Interleukin 6 Mediates the Lysophosphatidic Acid-regulated Cross-talk between Stromal and Epithelial Prostate Cancer Cells*

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The interaction between stromal and epithelial cells is critical for the initiation and progression of prostate cancer, but the molecular determinants responsible for the cross-talk between these two cell types remain largely unknown. Here, we used a co-culture cell assay to identify messengers involved in the cross-talk between human prostate stromal PS30 and epithelial LNCaP cells. Stimulation with lysophosphatidic acid (LPA) activates the mitogenic ERK signaling pathway in PS30, but not LNCaP, cells. The co-culture of PS30 and LNCaP cells results in the activation of ERK in LNCaP cells and that is further increased in response to stimulation with LPA. Physiologic relevance of the interaction between PS30 and LNCaP cells is demonstrated using LNCaP xenograft tumor assays. Animals implanted with a mixture of both cell types develop larger tumors with higher frequency compared with those injected with LNCaP cells alone. Conditioned medium transfer experiments reveal the PS30-derived inducing factor is soluble and promotes mitogenic ERK and STAT3 signaling pathways in LNCaP cells. Protein analysis demonstrates that treatment of the PS30 cells with LPA induces synthesis of interleukin 6 (IL-6). Antibody neutralization experiments reveal that IL-6 is responsible for the LPA-induced mitogenic signaling and growth of the LNCaP cells. Our findings reveal that the LPA-regulated secretion of IL-6 is an important messenger linking stromal and epithelial prostate cells, which may be exploited for the effective treatment of patients with advanced prostate cancer.

The existence of androgen-independent prostate tumors suggests that release of locally produced and/or circulating growth factors, which work through cellular receptors, can switch the prostate cells from a quiescent to an activated phenotype leading to cellular proliferation. The majority of prostate cancers arise from epithelial cells, and in tissue cultures, epithelial prostate cancer cells produce factors that act in an autocrine fashion to regulate their growth and survival (4, 5). It remains unclear whether autocrine mechanisms are relevant to the progression of prostate cancer in men. It is clear, however, that the cancerous prostate exhibits a morphologically altered stroma (6). The understanding of why stromal cells contribute to tumor growth remains incomplete, although a likely explanation is that they secrete growth-stimulating molecules that promote mitogenic activity of recipient epithelial cells. Support for this hypothesis is provided by the finding that in a murine xenograft model, prostate cancer epithelial cells form tumors more rapidly when mixed with stromal cells than when injected alone (9). It is not known how the stromal cells are activated in the cancerous human prostate and what growth factors they secrete.

Recent studies have shown that G protein-coupled receptors (GPCRs) and their immediate effectors, the heterotrimeric G proteins, are involved in prostate cancer (10). In vitro, stimulation of endogenous GPCRs for lysophosphatidic acid (LPA), bradykinin (BK), or endothelin 1 (ET-1), for example, induces the growth and survival of prostate cancer cells (11–15). Using a prostate cancer xenograft model, we recently demonstrated that inhibition of G protein signaling attenuates the growth of prostate tumors in animals (16). These findings strongly suggest the involvement of G proteins and their associated receptors in prostate tumorigenesis. Here, we tested the hypothesis that GPCRs exert their mitogenic effects by regulating the cross-talk between stromal and epithelial prostate cells. We found that stimulation with LPA induced the activation of mitogenic extracellular signal-regulated kinase 1 and 2 (ERK) in human prostate stromal PS30 but not in epithelial LNCaP cells. Conditioned medium (CM) obtained from LPA-stimulated PS30 cells activates ERK and the signal transducer and activator of transcription 3 (STAT3) in LNCaP cells. Protein analysis of CM from LPA-stimulated PS30 cells revealed the secretion of several growth factors, including interleukin 6 (IL-6). Antibody neutralization...
results demonstrated IL-6 to be the chief factor responsible for LPA-regulated cross-talk between the PS30 and LNCaP cells. Inhibition of IL-6 signaling abrogated PS30-induced mitogenic signaling and growth of LNCaP cells.

EXPERIMENTAL PROCEDURES

Materials—Antibodies were obtained as follows. Anti-human IL-6, anti-phospho-ERK, and anti-phospho-STAT3 were obtained from Cell Signaling (Beverly, MA), anti-ERK2 was from Upstate Biotechnology (Lake Placid, NY), and horseradish peroxidase-conjugated secondary antibodies were from Jackson ImmunoResearch (West Grove, PA). LPA was purchased from Sigma and recombinant human IL-6 from R&D Systems (Minneapolis, MN). Cell culture media and supplements were purchased from Invitrogen. All other reagents were standard laboratory grade. The plasmid encoding green fluorescent protein (GFP)-ERK2 was the kind gift of Dr. N. W. Bunnett (University of California, San Francisco).

