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Dishevelled: a masterful conductor of complex Wnt signals

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Abstract

The Dishevelled gene was first identified in *Drosophila* mutants with disoriented hair and bristle polarity [1–3]. The *Dsh* gene (*Dsh/Dvl*, in *Drosophila* and vertebrates respectively) gained popularity when it was discovered that it plays a key role in segment polarity during early embryonic development in *Drosophila* [4]. Subsequently, the vertebrate homolog of Dishevelled genes were identified in *Xenopus (Xdsh)*, mice (*Dvl1, Dvl2, Dvl3*), and in humans (*DVL1, DVL2, DVL3*) [5–10]. Dishevelled functions as a principal component of Wnt signaling pathway and governs several cellular processes including cell proliferation, survival, migration, differentiation, polarity and stem cell renewal. This review will revisit seminal discoveries and also summarize recent advances in characterizing the role of Dishevelled in both normal and pathophysiological settings.

Keywords

Wnt; Dishevelled; β-catenin; cancer; development; disease

1. Introduction

It is fascinating to consider how the identity of DVL is largely linked with its ability to integrate and relay complex Wnt signals in tissues and cells yet how it conducts this symphony of activity still remains poorly understood. While we know that the final outcome of Wnt signaling will depend on the abundance of and ratios of Wnt ligands, antagonists and receptors, DVL plays a key role in integrating and transmitting these instructions regardless of whether they are correct or aberrant in nature. This propagation of information may initiate a signaling cascade that ultimately leads to β-catenin stabilization or a β-catenin-independent effect. While this review will recap some of the landmark discoveries and

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recent advances in characterizing the role of Dishevelled, we point the reader to previous reviews that have highlighted its role in signal transduction [11, 12], developmental biology [3], and nuclear shuttling [13]. Additionally, the concept of the mystery that still surrounds DVL and what it means for it to be “activated” after more than two decades investigation was nicely addressed previously [14]. This review will discuss the function of DVL in the Wnt signaling pathway in normal and aberrant cellular contexts. It will also highlight novel roles within the nucleus and highlight new binding partners that have been discovered and novel mechanisms of post-translational regulation.

2. Function of DVL in Wnt signaling pathway

Early genetic studies demonstrated that Dishevelled proteins are involved in canonical (β-catenin-dependent) and non-canonical (β-catenin-independent) Wnt signaling pathways that govern the segment polarity in the fly. However, it was not clearly understood how DVL participates simultaneously in both pathways. It was later demonstrated that DVL acts as a branch-point and is an essential component of both arms of Wnt signaling [3]. In addition to the canonical and non-canonical pathways, DVL has been associated with other Wnt-related signaling pathways like the Wnt-GSKβ-microtubule, Wnt-calcium, Wnt-RYK (Related to tyrosine kinase), Wnt-aPKC (atypical Protein Kinase C), and Wnt-mTOR (mammalian target of rapamycin) signaling pathway [11].

2.1. Role of DVL in Canonical Wnt pathway

In the canonical Wnt signaling pathway (also called Wnt/β-catenin pathway), one model suggests that binding of Wnt to a seven-pass transmembrane Frizzled receptors helps recruit DVL to the plasma membrane [15]. Recruitment of DVL to the membrane provides a platform for Axin and GSK3β to bind and phosphorylate LRP5/6 thereby preventing constitutive degradation of β-catenin. Inhibition of Axin-mediated degradation by DVL allows β-catenin to accumulate in the nucleus where it serves as a coactivator for TCF to activate Wnt responsive genes (Figure 1). It is also important to note that DVL proteins have been shown to shuttle between the cytoplasm and nucleus [16–18]. A recent study reported that DVL proteins contain a conserved nuclear export sequence (NES) and a nuclear localization sequence (NLS) which is critical for its proper functioning in the canonical Wnt signaling pathway [18]. Another study demonstrated that interaction of DVL-2 with c-Jun and β-catenin, which was followed by formation of stable DVL-2/c-Jun/β-catenin/TCF complex leading to transcriptional activation of Wnt target genes in the nucleus [16] (Figure 1). In 2014, DVL-1 was shown to bind to a 2kb region upstream of the transcription start site of the Frizzled 7 gene in T-47D breast cancer cells. Interestingly, this binding was shown to be diminished with SIRT1/2 pharmacological inhibition, suggesting that DVL-1 protein levels and promoter occupancy could be regulated by at least one type of lysine deacetylase [19]. In addition, DVL was shown to modulate Wnt signaling by interacting with nuclear proteins such as HIPK1(Homeodomain-interacting protein kinase 1), xNET1 (Xenpous nucleotide exchange factor), and FOXKs (Forkhead box transcription factor) [20–22]. These studies elucidate the transcriptional function of DVL in the nucleus. A study in 2015 shed light on a possible mechanism of regulating DVL localization to the nucleus. Interestingly, they demonstrated that Forkhead box (FOX) transcription factors positively regulate Wnt/β-

catenin pathway by translocating DVL into the nucleus [22]. Therefore, there seems to be two pools of DVL in a cell – one in the nucleus and another in the cytoplasm regulating the canonical Wnt pathway in a cell.

2.2. Role of DVL in Non-canonical Wnt pathway

In the non-canonical Wnt signaling pathway (also called Wnt/PCP pathway), DVL plays a key role in governing polarity and cytoskeletal rearrangements of a cell. The Wnt signal is received by the Frizzled receptor which relays signal to DVL-Diego (Diversin in vertebrate) located distally, and Strabismus (Vangl in vertrebrates)-Prickle (Pk) located proximally in a cell, which helps define the polarity of an epithelial cell [11, 23–25].

In the non-canonical pathway, Dishevelled acts as a branchpoint for two independent pathways which leads to activation of small GTPase Rho and Rac (Figure 1). For the activation of the Rho branch of signaling, Wnt signal induces DVL to form a complex with Daam1 (Dishevelled associated activator of morphogenesis 1). The DVL-Daam1 complex further interacts with Rho guanine nucleotide exchange factor WGEF (weak-similarity GEF) which activates downstream effectors like Rho GTPase and Rho-associated kinase (ROCK) [26, 27]. Once activated, this pathway modifies actin and cytoskeleton architecture of a cell. In addition to activating Rho/ROCK, DVL activates the Rac GTPase independent of Daam1. Studies have reported that an activated Rac stimulates the downstream effector c-Jun N-terminal kinase (JNK) which regulates the polarity and movement of a cell during Xenopus gastrulation [28].

3. Involvement of DVL in other signaling pathways

It has been shown that DVL associates with proteins of other signaling pathways to regulate key cell processes. For instance, DVL regulates the cytoskeleton remodeling of a cell by inhibiting GSK3β and stabilizing microtubule-associated proteins MAP1B and MAP2 [29, 30]. Furthermore, DVL interacts with a Ring finger protein called XRNF185 to mediate cell migration during gastrulation. In the Wnt/ Ca^{2+} pathway, DVL proteins have also shown to cause an increase in intracellular calcium flux which leads to activation of various calcium-sensitive enzymes such as protein kinase C (PKC) (Figure 1), and calcium-calmodulin-dependent kinase (CamKII) [31]. Accumulation of calcium in a cell regulates tissue separation and convergent extension movements during early embryonic development [32]. DVL also participates in axonal repulsion and cell migration by physically interacting with Related to tyrosine kinase (RYK) receptor [33]. Additionally, DVL binds to and stabilizes atypical PKC (aPKC) which leads to microtubule assembly and axon formation. This study in hippocampal neurons demonstrated that downregulation of DVL reduced axon differentiation, whereas overexpression of DVL induced formation of multiple axons [34].

