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Multifaceted Interaction Between the Androgen and Wnt Signaling Pathways and the Implication for Prostate Cancer

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Abstract Androgen action in prostate and prostate cancer cells is dependent upon the androgen receptor (AR) protein that transcriptionally regulates the expression of androgen-dependent genes in the presence of a steroid ligand. Whereas the overall schema of androgen action mediated by this receptor protein appears to be relatively simple, androgen signaling is now known to be influenced by several other cell signal transduction pathways and here we review the evidence that the canonical Wnt signaling pathway also modulates androgen signaling at multiple levels. Wnt is a complex signaling pathway whose endpoint involves activation of transcription from LEF-1/TCF transcription factors and it is known to be involved in the development and progression of numerous human epithelial tumors including prostate cancer. β-catenin protein, a particularly critical molecular component of canonical Wnt signaling is now known to promote androgen signaling through its ability to bind to the AR protein in a ligand-dependent fashion and to enhance the ability of liganded AR to activate transcription of androgen-regulated genes. Under certain conditions, glycogen synthase kinase-3β (GSK-3β), a protein serine/threonine kinase that regulates β-catenin degradation within the Wnt signaling pathway, can also phosphorylate AR and suppress its ability to activate transcription. Finally, it was recently found that the human AR gene itself is a target of LEF-1/TCF-mediated transcription and that AR mRNA is highly upregulated by activation of Wnt signaling in prostate cancer cells. Paradoxically, Wnt activation also appears to stimulate Akt activity promoting an MDM-2-mediated degradation process that reduces AR protein levels in Wnt-stimulated prostate cancer cells. Collectively, this information indicates that the multifaceted nature of the interaction between the Wnt and the androgen signaling pathways likely has numerous consequences for the development, growth, and progression of prostate cancer. J. Cell. Biochem. 99: 402–410, 2006.

Key words: prostate cancer; androgen receptor; Wnt signaling; β-catenin; GSK-3β; Akt

The human prostate gland, a sexual accessory tissue of males, is dependent on male (androgenic) steroid hormones for its development and maturation. Likewise, the abnormal prostate growth diseases that are so commonly associated with male aging, prostate cancer and benign prostate hyperplasia, also develop and progress under the influence of androgenic steroids. Therapeutics for these disease conditions often utilize medical (drug) or even surgical procedures to reduce the levels of circulating androgen or to block their ability to activate the androgen-mediated cell signaling pathway in the diseased prostate cell. The integral relationship between androgenic steroids and the prostate in normal and disease states identifies the cellular androgen signaling pathway as a critical mediator of the biology of this tissue and an inviting target for therapeutic agents to prevent or suppress major prostate diseases. As we now understand it, the core molecular strategy of androgen signaling is

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relatively simple, yet this signaling pathway can be influenced and modulated by cross-talk with other cell signaling pathways and evidence is accumulating that these points of cross-talk might be key determinants of the abnormal behavior of the prostate cell in disease states. Here, we will discuss the multifaceted manner with which the canonical Wnt signaling pathway influences and modulates androgenic signaling and the implications of these interacting signaling pathways for prostate cancer development and progression.

An Overview of the Androgen Signaling Pathway and its Action in Prostate Cancer Cells

