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Review Article

Impact of cell plasticity on prostate tumor heterogeneity and therapeutic response

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Abstract: Epithelial-mesenchymal transition (EMT) is a dynamic process of lineage plasticity in which epithelial cancer cells acquire mesenchymal traits, enabling them to metastasize to distant organs. This review explores the current understanding of how lineage plasticity and phenotypic reprogramming drive prostate cancer progression to lethal stages, contribute to therapeutic resistance, and highlight strategies to overcome the EMT phenotype within the prostate tumor microenvironment (TME). Emerging evidence reveals that prostate tumor cells can undergo lineage switching, adopting alternative growth pathways in response to anti-androgen therapies and taxane-based chemotherapy. These adaptive mechanisms support tumor survival and growth, underscoring the need for deeper insights into the processes driving prostate cancer differentiation, including neuroendocrine differentiation and lineage plasticity. A comprehensive understanding of these mechanisms will pave the way for innovative therapeutic strategies. Effectively targeting prostate cancer cells with heightened plasticity and therapeutic vulnerability holds promise for overcoming treatment resistance and preventing tumor recurrence. Such advancements are critical for developing effective approaches to prostate cancer treatment and improving patient survival outcomes.

Keywords: Prostate cancer, differentiation, lineage plasticity, phenotypic reprogramming

Introduction

Prostate cancer represents a significant health challenge, being the most commonly diagnosed cancer and the second leading cause of cancer-related deaths among American men. Approximately 1 in 7 men will be diagnosed with prostate cancer in their lifetime [1]. The primary challenge in treating lethal prostate cancer lies in tumor recurrence following androgen-deprivation therapy (ADT), antiandrogen treatments, and chemotherapy, which contribute to high mortality rates. Addressing this challenge requires an urgent understanding of the mechanisms driving castration-resistant prostate cancer (CRPC), including those that operate independently of androgen receptor (AR) signaling, to develop targeted therapies and improve patient outcomes.

The tumor microenvironment (TME) plays a critical role in supporting cancer cell survival and invasion by activating key signaling pathways that inhibit anoikis, a form of cell death triggered by insufficient cell-extracellular matrix (ECM) interactions. The suppression of anoikis facilitates tumor cell invasion and metastatic colonization, as cancer epithelial cells and adjacent stromal cells, including endothelial cells and fibroblasts, adapt to survive without firm ECM attachment [2, 3]. Epithelial-mesenchymal transition (EMT), a process by which epithelial cells acquire mesenchymal, migratory, and invasive properties, is closely tied to anoikis resistance [4, 5]. In prostate cancer, EMT enables tumor cells to de-differentiate and invade, while mesenchymal-epithelial transition (MET) facilitates metastatic colonization and tumor recurrence [6, 7]. Loss of E-cadherin and

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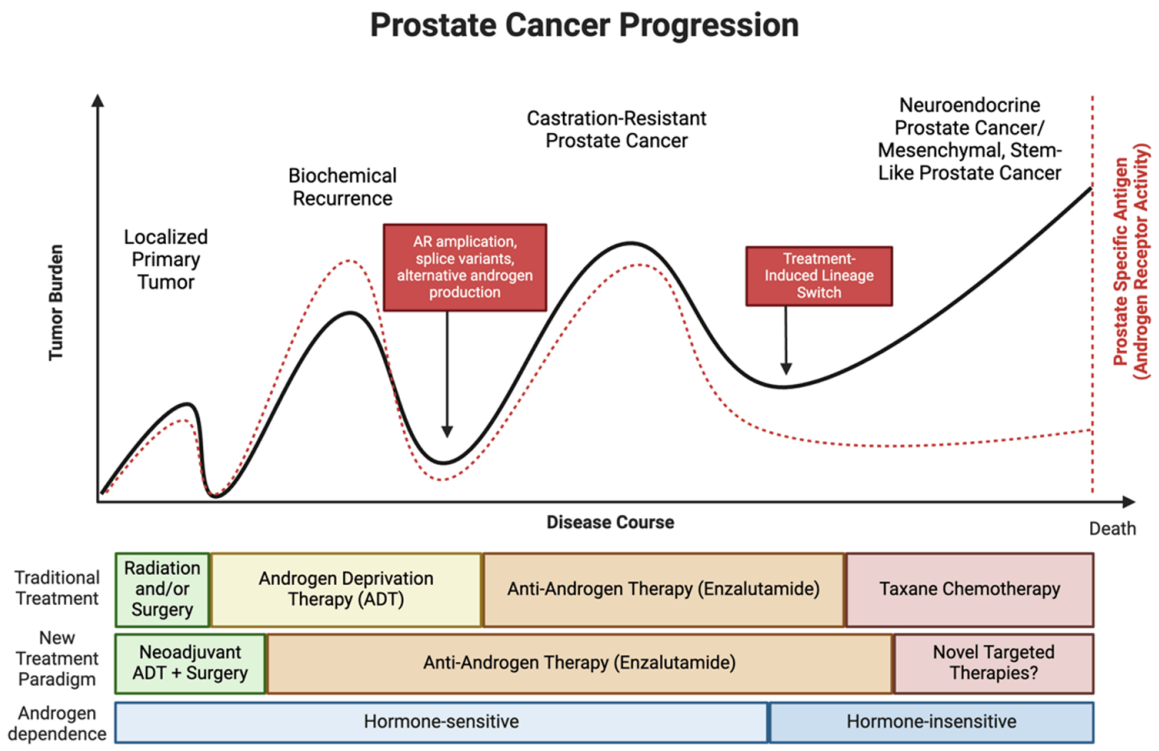

Figure 1. Natural history of prostate cancer progression. The progression of prostate adenocarcinoma can be clinically assessed by monitoring the levels of prostate-specific antigen (PSA) in the bloodstream. PSA is produced by the prostate epithelium and serves as a biomarker for androgen receptor (AR) activity and coincides with tumor burden/size as long as tumor express AR. As the disease advances and treatments are implemented, prostate tumors display reduced dependence on androgens due to abnormal reactivation of the AR or through lineage switch mechanisms. Novel anti-AR agent such as enzalutamide, apalutamide, or darolutamide, are now being implemented during hormone sensitive stages of prostate cancer. Loss of androgen dependency is associated with treatment failure and further disease progression.

disruption of adherens junctions during EMT further enhance metastatic progression and therapeutic resistance [6, 8]. Current treatment strategies predominantly target the AR signaling pathway through ADT or second-generation antiandrogens, such as enzalutamide, which directly inhibit AR activity. While these approaches initially reduce tumor size and prostate-specific antigen (PSA) levels [9], resistance inevitably develops, leading to the emergence of CRPC [10]. Mechanisms of resistance include AR amplification, the generation of AR splice variants, androgen-independent AR activation, and alternative androgen production [11, 12]. Furthermore, anti-androgen treatments can induce lineage plasticity in prostate cancer cells, reprogramming them toward stem-like or EMT-like states [13] and, in some cases, promoting neuroendocrine differentiation [14, 15]. These changes allow tumor cells to grow independently of AR signaling, further compounding treatment resistance.

Hyperactivation of AR signaling remains the primary driver of prostate tumorigenesis [16]. Initial treatments typically involve surgery or radiation to ablate the primary tumor, followed by ADT, which causes tumor shrinkage and suppresses PSA levels [9]. However, CRPC eventually arises, fueled by mechanisms that bypass AR dependency (**Figure 1**). Next-generation antiandrogens have been developed to counteract these pathways [17-19], yet resistance to these therapies is inevitable. Studies reveal that treatment-induced lineage plasticity is driven by transcriptional and epigenetic reprogramming [20-22], though the precise mechanisms underlying these changes remain incompletely understood due to the complexity of prostate cancer biology.

Unraveling the molecular drivers of lineage plasticity and phenotypic reprogramming in prostate cancer is critical for addressing therapeutic resistance and disease progression.

This knowledge will enable the development of novel strategies to overcome treatment resistance and improve survival outcomes for patients with advanced prostate cancer.

Signaling targets for EMT-directed therapy

Transcriptional activation pathways

Numerous epithelial-mesenchymal transition (EMT) transcription factors (EMT-TFs) have been identified as critical regulators of the EMT process. Key EMT-TFs include the zinc-finger homeobox (ZEB) family, SNAIL family, and TWIST family. These factors act in concert to decrease cell adhesion, disrupt cell polarity, and drive EMT and metastasis [23, 24]. The ZEB family, particularly ZEB1 and ZEB2, binds to E-box regions of the CDH1 promoter to suppress E-cadherin expression [25]. ZEB1 also represses Syndecan-1, a proteoglycan essential for maintaining epithelial integrity [26]. Elevated ZEB expression correlates with higher tumor grade and therapeutic resistance in prostate, bladder, breast, and other cancers [27]. Additionally, ZEB1 represses genes such as HUGL2 and Crumbs3, which are crucial for cell polarity [28]. The expression of ZEB is regulated by several pathways, including receptor tyrosine kinases (RTKs), TGF-β via SMAD signaling, Wnt, PI3K/Akt, and NF-κB pathways [29-31]. The SNAIL family, including SNAI1, SNAI2, and SNAI3, also suppresses CDH1 transcription upon nuclear accumulation, leading to reduced E-cadherin levels. Elevated SNAIL expression has been linked to high tumor grade and metastatic potential in prostate [32, 33], breast [34], ovarian [35], and hepatocellular cancers [36]. Notably, SNAIL promotes metastasis through both enhanced local invasion and immunosuppressive mechanisms [37].

TWIST1 and TWIST2, members of the helix-loop-helix family, drive EMT by directly suppressing CDH1 expression and increasing N-cadherin expression [38]. In prostate cancer, TGF-β1, BMP2, and BMP4 serve as key EMT drivers [39-41]. These ligands activate the TGF-β receptor complex, leading to SMAD-dependent transcription of EMT-TFs such as SNAIL, TWIST, and ZEB [42]. Additionally, TGF-β signaling activates alternative pathways, including PI3K/Akt, Ras, FAK, and Src, further promoting EMT [43, 44]. Growth factors such as HGF and IGF-1 utilize ERK signaling to enhance ZEB1 expression in prostate cancer cells [45], while PDGF has been shown to augment N-cadherin expression by suppressing E-cadherin during gastrulation [46]. Increased Src expression is associated with metastasis and castration-resistant prostate cancer (CRPC) [47, 48]. FGF and FGFR are also markedly overexpressed during the transition from androgen dependence to CRPC [49]. IL-6 secreted by prostate cancer cells induces cancer-associated fibroblasts to disrupt cell polarity in cancer cells, promoting EMT [50].

The Wnt pathway is another major EMT regulator. Binding of the Wnt ligand to lipoprotein receptor-related protein (LRP) phosphorylates LRP, recruiting Dishevelled and Axin, which allows β-catenin to translocate to the nucleus. Nuclear β-catenin binds to LEF-1, suppressing CDH1 and reducing E-cadherin expression [51, 52]. Wnt signaling also indirectly promotes SNAIL and TWIST expression via β-catenin nuclear activity [53, 54]. The Gli family of transcription factors, particularly Gli1, enhances SNAIL transcription [55] and has been implicated in EMT-mediated invasion of neuroendocrine tumors [56]. Hedgehog signaling activates Gli1 through the binding of the Hh ligand to PTCH receptors, leading to Smoothened-mediated Gli1 expression [57]. Epigenetic reprogramming further modulates EMT through repression of polycomb function, promoting tumor growth and tissue invasion [58]. Extracellular heat-shock protein (Hsp) 90, secreted by tumor cells, interacts with EZH2 to drive EMT and neuroendocrine differentiation via histone methylation (H3K27) [58].