It is evident that DVL plays a central role in propagating Wnt signaling pathway and can affect various development processes of a cell. Given its critical involvement in different pathways, DVL can be called a master integrator of diverse and complex signals.

4. DVL protein structure

All the DVL proteins ranging from drosophila to humans possess three conserved domains: an amino-terminal DIX domain, a central PDZ, and a carboxyl-terminal DEP domain [35]. In addition to these three domains, DVL harbors two regions with positively charged amino acid residues. The first one is a 'basic region' comprising of conserved serine and threonine residues, situated between the DIX and PDZ domains. The second is a 'proline-rich region' which is present downstream of the PDZ domain. These conserved domains mediate protein-protein interactions [36] and help DVL channel signals into either canonical or non-canonical Wnt pathway (Figure 2).

4.1. The DIX domain

Present on the N-terminal region of the DVL protein, it encodes 82–85 amino acids for human DVL proteins. The DIX domain is also found in proteins like Axin and coiled-coil protein DIX-domain-containing 1 (called DIXdc1 or Ccd1) [37]. The DVL proteins (both at endogenous and at overexpressed levels) have a striking ability to form cytoplasmic puncta (For review, see Gao and Chen 2010) [11]. The DIX domain mediates dynamic polymerization of DVL puncta which enables the DVL proteins to activate the Wnt/β-catenin pathway [35]. The DIX domain not only aids in assembly of signalosomes near the plasma membrane but also mediates protein-protein interactions. DVL protein can interact with Axin via DIX domain which inhibits Axin-promoted β-catenin destruction, thereby stabilizing β-catenin and inducing transcriptional activation of Wnt responsive genes [38]. The crystal structure of the DVL DIX domain has not been identified, however the DIX domain of rat Axin has been solved. Since the DIX domain of DVL and Axin share similarities, the structural properties of DVL DIX domain can be predicted. The DIX domain has five β–strands, one α–helix [39] with highly conserved amino acid residues which are critical for structural and functional roles of DVL. Mutations in some of the key residues (Y27D, F43S, V67A, K68A, E69A) have been shown to inhibit the canonical Wnt pathway [35, 40–42].

4.2. The PDZ domain

The central domain of the DVL proteins, usually encodes about 73 amino acids in each of the human DVL proteins. PDZ domain is named after the proteins in which it was first discovered – Post synaptic density-95/Discs large/Zonula-occludens-1. The PDZ domain mediates crucial protein-protein interactions and regulates multiple biological processes. For instance, it directly interacts with a conserved C-terminal region of Frizzled (KTXXXW) which is necessary for activation of Wnt pathway and for membrane localization of DVL proteins [43]. Considering its central location on DVL proteins, the PDZ domain appears to play an important role in both canonical and non-canonical Wnt pathway [44]. In fact, some studies suggest that the PDZ domain of DVL is involved in distinguishing between the two Wnt pathways [45, 46]. The PDZ domain comprises of 5 or 6 β–stands and 2 or 3 α–helices [47] with a conserved motif (R/K-XXX-G-φ-G-φ motif, where X represents any amino acid residue, and φ is hydrophobic residue) which plays a critical role in ligand binding and conformational properties of the DVL protein [47]. The special role of DVL PDZ domain has attracted a lot of attention. Using NMR spectroscopy, various compounds, peptides and

antagonists (3289–8625, NSC668036) have been synthesized which could selectively inhibit PDZ-domain interactions to down-regulate the downstream Wnt signaling pathway [11, 48–51]. Interestingly, an anti-tumor inhibitor called FJ9 has been developed which downregulates the canonical Wnt pathway by selectively inhibiting DVL-Fz interaction in human tumor cell lines [52].

4.3. The DEP domain

The Dishevelled, Egl-10, Pleckstrin (DEP) domain is the C-terminal domain of DVL and consists of 75 amino acids in the human DVL proteins. It has three α - helices, a β-hairpin "arm" and two short β-strands. The DEP domain enables interaction between DVL and DAAM1 (dishevelled associated activator of morphogenesis 1) thereby activating non-canonical signaling pathway. Recent studies have shown that DEP domain is responsible for targeting DVL proteins to the membrane upon Wnt signal stimulation [53]. Moreover, some evidences suggest that DEP domain is essential for the assembly of functional signalosomes and for Wnt signal transduction to the nucleus [54]. Based on structural studies, a strong electric dipole generated by K434, D445 and D448 residues on DEP domain is crucial for protein-protein interactions. Moreover, several basic residues present on the DEP domain (K408, K458, R461, R464, K465, K472 and K482) aid in membrane localization of DVL during planar epithelial polarization [55]. Mutations of these conserved residues not only disrupt membrane localization of DVL but also strongly inhibit Rho/Rac activation during convergent extension [55, 56].

In addition to these conserved regions, DVL possesses a nuclear localization signal (NLS) and a nuclear export signal (NES) (Figure 2). The NLS and NES regulate DVL cellular localization by shuttling it in and out of the nucleus. The NLS (represented by consensus sequence IxLT; where x is any amino acid) is located between the PDZ and DEP domain, whereas, the NES (represented by consensus sequence M/LxxLxL; where x is any amino acid) is present between the DEP and C-terminus of DVL protein. Recent findings suggest that nuclear localization of DVL is important for its function in the canonical Wnt pathway [16, 18].

5. DVL-associated proteins

Looking at the central position of DVL proteins in the Wnt signaling pathway, it is no surprise that DVL associates with number of proteins to carry out its diverse cellular functions. Several of the DVL binding partners have been discovered over the last few decades of research (Table 1) (for review see Gao and Chen, 2010; Wallingford and Habas, 2005; Wharton 2003 and Wnt homepage) [3, 11, 12]. This leads us to an important question about how DVL generates specificity to so many proteins? The answer lies in DVL's structural domains. The three conserved domains (DIX, PDZ and DEP) mediate protein-protein interaction and help DVL proteins to channel signals into either canonical or non-canonical Wnt pathway.

For instance, proteins like Axin and Frodo interact with DVL proteins via DIX domain leading to stabilization of canonical and non-canonical Wnt pathway [38, 57]. The DIX domain of DVL also interacts with itself to mediate canonical signaling pathway [38]. The

central PDZ domain acts as a scaffold for many proteins to propagate signals to downstream effector molecules. It switches between the canonical and non-canonical pathway by interacting with different binding partners. For activation of canonical pathway, PDZ domain of DVL interacts with β-arrestin, Casein Kinase 1, Casein Kinase 2, Frizzled and Protein Phosphatase 2C [16, 43, 58–65]. On the other hand, proteins like IDAX, CXXC5, Notch, and Naked cuticle behave as antagonist and repress the Wnt pathway [36, 66–74] (see Table 1 and Figure 3). Similarly, the DEP domain associates with various activators (APC, diversion, protein kinase C) and antagonists (Gβγ Prickle) to regulate non-canonical pathway (see Table 1 and Figure 3). Numerous other proteins like c-Jun, CTNNB1, KLHL12/Cullin-3, Lgl, and TIAM1 interact with Dishevelled [16, 75–79]. In 2010, the SIRT1 lysine deacetylase which is known to regulate cellular responses resulting from very diverse physiological stress, was shown to serve as an important regulator of Wnt signalling [80]. SIRT1 loss of function was shown to decrease the levels of all three DVLs. Furthermore, it was demonstrated that SIRT1 and DVL proteins complex in vivo and inhibition of SIRT1 led to changes in gene expression of Wnt target genes and Wnt-stimulated cell migration. This finding was the first to link the sirtuins with DVL directly and helped to explain SIRT1-mediated regulation diverse physiological responses given its connection with a key molecular scaffold. In 2013, a subsequent report probed the SIRT1-DVL connection in greater depth and demonstrated that SIRT1 and SIRT2 positively regulate the levels of Rac1-GTP and its activator, TIAM1 [78]. This report demonstrated that SIRT1 activity was critical for the DVL-1 and TIAM1 interaction in cancer cells and positively modulates the DVL/TIAM1/Rac axis and promote sustained pathway activation. Prior to these reports, SIRT1 had only been shown to mediate the epigenetic silencing of Wnt antagonists. Collectively these reports demonstrated that SIRT1 is a novel regulator of transient and constitutive Wnt signaling. However, the specific domain(s) to which they bind is not clearly understood (see Table 1 and Figure 3).

