Seminal plasma activates cyclooxygenase-2 and prostaglandin E₂ receptor expression and signalling in cervical adenocarcinoma cells

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Enhanced cyclooxygenase (COX) expression and prostaglandin E₂ (PGE₂) synthesis are regarded as promoters of neoplastic cell proliferation and angiogenesis. Expression of COX-2 and synthesis of PGE₂ are up-regulated in cervical carcinomas. In sexually active women, growth and invasiveness of neoplastic cervical epithelial cells may be also under the direct influence of PGE₂ present in seminal plasma. The aims of this study were to investigate the effect of seminal plasma and PGE₂ on the expression of COX-2 and expression and signalling of the PGE₂ receptor subtypes (EP1–EP4) in HeLa (cervical adenocarcinoma) cells. Treatment of HeLa cells with seminal plasma or PGE₂ resulted in up-regulation of COX-2 expression (P < 0.05). In addition, seminal plasma induced the mRNA expression of EP1, EP2 and EP4 receptors, whilst PGE₂ treatment of HeLa cells induced the expression of the EP4 receptor (P < 0.05). This was coincident with a rapid accumulation of adenosine 3',5'-cyclic monophosphate (cAMP) in HeLa cells stimulated with seminal plasma or PGE₂, which was greater in seminal plasma stimulated cells compared with PGE₂ stimulated cells (P < 0.05). Subsequently, we investigated whether the effect of seminal plasma on cAMP signalling in HeLa cells was mediated via the cAMP-linked EP2/EP4 receptors. Stimulation of HeLa cells with seminal plasma or PGE₂ resulted in an augmented cAMP accumulation in cells transfected with the EP2 or EP4 receptor cDNA compared with control transfected cells (P < 0.05). These data suggest that, in sexually active women, seminal plasma may play a role in modulating neoplastic cell function and cervical tumorigenesis.

Key words: cervical adenocarcinomas/cyclooxygenase/EP receptors/prostaglandin/semen plasma

Introduction

Uterine cervical cancer is a disease of multifactorial aetiology, generally found amongst sexually active women. Current evidence suggests that sexually transmitted infection of the benign cervical epithelium with human papilloma virus (HPV) is the main cause of the disease, however, several other factors including venereally transmitted disease, genital warts, genital herpes and trichomonas infection have also been recognized to play a role in the development and progression of cervical tumorigenesis (Brinton and Fraumeni, 1986; Brinton et al., 1987; McInerney, 1987; zur Hausen, 1991; Brinton, 1992; Munoz et al., 1992).

Recent studies have demonstrated that reproductive tract carcinomas, including carcinomas of the ovary, uterus and cervix, may be regulated by cyclooxygenase (COX) enzyme products (Dore et al., 1998; Ryu et al., 2000; Tong et al., 2000; Jabbour et al., 2001; Klimp et al., 2001; Kulkarni et al., 2001; Sales et al., 2001, 2002). Two distinct isoforms of the COX enzyme, COX-1 and COX-2, have been characterized (Hla and Neilson, 1992; Herschman, 1994; Vane et al., 1998). Both COX isoforms catalyse the rate-limiting step in the conversion of arachidonic acid to eicosanoids, a class of compounds which includes prostaglandins, thromboxanes and leukotrienes (DeWitt, 1991). COX-1 and COX-2 expression and prostaglandin E₂ (PGE₂) synthesis are elevated in numerous solid epithelial tumours, including carcinomas of the cervix (Sales et al., 2001, 2002), suggesting that both COX enzymes and their synthesized products, such as PGE₂, may be contributory towards the neoplastic process.

The biological actions of PGE₂ have been attributed to its interaction with G-protein-coupled seven-transmembrane-domain receptors (GPCRs) which belong to the rhodopsin superfamily of serpentine receptors (Coleman et al., 1994). Four main sub-types of PGE₂ receptors have been identified (EP₁, EP₂, EP₃, EP₄) and are known to utilize alternate, and in some cases opposing, intracellular pathways (Ashby, 1998). Recently, a direct role for PGE₂ and EP receptors has been ascertained in colorectal carcinomas. In this model, enhanced proliferative and tumorigenic effects are mediated by PGE₂ following interaction with the EP4 receptor (Sheng et al., 2001). Similarly, another study has demonstrated a role for PGE₂ and EP2 receptor in accelerating intestinal polyp formation in APCΔ¹¹⁰³² knock-out mouse models (Sonoshita et al., 2001). In cervical and endometrial carcinomas, elevated expression of the EP2 and EP4 receptors and enhanced adenosine 3',5'-cyclic monophosphate (cAMP) signalling has also been observed (Jabbour et al., 2001; Sales et al., 2001), further supporting the idea that prostanoids such as PGE₂, may regulate neoplastic cell function in reproductive tract carcinomas in an autocrine/paracrine manner.