The most critical molecular component of the androgen signaling pathway is the androgen receptor (AR) protein, a unique member of the nuclear steroid receptor gene family with a molecular mass of approximately 110 kd in size that preferentially utilizes dihydrotestosterone as its natural ligand [Heinlein and Chang, 2004]. Like the other members of the nuclear steroid receptor family, AR is a DNA-binding transcription factor that becomes active in its ligand-engaged form. The preferred ligand for AR is dihydrotestosterone, however, mutations have been frequently detected in human prostate tumor cells and in prostate cancer cell lines that alter the ligand specificity of the AR and allow for promiscuous activity in the presence of alternative steroid ligands that do not bind to the wild-type receptor protein [Dehm and Tindall, 2005; Javidan et al., 2005]. Like other steroid receptor proteins the AR protein can be categorically subdivided into modules of differing functional domains; whereas the N-terminal region contains structural information needed to form a transcriptionally active molecule (referred to as a transactivation domain), the central region contains the DNA-binding site, and the C-terminal region contains the ligand-binding site [Shen and Coetzee, 2005]. Ligand binding induces a conformational transition in the AR protein that facilitates disassociation of cytoplasmic AR from its chaperone, translocation of the protein into the nucleus where it homo-dimerizes and binds to definable DNA response elements that are similar to DNA response elements recognized by glucocorticoid and progesterone receptors; being that it preferentially binds to small regions of DNA containing palindromes of a 6-bp core sequence [typified by 5′-A-G-A-A-C-A-3′] that are separated by a 3 nucleotide spacer [Nelson et al., 1999]. Binding of AR dimers to these DNA elements modifies the secondary and tertiary structures of the proximal chromatin and attracts other transcriptional co-factors that further modifies the regional chromatin in a manner conducive to the onset of transcription of the adjoining gene unit. Whereas the spectrum of gene products regulated by AR-mediated transcription is not fully characterized there are some very well-characterized targets such as the human prostate-specific antigen (PSA) gene. The promoter element of this gene, when recombined upstream of a standard reporter gene (most often luciferase) in plasmid expression vectors can be used to quantify the activity of the androgen signaling pathway in any given cell type. Indeed, such reporter vectors have been very useful in identifying alternative molecular paradigms that influence or modify the activity of the canonical androgen signaling pathway in prostate cancer cells. These alternative mechanisms sometimes involve an interaction (of the AR) with alternate signaling pathways (exemplified by mitogen-activated protein kinase pathways such as those driven by Erb and IGF receptors) that selectively target certain amino acid residues of the AR protein for phosphorylation (thus modifying its transcriptional activity) or a direct interaction between the AR protein and other proteins (referred to as co-activators or co-repressors, depending upon the end effect on the androgen signaling process) [Heinlein and Chang, 2004; Dehm and Tindall, 2005; Javidan et al., 2005]. In this regard, it is the intent of this review to selectively focus on the growing awareness of the ability of the cellular Wnt signaling pathway and its individual molecular components to influence androgen signaling in prostate and prostate cancer cells and to highlight the implications of the complex interaction between these two unique signaling pathways for prostate cancer biology.

An Overview of the Wnt Signaling Pathway in Normal and Malignant Cells

The Wnt signaling pathway was initially defined through the study of unique developmental aberrations in Drosophila, Xenopus, and other organisms that were associated with mutations in genes now known to encode

proteins that are involved in the Wnt signaling process [Huelsken and Behrens, 2002]. The term Wnt was derived from the realization of the common relationship between the drosophila gene *wingless* (otherwise known as *wg*) and the mouse gene *int-1*, both of which encode protein ligands that are capable of initiating the Wnt signaling process. Wnt is a powerful and complex signaling pathway that is integrally involved in stem-cell renewal, embryonic development, and tissue differentiation and, as is becoming increasingly apparent, aberrant activity of the Wnt signaling pathway is also associated with tumorigenesis of several organ systems [Polakis, 2000; Lustig and Behrens, 2003; Logan and Nusse, 2004; Nusse, 2005; Reya and Clevers, 2005]. Like the androgen signaling process, canonical Wnt signaling is a means to control transcription of genes, particularly those that rely upon the LEF-1/TCF family of transcription factors for their expression. This family of transcription factors represents a group of proteins with DNA-binding activities that specifically recognize and bind to a contiguous 6 base concensus sequence, 5′-a/t-a/t-C-A-A-G-3′ that is found within the 5′ promoter regions of Wnt target genes [Roose and Clevers, 1999]. The known repertoire of Wnt (LEF-1/TCF) target genes includes some prominent gene products that regulate cellular proliferation including c-myc, jun, and cyclin D1; apoptotic regulators such as survivin; genes that influence cellular migratory behavior including uPA, MMP-7, and CD-44; genes that play a role in differentiation including FGF2, PPAR-δ, BMP-4, and c-Ret; and genes that have the potential to influence carcinogenesis including endothelin-1 and COX-2 [He et al., 1998; Mann et al., 1999; Tetsu and McCormick, 1999; Zhang et al., 2001]. More relevant for this review, it was recently shown that the human AR is also a direct gene target of LEF-1/TCF transcriptional activation, having at least three functional TCF recognition elements within a 2,000-bp region of its 5′ promoter [Yang et al., 2006]. Therefore, as will be discussed below, regulation of AR expression mRNA expression by TCF transcription factors identifies one of the mechanistic processes through which Wnt signaling is able to modulate the activity of the androgen signaling pathway in prostate and prostate cancer cells.

