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Wnt Signaling and Therapeutic Resistance in Castration-Resistant Prostate Cancer

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Abstract

Purpose of Review—Castration-resistant prostate cancer (CRPC) is a lethal form of prostate cancer (PCa) due to the development of resistance to androgen deprivation therapy and anti-androgens. Here, we review the emerging role of Wnt signaling in therapeutic resistance of CRPC.

Recent Findings—Convincing evidence have accumulated that Wnt signaling is aberrantly activated through genomic alterations and autocrine and paracrine augmentations. Wnt signaling plays a critical role in a subset of CRPC and in resistance to anti-androgen therapies. Wnt signaling navigates CRPC through PCa heterogeneity, neuroendocrine differentiation, DNA repair, PCa stem cell maintenance, epithelial-mesenchymal-transition and metastasis, and immune evasion.

Summary—Components of Wnt signaling can be harnessed for inhibiting PCa growth and metastasis and for developing novel therapeutic strategies to manage metastatic CRPC. There are many Wnt pathway-based potential drugs in different stages of pre-clinical development and clinical trials but so far, no Wnt signaling-specific drug has been approved by FDA for clinical use in CRPC.

Keywords

Prostate; Organoid; CRPC; Wnt signaling; Chemoresistance

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Introduction

According to GLOBOCAN 2020, prostate cancer (PCa) is the second-highest incidence and the sixth-highest in mortality rate in males worldwide [1, 2]. The current treatment protocol uses taxane-based drugs (docetaxel and cabazitaxel), hormonal therapies (abiraterone, apalutamide, and enzalutamide), radium-223 (radioisotope), and Sipuleucel-T (immunotherapy) [3•]. Novel drugs such as Poly-ADP ribose polymerase inhibitors (Olaparib and Rucaparib) and Lutetium-177 PSMA-617 (prostate-specific membrane antigen-617) are introduced for the treatment of a subset of patients with castration-resistant PCa (CRPC) with a deficiency in the DNA repair pathway and overexpression of PSMA, respectively. Despite advancements in PCa research and the improvement in survival, late-stage CRPC remains incurable because of therapeutic resistance [4•].

Aberrant activation in the Wnt signaling pathway plays a critical role in drug resistance, particularly to androgen deprivation therapy (ADT) and anti-androgens (e.g., abiraterone) [5]. Androgen receptor (AR) directly binds to β-catenin, a key Wnt pathway intermediate, and overexpression of AR in complex with β-catenin activates Wnt signaling [6]. RNA-sequencing (RNA-seq) analysis of enzalutamide-resistant cell lines and patient specimens suggest a strong interaction of β-catenin and AR and their involvement in enzalutamide resistance [7]. Whole genome exome-sequencing studies of tumor samples obtained by biopsy or at rapid autopsy revealed genomic aberrations in the Wnt signaling pathway in approximately 20% of CRPC metastases [8]. RNA-Seq of paired pre- and post-ADT biopsy samples and enzalutamide-resistant PCa specimens showed that the Wnt/β-catenin pathway is one of the most significantly altered pathways [9]. PCa patients who are resistant to Abiraterone treatment exhibited enrichment of activating mutations in the Wnt pathway compared to those responding to abiraterone [10]. RNA-Seq analysis of circulating tumor cells has implicated over-activity of non-canonical Wnts and their downstream components RhoA/Rac1/Cdc42 in antiandrogen resistance [11]. Integration of epigenetic and gene expression data to stratify PCa patients has identified a novel subtype of PCa, with low chromatin binding and AR activity, but with high activity of FGF and Wnt signaling and neuroendocrine (NE)-like gene expression [12].

The Subset of PCa with Overactivity of Wnt Signaling

PCa consists of a heterogeneous group of malignancies with distinct molecular footprints but linking the molecular background to clinical outcome is a great challenge. Genomic alterations need to be validated as molecular markers for the stratification of patients for efficient benefits from the drugs. The gene encoding speckle type poxvirus and zinc finger protein (SPOP) has an inactivating point mutation in 6–15% of the localized and metastatic PCa and appears to be an early event in prostate carcinogenesis. Steroid receptor coactivator 3 (SRC-3) promotes cell proliferation and AR-dependent transcriptional activity in PCa. SPOP, an E3 ubiquitin ligase adaptor, binds with SRC3 and facilitates protea-some-mediated degradation hence SPOP can be considered a tumor suppressor in wild-type form. When the SPOP is mutated, it is unable to engage with SRC-3, and hence AR-dependent transcriptional activity and cellular proliferation is promoted. The most frequently co-occurring mutations are adenomatous polyposis coli (APC), phosphatase and

tensin homolog (PTEN), and tumor protein p53 (TP53). SPOP mutated patients has lower homologous recombination deficient (HRD) and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3) pathway mutations compared to metastatic specimens and more Wnt pathway alterations compared to unselected primary PCa [13].

Based on assay for transposases accessible chromatin sequencing (ATAC-seq) and RNA sequencing (RNA-seq) data, CRPC was classified into four subtypes — AR dependent, neuroendocrine, Wnt dependent, and stem cell-like. Wnt dependent subtype is primarily driven by TCF/LEF (T-cell factor/lymphoid enhancer factor) transcription factors and the stem cell-like subtype is primarily driven by activator protein 1 (AP1) family transcription factors. AP1 interacts with Yes1 associated transcriptional regulator (YAP), Transcriptional coactivator with PDZ-binding motif (TAZ), and TEA domain family member (TEAD), and hence YAP, TAZ, and AP-1 can be used as novel drug targets in stem cell-like PCa subtypes. Stem cell-like subtype and Wnt-dependent subtypes had enrichment of fibroblast growth factor receptor (FGFR) signaling and expression of FGF ligands and receptors. In Wnt-dependent subtypes, the samples had hot spot mutations in β-catenin (CTNNB1), deletion in APC, and gain of R-Spondin 2 (RSPO2). RB1 loss was enriched in AR negative /low subtypes but there was no significant difference in PTEN and TP53 alterations among all four subtypes. AR independent subtypes had the worst prognosis indicating that RB1 alterations but not the TP53 and PTEN are linked to shorter survival in CRPCs. In the Wnt-dependent CRPC, transcription factor 7 like 2 (TCF7L2 or TCF4) was the most prominent transcription factor and some of the other involved TFs were lymphoid enhancer binding factor 1 (LEF1/LEF), transcription factor 7 (TCF7/TCF-1), and TCF7L1/TCF-3 [14••].

