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Review Article

Integrin signaling aberrations in prostate cancer

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Abstract: Integrins are cell surface receptors for extracellular matrix proteins and play a key role in cell survival, proliferation, migration and gene expression. Integrin signaling has been shown to be deregulated in several types of cancer, including prostate cancer. This review is focused on integrin signaling pathways known to be deregulated in prostate cancer and known to promote prostate cancer progression.

Key words: Focal adhesion kinase, PTEN, PI 3-kinase/AKT, Ras/Raf/MAPK, cdc2, survivin, Bcl-2

Introduction

Prostate cancer is a significant burden in western countries and has been predicted to account for more than 28,660 deaths and 186,320 new cases in 2008 [1]. Prostate cancer development proceeds through a series of defined states. These include prostatic intraepithelial neoplasia (PIN); high-grade PIN lesions, which usually develop prior to invasive cancer; androgen-sensitive invasive cancer and an androgen-independent castration-resistant state [2, 3]. The current therapies for prostate cancer involve surgery, androgen ablation, or the blockade of the androgen receptor; however, a significantly high percentage of treated prostate cancers eventually grows, despite either castration levels of androgen or the presence of anti-androgens. For these patients, radiation therapy is the only treatment available. Still, a large number of patients relapse.

Integrins are cell surface receptors for extracellular matrix proteins and play a key role in cell survival, proliferation, migration and gene expression. Integrin signaling has been shown to be deregulated in several types of cancer, including prostate cancer. In prostate cancer, tumor cells have a different surrounding matrix than normal cells; thus changes in the integrin profile may be functionally relevant and contribute to aberrant intracellular signaling [4-8]. Several studies have associated deregulation of integrin expression with the progression of prostate cancer to an advanced stage (**Table 1**) [4, 8-11]. This article reviews the literature on the major signaling pathways activated by integrins and their deregulation in prostate cancer.

Integrin deregulation in prostate cancer

Integrins are heterodimers consisting of α and β subunits. At this time, 24 heterodimers of the integrin family, consisting of 18 α and 8 β subunits, have been described [12, 13], and their ability to activate specific signaling pathways has been investigated [13]. Integrin signaling plays a key role in the alteration of cellular growth and tumor progression through the regulation of gene expression, apoptosis, cell adhesion, proliferation, migration and angiogenesis [14, 15], as well as proteinase expression [16]. Most α and β subunits have been shown to be downregulated in prostate cancer, whereas only α6, β1, β3 and β6 are upregulated [6]. Among the α subunits, several reports show that α3, α4, α5 and α7 are downregulated [17, 18]; α2 and α6 are aberrantly expressed, whereas there are no reports on the remaining subunits [6]. A unique

Table 1. Deregulated expression of integrin subunits in human prostate cancer and metastasis

Subunit	Adenocarcinoma	Metastasis	References
Up-Regulated			
α_6	unknown	↑	Knox et al., 1994 [11]; Bonkhoff et al., 1993 [19]; Nagle et al., 1995 [20]
α_{IIb} (truncated)	↑	unknown	Trikha et al, 1998 [33]
β_1	↑	unknown	Murant et al., 1997 [10]; Knox et al., 1994 [11]; Goel et al., 2007 [22]
β_3	↑	↑	Zheng et al., 1999 [30]
β_6	↑	↑	Li and Languino, 2007 [31]
Down-Regulated			
α_3, α_4 α_5	↓	unknown	Nagle et al., 1994 [18]
α_7	↓	unknown	Ren et al., 2007 [17]
β_{1C}	↓	unknown	Fornaro et al., 1996, 1998, 1999 [25-27]; Perlino et al., 2000 [28]
β_4	↓	unknown	Nagle et al., 1995 [20]; Davis et al., 2001 [23]; Allen et al., 1998 [24]
Other			
α_2	↓	↑	Nagle et al., 1994 [18]; Bonkhoff et al., 1993 [19]

This table shows the expression of integrin subunits found to be deregulated in human primary and metastatic prostate cancer.

expression pattern has been shown for α2, which is downregulated in prostate cancer, but upregulated in lymph node metastases as compared to primary lesions [18, 19]. An extensive analysis of α6 expression in prostate cancer shows that α6 expression is either maintained or overexpressed in prostate cancer, and increases in lymph node metastases [11, 19-21].

Among the β subunits, β1, β3, and β6 are upregulated, while β1C and β4 are downregulated in human prostate cancer [6, 20, 22-24]. No reports are available for β5, β7, and β8.

