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Integrin alpha-6 in Prostate Cancer

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Abstract

In Western populations, prostate cancer is one of the leading causes of cancer-related deaths in males, second only to lung cancer. Currently, relapse rates are still as high as 30% within 10 years of primary treatment, largely due to early micrometastatic progression in bone marrow. Patients with metastatic tumour progression have been shown to have significantly worse survival outcomes than their non-metastatic counterparts. The exact mechanism of tumour invasion in prostate cancer metastasis is poorly understood. Therefore, early diagnosis of aggressive prostate cancer has enormous potential to improve survival and quality of life, and there is a need for novel molecular markers in the early identification of malignant potential. Integrin α6 has been implicated in the migration and invasion processes of prostate tumour cells, and poses a potential target for future prostate cancer therapy

Keywords
prostate cancer, integrins, integrin alpha 6, ITGα6, cancer stem cells

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1. Introduction

In Western populations, prostate cancer is one of the leading causes of cancer-related deaths in males, second only to lung cancer [1]. In 2015, the Australian Bureau of Statistics reported more than 18,000 incidences of prostate cancer, with over 3000 deaths [2]. Despite this, the frequency of relapse is still as high as 30% within 10 years of primary treatment [3, 4, 5] of which a large portion is owed to early micrometastatic progression in bone marrow [6]. Studies have shown that the five-year survival rate of patients with contained prostate cancer is more than triple that of their metastatic counterparts [7]. As such, early diagnosis of aggressive prostate cancer has enormous potential to improve survival and quality of life [8, 9]. Currently, there are insufficient diagnostic tools to discriminate between indolent tumours and those with high propensity to metastasise. Therefore, there is a clinical imperative for novel molecular markers in the early identification of malignant potential, which could ultimately lead to the development of therapeutic interventions against cancer cell invasion and migration.

The existence of a stem cell subpopulation in the prostate has been well-documented and is proposed to reside within the basal cell compartment of the prostate gland [10, 11]. Their ability to self-renew and undergo multiple-lineage differentiation has led to studies about their tumorigenic properties. Over the past decade, however, the existence of a minor subpopulation of tumour cells known as cancer stem cells (CSCs) has been proposed. These CSCs are titled accordingly due to their capacity for self-renewal and invasion, as well as their differential ability to recapitulate the phenotype of their primary tumour [12, 13, 14]. Their stem cell-like characteristics have been suggested to be responsible for solid tumorigenesis, metastasis and even some resistance to chemotherapy, as a response to their ability to divide asymmetrically [15, 16, 17, 18, 19]. Understandably, targeting abnormal CSCs will necessarily be preceded by specific knowledge of marker proteins expressed in this subpopulation.

To date, studies have identified several putative markers of prostate stem cells, including a number of adhesion molecules known as integrins [20, 21, 22]. Research surrounding integrin involvement in cancer biology, and particularly prostate cancer progression, has attracted significant interest in recent decades. This review focuses specifically on one integrin, integrin α6 (ITGA6/CD49f), in light of the growing body of evidence suggesting its implication in prostate cancer susceptibility, CSC biology and tumour cell migration and metastasis. The aim of this review is to convey an overview of the biological function of integrin α6, present current evidence about its diagnostic and prognostic value and ultimately discuss the potential role of this integrin as a future target for drug design.

2. Materials and Methods

2.1 Search strategy and inclusion criteria

An electronic search of the MEDLINE and EMBASE databases was performed using the following MeSH and other keywords: integrin alpha6, alpha 6, alpha-6, alpha6, ITGA6, prostate cancer and prostate neoplasms. The search was restricted to articles in the English language. There was no limitation for publication year. Abstract submissions and studies for which integrin alpha 6 was not the primary focus were excluded. Studies were selected for inclusion if they contained empirical research that investigated integrin α6 natin prostate cancers and then judged on their focus on integrin alpha-6 and contribution to the review.