Under Wnt-unstimulated conditions, TCF-family transcription factors are generally found within the nucleus bound to their DNA recognition elements but they are transcriptionally inactive due to their association with a member of the groucho protein family that blocks their ability to capture the other chromatin-modifying proteins necessary for formation of an active transcription complex. The switch to a transcriptionally active complex requires nuclear entry and binding of the protein that is most integrally associated with the canonical Wnt signaling pathway, β-catenin. The 92 kd β-catenin protein is a critical co-factor in LEF-1/TCF-mediated transcription as its binding to the N-terminal domain of these transcription factors induces a conformational change that releases the groucho suppressor from the DNA-bound complex and facilitates recruitment of other proteins required for the formation of an active transcription complex and this activity represents the endpoint of Wnt signaling. A schematic presentation summarizing the various molecular components involved in LEF-1/TCF activation by the Wnt signaling pathway is presented in Figure 1.

The molecular components of the Wnt signaling pathway upstream of this endpoint function mainly to regulate the stability and nuclear penetrance of β-catenin. This activity involves a large repertoire of proteins that interact in a complex fashion, parts of which are still not thoroughly understood. In epithelial cells, β-catenin protein is stable when bound to the cytoplasmic domain of a classical cadherin (E-, N-, and P-cadherin), but it is rapidly degraded in the cytoplasm (in Wnt-unstimulated cells) by a multiprotein degradation complex anchored on an Axin-bound protein scaffold that contains a critical β-catenin-binding protein, adenomatous polyposis coli (APC), and multiple regulatory protein kinases including serine/threonine glycogen synthase kinase-3β (GSK-3β) and casein kinase Iα. Under Wnt-unstimulated conditions, free β-catenin is captured by this complex where it is sequentially phosphorylated at multiple serine/threonine residues within its N-terminal domain by the kinases of the degradation complex. Phosphorylated β-catenin attracts the β-tranducine repeat containing protein (β-TrCP), an F-box subunit of an ubiquitin ligase complex that then promotes ubiquitinylation of β-catenin rendering it an avid target for proteolysis by proteasomes. Thus, in Wnt-unstimulated cells, free β-catenin is rapidly degraded before it can enter the nucleus.

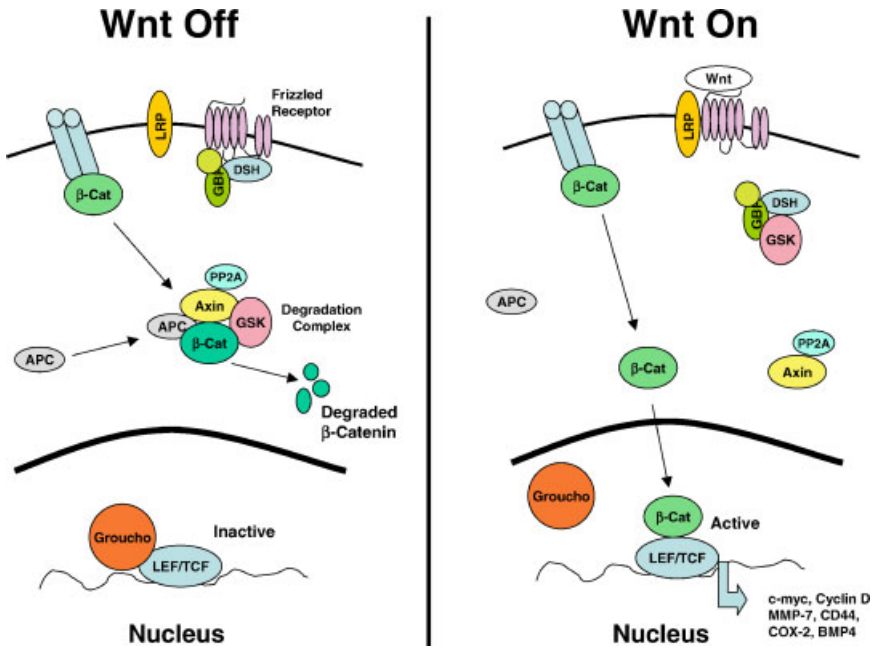

Fig. 1. Graphical depiction of the schema of the canonical Wnt signaling pathway. (**Left panel**) In the ''Wnt-Off'' state, TCF transcription factors are inert due to their association with a repressor (*groucho* protein) on their nuclear DNA binding sites. β-catenin, which is needed for release of the repressor protein, is captured by a degradation complex before it can enter the nucleus and is phosphorylated and subsequently ubiquitinylated and degraded by the proteasome. (**Right panel**) In the ''Wnt-On'' state, the binding of an activational Wnt to its Frizzled receptor enables the capture, phosphorylation and inactivation of GSK-3β by an alternative complex containing dishevelled protein and free β-catenin is able to enter the nucleus to complex with TCF, displacing groucho and enabling formation of an active transcription complex.

