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MINIREVIEW

Cross Talk between Wnt/β-Catenin and CIP2A/Plk1 Signaling in Prostate Cancer: Promising Therapeutic Implications

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Aberrant activation of the Wnt/β-catenin pathway and polo-like kinase 1 (Plk1) overexpression represent two common events in prostate cancer with relevant functional implications. This minireview analyzes their potential therapeutic significance in prostate cancer based on their role as androgen receptor (AR) signaling regulators and the pivotal role of the tumor suppressor protein phosphatase 2A (PP2A) modulating these pathways.

THE Wnt/β-CATENIN PATHWAY IN PROSTATE CANCER

Wnt signaling plays a critical role in development, and β-catenin represents a key downstream factor in the Wnt/β-catenin pathway. In the cytoplasm, β-catenin is a component of a protein complex that includes glycogen synthase kinase 3β (GSK-3β), axin, and adenomatosis polyposis coli (APC), and GSK-3β-dependent β-catenin phosphorylation induces its proteosomal degradation. After Wnt activation, β-catenin is stabilized and binds to the T-cell factor (Tcf)/lymphoid enhancer factor (Lef) family transcription factors, thereby leading to a transcriptional activation of multiple target genes (1, 2). Aberrant activation of the Wnt/β-catenin pathway is a common event in many tumor types such as colorectal, lung, liver, or ovarian cancer, through alterations affecting not only β-catenin but also other components as GSK-3β, axin, or APC. As a result, β-catenin accumulates and becomes transcriptionally active for proto-oncogenes related with cell proliferation and apoptosis (2–5).

A high number of studies have described the significance of the Wnt/β-catenin pathway in prostate cancer (PCa) progression and therapy-resistant state. Wnt1 and β-catenin upregulation has been reported in PCa cells and correlated with high Gleason score and serum prostate-specific antigen (PSA) levels, hormone-refractory PCa status, and metastatic disease (6, 7). Of note, it has been described as a gradual loss of nuclear β-catenin distribution that correlates with increasing Gleason grade (8). Consistent with its potential oncogenic role in PCa, Wnt/β-catenin has also been described to regulate both autophagy (9) and epithelial-mesenchymal transition through HIF-1α regulation (10, 11), and Wnt/β-catenin activation has been found to promote PCa progression *in vivo* (12). In contrast, Wnt/β-catenin inhibition by different strategies such as the small molecule PKF118-310 (13), the pyranocoumarin decursin (14), or miR-320 upregulation (15) has shown potent antitumor effects.

The activation of Wnt/β-catenin signaling seems to occur through different mechanisms than in other tumor types. Although mutations in axin have been identified and other mutations affecting β-catenin or APC are present at low levels, the loss or downregulation of cell adhesion components such as E-cadherin seems to play a dominant role in β-catenin activation (16–19). Moreover, a mutual inhibition between WNT11 and the androgen receptor (AR) has been reported, in which androgen depletion induces WNT11 activation that inhibits androgen-dependent but not androgen-independent cell growth (20).

Importantly, the involvement of the Wnt/β-catenin pathway in AR signaling and its role in PCa progression to an androgen-independent phenotype have been extensively studied. AR has been shown to signal through Wnt/β-catenin in a ligand-independent manner as an adaptation to castration levels of androgen (21). In fact, it has been reported that increased levels and nuclear colocalization *in vivo* of AR and β-catenin occur in castration-resistant PCa (CRPC), which supports an aberrant β-catenin-dependent AR activation in the progression to CRPC (22). Moreover, AR expression and Wnt/β-catenin activation correlate with aggressiveness and metastatic disease in PCa patients (23), and simultaneous inhibition of both pathways have shown promising antitumor properties in xenograft PCa models (24). However, β-catenin might also play important AR-independent oncogenic roles in CRPC, since high levels of nuclear β-catenin and low or no AR expression have been shown to define a subgroup of bone metastatic PCa patients (25). In addition, the Wnt/β-catenin pathway is involved in AKT activation, and overexpression of Wnt inhibitory factor 1 (WIF-1) leads to AKT inhibition, thereby inducing chemosensitivity in phosphatase and tensin homolog (PTEN)-mutated PCa cells (26). This event is of high importance, since AR together with AKT signaling provide a mechanism to escape the apoptosis induced after androgen withdrawal therapy in which loss of PTEN and GSK3β inhibition are key molecular events (27).

