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REVIEW ARTICLE

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# Signalling pathways in a nutshell: from pathogenesis to therapeutical implications in prostate cancer

Aviv Philip Goncharov[a,b#], Constantinos Dicusari Elissaiou[a#], Elad Ben Aharon Farzalla[a], Giorgi Akhvlediani[c,d,e], Nino Vashakidze[a] and Gvantsa Kharaishvili[f,g]

[a]Department of Clinical and Molecular Pathology, Palacky University, Olomouc, Czech Republic; [b]Department of Oncology, University Hospital, Olomouc, Czech Republic; [c]Faculty of Medicine, Georgian-American University, Tbilisi, Georgia; [d]American Hospital in Tbilisi, Tbilisi, Georgia; [e]Faculty of Medicine, University of Georgia, Tbilisi, Georgia; [f]Department of Human Morphology and Pathology, Medical Faculty, David Tvildiani Medical University, Tbilisi, Georgia; [g]Department of Clinical and Molecular Pathology, University Hospital, Olomouc, Czech Republic

**ABSTRACT**

From tumorigenesis to the establishment of local or metastatic high-grade tumours, an integral part of the cellular lifespan relies on various signalling pathways. Particular pathways that allow cells to proliferate by creating a network of new blood vessels have been documented, whereas other pathways are primarily involved with a migration to distant body parts, partially through the process of epithelial-mesenchymal transition (EMT). This review will discuss the different signalling pathways, such as TGF-β, Cripto-1, Wnt pathways, Hedgehog, Notch and NF-κB pathways, and how they promote tumour initiation and progression by influencing diverse cellular processes and EMT in general and in benign and malignant prostate tumours. This review will discuss only the critical pathways. Therefore, many other types of signalling pathways which are related to prostate cancer will not be discussed. Possibilities for further investigation will be mentioned, as many underlying mechanisms involved in these pathways have potential as targets in future tumour therapy. This review will also introduce some novel clinical trials relating to the inhibition of signalling pathways and their clinical outcomes.

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## 1. Background

Prostate cancer is the second most common tumour in men after skin cancer. It is considered the second most common cause of cancer-related deaths amongst men in the United States and fifth globally [1,2]. Prostate cancer classification and staging systems are based on clinical and laboratory evaluation, as well as imaging and histological classification [3].

According to treatment response and clinical and histopathological features, tumours may be classified as organ-confined, locally advanced, metastatic castration-sensitive prostate cancer (mCSPC), metastatic castration-resistant prostate cancer (mCRPC), or as a lethal disease [3–5].

mCRPC is further divided into five subgroups according to the histologic characteristics and the expression of androgen receptor (AR) and neuroendocrine (NE) markers: adenocarcinoma ($AR^+/NE^-$), double-positive ($AR^+/NE^+$), low AR ($ARL/NE^-$), neuroendocrine ($AR^-/NE^+$), and double-negative ($AR^-/NE^-$) [6].

The treatment lines vary between the types and are directly related to the extent of tumour progression. The epithelial-mesenchymal transition (EMT) is an integral stage in determining the invasive potential, progression, and aggressiveness of the tumour [7]. Our group has previously described the importance of the EMT process and its mechanism of action in benign and malignant prostate tumours. Initiation of the EMT process requires the activation of various signalling pathways within the cell. Later, cells reduce the expression of proteins such as E-cadherin, β- catenin, Desmoplakin, Syndecan, and several others. At the same time, proteins that are related to mesenchymal phenotypes, such as Vimentin, Fibronectin, Snail, and Slug, are upregulated [8]. A harsh tumour environment encourages the utilisation of different mechanisms to promote tumour survival and

**CONTACT** Gvantsa Kharaishvili gvantsa.kharaishvili@upol.cz Department of Clinical and Molecular Pathology, Palacky University, University Hospital, Olomouc, Czech Republic
[#]Authors with equal contribution.

proliferation. Changes in the tumour microenvironment are essential; therefore, it is important to point out the different mechanisms leading to EMT [9]. These pathways are located within various cell compartments and will affect the survival of the tumour and the prognosis of the patient. This article will thoroughly review the different signalling pathways and complex mechanisms that may affect the overall survival rate of prostate cancer patients and introduce novel treatment options available for clinicians.

## 2. TGF-β signalling pathway

Transforming growth factor (TGF) is a family of growth factors composed of several structurally similar polypeptides, including TGF-βs, activins, and BMPs [10]. They have diverse roles in regulating cell proliferation, differentiation, migration, and extracellular matrix deposition [11]. Mammalian organisms contain three distinct isoforms termed TGF-β1, TGF-β2, and TGF-β3, which function similarly *in vitro* but give rise to more than 30 different phenotypes upon their genetic deletion in mice [12].

TGF-β signalling begins with the ligation of its receptor (Figure 1). The human genome encodes seven type I receptors [i.e. ALK (activin receptor-like kinase 1–7)] and five type II receptors [i.e. TβRII (TGF-β type II receptor), ActR-II (activin type II receptor), ActR-IIB, BMPR-II (BMP type II receptor) and AMHR-II (MIS type II receptor)]. The type III receptor is an accessory receptor required for TGF- β1 assistance. Type I and II receptors contain an N-terminal extracellular ligand-binding domain, transmembrane, and cytoplasmic serine/threonine kinase domains. Upon ligand binding, the type II receptor kinase activates the type I receptor kinase through phosphorylation in the glycine-serine motif of the type I receptor. This activates the type I receptor kinase domain and propagates downstream signalling through the phosphorylation of receptor-activated Smads (R-Smads) in the canonical Smad pathway. Conversely, this may also trigger signalling through

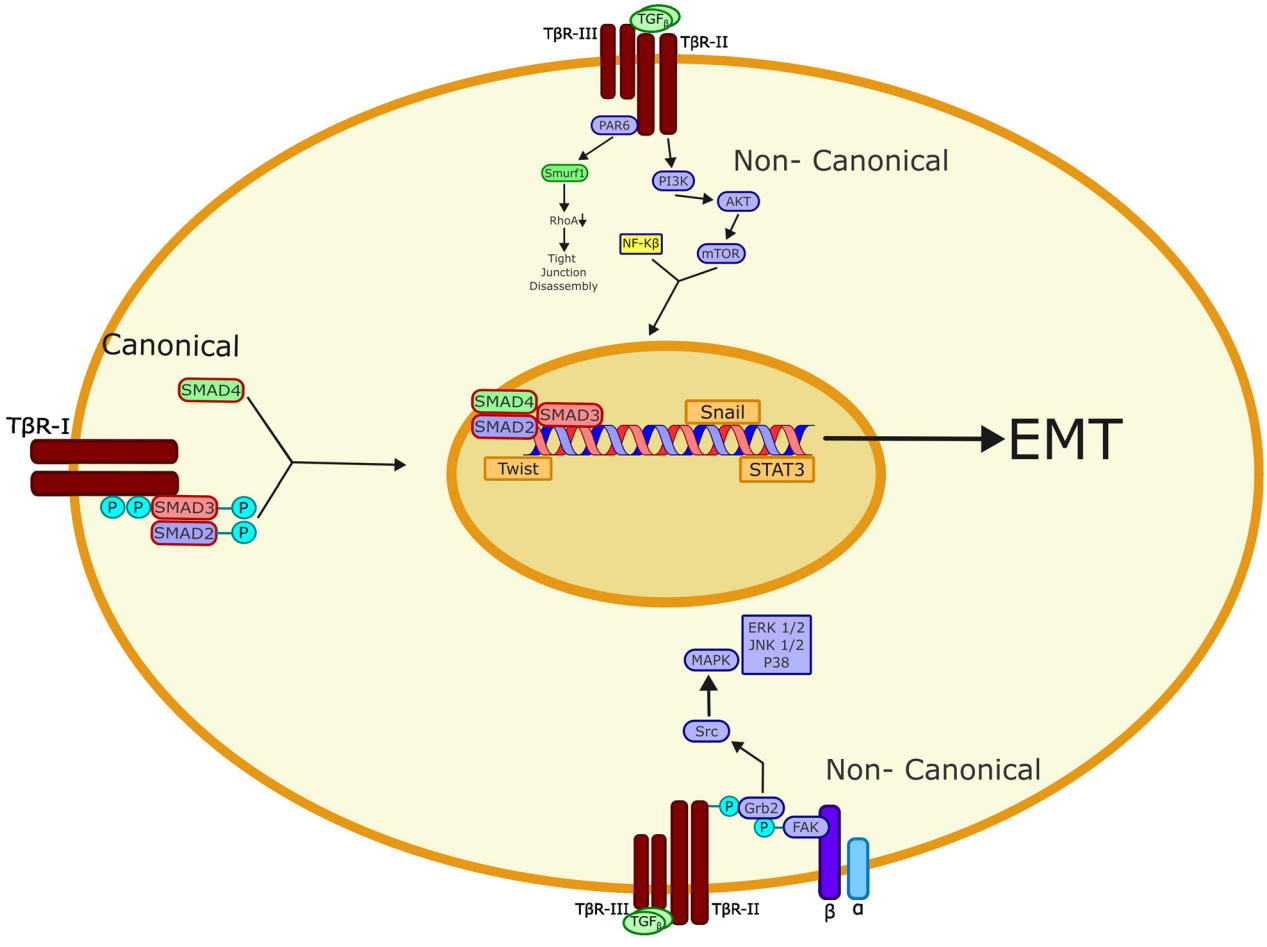


**Figure 1.** Canonical and noncanonical TGF-β signalling systems are coupled to EMT in mammary epithelial cells (please refer to the text in the 2nd section).

the mitogen-activated protein kinase (MAPK) pathway. The activated TGF-β – receptor complex phosphorylates R-Smads in their C-terminus. Activated R-Smads associate with a common-mediator Smad (Co-Smad), enter the nucleus, where Smads bind to DNA or communicate with transcriptional coactivators or corepressors. Inhibitory Smads (I-Smads), whose expression is induced by TGF-β, can inhibit the phosphorylation of R-Smads. I-Smads also recruit Smurf E3-ubiquitin ligases to the receptor complex, thus directing TGF-β receptors for degradation [10,13].

In addition to its ability to activate canonical Smad2/3-dependent pathways, TGF-β also regulates numerous 'non-canonical' effector systems, including (i) small GTP-binding proteins (Ras, Rho, Rac1); (ii) phosphoinositide-3-kinase (PI3K), AKT, and mTOR; (iii) MAP kinases and (iv) NF-κB and Cox-2 [14,15].

TGF-β-activated MAPK pathways include the extracellular signal-regulated kinases 1 and 2 (ERK1 and ERK2), the c-Jun N-terminal kinases 1 and 2 (JNK1 and JNK2), and the four p38 isoforms (α, β, γ and δ) [10].

Paradoxically, TGF-βs are known to be tumour suppressive [16], and TGF-β upregulation in many tumours is correlated with disease progression [17]. In normal epithelial cells and early tumour stages, TGFβ possesses antiproliferative properties which inhibit cell growth by inducing apoptosis. Loss of the antiproliferative responsiveness to TGF-β is often considered a leading step in cancer progression [18]. Interestingly, one study using a mouse skin model of chemical carcinogenesis showed that expression of TGF-β1 by keratinocytes relates to its dual function, which depends on the pathological state of the tumour. Before the onset of a malignant tumour, TGF-β1 acts as a tumour suppressor, but following tumorigenesis, it promotes tumour progression and invasiveness [19]. Although various carcinomas acquire mutations in several components of TGF-β, complete abrogation of TGF-β signalling is not a common occurrence in tumorigenesis. Additionally, exogenous TGF-β has been shown to promote tumour invasiveness [20].

TGF-β can promote tumorigenesis by modulating the tumour microenvironment and promoting EMT. This is due to its involvement in the critical processes of changing epithelial cellular adhesion molecules into mesenchymal molecules [21], high expression of metalloproteases [22], increased motility, and angiogenesis [23]. In addition, TGFβ stimulates the disassembly of tight junctions. Par6, a key component of epithelial polarity complexes, regulates tight junction assembly. TGFβ-ligand binding enables type II TGFβ receptor kinase, which is associated with occludins at tight junctions, to phosphorylate Par6. Phosphorylated Par6 allows for the recruitment of Smurf1, which in turn leads to ubiquitination and degradation of RhoA, a small GTPase family member responsible for stress fibre formation and the maintenance of apicobasal polarity and junctional stability [24]. In a study by Goby et al. loss or low levels of the type II TGF-β receptor correlated with high-grade tumours [25]. Although Smad4 is frequently inactivated in pancreatic cancers, the Smad genes rarely acquire mutations in humans. Thus, after cells are no longer prone to inhibition by TGF-β growth inhibitors, autocrine TGF-β signalling promotes tumour progression [26].

In the prostate, TGF-β plays several roles. Firstly, it is responsible for the embryonic development and differentiation of glandular epithelium. Interestingly, the signalling pathway between epithelial and mesenchymal cells involving TGF-β is directly involved in prostate morphogenesis. TGF-β also plays a role in the inhibition of cellular proliferation as well as the induction of apoptosis during homeostasis. Thus, loss of TGF-β is associated with carcinogenesis. Although it acts as an antiproliferative agent, it is also pro-oncogenic and potentiates metastasis when overexpressed in the late stages of prostate cancer [27]. Another study by Wang et al. showed the connection between TGF-β expression and benign prostatic hyperplasia (BPH). TGF-β signalling induces the expression of miR-223-3p, thus promoting BPH-1 cell viability and DNA synthesis, inhibiting apoptosis of BPH cells, and decreasing the pro-apoptotic molecules Bax/Caspase 3. Therefore, the inhibition of miR 223-3 P may be used as a therapeutic target for improving aggressive cases of BPH [28].

An effective therapy targeting TGF-β must focus on two crucial aspects of the cytokine activity: inhibition of the TGF-β mediated tumour progression in advanced metastatic prostate cancer and preservation of the growth-inhibitory function of the cytokine that is seen in the early stages of prostate tumorigenesis. The dual role of TGF-β in disease promotion and inhibition poses a challenge in the use of the pathway as a therapeutic target. The imbalance between Smad-dependent and Smad-independent signalling mediates the switch from tumour suppression to promotion. Thompson-Elliot et al. showed that AP-1 transcriptional regulators, Ski/SnoN, and PTEN proteins may play an essential role in the resistance to the effect of TGF-β on cellular proliferation in the prostate and other tumours [27]. Existing preclinical studies provide a possible understanding of the TGF-β signalling pathway in prostate tumorigenesis that may allow it to serve as a target for intervention. The use of neutralising antibodies, antisense oligonucleotides, and small molecule inhibitors of the kinase activity of the

receptor complexes have served as treatment options in studies targeting the TGF-β signalling pathway in a variety of human malignancies [29]. A recent clinical trial, No. NCT02452008 explores the possible use of TGF-β receptor inhibitors, Galunisertib and Enzalutamide, in mCRPC. This was an open-label randomised trial composed of two arms, where the first arm involved the combination of both drugs and the second arm involved Enzalutamide alone. The study observed progression-free survival in patients with mCRPC, the tumour marker kinetics, and the Overall Survival of the patients [30]. This trial is currently ongoing (phase 2), with no published results to date. Initially, activation of TGF-β target gene *PRRX2* facilitates the resistance to Enzalutamide. It was found that the gene tends to be overexpressed in double-negative prostate cancer (DNPC) and is associated with a reduced overall survival rate. Moreover, it was identified that *PRRX2* is related to changes in a few signalling pathways, such as CDK4/6/Rb/E2F and BCL2. Subsequently, Rodriguez et al. showed that prostate cancer previously treated with CDK4/6 and BCL2 inhibitors expressed reduced resistance to Enzalutamide [31].

