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Review

Epithelial-mesenchymal-transition regulators in prostate cancer: Androgens and beyond

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ABSTRACT

Castration resistant prostate cancer (CRPC) remains one of the leading causes of cancer deaths among men. Conventional therapies targeting androgen signaling driven tumor growth have provided limited survival benefit in patients. Recent identification of the critical molecular and cellular events surrounding tumor progression, invasion, and metastasis to the bone as well as other sites provide new insights in targeting advanced disease. Epithelial mesenchymal transition (EMT) is a process via which epithelial cells undergo morphological changes to a motile mesenchymal phenotype, a phenomenon implicated in cancer metastasis but also therapeutic resistance. Therapeutic targeting of EMT has the potential to open a new avenue in the treatment paradigm of CRPC through the reversion of the invasive mesenchymal phenotype to the well differentiated tumor epithelial tumor phenotype. Overcoming therapeutic resistance in metastatic prostate cancer is an unmet need in today's clinical management of advanced disease. This review outlines our current understanding of the contribution of EMT and its reversal to MET in prostate cancer progression and therapeutic resistance, and the impact of selected targeting of mechanisms of resistance via EMT towards a therapeutic benefit in patients with CRPC.

Contents

1. Introduction

Prostate cancer is the most common non-cutaneous malignancy among men, with an estimated 220,800 new cases diagnosed in the United States in 2015 [1] and a relatively low mortality rate in patients with favorable clinicopathological features [2]. Treatment of disseminated prostate tumors however, hinges on androgen deprivation therapy (ADT) with limited clinical outcomes. After an initial response, these patients eventually progress to an uniformly

Abbreviations: ADT, Androgen deprivation therapy; AR, Androgen receptor; CRPC, Castration resistant prostate cancer; DHT, Dihydrotestosterone; EGF, Epidermal growth factor; EMT, Epithelial mesenchymal transition; ERβ, Estrogen receptor β; FGF, Fibroblast growth factor; IGF, Insulin-like growth factor; MET, Mesenchymal epithelial transition; PDGF, Platelet derived growth factor; PI3 K, Phosphatidylinositol 3-OH kinase; PTEN, Phosphatase tensin homolog; RTK, Receptor tyrosine kinase; SHH, Sonic Hedgehog; TGFβ, Transforming growth factor β; TβR, TGFβ receptor; VEGF, Vascular endothelial growth factor.

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lethal state of castration resistant prostate cancer (CRPC) [3], reflecting biochemical or radiographic disease progression despite castrate levels of androgen [4]. Emergence of CRPC as a result of a complex interplay of events resulting in apoptosis evasion and consistent cell proliferation despite seemingly continued sequestration of canonical androgen signaling [5].

Advanced prostate cancer is associated with metastasis to the bone, which occurs in 90% [6] of patients, leading to disease morbidity [7]. Metastatic progression is a multistep process involving local invasion, dissemination, and colonization and re-establishment at a new location, contextual to a dynamic tumor microenvironment [8]. During tumorigenesis, the tumor microenvironment can exert influences on epithelial-mesenchymal transition (EMT), conferring invasive and migratory properties in primary tumor cells, ultimately resulting in metastasis [9,10]. EMT functionally contributes to therapeutic resistance, along with evasion of apoptosis and protection from immune surveillance [11]. Moreover, EMT induces stem cell-like properties tumor cells, conferring ability to differentiate into heterogeneous tumor populations [12]. The process is a remarkable display of cellular plasticity, driven by a network of molecular changes involving the tumor and its microenvironment. The reverse process, mesenchymal-epithelial transition (MET) results in a reversion back to a differentiated phenotype, and occurs during the process of tumor intravasation and colonization and seeding at the distant site of metastasis [13]. Understanding the mechanisms contributing to EMT induction in prostate cancer progression could provide insights into effective therapeutic strategies that could potentially prevent, or revert the metastatic process.

Abiraterone and enzalutamide, two potent androgen receptor (AR) signaling inhibitors currently deployed as standard-of-care CRPC therapies, offer improvements of four and five months respectively in terms of overall survival [14,15]. Resistance to first and second line taxane chemotherapy, docetaxel and cabazitaxel, respectively, is also inevitable in CRPC, highlighting the need to optimize both sequencing and combination of drugs currently FDA-approved for the treatment of CRPC. Recent evidence from this laboratory has shown that synergistic use of taxanes with AR inhibitors may overcome taxane resistance through mechanisms of EMT-MET cycling [16,17]. Reversal of EMT to MET, in combination with strategies of inhibition of androgen signaling holds promise in augmenting the treatment repertoire outcomes by inducing biochemical changes to the proliferative phenotype and overcoming therapeutic resistance.

