Biological Significance of Prolactin in Gynecologic Cancers

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Abstract

There is increasing evidence that prolactin (PRL), a hormone/cytokine, plays a role in breast, prostate, and colorectal cancers via local production or accumulation. Elevated levels of serum PRL in ovarian and endometrial cancers have been reported, indicating a potential role for PRL in endometrial and ovarian carcinogenesis. In this study, we show that serum PRL levels are significantly elevated in women with a strong family history of ovarian cancer. We show 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. PRL potentially induced proliferation in several ovarian and endometrial cancer cell lines. Binding of PRL to its receptor was followed by rapid phosphorylation of extracellular signal-regulated kinase (ERK) 1/2, mitogen-activated protein kinase (MAPK) pathway is also activated by PRL and may be involved in the proliferative effects of the hormone.

There is increasing evidence that PRL plays a causal role in several types of cancer via local production or accumulation. In rodents, hyperprolactinemia correlates with increased mammary tumorigenesis (7, 8), and PRL administration induces mammary tumors and sustains carcinogen-induced tumor growth (9). Dopamine is the physiologic inhibitor of PRL production. Recently, in a large retrospective cohort study, the use of dopamine antagonists (antipsychotics) resulted in a 16% increase in breast cancer, with a dose-response relationship between cumulative doses and greater risk (10). In a nested case-control study within the prospective Nurses’ Health Study cohort, a significant positive association was observed between plasma levels of PRL and postmenopausal breast cancer risk (11, 12). Association of elevated PRL serum levels with prostate cancer has also been documented (13).

Elevated PRL levels were recently reported in the sera of patients with ovarian (14) and endometrial (15) cancers. We hypothesize that elevated serum PRL could be a risk factor for ovarian and endometrial cancers. We propose a mechanism by which PRL promotes tumorigenesis by activating Ras oncogene, thus inducing malignant transformation of cells carrying mutations in tumor suppressor genes. We test this hypothesis by analyzing the differential expression of and response to the PRL/PRLR axis in human ovarian and endometrial carcinoma cells.

Introduction

Prolactin (PRL) is a 23-kDa protein that has a dual function: as a circulating hormone and as a cytokine. PRL is reportedly involved in more than 300 separate functions, including development of the mammary gland, lactation, implantation and pregnancy, angiogenesis, and regulation of immune function (reviewed in ref. 1). PRL is secreted by the pituitary gland and by multiple nonpituitary sites, including human ovarian follicular cells, decidualized stromal cells of the human endometrium, and normal peripheral blood lymphocytes (reviewed in ref. 2). The synthesis of extrapituitary PRL is driven by a different promoter than its pituitary counterpart (3), although the amino acid structure of pituitary and extrapituitary PRL seems to be identical (4).

PRL initiates signaling by binding to its cognate receptor, PRLR. The proximal transduction pathways activated during PRLR-associated signaling include the tyrosine kinases Jak2, Fyn, and Tec, the phosphatase SHP-2, the guanine nucleotide exchange factor Vav, and the signaling suppressor SOCS (5). In addition, as shown in rat GH4 neuroendocrine cells, the Ras/Raf/mitogen-activated protein kinase (MAPK) pathway is also activated by PRL and may be involved in the proliferative effects of the hormone.

Materials and Methods

Patient population. Sera from 167 patients with endometrial cancer were provided by Dr. Karen Lu (M. D. Anderson Cancer Center) and Gynecologic Oncology Group Blood Bank (Columbus, OH). Sera from 273 patients with endometrial cancer, 215 patients with stage I to II and 118 patients with stage III to IV ovarian cancer, 141 patients with benign pelvic disease, and 470 healthy controls were obtained from the Gynecologic Oncology Group Blood Bank. Sera from patients with high risk of developing ovarian cancer were from Drs. Andrew K. Godwin (n = 20) and David Fishman (n = 94). Sera of age-matched women with lung cancer (n = 75) were...
were blocked with H2O2, and EnVision+ System (Dako) was used for stain-

retrieval was performed using EDTA buffer (pH 8.0). After unmasking, slides

from patients with breast cancer (controls at

denote mean concentrations. ***, significance of differences between cases and

history of ovarian cancer. Horizontal lines and numbers over each distribution

ovarian and endometrial cancers compared with other cancers.

provided by Dr. Jill Siegfried (University of Pittsburgh Cancer Institute), sera

from patients with breast cancer (n = 219) were provided by Dr. Jeffrey

Marks (Duke Medical Center), and sera from women with pancreatic cancer (n = 101) were provided by Drs. Herbert Zeh III and Randall Brand (Uni-

versity of Pittsburgh Cancer Institute). All sera were collected during day-

time before surgery and anesthesia according to the same protocol.