In a review by Ottley et al. the implications of microRNA on non-canonical TGF-β pathway were investigated. MicroRNA has been shown to regulate and adjust many TGF-β superfamily members. Therefore, it was proposed that miRNA could target non-canonical Smad signalling factors. As a result, this process can potentially modulate the effects of TGF-β indirectly, providing novel therapeutic targets for advanced prostate cancer [32]. The Erk pathway is one of the potential adjuvant therapeutic targets found. Amongst these non-canonical Smad signalling pathways investigated, Erk5, in particular, showed promising results. Erk5 has been directly linked to human and murine prostate cancer. The article mentions a study carried out by Clapé et al. where it was found that Erk5 is a target of a microRNA class, specifically miR-143. An inverse correlation was identified, where levels of miR-143 decreased in prostate cancer progression both *in vitro* and *in vivo*, but Erk5 levels were significantly increased. The study also demonstrated that this inverse correlation and the significantly high Erk5 levels lead to higher rates of prostate cancer cell proliferation (Figure 2). This suggests the role of miR-143 as a potential tumour suppressor in prostate cancer [32].

R-smads, as mentioned earlier, are involved in the direct signalling of the TGF-β receptors. Erks normally inhibit the R-Smads, and miRNAs that target the Erk are decreased in prostate cancer [32]. An ectopic expression of Erk may have the potential to restore the growth-inhibitory effects of TGF-β in advanced prostate cancer. In addition to the Erk pathway, further investigations into the Rho pathway, another

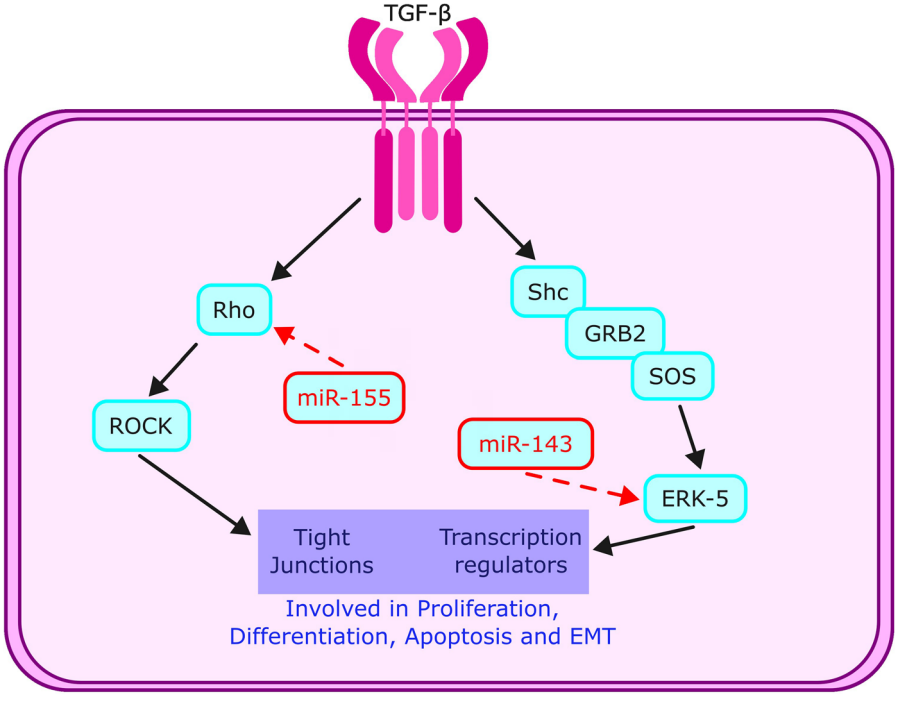


**Figure 2.** Non-canonical TGF-beta signalling pathways. miRNA class implications on non-canonical signalling pathways ERK and rho and the possibilities of fine-tuning, amplifying, or abrogating growth factor signalling.

non-canonical signalling factor, should be conducted to explore whether Rho pathways can be targeted by microRNA, particularly miR-155, in prostate cancer cells to successfully restore the effects of TGF-β [32].

Shou et al. discuss the various factors contributing to the slow progress toward targeted therapy. They highlight the duality of action and the prominence of adverse reactions as two key challenges impeding advancement. These obstacles, coupled with the relatively early stage of research, are likely the primary reasons why the downstream mechanisms of TGF-β remain insufficiently understood. They describe a few modes of action that may be used as a basis for developing this therapy. One such mode uses small molecule inhibitors of TGF-β tyrosine kinase that modify the interaction between ATP and its binding pocket, thus blocking SMAD2 and SMAD3. This treatment possibility does not appear to be effective since it exhibits poor pharmacokinetic and pharmacodynamic characteristics. Another possible treatment modality is through the use of monoclonal antibodies (MABs). These block TGF-β receptor binding ligands. MABs are expensive to produce routinely and, in this case, must work against the high affinity of TGF-β to the cell surface receptor complex. Also, there is no evidence that the MABs will be evenly and effectively distributed within the tumour. High-affinity ligand traps also exist; these were designed to eliminate TGF-β1 and TGF-β3 and, thereby, prevent the interaction between them and the transmembrane TβRII receptors. There is also a capability of inhibiting TGF-β synthesis by utilizing antisense oligonucleotides (ASOs). These are DNA or RNA sequences composed of short nucleotides (15–25 nucleotides). ASOs are a promising therapeutic modality nowadays not only because of their low toxicity profile but also because of their relatively high specificity and safety. Nevertheless, it has some clinical limitations due to its instability and low cell uptake. Eventually, it is suggested that inhibition of EMT in combination with cytotoxic drugs or radiotherapy will also inhibit the TGF-β signalling pathway and, therefore, will halt cancer progression. In many types of cancer, the combination of immune checkpoint inhibitors (ICI) or chimeric antigen receptor-T cell (CAR-T) therapies and TGF-β inhibitors is under trial [33].

## 3. Cripto-1 signalling pathway

Cripto-1 is a member of the epidermal growth factor (EGF)-CFC protein family that plays a role during early embryogenesis [34]. Cripto-1 is overexpressed in various human carcinomas and has a potential role in EMT [20]. *In vitro* and *in vivo* studies showed overexpression of Cripto-1 in mammary cells, which increased cell migration and tumorigenesis in mice [35].

In the Nodal canonical pathway, Cripto-1 acts as a cell surface co-receptor [36]. It possesses an ECF domain, which interacts with Nodal, and a CFC domain, which interacts with ALK4 or ALK7. This results in the transactivation of the ActRIIB receptor and the subsequent phosphorylation of activin type I receptors ALK4 or ALK7. The interaction of Cripto-1 through its CFC domain makes it crucial for the subsequent binding of Nodal to the ALK4/ActRIIB receptor complex, eventually leading to the phosphorylation of Smad2. Through activating the ActRI/ActRIIB complex, phosphorylation of cytoplasmic Smad2 and/or Smad3 becomes possible, which, after interacting with Smad4, leads to activation of the Smad pathway. The resulting transcriptional complexes interact with various transcriptional factors, e.g. FOXH1, which promotes transcription of certain genes and contributes to breast cancer cell invasion and growth [37].

Cripto-1 can also bind to glypican-1 in lipid raft-associated microdomains where signalling proteins such as c-SRC are found. This leads to the activation of the tyrosine kinase c-SRC pathway and the subsequent activation of MAPK and AKT in a Nodal-independent manner. Through the phosphorylation of ERKs by MEKs, MAPKs can enter the cell's nucleus and activate transcription factors, thus stimulating cell proliferation. The AKT signalling cascade also contributes to cell survival and proliferation by activating receptor kinases and a series of molecular interactions leading to its dissociation from the plasma membrane, followed by further signalling events [37]. Stimulation of cellular changes such as cell proliferation, migration and EMT by Cripto-1 depends on the latter's binding to Glypican-1 and the subsequent activation of c-SRC/MAPK/AKT signalling pathways [38].

Cripto-1 is significantly expressed in prostate cancer and is associated with its progression especially when comparing the expression between prostate cancer and BPH. Liu et al. showed that cripto-1 expression was lower in BPH and higher in prostate cancer [39]. According to Arnouk et al. 42% of prostate cancer tissues examined showed elevated levels of Cripto-1 [40]. Immunohistochemistry has shown that cripto-1 promotes EMT in prostate cancer by downregulating E-Cadherin and upregulating β-catenin. Additionally, there is a significant relationship between the expression of cripto-1 and prostate-specific antigen (PSA), Gleason grade, clinical staging, and metastasis in lymph nodes in patients with prostate cancer. Cripto-1

also actively participates in embryonic development and malignant tumour development and, later, promotes metastasis as part of the EMT. To demonstrate the involvement of Cripto-1 in the EMT process, the researchers silenced the transcription of the gene encoding Cripto-1 by using short hairpin RNA (shRNA), thus showing an increase in the expression of E-cadherin, an indicator of the reversal process of the EMT. Eventually, this showed a suppression of the prostate cancer's ability to migrate [39].

In another study by Liu et al. 138 prostate cancer and 67 BPH tissue samples were examined. It was revealed that the expression of Cripto-1 in malignant samples was significantly related to shorter Biochemical recurrence (BCR) free survival. Initially, out of 81 patients with PSA above 10 ng/ml, 32.10% ($p = 0.008$) of them were presented with overexpression of Cripto-1. A similar trend is seen with the Gleason score, where out of 71 patients with a Gleason score above 7, 30.99% ($p = .011$) were presented with overexpression of Cripto-1. A correlation between Cripto-1 overexpression and lymph node metastasis was established as well, with 15.79% overexpression ($p = .025$) in patients with metastatic disease [41]. Another interesting aspect is the development of radio-resistance in prostate cancer. It is described that a few cellular signalling mechanisms, such as p53, bcl-2, NF-kB, Cripto-1, and others, are responsible for radio-resistance. In their article, Tesar et al. showed that Cripto-1 is highly expressed in prostate cancer cells, which are radio and chemo-resistant. Additionally, the high expression of Cripto-1 is associated with a shorter survival without biochemical relapse, making it a potential target for immunotherapy [42].

Lawrence et al. showed that Nodal signalling and Cripto-1 are essential for the survival and growth of prostate tumours. The nodal signalling pathway is a member of TGF-β and is vital for promoting the growth of prostate cancer cells. In the study, immunohistochemistry was used to investigate the involvement of these signalling pathways in tumorigenesis. Cripto-1 mRNA and proteins were detected in all cells examined. A soluble form of Cripto-1 lacking a GPI anchor was detected and is associated with activation of the Nodal signalling pathway in many types of cancer, especially in breast and colon cancers [43].

## 4. Wnt signalling pathway

The Wingless-type (Wnt) signalling pathway is crucial for cell cycle regulation, stem cell renewal, cell proliferation, and differentiation. Dysregulation of Wnt signalling is associated with several hereditary and degenerative diseases and cancers [44].

Wnt signalling currently includes two major pathways: the first is the canonical or Wnt/β-catenin pathway (Figure 3), while the second is the non-canonical pathway, which does not involve β-catenin stabilisation. Another pathway exists as well that controls the orientation of mitotic spindles in Drosophila and Caenorhabditis elegans [45] and is similar to the pathways found in vertebrates [46].

### 4.1. Canonical wnt signalling pathway

The canonical Wnt pathway (Figure 3) regulates cellular responses through β-catenin. In the absence of Wnt ligand binding (Wnt signal), β-catenin is phosphorylated by casein kinase 1γ (CK1γ) and a multicomponent destruction complex [containing scaffolding proteins GSK3β (glycogen synthase kinase 3 β), AXIN and adenomatous polyposis coli (APC) protein]. After phosphorylation, β-catenin is then recognised by the E3 ubiquitin ligase β-TRCP (β-transducin repeat-containing protein) and targeted for rapid degradation in the cytoplasm *via* the ubiquitin-proteasome pathway. Low nuclear levels of β-catenin are maintained by nuclear exporters APC and AXIN, which shuttle β-catenin from the nucleus back to the cytoplasm [47]. Without the AXIN-based scaffold, β-catenin escapes capture, phosphorylation, and ubiquitination [48].

Wnt signalling is activated at the cell membrane where Wnt ligands form tertiary complexes with their respective frizzled receptors and transmembrane coreceptors LRP5 and LRP6. Co-factors such as R-spondin and Wise also take part in Wnt-receptor complex activity. Signalling proceeds through the protein Dishevelled, which enters the plasma membrane and initiates an interaction with frizzled receptors and other Dishevelled molecules [49,50]. Phosphorylation of the cytoplasmic tail of LRP5 or LRP6 and the formation of the Dishevelled polymer serve as mediators for the translocation of AXIN to the plasma membrane and inactivation of the destruction complex. Thus, β-catenin gradually accumulates in the cytoplasm and enters the nucleus, forming a complex with the T-cell factor or the lymphoid enhancer factor (TCF/LEF) family of transcription factors. The binding of β-catenin to transcription factors transactivates downstream target genes, such as *c-myc, urokinase-type plasminogen activator, cyclin D1, MMP-7, CD44, survivin, endothelin-1, Cox-2* and *–9, versican, periostin, fibronectin,* the *AR* gene, and others. These influence cell cycle regulation, invasion, and metastasis [51–56].