Wnt signaling in normal (non-malignant) cells is generally initiated by any of a family of secreted glycoprotein ligands, now referred to as Wnts, through their binding to cell surface receptor proteins which are members of the cysteine-rich, seven transmembrane domain *frizzled* (*fzd*) family. In human, the family of secreted Wnt glycoproteins includes 19 members varying from 350 to 400 amino acids in length [Miller, 2002]. There are 10 known human frizzled genes but only a subset of these are active in the transmission of canonical Wnt signaling activity [Huang and Klein, 2004]. Various combinations of Wnt ligand-*fzd* receptor complexes may result in a cascade of variable intracellular signaling allowing information transfer from extracellular signals into intracellular responses. When productively engaged in canonical Wnt signaling activation, the Wnt ligand-*fzd* receptor complex abrogates the activity of the β-catenin degradation complex by suppressing the activity of GSK-3β through a process that appears to require its sequestration into an alternate multiprotein complex containing the dishevelled (dsh) protein that itself phosphorylates GSK-3β rendering it inactive. In malignant cells, Wnt signaling can also be abnormally activated through mechanisms that involve mutations of key components of the pathway and this is best exemplified in colon cancer wherein mutations in the APC protein that binds β-catenin to the degradation complex or mutations of serine/threonine residues within the N-terminal domain of β-catenin itself, can suppress β-catenin degradation leading to constitutive activation of Wnt signaling even in the absence of Wnt ligand. Other human tumor systems that are associated with abnormal Wnt signaling include breast, head, and neck and oral cancers as well as melanoma.

Wnt Signaling and Prostate Cancer

In concordance with the evidence for the participation of canonical Wnt signaling in numerous human solid tumors mentioned above, evidence is also accumulating to indicate the involvement of abnormal Wnt signaling in prostate cancer development and/or progression [Yardy and Brewster, 2005]. Several different studies evaluating expression of Wnt

effectors in human prostate tumor specimens have reported an upregulation in the expression of Wnt ligands (Wnt−1, −2, and −5a) in cancer cells compared to normal prostate cells [Katoh, 2001; Chen et al., 2004; Glinsky et al., 2004] whereas another immunohistochemical study reported that expression of WIF1, an inhibitor of Wnt signaling was consistently downregulated in prostate tumor cells compared to normal [Wissmann et al., 2003]. Other immunohistochemical surveys have also found that the critical Wnt activator protein β-catenin is upregulated in expression or abnormally localized (in the cytoplasm or nucleus) of human prostate cancer cells indicating the likelihood of a "Wnt-On" state in such tumor cells [Chesire et al., 2002; de la Taille et al., 2003; Chen et al., 2004]. With regards to the specific cause for abnormal Wnt activation in prostate cancers, mutations in the APC or β-catenin genes similar to those found in colon cancer have also been detected in prostate cancers [Voeller et al., 1998; Chesire et al., 2000; Gerstein et al., 2002], although at a frequency that is relatively low (approximately 5%) compared to relatively high rate with which these types of mutations are found in colon cancer cells. Additionally, there is reason to believe that the high rate of PTEN deletion that is associated with prostate cancer development and progression might promote Wnt activation in prostate cancer cells. Loss of PTEN promotes the downstream activity of Akt and increases the ability of this conditional protein kinase to phosphorylate GSK-3β, effectively suppressing GSK-3β role in regulating the degradation of β-catenin [Mulholland et al., 2006]. Finally, there is evidence for at least one novel mechanism leading to Wnt activation in prostate cancer; specifically in association with the expression of an unusual Y-chromosome-linked member of the cadherin family, protocadherin-PC (PCDH-PC) (also referred to as PCDHY) that appears to endogenously upregulate Wnt signaling when expressed [Yang et al., 2005] though the precise mechanism of this effect has yet to be determined. Whereas abnormal activation of Wnt in adult cells has some very significant consequences related to the development of malignancy based upon the repertoire of growth-promoting and apoptosis-suppressing genes that are upregulated by this signaling pathway, the consequences are especially pertinent to prostate cancer because of the seemingly multiple nodes through which Wnt and its molecular components can influence androgenic signaling in these cells and these are described below.

