Modulation of Prostate Cancer Cell Attachment to Matrix by Versican

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Abstract

In this study, we examined whether versican, a recognized anti-cell adhesive molecule for various mesenchymal and nerve cell types, influences prostate cancer cell adhesion to extracellular matrix components. Prostate cancer cell adhesion to fibronectin, a major component of the stromal extracellular matrix, was inhibited by versican-rich conditioned medium (CM) from cultured human prostatic fibroblasts. In contrast, cancer cell attachment to laminin, a component of basement membranes, was not affected by the same CM. Consistent with versican being the active inhibitory factor in the CM, the integrity of chondroitin sulfate side chains and an ability to bind the RGD (Arg-Gly-Asp) peptide sequence of fibronectin were essential for the inhibition of prostate cancer cell attachment to fibronectin. Subsequent studies with versican purified from human prostate fibroblast CM confirmed its anti-adhesive activity. We conclude that versican is an important modulator of tumor cell attachment to the interstitial stromal matrix of the prostate, the latter being an essential step in cancer cell motility and local invasion of the prostatic stroma.

Introduction

The process of tissue invasion and metastasis involves changes to the integrity of basement membranes, structural composition of the interstitial ECM, and the cancer cell membrane, to facilitate detachment and migration of cancer cells through the stromal parenchyma and to gain access to the lymphatics and/or systemic circulation. Microenvironmental changes promoting cancer metastasis include: (a) changes to the composition of matrix glycoproteins and cellular integrin expression, on which cell adhesion and motility depend (2); (b) induced synthesis and activation of proteolytic enzymes to degrade the ECM, thereby facilitating the egress of motile cells through basement membranes and interstitial stroma (3); and (c) presence and release of bioactive fragments of ECM and/or growth factors that promote angiogenesis. Previous studies from this laboratory have shown that increased levels of the CS-proteoglycan versican in the peritumoral stroma of the prostate are predictive of prostate-specific antigen (PSA) relapse in patients definitively treated for clinical diagnosis of organ-confined prostate cancer (5, 6). Recently, we demonstrated a similar relationship to exist between elevated levels of versican in peritumoral mammary stroma and relapse in women with node-negative breast cancer (7). These findings suggest that increased expression of versican in the neoplastic prostate or breast stroma facilitates the local spread of tumor cells, potentially via destabilization of focal adhesion. Several reports have implicated versican in modulating cell adhesion and migration on ECM for a number of mesenchymal cell types, including osteosarcoma cells (8), malignant astrocytoma cells (9), malignant melanoma cells (10), neuronal cells (11), and fibroblasts (11, 12). Whether versican has an effect on matrix adhesion of adenocarcinoma cells, including prostate or breast cancer cells, is unknown. The aim of this study, therefore, was to determine whether versican, which is synthesized by cultured human prostatic fibroblasts, is able to modulate the attachment of prostate cancer cells to the principal matrix components, fibronectin, and laminin, in vitro.

Materials and Methods

Cell Lines. The human prostate adenocarcinoma cell lines LNCaP, PC3, and DU145, were purchased from the American Type Culture Collection (Manassas, VA). Each cell line was maintained in 80-mm flasks, in 10 ml of complete RPMI (i.e. RPMI 1640 supplemented with 4 mm l-glutamine, 100 μg/ml penicillin, 100 μg/ml streptomycin, and 2 μg/ml amphotericin B) plus 5% FBS at 37°C in an atmosphere of 5% CO₂ and 95% air. Cell passage was achieved by trypsinization (0.05% trypsin/0.02% EDTA) of near-confluent monolayer cultures.