Anthony et al. mentioned that constitutive activation of the Wnt signalling pathway is linked with the development of numerous cancers. It is supported by the

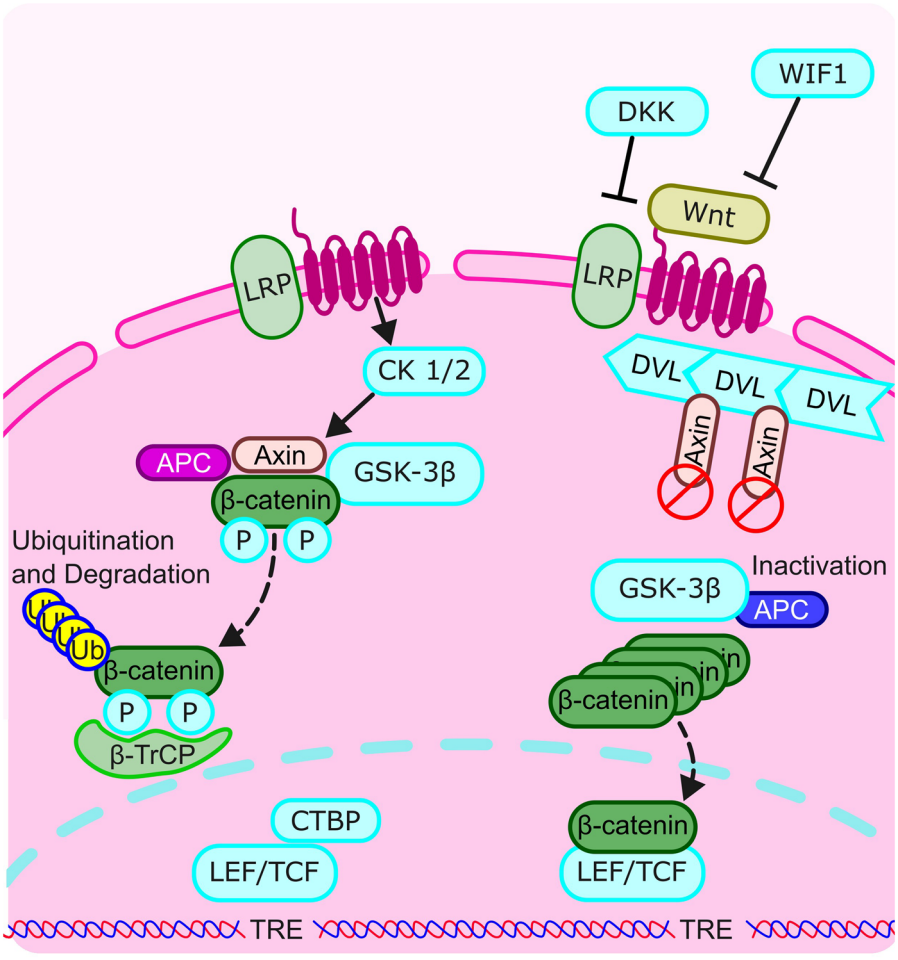


**Figure 3.** Canonical wnt signalling pathway (Kharaishvili et al. 2011).

evidence of inappropriate activation of the Wnt pathway in nearly 100% of all non-hereditary colorectal cancers. It is suggested that the reason is due to mutations in the destruction complex (e.g. gain-of-function of β-catenin or loss-of-function of APC/Axin) [57].

Aberrant β-catenin signalling is thought to be a very early step in colon cancer development. β-catenin's nuclear accumulation is observed during early stages of development in some types of cancers, such as Intestinal-type gastric carcinoma, as well as in more advanced stages of cancer progression [58,59]. Similarly, β-catenin delocalisation from the membrane to the cytoplasm is frequently observed at the early stages of breast carcinomas, but its nuclear localisation is associated with invasiveness [60]. Nuclear localisation of β-catenin was found in desmoid-type fibromatosis, solitary fibrous tumours, endometrial stromal sarcoma and synovial sarcoma [61].

Further investigations would lead to a better understanding of nuclear events driving Wnt signal transduction and the identification of nuclear factors that lead to Wnt signalling. This may result in better insights surrounding the mechanisms of the Wnt signal's propagation and contribute to the development of targeted interventions directed at the major activating mutations responsible for inappropriate activation of the Wnt pathway [57].

β-catenin-TCF activity can be modified by mammalian mitogen-activated protein (MAP) kinase pathway components: (1) transforming growth factor β-activated kinase (TAK1) and (2) NEMO-like kinase (NLK) [62]. TAK1 activates NLK, and the latter phosphorylates members of the TCF family. Phosphorylation alters the DNA-binding properties of the β–catenin–TCF complex and, in this way, blocks Wnt target gene activation. Input from the MAP kinase pathway can, therefore, negatively regulate the Wnt pathway in mammalian cells [63]

Besides TCF/LEF, Wnt signalling can modify other transcription factors, e.g. its role in the upregulation and downregulation of the NF-κB pathway [64]. Apart from the MAP kinase pathway, the Hedgehog pathway and the Notch signalling pathway are also involved in important interactions with the Wnt signalling pathway, which can include the development of various types of cancers, such as oral squamous cell carcinoma [65].

Furthermore, recent evidence by Kumar et al. suggests that a degree of crosstalk may also exist between Notch and other associated signalling pathways, such as the Hedgehog signalling pathway. In some cases, such as in glioblastoma, this can contribute to therapy resistance resulting from the decreased expression of GLI1 due to binding by Notch signalling target Hes1. In some cases, this may provide an avenue to overcome resistance, such as in the case of ovarian cancer where Notch Ligand Jagged 1 can crosstalk with Hedgehog and induce apoptosis *via* a decrease in GLI2. The notch may also regulate similar components of these pathways primarily by mTOR, STST3 and serine/threonine kinase Akt, as observed in its interaction with Hes3 and Sonic Hedgehog [66]

In human prostate cancer, the Wnt/β-catenin pathway is strongly associated with androgen/AR-directed therapy and chemotherapy resistance [67]. In murine studies, the AR signalling cascade and Wnt pathway are known to inhibit each other [68]. Shorning et al. showed that activating the β-catenin pathway in mice leads to prostate adenocarcinoma. Also, β-catenin activation can cooperate with PTEN deletion to promote prostate cancer progression, CRPC transition, and metastasis. As canonical WNT signalling mediates cellular β-catenin levels, the level of active β-catenin in a few cancer types and prostate cancer cells is regulated by the PI3K-AKT-mTOR cascade. This pathway also mediates β-catenin localisation and other factors interacting with β-catenin. In other types of cancer, such as melanoma, PTEN modulates β-catenin nuclear localisation and transcriptional activity *via* dissociation of β-catenin from the membrane attached to E-cadherin, thus increasing tumour formation and further metastasis [69]. One of the key tumour-promoting factors that can occur during the development of proteasomal degradation-resistant cells is a missense mutation or a frameshift deletion around S37, T41, and S45 in β-catenin. Another method could involve the upregulation of oncogenic target genes such as *CCND1* and *MYC*. A β-catenin transcription inhibitor, PKF118-310, was identified and appears to produce an antitumour effect on prostate cancer *in vitro* [70]. Kaplan et al. mention that Wnt and β-catenin regulate the EMT process in prostate cancers without TMPRSS2-ERG translocations. SOX2, for example, negatively correlates with E-cadherin expression while positively correlates with the mesenchymal protein α-SMA [71].

An interesting ongoing clinical trial (No. NCT03787056) at the Hospices Civilis de Lyon in France deals with the Wnt/β-catenin pathway from a different point of view. It is speculated that the canonical pathway activation may also be achieved by progastrin, a prohormone of gastrin that physiologically takes part in gastric acid secretion in the stomach. It has been shown that in many types of cancers, the *GAST* gene, which generally codes for gastrin, directly targets the Wnt/β-catenin pathway. The study tried to show the correlation between the high titer of Progastrin in blood and the stage of a few types of cancer, one of which included prostate cancer. The study aims to show the predictive value of progastrin kinetics during prostate cancer treatment [72]. Another article by Yashi et al. on the same issue, used Enzalutamide and Abiraterone Acetate and measured the plasma Progastrin levels. It showed that there was the highest change in PSA levels from baseline in the series of patients treated with Enzalutamide. Also, the PSA progression-free survival and Overall Survival (OS) in patients with elevated serum Progastrin were significantly worse compared to patients with low serum Progastrin. The OS rate was 17.5 months in patients with high serum progastrin levels, while in patients with low serum progastrin levels, the OS was 49.0 months. They suggest that there is a correlation between neuroendocrine pathways, especially Progastrin and the progression of CRPC and that Progastrin may play an essential role as a predictive value for patients undergoing therapy with AR axis-targeted (ARAT) agents [73].

Some researchers found the Wnt/β-catenin pathways to greatly impact prostate cancer cells' ability to acquire a metastatic form [68,74]. Although the connection between Wnt/β-catenin and metastatic disease is well established, the rate of mutations among patients with prostate cancer stands only at 12%–22% [75–77] and no mutations in β-catenin were observed after the acquisition of the metastatic form [78]. Pan et al. suggest that the uneven distribution of mutations in β-catenin and its nuclear localisation signify the involvement of other factors in the establishment of metastatic prostate cancer [79].

### 4.2. Non-canonical (β-catenin-independent) wnt signalling pathway

Wnts such as Wnt4, Wnt5a, and Wnt11 do not liberate β-catenin but signal noncanonically. The best characterised of these 'noncanonical' pathways are the Wnt/$Ca^{2+}$ pathway [80] and the planar polarity pathway [81]. Other noncanonical pathways include Wnt/Jnk and Wnt/Rho signalling [82].

Vertebrate noncanonical Wnt signalling requires frizzled receptors. Wnt ligand binding to frizzled can increase levels of intracellular calcium and activate two

$Ca^{2+}$-sensitive kinases: (1) calcium/calmodulin-dependent protein kinase II (CAMK2) and (2) protein kinase C (PKC). G-proteins and Drosophila dishevelled (dsh) are also involved in signal transduction by the Wnt/$Ca^{2+}$ pathway, and signalling specificity may be achieved *via* co-receptors, such as Knypek and Ror2 [83]. This pathway has been implicated in cellular movement processes required for embryonic patterning [84–86]. It also promotes ventral cell fate and antagonises dorsal cell fate during early Xenopus development, regulating gastrulation movements or heart and muscle development [87].

Noncanonical Wnt signalling pathways can overlap with each other. Wnt5a and Wnt11, which are involved in Planar Cell Polarity (PCP) signalling, can also activate calcium signalling [88]. Some PCP proteins, including flamingo (CELSR2), become localised to both the proximal and distal sides of the cell. However, other proteins, such as frizzled, dishevelled, and Rho, migrate to their location on the distal side, whereas prickle homolog 1 (PRICKLE1) and strabismus (STBMS1) localises to the proximal side. These proteins are required to ensure correct differentiation into proximal and distal parts and the subsequent development of correct polarity [89]. In vertebrates, this pathway requires Wnt ligands, such as silberblick (Wnt11 precursor) and pipe tail (Wnt5b), whereas no Wnt ligand is known to be involved in Drosophila PCP signalling. Sometimes, Wnt-receptor interaction requires the recruitment of additional co-factors. For example, secreted collagen glycoprotein Collagen triple helix repeat containing 1 (CTHRC1) can promote the formation of a Wnt-frizzled-Ror2 complex, activating the PCP pathway [90,91]. The Wnt-frizzled interaction may also be enhanced by proteoglycans, such as protein Dally in Drosophila, or inhibited by secreted proteins, including dickkopf 1 (DKK1), Cerberus (CER1) and SFRPs (secreted frizzled-related proteins) [92]. In some instances, the noncanonical Wnt pathway can inhibit canonical Wnt signalling. One example is competition for Dishevelled molecules that are shared between the two pathways [82]. Another example involves the Wnt5a-induced transcriptional upregulation of Siah2, which can stimulate β-catenin degradation [93].

A non-canonical Wnt signalling pathway was found to activate the PI3K-AKT-mTOR cascade, increasing the invasive potential of prostate cancer cells. Moreover, the Wnt receptor Frizzled2 may cause EMT by activating Fyn, which suppresses the AMPK-LKB1 signalling axis by blocking LKB1 redistribution to the cytoplasm; this ultimately results in an increase in tumorigenesis and further progression of invasive properties [69]. Shorning et al. describe new treatment lines for certain cancer types by blocking Wnt ligand secretion. One of these drugs is WNT974, which has passed through a phase 1 clinical trial and displayed both a manageable safety profile and suppressive activity upon the canonical pathway. The drug was not included in a clinical trial for prostate cancer patients. However, in a preclinical trial, the results have been promising and may indicate a significant level of efficacy for prostate cancer [69]. To date, although being an attractive target, Wnt signalling inhibitors are still in an early phase of development and have several limitations. One such limitation is the occurrence of the Wnt signalling pathway in physiological processes in the gastrointestinal tract (GIT), hematopoiesis, and others. Therefore, inhibiting the pathway may cause damage to normal physiological function [94]. Prostate cancer has been known to send metastases to the bone. One of the basic events of the metastatic process – EMT, is partially regulated by Wnt or β catenin signalling [71]. An interesting property of Wnt was described by Wang et al. who showed that Wnt5A is related to bone metastasis in prostate cancer in a mouse model. Other molecules, such as JNK, FZD4, and FZD8, were also described as contributors to prostate cancer invasion [95].

The invasion of prostate cancer to the bone is mediated by the canonical signalling pathway, particularly by its member FZD8. Li et al. showed that high-grade prostate cancer overexpresses FZD8, and thus, it was described that knockdown of FZD8 causes inhibition of bone metastases [96]. Ma et al. listed 46 genes associated with Wnt activation in mCRPC, including genes of the TGFβ pathway [97]. Kaplan et al. showed that *TMPRSS2* translocation-positive patients have a higher expression of FZD4 and other Wnt receptors. Furthermore, the upregulation of FZD4 led to the induction of EMT and decreased cell adhesion [71].

Similar to TGF-β, the Wnt signalling pathway is also involved in EMT and epithelial plasticity during embryonic development and cancer. Cells with β-catenin activation lose their polarity, morphologically disrupting cell-cell contacts and EMT [98,99]. Immunohistochemical studies demonstrate alternations of the actin cytoskeleton in these cells, indicating that nuclear β-catenin accumulation is functionally related to EMT in budding tumour cells at the tumour-host interface. Li and Zhou showed that β-catenin and Akt pathways were activated in Twist-overexpressing cells, and activation of β-catenin correlated with the expression of stem cell marker CD44 [100].

Canonical and noncanonical Wnt signalling pathways regulate the expression of structural proteins and

MMPs [101] to modify the surrounding matrix. Targets of canonical Wnt, among others, are *periostin, versican,* and *fibronectin,* mesenchyme-specific genes that are upregulated in breast, prostate, gastric and other cancers. Extracellular matrix, rich in these proteins, possesses anti-adhesive properties and can modify the proliferation and migration of different cell types [102–104].

One of the prominent regulatory proteins that mediates cross-talk between integrin-based cell-matrix adhesion and Wnt signalling is the integrin-linked kinase (ILK), which regulates the translocation of β-catenin to the nucleus independent of altering the expression level. It upregulates Lef-1 expression and downregulates GSK-3β activity, resulting in stabilised cytoplasmic/nuclear β-catenin. GSK3β, E-cadherin, and Slug play essential roles in EMT transition *via* Wnt/β-catenin signalling [55]. GSK3β is located at the junction of PI3K/AKT and Wnt/β-catenin/TCF survival pathways; it plays a critical role in cellular metabolism, growth, and proliferation [105].