Cell lines. Human endometrial carcinoma cell lines HEC-1A, AN3

CA, and RL95-2 and human ovarian carcinoma cell lines OVCAR3 and

SKOV3 were obtained from the American Type Culture Collection. Immor-

talized human normal ovarian epithelial (NOE) cells T29 and T80 were pro-

vided by Dr. Jinsong Liu, and immortalized noncancerous endometrial

fibroblasts were provided by Dr. Gil Mor.

Reagents. Cisplatin and Hoescht 33342 were purchased from Sigma-Al-

drich. Mouse monoclonal antibodies against human PRL and PRLR were

from AnaSpec, and Ras inhibitor α-hydroxy farnesyl phosphonic acid was

from Cayman Chemicals. Cancer and normal tissue microarrays (TMA)

from AnaSpec, and Ras inhibitor

were captured, extracted, and analyzed with ArrayScan II Data Acquisition

and Data Viewer version 3.0 (Cellomics) and Quattro Pro version 10.0.0

(Corel).

Flow cytometry analysis. Cells were preincubated in PBS/0.1% bo-

vine serum albumin (BSA) for 20 min before incubation with pri-

mary antibody (1:100 dilution in PBS/0.1% BSA) for 20 min. Flow

cytometry was performed using FACSscan using CellQuest software (Becton

Dickinson).

Proliferation assays. Cancer cells were plated onto 96-well plates at

2 × 10^4 per well. Next day, medium was changed to medium with 2% fetal

bovine serum, human recombinant PRL (hrPRL) was added to the final

concentration of 0 to 100 ng/mL, and cells were grown for additional

72 h. Cells were fixed, stained with Hoechst 33342, and counted using the

Cellomics ArrayScan HCS Reader (10× objective) as previously de-

scribed (17).

Apoptosis assays. Apoptosis was analyzed by flow cytometry using

FITC-conjugated Annexin V and propidium iodide and by analysis of cas-

pase activation using Fluorescent Poly-Caspases FLICA Apoptosis Detec-

tion kit FAM-VAD-FMK (Immunochemistry Technologies) as previously described (17).

Multiplex analysis of phosphoproteins. Analysis of phosphoproteins

was performed using multiplexing xMAP technology (Luminex Corp.). Tumor cells were stimulated with 10 ng/mL hrPRL for 0 to 30 min;

cell lysates were prepared using Bio-Rad Bio-Plex Cell Lyses kit and

analyzed using Bio-Rad 17-Plex Phosphoprotein kit for testing phospho-

proteins, Akt, ATF-2, extracellular signal-regulated kinase (ERK) 1/2,
glycogen synthase kinase-3α/B, c-Jun NH2-terminal kinase, p38 MAPK,
p65, p53, p70 S6 kinase, p90RSK, and TrkA according to the manufac-

turer's protocol.

Multiplex analysis of transcription factors. Tumor cells growing in

six-well plates were treated with 10 ng/mL PRL for 0 to 30 min. Nuclear

extracts were captured, prepared and transcription factor analysis was performed

according to the manufacturer's protocol using the Procarta Multiplex Trans-

scription Factor Assay kit (Panomics) designed for measuring activities of

NF-κB, AP1, AP2, CREB, HIF-1, STAT1, STAT3, STAT4, Oct, GATA,

ELK-1, FAST-1, p53, PAX-3, NF-1, NF-E2, NF-E1/YY1, ATF-2, ISRE, PAX-5,

AR, ETS/PEA, Ncx-2.5, E2F1, MyoD, PPAR, SMAD, RNX5/9M, BRN-3,

CBP, NF-Y, c-myc, ER, GR/P, FKHR, HNF-1, MEF-2, NFAT, and IRF tran-

scription factors.