2. The landscape of epithelial mesenchymal transition (EMT)

2.1. Markers featuring EMT

Phenotypic EMT is a normal physiological process that underlies many phases of embryonic development, whereby epithelial cells undergo morphological changes to acquire features that allow for migration and settlement in areas appropriate for the developmental process [18]. Its relevance in cancer progression was notably demonstrated in the context of the transcription factor SNAI1's ability to act as a repressor in the expression of the adhesion protein E-cadherin, promoting EMT in epithelial tumors [19,20]. E-cadherin, encoded by the gene *CDH1*, is essential in the maintenance of the epithelial phenotype, with a critical role as a Ca^{+2} dependent adhesion protein mediating intercellular adhesion and maintaining stable cell-to-cell junctions in both the normal and pathological state [21]. Specifically, E-cadherin forms connections between immunoglobulin domains and actin microfilaments via α- and β-catenin [21]. Repression of E-cadherin alone is sufficient to induce EMT [22], and loss thereof activates multiple transcriptional pathways that contribute to metastasis [23]. Loss of expression is frequently attributed to epigenetic changes caused by aberrant promoter methylation [24]. In prostate cancer, metalloprotease-mediated cleavage of the E-cadherin protein resulting in the dissociation of E-cadherin from the cadherin/catenin complex leads to cell invasion [25]. Loss of E-cadherin is a common feature of high grade prostate adenocarcinomas [26] and prognostic for survival [27]. Indeed, the *CDH1* gene resides on chromosome 16q, a site of frequent allelic loss in prostate cancers [28]. Interestingly, cadherin-11, an osteoblast Ca^{+2} dependent adhesion molecule, contributes to prostate metastases to bone, after a functional switch from E-cadherin to cadherin-11 in EMT [29]. Loss of E-cadherin is intimately coupled with production of the mesenchymal marker N-cadherin, a phenomenon, known as the "EN switch," that is frequently detected in aggressive prostate tumors [30,31]. N-cadherin is another member of the type I Cadherin family mediating cell-to-cell adhesion, but confers motility and invasiveness. In studies on breast cancer, N-cadherin is able to promote invasion despite presence of E-cadherin, suggesting that its effects override the suppressive properties of E-cadherin [32]. In prostate tumors, the EN switch occurs in high Gleason tumors [33], and is prognostic for time to biochemical failure and clinical recurrence. On its own, N-cadherin is a strong prognostic marker of clinical recurrence after radical prostatectomy [34] and emergence of CRPC. Furthermore, silencing N-cadherin suppresses prostate cancer growth and metastases, pointing to its therapeutic targeting value [35].

There are several other markers of phenotypic EMT that play physiologic roles in cell-to-cell dynamics. The cytoplasmic domain of cadherins associate with catenins, forming a complex that stabilizes cell-to-cell adhesion by mediating connections with the actin cytoskeleton. Expression levels of α- and β-catenins, the two most well characterized catenins, are downregulated in prostate cancers with strong correlation with clinical tumor grade and stage [36]. Vimentin is a type III intermediate filament protein expressed in mesenchymal cells and acts as dynamic tether that maintains cell integrity. Overexpressed in aggressive, hormone-insensitive prostate cancer cells [37], vimentin is known to enhance an invasive phenotype, yet by itself does not appear to confer migratory potential in vitro [38]. In clinical prostate cancer, co-expression of mesenchymal markers such as N-cadherin, vimentin, and fibronectin is uncommon in given tumor microenvironment; nevertheless, concomitant N-cadherin overexpression and E-cadherin downregulation in Gleason 4 prostate tumors, is a robust indicator the EN switch that characterizes poorly differentiated tumors[39].

2.2. Transforming growth factor-β (TGFβ): signaling master of EMT

The transforming growth factor β (TGFβ) is established as the master inducer of phenotypic EMT, with over 40 secreted ligands in its superfamily regulating these activities. In normal and premalignant cells, TGFβ acts as a potent tumor suppressor, promoting cell differentiation and apoptosis in an intricate dynamic. During tumor progression, however, TGFβ's suppressive properties are lost; cells now are able to exhibit a proliferative phenotype and initiate immune evasion, growth factor production, and EMT [40]. Cancer cells actively bypass the suppressive functions of TGFβ, either through inactivation of TGFβ receptors (blocking the entire system), or through repressing specific downstream elements that maintain the epithelial phenotype [41]. The factors influencing the transition from a tumor suppressive to enhancing role are yet to be fully understood, but the transcriptional factor homeoprotein Six1 has been implicated in this switch [42]. Canonical TGFβ signaling occurs through the initial binding of an active TGFβ ligand to type II receptors (TβRII), which in turn activates type I (TβRI) receptors to initiate signal