6. DVL post-translational modifications

6.1. DVL Phosphorylation

DVL transmits numerous diverse signals that lead to mutually exclusive cellular processes, yet much remains unknown about the manner in which it coordinates complex signals. Some progress has been made and post-translational regulation appears to be critical for specifying how molecular signals are routed. The most well studied post-translational modification of DVL proteins is phosphorylation. Early reports first demonstrated phosphorylation of *Drosophila* Dsh proteins in response to Wg stimulation [108]. A couple of years later, more investigation led to the report of Casein kinase 2 (CK2) as the first Dsh kinase to be identified in *Drosophila* [64]. These initial discoveries were followed by a series of reports across diverse species that identified other DVL kinases including casein kinase 1 (CK1) isoforms [61, 62, 109, 110], PAR1 [111], RIPK4 [106], NEK2 [112] and other kinases [11]. Phosphorylation of DVL appears to be a dynamic process where site-specific phosphorylation elicits divergent biological responses. For example, DVL regulates both β-catenin and planar cell polarity signals and site specific phosphorylation appears to control which of the competing signals is transmitted and the strength with which they are transmitted. Par1 and CKIε-mediated phosphorylation appears to activate the arm of DVL

signaling that promotes β-catenin signaling while simultaneously inhibiting the arm of DVL signaling that promotes JNK/PCP signaling [87, 113]. These studies and others demonstrated the critical role of multiple kinases such as CK1, CK2 and PAR1 in the Wnt pathway that can activate or inactivate DVL in a temporally sequential fashion [111]. Bernatik et al [111] reported that CK2 acts as a constitutive kinase whose activity is required for the further action of CK1ε to induce phosphorylation and TCF/LEF-driven transcription. This study proposed a multistep and multi-kinase model for DVL activation in the Wnt/β-catenin pathway which subsequently induces a de-activation mechanism driven by CK1δ/ε-mediated phosphorylation of DVL. The c-terminus of DVL has been implicated in the negative regulation of its own activity and of the Wnt pathway. Hyperphosphorylated DVL is also known to interact with Ror2 receptor-tyrosine kinase via its C-terminal and inactivate the canonical Wnt pathway [114]. Thus the C-terminal of DVL has been shown to be necessary and sufficient for canonical (and non-canonical) Wnt pathway inactivation.

6.2. DVL Ubiquitination

DVL ubiquitination has been linked with its degradation and activation. DVL is known to interact with proteins such as KLHL12-cullin3 complex which ubiquitinates and targets DVL for degradation [76]. The E3 ubiquitin ligase complex can polyubiquitinate and target DVL for proteasomal degradation causing an inhibition of the canonical Wnt pathway. Treatment of cells with MG132 increased the co-immunoprecipitation of KLHL12 with DVL in a Wnt3a-dependent manner [76]. ITCH is another E3-ubiquitin ligase belonging to the HECT-type E3 subfamily known to regulate DVL levels in cells by ubiquitination. ITCH negatively regulates canonical Wnt signaling by specifically targeting phosphorylated DVL for degradation [115]. Wnt-5a activation of JNK phosphorylates NEDDL4 which in turn ubiquitinates DVL for degradation via polyubiquitination at K-6, K-27 and K-29 [116]. Thus, NEDDL4 can act as a feedback regulator of Wnt pathway activation. Gao et al. [11] showed that DVL-2 can be targeted for degradation upon starvation-induced metabolic stress by Von-Hippel-Lindau protein (pVHL), an E3 ubiquitin ligase that promotes DVL-2 ubiquitination.

On the other hand, CYLD is a de-ubiquitinase and has been shown to negatively regulate β-catenin signaling. Knockdown of CYLD has been reported to stabilize β-catenin and induce β-catenin-responsive target gene activation [117]. This hyperactive Wnt signaling due to CYLD mutations was linked with human skin appendage tumors. Part of the proposed mechanism for this tumor promotion was tied to N-terminal K63-linked polyubiquitination of DVL which were proposed to potentiate the inactivation of the destruction complex and lead to β-catenin stabilization and translocation to the nucleus.

6.3. DVL methylation

Utilizing tandem mass spectrometry, Wu et al. showed that DVL-3 can be mono- or dimethylated on arginines located in DIX domain and the linker regions between DIX-PDZ and PDZ-DEP domains [118]. The precise role of DVL-3 methylation is not known but dimethylation of R698 was enhanced with Wnt3a stimulation for 15 minutes and returned to basal levels at 30 minutes.

7. Cancer associations

Wnt signaling and its association with cancer has been quite extensive in the study of intestinal and colorectal cancer, so we point the reader to previous reviews discussing this aspect of the cancer association [119–122]. In this section, we will focus primarily on the connection between Wnt signaling and breast cancer and some of the latest findings with other cancers beyond the GI tract. Somatic mutations and altered expression of Wnt ligands, antagonists or receptors can support tumorigenesis by influencing many hallmarks of cancer. Starting in the extracellular compartment, there are 19 mammalian Wnt ligands, and the genes encoding them show temporally restricted, tightly regulated, and localized expression patterns [123]. However, during tumor progression, this balance is perturbed, and altered Wnt signaling can serve as a potent stimulus for tumorigenesis. In mammals, Wnt was first identified as an oncogene in mouse mammary tumorigenesis [124]. Moreover, MMTV-Wnt-1 mice have been shown to possess a markedly expanded population of premalignant mammary tissue which is thought to arise from a discrete population of mammary stem cells [125, 126]. Wnt-1 was the first Wnt ligand demonstrated to cause mammary tumors. Early on, Wnt-1 expression was shown to cause striking changes in morphological and growth properties in mammary epithelial cell lines [127]. Wnt-1 was then shown to induce numerous mammary tumor formation *in vivo* [128] and was shown to transform primary human mammary epithelial cells alone without a cooperating oncogene [129]. Further study revealed that the Wnt-1 transgene preferentially induced mammary cancers from progenitor cells [130] and Wnt signaling regulated the amplification of mammary progenitor cells [131]. These Wnt-1 induced tumors contained heterogeneous cell types, expressing keratin 6 and Sca-1, and showed signs of selective targeting of mammary stem and/or progenitor cells. Further work addressing how Wnt-1 contributes to breast tumor heterogeneity demonstrated that Wnt-1 inhibits mouse mammary cell differentiation and upregulates Twist [132], a transcription factor that induces EMT to facilitate tumor metastasis [133]. However, what lies between Wnt-1 activation and the changes in programs of gene expression required for tumor formation is not known.

Interestingly, even in mice lacking ERα, Wnt-1 was shown to induce mammary gland hyperplasia and tumorigenesis, suggesting that the potency of this pathway to contribute to breast cancer may be especially relevant for the basal-like breast cancers which tend to be negative for ER, PR and do not show HER2 amplification [134]. Other Wnts such as Wnt-2, 3, 4 and 7B have now been shown to be differentially expressed in human breast tumors relative to normal tissue [135], and Wnt5a loss even correlates with loss of ERα while restoration of its expression restores tamoxifen sensitivity in ERα negative breast cancer cells [136].