Clonogenic/colony formation assays. Cells were plated at a density of

0.5 per well onto 96-well plates and cultured for 7 to 10 d. For col-

ony counting, cells were stained and stained with Coomassie brilliant

blue. The ability of cells to form colonies in soft agar was assessed

in methyl cellulose–based medium as described (18). Briefly, cells were

resuspended in 0.8% methyl cellulose–based medium (Stem Cell

Figure 1. Serum PRL levels in healthy women, women with endometrial,

ovarian, breast, lung, and pancreatic cancers, and women with strong family

history of ovarian cancer. Horizontal lines and numbers over each distribution

denote mean concentrations. ***, significance of differences between cases and

controls at P < 0.001. PRL concentrations are significantly (P < 0.001) higher in

ovarian and endometrial cancers compared with other cancers.
Technologies) and plated at $10^6$ per well in six-well plates coated with poly2-hydroxyethyl methacrylate (Sigma-Aldrich). Epidermal growth factor and basic fibroblast growth factor were added every day for 2 wk.

**Ras activation.** Cells grown in 100 mm$^2$ Petri dishes (75% of culture confluence) were treated with 10 ng/mL PRL for 0 to 30 min. Cell lysates were prepared and analyzed according to RasGTPase Activation ELISA kit (Upstate, Millipore).

Figure 2. Expression of PRL and PRLR in endometrial and ovarian cancer. A, RT-PCR analysis. Total RNA was isolated from normal pituitary tissue, normal endometrium (Normal), non–tumor-adjacent tissue surrounding endometrial (Endo) and ovarian tumors (NAT), and endometrial and ovarian tumors (Tumor). P, proximal transcript, expected size of 617 bp (red rectangle); D, distal transcript, expected size of 780 bp (blue rectangle). B, PRL expression by endometrial and ovarian carcinoma. Ovarian carcinoma cells, OVCAR3 and SKOV3, and endometrial carcinoma cells, HEC-1A, AN3 CA, and RL95-2, were stained with anti-PRL monoclonal antibody. Isotype-matched nonspecific antibody produced no staining (data not shown).

C, expression of PRLR in four human carcinoma cell lines. Cells were stained with rabbit polyclonal anti-PRLR antibody. Surface expression of PRLR was measured by flow cytometry. Bars, SE. D, expression of PRLR in tumors and healthy tissues. Ovarian cancer, endometrial cancer, and endometrial progression (hyperplasia) TMAs were stained with anti-PRLR antibody. Representative cores are presented.
Table 1. Expression of PRLR in normal and cancerous ovarian and endometrial tissue

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<th>Positive n</th>
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Abbreviations: CCC, clear cell carcinoma; Endo, endometrioid; M, mucinous; S, serous adenocarcinoma.

Results

PRL in sera of patients with ovarian and endometrial cancer. Circulating PRL concentrations were determined in sera of 167 patients with stage I to IV endometrial cancer, 273 patients with ovarian cancer, 141 patients with benign pelvic disease, and 470 age-matched healthy controls. Serum concentrations of PRL were significantly elevated in patients with endometrial and ovarian cancers and in women with benign pelvic disease compared with healthy controls ($P < 0.001$; Fig. 1). Mean serum PRL was significantly higher in women with ovarian and endometrial cancers compared with women with benign pelvic disease ($P < 0.001$). Serum PRL concentrations were equally high in patients with early- and late-stage cancers ($P > 0.1$; data not shown).

PRL levels in sera of age-matched women with lung, breast, and pancreatic cancers were analyzed for comparison (Fig. 1). Although mean circulating PRL concentrations in pancreatic and, to a lesser extent, lung and breast cancers were significantly higher than in the healthy group ($P < 0.001$), serum PRL levels were the highest in endometrial and ovarian cancers. This may indicate a specific role for PRL in peritoneal gynecologic cancers.

PRL levels are elevated in women with a family history of ovarian cancer. We have observed significantly elevated PRL levels in sera of 112 women with a strong (2 or more first relatives affected) family history of ovarian cancer (Fig. 1). Sixty-seven of 112 (60%) women showed PRL levels above 14 ng/mL, whereas in the general population only 22% of women have serum PRL levels above 14 ng/mL. The mean PRL concentration in the high-risk group was significantly ($P < 0.001$) higher compared with general population controls. This finding could be an important clue into the pathologic mechanisms underlying predispositions to cancer and preneoplastic processes.