Five β1 variant subunits, β1A, β1B, β1C, β1C-2, and β1D, generated by alternative splicing, have been described. Two variants, β1C and β1A, are shown to be expressed in benign prostatic epithelium. β1C is expressed at both protein and mRNA levels in benign prostatic epithelial cells, but is markedly downregulated in adenocarcinoma [25-28]. Fornaro et al. show that the expression of β1C integrin increases p^{27kip1} levels, a cell cycle inhibitor, as well as p^{27kip1} association with cyclin A [26]. In contrast, the findings that the expression of the β1A integrin variant is upregulated and is necessary for the cell's ability to grow in an

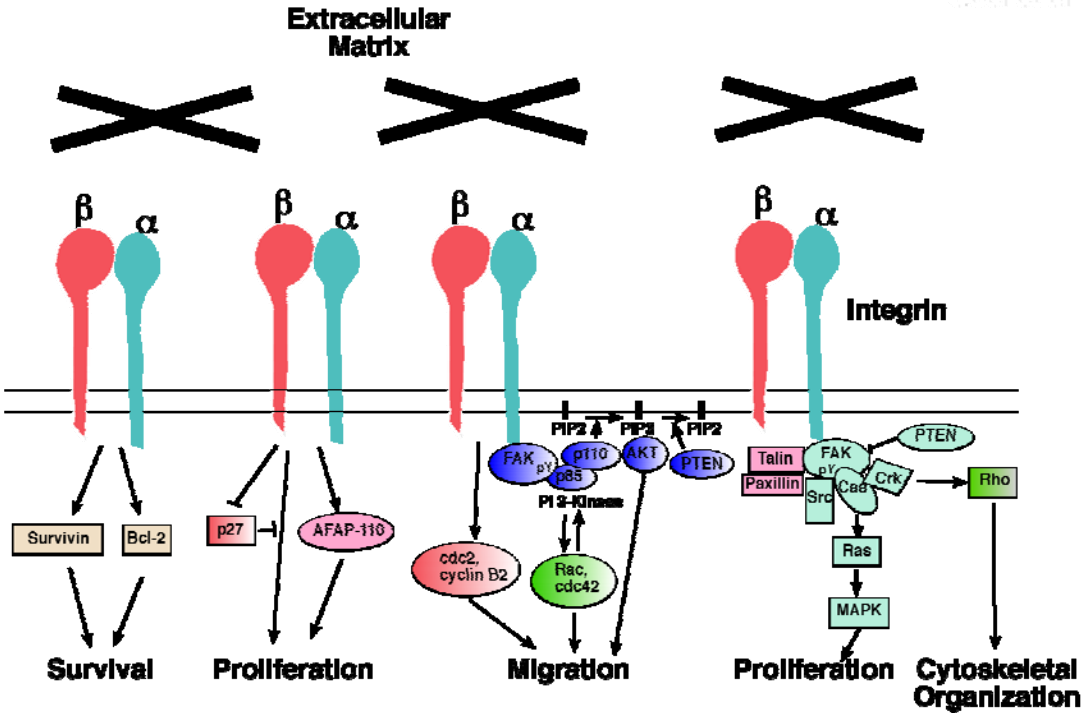

Figure 1. Integrin-dependent signaling pathways. Schematic drawing showing the signal transduction pathways regulated by integrins that control prostate cancer cell survival, proliferation, adhesion, migration, and cytoskeletal organization. For a detailed description of integrin downstream effectors like Rac, cdc42, Src, Cas, Rho and Crk, or cytoskeletal proteins like AFAP-110, talin and paxillin, readers should refer to previous articles [38, 86].

anchorage-independent manner [29], point to the important role that the β1A integrin may have during prostate cancer progression and will be helpful in formulating new therapeutic strategies.

Upregulation of αvβ3, αvβ6 and the truncated αIIb integrin variant has been described [6]. Zheng et al., using human prostate cancer cells isolated from 16 surgical specimens, show that these cells express αvβ3, whereas normal prostate epithelial cells do not [30]. Similarly, αvβ6 [31, 32] and the truncated αIIb integrin variant [33] are found to be expressed in adenocarcinoma.

The β1 and β3 integrin subunits are known to localize in focal contacts and to mediate spreading and cytoskeletal rearrangement in normal cells [12, 13]. However, when we either downregulated or upregulated these subunits by siRNA or ectopic expression analysis, we show that cancer cell spreading is not affected [29, 34]. These results demonstrate that the ability of the β1 and β3 subunits to promote cancer progression is independent of cell spreading.