The Frizzled and LRPs transmit extracellular signals and like the Wnts, members of both families of receptors contribute to tumorigenesis. For example, Wnt signaling through LRP6 was shown to be required for tumor formation and metastasis and was necessary for cancer cell self-renewal using *in vivo* models [137]. Moreover, inhibition of Wnt signaling resulted in re-expression of breast epithelial differentiation markers and repression of genes associated with EMT. A separate study revealed that expression of LRP6 is up-regulated in a subpopulation of human breast cancers and LRP6 inhibition in breast cancer cells reduces

Wnt signaling, cell proliferation, and *in vivo* tumor growth. Additionally, *in vivo* administration of an LRP6 antagonist was shown to markedly suppress growth of Wnt1 tumors without causing appreciable side effects [138]. Aberrant splicing of the other family member, LRP5, was shown to be resistant to inhibition via the extracellular secreted antagonist, DKK1 [139]. This mutant was found to be frequently expressed in breast tumors of different cancer stage (58–100%), and an anti-LRP5 antibody was shown to inhibit cell growth, and induce apoptosis in breast cancer cells expressing the mutant suggesting its potential as a new therapeutic target. Finally, in an elegant study, expression of LRP5 in mouse mammary stem cells was shown to be required to maintain the basal lineage [140]. This is important because LRP5 may serve as a single biomarker that has been demonstrated to be functionally involved in stem cell maintenance.

Extracellular Wnt ligands can interact with several key antagonists that are also secreted. Two families of antagonists include the secreted Frizzled related proteins (SFRPs), the Dickkopf proteins (DKKs) and the Wnt inhibitor factors (WIFs) [141–143]. The final outcome of extracellular Wnt signaling depends on the relative stoichiometry of ligands:receptors:antagonists. If the local concentration of Wnts extends beyond the buffering capacity of their antagonists, Wnt ligands bind the Fzd/LRP receptors and may initiate a signaling cascade that ultimately leads to β-catenin stabilization [142]. Antagonists of Wnt signaling participate in several dimensions of tumor suppression and their deregulation has been linked with tumorigenesis. For example, in 79 of 130 (61%) primary breast tumors the SFRP1 promoter was methylated and Kaplan-Meier analyses showed SFRP1 gene hypermethylation was associated with shorter patient OS (overall survival) with invasive breast cancer [144]. Further, analysis of 168 primary breast carcinomas revealed that 73% had a methylated SFRP5 promoter and strikingly, SFRP5 methylation was associated with reduced OS and was an independent risk factor affecting OS in a multivariate Cox proportional hazard model. Thus, the SFRPs are targeted for epigenetic inactivation in human breast cancer. Based on other studies this same trend is consistent for SFRP1, 2, 5, DKK1, WIF1 [145–147] suggesting that these gene silencing events may not be strictly random and stochastic, but rather part of a coordinated program of gene expression. Epigenetic silencing of Wnt inhibitors is another mechanism employed in tumor progression [148]. Promoter hypermethylation or histone deacetylation of Wnt inhibitory factors like *WIF1, sFRP1-5, DKK1 and DKK3* have been observed in breast, lung and colon cancers among others [146, 149, 150].

Inactivating or loss-of-function mutations in *APC*, a Wnt signaling protein classically known to cause familial adenomatous polyposis (FAP), can lead to colorectal cancer upon concurrent KRAS and p53 activation [151, 152]. Hyperactivation of the Wnt pathway in non-FAP colorectal cancer patients has also been reported due to *APC* and *β-catenin* mutations. Likewise, missense or other mutations of *β-catenin*, deletions and truncations of *Axin1* and mutations in *TCF4* are also seen in multiple cancer types including hepatocellular, medulloblastoma, colorectal, gastric, ovarian, pancreatic etc. [153].

Dishevelled alterations have now been reported for diverse cancer types. One report examined the protein levels in 67 human glioma and 3 normal brain specimens by Western blotting and immunohistochemistry. The DVL immunoreactivity score (IRS) was assessed to

investigate a possible association of DVL with the malignant phenotype in glioma. The DVL IRS increased significantly with the pathologic grade of glioma and the proliferation index and tumor invasion index were significantly higher for the DVL-positive group than the DVL-negative group. This study concluded that DVL overexpression may contribute to the malignant proliferation and invasion of human glioma [154].

The Wnt signaling pathway plays a critical role in normal cell development as well as in tumorigenesis [155]. Dishevelled proteins transduce the upstream signals from Frizzled receptors via PDZ domain to downstream components. Thus, the critical role of dishevelled PDZ domain makes it an ideal pharmaceutical target for treatment of various diseases. Since fibrotic lung exhibits aberrant activation of Wnt signaling pathway, a study showed that inhibiting the pathway at DVL level could be an effective approach for the treatment of fibrotic lung cancer. Their data demonstrated that a competitive inhibitor of DVL PDZ domain, called NSC668036, suppressed β-catenin driven gene transcription in fibroblasts. Furthermore, NSC668036 abolished TGF-β1 induced migration, proliferation, and expression of collagen I and α-smooth muscle actin (α-SMA) in pulmonary fibroblasts. In vivo studies concluded that NSC668036 significantly reduced collagen I, α-SMA, and TGF-β1 levels but increased expression of epithelial markers such as E-cadherin, CK19 and occludin that could inhibit pulmonary fibrogenesis [156]. Moreover, another study reported a novel DVL PDZ domain binding peptide ligand, known as pen-N3, which inhibits the Wnt/β-catenin pathway. This suggests that interference with DVL PDZ domains may be a suitable therapeutic strategy for inhibiting Wnt signaling in diseases that are dependent on DVL function [49]. On a similar note, a recent study reported that miR-103, a short non-coding RNA, down regulates DVL-1 by binding with its 3’ UTR region which results in β-catenin degradation and transcription inhibition of c-Myc. The study further demonstrated DVL-mediated mechanism of making tumor cells more sensitive for glucocorticoid-induced apoptosis in hematopoietic malignancies [157].

The nuclear localization of DVL proteins can play a critical role in tumorigenesis. A study reported that co-expression of IQGAP1, a key regulator of cell adhesion and migration, and DVL correlated with the lymph nodal metastasis and poor prognosis of NSCLC. Interestingly, coexpression of IQGAP1 and DVL in the cytoplasm and nucleus was reported to be significantly higher in lymph nodal metastases than in primary tumors, correlating with poor prognosis. Moreover, co-localization in the nucleus was proposed to play a critical role in the activation of canonical Wnt pathway [158]. A recent study demonstrated that Wnt5A represses ribosomal RNA (rRNA) synthesis in breast cancer cells by promoting nucleolar accumulation of DVL-1. The nucleolar DVL-1 proteins suppress tumor growth by negatively regulating rRNA synthesis through loss of SIRT-7 from chromatin regions containing rDNA [159]. Yet another study reported nuclear localization of DVL protein and demonstrated a protective role of DVL-2 in rheumatoid arthritis patients. This study explored the impact of DVL-2 on proliferation and inflammatory cytokine secretion in rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS). The authors demonstrated that over-expression of DVL-2 increased apoptosis and inhibited inflammatory cytokine secretion by RA-FLS, both in vivo and in vitro, possibly by downregulating NFκB pathway [160]. On other hand, a group proposed that loss of histone methyltransferase, SETD2, leads to upregulation of DVL-2 expression, thereby augmenting Wnt signaling to facilitate tumor malignancies.