Cell Growth and Transfection—Lymp node metastasis human prostate cancer LNCaP cells were obtained from the American Type Culture Collection (Manassas, VA). The PS30 human prostate stromal cell line was established at Duke University as described by Price et al. (17). The cells were maintained in RPMI 1640 medium containing 10% fetal calf serum supplemented with 100 μg/ml penicillin-streptomycin and cultured in a humidified atmosphere of 5% CO2 at 37 °C. For growth, the PS30 cells were seeded in 10-cm plates in standard culture medium for 48 h to allow attachment. Serum-free culture medium contained 100 μg/ml penicillin-streptomycin, 10 mM HEPES, and 0.1% bovine serum albumin. Transient transfection was carried out with 70%–80% confluent LNCaP cells using 1,2-dimyristyloxypropyl-3-dimethylhydroxyethyl ammonium bromide (Invitrogen), according to the manufacturer’s instructions. After transfection, the cells were detached with trypsin and equally divided into 6-well culture dishes. The cells were incubated in starvation medium (phenol red-free RPMI 1640 supplemented with 10 mM HEPES, and 0.1% bovine serum albumin). Transient transfection was carried out with 70%–80% confluent LNCaP cells using 1,2-dimyristyloxypropyl-3-dimethylhydroxyethyl ammonium bromide (Invitrogen), according to the manufacturer’s instructions. After transfection, the cells were detached with trypsin and equally divided into 6-well culture dishes. The cells were incubated in starvation medium (phenol red-free RPMI 1640 supplemented with 10 mM HEPES, and 0.1% bovine serum albumin) for 12–16 h prior to stimulation with agonist. For LNCaP-PS30 co-culture assays, the cells were mixed and seeded at a ratio of 4:1, LNCaP:PS30 cells. The activation of ERK in stromal and epithelial human prostate cells—PS30 cell monolayers were treated with agonist, or not, in starvation medium for 6 h or 24 h. CM was collected by aspiration, centrifuged to remove cell debris, and stored at 4 °C or −20 °C until further use.

**ERK and STAT3 Activation**—Serum-deprived cells were stimulated with agonist or PS30 CM at 37 °C for the indicated time. Reactions were terminated by direct addition of Laemmli lysis buffer. Equal amounts of protein (20–30 μg/lane) from each sample were separated on 4–20% SDS-polyacrylamide electrophoresis gels and transferred to nitrocellulose filters. ERK and STAT3 phosphorylation was detected by immunoblotting using phospho-specific ERK and STAT3 antibodies, exactly as described by Rue et al. (12). Phosphorylated ERK and STAT3 bands were visualized with ECL. Nitrocellulose filters were stripped of immunoglobulins and reprobed with ERK2 or STAT3 antibodies to confirm equal loading of protein.

**IL-6 Antibody Neutralization**—Neutralization of IL-6 in the CM was performed by adding 1 μg/ml of anti-IL-6 antibody for 1 h at 37 °C prior to application onto LNCaP cell monolayers (12). In control experiments, serum-free medium containing IL-6 was similarly exposed to the IL-6-neutralizing antibody. Another control included the treatment of PS30 cells with isotype-matched nonspecific antibodies. The monolayers were directly lysed in Laemmli sample buffer and prepared for immunoblotting as described (16).

**Xenograft Tumor Growth**—Tumor formation and growth were assessed using subcutaneous injection in intact animals as described by Bookout et al. (16). Briefly, a mixture of LNCaP (1 × 106) and PS30 (2.5 × 105) cells was resuspended in 50 μl of culture medium and 50 μl of Matrigel (Collaborative Biosciences, Bedford, MA) and injected subcutaneously into the flanks of 6–8-week-old Balbc athymic mice. Control samples included the injection of individual LNCaP (1 × 106) or PS30 (2.5 × 105) cells with Matrigel. Tumor volume was measured weekly with calipers, and tumor volume was determined using the formula \( V = \pi/6 \times (\text{larger diameter}) \times (\text{smaller diameter})^2 \). Each experiment consisted of 5 mice/group and was repeated two times. All animal experiments were done in accordance with the regulations of the Animal Institutional Review Board at Duke University.