Collection of Prostatic Fibroblast-CM. Primary isolates of fibroblasts from benign prostate tissues were derived as reported previously, using tissues obtained from patients treated by transurethral resection for voiding dysfunction (13). All of the prostate tissue samples were obtained via the Flinders Medical Centre-Repatriation General Hospital Tumor Bank after informed consent of the patients, and with approval of the Clinical Research Ethics Committee of the Flinders Medical Centre and the Repatriation General Hospital. The fibroblasts were cultured in 80-cm² flasks in 10 ml of complete RPMI plus 5% FBS at 37°C in an atmosphere of 5% CO₂ and 95% air. At near cell confluence, the culture medium was changed to complete RPMI containing 0.5% FBS and, then 24 h later, changed to serum-free conditions, i.e. complete RPMI medium containing ITS supplement. CM was harvested from the fibroblast cultures after an additional 72 h of culture. To reduce proteolytic degradation of bioactive molecules, the fibroblast CM was treated with protease inhibitors (0.01 μM EDTA, 0.02% sodium azide, 1 μM phenylmethylsulfonyl fluoride; Ref. 11). Fibroblast CM was concentrated 25-fold, using Centrisart 25 centrifuge tubes (Sartorius Biotechnology, Goettingen, Germany) with a 300,000 cutoff, at 4°C for 2 h at 2000 × g and was subsequently stored at −70°C for no longer than 2 weeks before assay. Control serum-free RPMI plus ITS collected from flasks containing no cells was treated in an identical manner to fibroblast CM. To provide an adequate quantity of versican for purification, 800 ml of CM was collected off prostate fibroblasts cultured 72 h in RPMI plus 5% FBS.

Versican Purification. Versican was isolated from prostate fibroblast CM using a combination of anion exchange and gel filtration chromatography. The CM was batch-absorbed to Q-Sepharose (10 ml/liter of medium; Amersham Pharmacia, Uppsala, Sweden) at 4°C overnight in the presence of protease inhibitors (11). Bound versican was batch-eluted with 2 M NaCl in the presence.
of protease inhibitors. The presence of versican was confirmed by immunoblotting with rabbit antibody raised against whole recombinant human versican (14) and described previously (13). Electrophoresis, electrol blotting and immunostaining for versican were performed as described previously (13). The versican-containing eluate was purified by gel chromatography on a Sephacryl S400 column (Amersham Pharmacia) equilibrated with PBS (pH 7.4). Five-ml fractions were eluted with the same buffer and concentrated 20-fold using Centriprep centrifugal filters (Amicon Bioseparations; Millipore, Bedford, MA) and Nanosep microconcentrators (Pall Gelman Laboratory, Ann Arbor, MI) with M, 50,000 and 300,000 cut-offs, respectively. The molecular integrity of the purified versican samples was determined by immunoblotting with the rabbit antibody to recombinant human versican (14). To determine the presence or absence of other CS proteoglycans in the CM and in the purified versican preparations, membranes were incubated in parallel with either rabbit anti-decorin (obtained from Dr. L. Fisher, NIH, Bethesda, MD; diluted 1:1000), or mouse monoclonal anti-CS epitopes (diluted 1:1000). Anti-CS epitopes used were 1B5 (C-0-S; Seikagaku Corporation, Tokyo, Japan), 2B6 (C-4-S; ICN Biochemicals, Aurora, OH), and 3B3 (C-6-S; ICN Biochemicals). Visualization was achieved by antirabbit IgG or antimouse IgG peroxidase-conjugated secondary antibodies (Bio-Rad Laboratories, CA) with enhanced chemiluminescence (ECL; Amersham, Little Chalfont, Buckinghamshire, England). Measurement of band staining intensity in immunoblots was achieved using α-Imager 2200 (α Innotech Corp., San Leandro, CA). Gels run in parallel were also stained with Stains All (Sigma) and Coomassie Blue dyes (Difco Laboratories, Surrey, United Kingdom) to confirm the absence of any other contaminating proteins.