PRL mRNA is expressed in endometrial or ovarian tumors. Because positive PRL protein staining could reflect PRL locally produced by tumor and by other sources, we investigated PRL expression in endometrial and ovarian tumors by analysis of PRL mRNA. Total RNA was isolated from normal pituitary tissue, normal ovary and endometrium, normal tissue surrounding ovarian and endometrial tumors, as well as ovarian and endometrial tumors. RT-PCR was performed using sense primers specific for pituitary proximal promoter and extrapituitary distal according to previously published procedure (16) and the results are presented in Fig. 2A. Pituitary gland expresses mostly proximal 617-bp transcript along with low levels of the distal 780-bp form. The normal endometrial tissue expressed both forms of PRL mRNA, whereas the non–tumor-adjacent tissue sample expressed only the distal transcript at high levels. All tested endometrial tumor samples expressed the proximal transcript with three of five also expressing the distant transcript; an example of which is shown. Normal ovary expressed low levels of proximal transcript and no expression of the distal transcript, whereas the non–tumor-adjacent ovarian tissue expressed both transcripts with the proximal being more prevalent. Tissue from five distinct ovarian tumors was analyzed with each expressing a unique mixture of expected and unexpected transcripts. The proximal transcript was observed in four of five tumors, although in two of these the expected band was present as a doublet (Fig. 2A; data not shown). One of these tumors expressed high levels of the proximal transcript (Fig. 2A). None of the tumors expressed appreciable levels of the distal transcript, although several products of unexpected sizes were observed from the RT-PCR reaction. The characterization of the unexpected transcripts and proximal transcript doublet observed here is the focus of ongoing investigation.

Expression of PRL and PRLR in cultured endometrial and ovarian carcinoma cells. Five human carcinoma cell lines were...
analyzed: endometrial carcinoma (HEC-1A, AN3 CA, and RL95-2) and ovarian carcinoma (OVCAR3 and SKOV3). PRL expression was assessed using Cellomics imaging cytometry, and expression of PRL was analyzed by flow cytometry. All five cell lines expressed PRL protein (Fig. 2B) and PRLR (Fig. 2C), although the expression levels varied.

**Expression of PRLR in ovarian and endometrial tumors.**

Expression of PRLR in tissue sections was analyzed by immunochemistry on TMA of ovarian tumors, normal ovarian epithelia, endometrial tumors, normal endometrium, noncancerous cancer-adjacent endometrium, endometrial hyperplasia, and endometritis. Expression of PRLR increased dramatically in ovarian and endometrial tumor (Fig. 2D). PRLR was highly expressed in all cancerous ovarian and endometrial tissues regardless of histology and grade (Table 1). Specifically, 80% of ovarian tumors were positive for PRLR with staining intensity varying from weak to moderate to strong. Serous, mucinous, and endometrioid tumors were mostly positive for PRLR (Table 1). None of 10 normal ovarian epithelia expressed PRLR. In endometrial cancer, 77% of tumors stained positively for PRLR with staining intensity varying from weak to moderate to strong, whereas only 13% of normal endometrial tissues (not cancer adjacent) were positive with staining intensity varying from weak to moderate. Noncancerous tumor-adjacent endometrium displayed 27% expression of PRLR with staining intensity varying from weak to moderate. Furthermore, increased expression of PRLR was observed in endometrial hyperplasia (Fig. 2D; Table 1) with 75% staining positive with an intensity of weak to moderate to strong. We have additionally observed high expression of PRLR in 75% of endometriosis with weak staining intensity. In both ovarian and endometrial cancers, PRLR expression was decreased in tumors of higher grade (Table 1). No association with stage could be observed in either cancer (Table 1).

**PRL induces proliferation in ovarian and endometrial carcinoma cell lines and protects cells from chemotherapy-induced apoptosis.** PRL at concentrations of 0.1 to 10 ng/mL was able to stimulate proliferation in all five studied cell lines (Fig. 3A). Preincubation with 1 ng/mL PRL for 1 hour significantly protected cells in all five lines from cisplatin-induced apoptosis (Fig. 3B for OVCAR3; similar results for other cell lines are not shown). Inhibition of PRL signaling by neutralizing antibody in unstimulated cells resulted in slower proliferation (Fig. 3C) but did not potentiate cisplatin-induced apoptosis or induce apoptosis/necrosis (data not shown).