In addition to endogenously synthesized PGE₂, sexually active women also come into contact with PGE₂ present in seminal plasma.
Prostaglandins are present in seminal plasma at 10 000-fold greater concentrations than that detected at the site of inflammation, and PGE2 is one of the predominant types detected (Templeton et al., 1978). Little is known of the effect of seminal plasma and seminal plasma prostaglandins, including PGE2, on the neoplastic cervical epithelium of sexually active women. Cervical tumorigenesis may thus be regulated in an autocrine/paracrine manner by PGE2 present in seminal plasma via PGE2–EP receptor interactions, initiation of intracellular signalling pathways and transcription of target genes involved in enhancing or sustaining cervical tumorigenesis.

The aims of this study were to determine the effect of seminal plasma and PGE2 on the expression of COX-2 and on the expression and signalling of the PGE2 receptors in HeLa cervical adenocarcinoma cells. In cervical carcinomas elevated PGE2 may act in an autocrine/paracrine manner via cAMP-linked PGE2 receptors to mediate an effect on target genes, such as COX-2. Thus, it would use the cAMP-dependent protein kinase pathway to activate adenylate cyclase and increase intracellular cAMP. This in turn may elevate expression of intracellular signalling pathways and transcription of target genes involved in enhancing or sustaining cervical tumorigenesis.

Materials and methods

Semen donors and preparation
Semena were obtained from healthy male volunteers by masturbation. The collected ejaculates were pooled and incubated at room temperature for 30 min prior to overlaying on a 100–500 per cent gradient. Seminal plasma was isolated from the pooled ejaculate by percoll density gradient centrifugation at 500 g for 20 min. The seminal plasma was added immediately to HeLa cell cultures at a final concentration of 1:50. At this dilution, seminal fluid has been reported to exert no effect on HeLa cell viability (Jeremias et al., 1997). Approval for the study was obtained from the University of Cape Town Research Ethics Committee, and informed consent was obtained from all patients prior to sample collection.

Cell culture
HeLa-S3 cells were purchased from BioWhittaker (Berkeley, UK) and were routinely maintained in Dulbecco’s modified Eagle’s medium nutrient mixture F-12 with Glutamax-1 and pyridoxine, supplemented with 10% fetal bovine serum and 1% antibiotics (stock 500 IU/ml penicillin and 500 µg/ml streptomycin) at 37°C and 5% CO2 (v/v). All experiments and cell treatments were performed on HeLa cells using culture medium containing no fetal bovine serum (serum-free conditions) or additional proteins.

Cell transfections
Cells were plated in 12-well dishes in complete medium and were allowed to attach and grow overnight. The EP2 receptor cDNA (a kind gift from Dr Karen Kedzie, Allergan, CA, USA) or EP4 receptor cDNA (a kind gift from Dr Mark Abramovitz, Merck Frosst Centre for Therapeutic Research, Canada) or empty vector (pCDNA3.1; Invitrogen, De Schelp, Netherlands) were transfected into the HeLa cell line at ~50% confluence using pfx-5 (Invitrogen) diluted in OptiMEM (Gibco, Life Technologies, Paisley, UK). Cells were incubated for 4 h at 37°C in 5% humidified CO2. Thereafter, the medium was replaced with fresh complete medium. Cells were allowed to grow for 48 h. Transfected cells were then stimulated either with a 1:50 dilution of seminal plasma or 300 nmol/l PGE2 and cAMP accumulation was measured by enzyme-linked immunosorbent assay (ELISA) using a CAMP kit.