**Prostate Cancer Cell Attachment.** Attachment of the prostate cancer cells LNCaP, PC3, and DU145 to ECM components was studied using an established assay (15). One hundred μl of fibronectin (Sigma; diluted to 10 μg/ml in PBS) or laminin (Sigma; diluted to 10 μg/ml in PBS) were independently added to the wells of 96-well tissue-culture microtiter plates (Nunc, Roskilde, Denmark). The plates were incubated for 60 min at room temperature, and the fluid was then aspirated. Subsequently, potential nonspecific cell adhesion to residual exposed plastic surface was blocked by addition of 200 μl of 10 mg/ml heat-denatured BSA (Sigma; 85°C for 10 min in PBS) solution. After washing the plates solution, the plates were washed with 100 μl of PBS. Twenty-five μl of control serum-free medium collected from flasks containing no cells, prostate fibroblast CM, or purified versican were then added to the appropriate wells. In some experiments, assays of cell attachment to fibronectin were repeated using fibroblast CM that had been pretreated with either 50 μg/ml RGD peptide (Sigma) or 2 units/ml enzyme ChABC (Sigma) for 2 h at 37°C. Purified versican was also pretreated with 50 μg/ml RGD peptide. The plates were then incubated at room temperature for 30 min, during the preparation of the prostate cancer cell suspensions (diluted in RPMI plus ITS). To facilitate accurate determination of cell attachment, each cell suspension was diluted to three working concentrations (1 × 10^5 cells/ml, 2.5 × 10^5 cells/ml and 5 × 10^5 cells/ml). Fifty μl of the cell suspensions were then added to the wells, and the plates were incubated for 60 min at room temperature, and the fluid was then aspirated. Subsequently, potential nonspecific cell adhesion to residual exposed plastic surface was blocked by addition of 200 μl of 10 mg/ml heat-denatured BSA (Sigma; 85°C for 10 min in PBS) solution to each well with 30-min incubation at room temperature. After aspiration of the BSA solution, the plates were washed with 100 μl of PBS. Twenty-five μl of control serum-free medium collected from flasks containing no cells, prostate fibroblast CM, or purified versican were then added to the appropriate wells. In some experiments, assays of cell attachment to fibronectin were repeated using fibroblast CM that had been pretreated with either 50 μg/ml RGD peptide (Sigma) or 2 units/ml enzyme ChABC (Sigma) for 2 h at 37°C. Purified versican was also pretreated with 50 μg/ml RGD peptide. The plates were then incubated at room temperature for 30 min, during the preparation of the prostate cancer cell suspensions (diluted in RPMI plus ITS). To facilitate accurate determination of cell attachment, each cell suspension was diluted to three working concentrations (1 × 10^5 cells/ml, 2.5 × 10^5 cells/ml and 5 × 10^5 cells/ml). Fifty μl of the cell suspensions were then added to the wells, and the plates were incubated for 30 min at 37°C in a 5% (v/v) CO₂ incubator, with lids removed to permit rapid gaseous equilibration. Unattached cells were removed by a single gentle aspiration using a micropipette. Subsequently, 100 μl of RPMI plus ITS were added to each well, and the residual number of cells per well were quantified by the MTT assay, as described previously (13). The inhibitory effect of the purified versican fractions (dilution range, 1:2 to 1:49) on prostate cancer cell attachment to fibronectin- and laminin-coated substrates was tested using DU145 cells.

**Statistical Analysis.** The Mann-Whitney U test was used to determine statistical significance between control and treatment groups. All of the analyses were performed using SPSS 10.0 for Windows software (SPSS Inc., Chicago, IL). Statistical significance was accepted at P < 0.05.

**Results**

**Effect of Prostate Fibroblast CM on Cancer Cell Attachment to Matrix-coated Substrate.** Concentrated CM had no significant effect on the number of LNCaP, PC3, or DU145 cells attached to laminin when compared with concentrated control serum-free RPMI medium (Fig. 1). This lack of effect of fibroblast CM on prostate cancer cell adhesion to laminin was observed for each cell line at three cell densities. In contrast, concentrated CM from the prostate fibroblasts significantly decreased the number of LNCaP, PC3, and DU145 cells attached to fibronectin, when compared with concentrated control serum-free RPMI medium (Mann-Whitney U Test, P > 0.05). Each data point is expressed as the number of attached cells (absorbance units) and represents the mean plus SD of eight replicates from two independent experiments.

**Specificity of Inhibition of Prostate Cancer Cell Attachment to Fibronectin by Fibroblast CM.** To determine the specificity of the inhibition of prostate cancer cell attachment to fibronectin observed in the presence of prostate fibroblast CM, the cell attachment assays were repeated using CM treated with either RGD peptide or ChABC. Treatment of concentrated CM with 50 μg/ml RGD peptide resulted in a significant reversal of the decrease in cell attachment induced by CM, for each prostate cancer cell line (Fig. 3, A–C). For PC3 and DU145 cells, but not for LNCaP cells, RGD treatment of the control
serum-free medium resulted in a significant reduction in prostate cancer cell attachment to fibronectin (Fig. 3, B and C). The attachment of DU145 cells to fibronectin appeared to be more sensitive than that of PC3 cells to the effect of RGD, irrespective of whether the substrate was treated with fibroblast CM or control serum-free medium. Treatment of concentrated fibroblast CM with ChABC mirrored the effects on cell attachment to fibronectin observed using RGD peptide (Fig. 3, A–C).