Their data demonstrated that SETD2 depletion enhanced mRNA expression and nuclear accumulation of DVL-2 which leads to hyper activation of Wnt signaling pathway resulting in colorectal cancer [161]. Therefore, the critical role of DVL in different cancer types makes it a suitable target for cancer therapy. Additional investigation of DVL expression in NSCLC revealed expression of all DVLs in primary tumors was 36.3% (41/113) for DVL-1, 36.3% (41/113) for DVL-2 and 41.6% (47/113) for DVL-3, while normal adult bronchial and alveolar epithelia showed negative expression of all these proteins. Moreover, the expression levels of all three DVL was significantly higher in adenocarcinomas than in squamous carcinomas, and were associated with poor tumor differentiation, and DVL-1 & DVL-3 were significantly higher in nodal metastases than in primary growths, with the DVL-1 expression correlating to β-catenin expression in the metastases [162]. Additionally, in a study of brain metastases that originated from primary lung carcinomas, the expression of DVL-1 and DVL-3 were analyzed by IHC. DVL-1 and DVL-3 showed over expression in brain metastasis in 87.1% and 90.3% of samples respectively. Nuclear staining was observed in 54.8% of cases for DVL-1 and 53.3% for DVL-3, and when DVL-1 and DVL-3 were up-regulated there was a significant increase in the number of cases with nuclear beta-catenin [163].

Yet another tumor type where DVL levels are altered is chronic lymphocytic leukemia (CLL). Khan et al reported that DVL-1, −2 & −3 were exclusively expressed in CLL cells as compared to normal peripheral blood mononuclear cells (PBMCs) [164]. The expression of DVL-1 and DVL-3 proteins was significantly more pronounced in progressive than in non-progressive disease ($p < 0.01$), whereas the level of DVL-2 was significantly higher in non-progressive as compared to progressive disease ($p < 0.001$). This alteration in DVL expression was also extended to breast cancers. Nagahata et al demonstrated amplification of DVL-1 in 13 of 24 primary breast cancers examined, and increased expression of this gene in 11 of those tumors in comparison to corresponding non-cancerous breast tissues. These data suggest that amplification and increased expression of the DVL-1 gene may play some role in human breast carcinogenesis through derangement of the Wnt signaling pathway [165]. A few years later in 2007, another report demonstrated an association between nuclear localization of DVL and β-catenin. Their analysis revealed that of the 98 IDCs analyzed, 30% of tumors displayed both nuclear and cytoplasmic staining of DVL, while 52% showed nuclear localization and demonstrated a significant association between nuclear localization of DVL and β-catenin [166]. Finally, in a study involving hepatocellular carcinoma (HCC), Western blotting and immunohistochemistry were used to measure DVL-2 protein expression in HCC and adjacent normal tissues of 101 patients. In this study, DVL-2 expression was found upregulated in HCC tissues compared to the adjacent normal tissues, and its expression level was significantly correlated with histological grade, metastasis, and vein invasion ($P = 0.009$) [167].

Interestingly, we performed a TCGA analysis of DVL-1, DVL-2 and DVL-3 expression across of 4 different types of cancer (Glioblastoma or GBM, Lung, Breast or BRCA and Liver or LIHC) that shows no dysregulation of DVL RNA expression in majority of those cancers compared to adjacent normal tissues except DVL-1 that appears to be downregulated in GBM and DVL-3 upregulated in lung cancer (Figure 4). Even though this data appears to be contradictory to the previous reports where DVL proteins are upregulated [154, 162, 165,

168], this suggests the important role of the post-transcriptional regulation of DVL proteins. For instance, few mechanisms like RNA transport and storage, RNA degradation and stability, or translational and protein stability may be altered in the tumor cells.

After post-transcriptional processing, the mature mRNA must be transported from the nucleus to the cytosol so that it can be translated into a protein, this step is a key point for regulation of gene expression. The different RNA species that are produced in the nucleus are exported through the nuclear pore complexes (NPCs) by nuclear transport proteins known as importins and exportins, which belong to the karyopherin-beta family proteins. The expression of karyopherin-beta proteins are dysregulated in multiple tumors such as in melanoma, pancreatic, breast, colon, gastric, prostate, esophageal, lymphoma and lung cancer which may have consequences in the differential expression in the tumor tissues with respect to the normal tissue [169]. On the other hand, RNA stability determines its half-life and therefore the time that would be available for translation. In cancer, among other pathological conditions, the dysregulation of RNA stability has been already reported to affect genes like growth factors, oncogenes, cell cycle regulators and inflammatory cytokines that can contribute to cancer development and/or progression [170, 171].

Post-translational modifications not only play a role in regulating the folding of proteins, their transport or function but also the stability of the protein. In this review, we show that DVL proteins can be phosphorylated, ubiquitinated, or methylated. Of these post-translational modifications, ubiquitination has a key role modulating DVL protein degradation [11, 76, 115]. The KLHL12-Cullin-3 ubiquitin ligase complex negatively regulates Dishevelled [76]. Interestingly, Cullin-3 act as tumor suppressor and is downregulated in lung, liver, and breast cancer [172–175] which may correlate with the elevated levels of DVL proteins in those cancers.

8. DVL and other human diseases

Since DVL is the central mediator of the Wnt signaling pathway that coordinate cell development processes and adult tissue homeostasis, it is certain that its deregulation can be linked with development disorders and syndromes. DVL was originally identified based on the phenotype of disorientation in wing hair of Drosophila. Later it was discovered that mutation in DVL signaling could perturb the segment polarity in Xenopus embryo [3]. All three DVL genes are broadly expressed in various tissues of the body. It is suggested that DVL genes work in network and there may be redundancy to some extent [176]. Several knockdown studies have been employed to elucidate the specific role of each DVL.

As a result of high similarity, DVL (DVL-1, −2 and −3) in mice and human have been proposed to have functional redundancy. Several mice models have been extensively used to understand the phenotype of DVL knockout mice. DVL-1 KO mice display normal skeletal phenotype but exhibit abnormal social interaction in nest building, and home cage huddling [177]. Additionally, lack of DVL-1 genes can induce myocardial infarction in mice [178]. Furthermore, recent studies consider DVL-1 as a candidate gene for cardiovascular malformations associated with 1p36 deletions [179]. While DVL-1 null mice showed unique feature in social interaction abnormalities, DVL-2 null mice display defects in cardiac

outflow tract formation. Almost half of the DVL-2 null die in perinatal period due to cardiac anomalies. In addition, DVL-2 null mice display defects in somite segmentation and neural tube closure [180].

DVL-3 null mice do not display any skeletal defects, however these mice die perinatally likely due to cardiac tract abnormalities. Knockdown studies of DVL-3 suggest that this gene is essential for cochlea and neural tube development [181]. To elucidate the specific roles of DVL genes, rescue studies were conducted. These studies indicate the double knockout mice have severe phenotype. For instance, double knockout of either DVL-1, DVL-2, DVL-3 lead to defect in cardiovascular outflow tract, neural crest development, cochlear defect and skeletal defects suggesting redundant roles between the DVL homologs. (Refer Gao et al., 2010 for review) [11, 181]. Interestingly, double knockout of DVL-1 and DVL-3 does not display neural tube defects which indicates that each DVL has a unique role to play. Aberrant expression of DVL genes have been linked to human disorders. In human development disorders, DVL-1 has been reported to be a candidate gene in Schwartz-Jampel syndrome, Charcot-Marie-Tooth disease type 2A and DiGeorge Syndrome [6, 182]. Additionally, over-expression of DVL-1 and DVL-3 have been linked to Hirschsprung's disease, a congenital disorder characterized by absence of ganglion cells in terminal regions of the gut during development [183].