Fibroblast growth factor mediates the osteoblastic progression of PCa cells into the bone. Many of the downstream genes of the Wnt pathway such as fibroblast growth factor 18 (FGF18), TCF4, neuronal cell adhesion molecule (NrCAM), SRY-box transcription factor 2 (SOX2), and bone morphogenetic protein 4 (BMP4) are overexpressed. β-catenin might act as the coactivator of AR, and it competes with TCF/LEF. D32G mutation in β-catenin enhances its localization to the nucleus and hence activates the Wnt signaling in AR negative CRPC cells. Hyaluronan synthase 2 (HAS2) acts as a downstream target of β-catenin in PCa and high β-catenin nuclear localization and low or no AR might define a subset of PCa patients with bone metastasis [15].

Tumor samples from seven patients having locally advanced or metastatic PCa were obtained before and after 22 weeks of ADT initiation. Among the different pathways activated in the development of ADT resistance, Wnt signaling was one of the overexpressed pathways and there was an observed overexpression of β-catenin in a subset of CRPC cells. Bioinformatic analysis using KEGG term Wnt signaling pathway resulted in largest number of upregulated genes among the cluster of upregulated cancer pathways. The Wnt signaling pathway is directly or indirectly regulated by androgens and specific components of Wnt signaling are implicated in AR signaling, ADT, and PCa progression [16]. The driver gene mutations that are more common in mCRPC compared to localized cancer can act as a candidate prognostic marker and the analysis of localized and metastatic tumors deciphered mutations in AR and its enhancer, TP53, MYC, ZNRF3, DNA-dependent protein kinase,

and catalytic subunit (PRKDC). The loss of ZNRF3 is associated with increased Wnt, cell cycle, and PRC1/2 activity [17].

Fatty acid synthase (FASN) is a key metabolic enzyme of lipogenesis, and it is overexpressed in many cancers, displays oncogenic roles, and induces resistance to apoptosis and cell proliferation. The role of FASN was explored in PCa by using immortalized prostate epithelial cells (iPrEC) overexpressing FASN. FASN increases the 14C acetate incorporation into palmitate in elevated Wnt-1 isogenic cells. The overexpression of FASN leads to cumulation of membranous and cytoplasmic β-catenin while knockdown of FASN results in the reduction of β-catenin. The overexpression of FASN in mice resulted in invasive tumor development and overexpression of β-catenin. There was a significant association between the FASN and cytoplasmic β-catenin immunostaining in human PCa samples [18•].

Whole genome sequencing of 23 PCa from 16 different lethal metastatic tumors and three high-grade primary carcinomas was performed to find the protein altering mutations that may fuel the PCa and induce metastasis. A subset of genes including TP53, delta like non-canonical notch ligand 1 (DLK2), glypican 6 (GPC6), and stromal cell derived factor 4 (SDF4) was recurrently altered across tumors from different individuals. A comparison of castration-resistant and castration-sensitive tumors derived from the same PCa deciphers that mutations in Wnt signaling is an important factor in the development of castration resistance. A comparison of exomes from castration resistance and castration sensitive xenografts of prostate tumors identified 12–50 genes with nonsynonymous mutations that were uniquely present in castration-resistant xenografts. When enrichment of mutations in genes encoding biochemical pathways in CRPC was analyzed, there was significant enrichment for genes of Wnt signaling pathways in castration-resistant tumors. Out of 86 mutations unique to CRPCs, each tumor had at least one mutation in a member of the Wnt signaling pathway genes. Some of the altered Wnt pathway genes were frizzled class receptor 6 (FZD6), glycogen synthase kinase 3 β (GSK3β), and WNT6 [19].

Wnt Signaling and Prostate Cancer Heterogeneity

PCa is a heterogeneous disease, and it has topographically and morphologically distinct tumor foci. The individual tumor foci can arise from clonally distinct abnormal tissues with no shared gene defects. The clinical, morphological, and molecular perspectives of PCa hint that an individual patient might harbor multiple genomically and phenotypically distinct primary prostate tumors and lethal metastatic PCa might arise from a single clone of the primary tumor. The intra-tumoral heterogeneity is now being given due consideration in the management of PCa. The PCa cells have a heterogeneous expression of the Wnt/β-catenin pathway and the PCa cells having active Wnt/β-catenin signaling, have cancer stem cell properties, slower cell cycle, higher resistance to docetaxel, and a higher expression of cancer stem cell markers. In normal prostate tissues, there is negligible nuclear staining of β-catenin but in prostatic intraepithelial neoplasia, there is a relatively increased cytoplasmic and nuclear staining of the β-catenin. There was heterogeneous β-catenin staining in the nucleus of a single duct indicating a heterogeneous activation of the Wnt signaling pathway in the tissues of PCa. Wnt signaling has graded increased activation during the PCa

progression. Wnt downstream gene LEF1 was also increased in a considerable percentage of PCa tissues. The PCa cells having a higher expression of Wnt signaling had a significantly higher sphere formation, more quiescent character, and a higher expression of stem cell markers such as B cell-specific Moloney murine leukemia virus integration site 1 (BMI) and CD44 [20].

A fast and flexible system was developed to introduce genetic alteration in prostate glands of mice using tissue electroporation. A subset of tumors in which p53 was altered, spontaneously developed the Wnt pathway alterations. Introduction of MYC overexpression and PTEN loss led to induction of PCa. Mice prostate having MYC overexpression and P53 deletion had Wnt pathway activation and the level of Wnt activity was related to metastatic spread. Mice having MYC, P53, and Apc deletion had increased nuclear β-catenin and TCF7 expression and APC disruption increased the metastasis spread [21].

