of an ancestral gene. PRL is a lactogenic hormone of 199 amino acids that is mainly produced by the anterior pituitary gland. PRL has multiple biological functions which include development, proliferation and differentiation of mammary gland cells, beginning and maintenance of lactation, immunoregulation, osmoregulation, behaviour and reproduction [1-4]. PRL plays a critical role in ductal branching at puberty, as well as lobuloalveolar development during pregnancy [5]. In addition to circulating PRL by pituitary PRL release, several human tissues also express PRL like epithelial and stromal breast tissue, prostate, skin, decidua, brain, some immune cells, adipocytes and several others [1]. Each of these functions requires expression of the PRL receptor in different extra-pituitary regions [1].

The prolactin receptor(PRLR) is a member of the cytokine receptor superfamily [6]. The PRLR contains 598amino acids(aa), which encoded by a gene on chromosome 5p13 - 14. The first step in the mechanism of action of PRL is the binding to a cell surface receptor. The ligand binds in a two-step process in which site 1 on PRL binds to one receptor molecule, after which a second receptor molecule binds to site 2 on the hormone, forming a homodimer consisting of PRL and two molecules of receptor (Bole-Feysot C., *et al.* 1998). The active ligand/receptor binding results in allosteric reorganization which brings JAK2 kinase into close proximity to the intracellular domain (BOX 1) of the receptor, enabling its phosphorylation. The phosphorylated JAK2 recruits several kinases and adaptor proteins which activate downstream signalling pathways such as JAK2-STAT5, JAK2-RUSH [7], Ras/raff/MAPK and PI3K. The JAK2/STAT5 pathway is one of the predominant pathways activated by PRLR to mediate transcriptional activation. PRL stimulated JAK2 activation results in the tyrosine phosphorylation of STAT5 and subsequent translocation of this protein into the nucleus, promoting transcription of numerous genes, for example, cytokine inducible SH2-containing protein, β-casein, c-myc protooncogene, and cyclin D1. Thus, these cascades result in endpoints such as differentiation, proliferation, survival and secretion [8].

PRLR isoforms and PRLR mutant model

There are several PRLR isoforms identified in humans, including the long form, an intermediate form, and two short forms. All of them generated through mRNA splicing [9,10]. Heterzygous (+/-) females show almost complete failure to lactate after delivery [11]. Homozygous (-/-) females are infertile due to multiple reproductive abnormalities [12,13]. A mutant of the PRLR which deleted a part of the extracellular domain formed mutant receptor dimers in a ligand-independent manner and constitutively activates protein gene expression. The expression of this constitutively active PRLR by transgenic mice induces a premature abnormal development of the mouse mammary gland, impaired termed differentiation and milk production, and then lactation failure at the end of pregnancy [14].

Clinically, familial puerperal alactogenesis due to isolated prolactin deficiency has been reported in 9 cases in the literature [15-20]. Isolated prolactin deficiency is a rare entity of disorder manifesting as failure of puerperal lactogenesis. Recent much interesting, Iwama and colleagues [19] reported a 39-year-old woman with puerperal alactogenesis after two deliveries and undetectable PRL. The patient serum contained autoantibodies that specifically recognized a subset of PRL-secreting cells. The patient was able to lactate fully after 17 days of treatment with rPRL 60 ug/kg every 12 hours, but alactogenesis is resumed after treatment was completed. Callejas., *et al.* [20] reported that one patient the ovulated-on clomiphene and became pregnant. In the 2nd trimester(TM) PRL was increased to 21. 8 ng/ml and third TM PRL was 119. 6ng/ml, as compared to initial 1. 7 - 2. 9 ng/ml. Acquired prolactin deficiency was found in patients with disorders of the hypothalamic-pituitary axis [21], especially in Cushing's disease treated and craniopharyngioma. Severe PRL deficiency was significantly associated with TSH, ACTH and GH deficiency [21,22]. Thyroid releasing hormone (TRH) and recombinant prolactin for treatment of poor puerperal lactation has been early established in rat and in available clinical trials [23-25].

Oncogenic activation of autocrine/paracrine PRL/PRL receptor signalling in breast tumorigenesis

The involvement of prolactin in human tumorigenesis has been long debated [26]. The tumorigenic potency of prolactin on the mammary gland was initially suggested 50 years ago based on the tumour growth-promoting effect of high circulating levels on spontaneous and chemical carcinogen-induced models of mammary carcinogenesis in rodents [27]. In human, epidemiological studies performed during the 1980s and 1990s with unable to reach unified conclusion [28,29-31]. Correlations between circulating PRL and breast cancer development and progression are conflicting, and reduction of pituitary PRL with bromocriptine does not alter the disease course [32].