Human tubulin beta class IVa (TUBB4A) is an important regulatory factor in the β-catenin pathway. TUBB4A, a member of the tubulin family, has been identified by Gao et al. as being highly expressed in aggressive forms of prostate cancer. The researchers demonstrated that CRISPR/Cas9-mediated knockdown of TUBB4A in various cell lines, both androgen-dependent and independent, leads to the arrest of tumour proliferation and migration, as well as the induction of DNA damage, evidenced by increased expression of γH2AX and 53BP1. Additionally, they reported that the interaction between TUBB4A and MYH9 reduces EMT by inhibiting GSK3β ubiquitination, thereby decreasing activation of the β-catenin pathway. This interaction forms a protective framework around the nucleus, safeguarding genetic material during cell migration. Deleting the TUBB4A gene has been associated with reduced tumour proliferation and metastatic potential by inhibiting the NF-κB, cyclin D1, and c-MYC signalling pathways. Furthermore, TUBB4A is implicated in other cancers, including ovarian cancer, and contributes to resistance to paclitaxel [106].

## 5. Hedgehog signalling pathway

Hedgehog (HH) signalling pathway regulates embryogenesis, adult tissue homeostasis, and carcinogenesis [107–109]. Sonic Hedgehog (SHH), Indian Hedgehog (IHH), and Desert Hedgehog (DHH) represent mammalian Hedgehog family ligands, consisting of an N-terminal signal peptide, Hedgehog core domain, and C-terminal processing domain. Patched family members (PTCH) are Hedgehog receptors, while Cdon homolog (CDON), Boc homolog (BOC), and growth arrest-specific 1 (GAS1) are Hedgehog coreceptors. Receptors are distantly related to Dispatch family members. Patched 1 and 2 (PTCH1 and PTCH2) do not directly transduce Hedgehog signals to the intracellular signalling cascade, but indirectly through Smoothened seven-transmembrane-type receptor. In the absence of Hedgehog signalling, GLI family zinc finger 1 (GLI1) is transcriptionally repressed, GSK3 and CK1 phosphorylate GLI2 for the FBXW11-mediated degradation, and GLI3 is processed to a cleaved repressor. In the presence of Hedgehog signalling, Smoothened is relieved from Patched-mediated suppression to induce MAP3K10 activation and suppressor of fused homolog (SUFU) inactivation. GLI activators then bind to the GACCACCCA motif for the transcriptional upregulation of target genes (Figure 4). *Hedgehog* target genes are involved in the HH signalling cascade, cell cycle regulation, cell fate determination, and stem cell signalling. Representative targets are: *GLI1*, *PTCH1*, *CCND1* and *2*, *SFRP1*, runt-related transcription factor (RUNX2), etc [110].

Constitutive overexpression of the HH pathway is observed in several cancers. For example, gain-of-function mutations underlie the nevoid basal cell carcinoma syndrome, in which affected individuals have an increased risk of developing medulloblastomas and basal cell carcinomas of the skin [111]. *PTCH* mutations are found in sporadic medulloblastomas, while *GLI1* overexpression is noted in various central nervous system tumours. Enhanced HH signalling has been described in small-cell lung cancers as well as oesophageal, gastric, and pancreatic cancers [112].

The Hedgehog signalling pathway plays a crucial role in the development and further progression of prostate cancer. Moreover, preclinical trials showed that inhibition of the pathway causes a reduction in metastasis. In some types of tumours, including prostate cancer, the Hedgehog pathway activation was present predominantly in the stroma and less so within the tumour cells, therefore suggesting a paracrine mechanism of action. The tumour secretes the Hedgehog ligand to the stroma, producing factors contributing to tumour progression and invasiveness [113]. However, it is important to note that this Hedgehog signalling imbalance may also occur in other contexts, such as resistance to Anti-Androgen therapy [114]. Sheng et al. reported that high Hedgehog-interacting protein levels are associated with high Gleason score and metastatic tumours [115]. Targeting the Hedgehog pathway may be a potential

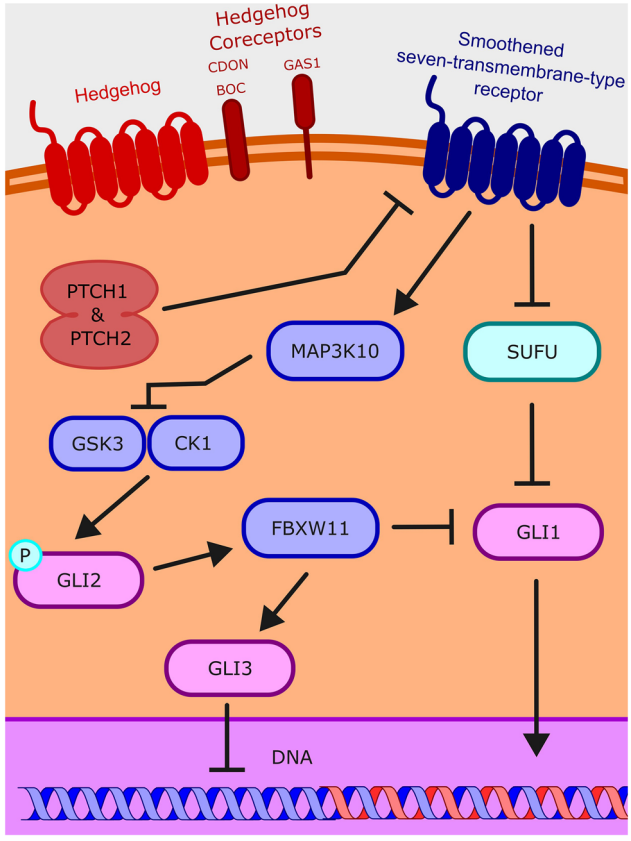


**Figure 4.** Schematic representation of hedgehog signalling Cascade. See the text for an explanation.

avenue for treatment, mainly due to the findings supporting the Hedgehog pathway's relation to radio-resistance. Generally, the response of the tissue to radiotherapy is influenced by several factors, such as repair of DNA damage, redistribution, and reoxygenation. Hedgehog signalling has been shown to interfere with each of these pathways, thereby contributing to the resistance of the tumour to radiotherapy. Several studies showed that the prognosis in prostate cancers expressing Hedgehog signalling after chemo-radiotherapy is significantly poorer than those that do not. Moreover, it has been demonstrated that Hedgehog signalling Inhibition may reduce the resistance to chemotherapy by targeting multidrug resistance and cancer stem cells. Interestingly, the SHH signalling pathway impairs DNA damage repair, creating a suitable environment for cancer proliferation and further radio-resistance due to its protection against ionising radiation [113].

An Interesting clinical trial was conducted at Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins on LDE225 (Sonidegib). Sonidegib is a drug that inhibits the Hedgehog pathway by binding to Smoothened, thus inhibiting the tumour's ability to proliferate and grow [116]. This randomised, two-arm, open-label prospective study dealt with the possible inhibition of the Hedgehog pathway with Sonidegib 800 mg/day vs patients who were merely under observation. All patients were characterized as high-risk prostate cancer patients and were actively undergoing radical prostatectomy. The researchers aimed to check the drug effect on the tumour characteristics, such as the proliferation and tissue infiltration rate. The expression of GLI1 has, in past studies, been measured as a representation of the Hedgehog pathway [117]. GLI1 and other markers were used for this purpose by Ross et al. when they performed their study on Sonidegib. In this way, it was possible to demonstrate that Sonidegib, as an Smo antagonist, was able to penetrate the prostatic tissue, resulting in the downregulation of the Hedgehog signalling pathway. These are but a few examples of ways in which this pathway can serve as a potential avenue for intervention. However, the clinical benefits often remain unclear. As was the case with Ross et al. where after four weeks of treatment, the PSA levels did not significantly change within the groups [118].

## 6. Notch signalling pathway

Notch signalling is one of the critical pathways implicated in the self-renewal of stem cells, cell fate

determination of progenitor cells, and terminal differentiation of proliferating cells. Notch-ligand binding induces cleavage of the Notch receptor [1–4] by metalloproteinase and γ-secretase to release the Notch intracellular domain (NICD). Canonical Notch signalling to the CSL-NICD-Mastermind complex inhibits the differentiation of stem cells or progenitor (transit-amplifying) cells. In contrast, non-canonical Notch signalling to the CSL-NICD-Deltex complex promotes the differentiation of progenitor cells [119]. Notch signalling transcriptionally activates *HES1-7*, *HEY1*, *HEY2*, and *HEYL* genes and the NF-κB-NICD complex to augment NF-κB signalling. Notch activity can be found in multiple cancer types. Notch signalling is aberrantly activated due to chromosomal translocation of NOTCH1 in acute lymphoblastic leukaemia [120], amplification and overexpression of NOTCH2 in medulloblastoma [121], chromosomal translocation of NOTCH3 in lung cancer [122], amplification and overexpression of NOTCH3 in ovarian cancer [123], and upregulation of JAG1 and NOTCH1 or down-regulation of NUMB in breast cancer. NUMB is a gene that, in conjunction with NOTCH, regulates balanced differentiation and proliferation, often acting as a tumour suppressor gene [124,125]. These characteristics seem to indicate that Notch signalling is oncogenic in various human tumours. On the other hand, Notch signalling has an anti-oncogenic role in cutaneous squamous cell and basal cell carcinomas and carcinoma of the uterine cervix [126,127], partially due to the interference with canonical Wnt signalling. Acar et al. detailed the mechanism involved in a 2020 study. Two distinct methods were discussed, culminating in *Wnt* inhibition by limiting β-catenin. Both pathways utilise membrane-bound ΔEGF_N1 and NICD proteins found in the nucleus. The first method begins with Deltex-mediated endocytosis of Notch, allowing it to act as an antagonist of β-catenin by sequestering it into the membrane. The second method is centred around Notch's ability to inhibit the transcription of β-catenin by forming a complex with NICD within the nucleus. While the location and specifics of each pathway may differ, both result in less β-catenin available to promote *Wnt* signalling [128]. Notch signalling activation also leads to transcriptional activation of NF-κB target genes, such as *IFN-γ*, through a direct association between NICD and NF-κB [129].

In recent studies, the Notch signalling pathway has been identified as a key regulator in the induction of EMT. Activation of the Notch signalling pathway predominantly in endothelial cells produces several characteristic changes affecting cell structure and function. Several Endothelial markers are down-regulated; these may include Tie1, Tie2, VE-cadherin, platelet-endothelial cell adhesion molecule 1 and endothelial NO synthase. At the same time, mesenchymal markers are Up-regulated, namely fibronectin, platelet-derived growth factor receptor and α-SMA. The key changes playing a major role that are consistent with mesenchymal transformation are PDGF-driven processes. Consequently, Notch signalling pathways can be involved in sub-reactions with associated molecules like Snail, Slug, Twist, TGF-β, FGF and PDGF and play an important role in the processes of EMT [130]. Stacy et al. describe the molecular mechanism involved. The Notch Transmembrane receptor-expressing cell encounters a Notch Ligand such as the Jagged 1 and 2, triggering the Proteolytic change of NOTCH to the NICD form. The NICD is subsequently cleaved and, after entering the nucleus, interacts with DNA-bound transcriptional repressor CBF-1-Suppressor of Hairless/Lag1 (CSL). This complex then combines with other co-activators to form the NOTCH-CSL-MAML complex, which recruits more Notch complexes that together increase the gene expression of Notch signalling upregulation. This includes the previously mentioned Snail and Slug [131].

In a study conducted by Orzechowzka et al. several groups were examined to check the relation between age and staging of prostate cancer. An overlap of 13 genes related to tumour progression from the NOTCH family between a group of patients below the age of 55 and those between 60 and 70 years old was identified. It was shown that decreased Notch activity is associated with slower progression of prostate cancer in the elderly and that Notch signalling targets the properties of aggressiveness and is modified according to the patient's age [132]. It is already known that there is a relationship between ageing and prostate cancer. The term used more recently is inflammaging-it describes a low-grade chronic sterile inflammatory process that contributes to the overactivation of the immune process, which may play a role in the carcinogenesis of the prostate. A study carried out by Zinger et al. showed that inflammaging, along with other changes within signalling molecules, stem cell impairment, and others, have been known to contribute to tumour development [133].

Hypoxia is one of the characteristics of prostate cancer and is associated with its progression and resistance to chemotherapy and radiotherapy. Inhibition of Notch increased the sensitivity to the treatment. Notch activity is strongly related to the expression of two essential markers of tumour hypoxia: Vascular endothelial growth factor (VEGF) and Hypoxia-induced factor 1α (HIF-1α). These markers facilitate neoangiogenesis

and thus are associated with poor prognosis in many types of cancer. A hypoxic microenvironment often leads to HIF-1α overexpression. This has been observed in a variety of human cancers, including prostate cancer and its associated metastases, usually as an increase in immunostaining. More recent evidence suggests that, under hypoxic conditions, HIF-1 α is recruited to notch-responsive promoters, leading to activation of transcriptional targets and a degree of regulation in cell differentiation. These conditions are especially relevant to prostate cancer as they are one of its most prominent characteristic states [134].

According to the study of May et al. and the review by Marignol et al. regarding the treatment resistance of prostate cancer, no studies have identified a role for the Notch signalling pathway in the response of prostate cancer cells to radiation. Nonetheless, proliferative activity and neuroendocrine differentiation have both been associated with the failure of radiation therapy in patients with prostate cancer, suggesting that the notch signalling pathway could potentially provide prognostic value [134].

Additional studies have been conducted to determine whether the Notch signalling pathway can be used as a novel therapeutic target. In this pathway, the Notch 1 receptor and jagged-1 ligand both play a central role in the progression and metastasis of prostate cancer. In these studies, the aim has been to downregulate the expression of notch 1 or jagged-1 encoding genes. Results seem to indicate that this may result in a decrease in prostate cancer cell invasion. Additionally, the downregulation of notch 1 and jagged-1, along with small interfering RNA (siRNA), has been associated with cell growth inhibition, including cell migration and invasion and potentially induction of apoptosis in some cases [134].

## 7. NF-κB signalling pathway

The transcription factor NF-κB, which was initially shown to be the main component in controlling innate and adaptive immunity, is presently considered a key molecule regulating apoptosis, mainly to prevent cell death. The ability of NF-κB to suppress apoptosis is one of the main NF-κB functions, which determines its ability to promote inflammation and involve this transcription factor in the pathogenesis of various inflammatory diseases, cancer therapy resistance and oncogenesis [135].

IKK complex, the inhibitor of kB kinase, comprises two catalytic components (IKKα and IKKβ) and one regulatory component (IKKγ). Activation of the IKKβ component occurs in response to stimuli such as CD40 ligand (CD40L), tumour-necrosis factor-α (TNF-α), lipopolysaccharide (LPS) or interleukin-1 (IL-1), leading to phosphorylation of IκB proteins (at two conserved serines) which are bound to the NF-κB heterodimers. The phosphorylation of IκB proteins triggers, as a result, the ubiquitin-dependent degradation of IκB by 26S proteasome, which leads to the nuclear translocation of RELA-p50 heterodimers as well as the transcription and activation of target genes. Activation of the IKKa component occurs in response to other stimuli, such as BAFF, and members constituting the TNF family, such as lymphotoxin β. This activation leads to the induction of phosphorylation of p100 (which is bound to RELB) at its two serine residues at its carboxyl terminus and subsequent ubiquitin-dependent degradation of the carboxy-terminal half of p100, which leads to the release of its amino-terminal half and the p52 polypeptide. Combined with the heterodimer partner of p100, RELB, the latter two translocate to the nucleus, leading to transcription activation [136].