Reference lists of all relevant articles were hand-searched for additional relevant studies. Titles and/or abstracts of relevant studies from this search strategy were screened by the author. Full-text articles were retrieved and screened when abstracts and titles were insufficient for determining inclusion or exclusion in the review.

3. Results

Eighteen relevant studies, published between 1994–2017 were included in this review. Six publications reported integrin α6 as a putative stem cell marker in prostate cancer, while two of the eighteen studies investigated its role in bony metastasis and invasion in a xenograft model. Five studies reported an association between increased expression of integrin α6 and metastatic progression and invasive phenotype of prostate cancer cell, although one study reported integrin α6 as a predictor of non-aggressive disease. Several studies were conducted by the same group of investigators.

Integrin α6 expression is persistent in invasive prostate cancer cell lines. The expression of this integrin is associated with aggressive phenotype, poor patient progression and increased metastasis. Its structural variant, integrin α6p is also reported to contribute to invasion and migration of prostate tumour cells on laminin.

4. Discussion

4.1 Structure of prostate - normal and neoplastic

The normal prostatic epithelium comprises of pseudostratified layers of luminal, basal and neuroendocrine cells [23] which form part of a duct-acinar system [24, 25]. These secretory epithelial cells are supported by the basal lamina, found at the epithelium-stroma interface [26, 27, 28]. The significance of the basal lamina is two-fold; a) structurally, it represents a physical barrier which must be breached in the context of metastasis [29, 30, 31] and b) functionally, its molecular composition of proteoglycans, collagens and non-collagenous glycoproteins such as laminin [32] lend

it to involvement in cellular processes such as attachment, migration and differentiation [33, 34]. This is consistent with evidence of altered composition, such as loss of collagen type VII [32, 35] and laminin B2t [36] in neoplastic basal lamina.

Currently, the exact cellular origin of CSCs is still widely debated. The greater expression of luminal cell markers on prostate cancer cells than basal cell markers has led to the hypothesis that prostate cancer arises from terminally differentiated luminal cells [37, 38]. However, there is also a belief that intermediate progenitors [39, 40] or subpopulations of multipotent stem cells from the basal epithelial layer may give rise to prostate cancer instead [41, 42]. Consequently, there still exists a paucity of accepted techniques used to characterize and isolate CSCs in prostate cancer tissue.

4.2 Structure and biological function of integrin-α6

Integrins are a large group of heterodimeric transmembrane glycoproteins that mediate interactions between cells and extracellular matrix (ECM) through molecular adhesion. They are comprised of one α subunit and one β subunit, which together determine ligand specificity and facilitate bidirectional signaling upon activation by ligands [43]. Each subunit contains an extracellular domain for ligand attachment, a transmembrane domain and a short tail within the cytoplasm [44]. This cytoplasmic tail interaction allows integrins to serve as sensors of dimensionality within the matrix [45] and transduce mechanical forces from the ECM into biochemical survival signals, resulting in the inhibition of a p53-regulated apoptotic pathway [46, 47]. Upon ligand binding, integrins complex with the cell membrane to form focal adhesions, consisting of signaling and adaptor proteins [48, 49]. These in turn engage relevant kinases to initiate downstream intracellular signaling cascades [44] such as the focal adhesion kinase (FAK) and the phosphatidylinositol 3-kinase (PI3K)/AKT pathways [50, 51] and thus regulate proliferation, migration, invasion and cell migration [45]. Additionally, crosstalk between the activation of AKT and p53 degradation via phosphorylation of Mdm2 has been discovered [52, 53]. Integrins play a critical role in numerous biological events involving ECM remodeling, including wound healing and embryonic development [54].