Nowadays, there are accumulating evidences that high circulating PRL levels are considered as a risk factor in breast cancer [30,33], and in other reproductive cancer such as endometrial ovarian and prostate [34,35]. Prolactin is not only secreted by their pituitary gland but is also produced locally in the majority of breast tumor and is thought to act in an autocrine and/or paracrine factor [1,36,37]. For instances, the PRL receptor and the sex steroid receptors were coexpressed in breast cancer [38, 39]. Cellular expression of hGHR and hPRLR mRNA in proliferative and neoplastic lesions of the breast [40, 41]. PRL and PRLR are expressed in human mammary carcinoma cells [42]. 80% of breast tumours stain positive for PRLR. 52%(33/63) of tumors PRL mRNA expression, and 58% (64/111) of breast cancers had hyperprolactinaemia (PRL 520.0 ng/ml) [43]. Breast tumours express higher levels of the PRLR than adjacent health tissue [2,36,44,45]. Notably, amplification of PRLR was identified in 4/4 cases of lobular carcinoma in situ (LCIS) and increased PRLR expression was found in an aggressive form of lobular carcinoma [46]. Moreover, a constitutively active genetic variant of the PRLR was identified in patients with breast tumours [47]. All these data indicate that breast cancer can produce PRL [43,48], and activated PRL/PRLR signalling act as a potent survival factor [49] and a major local growth promoter via autocrine/paracrine loop [43], then rapidly activate STAT5A /B through JAK2/STAT5/cyclin D1 pathway in mediating proliferative signal induced by PRL. This activation was increased by HOX A1 [42]. *In vitro*, in the presence of PRL at physiological concentration (20 ng/ml) as well as at pharmacological amounts (200 ng/ml), PRL significantly stimulated colony formation of human breast cancer cells 126% at lower dose and 159% at high dose respectively [61]. The effect of PRL was more pronounced in ER-positive tumours [62]. Thus, sustained PRL/PRLR oncogenic signalling has been implicated in mammary breast cancer including invasive and non-invasive breast cancer [50]. Otherwise, PRL/PRLR expression in tissues and serum has been found elevated in patients with cervical cancer [51,52], suggesting activated PRL/PRLR signalling as an important survival factor for cervical cancer [52].

In mice model, transgenic expression of prolactin results in increased tumour formation [37,53]. Prolactin potentiates TGFα induction of mammary neoplasia, bitransgenic mice harboring prolactin and TGFα increased the incidence and reduced the latency of preneoplastic lesions, with higher levels of phosphorylated ERK 1/2. The finding demonstrated that locally produced prolactin can strikingly potentiate the carcinogenic actions of another oncogene and modify ovarian hormone responsiveness [37]. Under the control of a hormonally nonresponsive promoter, neu-related lipocalin (NRL), in NRL-PRL transgenic mouse lineage, female virgin mice display mammary developmental abnormalities, mammary intraepithelial neoplasia's, and invasive neoplasms [5]. The tumours are of varied predominate, but papillary adenocarcinomas and adenosquamous neoplasms predominate. The invasive neoplasms had ERα positive and ERα negative populations, as occurs in human mammary tumours [5,54].

More studies, in transgenic mice overexpressing the rat PRL gene that have elevated levels of PRL (150 ng/ml) only binding to the PRLR and with normal IGF-I levels, all of the PRL transgenic female mice developed mammary carcinoma at 11-15 months of age [55]. Mice expressing the polyoma middle-T antigen oncogene developed tumours in the first weeks of life, but when crossed with PRL knockout mice they developed tumours significantly later (Vomachka., *et al*, 2000). Loss of mammary epithelial prolactin receptor also delays tumour formation by reducing cell proliferation in low-grade preinvasive lesions, the prolactin receptor was demonstrated to increase neoplasia and positively impact the transition to invasive carcinoma [56]. Using the prostate-specific rat probating (pb) promoters to drive expression of the rat PRL gene, pb-PRL transgenic males developed prostate hyperplasia [57-59]. Autocrine prl is expressed in 54% of hormone-refractory human prostate cancer and 62% prostate cancer metastasis. The key signalling proteins that mediate the biological effects of autocrine prl in prostate cancer are signal transducer and activation of transcription (stat)-5a/b via activation of Janus kinase-2 (JK2) [60]. Truthfully, by deleting 178 amino acids of the extracellular ligand-binding domain in human PRLR, expression of this deletion mutant in the IL-3-dependent murine myeloid cell line 32 Dcl3 or transfected into Nb2 cells resulted in the induction of growth factor-independent proliferation and constitutive activation of JAK2-STAT5, MAP kinase (ERK1 and ERK2) and loss of apoptosis in 32 D deleted 178 cells in the absence of mIL-3. This constitutive activation of 178 deleted PRLR mutant leads to oncogenic activation of the receptor due to the receptor to induce growth factor-independent proliferation of factor-dependent hematopoietic cells *in vitro* [61,62]. In clinic, targeting oncogenic receptor inhibitors [63-69], tamoxifen plus bromocriptine [32], and addition of G129R and Herceptin on HER2-overexpressing breast cancer were in trials [70-73]. These studies highlighted the ability of oncogenic PRL/PRLR-triggered pathway to promote mammary tumorigenesis in rodents.