Wnt and AR Interaction I: β-Catenin Is a Ligand-Dependent Co-Activator of AR

β-catenin binding is obligatory for activation of the transcriptional potential of the TCF family transcription factors. As is now demonstrated by numerous experimental paradigms involving co-immunoprecipitation or yeast-2-hybrid assays, β-catenin can also directly bind to the (steroid) ligand-engaged AR protein [Truica et al., 2000; Pawlowski et al., 2002; Yang et al., 2002; Song et al., 2003; Masiello et al., 2004] and this binding has a strong promoting effect on the ability of the AR to induce transcription of androgen-sensitive gene products. In this sense, β-catenin (wild-type or mutated) is considered to be a ligand-dependent co-activator of AR transcription. The binding of β-catenin to ligand-engaged AR facilitates the movement of β-catenin into the nucleus [Mulholland et al., 2002; Pawlowski et al., 2002] and β-catenin protein remains complexed to AR protein at its binding site on chromatin where it has been shown to be associated with the androgen-regulated element within the promoter region of the human PSA gene [Li et al., 2004]. Evaluation of other members of the steroid receptor family (specifically ER, PR, and GR) has not identified a similar interaction with β-catenin so this phenomenon is likely restricted to AR [Pawlowski et al., 2002]. β-catenin binds to the C-terminal end (within the activator function 2 region of the ligand-binding domain) of AR and, although this interaction is dependent upon steroid ligand engagement, it appears to be able to modify the ligand requirement of AR [Song et al., 2003]. β-catenin binding enables more efficient utilization of androstenedione or estradiol as agonists of androgen signaling and reduces the ability of bicalutamide to serve as an antagonist of the AR. It is of further interest that a truncated peptide of β-catenin (the C-terminal region) inhibits AR-mediated transcription suggesting a novel means through which one might exploit this interaction to suppress androgen signaling in a prostate cancer cell [Song and Gelmann, 2005]. Given that two types of transcription factors (TCF and AR) can bind to β-catenin it should not be surprising that there might be competition

for available β-catenin between these two proteins and, in this regards, high-level expression of AR has been shown to suppress activation of transcription by TCFs [Mulholland et al., 2003; Cronauer et al., 2005]. Thus, even though here we focus on the actions of Wnt on AR signaling, it is important to remember that there is mutual cross-talk between both of these signaling pathways that has important consequences for the human prostate cancer cell. Indeed, this mutual cross-talk is also apparent in the next node of interaction between Wnt and AR that involves another critical molecule in the Wnt signaling pathway, GSK-3β.

Wnt and AR Interaction II: GSK-3β Phosphorylates AR and Modulates its Activity

GSK-3β regulates β-catenin degradation and this function alone places it in the category of a tumor suppressor gene. More recently, GSK-3β was shown to be an AR-interacting protein and a (negative) regulator of AR-mediated transcription [Sharma et al., 2002; Salas et al., 2004; Wang et al., 2004]. This effect was first described in studies wherein overexpression of GSK-3β was linked to reduced expression of PSA in prostate cancer cells (LNCaP) as well as reduced ability of AR to activate expression of a luciferase reporter driven by an AR-dependent promoter. Secondly, it was demonstrated that exposure of prostate cancer cells to LiCl, a known GSK-3β inhibitor, abrogated the inhibitory effect of GSK3β expression. Further work from the same lab demonstrated that GSK-3β interacts with and phosphorylates AR in a manner that appears to impair the interaction between the NH2- and COOH-terminus of the protein that is essential for transcriptional activity. Subsequently, it was confirmed that LiCl can also increase AR-mediated transcription in the human CWR22rv-1 cell line that also endogenously expresses AR [Cronauer et al., 2005] although it should be noted that all of the above findings remain controversial given contradictory reports that GSK-3β has the ability to enhance AR function [Liao et al., 2004; Mazor et al., 2004], at least in some instances. Whereas all of this work suggests that GSK-3β influences AR activity, clearly more work is needed in this area to address the contradictory results. Certainly one aspect that might confuse the issue is the functional state of GSK-3β in the prostate cancer cell being evaluated. GSK-3β can itself be phosphorylated and inactivated either through the endogenous activity of the canonical Wnt signaling pathway or through the activity of Akt that also phosphorylates and inactivates GSK-3β (32). Both of these signaling pathways (Wnt and Akt) might be active in any given prostate cancer cell and they are certainly associated with more aggressive states of prostate cancer suggesting that the effects of endogenous GSK-3β might decrease in relevance for regulation of androgen signaling as the prostate cancer progresses to a more advanced stage.