The genes that are induced in response to NF-κB activation can be divided into four functional classes: genes whose products are involved in negative-feedback control of NF-κB activity; genes whose products serve various immunoregulatory functions; genes whose products inhibit caspase activation and apoptosis; and genes that promote cell proliferation [137]. NF-κB suppresses the expression of epithelial-specific genes *E-cadherin* and *desmoplakin* and induces mesenchymal vimentin in breast cancer cells [138].

It Is known that NF-κB signalling is activated in CRPC, with high levels in CRPC compared to the AR-dependent type. The high expression is induced by the activation of *PCAT1 via* knockdown, which increases the phosphorylation and subsequent decrease of NF-κB, ultimately inhibiting cell growth of CRPC. This finding was proved by the knockdown of PCAT1 which resulted decreased NF-κB in CRPC and inhibition of cell growth. On the other hand, cells that overexpressed PCAT1 also expressed high levels of NF-κB and were identified as tumours with poor prognosis. Also, PCAT1 binds to FKBP51, and the PCAT1/FKBP51 complex stabilises the FKBP51/IKK complex, leading to enhanced NF-κB signalling [139].

NF-κB is also known to induce EMT. It primarily mediates this process by downregulating the expression of E-cadherin [140]. NF-kB possesses a unique mutual interplay with β-catenin that can lead to several effects, such as activating Slug, ZEB1 and ZEB2, which consequently leads to a repression of E-cadherin and thus triggers a promotion of EMT [141]. An interesting association between NF-kB and EMT was

**Table 1.** Signalling pathways, clinical targets, implications and relevant clinical trials.

| Drug | Pathway | Target | Clinical Use | FDA-Approval[a] | Trial | Outcome | Clinical Trial ID and status | Reference |
|---|---|---|---|---|---|---|---|---|
| Galunisertib | • **TGFβ**<br>• The drug binds to TGFβR1 and thus inhibits TGFβ mediated signalling pathway | TGFβR1 | Not currently used. Under trials in many fields | – | • Combination with Capecitabin for CRC, lung, liver and breast cancers.<br>• Combination with Enzalutamide for prostate cancer. The combination showed positive results. | The combination with Enzalutamide in mice showed a significant suppression of tumour growth by increasing apoptosis, compared to a monotherapy. | NCT05700656<br>*Not yet recruiting*<br>NCT02452008<br>*Active, not recruiting* | Choi et al. [156] |
| Acetylsalicylic acid | Suppress the **NF-κB** signalling pathway by blocking the degradation of IκBα | IκBα | Anti-inflammatory, reduction of pain, fever, and is used in various clinical cases | + | • Prostate Cancer and other types of cancer.<br>• On trial in combination with traditional lines of treatment. | N/A | NCT00316927<br>*completed*<br>NCT03819101<br>*Recruiting* | Yu et al. [145] |
| Dexamethasone | Suppress the **NF-κB** signalling pathway by blocking the degradation of IκBα | IκBα | Anti-inflammatory | + | Prostate Cancer and other types of cancer | N/A | NCT00316927<br>*completed* | Yu et al. [145] |
| CWP232291 | • **Wnt/β-catenin**.<br>• Blocks the growth of the tumour in patients with CRPC by activation of the endoplasmic reticulum stress pathway | *Survivin* | Not currently used | – | • Prostate cancer<br>• Minimal effect in other types of cancer | N/A | NCT02426723<br>*completed* | Pak et al. [157] |
| WNT974 | • **Wnt/β-catenin**<br>• Blockage of Wnt ligand secretion | *AXIN2* | Not currently used | – | Prostate cancer | N/A | NCT01351103<br>*Active, not recruiting* | Shorning et al. [69] |
| Sonidegib | Inhibition of **Hedgehog** pathway by interaction with Smoothened | Smoothened | Locally advanced BCC | + | Prostate cancer | The drug penetrated the tissue and caused a > 60-fold suppression of the pathway. The clinical benefits are unclear. | NCT02111187<br>*Completed, with results* | Ross et al. [118] |
| Infliximab | • **NF-κB** | TNF-α | Immunosuppressant | + | Prostate cancer | N/A | N/A | Yu et al. [145] |
| Adalimumab | • The drugs bind to TNF-α to disrupt the pro-inflammatory cascade signalling | IκBα | Immunosuppressant | + | Prostate cancer, BPH | N/A | NCT06062875 (checked on BPH)<br>*Recruiting* | Yu et al. [145] |
| Golimumab | | TNF-α | Immunosuppressant | + | Prostate cancer- in combination with Apalutamide | N/A | NCT05960578<br>*Recruiting* | Yu et al. [145] |
| PF-03084014 γ-secretase inhibitor (GSI) | • **Notch** | • **Notch1.** Causes an arrest in cell cycle in S,G2/M phases | Not currently used | – | • In combination with Docetaxel for Prostate cancer.<br>• In trials for desmoid tumours | Results are irrelevant for prostate cancer | NCT01981551<br>A clinical trial in Desmoid tumours<br>*Completed, with results* | Cui et al. [158] |
| LGK974 (PORC inhibitor) | • **Wnt/β-catenin** | PORC | Not currently used | – | Prevent cellular proliferation and may be used as a preventative method rather than a treatment line | N/A | N/A | Yu et al. [159] |

(*Continued*)

**Table 1.** Continued.

| Drug | Pathway | Target | Clinical Use | FDA-Approval[a] | Trial | Outcome | Clinical Trial ID and status | Reference |
|---|---|---|---|---|---|---|---|---|
| Bortezomib | Suppress the **NF-κB** signalling pathway by blocking the Ubiquitin-Proteasome system | | Multiple Myeloma | + | Has a positive impact on PSA levels, but did not show positive results on CRPC | N/A | NCT00183937 *completed* | Nguyen et al. [160] |
| Marizomib | | | Grade IV diffuse astrocytic glioma; IDH-wildtype | + | Inhibits the progression of PC *in-vivo* and *in-vitro* | N/A | NCT00629473 *completed* | Nguyen et al. [160] |
| Ixazomib | | | Multiple Myeloma | + | | This phase 1 trial showed a limited antitumour effect and a manageable safety profile | NCT00830869 *Completed, with results* | Nguyen et al. [160] |
| PS1145 | NF-κB | IKK inhibition | Not currently used | – | Prostate Cancer and other types of cancer | N/A | N/A | Nguyen et al. [160] |
| BMS345541 | NF-κB | IKK inhibition | Not currently used | – | Prostate Cancer and other types of cancer | N/A | N/A | Nguyen et al. [160] |

N/A: Non-applicable.
[a]The *FDA approval* column relates to the general approval of the drug by the FDA and not specifically to prostate cancer.
[+]FDA approval exists; [–]FDA approval does not exist.

described by Tripathi et al.; Their study demonstrated that in androgen-independent and metastatic prostate cancer cells expressing NF-kB, the *DLC1* (Deleted in Liver Cancer 1) gene that acts as Rho GTPase-activating protein (RhoGAP), is associated with negative regulation of NF-kB. *DLC1* also suppresses the ubiquitination and degradation of the NF-κB inhibitor, IκBα. Therefore, they showed that tumours expressing the *DLC1* gene are associated with low rates of EMT [142].

A study by Zhou et al. showed the possible use of SAHA (suberoylanilide hydroxamic acid), a Histone deacetylase inhibitor, in *DCL1*-negative prostate cancer, as it was shown that the treatment reduced the tumour size by 75%–80% compared to the control group [143].

Jain et al. showed that inflammatory factors produced by LPS stimulation of blood cells enhance metastasis by activating NF-κB. A recurrent administration of Dexamethasone, a corticosteroid used in different inflammatory cases, did not suppress it *in vivo*. In a mouse model, injected LPS did not significantly influence the primary tumour size. Moreover, Dexamethasone-treated mice bearing MAT- LyLu tumour were shown to be associated with a higher incidence of metastasis regardless of LPS injection [144]. Other anti-inflammatory drugs such as Aspirin (acetylsalicylic acid) and sodium salicylate inhibit the NF-κB pathway by blocking the degradation of IκBα. These drugs are currently under different phases of clinical trial and are recommended for use in combination with chemotherapy or radiotherapy [145].

According to Jain et al. although no clear picture exists to show the exact involvement of NF-κB in the pathogenesis of prostate cancer is currently available, some therapeutic strategies may exist. The primary goal would be to interfere or otherwise block the NF-κB pathway; this direction seems promising for prostate cancer. The article proposes three key mechanisms that could serve as potential therapeutic strategies to this end. First, by inhibiting NF-κB, a possible treatment for NF-κB-positive but AR – negative CRPC may be devised. The second method involves inhibiting NF-κB to inhibit IKK2-dependent expression of proinflammatory cytokines, particularly during inflammatory reactions, preventing cellular damage. Lastly, recent evidence has surfaced supporting the importance of IKK1 in prostate cancer; this may position IKK1 as a potential therapeutic choice to treat CRPC. However, further research is likely required to explore the full potential of IKK1 as a therapeutic target [146].

San Ko et al. examined 101 prostate tissues with BPH using immunohistochemistry, but did not show

any correlation between NF-κB signalling and BPH [147].

However, the effects of NF-κB signalling are not limited to CRPC. Continuing research into this pathway has linked it with many other pathological states and cancer types. Additionally, a wide array of research conducted over the past several years has shown that the NF-κB signalling pathway plays an essential role in cellular and metabolic adaptations to environmental changes or imbalances that often characterise a wide range of chronic inflammatory diseases—including but not limited to Diabetes Mellitus type 2, Obesity, and autoimmune disorders [148]. The association with cancers has also been extensively studied; examples have been known to include H. Pylori Induced Gastric Cancer [149], Breast cancer [150], Ovarian cancer [151] and many others, usually resulting from increased NF-κB signalling due to external stimuli.

## 8. Clinical significance of targeting signalling pathways in prostate cancer

Many drugs that target different signalling pathways have undergone clinical trials or are currently under trial. Some of these drugs are indicated for other pathological states and have shown a positive effect on the overall survival rate. Table 1 reflects the current treatment possibilities and other clinical trials that will be used in the future under the United States Food and Drug Department (FDA) approval.

Even though drug development in this field is extensive, several problems still need to be overcome. Out of the list mentioned below, to date, no drugs have received formal FDA approval for the clinical indication of prostate cancer. The reason for this is primarily the off-target effects of these medications, which, in some of the proposed drugs, are still significant (e.g. drugs affecting the Wnt/β-catenin pathway) [139]. Other drugs that inhibit other signalling pathways have not been discussed. The AR pathways, for example, are FDA-approved and are currently used in clinics [94]. Therefore, more research is needed in this area.

As previously discussed, there is a consensus that combining ICIs with other therapeutic modalities, such as chemotherapy or radiation therapy, may enhance tissue responsiveness to treatment. In some cases, combining two ICIs, such as ipilimumab and nivolumab, is utilized for conditions like melanoma, pleural mesothelioma, and others. In other instances, particularly in non-small cell lung cancer (NSCLC), pembrolizumab is frequently combined with carboplatin [152]. In prostate cancer, Miller et al. report a survival benefit of 2.4 months with the combination of paclitaxel and prednisone. Additional therapeutic strategies may involve integrating androgen deprivation therapy (ADT) with radiotherapy, chemotherapy, immunotherapy, and other treatments [153]. Some mathematical models show that even though the combination of ADT with ICI expresses poor clinical efficacy in trials, higher doses can achieve effectiveness [154].

Resistance can emerge during treatment, presenting challenges in the management of prostate cancer with some drugs, such as ADT. Typically, ADT reduces dihydrotestosterone (DHT) levels, leading to apoptosis in some cancer cells. However, not all cells undergo programmed cell death; some enter a dormant state and adapt to the low androgen environment. These dormant cells can eventually proliferate and form colonies capable of metastasis. Resistance mechanisms involve upregulating AR expression through various signalling pathways, including NF-κB and PI3K/AKT. Additional resistance mechanisms have been observed with other drugs. For example, enzalutamide resistance may occur due to the *F876L* missense mutation or AR splice variants, while abiraterone resistance may involve CYP17A1 upregulation or alternative ligand synthesis [155]. The resistance mechanisms for the newer drugs listed in Table 1 remain unclear and are expected to be elucidated in future studies.

## 9. Conclusion

In conclusion, signalling pathways are crucial for tumorigenesis, especially for the ability of a tumour to sustain itself and later invade the basement membrane and metastasise. Many clinical trials have already attempted to block signalling pathways through the use of different drugs. Some have shown promising results, and some suggest that further investigation is required. However, several serum biomarkers explored may play an essential role in predicting possible outcomes such as Overall Survival rate. Various clinical trials have been conducted to identify signalling pathway inhibitors, but further research is required mainly due to the off-target effects seen in these drugs. Nevertheless, understanding the basic principles and mechanisms of the signalling pathways will serve as an essential background for developing further biomarkers and potentially new lines of treatment for prostate cancer and many other types of cancer.

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## Authors contributions

Conceptualization, G.K.; data curation, G.K., A.P.G., C.D.E., E.B.A; writing—original draft preparation, G.K., A.P.G., C.D.E.; writing—review and editing, G.K., A.P.G., C.D.E, E.B.A., N.V., G.A.; visualisation, A.P.G., C.D.E, E.B.A.; supervision, G.K.; All authors have read and agreed to the published version of the manuscript.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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## ORCID

Aviv Philip Goncharov http://orcid.org/0009-0001-1811-3535
Gvantsa Kharaishvili http://orcid.org/0000-0003-3618-6145

## Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

## References

[1] Rawla P, Rawla P. Epidemiology of prostate cancer. World J Oncol. 2019;10(2):63–89. https://www.wjon.org/index.php/wjon/article/view/1191 doi: 10.14740/wjon1191.

[2] Prostate Cancer. Prostate cancer information and overview. American Cancer Society; 2024 [cited 2024 Aug 30]. https://www.cancer.org/cancer/types/prostate-cancer.html.

[3] EAU Guidelines. Edn. Presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.

[4] Lin CY, Chuu CP. New classification may assist the development of targeted therapies for treatment-refractory castration-resistant prostate cancer. Transl Androl Urol. 2020;9(2):837–839. https://tau.amegroups.org/article/view/38875/html doi: 10.21037/tau.2020.03.24.

[5] Schaeffer EM, Srinivas S, Adra N, et al. Prostate cancer, version 4.2023, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2023;21(10):1067–1096. https://pubmed.ncbi.nlm.nih.gov/37856213/ doi: 10.6004/jnccn.2023.0050.