Real-time quantitative RT–PCR
Real-time quantitative RT–PCR was performed to determine COX-2 and EP receptor expression in HeLa cells. HeLa cells were grown in the presence or absence of a 1:50 dilution of seminal plasma or 300 nmol/l PGE2 and in the presence or absence of the dual COX enzyme inhibitor, indomethacin (used at a final concentration of 3 µg/ml) to exclude the effects of any endogenously synthesized PGE2. Cells were harvested with Tri-Reagent (Sigma; Sigma Chemical Company, Dorset, UK) as per the manufacturer’s protocol after 24, 48 and 72 h, for determination of COX-2 expression, and after 24 h for determination of EP receptor expression. For validation studies of EP2 and EP4 receptor expression in transfected cells, HeLa cells were grown for 48 h following transfection and harvested with Tri-Reagent (Sigma). RNA samples were reverse transcribed using MGeCl2 (5.5 mmol/l), dNTPs (0.5 mmol/l each), random hexamers (1.25 µmol/l), oligo-dT (1.25 µmol/l), RNAase inhibitor (0.4 IU/µl) and multiscribe reverse transcriptase (1.25 IU/µl; all from PE Biosystems, Warrington, UK). The mix was aliquoted into individual tubes (16 µl/tube) and template RNA was added (4 µl/tube of 250 ng/µl RNA). Samples were incubated for 60 min at 25°C, 45 min at 48°C and then at 95°C for 5 min. A reaction mix was made containing Taqman buffer (5.5 mmol/l MgCl2, 200 µmol/l dATP, 200 µmol/l dCTP, 200 µmol/l dGTP, 400 µmol/l dUTP), ribosomal 18S forward and reverse primers and probe (all at 50 nmol/l), forward and reverse primers for COX-2 or EP1, EP2, EP3 or EP4 receptor (300 nmol/l), COX-2 or EP1, EP2, EP3 or EP4 receptor probe (200 nmol/l), Amplerase UNG (0.01 IU/µl) and AmpillTaq Gold DNA Polymerase (0.025 IU/µl; all from PE Biosystems). A volume of 48 µl of reaction mix was aliquoted into separate tubes for each cDNA sample and 2 µl replicate of cDNA was added. After mixing, 23 µl of sample was added to the wells on a PCR plate. Each sample was added in duplicate. A no template control (containing water) was included in triplicate. Wells were sealed with optical caps and the PCR run on an ABI Prism 7700 using standard conditions (initial denaturation steps of 50 and 95°C for 2 and 10 min respectively, followed by 40 cycles of 95 and 60°C for 15 s and 1 min respectively). COX-2 and EP receptor primers and probe for quantitative PCR were designed using the PRIMER express program (PE Biosystems). The sequence of the COX-2 primers and probe were: forward, 5'-CCTTCTCTCTGTGGCTG TG-3'; reverse, 5'-ACAATCTCTATTGAAATCAGGAACT-3'; probe (FAM labelled), 5'-TGGCCGCTACTCTTCTGGTCA-3'. The sequence of the EP1 receptor primers and probe were: forward, 5'-AGATGTTGGGGCCAGCGTTT-3'; reverse, 5'-GCCACAAAACAGCATTG-3'; probe (FAM labelled), 5'-CAGCAAGTGGACGACACTCAG-3'. The sequence of the EP2 receptor primers and probe were: forward, 5'-GACCCGCTACCTAGCAGTGTCAT-3'; reverse, 5'-GAATACTGGACGCGGAGCA-3'; probe (FAM labelled), 5'-CCACCTCCTGCTGTCCTTCTGTTCGTC-3'. The sequence of the EP3 receptor primers and probe were: forward, 5'-GACCCGCTACCTACCTACATG-3'; reverse, 5'-AGAGGGAGGCGGCGGAGAAT-3'; probe (FAM labelled), 5'-AGCCGGGGCTCTTCCAACATATTTAAT-3'; probe (VIC labelled), 5'-TGGCCGGCAGCCAGTCTTCCTC-3'. Expression of COX-2 and EP receptors were normalized to RNA loading for each sample using the 18S ribosomal RNA as an internal standard. Fold induction of COX-2 and EP receptor expression was calculated by dividing the relative expression of COX-2 or EP receptors in cells incubated with seminal plasma or PGE2 by the relative expression of COX-2 and EP receptors in cells maintained in culture medium alone. Fold induction of EP2 and EP4 receptor expression in transfected cells was calculated by dividing the relative expression of EP2 or EP4 in cells transfected with EP2 or EP4 receptor cDNA by the relative expression of EP2 or EP4 in cells transfected with control cDNA. The data are presented as mean ± SEM from three independent experiments.