**Cell Proliferation**—LNCaP cells were detached with trypsin and diluted to 2.5 × 104 cells/ml in CM from LPA-treated, or not, PS30 cells. The cells were seeded into 6-well plates and allowed to grow for 5 days. Cell numbers were determined by counting viable cells using trypan blue exclusion and a hemocytometer (14, 15).

**RESULTS**

**LPA Regulates the Cross-talk between PS30 and LNCaP Cells**—Stimulation of human prostate stromal PS30 cells with LPA or BK (Fig. 1A) and ET-1 or EGF (Fig. 1B) induced the time-dependent phosphorylation of ERK. The magnitude of ERK activation by LPA, BK, and ET-1 was similar to that achieved in response to stimulation with EGF, demonstrating that these GPCR ligands exert a potent mitogenic response. Maximal activation of ERK was achieved within 5 min of GPCR stimulation and was sustained for about 30 min. Distinctly, stimulation of the androgen-dependent epithelial human prostate cancer LNCaP cells with the GPCR ligands did not promote the ERK phosphorylation (Fig. 1C).

Stimulation with EGF, used as positive control, induced the robust ERK phosphorylation in the LNCaP cells. These results demonstrate that stimulation with LPA, BK, and ET-1 activates ERK in stromal PS30 but not epithelial LNCaP prostate cells.

We took advantage of these observations to study the possible interaction between stromal and epithelial prostate cells with emphasis on the potential regulatory role of GPCRs. In the prostate gland, stromal cells may influence growth of epithelial cells either directly through physical contact between the two cell types or indirectly by secreting a soluble mediator. To explore these options, we examined ERK activation in a stromal-epithelial cell co-culture model system, using wild type PS30 cells and LNCaP cells stably expressing GFP fused to ERK2 (GFP-ERK2; Fig. 2A). Stimulation of the co-cultured cells with LPA induced the time-dependent increase in ERK phosphorylation in both cell types. LPA treatment induced maximal phosphorylation signal of the GFP-ERK2 in the LNCaP cells after 5 min of stimulation, returning to basal level within 30 min (Fig. 2B). A second peak of phosphorylated ERK
appeared after 30 min of LPA stimulation and was sustained for at least 60 min. The time course of ERK phosphorylation in the PS30 cells reached a maximum at 5–10 min before it began to decrease (Fig. 2B). Interestingly, the PS30, unlike LNCaP, cells did not show a secondary LPA-stimulated ERK phosphorylation peak. Direct stimulation of the GFP-ERK2-transfected LNCaP cells with LPA did not promote the ERK phosphorylation (Fig. 2C). Stimulation with EGF, used as positive control, promoted the robust phosphorylation of GFP-ERK2 and endogenous ERK (Fig. 2C). These data are consistent with the idea that stromal prostate cells promote mitogenic signaling in epithelial prostate cancer cells and that GPCR activation could enhance the mitogenic response.

Effect of Prostate Stromal CM on Epithelial Cells—To further characterize the factor(s) responsible for the cross-talk between the stromal and epithelial prostate cells, PS30 cells were stimulated with LPA, BK, or ET-1 followed by the collection of CM. The CM was clarified by centrifugation and added onto the LNCaP cells to determine ERK activation. Exposure of the LNCaP cells to the CM induced the time-regulated phosphorylation of ERK with the signal appearing after 30 min of stimulation (Fig. 2D). Thus, the cross-talk between stromal and epithelial prostate cells is mediated by a soluble factor(s) that is secreted in response to stimulating G protein-coupled receptors endogenously expressed in the stromal cells.

PS30 Cells Accelerate Formation of LNCaP Tumors—To investigate the possible physiologic impact of the cross-talk between the PS30 and LNCaP cells, we tested the hypothesis that co-inoculation of both cell types influences the frequency of tumor formation as well as tumor size in athymic mice. Fig. 3 shows that tumor take, defined as the number of formed tumors per total injections, was consistently higher in the animals receiving the LNCaP-PS30 cell mixture compared with animals receiving LNCaP cells alone (Fig. 3A). Similarly, the tumor size was larger when LNCaP cells were mixed with the PS30 cells, compared with LNCaP-alone tumors (Fig. 3B). Histologic tests revealed the tumors obtained from inoculating PS30-LNCaP cells resulted from increased growth of the LNCaP cells (and not the PS30 cells) and displayed increased blood vessel formation compared with tumors obtained from inoculating LNCaP cells alone. These results reinforce the idea that stromal prostate cells contribute to the growth of epithelial prostate cancer cells.

