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# Revisiting the Role of Wnt/β-catenin Signaling in Prostate Cancer

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## Abstract

The androgen receptor (AR) is a widely accepted therapeutic target in prostate cancer and multiple studies indicate that the AR and Wnt/β-catenin pathways intersect. Recent genome-wide analysis of prostate cancer metastases illustrate the importance of the Wnt/β-catenin pathway in prostate cancer and compel us to reexamine the interaction of the AR and Wnt/β-catenin signaling pathways. This review includes newer areas of interest such as non-canonical Wnt signaling and the role of Wnts in prostate cancer stem cells. The effort to develop Wnt modulating therapeutics, both biologics and small molecules, is also discussed.

### Keywords

Androgen Receptor; β-catenin; Prostate Cancer; Wnt Signaling

## 1. Introduction

β-catenin is an effector of the Wnt family of proteins, an evolutionarily conserved group of signaling molecules that regulate developmental and biological processes (Miller et al., 1999; Polakis, 2000; Wodarz and Nusse, 1998). In the absence of extracellular Wnt signals, cytoplasmic β-catenin is phosphorylated by glycogen synthase kinase 3 (GSK3) as part of a destruction complex including adenomatous polyposis coli (APC) and axin proteins. The phosphorylated β-catenin is then ubiquitinated and degraded. Wnt ligands bind their associated frizzled receptors in conjunction with cofactor lipoprotein receptor-related protein (LRP). Frizzled then signals to dishevelled (DVL) which inhibits the APC/axin/GSK3 destruction complex, thus stabilizing β-catenin and allowing its translocation to the nucleus. In the nucleus β-catenin binds the T cell factor (TCF) family of transcription factors to regulate expression of target genes. Aberrant Wnt/β-catenin signaling has been linked to a number of human cancers (Miyoshi and Hennighausen, 2003; Moon et al., 2004) including prostate cancer (PCa) (Beildeck et al., 2010; Wang et al., 2008; Yu et al., 2009). β-catenin

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mutations were identified in approximately 5% of PCa samples (Voeller et al., 1998). In the late 90s and early 2000s Wnt/β-catenin signaling became a focus of prostate cancer studies (Chesire and Isaacs, 2003).

The androgen steroid hormone receptor (AR) is the major therapeutic target in aggressive prostate cancer. In response to ligands such as 5α-dihydrotestosterone (DHT) the AR directs gene transcription. Therapeutics for late stage prostate cancer, such as enzalutamide and abiraterone, target the activity of the androgen receptor by blocking androgen synthesis or androgen/AR binding (Ryan et al., 2013; Tran et al., 2009). The AR and β-catenin were found to interact directly in yeast and mammalian two hybrid assays, and the interaction was localized to the ligand-binding domain of AR and the armadillo repeats of β-catenin (Pawlowski et al., 2002; Song et al., 2003; Yang et al., 2002). More recently, the crystal structure of β-catenin and the nuclear hormone receptor, LRH-1 (liver receptor homolog-1) protein interaction was solved, revealing three important β-catenin residues in the interaction (Y306, K345, and W383). Using pull down assays, it was shown that mutations in these residues could decrease β-catenin binding to LRH-1. These same mutations also inhibited β-catenin binding to the AR, providing further evidence of the AR and β-catenin protein interaction(Yumoto et al., 2012).

β-catenin has been shown in complex with the AR and could enhance AR signaling in PCa cells (Truica et al., 2000). Multiple other interactions have been discovered between the Wnt and AR signaling pathways (Figure 1). GSK-3 phosphorylates the AR with the potential to suppress AR signaling (Mazor et al., 2004; Salas et al., 2004; Wang et al., 2004). Wnt target gene Cyclin D1 can also repress AR signaling (Petre et al., 2002). Further, AR was recruited to the cMyc promoter and shown to interact with TCF4 independent of β-catenin (Amir et al., 2003). Importantly, at least three active LEF1/TCF binding sites exist in the promoter region of the AR gene and Wnt signaling can increase transcription of the AR (Yang et al., 2006).