Several studies have helped establish the fact that mutation in DVL genes can cause Robinow syndrome. Robinow Syndrome is a genetic disease which is characterized by skeletal abnormalities which can be caused by mutation in genes encoding components of Wnt signaling pathway [184]. White et al. uncovered that frameshift mutation in penultimate and final exons of DVL-1 and DVL-3 can be a common cause of autosomal-dominant Robinow syndrome [185, 186]. The data suggests that there are six frameshift mutations, out of which five are de-novo, leading to truncation of the C-terminal domain of DVL-1 disrupting the downstream canonical pathway [185]. Another study indicates that frameshift mutation on exon 15 replaces the C-terminal tail of DVL-1 with 142 highly basic amino acid. And these de-novo mutations on DVL-1 result in osteosclerotic form of Robinow syndrome [187]. To summarize, DVL plays an important role in development processes and mutations in DVL gene can lead to severe phenotypic defects.

9. Concluding remarks

Significant advances have been made regarding domain specific functions of DVL, the binding partners involved in molecular interactions, and the role it plays during development of diverse organisms. However, many significant gaps in knowledge remain regarding the mechanism by which Dishevelled relays information to different intracellular compartments, the role of post-translational regulation beyond phosphorylation and the functional significance of DVL nuclear localization. Given the central importance of this family of proteins to normal physiology and pathophysiology, many of these critical unknowns will likely be addressed in the years to come.

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Highlights

- The Dishevelled gene was first identified in Drosophila mutants with disoriented hair and bristle polarity and its study gained popularity when it was discovered to play a key role in segment polarity during early embryonic development. Further research revealed that Dishevelled (DVL) proteins function as principal components of Wnt signaling pathway in many organisms and govern several cellular processes including proliferation, survival, migration, differentiation and stem cell renewal. It is fascinating to consider how the identity of DVL is largely linked with its ability to integrate and relay complex Wnt signals in tissues and cells yet how it conducts this symphony of activity still remains poorly understood. Additionally, the concept of the mystery that still surrounds DVL and what it means for it to be “activated” after more than two decades investigation is addressed. This review discusses the function of DVL in the Wnt signaling pathway in normal and aberrant cellular contexts. It also highlights novel roles within the nucleus and discusses new binding partners that have been discovered and novel mechanisms of post-translational regulation.

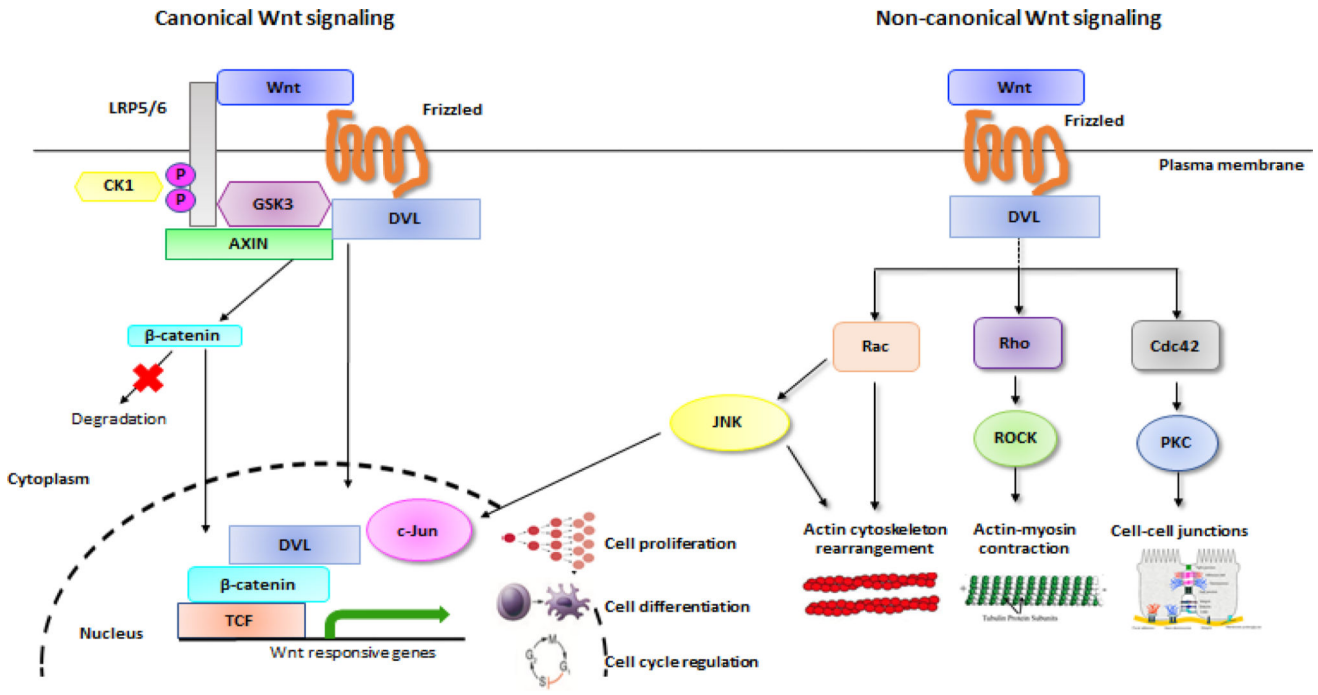


Figure 1. The role of DVL in canonical and non-canonical Wnt signaling pathway

In canonical Wnt pathway, DVL promotes clustering of Wnt-LRP5/6-Frizzled to form signalosomes, which results in phosphorylation of LRP5/6 and recruitment of Axin to the plasma membrane, further stabilizing the β–catenin levels in the cytoplasm. DVL has also been found to shuttle between the cytoplasm and the nucleus, acting as a transcriptional activator of Wnt target genes. In non-canonical pathway, Wnt-Frizzled complex interacts with DVL which relays signal to downstream effectors. Multiple pathways downstream of DVL regulate gene transcription, polarity and actin cytoskeleton remodeling of a cell.