Wnt and AR Interaction III: LEF-1/TCF Regulates Expression of AR mRNA and Protein

As was described in detail above, the canonical Wnt signaling pathway regulates the expression of genes that are targets of the LEF-1/TCF family of transcription factors. Recently, it was reported that there are at least 8 core' TCF-binding sites within a 2,000 basepair region of DNA immediately upstream of the transcription start site of the human AR gene [Yang et al., 2006]. A chromatin immunoprecipitation assay showed that three of these potential TCF-binding sites were apparently associated with β-catenin protein only under conditions when Wnt signaling was activated in LNCaP cells (following transduction with recombinant Wnt-1 expressing adenovirus or transfection with mutated β-catenin or PCDH-PC). This effect was consistent with the ability to show that luciferase expression from recombinant hAR promoter/luciferase reporter vectors containing these three β-catenin/TCF-binding sites was highly upregulated by Wnt activation and that site-specific mutations within the dominant TCF-binding site abrogated this upregulation following Wnt stimulation. Indeed, semi-quantitative RT-PCR measurements showed that hAR expression is upregulated from 12- to 16-fold by Wnt stimulation of LNCaP or CWR22rv-1 cells that endogenous expression hAR. This evidence now supports the idea that the human AR gene is a direct target of the Wnt signaling pathway and that Wnt activation in prostate cancer cells has the potential of strongly upreguating hAR mRNA expression.

Paradoxically, this same experimental study [Yang et al., 2006] showed that even though Wnt signaling upregulated AR mRNA, AR protein levels were reduced by up to 90% when

compared to control (non-Wnt activated) prostate cancer cells. Further study of this seemingly contradictory phenomenon supports the idea that Wnt signaling also upregulates an AR degradation pathway in the prostate cancer cell that appears to be mediated by and dependent upon the MDM2 protein that can bind to AR (as well as p53) in the phosphorylated state leading to its ubiquitinylation and degradation by the proteasome. Indeed, the application of proteasome inhibitors or an siRNA against MDM2 in Wnt-stimulated LNCaP cells increased AR protein levels to a range commensurate with the (12- to 16-fold) elevated level of AR mRNA in these cells.

Wnt and Androgen Signaling Cross-Talk: The Implications for Prostate Cancer

We have described above four major nodes through which the Wnt signaling pathway influences the activity of the androgen signaling pathway in the prostate cancer cell: (1) the β-catenin protein that is a key regulator of TCF-mediated transcription in the Wnt signaling pathway also promotes transcriptional activity of the AR protein in a ligand-dependent fashion; (2) GSK-3β, a serine/threonine protein kinase that is a critical regulator of β-catenin degradation in Wnt signaling can suppresses AR transcriptional activity, apparently through process that requires phosphorylation of the AR protein; (3) transcription of the human AR gene is upregulated by TCF-family transcription factors in a process that is activated through the canonical Wnt signaling pathway; and (4) expression of the human AR protein is downregulated through an AKT- and MDM2-mediated degradation process that is also apparently activated by Wnt signaling in prostate cancer cells. We have not even yet mentioned the evidence that at least one member of the TCF family (TCF4) has also been shown to bind to AR within its DNA-binding domain [Amir et al., 2003], though the effects of this binding on AR activity seemed to be, at least, less prominent than the other effects described above. For the most part, the interacting nodes of these two very dissimilar signaling pathways have differing effects; some potentiating androgen action whereas others are more likely to suppress androgen action and this implies the possibility that these multiply interacting nodes provide a means to increase or decrease androgen signaling as a function of controlled cell growth that may become unbalanced in the malignant prostate cell. While the importance of the androgen signaling pathway for prostate oncogenesis has long been known, its extensive and multifaceted interaction with the potentially oncogenic Wnt signaling pathway certainly suggests that this latter pathway may be more important to the natural history of prostate cancer development and progression that had previously been supposed.

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REFERENCES

Amir AL, Barua M, McKnight NC, Cheng S, Yuan X, Balk SP. 2003. A direct beta-catenin-independent interaction between androgen receptor and T cell factor 4. J Biol Chem 278:30828–30834.

Chen G, Shukeir N, Potti A, Sircar K, Aprikian A, Goltzman D, Rabbani SA. 2004. Upregulation of Wnt-1 and beta-catenin production in patients with advanced metastatic prostate carcinoma: Potential pathogenetic and prognostic implications. Cancer 101:1345–1356.

Chesire DR, Ewing CM, Sauvageot J, Bova GS, Isaacs WB. 2000. Detection and analysis of beta-catenin mutations in prostate cancer. Prostate 45:323–324.

Chesire DR, Ewing CM, Gage WR, Isaacs WB. 2002. In vitro evidence for complex modes of nuclear beta-catenin signaling during prostate growth and tumorigenesis. Oncogene 21:2679–2694.