Mechanisms of EMT navigate prostate cancer progression

Epithelial-mesenchymal transition (EMT) is marked by the loss of epithelial markers such as E-cadherin and β-catenin, and the gain of mesenchymal markers like N-cadherin, vimentin, and fibronectin [59]. These markers are not merely identifiers but play pivotal roles in maintaining epithelial integrity and driving mesenchymal phenotypes. E-cadherin and β-catenin, essential for adherens junctions, ensure cell polarity and epithelial cohesion [60]. EMT transcription factors (EMT-TFs), including ZEB, SNAIL, and TWIST families, orchestrate EMT by suppressing epithelial markers and promoting mesenchymal ones [61]. For instance, ZEB and

SNAIL bind E-box sequences in the CDH1 promoter to repress E-cadherin [62], while TWIST recruits nucleosome remodeling complexes to suppress epithelial markers [63], and upregulate mesenchymal markers like vimentin through Cullin2 circular RNAs [64]. Hypoxia-inducible factor 1α (HIF1α) and cytokines such as transforming growth factor β (TGF-β) are significant EMT initiators. HIF1α directly binds hypoxia response elements in the SNAIL1 promoter, driving its transcription [65], while hypoxia also upregulates ZEB1 in prostate cancer models [66].

Transforming growth factor β (TGF-β) signaling also regulates EMT. In healthy tissues, TGF-β can function as a tumor suppressor by phosphorylating SMAD proteins to regulate tissue differentiation and maintain tissue identity [67]. In its canonical pathway, TGF-β phosphorylates Smad proteins, which form complexes that translocate to the nucleus to regulate tissue differentiation genes, often acting as a tumor suppressor [68]. Loss of TGF-β receptor II (TGFBR2) is associated with higher Gleason scores, increased metastasis, and stemness-related genes like Sox2 and Nanog, highlighting the connection between EMT and lineage plasticity [69, 70]. Non-canonical TGF-β signaling activates PI3K/AKT and MAPK/ERK pathways, downregulating tight junction proteins and upregulating EMT TFs like SNAIL and SLUG, thereby promoting cell migration and invasion [71-74].

Receptor tyrosine kinases (RTKs) further propel EMT by activating key transcription factors and signaling pathways (**Figure 2**). Among RTKs, fibroblast growth factor receptor 1 (FGFR1) is particularly implicated in prostate cancer progression, EMT, and treatment resistance. FGFR1 is minimally expressed in normal prostate tissue but becomes prominent in adenocarcinoma [75]. Mouse models demonstrate that FGFR1 overexpression induces EMT-like gene signatures and promotes tumor aggressiveness, while FGFR1 loss reduces tumor growth [76, 77]. FGFR1 isoforms also play a role; the epithelial FGFR1 IIIb and mesenchymal FGFR1 IIIc isoforms contribute to EMT through crosstalk with TGF-β and Wnt signaling pathways, activating SNAIL and TWIST [75, 78]. FGFR1-mediated MAPK activation is particularly crucial in AR-null prostate tumors, driving anti-androgen therapy resistance [49] and promoting metastasis [79, 80]. Noncanonical FGFR ligands like Gremlin1 (GREM1), upregulated by ADT, activate FGFR1/MAPK signaling to induce stemness and suppress AR activity, further contributing to lineage plasticity and therapy resistance [49, 50, 80]. In TP53 and RB1 knockout models of prostate cancer cell plasticity, pathways involving FGFR1 and EMT expression were concurrently activated, leading to enzalutamide resistance [81]. These findings confirm that FGFR1 signaling also drives EMT and lineage plasticity in prostate cancer and serve as a potential pathway for treatment resistance. Other RTKs, such as EGFR and IGFR, also support EMT progression. EGFR enhances SNAIL stability by preventing its ubiquitination and promotes TWIST expression via HIF1α/STAT3 signaling [82, 83]. RTKs synergize with TGF-β signaling, amplifying EMT and promoting autocrine production of ligands to sustain their activation [84].

At the end of many signal transduction cascades lie the Signal Transducer and Activator of Transcription (STAT) family of proteins. Upon phosphorylation by tyrosine kinases, STATs are activated and enter the nucleus, where they bind DNA and promote transcription. In prostate cancer, STAT3 is of particular importance, as higher phospho-STAT3 levels are correlated with higher Gleason scores and increased bone metastases [85, 86]. During prostate cancer progression, STAT3 activation has been shown to be driven as well by TGF-β1 signaling and is able to directly upregulate TWIST expression through binding to the TWIST1 promoter in a HSP27-dependent manner [87, 88]. STAT3 is also part of the non-canonical, or β-catenin-independent Wnt signaling pathway. In this pathway, Wnt binds the Frizzled2 (Fzd2) receptor, which then activates STAT3 to promote EMT through its phosphorylation by Fyn tyrosine kinase [89]. In prostate cancer, non-canonical Wnt signaling was found to be elevated in high Gleason grade patient samples and promoted expression of the mesenchymal markers N-cadherin, vimentin while downregulating E-cadherin [90]. This pathway also includes the actin-cytoskeleton regulator ABI1, which interacts with Fyn and acts upstream of STAT3 (**Figure 2**). The loss of ABI1 was found to increase STAT3 phosphorylation, activation, and the expression of mesenchymal markers such

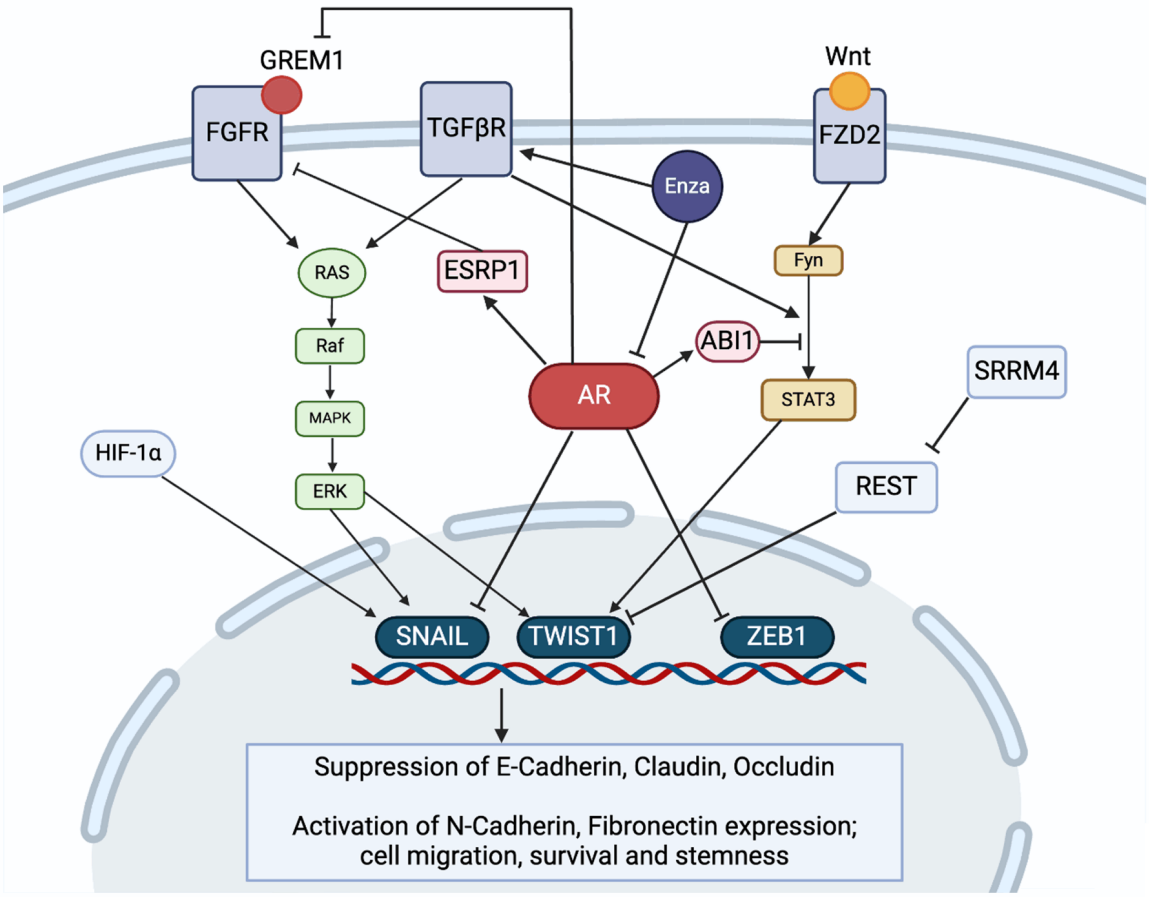

Figure 2. Pathways of EMT regulation in prostate cancer. EMT in prostate cancer has been shown to be regulated by various pathways, including non-canonical Wnt, receptor tyrosine kinase signaling pathways such as FGFR, and TGFβ signaling. Changes in alternative splicing factors, such as ESRP1 and SRRM4 also affect EMT. The loss of AR signaling due to Enza suppression has been shown to drive EMT progression through its interactions with many of these regulators.

as Slug and vimentin [91]. STAT3 has also been shown to be hyperactivated in TP53 and RB1 knockout models of prostate cancer plasticity, and promotes enzalutamide resistance through the expression of stemness markers such as SOX2 downstream of Janus kinase (JAK) activation [22, 81, 92]. As a result, STAT3 inhibitors were able to effectively target cancer stem cells in both *in vitro* and *in vivo* models of prostate cancer [93]. In this sense, STAT3 has been shown to be another master regulator of EMT and cancer progression through its interconnection between a wide network of pathways.

Alternative splicing in EMT

Alternative splicing also influences EMT by modulating epithelial and mesenchymal markers [94, 95]. Loss of epithelial splicing regulator proteins (ESRPs) and upregulation of RBFOX2 drive mesenchymal phenotypes [64, 65, 95, 96]. ESRPs maintain epithelial characteristics by regulating splicing events critical for cell adhesion and migration, such as FGFR2 isoforms. ESRP promotes the epithelial FGFR2 IIIb variant, while its loss enables the mesenchymal FGFR2 IIIc variant, inducing EMT and enhancing invasiveness [95, 97]. ESRP1 is also able to suppress the expression of pluripotency transcription factors such as OCT4, SOX2, and Nanog [98]. Thus, the loss of ESRP in EMT changes protein-protein interaction networks, leads to the increased mesenchymal features of cell invasion and migration, and the development of pluripotency needed to undergo transdifferentiation. Another RNA splicing mediated driver of EMT is the loss of repressor element 1 silencing transcription factor (REST). In heathy

tissues, REST serves to repress neuronal development and differentiation [99]. In neuroendocrine prostate cancer, the splicing factor SRRM4 can generate alternative splice isoforms of ABI1 [99] as well as nonfunctional isoform of REST, which then allows for the expression of various neuroendocrine markers [99, 100]. However, REST has also been shown to repress the expression of TWIST1 (**Figure 2**), and thus the loss of REST by SRRM4-mediated alternative splicing can promote both neuroendocrine differentiation and EMT [101].

The EMT-MET dynamic dictates metastatic behavior of prostate tumors

The primary metastatic site for prostate cancer is the bone, and progression to metastatic prostate cancer reduced the five-year survival rate to 30% [1]. The functional contribution of cell plasticity/phenotypic conversions to further advance prostatic tumor progression to metastasis, via facilitating migration, invasion, and colonization at distant sites continues to be a topic of focus for CRPC research [13]. EMT is a key determinant of cancer progression and for metastasis, associated with increased invasive potential and therapeutic resistance of tumors. Phenotypic reprogramming via EMT, involves the adoption of mesenchymal characteristics, loss of cell polarity and tight junctions [102]. The dynamic and reversible nature of EMT, and interconversion between epithelial and mesenchymal phenotypes contributes to both the dissemination of cancer cells from the primary tumor, and re-colonization at the metastatic site. These function of EMT in these processes are impacted by signaling in the tumor microenvironment and as a result of prostate cancer treatment (both ADT and taxane chemotherapy).