4.3 Integrin α6 structure

One integrin that has raised particular interest in the framework of prostate cancer progression is integrin α6. This mechanosensing integrin is encoded by the ITGα6 gene, and dimerizes with β1 or β4 chains to form either α6β1 or α6β4 complexes, respectively [55]. Both of these serve as receptors for the laminin family of ECM proteins, despite differing expressions and roles. α6β1 is widely expressed in epithelia and associated with strong anchorage and stabilization of skin tissue through hemidesmosome formation

[56, 57]. $\alpha 6\beta 4$ is involved in cellular migration such as embryogenic organ and tissue development [58, 59] and prominently identified on platelets, macrophages, lymphocytes and many epithelial cells [60].

4.4 Integrin-α6 function, regulation and expression

The major function of laminin-binding integrin-$\alpha 6$ is maintaining stable anchorage and structural integrity of skin and glandular epithelium whilst withstanding mechanical and shear stresses [61]. Mutations of the ITG$\alpha 6$ gene has been associated with basement separation and epithelial blistering of varying severity [62, 63, 64]. In the context of CSCs, integrin-$\alpha 6$ has also been demonstrated to play a key regulatory role in self-renewal, proliferation and tumour-formation capacity in glioblastoma stem cells cervical uterine cancer cells [65, 66].

Despite its important role in CSCs, there is a shortage in understanding of the molecular mechanisms involved in the regulation of integrin-$\alpha 6$. The limited current knowledge surrounding the stem cell self-renewal control by integrin-$\alpha 6$ derives mainly from studies in embryonic stem cells (ESCs) and breast CSCs. OCT4 and SOX2 are two pluripotent-related genes which maintain the self-renewal capacity of undifferentiated ESCs (67). Yu et al. (2012) revealed that increased expression of OCT4 and SOX2 led to upregulation of integrin-$\alpha 6$ expression, and demonstrated the regulation of integrin-$\alpha 6$ through the direct binding of OCT4 and SOX2 on specific regions of the integrin-$\alpha 6$ promoter [68].

In normal prostatic tissue, the basal lamina boasts a great diversity of molecular components, including collagen IV, VII, entactin, fibronectin, vitronectin, tenascin, laminin 5, 6, 7 (containing the $\alpha 3$ chain) and laminin 10-11 (containing $\alpha 5$ chain) (32, 69). Integrin-$\alpha 6$ is just one of a wide range of integrin receptor units which are polarised on the basal cell layer, adjacent to the basal lamina.

In human prostatic carcinoma, however, all but a select few components of the basal lamina are lost. As a result, there is a significant loss of the corresponding integrin units [70] which is consistent with the lack of integrin subunits observed on the tumour cell surface of invasive prostate carcinomas [36]. The $\alpha 6$ integrin is a notable exception to this, demonstrating a persistent expression in 69% of invasive prostate carcinomas [70].

4.5 Integrin-α6 expression and patient prognosis

In human prostate cancer, integrin $\alpha 6$ expression is preserved in a diffuse manner on the plasma membrane, rather than being polarised on the basal layers [36]. The progression of prostate tumour development generally begins with the emergence of precursor prostatic intraepithelial neoplasia lesions, followed by carcinoma in situ and eventually, extracapsular invasion into neighbouring structures and distant metastases sites [36]. Overwhelmingly, current evidence supports the theory that elevated expression

of integrin $\alpha 6\beta 1$ is correlated with an aggressive phenotype during tumour progression, poor patient prognosis and increased metastasis [6, 71, 72, 73, 74].

Rabinovitz, Nagle & Cress (1995) investigated the invasive phenotypic features of human prostate carcinoma cells by comparing the $\alpha 6$-high with $\alpha 6$-low cell subpopulations. In vitro assays were used to demonstrate a significantly higher rate of random migration on coated laminin in the $\alpha 6$-high sublines as compared with the $\alpha 6$-low sublines. $\alpha 6$-antibodies were then used to confirm the involvement of $\alpha 6$, and particularly $\alpha 6\beta 1$, as it was the primary distinguisher between $\alpha 6$-high with $\alpha 6$-low cells.