In addition to tissue culture models, multiple genetically engineered mouse models indicate that β-catenin plays a role in PCa progression. Overexpression of active β-catenin causes high-grade intraepithelial neoplasia and resistance to castration (Yu et al., 2009). β-catenin also cooperates with PTEN loss to promote invasive carcinoma (Francis et al., 2013). The transcription factor SOX9 has been shown to upregulate multiple components of the Wnt pathway suggesting a potential mechanism for the reactivation of Wnt signaling in PCa (Ma et al., 2016).

Taken together, all of the crosstalk between Wnt and AR signaling has led to many different proposals of what role the two pathways play in progression and maintenance of castration resistant prostate cancer (CRPC). Whether AR and Wnt/β-catenin act synergistically or in an opposing manner, is an important question in PCa biology. The role of Wnt signaling in PCa has been previously reviewed, most recently by Kypta and Waxman (2012); and Yokoyama et al (2014) (Beildeck et al., 2010; Chesire and Isaacs, 2003; Kypta and Waxman, 2012; Mulholland et al., 2005; Terry et al., 2006; Verras and Sun, 2006; Yardy and Brewster, 2005; Yokoyama et al., 2014). We do not comprehensively examine the information in these reviews here, but rather discuss the field in light of exciting new developments.

## 2. Genomic alterations in the Wnt/β-catenin pathway in prostate cancer

Advances in sequencing technology have recently enabled whole exome and whole genome sequencing of localized as well as metastatic PCa. (Barbieri et al., 2012; Grasso et al., 2012; Hieronymus and Sawyers, 2012). Such studies indicated that APC is one of the most significantly mutated genes in primary tumors. Sequencing of 50 lethal and heavily treated tissues obtained at autopsy showed mutations within the Wnt pathway in up to 50% of the samples (Grasso et al., 2012). An additional study included whole exome and transcriptome sequencing of bone or soft tissue biopsy from 150 CRPC affected individuals and demonstrated mutations in the Wnt signaling pathway in 18% of the cases (Robinson et al., 2015). These included activating mutations in beta-catenin as well as mutations and copy number alterations in APC. Mutations or copy number loss was also observed in RNF43 and ZNRF3, E3 ubiquitin ligases thought to negatively regulate the Wnt pathway. Interestingly, alterations of RNF43 and ZNRF3 were mutually exclusive with samples that exhibited alterations in APC (Robinson et al., 2015). The study also identified R-spondin genes fusions involving RSPO2, an activator of the canonical Wnt signaling pathway and important component of media used to generate organoids from patient derived PCa samples (Gao et al., 2014). These studies describing Wnt pathway alterations in the human PCa transcriptome challenge us to determine whether Wnt pathway alterations occur under selective pressure in the context of androgen deprivation or other treatment stresses and to determine whether Wnt/β-catenin and AR act together or separately to promote tumorigenesis.

## 3. Synergistic interaction of AR and β-catenin

The idea that AR and β-catenin directly interact and that β-catenin is an AR coactivator suggests that these proteins may act synergistically to regulate gene transcription. Importantly, the AR gene itself is a target of nuclear β-catenin action through TCF or the TCF family member, LEF1 that binds to the AR promoter (Li et al., 2009; Yang et al., 2006). The physical and functional interaction of AR and β-catenin has been described in a number of reports (Mulholland et al., 2002; Pawlowski et al., 2002; Song and Gelmann, 2005; Yang et al., 2002), along with characterization of the interaction of β-catenin, TIF2/GRIP1 and AR (Li et al., 2004; Song and Gelmann, 2005; Song et al., 2003; Yang et al., 2002). Crosstalk between the AR and β-catenin pathways was also observed in a hollow fiber model under castrate versus intact conditions (Wang et al., 2008). This study showed AR and β-catenin interaction and localization under castrate, but not non-castrate conditions.