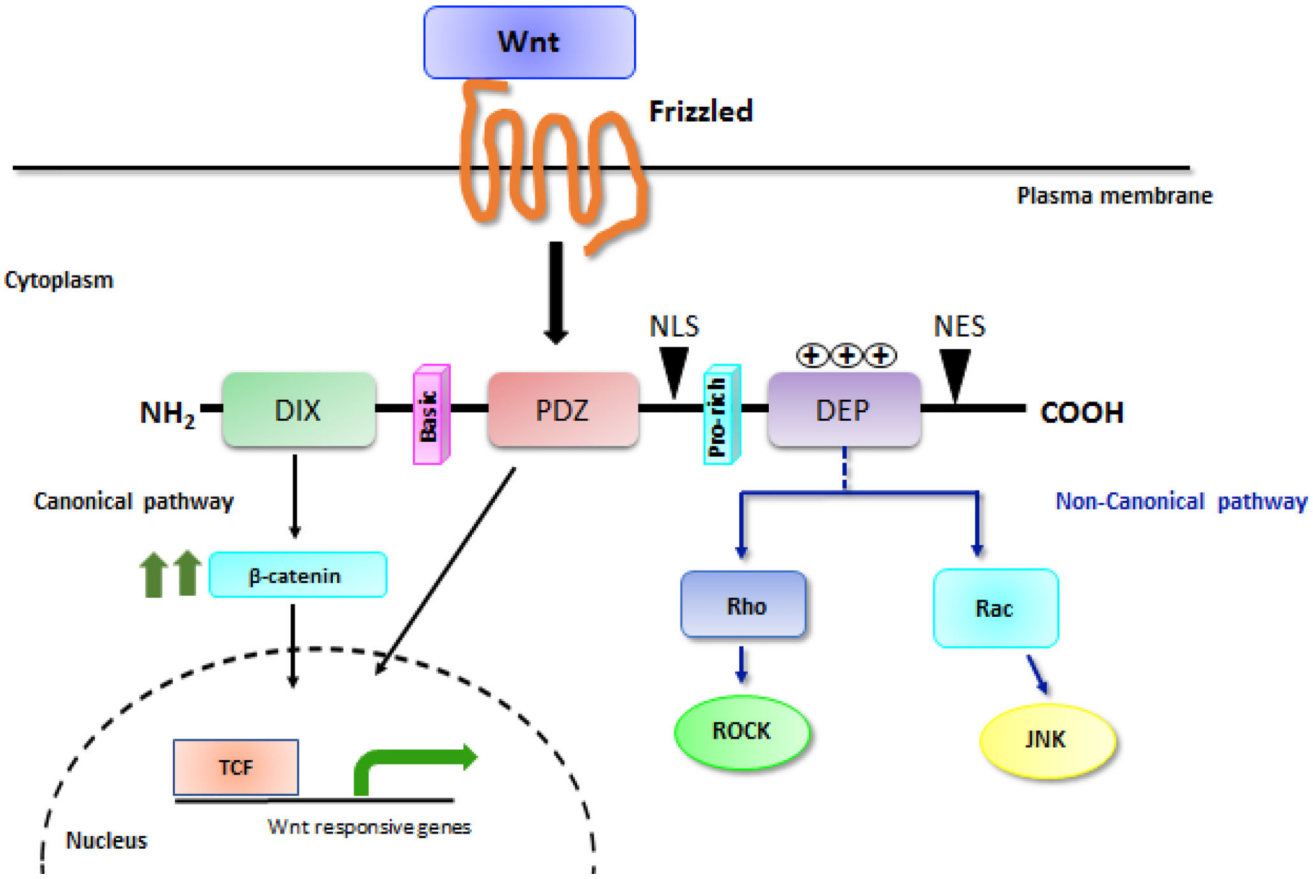


Figure 2. The structure of DVL proteins

DVL is made up of three conserved motifs namely an amino-terminal DIX domain, a central PDZ, and a carboxyl-terminal DEP domain. In addition to these three domains, DVL harbors two regions with positively charged amino acid residues (basic and proline-rich domain) plus a nuclear import (NLS) and a nuclear export signal (NES). The DIX and PDZ domain relay signal to canonical pathway (marked in black arrows), whereas DEP domain mainly regulates membrane localization of DVL and propagates non-canonical pathway (marked in blue arrows).

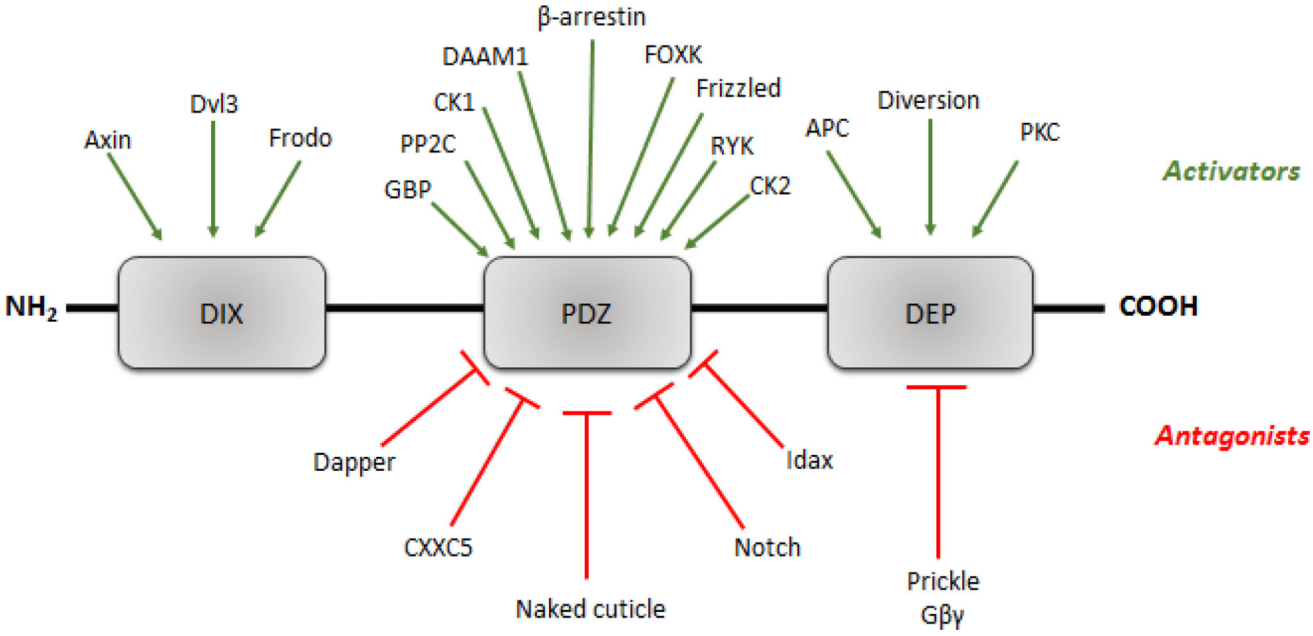
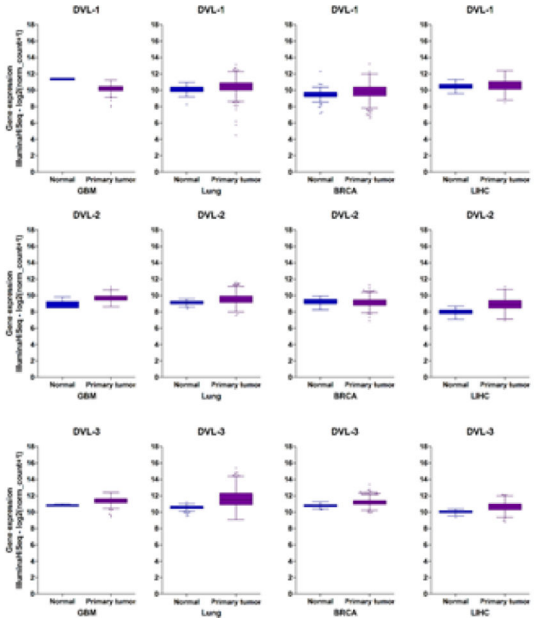


Figure 3. DVL binding partners

The agonists (marked in green arrows) and the antagonist (marked in red arrows) bind to specific domains of DVL to regulate Wnt pathway.