**Analysis of PRL signal transduction pathways in ovarian and endometrial carcinoma cell lines.** Phosphorylation of 17 phosphokinases (see Materials and Methods) was evaluated using multiplex bead-based immunoassay after 0- to 30-minute incubation with 10 ng/mL hrPRL. Of these 17 phosphokinases, ERK1/2, MEK1, STAT3, and CREB were phosphorylated within 15 minutes of incubation (Fig. 3E).

![Figure 3. Effects of PRL in ovarian and endometrial carcinoma cells.](image-url)

**Figure 3.** Effects of PRL in ovarian and endometrial carcinoma cells. A, PRL induces proliferation in ovarian and endometrial cancer cell lines. ovarian carcinoma cells, OVCAR3 and SKOV3, and endometrial carcinoma cells, HEC-1A, AN3 CA, and RL95-2, were treated with 0 to 10 ng/mL of hrPRL for 72 h, and cell counts were determined as described in Materials and Methods. B, PRL protects ovarian and endometrial tumor cells from chemotherapy-induced apoptosis. HEC-1B cells were untreated (C), treated with 5 μmol/L cisplatin (Cis) for 8 h, or pretreated with 10 ng/mL PRL for 1 h before treatment with cisplatin, stained with Annexin V/propidium iodide, and analyzed with flow cytometry as described in Materials and Methods. Similar data for OVCAR3 cells are not shown. C, effects of neutralizing anti-PRL and anti-PRLR antibodies on proliferation of ovarian carcinoma cells. OVCAR3 cells were incubated with neutralizing antibodies to PRL, PRLR, their combination, or IgG isotype control for 72 h and cell proliferation was assessed by imaging cytometry. D, PRL activates phosphokinases in ovarian and endometrial carcinoma cells. E, Ras activation. Cells were treated with 10 ng/mL hrPRL for 0 to 30 min and Rac activation was determined as described in Materials and Methods. *, P < 0.05; **, P < 0.001. Bars, SE.
5 minutes in OVCAR3 in response to PRL treatment, whereas in HEC-1A cells, ATF-2, MEK1, and p53 were phosphorylated (Fig. 3D).

Activation of 37 transcription factors (see Materials and Methods) following 5- to 30-minute incubation with 10 ng/ml hrPRL was analyzed using a multiplex bead-based assay. All 37 transcription factors were activated following 5- to 15-minute incubation with hrPRL in both ovarian and endometrial carcinoma cells, indicating direct effects of PRLR signaling on transcription factor activity (Supplementary Table S1).

Activation of Ras oncogene by PRL in ovarian and endometrial cells. The Ras gene family has been implicated in the development of endometrial and ovarian cancers (19–21). Ras genes often represent the last “hit” for complete transformation of SV40-immortalized but not yet transformed human ovarian cells (22). We have analyzed Ras activity in ovarian and endometrial cancer cell lines, OVCAR3 and RL95-2, and in an immortalized NOE cell line, T29, incubated with 10 ng/ml PRL for 0 to 30 minutes. PRL significantly activated Ras by 5 minutes of incubation in all three cell lines (Fig. 3E).

Chronic exposure to PRL induces malignant transformation in immortalized NOE and endometrial cell lines. To ascertain potential oncogenic function of PRL, we took advantage of the existing in vitro model developed by Liu and colleagues (22) wherein normal human ovarian epithelial cells were immortalized (but not transformed) by transfection with SV40 and hTERT cDNA, which disrupted the p53 and Rb pathways. We speculated that chronic exposure to PRL may activate Ras and result in malignant transformation of these cells. T29 cells were cultured in the presence of exogenous PRL at 10 and 100 ng/mL. After 2 weeks of incubation, we observed morphologic changes indicative of malignant transformation (i.e., uncontrolled growth of treated T29 cells seeded onto a confluent T29 monolayer and small rounded appearance of these cells; Fig. 4A). No such changes were observed in untreated cells even after prolonged (>8 weeks) culture. As an additional control, cells were also treated with CCL11, a chemokine that potently induces growth of ovarian cancer cells (23). No transformation was observed (data not shown). To confirm that PRL induced malignant transformation of immortalized NOE cells, their ability to form clones and to grow in soft agar was evaluated. PRL-treated cells showed a dramatically elevated capacity for both clonogenic growth and colony formation in semisolid medium. Whereas parental immortalized cells produced $0.33 \pm 0.21$ clones per plate, modified cells produced $20.2 \pm 0.87$ clones per plate (Fig. 4B). Similarly, whereas parental T29 cells did not form any colonies in semisolid agar, PRL-modified cells formed on average 55.0 ± 4.73 colonies per well of a six-well plate (Fig. 4C). Incubation of T29 cells with PRL in the presence of a specific Ras inhibitor, α-hydroxyfarnesyl phosphonic acid, dramatically abrogated the transforming effects of PRL (Table 2). Similar results were obtained using endometrial fibroblasts immortalized with hTERT (data not shown; ref. 24).

