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The Role of the Cell Adhesion Molecules (integrins / cadherins) in Prostate Cancer

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ABSTRACT

During prostate carcinogenesis the cellular adhesion molecules, i.e.; integrins and cadherins mediate aberrant interactions between glandular epithelial cells and the extracellular matrix. Several integrin α subunits are down-regulated, while β subunits are up-regulated. The expression of several cadherins and catenins has specific prognostic value. There is an association between the expression of the E-cadherin/catenin complex and high grade prostate cancer. Clinical trials evaluating the efficacy of integrin antagonists are ongoing with promising results. In this article we update the role of integrins and cadherins in prostate carcinogenesis and evaluate the therapeutic potential of their manipulation.

Key words: *cadherins; integrins; prostate cancer; review*
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INTRODUCTION

During prostate cancer (PCa) progression, precursor lesions will eventually progress to incurable androgen-independent metastatic disease (1). Among the alterations described in prostate carcinogenesis are aberrant interactions between glandular epithelial cells and the extracellular matrix (ECM), mediated by cell adhesion molecules (CAMs). CAMs are divided into four major categories: cadherins, integrins, selectins and members of the immunoglobulin superfamily. The majority of studies focus on the abnormal expression of cadherins and integrins. In this article, we update current knowledge and their role in prostate carcinogenesis and evaluate the therapeutic potential of manipulating these molecules.

ROLE OF INTEGRINS AND CADHERINS

Integrins

Integrins are transmembrane glycoprotein receptors for ECM proteins. They are composed of two subunits α and β, the combination of which gives them a different specificity and function. Currently, 26 members of the family of integrins have been described (18 α and 8 β subunits) (2). The extracellular domain of integrins has binding sites and upon interaction with the ECM, they form links between cells and ECM components.

Cadherins

Cadherins are transmembrane glycoproteins that mediate intercellular adhesion in the

presence of extracellular calcium (3). Cell-cell adhesion in cadherins is mainly mediated by homotypic interactions. There are about 20 different cadherin molecules currently classified and the most extensively studied are: E- (epithelial), N- (neural) and P- (placental) cadherins. The cadherin complex is composed of the following components: cadherin, intracellular components associated with cadherin (i.e. catenins), and the cytoskeleton (i.e. actin). Catenins (main types are: α-, β- and γ-) are cytoplasmic proteins that interact with the intracellular domain of cadherins, providing anchorage to the microfilament cytoskeleton.

EXPRESSION OF INTEGRINS IN PCA

α subunit

High Gleason score has been correlated with low and/or negative expression of integrin subunit α_3 (4). The expression of α6 subunit diminishes with increasing histologic grade, especially at sites of contact with the basement membrane (5). PCa demonstrates decreased positive staining for subunit α_7, with a further decrease in metastatic disease (6). Other α subunits that have been found down-regulated include α_2, α_4, α_5, and αv (2). Interestingly, $\alpha_{II\beta}$ subunit is expressed only in PCa and not in normal tissue (7).

β subunit

Five β_1 variant subunits have been described and two of them (β_{1C} and β_{1A}) are expressed in normal prostatic epithelium. Decreased β_{1C} steady-state mRNA levels were detected in 94% of PCa specimens compared with normal samples (8). Subunit β_{1A} has been found to be up-regulated in human PCa, as well as, in TRAMP (transgenic adenocarcinoma of mouse prostate) models (9). The expression of β1A promotes cell proliferation and survival by increasing the expression of insulin-like growth factor receptor type 1 (IGFR-1) (9).

Upregulation of β_3 and β_6 integrin subunits has been described in PCa. Studies have demonstrated expression of the heterodimeric complexes $\alpha v\beta_3$ and $\alpha v\beta_6$, in PCa specimens in contrast with normal controls (10). Integrin $\alpha_v\beta_3$ has been demonstrated to increase cdc2 kinase activity and cdc2 levels in PCA (11). Higher cdc2 levels result in increased cell migration mediated by interaction of cdc2 with cyclin B2 and phosphorylation of caldesmon. It is known that cdc2 and caldesmon are localized in the membrane ruffles of motile cells.