Within the primary tumor, prostate cancer cells remain unable to migrate with cell-cell adhesions formed by adherens and tight junctions (E-cadherin, integrins). As the master regulator of EMT, TGF-β can modulate the tumor microenvironment to facilitate cell invasion and progression to metastasis [103, 104]. TGF-β produced by tumor cells, immune cells and fibroblasts in the TME, can induce phenotypic transition to mesenchymal through transcriptional regulators of EMT including Snail, Zeb1, and Twist, leading to the degradation of adhesion molecules such as E-cadherin and detachment from the basement membrane [105, 106]. Simultaneously, this master regulator of EMT activates the cancer associated fibroblasts (CAFs) in the stroma to produce pro-angiogenic factors hypoxia-inducible factor (HIF-1α), and β-catenin transcriptionally promotes expression of vascular endothelial growth factor (VEGF) [107]. Induction of factors driving vascularity and angiogenesis promote the intravasation of prostate cancer cells through the basement membrane into the bloodstream, where these mesenchymal circulating tumor cells (CTCs) can travel to other organs at adjacent or distant sites [108]. EMT regulators Snail1, Snail2, and SLUG promote the degradation of the ECM by induction of matrix metalloproteases (MMPs) MT4-MMP and MMP2, while Snail1 suppresses expression of MMP9 [109, 110]. Recent studies suggest that some prostate cancer cells do not adhere to the specific roles of mesenchymal or epithelial phenotypes through progression of metastasis, and therefore there may be cells that exist in a hybrid EMT-MET state expressing both epithelial and mesenchymal markers such as E-cadherin and vimentin concurrently [111, 112]. Metastatic spread can be facilitated through expression of chemoattractant proteins such as CCL2, which can be suppressed by AR-signaling and can promote EMT directly or under the regulation of TGF-β [113, 114]. When the cancer cells in circulation reach the secondary organs, they must cross the endothelium to exit the bloodstream through extravasation. This process is stimulated by blood platelets, and there is some evidence for a feedback loop between TGF-β and transcription factor PRH/HHEX whereby a downregulation of PRH by TGF-β induced EMT and extravasation [115]. There is some evidence that EMT transcriptional regulator Twist1 promotes extravasation of cancer cells through integrin β1 [116]. Through reversal of EMT, prostate cancer cells re-differentiate towards the epithelial phenotype so generate secondary tumors. Tumor cells at secondary sites of solid tumors are often more poorly differentiated than the primary tumor of origin but share similar epithelial profiles [116, 117]. The interplay between cancer cells and the bone microenvironment by TGF-β drives metastatic spread. TGF-β released from the bone as a result of bone remodeling promotes cancer cell proliferation and osteoclast-mediated bone resorption in the metastatic site [118].

The role of androgen receptor signaling in prostate cancer EMT

The role of androgens and androgen deprivation therapies (ADT) in promoting EMT and stemness is complex and remains a topic of debate. Consistent with the understanding that prostate cancer development is androgen-driven, early studies suggested that androgens could promote the expression of EMT markers. For instance, androgen stimulation in prostate cancer cell lines has been shown to upregulate EMT transcription factors such as ZEB1 and TWIST1 [119-121]. This regulation is partly attributed to androgen response elements (AREs) upstream of the ZEB1 gene, implying direct androgen receptor (AR) involvement in its transcription [119, 122]. Interestingly, TWIST1 silencing also reduces AR expression, highlighting a reciprocal regulatory relationship between the two genes [123]. Conversely, suppression of AR signaling, such as through ADT or anti-androgen treatments, has been shown to induce EMT, increase stemness, promote metastasis, and facilitate lineage switching in prostate cancer. For example, N-cadherin is consistently upregulated in castration-resistant prostate cancer (CRPC) models but not in hormone-sensitive cell lines or xenografts [124]. Furthermore, physical and chemical castration in mouse models and prostate cancer organoids induces ZEB1 expression, accompanied by increased levels of mesenchymal markers such as N-cadherin and vimentin [125]. Notably, ZEB1 engages in a negative feedback loop with AR, suggesting that ZEB1 expression is not directly promoted by AR signaling but rather by its inhibition. Supporting this, ZEB1 ARE reporter assays are active even in AR-null prostate cancer cell lines [122]. SNAIL is another transcription factor regulated by AR signaling. In the C4-2 prostate cancer model, SNAIL expression is suppressed by dihydrotestosterone (DHT) treatment, with AR binding to the SNAI1 gene to repress its transcription [126]. Conversely, enzalutamide treatment induces SNAIL expression and upregulates mesenchymal markers such as N-cadherin, vimentin, and fibronectin in a reversible manner [126].

Enzalutamide has also been shown to enhance cell invasion via activation of TGF-β1/Smad3 signaling [127]. Inhibiting TGF-β receptor 1 reverses EMT and synergizes with enzalutamide treatment in preclinical transgenic mouse models of prostate cancer [30]. Similarly, under androgen deprivation environment, such as culturing LNCaP cells in charcoal-stripped serum, can result in the upregulation of EMT markers (N-cadherin, vimentin, and SNAIL) in stem-like cell populations compared to non-stem progenitors [128].

Anti-androgen treatment can activate STAT3 and non-canonical Wnt signaling pathways, further driving EMT progression. Loss of ABI1, an androgen-responsive gene downregulated by enzalutamide, has been linked to increased STAT3 activation [91, 129]. Furthermore, epithelial splicing regulators (ESRPs), which are androgen-responsive genes, are lost following ADT or anti-AR therapy [130]. Hence loss of AR signaling by ADT and anti-AR therapy could contribute to pluripotency and transdifferentiation, driving the epithelial-to-mesenchymal transition via alternative splicing in critical proteins like FGFR2 and others.

In summary, while AR signaling promotes EMT under certain conditions, AR inhibition via ADT or anti-androgen therapies often exacerbates EMT, stemness, and treatment resistance. These findings underscore the dual roles of AR signaling in prostate cancer progression and highlight the need for therapeutic strategies that address the complex interplay between EMT, stemness, and lineage plasticity.

The EMT-MET dynamics as a mechanism of therapeutic resistance

Prostate cancer, a hormonally responsive malignancy, relies on androgen signaling for growth. Standard treatments such as androgen deprivation therapy (ADT) and AR-targeted therapies (e.g., enzalutamide) aim to inhibit this pathway. However, resistance often develops, leading to castration-resistant prostate cancer (CRPC), where these therapies become ineffective (**Figure 1**). One mechanism underlying this progression is the induction of EMT during androgen deprivation.

A negative feedback loop between AR and ZEB1, a key transcriptional regulator of EMT, has been implicated in promoting EMT under androgen-deprived conditions [125]. In LNCaP cells cultured in androgen-depleted conditions, EMT is characterized by low E-cadherin, high

vimentin, elevated ZEB1 levels, and a reduction in miR-200b, a microRNA known to inhibit ZEB1 [131-133]. Several microRNAs associated with an epithelial phenotype, including miR-143, miR-145, miR-29b, miR-34b, and the miR-200 family, have been linked to resistance to ADT and docetaxel [134]. Similarly, in LNCaP tumor xenograft models, castration-resistant tumors exhibit upregulation of EMT regulator TWIST1 and other mesenchymal markers [135]. Clinically, biopsies from prostate cancer patients show increased N-cadherin expression after three months of ADT, supporting the role of EMT in therapy resistance [136].

In response to enzalutamide, EMT can be induced via upregulation of SNAIL, a transcription factor repressed by AR, and TGF-β expression, which facilitates survival in androgen-deprived environments [126, 137]. As a "master regulator" of EMT, TGF-β is heavily implicated in CRPC progression. Dysregulated TGF-β signaling, such as through a dominant negative TGF-β type II receptor (DNTGF-βRII), promotes increased tumor growth and reduced apoptosis after ADT in animal models. This aberrant signaling also enhances nuclear localization of AR and β-catenin, demonstrating crosstalk between TGF-β, AR, and EMT pathways in CRPC progression [31]. Interestingly, androgens can also induce EMT independently of TGF-β via SNAIL activation, with low AR content sensitizing cells to androgen-mediated EMT [120]. Furthermore, ADT leads to the accumulation of CCL2, a chemokine repressed by AR signaling, which is associated with EMT induction and increased resistance [113, 114].

Taxane chemotherapy further contributes to the phenotypic dynamics of EMT-MET and therapeutic resistance. TGF-β signaling drives resistance to taxanes, reducing docetaxel sensitivity in prostate cancer cells [138]. Mechanistically, TGF-β induces KLF5 acetylation, which upregulates and stabilizes the pro-survival protein Bcl-2, enhancing cell survival during docetaxel treatment [139]. However, in preclinical models of androgen-sensitive prostate cancer, cabazitaxel combined with enzalutamide induces EMT reversion toward an epithelial phenotype [140]. Similarly, in patient-derived xenograft models of therapeutically resistant CRPC, cabazitaxel treatment after ADT cessation restores an epithelial phenotype in circulating tumor cells [141]. The phenotypic interconversion between EMT and MET is not only central to taxane resistance and metastasis but may also reveal windows of therapeutic vulnerability [32]. Targeting this dynamic EMT-MET process offers a promising strategy to overcome resistance, which will be explored in the next section.

Neuroendocrine differentiation in prostate cancer: EMT-MET link in emergence of treatment-induced NEPC

CRPC initially remains androgen-sensitive and is treated with androgen receptor pathway inhibitors (ARPIs) such as enzalutamide and abiraterone [10]. However, prolonged ARPI therapy often leads to androgen resistance and neuroendocrine differentiation (NED) in CRPC cells [135]. These neuroendocrine-like cells lose AR expression and acquire neuroendocrine markers, such as chromogranin A, neuron-specific enolase, and synaptophysin [15, 142]. By escaping AR pathway inhibition, these cells continue to proliferate, resulting in treatment-induced neuroendocrine prostate cancer (T-NEPC), a lethal form of prostate cancer that arises in advanced stages of CRPC treatment [10]. The increasing use of potent ARPIs has contributed to a rise in T-NEPC incidence [10]. Emerging evidence suggests that epithelial-mesenchymal transition (EMT) and its reverse, mesenchymal-epithelial transition (MET), play critical roles in T-NEPC development [23, 143].

T-NEPC is characterized by overexpression of oncogenes such as AURKA and MYCN, which upregulate SOX and EZH2, promoting lineage plasticity and NED. These changes inhibit AR signaling and drive aggressive tumor behavior [144]. The loss of tumor suppressor genes TP53 and RB1 further exacerbates this process by enabling unchecked cell cycle progression and resistance to ADT [10]. Additionally, molecular pathways such as PI3K-AKT-mTOR and Wnt-ABI1-STAT3 are implicated in driving NED and tumor progression.

The EMT-MET interconversion dynamic is a fundamental molecular program involved in developmental processes, such as embryonic gastrulation and prostate gland formation [11]. In T-NEPC, tumors exhibit reprogramming to a pluripotent stem cell-like state, mediated by EMT-MET cycling [11]. Neuroendocrine cells

pass through hybrid transition states, co-expressing epithelial markers (e.g., E-cadherin, EPCAM) and mesenchymal markers (e.g., N-cadherin, cadherin-11) [20]. This hybrid phenotype allows rapid adaptation to environmental cues and facilitates phenotypic plasticity, a hallmark of T-NEPC.

Mechanisms driving EMT-MET interconversion in T-NEPC

Several mechanisms have been proposed as driving induction of EMT-MET interconversion dynamic in the development of T-NEPC. One of the mechanisms involves ADT-mediated induction of AR splice variants, such as for example AR-V7, which are linked to EMT activation and stem-cell-like characteristics [145]. Another key regulator of EMT-MET is the Abelson Interactor 1 (ABI1) gene. The ABI1 gene stabilizes the WAVE complex, which is critical for maintaining cell-cell adhesion. Loss of ABI1 reduces adhesion and increases cell migratory potential [91]. In prostate cancer cell models, ABI1 depletion activates non-canonical Wnt signaling, leading to STAT3 activation and transcription of EMT-related genes [129]. Importantly, ABI1 expression is suppressed by anti-AR treatments and in NEPC tumors, suggesting co-regulation between ABI1 and AR, and positioning ABI1 as a potential therapeutic target in NEPC [47].