Overall, these findings indicate that the expression of selective integrin subunits is deregulated during prostate cancer progression, and that these subunits are potential diagnostic markers in prostate cancer.

Activation of unique signaling pathways by integrins

The expression of the β1 and β3 subunits activates specific signaling pathways and supports distinct cancer cell functions [34, 35]. Analysis of the mechanism by which β1 may promote tumor growth in vivo, shows that β1 is uniquely required in cancer cells for the localization, expression and function of insulin-like growth factor type 1 receptor (IGF-IR), which is known to support cancer cell proliferation and surviv-

al [29, 35]. The mechanism proposed for β1 integrins' control of IGF-IR activity involves β1 recruiting specific adaptors to the plasma membrane, thus increasing the concentration of specific adaptors proximal to the growth factor receptor [35]. This study provides evidence that the β1 cytodomain plays an important role in mediating β1 integrin association with either insulin receptor substrate-1 (IRS-1) or Grb2-associated binder1 (Gab1)/SH2-containing protein-tyrosine phosphate 2 (Shp2), downstream effectors of IGF-IR. Specifically, β1A associates with IRS-1 and β1C with Gab1/Shp2 [29, 35, 36].

In parallel studies, we have discovered that β3 is uniquely required in cancer cells for increasing cdc2 levels, as well as cdc2 kinase activity. While β1 integrin expression does not increase cancer cell motility or cdc2 levels, and appears to predominantly modulate cell proliferation and survival, these effects are specific for β3. Higher levels of cdc2 result in increased cell migration mediated by the specific association of cdc2 with cyclin B2 and the phosphorylation of caldesmon, a substrate of cdc2. These results show that cdc2 acts as a downstream mediator of the αvβ3 integrin and promotes cancer cell migration [34]. In conclusion, the β1 and β3 integrins promote activation of selective signaling pathways that support prostate cancer progression.

Integrin downstream effectors

Since integrins lack catalytic activity, they depend on intracellular effector proteins to transduce signals [37, 38]. In this section, we discuss the major signaling effectors that are likely to contribute to prostate cancer progression (**Figure 1** and **Table 2**).

Focal adhesion kinase (FAK)

FAK is a non-receptor tyrosine kinase, which becomes activated upon integrin-extracellular matrix (ECM) interactions and integrin clustering [39, 40]. Upon phosphorylation, FAK interacts with several signaling proteins, including Src kinases, Cas, paxillin and Phosphoinositide 3-Kinase (PI 3-Kinase) [39, 40]. FAK signaling is altered in prostate cancer. In normal prostate, FAK expression is absent or weak in secretory epithelium and is expressed predominantly in the basal layers. Prostate carcinoma shows a greater expression of FAK compared to the secretory layer of normal prostate. FAK expression is further increased in invasive prostate cancer [41, 42].

A well established role for FAK is its ability to regulate cancer cell motility [43]. The expression of dominant negative FAK inhibits the migration of prostate carcinoma cells [44]. In our previous study, we show that the β3 integrin induces cell migration on vitronectin, which is mediated by FAK [30]. Recently, the role of FAK in cell migration has been confirmed by using an inhibitor of FAK phosphorylation, PF-573,228. This inhibitor fails to inhibit cell growth or to induce apoptosis. In contrast, treatment with PF-573,228 inhibits both chemotactic and haptotactic migration concomitant with the inhibition of focal adhesion turnover [45]. In addition, Dasatinib, an inhibitor of Src family kinases/Abl, blocks FAK and Cas signaling in human prostate cancer cells, resulting in the suppression of invasion, migration and adhesion of prostate cancer cells [46].

Bombesin is shown to stimulate PC-3 cell migration and tyrosine phosphorylation of FAK. In addition, bombesin also increases the association between FAK and the β1, β3 and β5 integrins [47]. Bombesin induces relocalization of FAK in focal contacts, followed by its tyrosine phosphorylation and the formation of actin lamellipodia. FAK inhibitors cause reduced cell motility upon bombesin treatment [48]. FAK is also required for bombesin stimulated activation of RhoA, a GTPase required for cell migration [49]. Another example of the role that FAK plays in cell migration is provided by Sumitomo et al., who use Neutral endopeptidase 24.11 (NEP) [50]. NEP is an enzyme which cleaves neuropeptides such as bombesin and endothelin-1. NEP treatment blocks bombesin and endothelin-stimulated cell migration and FAK phosphorylation. This study suggests that NEP expression results in the formation of a complex containing NEP, Lyn and PI 3-Kinase and this complex competitively blocks FAK/PI 3-Kinase interactions [50]. The FAK/PI 3-Kinase interactions are also shown to promote prostate cancer cell invasion: α5β1 interacts with the PHSRN sequence of fibronectin (FN), which induces FAK phosphorylation and FAK association with PI 3-Kinase, resulting in prostate cancer cell invasion [51]. FAK siRNA, or specific PI 3-Kinase inhibitors, block PHSRN-mediated invasion