AR was found to activate a Wnt reporter gene and to be recruited to the promoter of the Wnt target genes, myc and cyclin D1 (Schweizer et al., 2008). Further, a transgenic mouse model with overexpression of AR and stabilization of β-catenin, exhibited increased tumor growth (Lee et al., 2016). In actuality however, there is very little evidence beyond reporter gene assays and overexpression studies indicating the synergistic impact of these two proteins on gene transcription in an *in vivo* setting. Chromatin immunoprecipitation analysis has shown occupancy of both AR and β-catenin on selected endogenous target genes. AR occupancy was demonstrated at a TCF binding site on the Myc gene and occupancy of both β-catenin and AR were observed on the PSA promoter (Amir et al., 2003; Li et al., 2004; Liu et al.,

2008; Schweizer et al., 2008; Yang et al., 2006). Despite these studies indicating that AR and β-catenin appear to co-occupy promoters of a limited number of AR and β-catenin target genes the importance of the AR/β-catenin protein:protein interaction in execution of the AR-mediated program of gene transcription is unknown. Understanding the synergistic action of AR and β-catenin is hampered by the challenge of specifically interfering with their interaction and testing the effect on transcription. In particular, the chromatin binding sites of AR and β-catenin along with their overlap and functional significance has not yet been determined on a genome-wide scale.

## 4. Opposing interaction of the AR and β-catenin signaling pathways

There is a fair amount of evidence that the AR and Wnt/β-catenin signaling pathways may oppose one another. For example, ligand bound AR can inhibit β-catenin target gene expression (Chesire and Isaacs, 2002) and this may occur as a result of competition of AR and TCF for β-catenin binding (Mulholland et al., 2003). It is also possible that a compensatory mechanism can modulate Wnt/β-catenin and AR signaling where inhibition or activation of one can increase or decrease the other. We recently showed that androgen starvation resulted in activation of a Wnt reporter gene and enhanced interaction of β-catenin with TCF4 in PCa cells (Lee et al., 2015). These studies also demonstrated that activation of the Wnt reporter was suppressed by androgen treatment. *In vivo*, WNT16B is expressed in the prostate tumor microenvironment upon drug-induced damage and may promote resistant disease (Sun et al., 2012). The idea that the Wnt/β-catenin pathway is preferentially upregulated under conditions of androgen ablation is also supported by the finding that a Wnt/β-catenin reporter is activated in the proximal region of the mouse prostate in the castrate environment (Placencio et al., 2008). Consistent with this finding, a gene profiling comparison of the AR antagonist enzalutamide versus agonist DHT- treated LNCaP cells indicated that the Wnt pathway was the most highly overrepresented signaling pathway (Guerrero et al., 2013) in the enzalutamide treated samples suggesting that the Wnt pathway can compensate for loss of AR signaling. In prostate development, investigators have shown that the TCF family member, LEF1, is mutually exclusive with AR during branching morphogenesis and that treatment with an AR antagonist resulted in Wnt/LEF1 positive basal progenitor repopulation of the luminal compartment (Wu et al., 2011).

A reciprocal relationship between activated β-catenin and AR signaling was also demonstrated by compelling studies in mouse hair follicle cells (Kretzschmar et al., 2015; Leiros et al., 2012). Here the investigators use a combination of *in vitro* and *in vivo* approaches to show that AR negatively regulates the Wnt pathway (Kretzschmar et al., 2015). They show that AR activation reduced transcription of endogenous β-catenin target genes and conversely, that AR inhibition increased transcription of endogenous Wnt/β-catenin gene targets and promoted hair follicle proliferation and differentiation. The investigators suggest that the reciprocal relationship may be indirect through autocrine factors, proteins or microRNAs that regulate AR or β-catenin function.