TGF-β is a critical driver of EMT-MET interconversions, functionally activates serine-threonine membrane kinases, which phosphorylate Smad proteins. These Smad complexes translocate to the nucleus and regulate EMT-MET-related gene transcription. During ADT, AR downregulation enhances ZEB1 expression, inducing EMT and promoting mesenchymal characteristics. EMT transcription factors, such as SNAIL, SLUG, and TWIST, repress E-cadherin, disrupt epithelial integrity, and drive plasticity [23]. Additionally, TWIST suppresses apoptosis and promotes angiogenesis, further contributing to T-NEPC progression [23]. The interplay between EMT-MET dynamics, AR signaling, and lineage plasticity underscores the complex molecular mechanisms driving T-NEPC development. Understanding these processes provides a foundation for developing targeted therapies to combat this lethal form of prostate cancer.

Translational impact of lineage plasticity: in therapy and biomarker development

Targeting EMT-MET to overcome resistance: preclinical studies

Exploiting the dynamic interplay of EMT-MET in prostate cancer progression and therapeutic resistance offers a promising opportunity to enhance treatment responses and improve patient survival [9]. Understanding windows of susceptibility during these transitions may help optimize standard-of-care treatments without requiring significant regulatory changes.

Preclinical studies from our group have shown that cabazitaxel promotes MET, driving prostate cancer cells toward epithelial phenotypes [13]. This phenotypic shift reduces tumor invasiveness and may sensitize epithelial populations to further therapeutic interventions [32, 146, 147]. For example, androgen deprivation therapy (ADT), which targets the N-terminal transcriptional activity of AR, induces EMT-MET interconversions, leading to improved responses to docetaxel in preclinical models [148]. Sequencing ADT before taxane chemotherapy, such as cabazitaxel, has shown efficacy in androgen-sensitive prostate cancer [149]. However, this strategy is less effective in castration-resistant models. In recent studies, cabazitaxel administered after ADT cessation promoted an epithelial phenotype in patient-derived xenograft (PDX) models of CRPC, providing additional rationale for its use in therapeutic sequencing [141].

Upfront treatment with taxane chemotherapy, as demonstrated in the STAMPEDE trials, supports this approach clinically. Administering docetaxel within nine weeks of initiating ADT resulted in a 10-month survival benefit, a 22% reduction in mortality risk, and delayed metastatic progression [150, 151]. Targeting transcriptional regulators of EMT, such as TWIST, has also shown promise in enhancing taxane sensitivity, creating therapeutically vulnerable phenotypes [152]. While directly targeting EMT transcription factors poses challenges due to potential off-target effects, research has shifted toward inhibiting downstream effectors. For instance, monoclonal antibodies against the mesenchymal marker N-cadherin delayed tumor growth and progression in preclinical models by reducing activity in downstream path-

ways, including IL-6, IL-8, and AKT signaling [124]. Early clinical trials using Exherin (ADH-1), an antagonistic N-cadherin peptide, have shown delayed progression to castration resistance with modest improvements in CRPC outcomes [136, 153].

Further research is needed to elucidate the precise role of EMT-MET dynamics in the development of treatment-induced neuroendocrine prostate cancer (T-NEPC). Targeting programs related to neuroendocrine differentiation (NED) and EMT-MET cycling may offer novel therapeutic avenues. Promising approaches include inhibitors of MYCN/AURKA, EZH2 [15, 20] and the Wnt-ABI1-STAT3 pathway, as well as blockers of IL-6-STAT3 and mTOR signaling [91]. These strategies hold potential to mitigate therapeutic resistance and improve outcomes in aggressive, treatment-resistant prostate cancer.

Clinical trials exploiting EMT-targeted therapy

Efforts to target epithelial-mesenchymal transition (EMT) pathways in metastatic castration-resistant prostate cancer (mCRPC) have focused on impairing EMT-MET signaling to improve progression-free survival (PFS). To date, 22 clinical trials have investigated EMT-targeted therapies in mCRPC (**Table 1**). While these studies demonstrate the potential for EMT-targeted approaches, they also underscore the challenges associated with these therapies.

CCL2 and interleukin-6 (IL-6) inhibitors: The earliest trials, initiated in 2012, explored CCL2 inhibition using Carlumab in patients with mCRPC who had failed docetaxel therapy (NCT00992186). Unfortunately, Carlumab monotherapy did not improve PFS [154]. Subsequent trials shifted focus to IL-6 inhibitors, such as Siltuximab. While Siltuximab showed modest anti-tumor activity in patients pretreated with taxanes (NCT00433446) [155], a phase 2 non-randomized trial combining Siltuximab with mitoxantrone/prednisone demonstrated no improvement in PFS compared to mitoxantrone/prednisone alone (NCT00385827). Consequently, this trial was discontinued due to lack of efficacy. The results of a Siltuximab-docetaxel combination trial are still pending (NCT00401765).

Heat Shock Protein (Hsp) inhibitors: Hsp inhibitors targeting Hsp27 and Hsp90 were explored for their potential to disrupt EMT. Apatorsen, an Hsp27 inhibitor, demonstrated good tolerability with minimal adverse effects in a phase 1 trial (NCT00487786) [156], leading to phase 2 trials. However, in a non-randomized trial, Apatorsen combined with prednisone did not improve PFS compared to prednisone alone (NCT01120470). Another trial combining Apatorsen with abiraterone and prednisone was terminated due to low patient accrual (NCT01681433). Hsp90 inhibitors Ganetespib and Onalespib were also evaluated, but neither showed clinical efficacy as monotherapy or in combination therapy (NCT01270880, NCT01685268).

Receptor tyrosine kinase (RTK) and tyrosine kinase (TK) inhibitors: Given the central role of RTKs in EMT signaling, RTK and TK inhibitors have also been investigated. Dovitinib, an RTK inhibitor, showed modest anti-tumor activity in a trial where chemo-naïve patients benefitted the most (NCT01741116) [157]. However, another Dovitinib trial combining it with ADT was discontinued due to budgetary constraints (NCT02065323). Similarly, direct TK inhibitors such as Dasatinib (NCT00744497, NCT01990196) and Masitinib (NCT03761225) did not yield favorable results [158].

Emerging therapies and future directions

Hsp inhibition has also been investigated in the context of EZH2, a downstream effector of Hsp that promotes EMT. Drugs such as CPI-1205, Mevrometostat, and Tezmetostat are currently being studied in mCRPC. Preliminary results with Mevrometostat combined with enzalutamide are promising (NCT03480646, NCT03460977, NCT04179864). Similarly, trials investigating TGF-β receptor inhibitors (Galunisertib, NCT02452008) and polycomb receptor complex 2 inhibitors (ORIC-944, NCT05413421) are ongoing (**Table 1**).

The limited success of EMT-targeted therapies can be attributed to several factors. Most clinical trials targeted single EMT pathways, which may have allowed compensation by alternative pathways, limiting efficacy. Additionally, economic constraints led to the termination of some trials, highlighting the financial challenges of developing novel drugs. Despite these setbacks, these therapies were generally well-tolerated, suggesting that EMT-targeted strate-

Table 1. Summary of clinical trials exploring epithelial-mesenchymal transition targeted therapy

NCT Number	Year	Drug	Target	Phase	Design	Status	Outcome of Interest	Findings
NCT00992186	2012	Carlumab	CCL2	Phase 2	Single-arm	Completed	Progression-free survival of patients with CRPC who were previously treated with Docetaxel	Carlumab was well tolerated, but did not show antitumor activity as a monotherapy against CRPC
NCT00433446	2013	Siltuximab	Interleukin 6	Phase 2	Single-arm	Completed	Progression-free survival after receiving Siltuximab in patients with CRPC who received prior taxane therapy	Siltuximab resulted in 3.8% PSA response rate, and 23% of patients had stable disease as per the RECIST criteria. Baseline elevated IL6 was associated with poorer prognosis
NCT00385827	2014	Siltuximab	Interleukin 6	Phase 2	Two-arm nonrandomized	Terminated	Progression-free survival after receiving Siltuximab + mitoxantrone/prednisone versus mitoxantrone/prednisone alone	Though Siltuximab was well tolerated, there was no improvement in progression-free survival and so the study was terminated
NCT00401765	2014	Siltuximab	Interleukin 6	Phase 1	Single-arm	Completed	Safety and efficacy of using Siltuximab in combination with Docetaxel in patients with CRPC	No results posted
NCT00487786	2016	Apatorsen	Heat Shock Protein 27 inhibitor	Phase 1	Single-arm	Completed	Safety and Efficacy of Apatorsen monotherapy in patients with CRPC, breast, ovary, lung, or bladder cancer	Apatorsen was well tolerated and can be safely administered
NCT01120470	2019	Apatorsen	Heat Shock Protein 27 inhibitor	Phase 2	Two-arm	Completed	Progression-free survival of apatorsen with prednisone compared to prednisone alone in chemo-naïve patients	The addition of apatorsen did not increase progression-free survival when compared to prednisone alone
NCT01681433	2022	Apatorsen	Heat Shock Protein 27 inhibitor	Phase 2	Two-arm	Terminated	Progression-free survival of patients receiving Abiraterone and prednisone with apatorsen compared to abiraterone and prednisone alone	Study terminated due to lack of accrual
NCT01270880	2018	Ganetespib	Heat Shock Protein 90 inhibitor	Phase 1	Single-arm	Completed	Six-month progression-free survival after Ganetespib in men with CRPC who received prior docetaxel therapy	As a single therapy, Ganetespib did not prolong progression free survival. All patients had disease progression by 6 months
NCT01685268	2019	Onalespib	Heat Shock Protein 90 inhibitor	Phase 1 and 2	Two-arm stratified by regimens	Completed	Tolerability and antitumor activity of onalespib in combination with abiraterone/prednisone	Onalespib with abiraterone/prednisone showed mild evidence of biological effect, but no clinical effect
NCT02065323	2015	Dovitinib	Receptor Tyrosine Kinase inhibition	Phase 2	Two-arm	Withdrawn	Progression-free survival in patients with mCRPC after Dovitinib therapy with ADT in comparison to ADT alone	Terminated due to budgetary considerations and length of development
NCT01741116	2018	Dovitinib	Receptor Tyrosine Kinase inhibition	Phase 2	Single-arm	Completed	Progression-free survival in patients with mCRPC after 16 weeks of Dovitinib therapy	Dovitinib showed modest anti-tumor activity with manageable toxicity. Patients who were chemo-naïve benefitted more
NCT01994590	2019	Dovitinib	Receptor Tyrosine Kinase inhibition	Phase 2	Single-arm	Terminated	Progression-free survival in patients with mCRPC after Dovitinib therapy in combination with Abiraterone	Study terminated as sponsor stopped supplying the drug
NCT00744497	2016	Dasatinib	Tyrosine kinase inhibitor	Phase 3	RCT	Completed	Overall survival after Docetaxel + Dasatinib in comparison to Placebo	The addition of dasatinib did not increase overall survival
NCT03761225	2021	Masitinib	Tyrosine kinase inhibitor	Phase 3	RCT	Completed	Progression-free survival after Docetaxel + Masitinib in comparison to Docetaxel + Placebo	No results posted
NCT01990196	2023	Degarelix, Enzalutamide, Trametinib, Dasatinib	Src and/or MEK inhibition of tyrosine kinase	Phase 2	Two-arm nonrandomized	Active, not recruiting	Change in molecular signature after AR inhibition with and without SRC and/or MEK inhibition	No results posted

NCT00887640	2014	Temsirolimus	mTOR, VEGF	Phase 2	Single-arm	Terminated	Impact of Temsirolimus on CTC count at 8 weeks	Study terminated
NCT03480646	2021	CPI-1205	EZH2 inhibitor	Phase 1 and 2	Two-arm	Unknown	To assess safety and efficacy of CPI-1205, and to assess its antitumor activity in combination with enzalutamide or abiraterone/prednisone	Unknown
NCT03460977	2024	Mevrometostat	EZH2 inhibitor	Phase 1 and 2	Single-arm	Recruiting, preliminary findings posted	Safety and efficacy of Mevrometostat in combination with enzalutamide + ADT	Mevremostat + enzalutamide shows promising activity in combination with ADT with manageable adverse effect profile
NCT04179864	2024	Tazemetostat	EZH2 inhibitor	Phase 1 and 2	Single-arm	Active, not recruiting	Safety and efficacy of Tazemetostat in combination with Enzalutamide or Abiraterone/Prednisone	No results posted
NCT05413421	2023	ORIC-944	Polycomb receptor complex 2 inhibitor	Phase 1	Single-arm	Recruiting	Safety and preliminary antitumor activity of ORIC-944 in patients with mCRPC	No results posted
NCT02204943	2018	Radium-223	Osteoblastic plasticity of CRPC	Phase 2	Single-arm	Completed	Impact of Radium-223 on CTC B-ALP levels	CTC B-ALP expression was decreased in 31% of men
NCT02452008	2024	Galunisertib	TGF-β Receptor Inhibitor	Phase 2	RCT	Active, not recruiting	Progression-free survival after enzalutamide + Galunisertib compared to enzalutamide alone	No results posted

gies could be safely integrated into mCRPC treatment regimens. Future clinical trials should focus on combining drugs that target convergent EMT pathways to enhance efficacy while maintaining cost-effectiveness. Moreover, given the role of TGF-β receptor activity and long non-coding RNAs in regulating cancer cell apoptosis, future studies could prioritize apoptosis as a primary endpoint to better evaluate therapeutic effectiveness [104, 159-162]. Future clinical trials exploring the combination of drugs blocking convergent EMT pathways, which are cost-effective, and can demonstrate the efficacy of mono- or combination therapies may provide mCRPC patients with an alternate and safe form of therapy, thereby blocking progression to advanced disease and improving survival.