Table 2. Aberrant Integrin-Dependent Pathways in Prostate Cancer

Downstream Effectors	Expression/Activity	Prostate cancer stage	References
FAK	upregulated expression	invasive cancer and metastasis	Rovin et al, 2002 [41]; Tremblay et al, 1996 [42]
MAP kinase	increased kinase activity	androgen-independent state	Bakin et al, 2003 [53]
PTEN	downregulated expression	cancer and metastasis	Schmitz et al, 2007 [61]
AKT	increased kinase activity	cancer with high Gleason score	Sun et al, 2001 [67]; Malik et al, 2002 [68]
Survivin	upregulated expression	PIN, primary tumors and metastasis	Shariat et al, 2004 [71]; Krajewska et al, 2003 [72]; Kishi et al, 2004 [73]
Bcl-2	upregulated expression	PIN, primary tumors and metastasis from recurrent cancer	Colombel et al, 1993 [76]; Zellweger et al, 2005 [77]; Krajewska et al, 1996 [78]

Signaling proteins and inhibitors of apoptosis known to be regulated by integrins and to affect prostate cancer progression are shown. FAK, Focal adhesion kinase; PTEN, phosphatase and tensin homolog; MAP kinase, mitogen-activated protein kinase.

[51]. Overall, these studies highlight a crucial role for the FAK in prostate cancer cell invasion mediated by integrins.

Ras/Raf/MAP kinase

Mitogen-activated protein (MAP) kinases, the principal effectors of Ras and known downstream effectors of integrins, are major regulators of cell proliferation and cell differentiation [52]. Although Ras and Raf mutations are not common in prostate cancer, it is known that the activation of the Ras/MAP kinase pathway might be sufficient for progression towards the androgen-independent state [53, 54]. A high ERK/p38 activity ratio favors prostate tumor growth and activation of α5β1 integrin is proposed as a determinant of the in vivo growth promoting activity of a high ERK/p38 ratio [55]. Furthermore, inhibition of MAP kinase, using U0126, decreases α6 integrin mRNA levels in androgen-independent prostate cancer cells [56]. Thus, blocking MAP kinase activation provides an important tool to regulate integrin signaling during prostate cancer progression.

PTEN

PTEN, a dual specificity phosphatase, has the ability to dephosphorylate inositol phospholipids such as phosphatidylinositol-3,4,5-triphosphate (PIP3) and, as a consequence, negatively regulates AKT activation. By virtue of its ability to inhibit the AKT pathway, PTEN acts as a tumor suppressor [57]. The Pten gene is frequently deleted or mutated in human cancers and is shown to be involved in the regulation of cell migration on integrin substrates [58]. In 1997, PTEN was cloned from the 10q23 region, a region frequently targeted by loss of heterozygosity in advanced cancer [59, 60]. PTEN alterations are common in prostate cancer. Recently, Schmitz et al. have shown that 23% of patients with first time diagnoses lost PTEN expression, and 59% of patients with lymph node metastasis no longer express PTEN. These findings suggest that loss of PTEN expression is a possible early prognostic marker for prostate cancer metastasis [61].

Overexpression of PTEN inhibits cell migration, whereas antisense to PTEN enhances cell migration. These effects are suggested to be mediated by FAK regulation, since overexpression of FAK partially antagonizes the effects of PTEN. Thus, PTEN phosphatase may function as a tumor suppressor by negatively regulating cell interactions with the ECM, mediated by integrins [58]. PTEN is shown to regulate the adhesion and proliferation of LNCaP-C4-2 prostate cancer cells stimulated by vascular endothelial growth factor [62]. PTEN expression inhibits LNCaP-C4-2 cell migration toward calvaria-conditioned medium, but has no effect on migration toward lung-conditioned medium, and this inhibitory effect is dependent on PTEN lipid phosphatase activity [63]. All these studies suggest that PTEN downregula-

tion contributes to integrin activation of signaling pathways that mediate cancer progression, although the mechanisms underlying this cross-talk remain to be investigated.