Wnt Signaling and Neuroendocrine Differentiation

Neuroendocrine (NE) differentiation in PCa is a phenotypic change in PCa cells wherein PCa cells transdifferentiate into neuroendocrine like cells. NE like cells do not express androgen receptors, or prostate-specific antigens, and are highly resistant to the treatment. NE like cells secrete multiple growth hormones and peptide hormones that support the growth of neighbor tumor cells. Neuroendocrine differentiation (NED) is associated with disease progression and poor prognosis. Androgen deprivation therapy, chemotherapy, and radiotherapy are shown to induce NED in PCa. Therapy induced NED can lead to the development of drug resistance. NE cells are widely distributed in the prostate, and they are thought to arise from endodermal-derived pluripotent prostatic stem cells. They are involved in prostatic growth and differentiation as well as in homeostatic regulation of the secretory process. The majority of primary conventional PCa contain scattered NE cells and metastatic PCa has NE marker positive cells and lacks androgen receptors. There is an increased expression of neuroendocrine markers in enzalutamide resistant PCa cell lines. TCF4 mediated neuroendocrine differentiation and neuroendocrine markers were elevated in enzalutamide resistant PCa tissues. In the enzalutamide-resistant cell line (LNCaP-EnzR), NED markers such as chromogranin A, neuron-specific enolase, and parathyroid hormone like hormone (PTHrP) were increased compared to LNCaP maintained in charcoal stripped FBS (LNCaP-csFBS). The mRNA level of TCF4 and POU2F2 was higher in LNCaP-EnzR which has a TF binding site in the promoter of NED markers. Cells overexpressing TCF4 demonstrated an increased level of NED markers and TCF4 expressing cells were resistant to enzalutamide [22]. NED is associated with Wnt signaling activation and it is observed after the ADT failure in prostatic adenocarcinoma. ADT mediated upregulation of TCF7L1 increases the cytokine response and enhances the neuroendocrine differentiation of PCa by activation of CXC chemokine receptor 2 (CXCR2) signaling. ADT induces Wnt4 and TCF7L1 to enhance interleukin-8 (IL-8) and CXCR2 expressions. TCF7L1 binds regulatory sequences of IL-8 and CXCR2 by activation of Wnt4 and upregulates IL-8/CXCR2 driven NED and cell motility [23].

Protocadherin-PC (PCDH-PC), a Y chromosome gene, is selectively expressed in apoptosis and hormone-resistant human PCa cells. PCDH-PC transfected LNCaP cells or cells

grown in androgen-free medium transdifferentiated into neuroendocrine-like cells showing higher expression of neuron-specific enolase and chromogranin-A. LNCaP cells transfected with stabilized β-catenin also show neuroendocrine transdifferentiation. Wnt 11 is overexpressed in PCa but it is repressed by the androgens. Wnt-11 induces cell invasion and neuroendocrine-like differentiation. Wntless (WLS), a Wnt secretion mediator, drives NEPC and WLS is a transcriptional target of AR. WLS is overexpressed in CRPC and NEPC cancer tissues [24].

Wnt Signaling and DNA Repair

DNA repair is an essential component for the proper maintenance of genomic integrity. Cancer cells are dependent on DNA repair regulation for their survival. Wnt signaling interacts with DNA damage response at different levels. DNA dependent protein kinase (DNAPK), a pivotal component of DNA repair machinery, plays an important role in the metastatic progression of high risk PCa. The inhibition of DNAPK suppresses the growth of AR-dependent as well as AR-independent PCa cells [25•]. Wnt signaling is the top pathway associated with DNAPK in gene set enrichment analysis. DNAPK interacts with LEF1, a Wnt transcription factor, and is critical for LEF1 mediated transcription. DNAPK expression level is not only associated with metastatic progression but also with the decreased rates of PCa specific survival and overall survival. DNAPK can act as a prognostic indicator in luminal and basal subtypes of PCa which are AR-independent. The expression of DNAPK and β-catenin is strongly correlated in clinical samples. The knockdown of DNAPK in LNCaP cells in androgen-depleted conditions causes the suppression of Wnt signaling genes suggesting that DNAPK knockdown prevents the emergence of ADT resistant LNCaP cells. Inhibition of DNAPK reduces the Wnt induced invasion and migration in CRPC cells and reduces active β-catenin and c-myc proteins [25•].

APC a negative regulator of the Wnt pathway can regulate chemotherapeutic response by interacting with DNA repair proteins, DNA replication proteins tubulins, and other cell components. APC can block or enhance DNA repair based on specific DNA damage, repair pathway, and stage of tumor development [26]. Wnt signaling interaction with DNA repair components can be targeted to treat PCa and/or deal with the resistance in PCa [27].

Wnt Signaling Components Dysregulated in Prostate Cancer

Activating mutation in β-catenin genes (CTNNB1) or inactivation of APC and AXIN1 is very common in other cancers but these mutations are uncommon in PCa (Table1). Genetic changes activating the Wnt/β-catenin signaling pathway are more common in CRPC compared to the treatment naïve PCa. Dysregulation in CTNNB1 is present in 12% of CRPC patients and APC mutation in 22% of CRPC but none of the localized untreated prostate tumors. A multi-institutional study has revealed that 18% of CRPC patients had alterations in APC and CTNNB1 genes [28]. There is also a link between the gene variants of APC and reduced PSA free survival and PCa development. The overactivation of the Wnt pathway by the stabilization of β-catenin or mutation in APC leads to the development of prostate intraepithelial neoplasia. LEF1 transcription factor which is a binding partner of β-catenin is upregulated in androgen independent prostate tumors. LEF1 and β-catenin co-expression

is involved in malignant transformation as well as metastasis of PCa. Co-expression of cytoplasmic β-catenin and AR is correlated with disease progression, PSA levels, higher Gleason grade. Wnt1 mRNA is highly expressed in advanced PCa and Wnt5A is found to be upregulated and accelerates cancer invasion. The haploinsufficiency of Wnt-5A prevents early onset and lethality in the mouse model of PCa but in contradiction, there are reports which suggest a correlation between Wnt-5A expression and a better outcome in PCa of low grade. Wnt-5A has an inhibitory effect on canonical Wnt signaling and activates the noncanonical Wnt signaling thus having a context dependent effect in different types of cancer. Wnt-5A mRNAs are present in the circulating tumor cells of CRPC patients. Wnt-7B which is overexpressed in PCa is one of the AR target genes in CRPC and it activates noncanonical Wnt signaling [29].