[6] Lundberg A, Zhang M, Aggarwal R, et al. The genomic and epigenomic landscape of double-negative metastatic prostate cancer. Cancer Res. 2023;83(16):2763–2774. https://pmc.ncbi.nlm.nih.gov/articles/PMC10425725/ doi: 10.1158/0008-5472.CAN-23-0593.

[7] Montanari M, Rossetti S, Cavaliere C, et al. Epithelial-mesenchymal transition in prostate cancer: an overview. Oncotarget. 2017;8(21):35376–35389. https://www.oncotarget.com/article/15686/text/ doi: 10.18632/oncotarget.15686.

[8] Goncharov AP, Vashakidze N, Kharaishvili G. Epithelial-mesenchymal transition: a fundamental cellular and microenvironmental process in benign and malignant prostate pathologies. Biomedicines. 2024;12(2):418. https://www.mdpi.com/2227-9059/12/2/418 doi: 10.3390/biomedicines12020418.

[9] Baghban R, Roshangar L, Jahanban-Esfahlan R, et al. Tumor microenvironment complexity and therapeutic implications at a glance. Cell Commun Signal. 2020;18(1):59. doi: 10.1186/s12964-020-0530-4.

[10] Leivonen SK, Kähäri VM. Transforming growth factor-beta signaling in cancer invasion and metastasis. Int J Cancer. 2007;121(10):2119–2124. https://pubmed.ncbi.nlm.nih.gov/17849476/ doi: 10.1002/ijc.23113.

[11] Massagué J, Blain SW, Lo RS. TGFbeta signaling in growth control, cancer, and heritable disorders. Cell. 2000;103(2):295–309. https://pubmed.ncbi.nlm.nih.gov/11057902/ doi: 10.1016/s0092-8674(00)00121-5.

[12] Chang H, Brown CW, Matzuk MM. Genetic analysis of the mammalian transforming growth factor-beta superfamily. Endocr Rev. 2002;23(6):787–823. https://pubmed.ncbi.nlm.nih.gov/12466190/ doi: 10.1210/er.2002-0003.

[13] Taylor MA, Parvani JG, Schiemann WP. The pathophysiology of epithelial-mesenchymal transition induced by transforming growth factor-beta in normal and malignant mammary epithelial cells. J Mammary Gland Biol Neoplasia. 2010;15(2):169–190. https://pubmed.ncbi.nlm.nih.gov/20467795/ doi: 10.1007/s10911-010-9181-1.

[14] Zavadil J, Bitzer M, Liang D, et al. Genetic programs of epithelial cell plasticity directed by transforming growth factor-beta. Proc Natl Acad Sci U S A. 2001;98(12):6686–6691. https://pubmed.ncbi.nlm.nih.gov/11390996/ doi: 10.1073/pnas.111614398.

[15] Neil JR, Johnson KM, Nemenoff RA, et al. Cox-2 inactivates Smad signaling and enhances EMT stimulated by TGF-beta through a PGE2-dependent mechanisms. Carcinogenesis. 2008;29(11):2227–2235. https://pubmed.ncbi.nlm.nih.gov/18725385/ doi: 10.1093/carcin/bgn202.

[16] Markowitz SD, Roberts AB. Tumor suppressor activity of the TGF-beta pathway in human cancers. Cytokine Growth Factor Rev. 1996;7(1):93–102. https://pubmed.

ncbi.nlm.nih.gov/8864357/ doi: 10.1016/1359-6101(96)00001-9.
[17] Furler RL, Nixon DF, Brantner CA, et al. TGF-β sustains tumor progression through biochemical and mechanical signal transduction. Cancers. 2018;10(6):199. https://www.mdpi.com/2072-6694/10/6/199/htm doi: 10.3390/cancers10060199.
[18] Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000; 100(1):57–70. https://pubmed.ncbi.nlm.nih.gov/10647931/ doi: 10.1016/S0092-8674(00)81683-9.
[19] Dumont N, Arteaga CL. Transforming growth factor-beta and breast cancer: tumor promoting effects of transforming growth factor-beta. Breast Cancer Res. 2000;2(2):125–132. https://pubmed.ncbi.nlm.nih.gov/11250702/ doi: 10.1186/bcr44.
[20] Pardali K, Moustakas A. Actions of TGF-beta as tumor suppressor and pro-metastatic factor in human cancer. Biochim Biophys Acta. 2007;1775(1):21–62. https://pubmed.ncbi.nlm.nih.gov/16904831/ doi: 10.1016/j.bbcan.2006.06.004.
[21] Hao Y, Baker D, Dijke PT. TGF-β-mediated epithelial-mesenchymal transition and cancer metastasis. Int J Mol Sci. 2019;20(11):2767. doi: 10.3390/ijms20112767.
[22] Krstic J, Santibanez JF. Transforming growth factor-beta and matrix metalloproteinases: functional interactions in tumor stroma-infiltrating myeloid cells. Sci World J. 2014;2014:1–14. doi: 10.1155/2014/521754.
[23] Baba AB, Rah B, Bhat GR, et al. Transforming growth factor-beta (TGF-β) signaling in cancer-a betrayal within. Front Pharmacol. 2022;13:791272. doi: 10.3389/fphar.2022.791272.
[24] Zavadil J, Böttinger EP. TGF-beta and epithelial-to-mesenchymal transitions. Oncogene. 2005;24(37):5764–5774. https://pubmed.ncbi.nlm.nih.gov/16123809/ doi: 10.1038/sj.onc.1208927.
[25] Gobbi H, Arteaga CL, Jensen RA, et al. Loss of expression of transforming growth factor beta type II receptor correlates with high tumour grade in human breast in-situ and invasive carcinomas. Histopathology. 2000;36(2):168–177. https://onlinelibrary.wiley.com/doi/full/10.1046/j.1365-2559.2000.00841.x doi: 10.1046/j.1365-2559.2000.00841.x.
[26] Ahmed S, Bradshaw AD, Gera S, et al. The TGF-β/Smad4 signaling pathway in pancreatic carcinogenesis and its clinical significance. J Clin Med. 2017;6(1):5. doi: 10.3390/jcm6010005.
[27] Thompson-Elliott B, Johnson R, Khan SA. Alterations in TGFβ signaling during prostate cancer progression. Am J Clin Exp Urol. 2021;9(4):318–328.
[28] Wang Z, Zhang Y, Zhao C, et al. The miR-223-3p/MAP1B axis aggravates TGF-β-induced proliferation and migration of BPH-1 cells. Cell Signal. 2021;84:110004. doi: 10.1016/j.cellsig.2021.110004.
[29] Jones E, Pu H, Kyprianou N. Targeting TGF-β in prostate cancer: therapeutic possibilities during tumor progression. Expert Opin Ther Targets. 2009;13(2):227–234. https://www.tandfonline.com/doi/abs/10.1517/14728220802705696 doi: 10.1517/14728220802705696.
[30] Study Details. Study of TGF-β receptor inhibitor galunisertib (LY2157299) and enzalutamide in metastatic castration-resistant prostate cancer. ClinicalTrials.gov; 2024. https://clinicaltrials.gov/study/NCT02452008.
[31] Rodríguez Y, Unno K, Truica MI, et al. A genome-wide CRISPR activation screen identifies PRRX2 as a regulator of enzalutamide resistance in prostate cancer. Cancer Res. 2022;82(11):2110–2123. https://pubmed.ncbi.nlm.nih.gov/35405009/ doi: 10.1158/0008-5472.CAN-21-3565.
[32] Ottley E, Gold E. microRNA and non-canonical TGF-β signalling: implications for prostate cancer therapy. Crit Rev Oncol Hematol. 2014;92(1):49–60. doi: 10.1016/j.critrevonc.2014.05.011.
[33] Shou M, Zhou H, Ma L. New advances in cancer therapy targeting TGF-β signaling pathways. Mol Ther Oncolytics. 2023;31:100755. http://www.cell.com/article/S2372770523001043/fulltext doi: 10.1016/j.omto.2023.100755.
[34] Castro NP, Rangel MC, Nagaoka T, et al. Cripto-1: at the crossroads of embryonic stem cells and cancer. Embryonic stem cells – Basic biology to bioengineering; 2011 [cited 2024 Aug 30]. https://www.intechopen.com/chapters/19271.
[35] Rodrigues Sousa E, Zoni E, Karkampouna S, et al. A multidisciplinary review of the roles of cripto in the scientific literature through a bibliometric analysis of its biological roles. Cancers. 2020;12(6):1480. https://www.mdpi.com/2072-6694/12/6/1480/htm doi: 10.3390/cancers12061480.
[36] Nickel J, Ten Dijke P, Mueller TD. TGF-β family co-receptor function and signaling. Acta Biochim Biophys Sin. 2018;50(1):12–36. doi: 10.1093/abbs/gmx126.
[37] Ishii H, Afify SM, Hassan G, et al. Cripto-1 as a potential target of cancer stem cells for immunotherapy. Cancers. 2021;13(10):2491. https://www.mdpi.com/2072-6694/13/10/2491/htm doi: 10.3390/cancers13102491.
[38] Bianco C, Rangel MC, Castro NP, et al. Role of cripto-1 in stem cell maintenance and malignant progression. Am J Pathol. 2010;177(2):532–540. doi: 10.2353/ajpath.2010.100102.
[39] Liu Y, Qin Z, Yang K, et al. Cripto-1 promotes epithelial-mesenchymal transition in prostate cancer via Wnt/β-catenin signaling. Oncol Rep. 2017;37(3):1521–1528. https://pubmed.ncbi.nlm.nih.gov/28098905/ doi: 10.3892/or.2017.5378.
[40] Arnouk H, Yum G, Shah D. Cripto-1 as a key factor in tumor progression, epithelial to mesenchymal transition and cancer stem cells. Int J Mol Sci. 2021;22(17):9280. https://www.mdpi.com/1422-0067/22/17/9280/htm doi: 10.3390/ijms22179280.
[41] Liu YAN, Wang J, Yang T, et al. Overexpression levels of cripto-1 predict poor prognosis in patients with prostate cancer following radical prostatectomy. Oncol Lett. 2019;18(3):2584–2591. https://pubmed.ncbi.nlm.nih.gov/31452743/ doi: 10.3892/ol.2019.10555.
[42] Tesar EC, Mikolasevic I, Skocilic I, et al. Prostate cancer scoring index for risk of progression of radioresistant disease. JPM. 2023;13(5):870. https://www.mdpi.com/2075-4426/13/5/870/htm doi: 10.3390/jpm13050870.

[43] Lawrence MG, Margaryan NV, Loessner D, et al. Reactivation of embryonic nodal signaling is associated with tumor progression and promotes the growth of prostate cancer cells. Prostate. 2011;71(11):1198–1209. doi: 10.1002/pros.21335.

[44] Haseeb M, Pirzada RH, Ul Ain Q, et al. Wnt signaling in the regulation of immune cell and cancer therapeutics. Cells. 2019;8(11):1380. https://www.mdpi.com/2073-4409/8/11/1380/htm doi: 10.3390/cells8111380.

[45] Jones SE, Jomary C. Secreted Frizzled-related proteins: searching for relationships and patterns. Bioessays. 2002;24(9):811–820. https://pubmed.ncbi.nlm.nih.gov/12210517/ doi: 10.1002/bies.10136.

[46] Lechler T, Mapelli M. Spindle positioning and its impact on vertebrate tissue architecture and cell fate. Nat Rev Mol Cell Biol. 2021;22(10):691–708. https://pubmed.ncbi.nlm.nih.gov/34158639/ doi: 10.1038/s41580-021-00384-4.

[47] Moon RT, Brown JD, Yang-Snyder JA, et al. Structurally related receptors and antagonists compete for secreted Wnt ligands. Cell. 1997;88(6):725–728. https://pubmed.ncbi.nlm.nih.gov/9118212/ doi: 10.1016/s0092-8674(00)81915-7.

[48] Yardy GW, Brewster SF. Wnt signalling and prostate cancer. Prostate Cancer Prostatic Dis. 2005; 8(2):119–126. https://pubmed.ncbi.nlm.nih.gov/15809669/ doi: 10.1038/sj.pcan.4500794.

[49] Bilić J, Huang Y-L, Davidson G, et al. Wnt induces LRP6 signalosomes and promotes dishevelled-dependent LRP6 phosphorylation. Science. 2007; 316(5831):1619–1622. https://pubmed.ncbi.nlm.nih.gov/17569865/ doi: 10.1126/science.1137065.

[50] Schwarz-Romond T, Fiedler M, Shibata N, et al. The DIX domain of Dishevelled confers Wnt signaling by dynamic polymerization. Nat Struct Mol Biol. 2007;14(6):484–492. https://pubmed.ncbi.nlm.nih.gov/17529994/ doi: 10.1038/nsmb1247.

[51] He TC, Sparks AB, Rago C, et al. Identification of c-MYC as a target of the APC pathway. Science. 1998;281(5382):1509–1512. https://pubmed.ncbi.nlm.nih.gov/9727977/ doi: 10.1126/science.281.5382.1509.

[52] Shtutman M, Zhurinsky J, Simcha I, et al. The cyclin D1 gene is a target of the beta-catenin/LEF-1 pathway. Proc Natl Acad Sci U S A. 1999;96(10):5522–5527. https://pubmed.ncbi.nlm.nih.gov/10318916/ doi: 10.1073/pnas.96.10.5522.

[53] Carlson ME, Conboy MJ, Hsu M, et al. Relative roles of TGF-beta1 and Wnt in the systemic regulation and aging of satellite cell responses. Aging Cell. 2009;8(6):676–689. https://pubmed.ncbi.nlm.nih.gov/19732043/ doi: 10.1111/j.1474-9726.2009.00517.x.

[54] Rahmani M, Read JT, Carthy JM, et al. Regulation of the versican promoter by the beta-catenin-T-cell factor complex in vascular smooth muscle cells. J Biol Chem. 2005;280(13):13019–13028. https://pubmed.ncbi.nlm.nih.gov/15668231/ doi: 10.1074/jbc.M411766200.

[55] Haertel-Wiesmann M, Liang Y, Fantl WJ, et al. Regulation of cyclooxygenase-2 and periostin by Wnt-3 in mouse mammary epithelial cells. J Biol Chem. 2000; 275(41):32046–32051. https://pubmed.ncbi.nlm.nih.gov/10884377/ doi: 10.1074/jbc.M000074200.

[56] ten Berge D, Koole W, Fuerer C, et al. Wnt signaling mediates self-organization and axis formation in embryoid bodies. Cell Stem Cell. 2008;3(5):508–518. https://pubmed.ncbi.nlm.nih.gov/18983966/ doi: 10.1016/j.stem.2008.09.013.

[57] Anthony CC, Robbins DJ, Ahmed Y, et al. Nuclear regulation of Wnt/β-catenin signaling: it's a complex situation. Genes 2020;11(8):886. doi: 10.3390/genes11080886.

[58] Gavert N, Ben-Ze'ev A. Beta-catenin signaling in biological control and cancer. J of Cellular Biochemistry. 2007;102(4):820–828. https://pubmed.ncbi.nlm.nih.gov/17854061/ doi: 10.1002/jcb.21505.