PI 3-Kinase/AKT pathway

PI 3-Kinase is a major downstream component of the integrin and growth factor signaling pathways [64, 65]. PI 3-Kinase catalyzes the production of the lipid secondary messenger PIP3 at the cell membrane. PIP3, in turn, contributes to the recruitment and activation of a wide range of downstream targets, including the serine-threonine protein kinase AKT [64]. Several studies show that integrin-mediated activation of PI 3-Kinase plays a crucial role in cancer cell survival, preventing anoikis and promoting cell migration (for review, [37, 66]). AKT1 kinase activity is significantly increased in primary carcinomas of the prostate [67]. AKT activation, assessed by immunohistochemical staining of human prostate cancer biopsies, shows greater intensity in high Gleason grade compared to PIN and all other grades of prostate cancer [68]. Similarly, using protein microarrays, it is shown that prostate cancer progression is associated with increased phosphorylation of AKT [69]. Although AKT promotes several integrin-mediated functions, our studies indicate a predominant role for the PI 3-Kinase/AKT pathway in prostate cancer cell migration [70].

Survivin/Bcl-2

Survivin, an important member of the inhibitor of apoptosis family, is a dual regulator of cell proliferation and cell viability. Survivin is expressed in embryonic and fetal organs, but is undetectable in most differentiated tissues. Survivin is shown to be upregulated in prostate cancer, especially in aggressive forms, such as high grade carcinoma and metastasis [71-73]. We demonstrate that β1 integrin engagement by FN upregulates the expression of survivin, and increases protection from apoptosis induced by the TNF-α in aggressive prostate cancer cells. The expression of dominant negative survivin counteracts the ability of FN to protect cells from undergoing apoptosis. We also show that the regulation of survivin levels by integrins is mediated by the AKT pathway [74]. It should be noted that in addition to integrin-ECM interactions, IGF/mTOR signaling and anti-androgen therapy are associated with the modulation of survivin levels in prostate cancer [75].

Bcl-2 is another important regulator of cell survival. Bcl-2 expression is restricted to the basal cells in normal and hypertrophic prostate glands, but all epithelial cells in areas of PIN express Bcl-2 [76]. All primary prostatic carcinomas and metastases obtained from hormone-refractory tumors are shown to express Bcl-2 [76-78]. This suggests that they may protect tumor cells from apoptosis induced in response to radiotherapy or chemotherapy. Integrin ligation, specifically by α5β1 and αvβ3, but not αvβ1, stimulates Bcl-2 expression via the FAK and PI 3-Kinase pathways [79, 80]. This integrin-mediated regulation of Bcl-2 is also controlled by the activation of Ca2+/calmodulin-dependent protein kinase IV, NF-kappaB and CREB transcription factors [79, 80]. Bcl-2 is also known to suppress anoikis induced by quinazoline based α1-adrenoceptor antagonists in prostate cancer cells [81].

All these recent studies highlight a crucial role for survivin and Bcl-2 in prostate cancer cell survival mediated by integrins.

Conclusions and future studies

The studies reviewed here indicate that designing new diagnostic and therapeutic approaches for prostate cancer, based on inhibitors of integrin functions or of integrin downstream signaling, will prove to be a successful strategy. However, the molecular pathways by which integrins contribute to prostate cancer progression, and in general, the molecular mechanisms that promote this disease remain to be fully investigated. Several areas of research appear under-investigated. Among others, a major effort is needed to study the mechanisms by which integrins are deregulated in prostate cancer and to characterize integrin-mediated pathways which support survival of prostate cancer stem cells. Furthermore, new preclinical studies to test the efficacy of integrin inhibitors in prostate cancer are necessary. For this purpose, prostate cancer mouse models, such as the TRAMP mouse or the mouse which carries a conditional Pten deletion in the prostate are useful tools. Future studies will also take advantage of the use of recently developed novel small animal molecular imaging approaches, such as biolumines-

cence imaging (BLI) [82, 83]. A very innovative study, using BLI in mice that ubiquitously express luciferase (FLASH, firefly luciferase activated systemically in homozygotes), proves that we can increase our ability to detect tumor response to therapeutic agents like siRNAs [84, 85].

In conclusion, studies aimed at elucidating the mechanisms by which deregulation of integrin-mediated signaling pathways occurs in prostate cancer will provide novel therapeutic approaches for this disease.

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