Wnt binding proteins, Wnt inhibitory factor 1 (WIF1), and secreted frizzled related protein 1 (sFRP1) are inversely correlated with β-catenin levels and these are favorable prognostic markers for PCa. SFRP1 and SFRP5 expressions are low in PCa but the expression of SFRP4 is increased. SFRP2 expression is suppressed by promoter hypermethylation. sFRPs also might have a context dependent effect on the Wnt signaling pathway and sometime instead of inhibiting the Wnt pathway it might induce or potentiate the tumor promoting functions of the Wnt signaling pathway [48]. Dickkopf (DKK) proteins can act as the activator of carcinogenesis despite their function as Wnt inhibitors. Higher expression of DKK1 in the serum of PCa patients is associated with poor prognosis in the patients and higher expression of DKK1 promotes the tumor growth and bone metastasis of the prostate tumors. DKK1 suppresses the canonical Wnt signaling and promotes the non-canonical Wnt signaling. DKK1 can also have the Wnt signaling independent effect on the enhancement of cell proliferation through some novel receptors. In PCa, higher expression of DKK1 is associated with poor patient prognosis and promotes tumor growth and bone metastasis. DKK1 can inhibit the canonical Wnt signaling and promote the noncanonical Wnt signaling but it can also act independently of the Wnt signaling pathway by acting on various cell receptors [49]. Inactivating mutations in ring finger protein 43 (RNF43) and Zinc and ring finger 3 (ZNRF3) and upregulation of RSPO2 is observed in certain cases of CRPC [50].

Wnt Signaling in Stem Cells and Organoids

The Wnt signaling pathway is one of the evolutionarily conserved cell-cell interaction pathways and it has been shown to play an important role in cancer stem cell renewal cell proliferation, and differentiation during embryonic development and tissue homeostasis [51–53]. The intestine, skin, and bone are the three best-studied tissues where Wnt signaling has been shown to play an important role in stem cell functions. Wnt target genes are also expressed in the stomach, liver, and mammary gland [54].

The growth factors for the development of different organoids might vary in composition but the requirement of Wnt and Rspo or their combination is required for most of the organoids [55, 56]. Adult stem cells and patient-derived organoids can be used to understand the regulatory mechanism of the Wnt signaling pathway in different physiological and pathological contexts and disease progression [57]. Patient-derived organoids can be used for studying the growth and sensitiveness of the Wnt pathway and small molecule inhibitors

can be tested for their clinical utility [58, 59]. Adult stem cell derived organoids are known to be dependent on the Wnt signaling pathway for the continuity of stem cell character, growth and division, and formation of differentiated and specialized cells [60]. The prostate organoids can also help in the study of disease pathogenesis, drug resistance studies, novel and repurposed drug screening, and personalized treatment of the patients [61]. Wnt5a suppresses the size of prostate organoids better in presence of R-spondin [62]. In the prostate organoid culture of basal cells, it was shown that dihydrotestosterone can antagonize the R-spondin mediated organoid growth. In the organoid, androgen signaling downregulated the expression of Wnt signaling and its downstream target genes. Dihydrotestosterone was shown to enhance the AR and β–catenin binding in the nucleus of the prostate organoid which can explain the reason why androgen signaling keeps Wnt signaling in check [63]. Prostate stromal cells secrete Wnt ligands that enhance the cell proliferation of prostate epithelial cells. To get a better insight into the roles of Wnt signaling in PCa pathogenesis and drug resistance, Wnt signaling components can be suppressed or overactivated using CRISPR/Cas9 technology in the prostate organoids and its downstream effect or the cause of the drug resistance can be screened [64].

Wnt Signaling in Antiandrogen Therapy

PCa growth and maintenance are highly dependent on androgen hormones and androgen receptors. Some of the well explored mechanisms of AR dependent resistance are amplification of AR, mutations in AR, AR splice variants generation, increase in androgen hormone production, and changes in co-activator and co-repressors of AR. Among the AR independent mechanisms, Wnt signaling pathway has been shown to play a very important role in the development of drug resistance in PCa. APC/RNF43 mutations are independently associated with PSA progression and CTNNB1 mutations are non-significantly associated with the progression. PCa patients harboring Wnt pathway activation (activating mutation in CTNNB1 or inactivating mutation in APC or RNF43 have a bad outcome to first-line abiraterone/enzalutamide treatment [65].

Sampling the circulating tumor cells (CTC) in patients treated with enzalutamide had significant enrichment in noncanonical Wnt signaling and the source of noncanonical Wnt5A and Wnt7B mRNA were the subset of tumor cells and not the surrounding stromal cells. Thus, in the case of AR inhibition, noncanonical Wnt signaling can provide a survival signal to the PCa cells. Survival of AR-positive LNCaP cells was enhanced on ectopic expression of noncanonical Wnt ligands Wnt4, Wnt11, Wnt5A, and Wnt7B in the presence of enzalutamide. The noncanonical Wnt signaling genes such as Wnt5a, Ras homolog family member A (RhoA), and Rho-kinase (ROCK) were overexpressed in enzalutamide resistant PCa cells in comparison to enzalutamide sensitive counterparts. The frequency of driver mutations in TP53, Wnt, and cell cycle genes is increased in metastatic castration sensitive PCa [45]

E3 ubiquitin ligase identified by differential display (EDD) acts on protein by adding ubiquitin and regulates cell proliferation and tumorigenesis. EDD is upregulated in docetaxel resistant CRPC and knockdown of EDD reverses the docetaxel resistance. The Wnt signaling is overexpressed in docetaxel resistant CRPC cells and it is promoted by EDD.

The inhibition of Wnt signaling by knockdown of β-catenin diminishes the EDD-mediated docetaxel resistance [66].

DAB2 Interacting Protein (DAB2IP) knockdown in cells leads to resistance to several anticancer drugs but the increased DAB2IP in C4-2 cells increased the drug sensitivity. DAB2IP blocks the crosstalk between Wnt/β-catenin and IGF-I signaling and leads to the suppression of early growth response 1 (Egr-1). DAB2IP and Egr-1 expression are inversely related and DAB2IP expression level is positively related to drug sensitivity and negatively related to the expression of Clusterin, an antiapoptotic factor [67].

Wingless-type MMTV integration site family member 16B (WNT16B) expression in prostate tumor microenvironment diminishes the effect of cytotoxic chemotherapy drugs and promotes cancer cell growth and drug resistance in vivo. DNA damage increases the expression of WNT16B protein expression, and it is elevated in the extracellular medium of radiation or chemotherapy treated prostate fibroblast cells. WNT16B is slightly increased in epithelial cells but other Wnt family members were not significantly altered in prostate fibroblast cells [34].