## 5. Wnt/β-catenin driven prostate cancer stem cell growth

Recent studies have shown that small subpopulations of cancer cells, termed “cancer stem cells (CSCs)” or “tumor-initiating cells” based on their ability to self-renew as well as differentiate to a daughter cell type, play a critical role in both initiation and maintenance of tumors. It has been suggested that these cells are resistant to conventional chemotherapy and radiation, making it important to develop therapeutic approaches to selectively target them (Chandler and Lagasse, 2010; Korkaya and Wicha, 2010), perhaps by interfering with cell specific signaling pathways that regulate self-renewal. In PCa, it is possible that CSCs survive after androgen ablation therapy, causing castration-resistant disease (Lawson and Witte, 2007). Growing evidence shows that Wnt/β-catenin signaling is highly active in CSCs, and may have a role in prostate stem cell self-renewal (Bisson and Prowse, 2009; Korkaya et al., 2009). In addition, lineage tracing studies showed that Lgr5, a Wnt target gene, is expressed in an adult prostate stem cell population and that Lgr5 positive stem cells are castration resistant (Wang et al., 2015).

## 6. Emerging importance of the non-canonical Wnt pathway in prostate cancer

Non-canonical Wnt signaling pathways, which are β-catenin independent, may also promote PCa. Isolation and single cell RNA sequencing of circulating tumor cells from individuals with metastatic PCa showed upregulation of non-canonical Wnt signaling in persons treated with enzalutamide (Miyamoto et al., 2015). Further, the non-canonical Wnt activator WNT5A increased proliferation of LNCaP cells treated with enzalutamide. Multiple other reports have found WNT5A to be important in castration resistant disease. A study of 156 individuals with bone metastasis and treated with androgen deprivation therapy demonstrated expression of bone morphogenetic protein-6 induced by WNT5A, suggesting a potential mechanism for castration resistance (Lee et al., 2014). Another study found that haploinsufficiancy of WNT5A reduced the growth of prostate tumors in a mouse model and also confirmed the increased presence of WNT5A in human prostate tumors relative to benign prostatic hyperplasia (Takahashi et al., 2011). In addition, Frizzled2, Ror2, and protein kinase D were proven important in WNT5A induced cell invasiveness (Yamamoto et al., 2010). WNT5A also induced increased $Ca^{2+}$ and $Ca^{2+}$/calmodulin dependent protein kinase activity resulting in actin cytoskeleton remodeling (Wang et al., 2010). Hypomethylation of the WNT5A gene has been suggested as a potential mechanism for its increased activity (Wang et al., 2007). With exciting new technologies, such as the ability to analyze circulating tumor cells, our understanding of the importance of both canonical and non-canonical Wnt signaling in castration resistant disease will only grow, hopefully enabling the development of much needed new treatments.

## 7. Challenges and successes in targeting nuclear Wnt/β-catenin signaling

While the exact mechanism of Wnt activation in PCa may be uncertain, it is clear that Wnt signaling is an attractive pathway to target in castration resistant disease. Given the role of the Wnt pathway in many disease mechanisms, including many types of cancer, there has been a large effort to develop Wnt modulators as treatments for disease (Kahn, 2014; Zhang

and Hao, 2015). Multiple older FDA approved drugs such as Lithium and Celecoxib, were found to modulate Wnt signaling, but the majority of the newly developed potential therapeutics have yet to reach clinical trials (Kahn, 2014).

Several monoclonal antibodies are in trials for diseases where Wnt signaling is important. Romosozumab is one of the closest to the clinic and has proven successful in phase 2 clinical trials in osteoporotic women (McClung et al., 2014). Romosozumab binds sclerostin, an extracellular inhibitor of Wnt signaling secreted by osteocytes, causing an increase in Wnt signaling in osteoblasts resulting in increased bone formation. Biologics that can inhibit Wnt signaling have also been developed for cancer. Vantictumab (OMP18R5) is a monoclonal antibody, targeting Frizzled receptors 1, 2, 5, 7, and 8, that was shown to reduce the growth of breast, pancreatic, colon, and lung tumors in xenograft models (Gurney et al., 2012). Ipafricept (OMP-54F28) is a solubilized Frizzled 8 fusion receptor with a human IgG1 Fc fragment designed to sequester extracellular Wnts that also showed promise in preclinical xenograft models (Fischer et al., 2015; Le et al2015). Vantictumab and Ipafricept, both owned by OncoMed Pharmaceuticals, are currently in phase one clinical trials (Fischer et al., 2015; Zhang et al., 2016; Zhang and Hao, 2015).