Cronauer MV, Schulz WA, Ackermann R, Burchardt M. 2005. Effects of WNT/beta-catenin pathway activation on signaling through T-cell factor and androgen receptor in prostate cancer cell lines. Int J Oncol 26:1033–1040.

de la Taille A, Rubin M, Chen M-W, Vacherot F, Gil-Diez de Medina S, Burchardt M, Buttyan R, Chopin D. 2003. β-catenin related anomalies in apoptosis-resistant and hormone-refractory prostate cancer. Clin Cancer Res 9: 1801–1807.

Dehm SM, Tindall DJ. 2005. Regulation of androgen signalling in prostate cancer. Exp Rev Anticancer Ther 5:63–74.

Gerstein AV, Ameida TA, Zhao G, Chess E, Shih IM, Buhler K, Pienta K, Rubin MA, Vessella R, Papadopoulos N. 2002. APC/CTNNB1 (beta-catenin) pathway alterations in human prostate cancers. Genes Chrom Cancer 34: 9–16.

Glinsky GV, Glinskii AB, Stephenson AJ, Hoffman RM, Gerald WL 2004. Gene expression profiling predicts clinical outcome of prostate cancer. J Clin Invest 113:806–808.

He TC, Sparks AB, Rago C, Hermeking H, Zawel L, da Costa LT, Morin PJ, Vogelstein B, Kinzler KW. 1998.