Growth of PRL-transformed T29 in nude mice. We assessed the tumorigenic potential of parental and PRL-transformed T29 cells in a SCID-beige mouse model. Ten mice received bilateral s.c. injections of $5 \times 10^6$ PRL-transformed or nontransformed H29 cells. Two weeks after injection, tumors appeared at the site of inoculation of PRL-modified cells. These tumors grew progressively in all mice (Fig. 4D). Mice were sacrificed when tumor exceeded 1.5 cm in diameter. In contrast, none of the 10 mice showed tumor formation at the site of inoculation of PRL-untreated parental T29 cells.

Figure 4. PRL promotes malignant transformation in immortalized NOE H29 cells. A, effects of chronic exposure to PRL on morphology of immortalized NOE cells. H29 cells were incubated with 100 ng/ml PRL for 0 to 20 d. The experiment was repeated 18 times. Black arrows, untransformed parental T29 cells; white arrows, PRL-transformed cells. B and C, PRL-modified H29 cells exhibit higher capacity for clonogenic growth (B) and semisolid medium colony formation (C). D, dynamics of tumor growth in SCID mice injected with PRL-transformed and parental T29 cells.
Discussion

In this study, we show the potential critical role of a hormone/cytokine, PRL, as a tumor promoter and risk factor in ovarian and endometrial cancers. Serum PRL levels are dramatically elevated in women suffering from ovarian and endometrial cancers, making it a strong biomarker for these cancers (14, 15). The use in this study of samples drawn before the admission of anesthesia and surgery eliminates the effect of these confounders shown to boost serum PRL (25). Although one might suspect that elevated blood PRL may reflect an increase in production of pituitary hormones as a result of stress related to cancer diagnosis, several lines of evidence argue against it. First, as we show here, circulating PRL is elevated to a different extent in different cancers. Second, several studies of stress-induced increase in blood PRL in healthy subjects concluded that PRL responses to purely psychological stress are rarely seen (26, 27).

We observed a dramatic increase in expression of PRLR in both ovarian and endometrial tumors compared with healthy tissues, indicating a critical role of PRL signaling for tumor growth and maintenance. Although PRL itself was not overexpressed in either cancerous endometrium or ovarian epithelium, high serum levels of PRL should be sufficient for activating PRL signaling in tumors. These increased levels of serum PRL must originate either from pituitary or from alternative extrapituitary sources such as lymphocytes.

Significant up-regulation of PRLRs could be responsible for increased PRL signaling in ovarian and endometrial tumors, leading to increased tumor proliferation and cell survival. In addition, PRL may play several other active roles in tumor development by stimulating angiogenesis (28) and activating pathways involved in cellular adhesion and motility (29, 30). We observed a reverse correlation between tumor grade and expression of PRLR in both ovarian and endometrial tumors and no association of PRLR with cancer stage. A similar relationship with tumor grade was reported in ovarian and endometrial tumors and no association of PRLR with carcinogenic pathways. Such work could lead to the use of PRL as a risk factor for ovarian, endometrial, and potentially other cancers.

In summary, our findings indicate an important role for PRL in ovarian and endometrial tumorogenesis. Ongoing efforts should seek to characterize the role of PRL in specific and nonspecific tumorigenic pathways. Such work could lead to the use of PRL as a risk factor for ovarian, endometrial, and potentially other cancers.

Disclosure of Potential Conflicts of Interests

No potential conflicts of interest were disclosed.

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References

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Table 2. Effect of Ras inhibition on the PRL-induced transformation of T29 cells

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Prolactin in Gynecological Cancers


Biological Significance of Prolactin in Gynecologic Cancers
Vera V. Levina, Brian Nolen, YunYun Su, et al.

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