Characterization of Prostate Fibroblast CM Collected in RPMI + ITS. Versican isoforms V0 and V1 (M_r ~400,000) were identified in 25-fold concentrated CM as a broad band because of incomplete resolution of the versican isoforms (Fig. 3D, left panel). Decorin was also present in the concentrated CM as two isoforms (Fig. 3, D, middle panel). The sizes of the decorin core proteins identified (M_r 45,000 and 55,000) were in agreement with those in previous studies (16). Identical banding patterns were obtained on immunoblotting with antibodies to three different CS epitopes that react to the variously sulfated CS stubs remaining after ChABC digestion (i.e., 1B5, C-0-S; 2B6, C-4-S; and 3B3, C-6-S). Fig. 3D, right panel, depicts a representative immunoblot, illustrating that four bands (M_r ~400,000, 260,000, 210,000, and 180,000) were detected.

The band observed at M_r ~400,000 is consistent with versican core protein. The identities of the other CS-containing proteins is not known.

Characterization and Cell Attachment-inhibitory Activity of Purified Versican Fractions. To produce the quantity of versican that was sufficient for purification, CM was collected from prostate fibroblasts that were cultured in RPMI plus 5% FBS instead of RPMI plus ITS. Fig. 4 illustrates the characterization and inhibitory activity for DU145 cell attachment to fibronectin of sequential fractions during the purification of versican. Immunoblotting of unconcentrated CM from fibroblasts grown in FBS-containing medium using rabbit antibody to recombinant human versican (Fig. 4A, Lane 1) demonstrated the presence of two versican isoforms. After adsorption to Q-Sepharose and elution with 2 M NaCl, a broad band that reflected incomplete resolution of the versican isoforms because of overloading of the gel was observed (Lane 2). Versican V0 and V1 isoforms were observed in the sequential fractions 6–12 eluted from the Sephacryl S400 gel filtration column, with no evidence of proteolytic degradation. Fractions 7 + 8, 9 + 10, and 11 + 12 were individually pooled and concentrated 20-fold for characterization and testing.

Immunoblotting of fractions 7 + 8, 9 + 10, and 11 + 12 using antibodies to the three CS epitopes (C-0-S, C-4-S, and C-6-S) again yielded identical blots. Fig. 4B depicts a representative immunoblot using antisera C-4-S. Two bands only (M_r ~400,000 and 180,000) were detected. The band observed at M_r ~400,000 is consistent with versican core protein. The identity of the M_r 180,000 band present in the CM and versican purified fractions is not known. Quantitation of fractions 7 + 8 and 9 + 10 in the immunoblot (Fig. 4D) indicated that although there was no difference between the amount of the M_r 180,000 CS proteoglycan, the difference in the relative concentration of versican between the fractions was 5-fold. Two isoforms of decorin were present after gel filtration in the concentrated fraction 11 + 12 (Fig. 4C). Decorin was not present, however, in the concentrated fractions 7 + 8 or 9 + 10, which contained the greater proportion of versican and which were used for determining the inhibitory activity for DU145 cell attachment. Parallel electrophoresis gels stained with Stains All and Coomassie Blue dyes confirmed the absence of any other contaminating proteins in fractions 7 + 8 and 9 + 10 (data not shown).

Purified versican fractions 7 + 8 and 9 + 10 both inhibited the attachment of DU145 cells to fibronectin- (Fig. 4D), but not to laminin-coated substrates (data not shown). The dose-response plots indicate that the level of inhibitory activity decreases as the dilution increases for both fractions. The data also indicate that the relative amount of inhibitory activity in fraction 7 + 8 is 5-fold greater than that of fraction 9 + 10. Similar to the original concentrated CM harvested in ITS (Fig. 3C), the attachment-inhibitory activity of fractions 7 + 8 and 9 + 10 for DU145 cells was abrogated by 50 μg/ml RGD peptide (data not shown).