POLO-LIKE KINASE 1: MOLECULAR SIGNALING AND FUNCTIONAL ROLE

The polo-like kinases (Plk) constitute a family of serine/threonine phosphatases that includes five members (from Plk-1 to Plk-5), all

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of them containing an N-terminal kinase domain and two C-terminal polo box domains (28). Plk-1 is the best-characterized member of the Plk family due to the fact that Plk-1 is a protein required for the successful completion of mitosis. In fact, Plk-1 silencing has been reported to disrupt embryonic development by impairing the formation of polar bodies and a correct meiotic chromosome separation (29–31). Moreover, Plk-1-dependent cyclin B1 phosphorylation promotes the nuclear translocation of the Cdc2/cyclin B1 complex which represents a key event for M-phase coordination and G_2/M transition (30, 31).

Consistent with its role in mitosis, enhanced Plk1 activity is observed in those cells with high mitotic rates including tumor cells. Thus, Plk1 overexpression has been reported in a wide variety of tumor types (see Table S1 in the supplemental material) (32–64) and associated with poor patient outcomes in many of those cancers (32–36, 39, 40, 44, 45, 50–53, 58, 59, 65). Of note, Plk-1 upregulation is observed in many types of human cancers since it phosphorylates and inactivates the tumor suppressor p53 (66) and also causes the p53 inactivation and/or degradation in an MDM2, GTSE1 (G_2- and S-phase-expressed 1 protein), and Topo-1 binding protein-dependent manner (67–70).

Interestingly, Plk1 has also been reported to be commonly overexpressed in prostate cancer (PCa), and it correlates with tumor progression and poor patient outcomes (71). The first pieces of evidence about the oncogenic role of Plk-1 in PCa were documented by Reagan-Shaw and Ahmad (72). These authors found enhanced Plk1 levels in PCa cells compared to normal prostate epithelial cells and observed that Plk1 depletion decreased cell viability and promoted apoptosis in PCa cells but had no effects in normal cells. Moreover, Plk1 inhibition in androgen-insensitive PCa has been reported to induce necroptosis (73) and cause mitotic arrest and defects in both cytokinesis and centrosome formation of PCa cells (72). These findings are consistent with the data published in many other tumor types, in which tumor growth inhibition and enhanced apoptosis have been observed in preclinical studies using Plk-1 specific small interfering RNAs (74–86). Another interesting issue of therapeutic relevance is that Plk-1 inhibition has been reported to enhance both radiation and anticancer drug efficacy in many tumor types (87–92). Moreover, Plk1 overexpression has been shown to be critical for PTEN-depleted cells to adapt to mitotic stress, thereby facilitating the loss of PTEN-induced PCa formation (93), and its inhibition has been described to enhance the anticancer activity of metformin (94).

EMERGING RELEVANCE OF THE CIP2A/Plk1/AR AXIS: COTARGETING Plk1 AND β-CATENIN AS A NOVEL THERAPEUTIC STRATEGY FOR TREATING CRPC

It has recently been reported that the use of the Wnt/β-catenin signaling inhibitor IWR-1 has synergistic antitumor effects in combination with the Plk1 inhibitor BI2536 both *in vitro* and *in vivo* (95). However, the molecular mechanisms involved in both Plk1 and β-catenin regulation are still not fully understood, and their therapeutic value as novel molecular targets in CRPC is also not known. In this line of thinking, CIP2A has recently been reported to positively regulate both Plk1 stability and activity, determining its function in cell cycle progression (96). CIP2A has also been reported to be widely overexpressed in PCa patients, and it has been proposed as a candidate therapeutic target in this disease (96). Protein phosphatase 2A (PP2A) dephosphorylates β-catenin, impairing its degradation (97, 98). As CIP2A is a potent

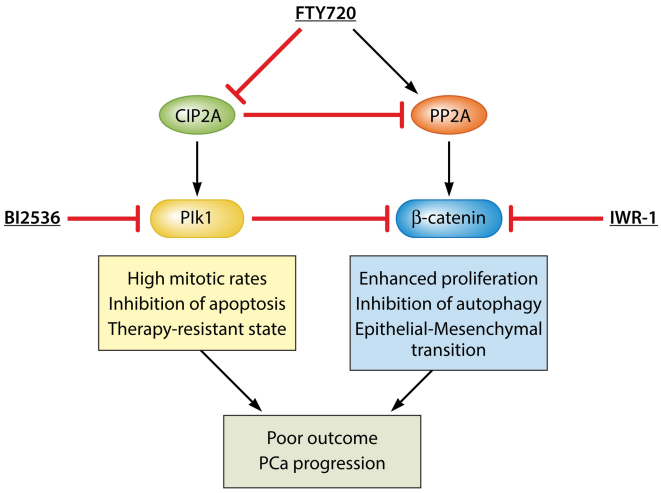

FIG 1 Schematic view of the cross talk between the Wnt/β-catenin and CIP2A/Plk1 pathways in PCa.