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Disclosure of conflict of interest

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Abbreviations

ADT, Androgen deprivation therapy; AR, Androgen receptor; ARPIs, Androgen receptor pathway inhibitors; CAFs, Cancer associated fibroblasts; CRPC, Castration resistant prostate cancer; CTCs, Circulating tumor cells; ECM, Extracellular matrix; EMT, Epithelial-mesenchymal transition; ESRP, Epithelial splicing receptor protein; LHRH, Leuteinising hormone-releasing hormone; mCRPC, Metastatic castration resistant prostate cancer; MET, Mesenchymal-epithelial transition; NED, Neuroendocrine differentiation; NEPC, Neuroendocrine prostate cancer; PCa, Prostate cancer; PDX, Patient derived xenograft; PIN, Prostatic intraepithelial neoplasia; PSA, Prostate specific antigen; RTKs, Receptor tyrosine kinases; STAT, Signal Transducer and Activator of Transcription; TFs, Transcription factors; TK, Tyrosine kinase; TME, Tumor microenvironment; T-NEPC, Treatment induced neuroendocrine prostate cancer.

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References

[1] Siegel RL, Giaquinto AN and Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024; 74: 12-49.

[2] Frisch SM and Screaton RA. Anoikis mechanisms. Curr Opin Cell Biol 2001; 13: 555-62.

[3] Rennebeck G, Martelli M and Kyprianou N. Anoikis and survival connections in the tumor microenvironment: is there a role in prostate cancer metastasis? Cancer Res 2005; 65: 11230-5.

[4] Thiery JP, Acloque H, Huang RY and Nieto MA. Epithelial-mesenchymal transitions in development and disease. Cell 2009; 139: 871-90.

[5] Kalluri R and Weinberg RA. The basics of epithelial-mesenchymal transition. J Clin Invest 2009; 119: 1420-8.

[6] Kyprianou N. ASK-ing EMT not to spread cancer. Proc Natl Acad Sci U S A 2010; 107: 2731-2.

[7] Singh A and Settleman J. EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer. Oncogene 2010; 29: 4741-51.

[8] Kong D, Banerjee S, Ahmad A, Li Y, Wang Z, Sethi S and Sarkar FH. Epithelial to mesenchymal transition is mechanistically linked with stem cell signatures in prostate cancer cells. PLoS One 2010; 5: e12445.

[9] Knudsen KE and Scher HI. Starving the addiction: new opportunities for durable suppression of AR signaling in prostate cancer. Clin Cancer Res 2009; 15: 4792-8.

[10] Akamatsu S, Inoue T, Ogawa O and Gleave ME. Clinical and molecular features of treatment-related neuroendocrine prostate cancer. Int J Urol 2018; 25: 345-51.

[11] Grant CM and Kyprianou N. Epithelial mesenchymal transition (EMT) in prostate growth and tumor progression. Transl Androl Urol 2013; 2: 202-11.

[12] Davies AH, Beltran H and Zoubeidi A. Cellular plasticity and the neuroendocrine phenotype in prostate cancer. Nat Rev Urol 2018; 15: 271-86.

[13] Beltran H, Hruszkewycz A, Scher HI, Hildesheim J, Isaacs J, Yu EY, Kelly K, Lin D, Dicker A, Arnold J, Hecht T, Wicha M, Sears R, Rowley D, White R, Gulley JL, Lee J, Diaz Meco M, Small EJ, Shen M, Knudsen K, Goodrich DW, Lotan T, Zoubeidi A, Sawyers CL, Rudin CM, Loda M, Thompson T, Rubin MA, Tawab-Amiri A, Dahut W and Nelson PS. The role of lineage plasticity

in prostate cancer therapy resistance. Clin Cancer Res 2019; 25: 6916-24.
[14] Epstein JI, Amin MB, Beltran H, Lotan TL, Mosquera JM, Reuter VE, Robinson BD, Troncoso P and Rubin MA. Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. Am J Surg Pathol 2014; 38: 756-67.
[15] Beltran H, Rickman DS, Park K, Chae SS, Sboner A, MacDonald TY, Wang Y, Sheikh KL, Terry S, Tagawa ST, Dhir R, Nelson JB, de la Taille A, Allory Y, Gerstein MB, Perner S, Pienta KJ, Chinnaiyan AM, Wang Y, Collins CC, Gleave ME, Demichelis F, Nanus DM and Rubin MA. Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. Cancer Discov 2011; 1: 487-95.
[16] Huggins C and Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin 1972; 22: 232-40.
[17] Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L and de Bono JS; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367: 1187-97.
[18] de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB Jr, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Fléchon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM and Scher HI; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011; 364: 1995-2005.
[19] Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, Wongvipat J, Smith-Jones PM, Yoo D, Kwon A, Wasielewska T, Welsbie D, Chen CD, Higano CS, Beer TM, Hung DT, Scher HI, Jung ME and Sawyers CL. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009; 324: 787-90.
[20] Davies A, Nouruzi S, Ganguli D, Namekawa T, Thaper D, Linder S, Karaoğlanoğlu F, Omur ME, Kim S, Kobelev M, Kumar S, Sivak O, Bostock C, Bishop J, Hoogstraat M, Talal A, Stelloo S, van der Poel H, Bergman AM, Ahmed M, Fazli L, Huang H, Tilley W, Goodrich D, Feng FY, Gleave M, He HH, Hach F, Zwart W, Beltran H, Selth L and Zoubeidi A. An androgen receptor switch underlies lineage infidelity in treatment-resistant prostate cancer. Nat Cell Biol 2021; 23: 1023-34.
[21] Ku SY, Rosario S, Wang Y, Mu P, Seshadri M, Goodrich ZW, Goodrich MM, Labbé DP, Gomez EC, Wang J, Long HW, Xu B, Brown M, Loda M, Sawyers CL, Ellis L and Goodrich DW. Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance. Science 2017; 355: 78-83.
[22] Mu P, Zhang Z, Benelli M, Karthaus WR, Hoover E, Chen CC, Wongvipat J, Ku SY, Gao D, Cao Z, Shah N, Adams EJ, Abida W, Watson PA, Prandi D, Huang CH, de Stanchina E, Lowe SW, Ellis L, Beltran H, Rubin MA, Goodrich DW, Demichelis F and Sawyers CL. SOX2 promotes lineage plasticity and antiandrogen resistance in TP53- and RB1-deficient prostate cancer. Science 2017; 355: 84-8.
[23] Dicken H, Hensley PJ and Kyprianou N. Prostate tumor neuroendocrine differentiation via EMT: the road less traveled. Asian J Urol 2019; 6: 82-90.
[24] Broster SA and Kyprianou N. Epithelial-mesenchymal transition in prostatic disease. Future Oncol 2015; 11: 3197-206.
[25] Eger A, Aigner K, Sonderegger S, Dampier B, Oehler S, Schreiber M, Berx G, Cano A, Beug H and Foisner R. DeltaEF1 is a transcriptional repressor of E-cadherin and regulates epithelial plasticity in breast cancer cells. Oncogene 2005; 24: 2375-85.
[26] Farfán N, Ocarez N, Castellón EA, Mejía N, de Herreros AG and Contreras HR. The transcriptional factor ZEB1 represses Syndecan 1 expression in prostate cancer. Sci Rep 2018; 8: 11467.
[27] Perez-Oquendo M and Gibbons DL. Regulation of ZEB1 function and molecular associations in tumor progression and metastasis. Cancers (Basel) 2022; 14: 1864.
[28] Aigner K, Dampier B, Descovich L, Mikula M, Sultan A, Schreiber M, Mikulits W, Brabletz T, Strand D, Obrist P, Sommergruber W, Schweifer N, Wernitznig A, Beug H, Foisner R and Eger A. The transcription factor ZEB1 (deltaEF1) promotes tumour cell dedifferentiation by repressing master regulators of epithelial polarity. Oncogene 2007; 26: 6979-88.
[29] Gheldof A, Hulpiau P, van Roy F, De Craene B and Berx G. Evolutionary functional analysis and molecular regulation of the ZEB transcription factors. Cell Mol Life Sci 2012; 69: 2527-41.
[30] Paller C, Pu H, Begemann DE, Wade CA, Hensley PJ and Kyprianou N. TGF-β receptor I inhibitor enhances response to enzalutamide in a pre-clinical model of advanced prostate cancer. Prostate 2019; 79: 31-43.
[31] Pu H, Begemann DE and Kyprianou N. Aberrant TGF-β signaling drives castration-resistant prostate cancer in a male mouse model of