Discussion

The observation that versican-rich CM, derived from primary cultures of prostate fibroblasts, significantly decreased the attachment of prostate cancer cells to fibronectin-coated substrate in an RGD- and ChABC-sensitive manner, provides evidence that versican potentially is a key regulator of prostate cancer cell attachment. Analysis of fractions after chromatographic purification of CM indicated that the inhibitory component for cell attachment is most likely attributable to versican. The capacity of versican to inhibit cellular attachment seems to be substrate-dependent because cell binding to laminin is unaffected. These findings are consistent with other studies that demonstrate versican selectively interferes with stromal cell binding to
matrix components. For instance, the adhesive capacity of L929 fibroblasts, neonatal dorsal root ganglion neurons, and Schwann cells was reduced when versican was substrate coated in a mixture with fibronectin but not in mixtures with laminin or collagen types I or IV (11). Other studies report that melanoma cell adhesion to fibronectin and collagen type I substrates is inhibited by versican (10). ELISA of versican binding to solid-phase coatings of ECM components indicated that versican bound specifically to fibronectin and collagen type I but not to laminin or collagen type IV (17). Collectively, these observations suggest that versican modulates cancer cell attachment via binding to components of interstitial tissue matrix rather than to basement membrane.

The effect of versican in fibroblast CM on cell attachment was most pronounced for the two androgen-insensitive cell lines, PC3 and DU145. The differential capacity of versican to inhibit fibronectin binding by the three prostate cancer cell lines may be a function of specific integrin-expression profiles for each cell line (18). The RGD tripeptide sequence of fibronectin, a recognized inhibitor of classical cell binding to fibronectin (19), was found to completely (LNCaP) or partially (PC3, DU145) reverse the inhibition of prostate cancer cell binding induced by fibroblast CM. This is consistent with versican specifically interfering with cell binding to fibronectin via an RGD-dependent mechanism. In the absence of fibroblast CM, RGD peptide was found to partially inhibit PC3 and DU145 cell attachment to fibronectin, consistent with the inhibition of cell attachment via the binding of RGD peptide to the integrin receptors $\alpha_5\beta_1$, $\alpha_6\beta_1$, and $\alpha_\beta_1$ present on the surface of malignant prostate epithelial cells (20, 21). Interestingly, the degree of inhibition of cell attachment for PC3 and DU145 is greater when control medium rather than versican-containing fibroblast CM is treated with RGD. This suggests that,
rather than an additive inhibitory effect in the presence of both RGD and versican, RGD binds to versican and thereby effectively reduces the inhibitory capacity for cell binding of both molecules. In contrast to PC3 and DU145 cells, attachment of LNCaP cells to fibronectin was not inhibited by RGD peptide in the absence of fibroblast CM. Again, this is suggestive of differing profiles of integrin expression among the three cell lines; for example, expression of α₃β₁ integrin by LNCaP cells could result in non-RGD-dependent binding to fibronectin (20, 21). However, the inhibition of LNCaP cell binding by fibroblast CM was completely reversed by the addition of RGD, suggesting that the anti-cell adhesive capacity of versican is abrogated by its binding of the peptide. An earlier study suggested that versican binds to a fibronectin fragment lacking the RGD sequence, and that steric hindrance or conformational disturbance of the adjacent RGD cell-binding site results in the inhibition of adhesion (11). However, if LNCaP cells bind to fibronectin in an RGD-independent manner, and this interaction can be inhibited by versican as suggested in the present study, then it appears that versican may be capable of acting in both an RGD-dependent and an RGD-independent manner, depending on both the cellular and microenvironmental context.

Previous studies have indicated that the cell-adhesion-inhibitory properties of versican are dependent on the presence of the CS side chains, as shown by the loss of activity after digestion with ChABC (11). In this study, digestion of the CS side chains of proteoglycans present in the fibroblast CM by ChABC led to a partial reversal of the inhibition of prostate cancer cell attachment to fibronectin. This suggests the presence of at least one CS proteoglycan in fibroblast CM. The fact that ChABC significantly inhibited the binding of PC3 and DU145 cells to fibronectin in control medium (i.e., in the absence of fibroblast-derived proteoglycans) suggests the involvement of an additional CS proteoglycan in cell attachment, one that is integral to the cancer cell membrane. A likely candidate is CD44, previously demonstrated to be present on the cell surface of PC3 and DU145 but not of LNCaP cells (22).