Western blotting
Cells were seeded in 5 cm dishes and allowed to attach overnight. The following day, the culture medium was replaced with serum-free medium or serum-free medium containing either a 1:50 dilution of seminal plasma or 300 nmol/l PGE2. Cells were grown for 24, 48 and 72 h and harvested by lysis in protein lysis buffer (150 mmol/l NaCl, 10 mmol/l Tris–HCl pH 7.4, 1 mmol/l EDTA, 1% Triton X-100, 0.1% SDS) and centrifugation. The clarified lysate was removed to a new tube for protein quantification and SDS–PAGE. The protein content in the supernatant fraction was determined using the Bio-Rad, Hemel Hempstead, UK. A total of 20 µg of protein was resuspended in 20 µl of sample buffer (125 mmol/l Tris–HCl pH 6.8, 2% SDS, 5% β-mercaptoethanol, 10% glycerol, 0.02% bromophenol blue). Samples were boiled at 95°C for 5 min and separated by 10% SDS–PAGE. The proteins were transferred to nitrocellulose membranes at 75 V for 1 h. Membranes were blocked in 5% milk in Tris-buffered saline (10 mmol/l Tris, 150 mmol/l NaCl, pH 7.5) for 1 h and incubated with mouse monoclonal antibodies against COX-2 (1:1000 dilution) and EP receptors (1:500 dilution) in 1% milk in Tris-buffered saline for 1 h. Membranes were washed 3 times with 1% milk in Tris-buffered saline for 5 min each wash. Membranes were then incubated with donkey anti-mouse IgG HRP conjugate (1:1000 dilution) for 1 h, washed again for 15 min before incubation with chemiluminescent substrate (Merck Darmstadt, Germany) for 1 min. Membranes were exposed on Biomax MR X-ray film (Kodak) for 20 s to 5 days depending on signal strength.
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PGE₂ stimulation and cAMP measurement

EP receptor signalling was assessed by measuring cAMP accumulation following stimulation of cells with either seminal plasma or PGE₂. Cells (2×10⁵) were plated in 6-well dishes containing 4 ml/well of complete medium. Cells were allowed to attach overnight. Thereafter, the culture medium was replaced and removed with serum-free medium containing 3-isobutyl-1-methylxanthine (IBMX; Sigma) to a final concentration of 1 mmol/l for 40 min at 37°C. Cells were then stimulated with a 1:50 dilution of seminal plasma or 300 nmol/l PGE₂ for 5, 10 or 15 min respectively, or left unstimulated. Following stimulation, the medium was removed and the cells lysed in 0.1 mol/l HCl. cAMP concentration was quantified by ELISA using a cAMP kit (Biomol; Affiniti, Exeter, UK) as per the manufacturer’s protocol and normalized to the protein concentration of the lysate. Protein concentrations were determined using protein assay kits (Bio-Rad). The data are presented as mean ± SEM from three independent experiments.

Statistical analysis

The data in this study were analysed by ANOVA using StatView 5.0 (Abacus Concepts, Berkeley, CA, USA).

Results

Seminal plasma and PGE₂ induces COX-2 expression in HeLa cells

The effects of seminal plasma and PGE₂ on COX-2 expression in HeLa cells were investigated by real-time quantitative RT–PCR (Figure 1A, B) and Western blot analysis (Figure 2A, B). HeLa cells were treated with seminal plasma or PGE₂ or maintained untreated in culture medium (control cells) for 24, 48 and 72 h respectively. Real-time quantitative RT–PCR analysis revealed a 20.25 ± 5.38- and 4.3 ± 0.75-fold induction of COX-2 mRNA in HeLa cells treated with seminal plasma (Figure 1A) for 24 or PGE₂ (Figure 1B) for 72 h respectively (P < 0.05). Co-treatment of HeLa cells with 3 μg/ml indomethacin (a dual COX enzyme inhibitor) showed no significant reduction in induced COX-2 mRNA expression. Western blot analysis revealed 8 ± 3.78- and 3.7 ± 0.78-fold induction of COX-2 protein expression in HeLa cells following treatment with seminal plasma for 24 h (Figure 2A) or PGE₂ for 72 h (Figure 2B) respectively (P < 0.05). No significant elevation in COX-1 protein was observed as determined by Western blot analysis. Cells were normalized for protein loading against β-actin on the same blot.