Targeting the protein:protein interactions of the central Wnt mediator, β-catenin, and its activating partners is another potential therapeutic approach and has been undertaken by multiple groups. An example is the small molecules ICG-001 and PRI-724 that inhibit the binding of β-catenin to its co-activator CREB-binding protein (CBP), which in a balancing act with binding partner p300, causes stem cells to proliferate and remain potent (Lenz and Kahn, 2014). While ICG-001 has toxicity and stability issues, PRI-724, a second generation CBP/β-Catenin antagonist from Prism and Eisai Pharmaceuticals, showed an acceptable toxicity profile in phase one trials and is currently in trials for refractory colorectal cancer, refractory pancreatic cancer, and for hematologic malignancies (El-Khoueiry et al., 2013; Lenz and Kahn, 2014; Sasaki et al., 2013). It is not known what effect PRI-724 might have in PCa.

Wnt inhibitors that interfere with the β-catenin TCF/LEF interaction were also isolated in a high throughput screen for small molecules that interfered with Wnt reporter gene activity (Gonsalves et al., 2011). In collaboration with the DasGupta laboratory, we found that the small molecule inhibitor of β-catenin responsive transcription-3 (iCRT3), disrupted both β-catenin/TCF and β-catenin/AR interaction (Lee et al., 2013). Treatment with iCRT3 also resulted in decreased occupancy of β-catenin on the AR promoter and diminished AR and β-catenin target gene expression. In addition, iCRT-3 also inhibited xenograft tumor growth and blocked renewal of AR antagonist-resistant sphere-forming cells.

While there has not been extensive testing of Wnt modulators in clinical trials for CRPC, multiple drugs have also been tested in preclinical PCa cell models. A small molecule targeting dishevelled, 3289–8625, inhibited PC-3 cell proliferation (Grandy et al., 2009). Growth of DU145 cells can be inhibited by IWR-3, which stabilizes Axin leading to increased proteosomal β-catenin destruction (Chen et al., 2009). Salinomycin and Niclosamide, LRP6 antagonists, suppress both cell growth of AR negative PC3 and DU145 cells (Lu and Li, 2014; Lu et al., 2011).

While considerable effort has been expended toward the isolation of small molecule inhibitors of the Wnt/β-catenin in cancer biology (Anastas and Moon, 2013), there is still a need for further development. Some compounds were identified in cell-free assays so their *in vivo* use is uncertain (Lepourcelet et al., 2004). Others, such as ICG-001 and PRI-724, that interfere with β-catenin/CBP interaction (Emami et al., 2004), raise concerns because of the multitude of CBP interacting proteins. Compounds such as XAV939 that affect the stability and expression of β-catenin have also been investigated (Chen et al., 2009; Huang et al., 2009; Thorne et al., 2010) but run the risk of destabilizing β-catenin at the cell membrane, resulting in pleiotropic, non-specific effects. Finally small molecules that influence pathway activity at the level of ligand secretion could modulate activity of non-canonical Wnt pathways in addition to the β-catenin-dependent arm of Wnt signaling (Chen et al., 2009; Dodge et al., 2012).