Identification of Factors in Stromal Cell CM—Initial attempts to identify secreted PS30 factors were carried out by analyzing protein bands (one-dimensional gel) and spots (two-dimensional gel) using peptide mass fingerprinting and mass spectrometry. Data base searches identified many proteins, but none had growth-promoting characteristics (data not shown), suggesting our proteomic approach may be limited for the detection of low abundance mitogenic factors. We used growth factor/cytokine array analysis as an alternative approach to identify the growth factor(s) present in the PS30 CM. Fig. 4A lists the various cytokines and peptide growth factors spotted on the filter. Fig. 4B shows the immunoreactivity of the cytokines and growth factors present in the
CM obtained from LPA-treated, or not, PS30 cells. The array spots were analyzed by Scan-Analyze, and the intensity of each spot was compared with respective spots in the control array. Levels of granulocyte-macrophage colony-stimulating factor (Fig. 4A, GM-CSF), growth-related oncogene (GRO), IL-6, -8, and -16, oncostatin M (OSM), vascular endothelial growth factor (VEGF), fibroblast growth factors 4 and 9 (FGF4, FGF9), glial cell-derived neurotrophic factor (GDNF), insulin-like growth factor-binding proteins 2 and 4 (IGFBP2 and 4), interferon γ-inducible protein 10 (IP10), leukemia inhibitory factor (LIF), and transforming growth factor β2 (TGFβ2) were all significantly increased in the LPA-treated (compared with unstimulated) samples (Fig. 4B). We validated the cytokine array results by determining the levels of secreted IL-6 using Western blot analysis. CM obtained from PS30 cells treated with LPA for 24 h showed 2–3-fold higher levels of IL-6 compared with the control CM (Fig. 4C).

**IL-6 Mediates LPA-regulated Cross-talk between PS30 and LNCaP Cells**—Our results show that CM from LPA-stimulated PS30 cells induced ERK activation in the LNCaP cells (Fig. 2D) and contained IL-6 (Fig. 4, B and C). We tested whether IL-6 is the CM-expressed growth factor responsible for ERK activation.

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**Fig. 3. Effect of PS30 cells on the formation of LNCaP tumors in mice.** LNCaP cells (1.0 × 10⁶) alone or together with PS30 (2.5 × 10⁵) cells were injected subcutaneously with Matrigel into the flanks of 6–8-week-old Balb/c athymic mice. The graphs show: A, tumor take, defined as the fraction of tumors formed per total injections and B, mean tumor volume, measured using calipers and calculated using the formula, v = π/6 × (long dimension) × (short dimension)². Shown are curves representing the average tumor take (A) and tumor size (B) of 10 mice for each of the LNCaP-PS30 and LNCaP alone groups.

**Fig. 4. LPA regulates secretion of IL-6 from PS30 cells.** A, human growth factor/cytokine array map showing the growth factors and cytokines spotted on the filter. B, detection of multiple factors expressed in conditioned medium from LPA-stimulated and nonstimulated PS30 cells. The membrane was incubated with CM and analyzed as described under “Experimental Procedures.” C, LPA increases the expression of IL-6 in PS30 CM. Serum-starved PS30 cells were treated with LPA (10 μM) for 24 h followed by the collection of CM. Proteins were concentrated by ammonium sulfate precipitation, separated on 4–20% SDS-PAGE, and probed for IL-6 expression by immunoblotting. Purified recombinant human IL-6 (rIL6) was used as a control. Immunoblots are representative of three independent experiments. NS, not stimulated.
in the LNCaP cells. CM was mixed with 1 μg/ml neutralizing IL-6 antibodies for 1 h prior to application onto the LNCaP cells to assay ERK and STAT3 phosphorylation. Results show that neutralization of IL-6 was dramatically reduced but did not totally eliminate the CM-induced ERK activation (Fig. 5A). These results suggest that other growth factors may be present in the CM and contribute to ERK phosphorylation. On the other hand, neutralizing the IL-6 activity obliterated the CM-induced STAT3 phosphorylation (Fig. 5B), demonstrating that IL-6 is the chief CM-expressed factor responsible for STAT3 activation. Direct stimulation with IL-6, used as a positive control, induced the ERK and STAT3 activation. As expected, the IL-6-induced ERK and STAT3 phosphorylation was inhibited in the presence of IL-6-neutralizing antibodies. Together, these results suggest that IL-6 is a major mitogenic growth factor secreted from PS30 cells in response to stimulation with the GPCR ligand LPA.