Multiple fibroadenomas (MFA) are benign breast tumours which appear most frequently in young women, including at puberty, which prl has well-recognized proliferative actions on the breast. Bogorad., *et al.* and benign breast diseases study group [47]. identified four patients harboring a heterozygous missense mutation in the exon 6 of the PRLR gene leads to I146L substitution in its extracellular domain. Mutation I146L encodes a constitutively activate PRLR, and increased STAT5 signalling was phosphorylated in the absence of prl. Ba/F-PRLR I146L cells survived and autonomous growth irrespective of the addition of prl. Thus, constitutive activity, phosphorylated STAT5 contributes to the pathogenesis of MFAs.

Mutant prolactin receptor and familial hyperprolactinemia

Hyperprolactinoma is usually due to tumors in the anterior pituitary gland and occurs occasionally in hereditary multiple endocrine neoplasia syndromes. Several growth factors, including dysregulated receptors for fibroblast growth factor (FGF), dopamine, estrogen, and hypothalamic hormones have been implicated predominantly in prolactinoma pathogenesis. Estrogen-induced pituitary tumor transforming gene (PTTG) through its receptor and by stimulation of FGF regulate prolactin synthesis and secretion. Pituitary pttg expression is induced by both bFGF and estrogen, and pttg expression coincides with the early lactotrophic hyperplastic response, angiogenesis and prolactinoma development [74-76].

When examined, elevated prolactin receptor levels were found in PRL-secreting pituitary adenoma [77]. Recently, a heterozygous mutation in the prolactin gene resulting in an amino acid change from histidine to arginine at codon 188 (His188Arg) was identified in familial hyperprolactinemia [78]. This substitution that disrupted the high affinity ligand- binding interface of the prolactin receptor, leads to a loss of downstream signalling by JAK2-STAT5. Thus, the familial hyperprolactinemia appears to be due to a germline, loss-of-function mutation in PRLR, and cause prolactin insensitivity [78].

Conclusion

over the past five decades, although there is a long debated, increasing evidences suggest a growth promoter role for activated PRL/PRLR in breast and prostate tumorigenesis. PRL can induce growth and survival of cancer cells and tissues in several experimental settings. In mice, transgenic expression of PRL on breast and/or prostate leads to enhanced epithelial hyperplasia and dysplasia, with amplification of basal/stem cells which recently known as cancer-initiating cells. Also, activation of the prolactin receptor (PRLR) is sufficient for induction of mammary carcinomas in mice [55]. In PRLR knockout transplants [56] the area of neoplasia was significantly smaller (7 vs 17% at 22 weeks, $p < 0.001$). Tumour latency increased (289 days vs 236 days, $p < 0.001$)[56]. These, and other experience, have uncovered that prl alone at high level produce mammary tumours. By deleting the extracellular ligand-binding domain in human PRLR resulted in the induction of growth factor- independent proliferation and constitutive activation of JAK2-STAT5, MAP kinases, which highlighted the ability of oncogenic PRL/PRLR promote breast tumorigenesis in rodent [62]

Available clinical data point to a role of local (autocrine/paracrine) PRL in the induction of disease progression [42]. Higher cellular expression of PRLR predominantly in steroid hormone receptor positive breast cancer cells and tumors. In particular, elevated PRLR levels were shown in PRL-secreting tumours from patients with markedly increased serum PRL levels [77]. Prolactinomas are the most common cause of hyperprolactinemia [79], and hyperprolactinemia caused prostate hyperplasia and stromal accumulation of inflammatory cells [80]. Another, in four patients with MFA, mutant PRLR I146L was identified in its extracellular domain, and with increased STAT5 signalling [47]. Thus, targeting activated PRLR/STAT5 oncogenic signalling may provide an alternative therapy for the treatment of breast and/or prostate cancer, and small molecule inhibitors directed against the tyrosine kinase JAK2 upstream of STAT5. This is testable.

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