endogenous PP2A inhibitor, CIP2A upregulation might indirectly lead to reduced β-catenin levels via PP2A inactivation, reinforcing the Plk1-dependent β-catenin inhibition (95). However, the upregulation of both Plk1 and β-catenin in PCa cells and its correlation with progression and advanced disease have been well established (6, 7, 12, 71, 72), despite the fact that one would expect a correlation between CIP2A/Plk1 upregulation with reduced β-catenin levels. Therefore, these observations would support the use of Wnt/β-catenin inhibitors together with CIP2A/Plk1-inactivating drugs, since inhibition of CIP2A/Plk1 could reinforce Wnt/β-catenin activation as an unwanted side effect. Interestingly, CIP2A has been identified as a molecular target and key determinant of FTY720 action (99, 100). However, the precise molecular mechanism by which FTY720 induces CIP2A downregulation remains to be investigated. In fact, FTY720 is a FDA-approved drug that has shown marked antitumor effects in prostate cancer cells (99) and that represents a good candidate to target the CIP2A/Plk1/AR signaling axis in CRPC. A schematic view of cross talk between the Wnt/β-catenin and CIP2A/Plk1 pathways in prostate cancer is shown in Fig. 1. The potential synergistic effect of FTY720 used in combination with Wnt/β-catenin inhibitors has yet to be investigated. Taxanes such as docetaxel, cabazitaxel, and paclitaxel are currently used as standard chemotherapy agents in CRPC. However, the ultimate development of resistance is a therapeutic challenge and an inevitable event in CRPC patients (101). Importantly, CIP2A silencing has been found to decrease proliferation, promote apoptosis, and enhance the sensitivity of prostate cancer cells to cabazitaxel treatment (102). Plk1 downregulation or ectopic expression of miRNA-100, a negative Plk1 regulator, has been reported to enhance sensitivity to docetaxel by impairing proliferation and inducing apoptosis and cell cycle arrest (103). This therapeutic value of targeting Plk1 to overcome docetaxel resistance has been reported to be mediated by its regulatory role on CDC25C (104). Moreover, 4E-BP1 depletion increases paclitaxel-induced antitumor effects, and its role in mitotic progression is modulated by its direct interaction and phosphorylation by Plk1 (105, 106). Therefore, downregulation of CIP2A/Plk1 could contribute to sensitizing PCa cells to taxane-based therapy through different mitosis-related proteins such as

CDC25C or 4E-BP1. Thus, the potential role of the CIP2A/Plk1 axis and Wnt/β-catenin in the development of resistance to taxane-based therapies is therefore a very interesting issue to be further addressed.

Furthermore, reactivation of the AR pathway is a key molecular event in the progression to CRPC. As described above, β-catenin has been reported to induce activation of AR signaling, and Plk1 inhibition led to reduced AR activity, impairing tumor growth in LNCaP CRPC xenografts. Castration-associated Plk1 overexpression induces activation of the AR pathway through a transcriptionally AR upregulation. At the molecular level, Plk1 activates AKT, leading to AKT-mediated phosphorylation and nuclear accumulation of the transcription factor Twist1 that increases AR expression through binding to E-boxes in the AR promoter (107). Moreover, the use of an AR antagonist reduced Plk1 levels, which reveals the existence of a reciprocal Plk1/AR regulation (108). Therefore, the finding of a Plk1-dependent regulation of β-catenin reveals a novel regulation circuitry linking β-catenin, Plk1, and AR signaling in prostate cancer. Mechanistically, Plk1 phosphorylation of the negative β-catenin regulator axin2 promotes β-catenin degradation by enhancing the binding between β-catenin and GSK3β (95). The mutual regulation between these pathways and the role that other actors as CIP2A would be playing here could have important therapeutic implications that merits discussion. Thus, the different AR inhibitory therapies would lead to a concomitant Plk1 inactivation, suggesting that Wnt/β-catenin and Plk1 inhibitors could have antagonistic effects in combination with AR inhibitors that should be investigated. Altogether, the use of CIP2A/Plk1/AR-inactivating drugs such as FTY720 in combination with Wnt/β-catenin inhibitors represents a novel therapeutic approach in CRPC that warrants further investigation.

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