Up-regulation of EP receptor mRNA expression by seminal plasma and PGE₂

The effects of seminal plasma (Figure 3A) and PGE₂ (Figure 3B) on mRNA expression on the four subtypes of PGE₂ receptors, namely EP1–EP4, were investigated by real-time quantitative RT–PCR analysis. Treatment of HeLa cells with seminal plasma for 24 h significantly induced the mRNA expression of EP1, EP2 and EP4 receptors (5 ± 1.2-, 12.5 ± 3.6- and 7.8 ± 2.26-fold induction respectively; Figure 3A, solid bars; P < 0.05), but had no significant effect on the expression of the EP3 receptor mRNA. Co-treatment of HeLa cells with indomethacin abolished the up-regulated mRNA expression of EP1, EP2 and EP4 receptors (Figure 3A, open bars; P < 0.01). There was no significant alteration in expression of EP1, EP2 or EP3 receptor mRNAs in response to treatment with PGE₂ for 24 h (Figure 3B, solid bars; P > 0.05). However, PGE₂ significantly induced the expression of the EP4 receptor mRNA (4.1 ± 2.26-fold induction, solid bars; P < 0.05). Co-treatment of cells with the dual COX enzyme inhibitor, indomethacin, abolished the induced expression of PGE4 receptor mRNA (P < 0.01), but failed to elicit any significant effect on the mRNA expression of EP1, EP2 or EP3 receptors (Figure 3B, open bars; P > 0.05).

cAMP production in HeLa cells in response to seminal plasma and PGE₂

cAMP signalling in HeLa cells was determined following stimulation of HeLa cells with seminal plasma or exogenous PGE₂ (Figure 4). A rapid accumulation of cAMP was observed after 5 min of stimulation with seminal plasma or PGE₂; the accumulation was
greater in seminal plasma stimulated cells compared with PGE2 stimulated cells (31 ± 10.2 versus 11.33 ± 1.92 pmol cAMP/mg protein respectively; \( P < 0.05 \)).

cAMP production in EP2 or EP4 receptor transfected HeLa cells in response to seminal plasma or PGE2

HeLa cells were transiently transfected with either the EP2 or EP4 receptor cDNA or control cDNA. Real-time quantitative RT–PCR analysis revealed a 5.31 ± 0.58- and 6.7 ± 0.91-fold overexpression of EP2 and EP4 receptor mRNA expression in HeLa cells transfected with EP2 or EP4 receptor cDNA respectively, after 48 h (Figure 5A; \( P < 0.05 \)). cAMP signalling via the EP2/EP4 receptors was ascertained following transient transfection of HeLa cells with either the EP2 or EP4 receptor cDNA or control cDNA, and stimulation with seminal plasma (Figure 5B) or PGE2 (Figure 5C). Treatment of HeLa cells with seminal plasma (Figure 5B) resulted in a rapid accumulation of cAMP after 5 min in cells transfected with the EP2 or EP4 receptor cDNAs (33.3 ± 1.25 and 26 ± 2.92 pmol cAMP/mg protein respectively; \( P < 0.05 \)) compared with cells transfected with control cDNA (20 ± 2.3 pmol cAMP/mg protein). Similarly, stimulation of transfected HeLa cells with 300 nmol/l PGE2 (Figure 5C) revealed a rapid augmented accumulation of cAMP in cells transfected with the EP2 or EP4 receptor cDNAs (25.69 ± 1 and 34.63 ± 6.5 pmol cAMP/mg protein respectively; \( P < 0.05 \)) compared with cells transfected with control cDNA (13.3 ± 0.64 pmol cAMP/mg protein).