prostate tumorigenesis. Endocrinology 2017; 158: 1612-22.
[32] Stylianou N, Lehman ML, Wang C, Fard AT, Rockstroh A, Fazli L, Jovanovic L, Ward M, Sadowski MC, Kashyap AS, Buttyan R, Gleave ME, Westbrook TF, Williams ED, Gunter JH, Nelson CC and Hollier BG. A molecular portrait of epithelial-mesenchymal plasticity in prostate cancer associated with clinical outcome. Oncogene 2019; 38: 913-34.
[33] Smith BN and Odero-Marah VA. The role of Snail in prostate cancer. Cell Adh Migr 2012; 6: 433-41.
[34] Olmeda D, Moreno-Bueno G, Flores JM, Fabra A, Portillo F and Cano A. SNAI1 is required for tumor growth and lymph node metastasis of human breast carcinoma MDA-MB-231 cells. Cancer Res 2007; 67: 11721-31.
[35] Jin H, Yu Y, Zhang T, Zhou X, Zhou J, Jia L, Wu Y, Zhou BP and Feng Y. Snail is critical for tumor growth and metastasis of ovarian carcinoma. Int J Cancer 2010; 126: 2102-11.
[36] Min AL, Choi JY, Woo HY, Kim JD, Kwon JH, Bae SH, Yoon SK, Shin SH, Chung YJ and Jung CK. High expression of Snail mRNA in blood from hepatocellular carcinoma patients with extrahepatic metastasis. Clin Exp Metastasis 2009; 26: 759-67.
[37] Kudo-Saito C, Shirako H, Takeuchi T and Kawakami Y. Cancer metastasis is accelerated through immunosuppression during Snail-induced EMT of cancer cells. Cancer Cell 2009; 15: 195-206.
[38] Vesuna F, van Diest P, Chen JH and Raman V. Twist is a transcriptional repressor of E-cadherin gene expression in breast cancer. Biochem Biophys Res Commun 2008; 367: 235-41.
[39] Deng G, Chen Y, Guo C, Yin L, Han Y, Li Y, Fu Y, Cai C, Shen H and Zeng S. BMP4 promotes the metastasis of gastric cancer by inducing epithelial-mesenchymal transition via ID1. J Cell Sci 2020; 133: jcs237222.
[40] Pang MF, Georgoudaki AM, Lambut L, Johansson J, Tabor V, Hagikura K, Jin Y, Jansson M, Alexander JS, Nelson CM, Jakobsson L, Betsholtz C, Sund M, Karlsson MC and Fuxe J. TGF-β1-induced EMT promotes targeted migration of breast cancer cells through the lymphatic system by the activation of CCR7/CCL21-mediated chemotaxis. Oncogene 2016; 35: 748-60.
[41] Gogola S, Rejzer M, Bahmad HF, Abou-Kheir W, Omarzai Y and Poppiti R. Epithelial-to-mesenchymal transition-related markers in prostate cancer: from bench to bedside. Cancers (Basel) 2023; 15: 2309.
[42] Guo Y and Kyprianou N. Overexpression of transforming growth factor (TGF) beta1 type II receptor restores TGF-beta1 sensitivity and signaling in human prostate cancer cells. Cell Growth Differ 1998; 9: 185-93.
[43] Huang F and Chen YG. Regulation of TGF-β receptor activity. Cell Biosci 2012; 2: 9.
[44] Du Z and Lovly CM. Mechanisms of receptor tyrosine kinase activation in cancer. Mol Cancer 2018; 17: 58.
[45] Graham TR, Zhau HE, Odero-Marah VA, Osunkoya AO, Kimbro KS, Tighiouart M, Liu T, Simons JW and O'Regan RM. Insulin-like growth factor-I-dependent up-regulation of ZEB1 drives epithelial-to-mesenchymal transition in human prostate cancer cells. Cancer Res 2008; 68: 2479-88.
[46] Yang X, Chrisman H and Weijer CJ. PDGF signalling controls the migration of mesoderm cells during chick gastrulation by regulating N-cadherin expression. Development 2008; 135: 3521-30.
[47] Drake JM, Graham NA, Stoyanova T, Sedghi A, Goldstein AS, Cai H, Smith DA, Zhang H, Komisopoulou E, Huang J, Graeber TG and Witte ON. Oncogene-specific activation of tyrosine kinase networks during prostate cancer progression. Proc Natl Acad Sci U S A 2012; 109: 1643-8.
[48] Tatarov O, Mitchell TJ, Seywright M, Leung HY, Brunton VG and Edwards J. SRC family kinase activity is up-regulated in hormone-refractory prostate cancer. Clin Cancer Res 2009; 15: 3540-9.
[49] Bluemn EG, Coleman IM, Lucas JM, Coleman RT, Hernandez-Lopez S, Tharakan R, Bianchi-Frias D, Dumpit RF, Kaipainen A, Corella AN, Yang YC, Nyquist MD, Mostaghel E, Hsieh AC, Zhang X, Corey E, Brown LG, Nguyen HM, Pienta K, Ittmann M, Schweizer M, True LD, Wise D, Rennie PS, Vessella RL, Morrissey C and Nelson PS. Androgen receptor pathway-independent prostate cancer is sustained through FGF signaling. Cancer Cell 2017; 32: 474-89.e6.
[50] Giannoni E, Bianchini F, Masieri L, Serni S, Torre E, Calorini L and Chiarugi P. Reciprocal activation of prostate cancer cells and cancer-associated fibroblasts stimulates epithelial-mesenchymal transition and cancer stemness. Cancer Res 2010; 70: 6945-56.
[51] Patel S, Alam A, Pant R and Chattopadhyay S. Wnt signaling and its significance within the tumor microenvironment: novel therapeutic insights. Front Immunol 2019; 10: 2872.
[52] Kim K, Lu Z and Hay ED. Direct evidence for a role of beta-catenin/LEF-1 signaling pathway in induction of EMT. Cell Biol Int 2002; 26: 463-76.
[53] Zucchini-Pascal N, Peyre L and Rahmani R. Crosstalk between beta-catenin and snail in

the induction of epithelial to mesenchymal transition in hepatocarcinoma: role of the ERK1/2 pathway. Int J Mol Sci 2013; 14: 20768-92.
[54] Wu ZQ, Li XY, Hu CY, Ford M, Kleer CG and Weiss SJ. Canonical Wnt signaling regulates Slug activity and links epithelial-mesenchymal transition with epigenetic Breast Cancer 1, Early Onset (BRCA1) repression. Proc Natl Acad Sci U S A 2012; 109: 16654-9.
[55] Fendrich V, Waldmann J, Esni F, Ramaswamy A, Mullendore M, Buchholz M, Maitra A and Feldmann G. Snail and Sonic Hedgehog activation in neuroendocrine tumors of the ileum. Endocr Relat Cancer 2007; 14: 865-74.
[56] Li X, Deng W, Nail CD, Bailey SK, Kraus MH, Ruppert JM and Lobo-Ruppert SM. Snail induction is an early response to Gli1 that determines the efficiency of epithelial transformation. Oncogene 2006; 25: 609-21.
[57] Jing J, Wu Z, Wang J, Luo G, Lin H, Fan Y and Zhou C. Hedgehog signaling in tissue homeostasis, cancers, and targeted therapies. Signal Transduct Target Ther 2023; 8: 315.
[58] Nolan KD, Franco OE, Hance MW, Hayward SW and Isaacs JS. Tumor-secreted Hsp90 subverts polycomb function to drive prostate tumor growth and invasion. J Biol Chem 2015; 290: 8271-82.
[59] Mani SA, Guo W, Liao MJ, Eaton EN, Ayyanan A, Zhou AY, Brooks M, Reinhard F, Zhang CC, Shipitsin M, Campbell LL, Polyak K, Brisken C, Yang J and Weinberg RA. The epithelial-mesenchymal transition generates cells with properties of stem cells. Cell 2008; 133: 704-15.
[60] Harris TJ and Tepass U. Adherens junctions: from molecules to morphogenesis. Nat Rev Mol Cell Biol 2010; 11: 502-14.
[61] Brabletz T, Kalluri R, Nieto MA and Weinberg RA. EMT in cancer. Nat Rev Cancer 2018; 18: 128-34.
[62] Saitoh M. Transcriptional regulation of EMT transcription factors in cancer. Semin Cancer Biol 2023; 97: 21-9.
[63] Yu X, He T, Tong Z, Liao L, Huang S, Fakhouri WD, Edwards DP and Xu J. Molecular mechanisms of TWIST1-regulated transcription in EMT and cancer metastasis. EMBO Rep 2023; 24: e56902.
[64] Meng J, Chen S, Han JX, Qian B, Wang XR, Zhong WL, Qin Y, Zhang H, Gao WF, Lei YY, Yang W, Yang L, Zhang C, Liu HJ, Liu YR, Zhou HG, Sun T and Yang C. Twist1 regulates vimentin through Cul2 circular RNA to promote EMT in hepatocellular carcinoma. Cancer Res 2018; 78: 4150-62.
[65] Zhu GH, Huang C, Feng ZZ, Lv XH and Qiu ZJ. Hypoxia-induced snail expression through transcriptional regulation by HIF-1α in pancreatic cancer cells. Dig Dis Sci 2013; 58: 3503-15.
[66] Bery F, Figiel S, Kouba S, Fontaine D, Guéguinou M, Potier-Cartereau M, Vandier C, Guibon R, Bruyère F, Fromont G and Mahéo K. Hypoxia promotes prostate cancer aggressiveness by upregulating EMT-Activator Zeb1 and SK3 channel expression. Int J Mol Sci 2020; 21: 4786.
[67] Derynck R and Akhurst RJ. Differentiation plasticity regulated by TGF-beta family proteins in development and disease. Nat Cell Biol 2007; 9: 1000-4.
[68] Nakazawa M and Kyprianou N. Epithelial-mesenchymal-transition regulators in prostate cancer: androgens and beyond. J Steroid Biochem Mol Biol 2017; 166: 84-90.
[69] Kim IY, Ahn HJ, Lang S, Oefelein MG, Oyasu R, Kozlowski JM and Lee C. Loss of expression of transforming growth factor-β receptors is associated with poor prognosis in prostate cancer patients. Clin Cancer Res 1998; 4: 1625-30.
[70] Hao Y, Bjerke GA, Pietrzak K, Melhuish TA, Han Y, Turner SD, Frierson HF Jr and Wotton D. TGFβ signaling limits lineage plasticity in prostate cancer. PLoS Genet 2018; 14: e1007409.
[71] Wang K, Pascal LE, Li F, Chen W, Dhir R, Balasubramani GK, DeFranco DB, Yoshimura N, He D and Wang Z. Tight junction protein claudin-1 is downregulated by TGF-β1 via MEK signaling in benign prostatic epithelial cells. Prostate 2020; 80: 1203-15.
[72] Lamouille S and Derynck R. Cell size and invasion in TGF-beta-induced epithelial to mesenchymal transition is regulated by activation of the mTOR pathway. J Cell Biol 2007; 178: 437-51.
[73] Zhang YE. Non-Smad pathways in TGF-beta signaling. Cell Res 2009; 19: 128-39.
[74] Hamidi A, Song J, Thakur N, Itoh S, Marcusson A, Bergh A, Heldin CH and Landström M. TGF-β promotes PI3K-AKT signaling and prostate cancer cell migration through the TRAF6-mediated ubiquitylation of p85α. Sci Signal 2017; 10: eaal4186.
[75] Sahadevan K, Darby S, Leung HY, Mathers ME, Robson CN and Gnanapragasam VJ. Selective over-expression of fibroblast growth factor receptors 1 and 4 in clinical prostate cancer. J Pathol 2007; 213: 82-90.
[76] Acevedo VD, Gangula RD, Freeman KW, Li R, Zhang Y, Wang F, Ayala GE, Peterson LE, Ittmann M and Spencer DM. Inducible FGFR-1 activation leads to irreversible prostate adenocarcinoma and an epithelial-to-mesenchymal transition. Cancer Cell 2007; 12: 559-71.
[77] Yang F, Zhang Y, Ressler SJ, Ittmann MM, Ayala GE, Dang TD, Wang F and Rowley DR. FGFR1 is essential for prostate cancer progression and metastasis. Cancer Res 2013; 73: 3716-24.
[78] Carstens JL, Shahi P, Van Tsang S, Smith B, Creighton CJ, Zhang Y, Seamans A, Seetham-

magari M, Vedula I, Levitt JM, Ittmann MM, Rowley DR and Spencer DM. FGFR1-WNT-TGF-β signaling in prostate cancer mouse models recapitulates human reactive stroma. Cancer Res 2014; 74: 609-20.

[79] Labanca E, Yang J, Shepherd PDA, Wan X, Starbuck MW, Guerra LD, Anselmino N, Bizzotto JA, Dong J, Chinnaiyan AM, Ravoori MK, Kundra V, Broom BM, Corn PG, Troncoso P, Gueron G, Logothethis CJ and Navone NM. Fibroblast growth factor receptor 1 drives the metastatic progression of prostate cancer. Eur Urol Oncol 2022; 5: 164-75.

[80] Cheng C, Wang J, Xu P, Zhang K, Xin Z, Zhao H, Ji Z, Zhang M, Wang D, He Y, Jing N, Fan L, Liu K, Li F, Liu C, Gong Y, Cui S, Sun Z, Sun D, Yao X, Li H, Zhang J, Zhang P, Dong B, Xue W, Qian X, Gao WQ and Zhu HH. Gremlin1 is a therapeutically targetable FGFR1 ligand that regulates lineage plasticity and castration resistance in prostate cancer. Nat Cancer 2022; 3: 565-80.

[81] Chan JM, Zaidi S, Love JR, Zhao JL, Setty M, Wadosky KM, Gopalan A, Choo ZN, Persad S, Choi J, LaClair J, Lawrence KE, Chaudhary O, Xu T, Masilionis I, Linkov I, Wang S, Lee C, Barlas A, Morris MJ, Mazutis L, Chaligne R, Chen Y, Goodrich DW, Karthaus WR, Pe'er D and Sawyers CL. Lineage plasticity in prostate cancer depends on JAK/STAT inflammatory signaling. Science 2022; 377: 1180-91.