Identification of c-myc as a target of the APC pathway. Science 281:1509–1512.
Heinlein CA, Chang C. 2004. Androgen receptors in prostate cancer. Endocr Rev 25:276–308.
Huang HC, Klein PS. 2004. Gen Biol 5:234 (E-Publication).
Huelsken J, Behrens J. 2002. The Wnt signaling pathway. J Cell Sci 115:3977–3988.
Javidan J, Deitch AD, Shi X-B, de Vere White RW. 2005. The androgen receptor and mechanisms for androgen independence in prostate cancer. Cancer Invest 23:420–528.
Katoh M. 2001. Frequent up-regulation of WNT2 in primary gastric cancer and colorectal cancer. Int J Oncol 19:1003–1007.
Li H, Kim JH, Koh SS, Stallcup MR. 2004. Synergistic effects of coactivators GRIP1 and beta-catenin on gene activation: Cross-talk between androgen receptor and Wnt signaling pathways. J Biol Chem 279:4212–4220.
Liao X, Thrasher JB, Holzbeierlein J, Stanley S, Li B. 2004. Glycogen synthase kinase-3beta activity is required for androgen-stimulated gene expression in prostate cancer. Endocrinology 145:2941–2949.
Logan CY, Nusse R. 2004. The Wnt signaling pathway in development and disease. Ann Rev Cell Devel Biol 20: 781–810.
Lustig B, Behrens J. 2003. The Wnt signaling pathway and its role in tumor development. J Cancer Res Clin Oncol 129:199–221.
Mann B, Gelos M, Siedow A, Hanski ML, Gratchev A, Ilyas M, Bodmer WF, Moyer MP, Riecken EO, Buhr HJ, Hanski C. 1999. Target genes of beta-catenin-T cell-factor/lymphoid-enhancer-factor signaling in human colorectal carcinomas. Proc Natl Acad Sci USA 96:1603–1608.
Masiello D, Chen SY, Xu Y, Verhoeven MC, Choi E, Hollenberg AN, Balk SP. 2004. Recruitment of beta-catenin by wildtype or mutant androgen receptors correlates with ligand stimulated growth of prostate cancer cells. Mol Endocrinol 18:2388–2401.
Mazor M, Kawano Y, Zhu H, Waxman J, Kypta RM. 2004. Inhibition of glycogen synthase kinase-3 represses androgen receptor activity and prostate cancer cell growth. Oncogene 23:7882–7892.
Miller JR. 2002. The Wnts. Gen Biol 3: Reviews 3001.1-3001.15 (E-Publication).
Mulholland DJ, Cheng H, Reid K, Rennie PS, Nelson CC. 2002. The androgen receptor can promote beta-catenin nuclear translocation independently of adenomatous polyposis coli. J Biol Chem 277:17933–17943.
Mulholland DJ, Read JT, Rennie PS, Cox ME, Nelson CC. 2003. Functional localization and competition between the androgen receptor and T-cell factor for nuclear beta-catenin: A means for inhibition of the Tcf signaling axis. Oncogene 22:5602–5613.
Mulholland DJ, Dedhar S, Wu H, Nelson CC. 2006. PTEN and GSK3beta: Key regulators of progression to androgen-independent prostate cancer. Oncogene 25: 329–337.
Nelson CC, Hendy SC, Shukin RJ, Cheng H, Bruchovsky N, Koop BF, Rennie PS. 1999. Determinants of DNA sequence specificity of the androgen, progesterone and glucocorticoid receptors: Evidence for differential steroid receptor response elements. Mol Endocrin 13:2090–2107.
Nusse R. 2005 Wnt signalling in disease and in development. Cell Res 15:28–32.
Pawlowski JE, Ertel JR, Allen MP, Xu M, Butler C, Wilson EM, Wierman ME. 2002. Liganded androgen receptor interaction with beta-catenin: Nuclear co-localization and modulation of transcriptional activity in neuronal cells. J Biol Chem 277:20702–20710.
Polakis P. 2000. Wnt signaling and cancer. Genes Dev 14: 1837–1851.
Reya T, Clevers H. 2005. Wnt signalling in stem cells and cancer. Nature 434:343–350.
Roose J, Clevers H. 1999. TCF transcription factors: Molecular switches in carcinogenesis. Biochim Biophys Acta 1424:23–37.
Salas TR, Kim J, Vakar-Lopez F, Sabichi AL, Troncoso P, Jenster G, Kikuchi A, Chen SY, Shemshedini L, Suraokar M, Logothetis CJ, DiGiovanni J, Lippman SM, Mentor DG. 2004. Glycogen synthase kinase-3 beta is involved in the phosphorylation and suppression of androgen receptor activity. J Biol Chem 279:19191–19200.
Sharma M, Chuang WW, Sun Z. 2002. Phosphatidylinositol 3-kinase/Akt stimulates androgen pathway through GSK3beta inhibition and nuclear beta-catenin accumulation. J Biol Chem 277:30935–30941.
Shen HC, Coetzee GA. 2005. The androgen receptor: Unlocking secrets of its unique transactivation domain. Vit Horm 71:301–319.
Song LN, Gelmann EP. 2005. Interaction of beta-catenin and TIF2/GRIP1 in transcriptional activation by the androgen receptor. J Biol Chem 280:37853–37867.
Song LN, Herrell R, Byers S, Shah S, Wilson EM, Gelmann EP 2003. Beta-catenin binds to the activation function 2 region of the androgen receptor and modulates the effects of the N-terminal domain and TIF2 on ligand-dependent transcription. Mol Cell Biol 23:1674–1687.
Tetsu O, McCormick F. 1999. Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells. Nature 398:422–6.
Truica CI, Byers S, Gelmann EP. 2000. Beta-catenin affects androgen receptor transcriptional activity and ligand specificity. Cancer Res 60:4709–4713.
Voeller HJ, Truica CI, Gelmann EP. 1998. Beta-catenin mutations in human prostate cancer. Cancer Res 58: 2520–2523.
Wang L, Lin HK, Hu YC, Xie S, Yang L, Chang C. 2004. Suppression of androgen receptor-mediated transactivation and cell growth by the glycogen synthase kinase 3 beta in prostate cells. J Biol Chem 279:32444–32452.
Wissmann C, Wild PJ, Kaiser S, Roepcke S, Stoehr R, Woenckhaus M, Kristiansen G, Hsieh JC, Hofstaedter F, Hartmann A, Knuechel R, Rosenthal A, Pilarsky C. 2003. WIF1, a component of the Wnt pathway, is down-regulated in prostate, breast lung and bladder cancer. J Pathol 201:204–212.
Yang F, Li X, Sharma M, Sasaki CY, Longo DL, Lim B, Sun Z. 2002. Linking beta-catenin to androgen-signaling pathway. J Biol Chem 277:11336–11344.
Yang X, Chen M-W, Terry S, Vacherot F, Chopin DK, Bemis DL, Kitajewski J, Benson MC, Guo Y, Buttyan R. 2005. A human- and male-specific protocadherin that acts through the Wnt signalling pathway to induce neuroendocrine differentiation of prostate cancer cells. Cancer Res 65:5263–5271.

Yang X, Chen M-W, Terry S, Vacherot F, Bemis DL, Capodice J, Kitajewski J, de la Taille A, Benson MC, Guo Y, Buttyan R. 2006. Complex regulation of human androgen receptor expression by Wnt signaling in prostate cancer cells. Oncogene (Online publication Feb 2006).

Yardy GW, Brewster SF. 2005. Wnt signalling and prostate cancer. Prostate Cancer Prostate Dis 8:119–126.

Zhang T, Otevrel T, Gao Z, et al. 2001. Evidence that APC regulates survivin expression: A possible mechanism contributing to the stem cell origin of colon cancer. Cancer Res 61:8664–8667.