The AR-positive and androgen-sensitive LNCaP cells and C4-2B cells grown in supplemented media with charcoal-stripped medium resulted in overexpression of WLS proteins and it was reversed by R1881, a synthetic androgen. There was increased phosphorylation of LRP6, an early step in the activation of Wnt signaling and there was an accumulation of β-catenin in the nucleus of the cancer cells. Proteomic screening with the Wnt signaling phospho specific antibodies revealed that several phosphoproteins of noncanonical Wnt signaling such as PKC, JNK, and AKT were downregulated by WLS silencing and PKC had the most phosphorylation sites affected by WLS knockdown [68].

Metastatic CRPC patients underwent the whole genome and RNA sequencing before abiraterone acetate/prednisone (AA/P) treatment and genomic alterations associated with AA/P resistance were analyzed. After 12 weeks, the primary resistance was investigated using serum prostate-specific antigen, and bone and computerized tomography imaging. Genes in the Wnt/β-catenin pathway were having frequent mutation and negative regulators of Wnt signaling were deleted or had lower expression at mRNA level [69]. AR activation can prevent the interaction between β-catenin and TCF/LEF hence suppressing the Wnt signaling pathway. AR signaling suppresses the TCF7 by miR 1 mediated downregulation of TCF7 and overexpression of TCF7 or disruption of miR-1 promotes androgen-independent proliferation of PCa cells [70].

The second generation of anti-androgen therapy is widely used as a new strategy for the treatment of CRPC but it is linked to the development of spinal epidural lipomatosis. The pathophysiology of adipose tissue growth after the treatment with second-generation antiandrogen therapy involves canonical as well as noncanonical Wnt signaling pathways [71]. Wnt signaling pathway gene transcriptomic signature reveals that Wnt signaling genes are significantly higher in enzalutamide resistant patients and genomic alteration in CTNNB1 is the main player in the process [37]. β-catenin upregulation is partially caused by βTrCP mediated ubiquitination and activation of Wnt signaling in enzalutamide

sensitive cancer cells leading to drug resistance [72]. Wnt pathway signature is enriched in enzalutamide-resistant C4-2B-MDVR (MDVR) cells compared to parental C4-2B cells. MDVR cells had upregulated Wnt signaling pathways and overexpression of WLS. The suppression of WLS has decreased the Wnt signaling pathway, induces cell death in PCa cells, and re-sensitized enzalutamide resistant cells to the drug treatment [73].

Inhibition of protein kinase C δ (PKCδ) activates the Wnt/β-catenin pathway and Aurora kinase A. In the absence of PKCδ, the combined treatment with paclitaxel and Wnt/β-catenin inhibitor improves the response of paclitaxel by inducing more cell death. The high Gleason score PCa has suppressed PKCδ, higher β-catenin, inactivation of GSK3β, and higher Aurora kinase and Mcl-1. In PKCδ silenced PC3 and LNCaP cells, the β-catenin target genes c-Myc and cyclin D1 both were increased and Aurora kinase A and phsopho-Akt were high. Paclitaxel treatment decreased the active β-catenin but there was no change in total β-catenin level. Primary prostate tumor samples studied by immunostaining had shown different levels of cytoplasmic expression of PKCδ, Aurora kinase A, phosphoGSK3β, and Mcl-1 proteins, and β-catenin had active nuclear localization. The expression of PKCδ was correlated with the expression of β-catenin, Aurora kinase A, phosphoGSK3β, and Mcl-1 expression [74]. The patients having circulating tumor cell (CTC) AR-V7 positive mCRPC show the worst result when treated with enzalutamide/abiraterone however most of the men lack CTC AR-V7 [75]. After the progression despite abiraterone/enzalutamide treatment, clonal evolution of CTCs was shown to harbor TP53 mutation and gain of ATM, KDM6A, and MYC, and loss of nuclear receptor corepressor 1 (NCOR1), PTEN, RB1, and runt-related transcription factor 2 (RUNX2) [76].

Wnt Signaling in Stem Cells and Epithelial Mesenchymal Transition Related Resistant Mechanisms

Epithelial mesenchymal transition (EMT) is a molecular program that controls cell morphology and function in embryonic development and tissue differentiation. EMT is involved in tumor development, invasion, and metastasis. Wnt signaling pathway is one of the major signaling pathways which has an established role in the induction of epithelial-mesenchymal transition in cancer. Endothelial cell-specific molecule 1 (ESM1), a secretory proteoglycan, promotes Wnt signaling and is positively related to PCa stemness and progression. Elevated ESM1 correlates with poor survival and metastasis. Nuclear ESM1 interacts with β-catenin to stabilize the β-catenin-TCF4 complex and activates Wnt signaling and promotes PCa stemness. Further, it was shown that β-catenin interacts with ESM1 through the ARM domain, primarily the region repeats 3–8 and cysteine rich region, especially 1–46 amino acids [77].

Protein kinase cAMP-dependent type II regulatory subunit beta (PRKAR2B) is upregulated in CRPC and induces metastasis. PRKAR2B is markedly increased in androgen independent LNCaP cell line and mCRPC tissues compared to LNCaP cells and primary PCa tissues. PRKAR2B induces invasion and metastasis and is correlated with Gleason score and lymph node metastasis in PCa. PRKAR2B suppresses E-cadherin and induces Vimentin, N cadherin, and Fibronectin. PRKAR2B induces Wnt signaling and inhibition of Wnt

signaling suppresses PRKAR2B induced EMT and invasion. Androgen independent LNCaP (LNCaP-AI) had increased AR expression and PRKAR2B. PRKAR2B expression was very high in mCRPC tissues compared to primary PCa tissue. Inhibition of Wnt signaling by IWR-1 suppressed PRKAR2B induced EMT and invasion [78].