[82] Liu ZC, Chen XH, Song HX, Wang HS, Zhang G, Wang H, Chen DY, Fang R, Liu H, Cai SH and Du J. Snail regulated by PKC/GSK-3β pathway is crucial for EGF-induced epithelial-mesenchymal transition (EMT) of cancer cells. Cell Tissue Res 2014; 358: 491-502.

[83] Cho KH, Choi MJ, Jeong KJ, Kim JJ, Hwang MH, Shin SC, Park CG and Lee HY. A ROS/STAT3/HIF-1α signaling cascade mediates EGF-induced TWIST1 expression and prostate cancer cell invasion. Prostate 2014; 74: 528-36.

[84] Grünert S, Jechlinger M and Beug H. Diverse cellular and molecular mechanisms contribute to epithelial plasticity and metastasis. Nat Rev Mol Cell Biol 2003; 4: 657-65.

[85] Mora LB, Buettner R, Seigne J, Diaz J, Ahmad N, Garcia R, Bowman T, Falcone R, Fairclough R, Cantor A, Muro-Cacho C, Livingston S, Karras J, Pow-Sang J and Jove R. Constitutive activation of Stat3 in human prostate tumors and cell lines: direct inhibition of Stat3 signaling induces apoptosis of prostate cancer cells. Cancer Res 2002; 62: 6659-66.

[86] Don-Doncow N, Marginean F, Coleman I, Nelson PS, Ehrnström R, Krzyzanowska A, Morrissey C, Hellsten R and Bjartell A. Expression of STAT3 in prostate cancer metastases. Eur Urol 2017; 71: 313-6.

[87] Cho KH, Jeong KJ, Shin SC, Kang J, Park CG and Lee HY. STAT3 mediates TGF-β1-induced TWIST1 expression and prostate cancer invasion. Cancer Lett 2013; 336: 167-73.

[88] Shiota M, Bishop JL, Nip KM, Zardan A, Takeuchi A, Cordonnier T, Beraldi E, Bazov J, Fazli L, Chi K, Gleave M and Zoubeidi A. Hsp27 regulates epithelial mesenchymal transition, metastasis, and circulating tumor cells in prostate cancer. Cancer Res 2013; 73: 3109-19.

[89] Gujral TS, Chan M, Peshkin L, Sorger PK, Kirschner MW and MacBeath G. A noncanonical Frizzled2 pathway regulates epithelial-mesenchymal transition and metastasis. Cell 2014; 159: 844-56.

[90] Sandsmark E, Hansen AF, Selnæs KM, Bertilsson H, Bofin AM, Wright AJ, Viset T, Richardsen E, Drabløs F, Bathen TF, Tessem MB and Rye MB. A novel non-canonical Wnt signature for prostate cancer aggressiveness. Oncotarget 2017; 8: 9572-86.

[91] Nath D, Li X, Mondragon C, Post D, Chen M, White JR, Hryniewicz-Jankowska A, Caza T, Kuznetsov VA, Hehnly H, Jamaspishvili T, Berman DM, Zhang F, Kung SHY, Fazli L, Gleave ME, Bratslavsky G, Pandolfi PP and Kotula L. Abi1 loss drives prostate tumorigenesis through activation of EMT and non-canonical WNT signaling. Cell Commun Signal 2019; 17: 120.

[92] Deng S, Wang C, Wang Y, Xu Y, Li X, Johnson NA, Mukherji A, Lo UG, Xu L, Gonzalez J, Metang LA, Ye J, Tirado CR, Rodarte K, Zhou Y, Xie Z, Arana C, Annamalai V, Liu X, Vander Griend DJ, Strand D, Hsieh JT, Li B, Raj G, Wang T and Mu P. Ectopic JAK-STAT activation enables the transition to a stem-like and multilineage state conferring AR-targeted therapy resistance. Nat Cancer 2022; 3: 1071-87.

[93] Canesin G, Maggio V, Palominos M, Stiehm A, Contreras HR, Castellón EA, Morote J, Paciucci R, Maitland NJ, Bjartell A and Hellsten R. STAT3 inhibition with galiellalactone effectively targets the prostate cancer stem-like cell population. Sci Rep 2020; 10: 13958.

[94] Pradella D, Naro C, Sette C and Ghigna C. EMT and stemness: flexible processes tuned by alternative splicing in development and cancer progression. Mol Cancer 2017; 16: 8.

[95] Roy Burman D, Das S, Das C and Bhattacharya R. Alternative splicing modulates cancer aggressiveness: role in EMT/metastasis and chemoresistance. Mol Biol Rep 2021; 48: 897-914.

[96] Venables JP, Brosseau JP, Gadea G, Klinck R, Prinos P, Beaulieu JF, Lapointe E, Durand M, Thibault P, Tremblay K, Rousset F, Tazi J, Abou Elela S and Chabot B. RBFOX2 is an important regulator of mesenchymal tissue-specific splic-

ing in both normal and cancer tissues. Mol Cell Biol 2013; 33: 396-405.
[97] Kwabi-Addo B, Ropiquet F, Giri D and Ittmann M. Alternative splicing of fibroblast growth factor receptors in human prostate cancer. Prostate 2001; 46: 163-72.
[98] Fagoonee S, Bearzi C, Di Cunto F, Clohessy JG, Rizzi R, Reschke M, Tolosano E, Provero P, Pandolfi PP, Silengo L and Altruda F. The RNA binding protein ESRP1 fine-tunes the expression of pluripotency-related factors in mouse embryonic stem cells. PLoS One 2013; 8: e72300.
[99] Li Y, Donmez N, Sahinalp C, Xie N, Wang Y, Xue H, Mo F, Beltran H, Gleave M, Wang Y, Collins C and Dong X. SRRM4 drives neuroendocrine transdifferentiation of prostate adenocarcinoma under androgen receptor pathway inhibition. Eur Urol 2017; 71: 68-78.
[100] Li Y, Zhang Q, Lovnicki J, Chen R, Fazli L, Wang Y, Gleave M, Huang J and Dong X. SRRM4 gene expression correlates with neuroendocrine prostate cancer. Prostate 2019; 79: 96-104.
[101] Chang YT, Lin TP, Campbell M, Pan CC, Lee SH, Lee HC, Yang MH, Kung HJ and Chang PC. REST is a crucial regulator for acquiring EMT-like and stemness phenotypes in hormone-refractory prostate cancer. Sci Rep 2017; 7: 42795.
[102] Dongre A and Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. Nat Rev Mol Cell Biol 2019; 20: 69-84.
[103] Tu WH, Thomas TZ, Masumori N, Bhowmick NA, Gorska AE, Shyr Y, Kasper S, Case T, Roberts RL, Shappell SB, Moses HL and Matusik RJ. The loss of TGF-beta signaling promotes prostate cancer metastasis. Neoplasia 2003; 5: 267-77.
[104] Pu H, Collazo J, Jones E, Gayheart D, Sakamoto S, Vogt A, Mitchell B and Kyprianou N. Dysfunctional transforming growth factor-beta receptor II accelerates prostate tumorigenesis in the TRAMP mouse model. Cancer Res 2009; 69: 7366-74.
[105] Ricciardi M, Zanotto M, Malpeli G, Bassi G, Perbellini O, Chilosi M, Bifari F and Krampera M. Epithelial-to-mesenchymal transition (EMT) induced by inflammatory priming elicits mesenchymal stromal cell-like immune-modulatory properties in cancer cells. Br J Cancer 2015; 112: 1067-75.
[106] Lamouille S, Xu J and Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. Nat Rev Mol Cell Biol 2014; 15: 178-96.
[107] Lopez-Novoa JM and Nieto MA. Inflammation and EMT: an alliance towards organ fibrosis and cancer progression. EMBO Mol Med 2009; 1: 303-14.
[108] Huang Y, Hong W and Wei X. The molecular mechanisms and therapeutic strategies of EMT in tumor progression and metastasis. J Hematol Oncol 2022; 15: 129.
[109] Huang CH, Yang WH, Chang SY, Tai SK, Tzeng CH, Kao JY, Wu KJ and Yang MH. Regulation of membrane-type 4 matrix metalloproteinase by SLUG contributes to hypoxia-mediated metastasis. Neoplasia 2009; 11: 1371-82.
[110] Ota I, Li XY, Hu Y and Weiss SJ. Induction of a MT1-MMP and MT2-MMP-dependent basement membrane transmigration program in cancer cells by Snail1. Proc Natl Acad Sci U S A 2009; 106: 20318-23.
[111] Liao TT and Yang MH. Hybrid epithelial/mesenchymal state in cancer metastasis: clinical significance and regulatory mechanisms. Cells 2020; 9: 623.
[112] Kolijn K, Verhoef EI and van Leenders GJ. Morphological and immunohistochemical identification of epithelial-to-mesenchymal transition in clinical prostate cancer. Oncotarget 2015; 6: 24488-98.
[113] Tsai YC, Chen WY, Abou-Kheir W, Zeng T, Yin JJ, Bahmad H, Lee YC and Liu YN. Androgen deprivation therapy-induced epithelial-mesenchymal transition of prostate cancer through downregulating SPDEF and activating CCL2. Biochim Biophys Acta Mol Basis Dis 2018; 1864: 1717-27.
[114] Izumi K, Fang LY, Mizokami A, Namiki M, Li L, Lin WJ and Chang C. Targeting the androgen receptor with siRNA promotes prostate cancer metastasis through enhanced macrophage recruitment via CCL2/CCR2-induced STAT3 activation. EMBO Mol Med 2013; 5: 1383-401.
[115] Marcolino E, Siddiqui YH, van den Bosch M, Poole AW, Jayaraman PS and Gaston K. Blood platelets stimulate cancer extravasation through TGFβ-mediated downregulation of PRH/HHEX. Oncogenesis 2020; 9: 10.
[116] Tsai JH and Yang J. Epithelial-mesenchymal plasticity in carcinoma metastasis. Genes Dev 2013; 27: 2192-206.
[117] Papanikolaou S, Vourda A, Syggelos S and Gyftopoulos K. Cell plasticity and prostate cancer: the role of epithelial-mesenchymal transition in tumor progression, invasion, metastasis and cancer therapy resistance. Cancers (Basel) 2021; 13: 2795.
[118] Buijs JT, Stayrook KR and Guise TA. The role of TGF-β in bone metastasis: novel therapeutic perspectives. Bonekey Rep 2012; 1: 96.
[119] Anose BM and Sanders MM. Androgen receptor regulates transcription of the ZEB1 transcription factor. Int J Endocrinol 2011; 2011: 903918.
[120] Zhu ML and Kyprianou N. Role of androgens and the androgen receptor in epithelial-mes-