## 8. Conclusion

New genome wide studies have highlighted the importance of the interaction between the Wnt/β-catenin and AR signaling in PCa. The interaction has yielded much research over the last 15+ years with many studies detailing its relevance in metastatic disease and the development of castration resistance. Although evidence exists for both synergistic and opposing interactions between β-catenin and AR, their combined role remains unclear. This is particularly true in separating out the importance of the AR/β-catenin protein:protein association from the effects of β-catenin/Wnt control of AR mRNA transcription. Other related research areas are also coming to light as important in PCa, including Wnt effects on cancer stem cells and the role of non-canonical Wnt signaling in castration resistance. Even with some mechanistic uncertainties, continuing progress is being made in the development of Wnt modulating therapeutics. The ongoing refinement of Wnt/β-catenin's role in PCa and its influence on the AR will only help this effort.

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## Highlights

- Description of interactions of the Wnt/β-catenin and AR signaling in prostate cancer.
- The interaction may be synergistic or opposing depending on context.
- Prostate cancer stem cells and non-canonical Wnt signaling in PCa also discussed.
- The status of Wnt modulating therapeutics in relation to cancer is detailed.

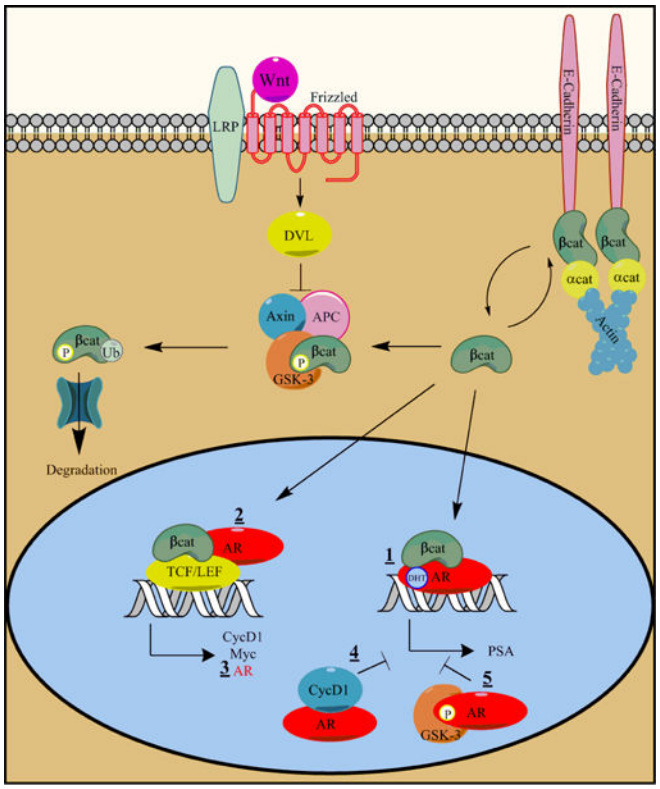


**Figure 1. Crosstalk between Wnt signaling and the Androgen Receptor**

A simplified view of canonical Wnt signaling: Cytoplasmic β-catenin (βcat), when not bound to E-cadherin at the cell membrane, is phosphorylated by GSK-3 in complex with the proteins adenomatous polyposis coli (APC) and Axin. Phosphorylated β-catenin is then ubiquitinated and degraded by the proteasome. In the presence of a Wnt extracellular signal, through Frizzled receptors in complex with LRP, disheveled (DVL) inhibits the β-catenin phosphorylation complex. This stabilizes β-catenin which translocates to the nucleus activating transcription factors of the TCF/LEF family. Multiple intersections of the Wnt pathway have been shown in PCa: 1- β-catenin binds AR directly and can enhance its transcriptional activity; 2- the AR can be recruited to the promoter of TCF/LEF target genes like CycD1 and Myc; 3- β-catenin/TCF bind to the promoter of AR itself, activating AR mRNA transcription; 4- β-catenin/TCF target gene CycD1 can inhibit AR mediated transcription; and 5- GSK-3 can phosphorylate AR leading to a decrease in AR mediated transcription (Amir et al., 2003; Kypta and Waxman, 2012; Mazor et al., 2004; Pawlowski et al., 2002; Petre et al., 2002; Salas et al., 2004; Song et al., 2003; Wang et al., 2004; Yang et al., 2002; Yang et al., 2006).