[59] Kushima R, Tsukashita S, Hattori T. Role of immunohistochemical expression of beta-catenin and mucin in stomach cancer. In: *Handbook of immunohistochemistry and in situ hybridization of human carcinomas*. vol. 4. London: Elsevier; 2006. p. 157–160.

[60] Uchino M, Kojima H, Wada K, et al. Nuclear β-catenin and CD44 upregulation characterize invasive cell populations in non-aggressive MCF-7 breast cancer cells. BMC Cancer. 2010; 10(1):414. doi: 10.1186/1471-2407-10-414.

[61] Ng TL, Gown AM, Barry TS, et al. Nuclear beta-catenin in mesenchymal tumors. Mod Pathol. 2005;18(1):68–74. https://pubmed.ncbi.nlm.nih.gov/15375433/ doi: 10.1038/modpathol.3800272.

[62] Ishitani T, Ninomiya-Tsuji J, Nagai S, et al. The TAK1-NLK-MAPK-related pathway antagonizes signalling between beta-catenin and transcription factor TCF. Nature. 1999;399(6738):798–802. https://pubmed.ncbi.nlm.nih.gov/10391247/ doi: 10.1038/21674.

[63] Voronkov A, Krauss S. Wnt/beta-catenin signaling and small molecule inhibitors. CPD. 2012;19(4):634–664. doi: 10.2174/13816128130406.

[64] Ma B, Hottiger MO. Crosstalk between Wnt/β-Catenin and NF-κB signaling pathway during inflammation. Front Immunol. 2016;7:378. https://pubmed.ncbi.nlm.nih.gov/27713747/ doi: 10.3389/fimmu.2016.00378.

[65] Patni AP, Harishankar MK, Joseph JP, et al. Comprehending the crosstalk between Notch, Wnt and Hedgehog signaling pathways in oral squamous cell carcinoma - clinical implications. Cell Oncol. 2021;44(3):473–494. https://pubmed.ncbi.nlm.nih.gov/33704672/ doi: 10.1007/s13402-021-00591-3.

[66] Kumar V, Vashishta M, Kong L, et al. The role of Notch, Hedgehog, and Wnt Signaling pathways in the resistance of tumors to anticancer therapies. Front Cell Dev Biol. 2021;9:650772. doi: 10.3389/fcell.2021.650772.

[67] Zhang Z, Cheng L, Li J, et al. Inhibition of the Wnt/β-catenin pathway overcomes resistance to enzalutamide in castration-resistant prostate cancer. Cancer Res. 2018;78(12):3147–3162. https://pubmed.ncbi.nlm.nih.gov/29700003/ doi: 10.1158/0008-5472.CAN-17-3006.

[68] Patel R, Brzezinska EA, Repiscak P, et al. Activation of β-catenin cooperates with loss of Pten to drive AR-independent castration-resistant prostate cancer. Cancer Res. 2020;80(3):576–590. https://pubmed.ncbi.nlm.nih.gov/31719098/ doi: 10.1158/0008-5472.CAN-19-1684.

[69] Shorning BY, Dass MS, Smalley MJ, et al. The PI3K-AKT-mtor pathway and prostate cancer: at the crossroads

of AR, MAPK, and WNT Signaling. Int J Mol Sci. 2020;21(12):1–47. https://pubmed.ncbi.nlm.nih.gov/32630372/

[70] Katoh M. Multi-layered prevention and treatment of chronic inflammation, organ fibrosis and cancer associated with canonical WNT/β-catenin signaling activation. Int J Mol Med. 2018;42(2):713–725. https://pubmed.ncbi.nlm.nih.gov/29786110/ doi: 10.3892/ijmm.2018.3689.

[71] Kaplan Z, Zielske SP, Ibrahim KG, et al. Wnt and β-catenin signaling in the bone metastasis of prostate cancer. Life. 2021;11(10):1099. https://www.mdpi.com/2075-1729/11/10/1099/htm doi: 10.3390/life11101099.

[72] Study Details. Predictive value of progastrin titer at diagnosis and of progastrin kinetics during treatment in cancer patients. ClinicalTrials.gov; 2024. https://www.clinicaltrials.gov/study/NCT03787056.

[73] Yashi M, Nishihara D, Yokoyama M, et al. Plasma progastrin-releasing peptide level shows different predictive profiles for treatment response by androgen receptor axis-targeted agents in patients with metastatic castration-resistant prostate cancer. Cancer Rep. 2023;6(3):e1762. https://pubmed.ncbi.nlm.nih.gov/36470854/ doi: 10.1002/cnr2.1762.

[74] Chen G, Shukeir N, Potti A, et al. Up-regulation of Wnt-1 and beta-catenin production in patients with advanced metastatic prostate carcinoma: potential pathogenetic and prognostic implications. Cancer. 2004;101(6):1345–1356. https://pubmed.ncbi.nlm.nih.gov/15316903/ doi: 10.1002/cncr.20518.

[75] Robinson D, Van Allen EM, Wu Y-M, et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015;161(5):1215–1228. http://www.cell.com/article/S0092867415005486/fulltext doi: 10.1016/j.cell.2015.05.001.

[76] Beltran H, Yelensky R, Frampton GM, et al. Targeted next-generation sequencing of advanced prostate cancer identifies potential therapeutic targets and disease heterogeneity. Eur Urol. 2013;63(5):920–926. https://pubmed.ncbi.nlm.nih.gov/22981675/ doi: 10.1016/j.eururo.2012.08.053.

[77] Grasso CS, Wu Y-M, Robinson DR, et al. The mutational landscape of lethal castrate resistant prostate cancer. Nature. 2012;487(7406):239–243. doi: 10.1038/nature11125.

[78] Voeller HJ, Truica CI, Gelmann EP. Beta-catenin mutations in human prostate cancer. Cancer Res. 1998;58(12):2520–2523.

[79] Pan K-F, Lee W-J, Chou C-C, et al. Direct interaction of β-catenin with nuclear ESM1 supports stemness of metastatic prostate cancer. Embo J. 2021;40(4):e105450. https://www.embopress.org/doi/10.15252/embj.2020105450 doi: 10.15252/embj.2020105450.

[80] Kühl M. Non-canonical Wnt signaling in Xenopus: regulation of axis formation and gastrulation. Semin Cell Dev Biol. 2002;13(3):243–249. doi: 10.1016/s1084-9521(02)00050-2.

[81] McEwen DG, Cox RT, Peifer M. The canonical Wg and JNK signaling cascades collaborate to promote both dorsal closure and ventral patterning. Development. 2000;127(16):3607–3617. https://pubmed.ncbi.nlm.nih.gov/10903184/ doi: 10.1242/dev.127.16.3607.

[82] Veeman MT, Axelrod JD, Moon RT. A second canon: functions and mechanisms of β-catenin-independent Wnt signaling. Dev Cell. 2003;5(3):367–377. doi: 10.1016/s1534-5807(03)00266-1.

[83] Turashvili G, Bouchal J, Burkadze G, et al. Wnt signaling pathway in mammary gland development and carcinogenesis. Pathobiology. 2006;73(5):213–223. doi: 10.1159/000098207.

[84] Slusarski DC, Corces VG, Moon RT. Interaction of Wnt and a Frizzled homologue triggers G-protein-linked phosphatidylinositol signalling. Nature. 1997;390(6658):410–413. https://pubmed.ncbi.nlm.nih.gov/9389482/ doi: 10.1038/37138.

[85] Ahumada A, Slusarski DC, Liu X, et al. Signaling of rat Frizzled-2 through phosphodiesterase and cyclic GMP. Science. 2002;298(5600):2006–2010. https://pubmed.ncbi.nlm.nih.gov/12471263/ doi: 10.1126/science.1073776.

[86] Sheldahl LC, Park M, Malbon CC, et al. Protein kinase C is differentially stimulated by Wnt and Frizzled homologs in a G-protein-dependent manner. Curr Biol. 1999;9(13):695–698. doi: 10.1016/s0960-9822(99)80310-8.

[87] Pandur P, Läsche M, Eisenberg LM, et al. Wnt-11 activation of a non-canonical Wnt signalling pathway is required for cardiogenesis. Nature. 2002;418(6898):636–641. https://pubmed.ncbi.nlm.nih.gov/12167861/ doi: 10.1038/nature00921.

[88] Heisenberg CP, Tada M, Rauch GJ, et al. Silberblick/Wnt11 mediates convergent extension movements during zebrafish gastrulation. Nature. 2000;405(6782):76–81. https://pubmed.ncbi.nlm.nih.gov/10811221/ doi: 10.1038/35011068.

[89] Veeman MT, Slusarski DC, Kaykas A, et al. Zebrafish prickle, a modulator of noncanonical Wnt/Fz signaling, regulates gastrulation movements. Curr Biol. 2003;13(8):680–685. https://pubmed.ncbi.nlm.nih.gov/12699626/ doi: 10.1016/s0960-9822(03)00240-9.

[90] van Amerongen R, Nusse R. Towards an integrated view of Wnt signaling in development. Development. 2009;136(19):3205–3214. https://pubmed.ncbi.nlm.nih.gov/19736321/ doi: 10.1242/dev.033910.

[91] Yamamoto S, Nishimura O, Misaki K, et al. Cthrc1 selectively activates the planar cell polarity pathway of Wnt signaling by stabilizing the Wnt-receptor complex. Dev Cell. 2008;15(1):23–36. https://pubmed.ncbi.nlm.nih.gov/18606138/ doi: 10.1016/j.devcel.2008.05.007.

[92] Kharaishvili G, Simkova D, Makharoblidze E, et al. Wnt signaling in prostate development and carcinogenesis. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2011;155(1):11–18. https://pubmed.ncbi.nlm.nih.gov/21475372/ doi: 10.5507/bp.2011.016.

[93] Topol L, Jiang X, Choi H, et al. Wnt-5a inhibits the canonical Wnt pathway by promoting GSK-3-independent beta-catenin degradation. J Cell Biol. 2003;162(5):899–908. https://pubmed.ncbi.nlm.nih.gov/12952940/ doi: 10.1083/jcb.200303158.

[94] He Y, Xu W, Xiao YT, et al. Targeting signaling pathways in prostate cancer: mechanisms and clinical trials. Signal Transduct Target Ther. 2022;7(1):198. https://

www.nature.com/articles/s41392-022-01042-7 doi: 10.1038/s41392-022-01042-7.
[95] Wang Y, Singhal U, Qiao Y, et al. Wnt signaling drives prostate cancer bone metastatic tropism and invasion. Transl Oncol. 2020;13(4):100747. doi: 10.1016/j.tranon.2020.100747.
[96] Li Q, Ye L, Zhang X, et al. FZD8, a target of p53, promotes bone metastasis in prostate cancer by activating canonical Wnt/β-catenin signaling. Cancer Lett. 2017;402:166–176. doi: 10.1016/j.canlet.2017.05.029.
[97] Ma F, Arai S, Wang K, et al. Autocrine canonical Wnt signaling primes noncanonical signaling through ROR1 in metastatic castration-resistant prostate cancer. Cancer Res. 2022;82(8):1518–1533. https://pubmed.ncbi.nlm.nih.gov/35131873/ doi: 10.1158/0008-5472.CAN-21-1807.
[98] Mariadason JM, Bordonaro M, Aslam F, et al. Down-regulation of beta-catenin TCF signaling is linked to colonic epithelial cell differentiation. Cancer Res. 2001;61(8):3465–3471. https://pubmed.ncbi.nlm.nih.gov/11309309/
[99] Naishiro Y, Yamada T, Takaoka AS, et al. Restoration of epithelial cell polarity in a colorectal cancer cell line by suppression of beta-catenin/T-cell factor 4-mediated gene transactivation. Cancer Res. 2001;61(6):2751–2758.
[100] Li J, Zhou BP. Activation of β-catenin and Akt pathways by Twist are critical for the maintenance of EMT associated cancer stem cell-like characters. BMC Cancer. 2011;11(1):49. https://pubmed.ncbi.nlm.nih.gov/21284870/ doi: 10.1186/1471-2407-11-49.
[101] Schambony A, Kunz M, Gradl D. Cross-regulation of Wnt signaling and cell adhesion. Differentiation. 2004;72(7):307–318. doi: 10.1111/j.1432-0436.2004.07207002.x.
[102] Sasaki H, Yu C-Y, Dai M, et al. Elevated serum periostin levels in patients with bone metastases from breast but not lung cancer. Breast Cancer Res Treat. 2003;77(3):245–252. https://pubmed.ncbi.nlm.nih.gov/12602924/ doi: 10.1023/a:1021899904332.
[103] Zheng P-S, Wen J, Ang LC, et al. Versican/PG-M G3 domain promotes tumor growth and angiogenesis. FASEB J. 2004;18(6):754–756. https://pubmed.ncbi.nlm.nih.gov/14766798/ doi: 10.1096/fj.03-0545fje.
[104] Nikitovic D, Zafiropoulos A, Katonis P, et al. Transforming growth factor-beta as a key molecule triggering the expression of versican isoforms v0 and v1, hyaluronan synthase-2 and synthesis of hyaluronan in malignant osteosarcoma cells. IUBMB Life. 2006;58(1):47–53. https://pubmed.ncbi.nlm.nih.gov/16540432/ doi: 10.1080/15216540500531713.
[105] Kim L, Kimmel AR. GSK3, a master switch regulating cell-fate specification and tumorigenesis. Curr Opin Genet Dev. 2000;10(5):508–514. doi: 10.1016/s0959-437x(00)00120-9.
[106] Gao S, Wang S, Zhao Z, et al. TUBB4A interacts with MYH9 to protect the nucleus during cell migration and promotes prostate cancer via GSK3β/β-catenin signalling. Nat Commun. 2022;13(1):2792. https://www.nature.com/articles/s41467-022-30409-1 doi: 10.1038/s41467-022-30409-1.
[107] Iriana S, Asha K, Repak M, et al. Hedgehog signaling: implications in cancers and viral infections. Int J Mol Sci. 2021;22(3):1042. https://www.mdpi.com/1422-0067/22/3/1042/htm doi: 10.3390/ijms22031042.
[108] Jing J, Wu Z, Wang J, et al. Hedgehog signaling in tissue homeostasis, cancers, and targeted therapies. Signal Transduct Target Ther. 2023;8(1):315. https://www.nature.com/articles/s41392-023-01559-5 doi: 10.1038/s41392-023-01559-5.
[109] Petrova R, Joyner AL. Roles for Hedgehog signaling in adult organ homeostasis and repair. Development. 2014;141(18):3445–3457. doi: 10.1242/dev.083691.
[110] Ingham PW. Hedgehog signaling. Curr Top Dev Biol. 2022;149:1–58. https://pubmed.ncbi.nlm.nih.gov/35606054/ doi: 10.1016/bs.ctdb.2022.04.003.
[111] Onodera S, Nakamura Y, Azuma T. Gorlin syndrome: recent advances in genetic testing and molecular and cellular biological research. Int J Mol Sci. 2020;21(20):7559. https://www.mdpi.com/1422-0067/21/20/7559/htm doi: 10.3390/ijms21207559.
[112] Miller SJ, Lavker RM, Sun TT. Interpreting epithelial cancer biology in the context of stem cells: tumor properties and therapeutic implications. Biochim Biophys Acta. 2005;1756(1):25–52. https://pubmed.ncbi.nlm.nih.gov/16139432/ doi: 10.1016/j.bbcan.2005.07.003.
[113] Gonnissen A, Isebaert S, Haustermans K. Hedgehog signaling in prostate cancer and its therapeutic implication. Int J Mol Sci. 2013;14(7):13979–14007. https://www.mdpi.com/1422-0067/14/7/13979/htm doi: 10.3390/ijms140713979.
[114] Efstathiou E, Karlou M, Wen S, et al. Integrated Hedgehog signaling is induced following castration in human and murine prostate cancers. Prostate. 2013;73(2):153–161. https://onlinelibrary.wiley.com/doi/full/10.1002/pros.22550 doi: 10.1002/pros.22550.
[115] Sheng T, Li C, Zhang X, et al. Activation of the hedgehog pathway in advanced prostate cancer. Mol Cancer. 2004;3(1):29. https://molecular-cancer.biomedcentral.com/articles/10.1186/1476-4598-3-29 doi: 10.1186/1476-4598-3-29.
[116] De SK. Targeted therapy: small molecules. In: Medicines for cancer; 2023. p. 205–411 [cited 2024 Aug 30]. https://linkinghub.elsevier.com/retrieve/pii/B9780443133121000027.
[117] Study Details. A pre surgical study of LDE225 in men with high-risk localized prostate cancer. ClinicalTrials.gov. 2024 [cited 2024 Feb 18]. https://clinicaltrials.gov/study/NCT02111187.
[118] Ross AE, Hughes RM, Glavaris S, et al. Pharmacodynamic and pharmacokinetic neoadjuvant study of hedgehog pathway inhibitor Sonidegib (LDE-225) in men with high-risk localized prostate cancer undergoing prostatectomy. Oncotarget. 2017;8(61):104182–104192. doi: 10.18632/oncotarget.22115.
[119] Katoh M, Katoh M. Notch signaling in gastrointestinal tract. Int J Oncol. 2007;30(1):247–251. doi: 10.3892/ijo.30.1.247/abstract
[120] Ellisen LW, Bird J, West DC, et al. TAN-1, the human homolog of the Drosophila notch gene, is broken by