Severely compromised immunodeficient mice were then used to assess the invasion and migration capacity of the $\alpha 6$ sublines in vivo. $\alpha 6$-high subpopulations were found to exhibit a significantly higher rate of invasion through the laminin-rich mice diaphragm, as characterized by several basement membrane breaching points. These findings are consistent with evidence suggesting an association between increasing prostatic intraepithelial neoplasia grades and progressive basal cell disruption [75].

This could be partially explained by the role of the integrin-ECM interaction in providing traction for tumour cell invasion during dissociation of the cell from ECM proteins at the leading edge of the cell migratory path [76, 77] or the extracapsular escape facilitated by laminin-coated nerves [72]. However, this is conflicted by some evidence noting an association between high expression levels of integrin $\alpha 6$ and lowered recurrence rate, disease-associated death following radical prostatectomy, as well as other non-aggressive tumour features such as low Gleason score ($<$7), serum PSA levels of 10ng/mL and pT2 stage [78]. Integrin $\alpha 6$ has also been shown to be a predictor of biochemical and local recurrence of prostate cancer [79].

More recently, a novel structural variant of integrin $\alpha 6$, called integrin $\alpha 6$p has been identified [7]. This is formed by post-translational proteolytic cleavage of the ligand-binding extracellular domain by urokinase-type plasminogen activator (uPA) on the tumour cell surface [70, 80]. The cleavage of integrin $\alpha 6$ contributes to invasion and migration of the tumour cell on laminin, whilst in vitro and in vivo studies of integrin $\alpha 6$p have shown that inhibition of the cleavage function significantly hinders tumour migration within the bone [81, 82] and encourages the formation of curative-type bone lesions [73, 83, 84]. These results highlight the prevention of integrin $\alpha 6$p production as a potential novel treatment strategy for delaying disease progression within the bone.

4.6 Integrin-targeted modalities for prostate cancer treatment in lab and future directions

Given the growing recognition of integrins' roles in facilitating prostate cancer invasion and metastasis, there has been increasing research into future treatment modalities targeted at these adhesion molecules. Various groups

have developed pre-clinical models to investigate the functional significance of targeting integrin $\alpha6$. For example, King 2008 demonstrated the reduced tumour cell migration and onset and degree of bone pain and fractures in xenograft mouse models injected with uncleaved integrin $\alpha6$ ($\alpha6$pB1) as compared with cleaved ($\alpha6$B1) [85]. A similar model has since been used by Landowski 2014, in testing an integrin $\alpha6$ functional blocking monoclonal antibody, called J8H [6]. The results of this study showed promising outcomes of J8H in blocking tumour progression and subsequently improving survival outcomes without impacting cell adhesion to laminin. Despite this, currently there are only four drugs that have passed Phase II trial for treatment of metastatic prostate cancer (Cilengitide, Etaracizumab, Intetumumab and Abituzumab) [86]. One reason for this limited number of integrin antibodies in clinical trial is the difficulty posed by their bidirectional nature of cell signalling, as targeting these integrins may lead to the altered expression and function of other receptors [86]. Furthermore, most integrins are not constitutively active, and therefore, change their expression in response to changes in external stimuli, including therapy. This complicates integrin antagonism, and could limit clinical effectiveness of targeted therapy.

5. Conclusion

The need for early detection and prevention of tumour cell metastasis drives the search for greater diagnostic and prognostic biomarkers in prostate cancer. Integrin-targeted treatment presents as a promising area in which drug development may have a significant impact on patient survival. There is still much to learn about the role of integrins in prostate tumour cell migration and invasion, and the clinical significance of integrin inhibition in prostate cancer is still unclear. Whilst the pool of preclinical evidence supporting a role for integrin $\alpha6$ in prostate cancer invasion, future clinical studies of bony metastasis prevention via integrin inhibition are required. Combined therapy of integrin treatment with radiotherapy is also a consideration for future research, as it has the potential to increase prostate tumour sensitivity to radiation and drug therapies [87]. A greater understanding of integrin signalling and expressional changes modulates our prospects of developing targeted biological interventions to slow prostate cancer progression.

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