			n	Mean ± SEM	Difference between means	F test to compare variances: P value		Unpaired t test	t	P value		Fold change(log2FC)	
GBM	DVL-1	Normal	5	11.364 ± 0.054	1.185 ± 0.066	0.0141	*	Welch-corrected t	17.93111	P<0.0001	***	1.185	downregulated
		Primary tumor	167	10.179 ± 0.037									
	DVL-2	Normal	5	8.809 ± 0.261	-0.876 ± 0.188	0.1811	ns	Unpaired t test	4.656517	P<0.0001	***	-0.876	
		Primary tumor	167	9.685 ± 0.031									
	DVL-3	Normal	5	10.823 ± 0.049	-0.548 ± 0.061	0.0119	*	Welch-corrected t	8.921578	P<0.0001	***	-0.548	
		Primary tumor	167	11.371 ± 0.036									
Lung	DVL-1	Normal	110	10.093 ± 0.039	-0.349 ± 0.046	P<0.0001	***	Welch-corrected t	7.543055	P<0.0001	***	-0.350	
		Primary tumor	1017	10.443 ± 0.024									
	DVL-2	Normal	110	9.142 ± 0.022	-0.427 ± 0.029	P<0.0001	***	Welch-corrected t	14.59219	P<0.0001	***	-0.428	
		Primary tumor	1017	9.569 ± 0.019									
	DVL-3	Normal	110	10.555 ± 0.027	-1.086 ± 0.040	P<0.0001	***	Welch-corrected t	26.70771	P<0.0001	***	-1.087	upregulated
		Primary tumor	1017	11.642 ± 0.030									
BRCA	DVL-1	Normal	114	9.446 ± 0.060	-0.404 ± 0.065	0.0022	**	Welch-corrected t	6.150027	P<0.0001	***	-0.405	
		Primary tumor	1097	9.851 ± 0.024									
	DVL-2	Normal	114	9.266 ± 0.033	0.130 ± 0.037	P<0.0001	***	Welch-corrected t	3.519618	0.0006	***	0.131	
		Primary tumor	1097	9.135 ± 0.015									
	DVL-3	Normal	114	10.801 ± 0.017	-0.409 ± 0.021	P<0.0001	***	Welch-corrected t	19.2067	P<0.0001	***	-0.409	
		Primary tumor	1097	11.210 ± 0.012									
LIHC	DVL-1	Normal	50	10.467 ± 0.055	-0.130 ± 0.065	P<0.0001	***	Welch-corrected t	1.98518	0.05	*	-0.130	
		Primary tumor	371	10.597 ± 0.035									
	DVL-2	Normal	50	7.964 ± 0.053	-0.960 ± 0.064	P<0.0001	***	Welch-corrected t	14.90356	P<0.0001	***	-0.960	
		Primary tumor	371	8.924 ± 0.035									
	DVL-3	Normal	50	10.035 ± 0.027	-0.638 ± 0.039	P<0.0001	***	Welch-corrected t	16.0836	P<0.0001	***	-0.638	
		Primary tumor	371	10.673 ± 0.028									

Figure 4. DVL mRNA expression in GBM, Lung, BRCA and LIHC

DVL-1, DVL-2 and DVL-3 RNA-seq data were analyzed using TCGA downloaded from Xena tool of UCSC Cancer Genomics Browser (http://xena.ucsc.edu/). Normalized RNA expression is plotted as log2 (norm_count+1). Dysregulated DVL expression between tumor and normal tissue were identified using t-test (p value < 0.001, log2FC > 1 or < −1).

Table 1

DVL-protein binding partners

Binding partner	Pathway	Regulation	Function	References
DIX-domain binding proteins				
Axin	Canonical	Positive	β-catenin stability	[38]
Dishevelled	Canonical, non-canonical (PCP/Ca^{2+})	Positive	Enhances the ability of DVL activate Wnt pathway	[38]
Frodo	Canonical, Non-canonical	Positive	Secondary axis formation in Xenopus embryo	[57]
PDZ-domain binding proteins				
β-arrestin	Non-canonical (PCP)	Positive	Endocytosis of Frizzled receptor, β-catenin stability and activation of LEF transcription factor	[58–60]
Casein Kinase 1	Canonical	Positive	Stimulate canonical pathway by phosphorylating DVL proteins	[61–63]
Casein Kinase 2	Canonical	Positive	Stimulate canonical pathway by phosphorylating DVL proteins	[64]
CFTR	Canonical	Negative	Interacts with DVL-2, negatively regulates Wnt pathway	[81]
CXXC5	Canonical	Negative	BMP4-induced inhibitor of Wnt Signaling in neural stem cell. Also plays a significant role in osteoblast differentiation and wound healing.	[36, 66–68]
DAAM1	Non-canonical (PCP)	Positive	Rho A activation (Binds to both PDZ and DEP domain)	[26]
Dapper	Canonical, non-canonical (PCP)	Negative	Induces DVL degradation (Binds to both PDZ and DEP domain)	[82, 83]
Diego	Non-canonical (PCP)	Positive	Affects orientation of Drosophila wing hairs	[84]
FOXK1, FOXK2 (Forkhead box)	Canonical	Positive	Translocates DVL-2 to nucleus	[22]
Frizzled	Canonical, Non-canonical	Positive	Transduction of Wnt signal from Fz to downstream components, membrane targeting of Dishevelled	[43]
GSK3β-binding protein/Frat	Canonical, Non-canonical	Positive	Dissociation of Axin-GSK3β complex, activation of JNK	[85, 86]
IDAX/CXXC4	Canonical	Negative	Regulate embryonic axis formation in Xenopus	[69]
Naked Cuticle	Non-canonical (PCP)	Negative	Repress Wnt pathway	[70, 71]
Notch	Non-canonical (PCP)	Negative	Regulate cell development in Drosophila eye, crosstalk between PCP and Notch pathway	[72–74]
PAR1	Canonical, Non-canonical (PCP)	Positive / Negative	Phosphorylation of Dishevelled	[87–89]

Binding partner	Pathway	Regulation	Function	References
Protein Phosphatase 2C	Canonical	Positive	Positively regulates Wnt signals by dephosphorylating Axin	[65]
RYK	Canonical	Positive	Essential for neurite outgrowth, activates T cell factor induced by Wnt ligands	[33]
Strabismus	Canonical, Non-canonical	Negative / Positive	Regulates planar cell polarity, morphogenetic movement and neural gene expression during gastrulation	[90, 91]
TMEM88	Canonical	Negative	Disrupts canonical Wnt signaling	[92]
DEP-domain binding proteins				
APC	Non-canonical	Positive	Stabilization of microtubule, enhance cell migration	[93]
Diversion	Non-canonical	Positive	Regulates heart formation and gastrulation movements in zebrafish embryogenesis	[94]
Ephrin B1	Non-canonical (PCP)	Positive	Regulates PCP pathway for cell movement and cell repulsion	[95–97]
Gpy	Canonical	Positive / Negative	Membrane localization of Dishevelled, and lysosomal degradation	[98, 99]
Prickle	Canonical, Non-canonical (PCP)	Negative	Degradation of DVL-3, regulate planar cell polarity	[84, 100, 101]
Protein Kinase C	Canonical/Non-canonical	Positive	Regulate convergent extension movements, phosphorylation and stabilization of DVL proteins	[102, 103]
Other associated proteins				
c-Jun	Canonical	Positive	Activates β-catenin/TCF mediated transcription of Wnt target genes in the nucleus	[16]
CTNNB1	Canonical	Positive	Activate transcription of Wnt target genes	[16, 75]
KLHL12/Cullin-3	Canonical	Negative	Degradation of Dishevelled 3	[76]
IQGAP1	Canonical	Positive	Promotes nuclear localization of Dishevelled which sequentially activates Wnt target genes	[104]
Lgl	Non-canonical	N/A	Regulate apical basal polarity	[77]
NFκB	NFκB signaling	Negative	DVL-1 (C-terminus) binds to p65 in nucleus and inhibits NFκB activation	[105]
RIPK4	Canonical	Positive	Stimulates Wnt pathway by phosphorylating DVL proteins	[106]
RNF185	Canonical	Negative	Negatively modulates osteoblast differentiation through ubiquitination and degradation of DVL-2	[107]
SIRT1	Canonical/Non-canonical	Positive	Positively regulates Wnt signaling via DVL proteins	[80]

Binding partner	Pathway	Regulation	Function	References
TIAM1 (T-cell lymphoma invasion and metastasis 1)	Non-canonical	Positive	Mediates cell migration via Rac activation, required for neuron differentiation	[78, 79]

*

Note: The table summarizes the list of proteins which bind to Dishevelled, categorized by the region of interaction with Dishevelled. The table further describes the pathway affected and the functional significance of the interaction between DVL and its associated proteins.