The presence of versican, decorin, and, potentially, three other CS proteoglycans (or fragments of proteoglycan at M₉, 150,000, 210,000, and 260,000) was observed in the original CM from fibroblasts cultured in ITS. Only versican and a M₉, 180,000 proteoglycan were present after chromatographic purification of CM obtained from FBS-cultured fibroblasts. The band at M₉, 400,000 observed with antibodies to the CS epitopes (C-0-S, C-4-S, C-6-S) reflects the composition of the side-chain stubs remaining on the versican core protein after the ChABC treatment that was required to permit electrophoretic migration (13). The bands of M₉, ranging from 180,000, to 260,000, detected using antibodies to CS epitopes, most likely are not glycosylated breakdown products of versican because none are detected by immuno blotting using polyclonal rabbit antibody to recombinant human versican. Whereas the 180,000 M₉ proteoglycan was not completely removed by column chromatography from the CM derived from fibroblasts cultured in FBS, it is unlikely that this protein plays a role in the inhibition of prostate cancer cell attachment to fibronectin because the concentration of versican and the inhibitory activity for

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INHIBITION OF PROSTATE CANCER CELL ADHESION BY VERSICAN

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Fig. 4. Characterization and biological activity of chromatographically purified versican. A, immunoblotting of fractions generated during purification of versican using antibody to recombinant human versican. Unconcentrated CM from prostate fibroblasts cultured in RPMI plus FBS (20 μl loaded, Lane 1), 2 M NaCl eluate from Q-Sepharose (20 μl loaded, Lane 2), and fractions 6–12 from Sephacryl S400 (20 μl loaded, Lanes 3–9) all contain versican isoforms V0 and V1 (M₉, ~400,000). B, immunoblotting of fractions generated during purification of versican using antibody to C-4-S. Concentrated CM (10 μl loaded, Lane 2) from prostate fibroblasts cultured in RPMI plus FBS, and fractions 7 + 8, 9 + 10, and 11 + 12 (1 μl of 20× concentrate loaded, Lanes 3–5) from Sephacryl S400 contain two core proteins with CS stubs (M₉, 400,000 and 180,000). The band of M₉, ~400,000 is consistent with versican. The identity of the M₉, 180,000 band is unknown. C, immunoblotting of fractions generated by gel filtration using antibody to human decorin. Decorin was absent from pooled fractions 7 + 8 and 9 + 10 (1 μl of 20× concentrate loaded, Lanes 1–2), but was present in pooled fraction 11 + 12 (1 μl of 20× concentrate loaded, Lane 3). D, dose-response curves for effect of pooled versican-containing fractions 7 + 8 and 9 + 10 isolated from prostate fibroblast CM, on attachment of DU145 prostate cancer cells to substrate coated with fibronectin. *, significantly different from control, i.e., RPMI medium was not conditioned by fibroblasts. Dilution, 1:49 of fraction 7 + 8 not significantly different from dilution 1:9 of fraction 9 + 10. kDa, M₉ in thousands.
attachment of DU145 cells to fibronectin in dose-response experiments were both 5-fold greater in fraction 7 + 8 compared with fraction 9 + 10, whereas the concentration of the $M_r$ 180,000 proteoglycan was unchanged between the fractions.

Our previous studies (13) indicated that CM from prostate cancer cells has the ability, via cancer cell-secreted transforming growth factor $\beta_1$ (TGF-$\beta_1$), to increase the accumulation of versican during the culture of prostatic fibroblasts. In light of the present studies, we propose a positive feedback model that facilitates local invasion of prostate cancer cells in vivo. The production of soluble mediators such as TGF-$\beta_1$ by prostate cancer cells potentially induces the deposition of versican by fibroblasts into the peritumoral neoplastic stromal matrix. Prostate cancer cells could assemble the fibroblastic versican into the pericellular sheet to modulate focal cell adhesion and cellular motility, thereby facilitating local invasion.

This model is supported by recent studies demonstrating that the attachment of prostate cancer cells to bone marrow endothelial cells can be modulated by hyaluronic acid and another hyaluronan-aggregating proteoglycan, aggregan, from bovine cartilage (23). Collectively, these findings suggest that the versatile role of versican and other molecules involved in modulating prostate cancer cell adhesion and motility may lead to new strategies for controlling the local spread of tumor cells in patients with clinically organ-confined prostate cancer.

References


* C. Ricciardelli, unpublished observations.
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