In Vitro Effects of CM on Epithelial Cell Growth—To further implicate the effect of stromal factors on LNCaP cell growth, we used CM collected from PS30 cells pretreated, or not, with LPA. The LNCaP cells were exposed to the CM for 48 h before cell numbers were determined. Fig. 6 shows that CM from LPA-treated PS30 cells supported the growth of LNCaP cells; about 2-fold increase compared with nonstimulated PS30 CM. Importantly, the CM-mediated LNCaP cell growth was attenuated in the presence of IL-6-neutralizing antibodies. However, the nonstimulated PS30 CM still induced LNCaP cell growth compared with cells cultured in starvation medium. Together, these results suggest that IL-6 mediates, at least in part, the LPA-regulated cross-talk between PS30 and LNCaP prostate cells to promote cell growth.

DISCUSSION

G protein-coupled receptors are increasingly viewed as critical regulators of autocrine- and/or paracrine-based mechanisms that control cell growth (10). The GPCRs may perform this function by (i) increasing the gene expression of growth factors (18) or (ii) regulating the activity of matrix metalloproteinases (19), which cleave plasma membrane-anchored propeptides to produce soluble and biologically active growth factors (20). The major finding of this study was that activation of GPCRs expressed in prostate stromal cells induced the secretion of factors that promoted mitogenic signaling of prostate epithelial cells. Hence, GPCRs regulate the cross-talk between stromal and epithelial prostate cells, which plays an important role in the initiation and progression of prostate cancer (6–8).

The LPA-regulated cross-talk between PS30 and LNCaP cells is mediated largely by the secretion of IL-6 from the PS30 cells. Neutralization of IL-6 activity abrogated the CM-induced ERK and STAT3 activation and LNCaP cell growth. Clinical studies show that plasma levels of IL-6 are increased in patients with prostate cancer (21), suggesting a potential role for IL-6 in the initiation and/or progression of the disease. However, the source of IL-6 and the regulation of its secretion remain unclear. In tissue cultures, IL-6 can be detected in the supernatants of androgen-independent prostate cancer PC3 and DU145 (22) but not androgen-dependent LNCaP (23) cells. Our results provide direct evidence that prostate stromal cells are a major source of IL-6 and that activated GPCRs serve as important regulators of IL-6 production. We propose that GPCRs act as master regulators controlling the secretion of the “second messenger” IL-6 that, in turn, supports the growth of epithelial prostate cancer cells.

Growth of normal and malignant prostate cells is controlled by the androgen receptor (AR). In patients with advanced prostate cancer, the AR is activated despite the presence of hormonal therapies that reduce circulating androgen levels (24), suggesting the AR can be activated by factors other than androgens. In tissue cultures, IL-6 has been demonstrated to activate the AR and promote prostate cancer cell growth. Mechanisms involved in the IL-6-mediated activation of AR are not clear but may involve ErbB2 (25), ERK (26), or STAT3 (27). Pharmacologic inhibition of ERK or STAT3 diminishes the IL-6-mediated activation of AR and subsequent LNCaP cell growth (26, 27). Our data show that CM from LPA-stimulated PS30 cells induces ERK and STAT3 activation and growth of the LNCaP cells. However, inhibition of ErbB family activation does not affect the CM-induced ERK phosphorylation in the LNCaP cells (data not shown). Thus, it is likely the CM-mediated LNCaP cell growth proceeds via activated ERK, STAT3, and AR. In support of this conclusion is our finding that CM from GPCR-stimulated PS30 cells activates a luciferase reporter gene that is under the control of AR (data not shown).

How do activated GPCRs in the stromal cells induce secretion of IL-6? Ligands for several GPCRs have been documented to stimulate secretion of IL-6, including BK in airway smooth muscle (28) and ET-1 (29) and angiotensin (30) in vascular smooth muscle cells. In all cases, the GPCRs appear to exert their effects on IL-6 expression at a pretranslational level. Indeed, IL-6 gene expression is under the control of the tran-
scription factors, nuclear factor κB and activator protein 1 (23).
In prostate cancer cells, stimulation with LPA increases the activity of a luciferase reporter that is under the control of nuclear factor κB (data not shown).

In conclusion, the results of the present study show that GPCR stimulation activates stromal cells to secrete factors that regulate growth of epithelial prostate cancer cells. Based on these findings, we suggest that GPCRs regulate the mitogenic behavior of prostate cells, at least in part, by controlling the cross-talk between stromal and epithelial cells. Establishing a role for GPCRs in prostate cancer will hopefully uncover new mechanisms and lead to the design of new therapeautic agents for the better treatment of this common disease.

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