Discussion

COX enzyme expression is elevated in numerous reproductive tract carcinomas, including cervical carcinoma, endometrial adenocarcinoma and ovarian adenocarcinoma (Dore et al., 1998; Ryu et al., 2000; Tong et al., 2000; Jabbour et al., 2001; Klimp et al., 2001; Kulkarni et al., 2001; Sales et al., 2001, 2002). In cervical and endometrial carcinomas, enhanced expression of COX enzymes is associated with an elevated synthesis of PGE2 in neoplastic epithelial and endothelial cells (Jabbour et al., 2001; Sales et al., 2001), suggesting that COX enzyme products such as PGE2 may be involved in neoplastic cell transformation and reproductive tract tumorigenesis. This study reports up-regulated expression of COX-2, but not COX-1, in HeLa (cervical adenocarcinoma) cells by seminal plasma and PGE2 as determined by real-time quantitative RT–PCR and Western blot analysis. The positive feedback effect of PGE2 in inducing expression of COX-2 has been demonstrated in several
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manner to enhance COX-2 expression. Moreover, the mechanism of action of seminal plasma and PGE₂ in inducing expression of COX-2 may involve differential regulation of COX-2 transcription and mRNA stability.

PGE₂ exerts its autocrine/paracrine effect by binding to prostanoid G-protein-coupled transmembrane receptors of which four pharmacologically classified subtypes have been described (namely EP1–EP4). We investigated the effect of seminal plasma and PGE₂ on the expression of the subtypes of EP receptors in HeLa cells. Treatment of HeLa cells with seminal plasma or PGE₂ significantly up-regulated the mRNA expression of the EP1, EP2 and EP4 receptors or EP4 receptor respectively. Co-treatment of HeLa cells with the dual COX enzyme inhibitor, indomethacin, significantly inhibited the up-regulation of receptor mRNA expression, suggesting that the observed up-regulation was a result of enhanced COX-2 expression in HeLa cells, mediated by seminal plasma or exogenous PGE₂. Previous studies have demonstrated up-regulated EP receptor expression in cervical and endometrial carcinomas coincident with elevated cAMP signalling (Jabbour et al., 2001; Sales et al., 2001). In addition, a direct role for EP receptors in tumorigenesis has been reported recently in mediating proliferation and tumorigenesis in colon carcinoma cells (Sheng et al., 2001), as well as accelerating intestinal polyp formation in APCΔ716 knock-out mouse models (Sonoshita et al., 2001). It is likely that in sexually active women, exposure to seminal plasma prostanoids may act in a similar manner in cervical carcinomas to enhance or sustain tumorigenesis following ligand–receptor binding and activation of intracellular signal transduction pathways.

One of the signal transduction pathways associated with EP receptor function is the cAMP pathway. Treatment of HeLa cells with seminal plasma or PGE₂ resulted in a rapid cAMP accumulation, which was augmented in the cells stimulated with seminal plasma compared with cells stimulated with PGE₂. In order to determine whether seminal plasma prostanoids were partially responsible for the observed cAMP signalling in HeLa cells, we transiently transfected HeLa cells with the EP2 or EP4 receptor cDNA [which activate adenylyl cyclase and cAMP signalling (Ashby, 1998)] and subsequently treated the cells with seminal plasma or PGE₂. A rapid accumulation of cAMP was observed in EP2/EP4 transfected cells, and was greater than that detected in control transfected cells. Taken together, these data confirm that seminal plasma prostanoids, including PGE₂, may modulate cervical tumorigenesis in an autocrine/paracrine manner via the COX-2/PGE₂ biosynthetic pathway. It is noteworthy that seminal plasma is a heterogeneous fluid and the difference in kinetics observed between PGE₂ and seminal plasma in regulating COX-2 and EP receptor expression and signalling could suggest that other factors and effectors of signal transduction pathways may be functioning in synergy with PGE₂ to modulate neoplastic cervical epithelial cell function. These factors may include other prostanoid derivatives of the E series (PGE and 19-hydroxy-PGE), which may be acting in combination to shift the kinetics of signal transduction in cervical carcinoma cells. Further studies into the elucidation of the effect of the various components of seminal plasma, on normal and HPV-transformed cervical epithelial cells, may augment our understanding of the role of seminal plasma in progression of cervical pathologies in sexually active women. These studies are currently underway in our laboratory to elucidate the differential effects of the various components of seminal plasma on modulation of the COX/PGE biosynthetic pathway.

Thus, in conclusion, enhanced ligand–receptor binding of seminal plasma prostanoids, specifically prostanoids of the E series, brought about by prolonged exposure of neoplastic cervical epithelial cells to seminal plasma, may modulate cervical tumorigenesis by enhancing transcription of target genes such as COX-2 and prostanoid receptors.
This in turn initiates signal transduction pathways, such as the cAMP pathway, and transcription of target genes that may modulate cervical tumorigenesis.

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References


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