chromosomal translocations in T lymphoblastic neoplasms. Cell. 1991;66(4):649–661. https://pubmed.ncbi.nlm.nih.gov/1831692/ doi: 10.1016/0092-8674(91)90111-b.

[121] Fan X, Mikolaenko I, Elhassan I, et al. Notch1 and notch2 have opposite effects on embryonal brain tumor growth. Cancer Res. 2004;64(21):7787–7793. https://pubmed.ncbi.nlm.nih.gov/15520184/ doi: 10.1158/0008-5472.CAN-04-1446.

[122] Dang TP, Gazdar AF, Virmani AK, et al. Chromosome 19 translocation, overexpression of Notch3, and human lung cancer. J Natl Cancer Inst. 2000;92(16):1355–1357. https://pubmed.ncbi.nlm.nih.gov/10944559/ doi: 10.1093/jnci/92.16.1355.

[123] Park JT, Li M, Nakayama K, et al. Notch3 gene amplification in ovarian cancer. Cancer Res. 2006;66(12):6312–6318. https://pubmed.ncbi.nlm.nih.gov/16778208/ doi: 10.1158/0008-5472.CAN-05-3610.

[124] Reedijk M, Odorcic S, Chang L, et al. High-level coexpression of JAG1 and NOTCH1 is observed in human breast cancer and is associated with poor overall survival. Cancer Res. 2005;65(18):8530–8537. https://pubmed.ncbi.nlm.nih.gov/16166334/ doi: 10.1158/0008-5472.CAN-05-1069.

[125] Pece S, Serresi M, Santolini E, et al. Loss of negative regulation by Numb over Notch is relevant to human breast carcinogenesis. J Cell Biol. 2004;167(2):215–221. https://pubmed.ncbi.nlm.nih.gov/15492044/ doi: 10.1083/jcb.200406140.

[126] Radtke F, Raj K. The role of Notch in tumorigenesis: oncogene or tumour suppressor? Nat Rev Cancer. 2003;3(10):756–767. https://pubmed.ncbi.nlm.nih.gov/14570040/ doi: 10.1038/nrc1186.

[127] Proweller A, Tu L, Lepore JJ, et al. Impaired notch signaling promotes de novo squamous cell carcinoma formation. Cancer Res. 2006;66(15):7438–7444. https://pubmed.ncbi.nlm.nih.gov/16885339/ doi: 10.1158/0008-5472.CAN-06-0793.

[128] Acar A, Hidalgo-Sastre A, Leverentz MK, et al. Inhibition of Wnt signalling by Notch via two distinct mechanisms. Sci Rep. 2021;11(1):9096. https://www.nature.com/articles/s41598-021-88618-5 doi: 10.1038/s41598-021-88618-5.

[129] Shang Y, Smith S, Hu X. Role of Notch signaling in regulating innate immunity and inflammation in health and disease. Protein Cell. 2016;7(3):159–174. doi: 10.1007/s13238-016-0250-0.

[130] Wang Z, Li Y, Kong D, et al. The role of Notch signaling pathway in epithelial-mesenchymal transition (EMT) during development and tumor aggressiveness. Curr Drug Targets. 2010;11(6):745–751. https://pubmed.ncbi.nlm.nih.gov/20041844/ doi: 10.2174/138945010791170860.

[131] Stacy AJ, Craig MP, Sakaram S, et al. ΔNp63α and microRNAs: leveraging the epithelial-mesenchymal transition. Oncotarget. 2017;8(2):2114–2129. https://www.oncotarget.com/article/13797/text/ doi: 10.18632/oncotarget.13797.

[132] Orzechowska MJ, Anusewicz D, Bednarek AK. Age- and stage-dependent prostate cancer aggressiveness associated with differential Notch signaling. Int J Mol Sci. 2022;24(1):164. https://pubmed.ncbi.nlm.nih.gov/36613607/ doi: 10.3390/ijms24010164.

[133] Zinger A, Cho WC, Ben-Yehuda A. Cancer and aging – the inflammatory connection. Aging Dis. 2017;8(5):611–627. doi: 10.14336/AD.2016.1230.

[134] Marignol L, Rivera-Figueroa K, Lynch T, et al. Hypoxia, notch signalling, and prostate cancer. Nat Rev Urol. 2013;10(7):405–413. https://pubmed.ncbi.nlm.nih.gov/23712204/ doi: 10.1038/nrurol.2013.110.

[135] Torchinsky A, Toder V. To die or not to die: the function of the transcription factor NF-kappaB in embryos exposed to stress. Am J Reprod Immunol. 2004;51(2):138–143. https://pubmed.ncbi.nlm.nih.gov/14748840/ doi: 10.1046/j.8755-8920.2003.00134.x.

[136] Häcker H, Karin M. Regulation and function of IKK and IKK-related kinases. Sci STKE. 2006;2006(357):re13. https://www.science.org/doi/10.1126/stke.3572006re13

[137] Karin M, Cao Y, Greten FR, et al. NF-kappaB in cancer: from innocent bystander to major culprit. Nat Rev Cancer. 2002;2(4):301–310. https://pubmed.ncbi.nlm.nih.gov/12001991/ doi: 10.1038/nrc780.

[138] Chua HL, Bhat-Nakshatri P, Clare SE, et al. NF-κB represses E-cadherin expression and enhances epithelial to mesenchymal transition of mammary epithelial cells: potential involvement of ZEB-1 and ZEB-2. Oncogene. 2007;26(5):711–724. https://www.nature.com/articles/1209808 doi: 10.1038/sj.onc.1209808.

[139] Shang Z, Yu J, Sun L, et al. LncRNA PCAT1 activates AKT and NF-κB signaling in castration-resistant prostate cancer by regulating the PHLPP/FKBP51/IKKα complex. Nucleic Acids Res. 2019;47(8):4211–4225. https://pubmed.ncbi.nlm.nih.gov/30773595/ doi: 10.1093/nar/gkz108.

[140] Oh A, Pardo M, Rodriguez A, et al. NF-κB signaling in neoplastic transition from epithelial to mesenchymal phenotype. from:/pmc/articles/PMC10585759/. Cell Commun Signal. 2023;21(1):291. doi: 10.1186/s12964-023-01207-z.

[141] Solanas G, Porta-de-la-Riva M, Agustí C, et al. E-cadherin controls β-catenin and NF-κB transcriptional activity in mesenchymal gene expression. J Cell Sci. 2008;121(Pt 13):2224–2234. doi: 10.1242/jcs.021667.

[142] Tripathi V, Popescu NC, Zimonjic DB. DLC1 suppresses NF-κB activity in prostate cancer cells due to its stabilizing effect on adherens junctions. Springerplus. 2014;3(1):27. https://springerplus.springeropen.com/articles/10.1186/2193-1801-3-27 doi: 10.1186/2193-1801-3-27.

[143] Zhou X, Yang XY, Popescu NC. Preclinical evaluation of combined antineoplastic effect of DLC1 tumor suppressor protein and suberoylanilide hydroxamic acid on prostate cancer cells. Biochem Biophys Res Commun. 2012;420(2):325–330. doi: 10.1016/j.bbrc.2012.02.158.

[144] Jain S, Dash P, Minz AP, et al. Lipopolysaccharide (LPS) enhances prostate cancer metastasis potentially through NF-κB activation and recurrent dexamethasone administration fails to suppress it in vivo. Prostate. 2019;79(2):168–182. https://pubmed.ncbi.nlm.nih.gov/30264470/ doi: 10.1002/pros.23722.

[145] Yu H, Lin L, Zhang Z, et al. Targeting NF-κB pathway for the therapy of diseases: mechanism and clinical

study. Signal Transduct Target Ther. 2020;5(1):209. https://www.nature.com/articles/s41392-020-00312-6 doi: 10.1038/s41392-020-00312-6.

[146] Jain G, Cronauer MV, Schrader M, et al. NF-κB signaling in prostate cancer: a promising therapeutic target? World J Urol. 2012;30(3):303–310. https://link.springer.com/article/10.1007/s00345-011-0792-y doi: 10.1007/s00345-011-0792-y.

[147] Ko YS, Pyo JS, Cho WJ. Roles of NF-κB activation in benign prostatic hyperplasia and association between NF-κB and HIF-1α. Pathol Res Pract. 2022;237:154021. https://pubmed.ncbi.nlm.nih.gov/35901596/ doi: 10.1016/j.prp.2022.154021.

[148] Capece D, Verzella D, Flati I, et al. NF-κB: blending metabolism, immunity, and inflammation. Trends Immunol. 2022;43(9):757–775. https://pubmed.ncbi.nlm.nih.gov/35965153/ doi: 10.1016/j.it.2022.07.004.

[149] Chen B, Liu X, Yu P, et al. H. pylori-induced NF-κB-PIEZO1-YAP1-CTGF axis drives gastric cancer progression and cancer-associated fibroblast-mediated tumour microenvironment remodelling. Clin Transl Med. 2023;13(11):e1481. https://onlinelibrary.wiley.com/doi/full/10.1002/ctm2.1481 doi: 10.1002/ctm2.1481.

[150] Zhang M, Liu ZZ, Aoshima K, et al. CECR2 drives breast cancer metastasis by promoting NF-κB signaling and macrophage-mediated immune suppression. Sci Transl Med. 2022;14(630):eabf5473. https://pubmed.ncbi.nlm.nih.gov/35108062/ doi: 10.1126/scitranslmed.abf5473.

[151] Lin S-C, Liao Y-C, Chen P-M, et al. Periostin promotes ovarian cancer metastasis by enhancing M2 macrophages and cancer-associated fibroblasts via integrin-mediated NF-κB and TGF-β2 signaling. J Biomed Sci. 2022;29(1):109. https://jbiomedsci.biomedcentral.com/articles/10.1186/s12929-022-00888-x doi: 10.1186/s12929-022-00888-x.

[152] Voronova V, Vislobokova A, Mutig K, et al. Combination of immune checkpoint inhibitors with radiation therapy in cancer: a hammer breaking the wall of resistance. Front Oncol. 2022;12:1035884. doi: 10.3389/fonc.2022.1035884.

[153] Miller DR, Ingersoll MA, Teply BA, et al. Combination treatment options for castration-resistant prostate cancer. Prostate Cancer; 2021 [cited 2024 Aug 30]. https://pubmed.ncbi.nlm.nih.gov/34181378/.

[154] Siewe N, Friedman A. Combination therapy for mCRPC with immune checkpoint inhibitors, ADT and vaccine: a mathematical model. PLOS One. 2022;17(1):e0262453. doi: 10.1371/journal.pone.0262453.

[155] Nakazawa M, Paller C, Kyprianou N. Mechanisms of therapeutic resistance in prostate cancer. Curr Oncol Rep. 2017;19(2):13. https://pubmed.ncbi.nlm.nih.gov/28229393/ doi: 10.1007/s11912-017-0568-7. [InsertedFromOnline

[156] Choi HY, Chang JE, Choi HY, et al. Targeted therapy for cancers: from ongoing clinical trials to FDA-approved drugs. Int J Mol Sci. 2023;24(17):13618. https://www.mdpi.com/1422-0067/24/17/13618/htm doi: 10.3390/ijms241713618.

[157] Pak S, Park S, Kim Y, et al. The small molecule WNT/β-catenin inhibitor CWP232291 blocks the growth of castration-resistant prostate cancer by activating the endoplasmic reticulum stress pathway. J Exp Clin Cancer Res. 2019;38(1):342. 1–13. https://jeccr.biomedcentral.com/articles/10.1186/s13046-019-1342-5 doi: 10.1186/s13046-019-1342-5.

[158] Cui D, Dai J, Keller JM, et al. Notch pathway inhibition using PF-03084014, a γ-secretase inhibitor (GSI), enhances the anti-tumor effect of docetaxel in prostate cancer. Clin Cancer Res. 2015;21(20):4619–4629. doi: 10.1158/1078-0432.CCR-15-0242.

[159] Yu F, Yu C, Li F, et al. Wnt/β-catenin signaling in cancers and targeted therapies. Signal Transduct Target Ther. 2021;6(1):307. doi: 10.1038/s41392-021-00701-5.

[160] Nguyen DP, Li J, Yadav SS, et al. Recent insights into NF-κB signalling pathways and the link between inflammation and prostate cancer. BJU Int. 2014;114(2):168–176. https://pubmed.ncbi.nlm.nih.gov/24215139/ doi: 10.1111/bju.12488.