enchymal transition and invasion of prostate cancer cells. FASEB J 2010; 24: 769-77.
[121] Eide T, Ramberg H, Glackin C, Tindall D and Taskén KA. TWIST1, a novel androgen-regulated gene, is a target for NKX3-1 in prostate cancer cells. Cancer Cell Int 2013; 13: 4.
[122] Mooney SM, Parsana P, Hernandez JR, Liu X, Verdone JE, Torga G, Harberg CA and Pienta KJ. The presence of androgen receptor elements regulates ZEB1 expression in the absence of androgen receptor. J Cell Biochem 2015; 116: 115-23.
[123] Shiota M, Yokomizo A, Tada Y, Inokuchi J, Kashiwagi E, Masubuchi D, Eto M, Uchiumi T and Naito S. Castration resistance of prostate cancer cells caused by castration-induced oxidative stress through Twist1 and androgen receptor overexpression. Oncogene 2010; 29: 237-50.
[124] Tanaka H, Kono E, Tran CP, Miyazaki H, Yamashiro J, Shimomura T, Fazli L, Wada R, Huang J, Vessella RL, An J, Horvath S, Gleave M, Rettig MB, Wainberg ZA and Reiter RE. Monoclonal antibody targeting of N-cadherin inhibits prostate cancer growth, metastasis and castration resistance. Nat Med 2010; 16: 1414-20.
[125] Sun Y, Wang BE, Leong KG, Yue P, Li L, Jhunjhunwala S, Chen D, Seo K, Modrusan Z, Gao WQ, Settleman J and Johnson L. Androgen deprivation causes epithelial-mesenchymal transition in the prostate: implications for androgen-deprivation therapy. Cancer Res 2012; 72: 527-36.
[126] Miao L, Yang L, Li R, Rodrigues DN, Crespo M, Hsieh JT, Tilley WD, de Bono J, Selth LA and Raj GV. Disrupting androgen receptor signaling induces snail-mediated epithelial-mesenchymal plasticity in prostate cancer. Cancer Res 2017; 77: 3101-12.
[127] Lin TH, Lee SO, Niu Y, Xu D, Liang L, Li L, Yeh SD, Fujimoto N, Yeh S and Chang C. Differential androgen deprivation therapies with anti-androgens casodex/bicalutamide or MDV3100/Enzalutamide versus anti-androgen receptor ASC-J9(R) Lead to promotion versus suppression of prostate cancer metastasis. J Biol Chem 2013; 288: 19359-69.
[128] Zhifang M, Liang W, Wei Z, Bin H, Rui T, Nan W and Shuhai Z. The androgen receptor plays a suppressive role in epithelial-mesenchymal transition of human prostate cancer stem progenitor cells. BMC Biochem 2015; 16: 13.
[129] Porter BA, Li X, Arya N, Zhang F, Kung SHY, Fazli L, Oo HZ, Li Y, Marincin K, Kukkonen K, Urhonen H, Ortiz MA, Kemraj AP, Corey E, Dong X, Kuznetsov VA, Nykter M, Gleave ME, Bratslavsky G, Urbanucci A, Frueh D, Bah A and Kotula L. ABI1 regulates transcriptional activity of Androgen Receptor by novel DNA and AR binding mechanism. bioRxiv 2023; 2023.05.26.542350.
[130] Munkley J, Li L, Krishnan SRG, Hysenaj G, Scott E, Dalgliesh C, Oo HZ, Maia TM, Cheung K, Ehrmann I, Livermore KE, Zielinska H, Thompson O, Knight B, McCullagh P, McGrath J, Crundwell M, Harries LW, Daugaard M, Cockell S, Barbosa-Morais NL, Oltean S and Elliott DJ. Androgen-regulated transcription of ESRP2 drives alternative splicing patterns in prostate cancer. Elife 2019; 8: e47678.
[131] Tso CL, McBride WH, Sun J, Patel B, Tsui KH, Paik SH, Gitlitz B, Caliliw R, van Ophoven A, Wu L, deKernion J and Belldegrun A. Androgen deprivation induces selective outgrowth of aggressive hormone-refractory prostate cancer clones expressing distinct cellular and molecular properties not present in parental androgen-dependent cancer cells. Cancer J 2000; 6: 220-33.
[132] Singh S, Sadacharan S, Su S, Belldegrun A, Persad S and Singh G. Overexpression of vimentin: role in the invasive phenotype in an androgen-independent model of prostate cancer. Cancer Res 2003; 63: 2306-11.
[133] Xu G, Wu J, Zhou L, Chen B, Sun Z, Zhao F and Tao Z. Characterization of the small RNA transcriptomes of androgen dependent and independent prostate cancer cell line by deep sequencing. PLoS One 2010; 5: e15519.
[134] Li F and Mahato RI. MicroRNAs and drug resistance in prostate cancers. Mol Pharm 2014; 11: 2539-52.
[135] Shiota M, Itsumi M, Takeuchi A, Imada K, Yokomizo A, Kuruma H, Inokuchi J, Tatsugami K, Uchiumi T, Oda Y and Naito S. Crosstalk between epithelial-mesenchymal transition and castration resistance mediated by Twist1/AR signaling in prostate cancer. Endocr Relat Cancer 2015; 22: 889-900.
[136] Jennbacken K, Tesan T, Wang W, Gustavsson H, Damber JE and Welén K. N-cadherin increases after androgen deprivation and is associated with metastasis in prostate cancer. Endocr Relat Cancer 2010; 17: 469-79.
[137] Liu Q, Tong D, Liu G, Xu J, Do K, Geary K, Zhang D, Zhang J, Zhang Y, Li Y, Bi G, Lan W and Jiang J. Metformin reverses prostate cancer resistance to enzalutamide by targeting TGF-β1/STAT3 axis-regulated EMT. Cell Death Dis 2017; 8: e3007.
[138] Marín-Aguilera M, Codony-Servat J, Kalko SG, Fernández PL, Bermudo R, Buxo E, Ribal MJ, Gascón P and Mellado B. Identification of docetaxel resistance genes in castration-resistant prostate cancer. Mol Cancer Ther 2012; 11: 329-39.

[139] Li Y, Zhang B, Xiang L, Xia S, Kucuk O, Deng X, Boise LH and Dong JT. TGF-β causes Docetaxel resistance in Prostate Cancer via the induction of Bcl-2 by acetylated KLF5 and Protein Stabilization. Theranostics 2020; 10: 7656-70.
[140] Martin SK, Pu H, Penticuff JC, Cao Z, Horbinski C and Kyprianou N. Multinucleation and mesenchymal-to-epithelial transition alleviate resistance to combined cabazitaxel and antiandrogen therapy in advanced prostate cancer. Cancer Res 2016; 76: 912-26.
[141] Archer M, Begemann D, Gonzalez-Kozlova E, Nepali PR, Labanca E, Shepherd P, Dogra N, Navone N and Kyprianou N. Kinesin facilitates phenotypic targeting of therapeutic resistance in advanced prostate cancer. Mol Cancer Res 2024; 22: 730-45.
[142] Parimi V, Goyal R, Poropatich K and Yang XJ. Neuroendocrine differentiation of prostate cancer: a review. Am J Clin Exp Urol 2014; 2: 273-85.
[143] Quintanal-Villalonga Á, Chan JM, Yu HA, Pe'er D, Sawyers CL, Sen T and Rudin CM. Lineage plasticity in cancer: a shared pathway of therapeutic resistance. Nat Rev Clin Oncol 2020; 17: 360-71.
[144] Li Q, Zhang CS and Zhang Y. Molecular aspects of prostate cancer with neuroendocrine differentiation. Chin J Cancer Res 2016; 28: 122-9.
[145] Ge R, Wang Z, Montironi R, Jiang Z, Cheng M, Santoni M, Huang K, Massari F, Lu X, Cimadamore A, Lopez-Beltran A and Cheng L. Epigenetic modulations and lineage plasticity in advanced prostate cancer. Ann Oncol 2020; 31: 470-9.
[146] Dudas J, Ladanyi A, Ingruber J, Steinbichler TB and Riechelmann H. Epithelial to mesenchymal transition: a mechanism that fuels cancer radio/chemoresistance. Cells 2020; 9: 428.
[147] Moreno-Bueno G, Portillo F and Cano A. Transcriptional regulation of cell polarity in EMT and cancer. Oncogene 2008; 27: 6958-69.
[148] Martin SK, Banuelos CA, Sadar MD and Kyprianou N. N-terminal targeting of androgen receptor variant enhances response of castration resistant prostate cancer to taxane chemotherapy. Mol Oncol 2014; 9: 628-39.
[149] Begemann D, Wang Y, Yang W and Kyprianou N. Androgens modify therapeutic response to cabazitaxel in models of advanced prostate cancer. Prostate 2020; 80: 926-37.
[150] Carthon BC and Antonarakis ES. The STAMPEDE trial: paradigm-changing data through innovative trial design. Transl Cancer Res 2016; 5 Suppl: S485-S490.
[151] Clarke NW, Ali A, Ingleby FC, Hoyle A, Amos CL, Attard G, Brawley CD, Calvert J, Chowdhury S, Cook A, Cross W, Dearnaley DP, Douis H, Gilbert D, Gillessen S, Jones RJ, Langley RE, MacNair A, Malik Z, Mason MD, Matheson D, Millman R, Parker CC, Ritchie AWS, Rush H, Russell JM, Brown J, Beesley S, Birtle A, Capaldi L, Gale J, Gibbs S, Lydon A, Nikapota A, Omlin A, O'Sullivan JM, Parikh O, Protheroe A, Rudman S, Srihari NN, Simms M, Tanguay JS, Tolan S, Wagstaff J, Wallace J, Wylie J, Zarkar A, Sydes MR, Parmar MKB and James ND. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. Ann Oncol 2019; 30: 1992-2003.
[152] Kwok WK, Ling MT, Lee TW, Lau TC, Zhou C, Zhang X, Chua CW, Chan KW, Chan FL, Glackin C, Wong YC and Wang X. Up-regulation of TWIST in prostate cancer and its implication as a therapeutic target. Cancer Res 2005; 65: 5153-62.
[153] Yarom N, Stewart D, Malik R, Wells J, Avruch L and Jonker DJ. Phase I clinical trial of Exherin (ADH-1) in patients with advanced solid tumors. Curr Clin Pharmacol 2013; 8: 81-8.
[154] Pienta KJ, Machiels JP, Schrijvers D, Alekseev B, Shkolnik M, Crabb SJ, Li S, Seetharam S, Puchalski TA, Takimoto C, Elsayed Y, Dawkins F and de Bono JS. Phase 2 study of carlumab (CNTO 888), a human monoclonal antibody against CC-chemokine ligand 2 (CCL2), in metastatic castration-resistant prostate cancer. Invest New Drugs 2013; 31: 760-8.
[155] Dorff TB, Goldman B, Pinski JK, Mack PC, Lara PN Jr, Van Veldhuizen PJ Jr, Quinn DI, Vogelzang NJ, Thompson IM Jr and Hussain MH. Clinical and correlative results of SWOG S0354: a phase II trial of CNTO328 (siltuximab), a monoclonal antibody against interleukin-6, in chemotherapy-pretreated patients with castration-resistant prostate cancer. Clin Cancer Res 2010; 16: 3028-34.
[156] Chi KN, Yu EY, Jacobs C, Bazov J, Kollmannsberger C, Higano CS, Mukherjee SD, Gleave ME, Stewart PS and Hotte SJ. A phase I dose-escalation study of apatorsen (OGX-427), an antisense inhibitor targeting heat shock protein 27 (Hsp27), in patients with castration-resistant prostate cancer and other advanced cancers. Ann Oncol 2016; 27: 1116-22.
[157] Choi YJ, Kim HS, Park SH, Kim BS, Kim KH, Lee HJ, Song HS, Shin DY, Lee HY, Kim HG, Lee KH, Lee JL and Park KH. Phase II study of dovitinib in patients with castration-resistant prostate cancer (KCSG-GU11-05). Cancer Res Treat 2018; 50: 1252-9.
[158] Araujo JC, Trudel GC, Saad F, Armstrong AJ, Yu EY, Bellmunt J, Wilding G, McCaffrey J, Serrano SV, Matveev VB, Efstathiou E, Oudard S, Morris MJ, Sizer B, Goebell PJ, Heidenreich A, de Bono JS, Begbie S, Hong JH, Richardet E, Gallardo E,

Paliwal P, Durham S, Cheng S and Logothetis CJ. Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): a randomised, double-blind phase 3 trial. Lancet Oncol 2013; 14: 1307-16.

[159] Yuen HF, Chua CW, Chan YP, Wong YC, Wang X and Chan KW. Significance of TWIST and E-cadherin expression in the metastatic progression of prostatic cancer. Histopathology 2007; 50: 648-58.

[160] Wang D, Ding L, Wang L, Zhao Y, Sun Z, Karnes RJ, Zhang J and Huang H. LncRNA MALAT1 enhances oncogenic activities of EZH2 in castration-resistant prostate cancer. Oncotarget 2015; 6: 41045-55.

[161] Huang G, Osmulski PA, Bouamar H, Mahalingam D, Lin CL, Liss MA, Kumar AP, Chen CL, Thompson IM, Sun LZ, Gaczynska ME and Huang TH. TGF-β signal rewiring sustains epithelial-mesenchymal transition of circulating tumor cells in prostate cancer xenograft hosts. Oncotarget 2016; 7: 77124-37.

[162] Guo Y and Kyprianou N. Restoration of transforming growth factor beta signaling pathway in human prostate cancer cells suppresses tumorigenicity via induction of caspase-1-mediated apoptosis. Cancer Res 1999; 59: 1366-71.