The role of bone morphogenetic factor 6 (BMP6) was investigated in the development of CRPC in the context of bone metastasis. The median time to the emergence of PSA progression was shorter in men with bone metastasis than in those without bone metastasis [79]. The skeletal microenvironment could trigger resistance to castration in PCa cells. BMP6 mediated cellular proliferation of PCa cells in androgen reduced media requires BMP-RII, ALK2, Smad5, and β-catenin. Wnt5A factor secreted by bone marrow stromal cell line induces the BMP6 expression in PCa cells in androgen deprived conditions. Wnt5A induces BMP6 expression through the NF-kB noncanonical Wnt pathway [80]. Aryl hydrocarbon receptor and RUNX1 which are linked to stem cell maintenance, and ROR1, a noncanonical Wnt5a coreceptor are involved in PCa stemness and primes for noncanonical Wnt signaling through ROR1. Autocrine Wnt production acts as a nongenomic driver for noncanonical and canonical Wnt signaling in PCa [81]. Cuprous oxide nanoparticles (CONPs) decreased the expression of stem cell transcription factors Oct4, Sox2, and KLF4. CONP was able to suppress Wnt1A, FZD7, cMYC, and Cyclin D1 in PC3 cells in a dose-dependent manner. CONPs induce selective apoptosis and inhibit cancer cell growth in CRPC. It also inhibits the stemness and Wnt signaling pathway in PCa cells [82].

We have also demonstrated that the expression of secreted Wnt inhibitors, such as FrzB and WIF1, was loss in CRPC cell lines and re-expression of FrzB and WIF1 in CRPC cell lines reverses the EMT process by increasing the expression of E-cadherin and downregulation of N-Cadherin and inhibits cell migration and invasion leading to potent antitumor effects in xenograft models [83••, 84].

Cancer cells shift to less efficient glycolysis from oxidative phosphorylation to fuel the aggressive proliferation. Cancer stem cells (CSCs) show a metabolic shift depending on the cancer type and can be highly glycolytic or dependent on oxidative phosphorylation [85]. Wnt signaling is known to promote glycolysis and tumor growth hence the effect of Wnt antagonist secreted frizzled-related protein 4 (sFRP4) on CSC metabolism was investigated. sFRP4 plays an important role in basal glucose uptake in CSCs in PCa cell lines. CSCs treated with sFRP4 show metabolic reprogramming by relocating metabolic flux between glycolysis and oxidative phosphorylation. sFRP4 treatment dysregulate cell proliferation and affects viability through glucose transporter, pyruvate conversion, mammalian target of rapamycin, and apoptosis [86].

Wnt Signaling and Immune Evasion

PCa is generally a slow progressing disease and hence the use of immune based therapy should provide an advantage for the treatment of advanced PCa and induce antitumor immunity. Cancer immunotherapy efficacy in PCa is low due to the complex immune evasion mechanism (IEM). In an integrative analysis of RNA-seq data for prostate adenocarcinoma from TCGA, eight clusters with different IEM combinations

were identified. Prostate tumors utilize different combinations of IEM to evade the immune system. The majority of PCa patients had immunological ignorance, upregulated cytotoxic T lymphocyte-associated protein 4 (CTLA4), and upregulated decoy receptor 3 (DcR3). PCa expresses prostate-associated antigens such as prostate-specific antigen (PSA), prostate-specific membrane antigen (PSMA), prostate stem-cell antigen, and prostatic acid phosphatase (PAP) but these self-antigens do not induce an immune response. The prostate has an immunosuppressive tumor microenvironment and hence immunotherapies have very diminished efficacy in PCa treatment [87•].

Double negative prostate cancer (DNPC), an advanced CRPC without AR receptor and neuroendocrine signaling, is prevalent in patients treated with AR signaling inhibitors. DNPC has increased Dickkopf-1 (DKK1) expression relative to PSA in mCRPC. DKK1 expression is regulated by Wnt signaling and correlates with Wnt signaling mutations and low PSA mRNA in mCRPC biopsies. DKK1 high mCRPC tumors are infiltrated with a higher number of quiescent NK cells and a lower number of activated NK cells. Patients with mCRPC and a low level of PSA have a higher level of circulating DKK1. When Wnt signaling was activated by overexpression of mutant stabilized β-catenin or knockdown of APC, DKK1 mRNAs were significantly increased along with AXIN2, a well-known Wnt target gene. Wnt signaling acts as an upstream regulator of DKK1 in PCa [88]. Bone morphogenetic protein 6 (BMP6) induces CRPC via tumor-infiltrating macrophages and Wnt5A/BMP6 loop in PCa bone metastasis leads to resistance against androgen. Wnt5A is associated with increased expression of CCL2 in LNCaP and it is mediated by MAPK/ERK pathways. Overexpression of Wnt5A in LNCaP cells lead to castration resistance and the resistance was nullified by the removal of macrophages. A high level of Wnt5A is correlated with an increased level of CCL2 and BMP6 [89].

Noncanonical Wnt Signaling in Prostate Cancer

The noncanonical Wnt signaling is well known to be involved in embryonic development and growth but their role in cancer is emerging. A newly discovered non canonical Wnt signaling pathway mediated through Wnt5/Fzd2 is shown to induce EMT in cancer. Increased activity of Wnt5a/Fzd2 is observed in prostate cancer and it is associated with increased EMT marker and higher Gleason score in prostate cancer [90]. Noncanonical Wnt signaling is activated in Cabazitaxel resistant DU145 prostate cancer cells [91] . Wnt5a is highly expressed in prostate tumor tissue and cancer cell lines. Wnt 5a regulates cytoskeleton through Wnt/Ca + 2/CaMKII axis in prostate cells and inhibition of CaMKII inhibits cell motility and wound healing in-vitro [92]. Increased activation of noncanonical Wnt5a/Fzd2 pathway stimulates the Wnt pathway and it enhances the EMT and metastasis [93]. Noncanonical Wnt11 is overexpressed in aggressive prostate tumors, hormone independent prostate cancer cells and poorly differentiated prostate cancer. Wnt11 might affect transcription independent of AR and regulates LNCaP cell growth. Diminished androgen activates Wnt11 dependent pathways and inhibits androgen dependent cell growth. Wnt11 is correlated with Wnt receptor Fzd8 in prostate cancer and Fzd8 interacts and colocalizes with Wnt11 [94]. Fzd8 knockdown leads to inhibition of organoid cell growth, EMT marker expression, cell migration, and invasion. The extracellular domain of Fzd8 interacts with TGFβ receptor 1 and regulates downstream Smad pathways [95]. Hence the

noncanonical Wnt signaling seems to be playing an important role in prostate cancer and it can be further harnessed to find potential drug targets for prostate cancer management.