EXPRESSION OF CADHERINS IN PCA

Cadherins

It has been demonstrated that tumor tissues exhibit decreased levels of E-cadherin (12). The expression of this cadherin was significantly correlated with histological differentiation and bones metastasis, but not with lymphatic or vascular invasion (13). Several studies have demonstrated an association between the expression of the E-cadherin/catenin complex and high grade PCa (14). Richmond et al. (15) demonstrated that abnormal expression of the E-cadherin/α-catenin complex was significantly correlated with Gleason score and with a lower survival outcome. In a recent study it has been demonstrated that there is a significant decrease of membrane expression of E-cadherin/β-catenin complex and an increase of cytoplasmatic and nuclear location of the same complex, in high Gleason score prostate cancer (16). A low E-cadherin to high N-cadherin expression switch has been correlated with progression of PCa and high mortality. N-cadherin is not expressed in normal prostate tissue; however, in PCa it has been detected especially in poorly differentiated areas (17). Also, in a number of metastatic lesions, N-cadherin has been found to be homogeneously expressed.

Prostatic tumor tissues were demonstrated to exhibit decreased levels of P-cadherin (12) even when compared with the reduced expression in benign prostatic hyperplasia (BPH). Furthermore, Cadherin-11 is expressed in the stroma of all PCa specimens. A recent study has show the absence of cadherin-10 in irregular cancer profiles in contrast with normal glandular profiles (18).

Catenins

Aberrant expression of all main three catenin types (α, β- and γ-catenin) has been associated with

extra prostatic extension (14). The expression of α-catenin seems to have prognostic value in both local and locally advanced PCa (14,15). The abnormality in α-catenin expression has been found to be associated with high Gleason score, perineural invasion and poor survival. Furthermore, the expression of α-catenin in PCa is up-regulated not only in comparison with normal tissue, but also when compared with the elevated expression in BPH. Hyperplastic prostates differ from normal prostates in the weaker immunoreactions of the two catenins β- and γ- , as well as, in the intracellular distribution of them (19). A recent study has demonstrated that the membranous overexpression of β-catenin is significantly associated with the metastatic prostate cancer cells in the bone and that the high frequency of expression suggests its involvement in the intercellular adhesion of the metastatic cells in the bone. Furthermore, studies have demonstrated that δ-catenin is overexpressed in PCa and is correlated positively with increasing Gleason scores (14).

CLINICAL IMPLICATIONS

Clinical trials that evaluate the efficacy of integrin antagonists as PCa therapeutics are ongoing. Cilengitide, a cyclic Arg-Gly-Asp peptide that inhibits $\alpha v\beta_3$ and $\alpha v\beta_5$, is a promising antagonist of αv integrins. A recent randomized phase II trial assessed the efficacy of different doses of Cilengitide in metastatic hormone refractory PCa patients (20). Forty-four patients were randomized to Cilengitide 500 mg or 2,000 mg IV twice weekly. Median number of cycles was three in both arms and at 6 months two patients on the 500 mg arm and five on the 2,000 mg arm had not progressed, while there was no grade 4 toxicity.

Monoclonal antibodies that inhibit αv integrins have also been studied, usually in conjunction with standard chemotherapy. CNTO 95, an αv integrin monoclonal antibody, was administered (10 mg/kg, once weekly) in combination with docetaxel and prednisone and appeared to be well tolerated (21). MEDI-522 is an antibody against the $\alpha_v\beta_3$ integrin that is being studied in a randomized phase II in combination with docetaxel, prednisone and zoledronic acid [unpublished data].

It is questionable if E-cadherin, β-catenin or α-catenin, can be used individually as prognostic markers. However, a combination of these proteins may be of clinical use as in other tumors (i.e. liver, colorectal). Apigenin is a plant flavone that blocks β-catenin signaling and has been found to suppress prostate carcinogenesis in TRAMP mice (22). Another study (23) has suggested that therapeutic strategies blocking cadherin-11 expression or function, such as anti-cadherin-11 antibodies, may be considered when applying androgen-ablation therapy, because androgen deprivation up-regulates cadherin-11 expression in PCa, and this may contribute to the metastasis of PCa. Finally, a study (24) examined the potential of an N-cadherin inhibitor: ADH1, in reducing tumor angiogenesis ex vivo and delaying tumor progression in vivo. Relevant results have demonstrated that ADH1, does not display antiangiogenic activity in a rat aortic ring assay or antitumor potential in a PC3 subcutaneous xenograft tumor model. Cytotoxic activity was detected in human umbilical vein endothelial cells, PC3, and Tsu-Pr1 cells.

CONCLUSIONS

The molecular pathways by which integrins and cadherins contribute to PCa progression need to be further elucidated. The expression of several cadherins and catenins has specific prognostic value that could be standardized. Finally, designing novel therapeutic approaches based on inhibiting integrin expression and/or downstream signaling is likely to be a promising strategy.

CONFLICT OF INTEREST

None declared.

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