Wnt Signaling Targeted Therapy

The subset of cancers having overexpression of the Wnt signaling pathway can be theoretically managed by Wnt inhibitors. This basic idea has generated a lot of interest in the development of novel Wnt inhibitors [96, 97]. IWPs and LGK974 have been shown to block Porcupine resulting in inhibition of Wnt ligand secretion [98]. Mutation of RNF43 results in dependency of pancreatic adenocarcinoma on Wnt ligands [99] and mutation of RNF43 and R-spondin fusion proteins in colorectal cancer is a predictor of effective treatment [100]. A clinical trial for LGK974 was conducted in metastatic colorectal cancer having mutations in RNF43 and R-spondin fusion proteins [101]. Porcupine inhibitor ETC-159 was shown to prevent the growth of R-spondin fusionpositive CRC [102]. OMP-54F28 is a fusion protein that can inhibit the Wnt ligands and reduces the size of the xenografts and tumors in hepatocellular carcinoma and ovarian cancer [103]. OMP131R10 is also believed to be a promising candidate against colorectal cancer [104]. OMP18R5 is an antibody designed to block five different types of Fzd receptors [105]. OTSA 101 is a radioactive anti-Fzd10 antibody undergoing clinical trial for advanced synovial sarcoma [106]. PRI-724 and ICG-001 target the β-catenin and CBP complex formation and enhance the β-catenin/p300 complex formation in ALL cells [107]. XAV939, a tankyrase inhibitor that stabilizes Axin, acts as a Wnt inhibitor [108]. Foxy-5 and Box-5 have been developed as Wnt5a analogs to control Wnt5a-directed signaling and suppress metastasis [109]. Recent studies have identified several cancer-specific Wnt signaling regulators which might be a druggable vulnerabilities to treat Wnt signaling dependent cancers. In the strive to get Wnt signaling suppressed, potential therapeutic agents have been tried against various components of Wnt signaling pathway. Some of the important and promising clinical trial drugs are against the major and important Wnt signaling components such as porcupine, Wnt-receptor interaction, and β-catenin. LGK974 and ETC-159 act as porcupine inhibitors [110], Ipafricept (OMP-54F28) binds to Wnt ligand and interfere its binding with the receptor [111], Vantictumab (OMP-18R5) interacts with Frizzled receptors to inhibit the Wnt ligands [112]. PRI-724 blocks the interaction between β-catenin and CBP [113], and CWP232291 (CWP291) acts on Wnt/β-catenin transcriptional products [114]. Several drugs clinically approved for other diseases have been repurposed as Wnt signaling inhibitors and they can be utilized for Wnt dependent cancer treatment such as loop diuretic drug Ethacrynic Acid [115], antiparasitic drug Pyrvinium pamoate [116], psychotic disease drug Pimozide [116], NSAID drug Celecoxib [117], and anti-parasitic drug Niclosamide [118]. Looking at the promising clinical drugs and repurposed drugs it gives a positive hope that we will get Wnt targeting clinically approved drugs very soon and hopefully they could be utilized in Wnt fueled prostate cancer as well.

The evolutionarily conserved Wnt pathway is crucial in normal embryonic development in most of the tissue and organ system. The Wnt signaling is involved in the development of the brain, eye, spinal cord, bone, cartilage, skin, lung, teeth, mammary gland, gut, heart, liver, kidney pancreas, and hematopoietic and reproductive system [119]. In the adults, Wnt signaling is involved in tissue homeostasis and skin and hair regeneration [120]. Wnt

signaling is involved in liver and lung repair after injury to maintain the organ function and neurogenesis in adults [121]. Wnt signaling plays an important role in cell migration, genetic stability, and apoptosis. Wnt signaling dysregulation is associated with many types of cancer, and other diseases like fibrosis, metabolic disorders, and neurodegenerative disorders [122]. Hence, getting a Wnt targeting drugs will be a great arsenal for management of various diseases but looking at the wide roles played by Wnt signaling, the side effects and toxicity seem unavoidable. Some of the challenges in targeting Wnt signaling is 19 types of Wnt ligands [123], more than 15 receptors and coreceptors distributed over seven protein families in mammals [124]. Components of Wnt signaling pathway also might act independently of β-catenin [125]. Wnt proteins can also initiate alternative responses collectively known as non-canonical Wnt signaling pathway. Crosstalk from non Wnt factors can also influence the nuclear β-catenin accumulation [126]. This diversity in ligand and receptor helps the pathway easily adapt and develop an alternative mechanism to bypass the therapeutic inhibition.

Wnt signaling being one of the crucial signaling pathways involved in development, its targeting can have devastating effect on embryonic patterning similar to hedgehog inhibitor induced cyclopia [127] and thalidomide induced phocomelia [128]. Wnt4 is involved in development of female reproductive system and during mammalian embryogenesis Wnt4 is expressed in the gonads of both sexes and downregulated in male gonad later [129]. The FDA-approved Hedgehog signaling inhibitor vismodegib that antagonizes Smoothened has been shown to have side effects such as muscle spasms and cramps, alopecia, diarrhea, dysgeusia, weight loss, and fatigue. But these side effects are reversible after the treatment or over or can be clinically managed [130]. We believe that similar manageable side effects are expected with Wnt inhibitors in cancer treatment. Wnt signaling is a major pathway that maintains the stem cells hence targeting the activated Wnt signaling in cancer stem cells can also have severe effects on the normal somatic stem cells of different organs of the body.

In short, Wnt signaling, which is involved in maintenance of multiple physiological and regulatory pathways, is dysregulated in many diseases including cancer. There is enormous effort to develop Wnt signaling target based therapeutic drugs but so far there is no clinically approved Wnt target specific drugs. The great excitement and potential in the preclinical and clinical trials of Wnt inhibitors in different types of cancer gives us a hope that soon Wnt dependent or regulated PCa will also be managed well using these drugs.

Conclusion

Wnt signaling is extensively involved in CRPC development and progression and the resistance to anti-androgen through multiple mechanisms as summarized in Fig. 1. Therapeutic manipulation of the pathway can be useful for CRPC management. Wnt signaling implications in prostate carcinogenesis can be studied using organoid models of PCa and prostate organoids can be helpful in drug screening and personalized treatment plans. In anti-androgen therapy resistant PCa, the non-canonical Wnt signaling pathway is emerging as a potential new target.

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•• Of major importance

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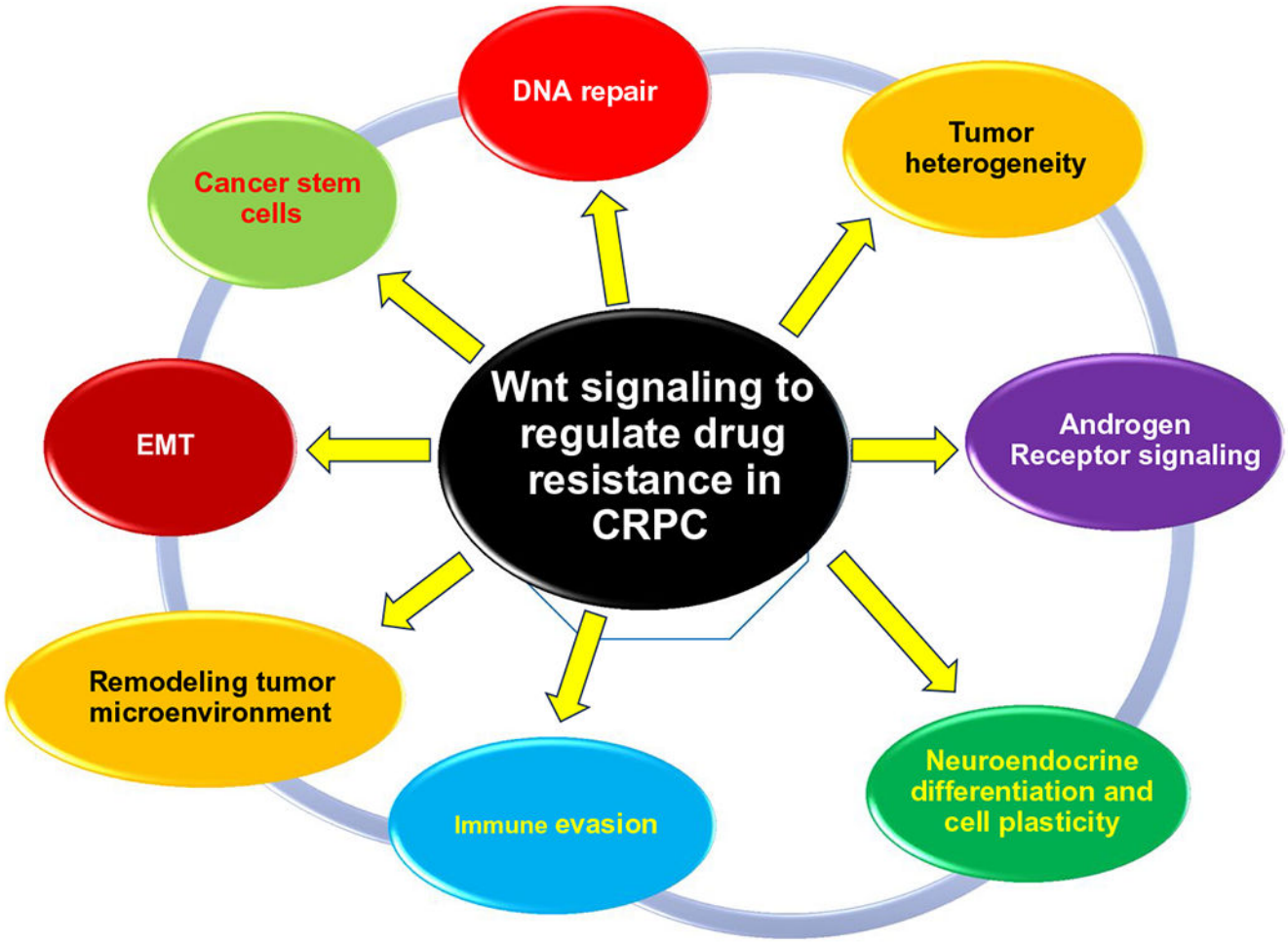

Fig. 1.

A schematic presentation of Wnt signaling to regulate drug resistance in CRPC through multiple mechanisms. (1) Wnt/β-catenin signaling can interact with androgen receptor signaling to affect the responses to ADT and anti-androgens. (2) A subset of CRPC tumors have high activities of Wnt signaling due to the dysregulation of multiple Wnt signaling components in CRPC. (3) Wnt transcriptional factor LEF1 interacts with DNAPK to affect DNA repair process and androgen receptor signaling. (4) Wnt signaling plays a key role in the EMT process and cancer stem cells and inhibition of Wnt signaling by secreted inhibitors, such as Frzb and WIF1, can reverse the process of EMT and reduce invasiveness of CRPC. (5) Prostate cancer tumor microenvironment secretes several canonical and non-canonical Wnts leading to anti-androgen resistance and immune evasion. (6) Wnt signaling is involved in cell plasticity and neuroendocrine transdifferentiation through Wntless and Wnt transcriptional factor TCF4

Table 1

Wnt signaling dysregulation in prostate cancer

CTNNB1	**Activating mutation**	**Progression of disease and CRPC development [30]**
APC	Inactivating mutation	Advanced stage of cancer and CRPC development [31]
Wnt-5A	Overexpression	CRPC, metastasis, recurrence [32]
Wnt-7B	Overexpression	[33]
Wnt-16B	Overexpression	Drug resistance [34]
Wnt-11	Overexpression	Invasion and metastasis[35]
ROR1	Overexpression	[36]
FZD2	Overexpression	Recurrence, CRPC development [37]
FZD4	Overexpression	EMT [38]
FZD5	Overexpression	Noncanonical Wnt signaling [39]
FZD8	Overexpression	Noncanonical and canonical Wnt signaling[40]
sFRP1	suppression	Survival is decreased[41]
sFRP2	overexpression	Resistance to therapy[42]
DKK1	Overexpression	Metastasis [43, 44]
DKK3	Suppression	Inhibition of metastasis and growth [45]
ZNRF3 or RNF43	Inactivating mutation	Enhance Wnt signaling [46]
RSPO2	Overexpression	Enhance Wnt signaling [47]