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# The Wnt signaling pathways and cell adhesion

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## 1. ABSTRACT

In multicellular organisms, the processes of tissue and organ formation are governed by morphogenetic signaling pathways. The Wnt pathways regulate morphogenesis by controlling cell adhesion and migration; processes that when corrupted, lead to tumorgenesis. It is well known that the Wnt signaling pathways affect adhesion and migration via downstream effectors. Canonical Wnt signaling regulates cell adhesion by regulating the stability of beta-Catenin, a component of the adherens junction. Whereas, non-canonical signaling modulates cytoskeletal dynamics by regulating the activity of downstream effectors that function to organize the cytoskeleton. Recent studies have uncovered a multitude of points of crosstalk between the Wnt pathways and the mechanisms that control cellular architecture, from the level of receptors to the level of transcription. At the same time, cellular mechanisms that are responsible for the regulation of adhesion and migration also function to modulate the activity of several Wnt pathway components. Uncovering these points of crosstalk may lead to better understanding and treatment of the processes that can lead to tumorgenesis.

## 2. INTRODUCTION

The proper development and formation of organs in multicellular organisms depends on the formation of precise signaling gradients and well defined cell and tissue polarity. Pathways that are responsible for the development and maintenance of complex organisms include Wnt, TGF-beta, Hedgehog, Hippo and Notch; which both regulate and are regulated by signaling gradients. During the development of an embryo, signaling molecules (or morphogens) are localized to or secreted from specific cells. This leads to a gradient where the levels of morphogen are high at the source, and lower the further away from the source. This morphogen gradient leads to differential signaling to downstream targets, enabling the precise co-ordination of tissue and organ formation (morphogenesis). Morphogens are usually received by receptors that function to transduce the signal to a multitude of effector molecules, resulting in the regulation of transcription factors or molecules that control cell adhesion.

Until recently, it was thought that signal transduction throughout these developmental pathways

acted in a linear manner, with minimal crosstalk. However, increasing evidence is uncovering complex levels of interactions (1-5).

Pathways controlling development are precisely modulated by a multitude of inputs, and corruption of this process often leads to tumorigenesis. Indeed, genes that are found mutated in cancers are often found to be key regulators of development (6-8). Understanding interactions and cross-talk between pathways that determine the complex physiology of multicellular organisms, will allow new avenues for the therapeutic manipulation of diseases such as cancer.

## 3. CELL-CELL ADHESION

Epithelia accomplish highly specialized functions that require cellular polarization on both a planar and apical-basal axis. Planar polarity is the polarization of cells within the plane of the epithelium (Section 4.2). While apical-basal polarity is manifested as a precise localization of molecules throughout the plasma membrane and specialized structures within the cell. The plasma membrane is polarized into apical, lateral and basolateral domains, each containing conserved and highly specialized complexes that mediate cell-cell adhesion and communication. The apical membrane is established by the Par (Par3/Par6/aPKC) and Crumbs (Crumbs1/PATJ/PALS) complexes, and basolateral domain is established by the Scribble (Scribble, Discs large (Dlg) and Lethal giant larvae (Lgl)) complex. Par1 regulates microtubule (MT) arrangement and Par4 (LKB1) controls the polarity of the cytoskeleton (9, 10). Epithelial cells adhere tightly to each other to form sheets and are connected to each other via a series of intercellular junctions, termed tight junctions (TJs), adherens junctions (AJs), desmosomes and gap junctions. TJs are usually located towards the apical end of the cells, whereas the AJs, desmosomes and gap junctions are located within the basolateral domain. Polarized epithelial cells are responsible for maintaining the structural integrity of tissues, the ability of cells to organize themselves into specialized tissues and organs, and for regulating the communication between cells via the movement of ions, water and macromolecules (reviewed in 11, 12, 13) (Figure 1A).

### 3.1. Tight junctions

Structurally, TJs function as a barrier to paracellular diffusion between apical and basolateral surfaces of epithelial sheets. TJs also coordinately receive and transmit information back to the cell interior to regulate cellular assembly and function or to regulate gene expression. The Par6-Par3-atypical Protein Kinase C (aPKC or PKCzeta) complex regulates the formation of the TJs junctional structures (14). TJs are composed of a range of transmembrane proteins, including JAMs (junction adhesion molecules), Claudins (24 family members), Occludin and Tricellulin. Many of these transmembrane proteins interact with proteins in the cytoplasm via PDZ (PSD/DlgA/ZO-1)-binding domains present in their cytosolic domains and PDZ domains of intracellular cell polarity proteins such as ZO-1, ZO-2, ZO-3, PAR-3, PAR-6, Pals1 and PATJ (Figure 1B). TJs also associate with the Actin cytoskeleton and a range of signaling molecules such as Rho GTPases (e.g. Rac1 and Cell division cycle 42 (Cdc42)) and PKC isoforms. Such interactions are instrumental for TJ formation and processes requiring junctional reorganization, such as those that occur during morphogenesis and cell movement (reviewed in 11, 15).

### 3.2. Adherens junctions

AJs are dedicated sites of cell contact that function to link the Actin cytoskeleton, and the microtubule network with specialized membrane sites of vesicle transport (exocyst) and intercellular communication. The AJ is a dynamic structure composed of a family of transmembrane Cadherin (Calcium-dependent adhesion) proteins (epithelial (E), neuronal (N), placental (P), vascular endothelial (VE), etc.) that dimerize in a calcium ($Ca^{2+}$) dependent manner. Cadherins at the plasma membrane interact with beta-Catenin, and alpha-Catenin physically links the complex to microtubules and the Actin cytoskeleton (16, 17). The small GTPase family are key regulators of Cadherin based adhesion; signaling leads to the clustering of these Cadherin–Catenin complexes and thereby leading to Actin remodeling (reviewed in 18) (Figure 1C). Another major component of the AJ is the Nectin-Afadin complex that also links to Actin and has similar activities as the Cadherin-Catenin complexes. Nectins in concert with Integrin alpha(v)beta(3) at the AJ regulate activation of PKC, Focal Adhesion Kinase (FAK), Src, members of the Rho family of small GTPases (Rap1, Cdc42, and Rac) and thereby Actin reorganization and the formation of the cell-cell junctions (19, 20).

Merlin is a FERM (4.1, Ezrin, Radixin, Moesin) domain-containing protein and is also responsible for the establishment of the AJ. It associates directly with alpha-Catenin and links it to Par3 thereby linking the AJ to the Par3/Par6/aPKC complex (21). Merlin is also required for contact inhibition of proliferation (22, 23).

### 3.3. Desmosomes and gap junctions

Desmosomes are a specialized adhesive junction that interacts with the cytoskeleton and are found expressed in tissues that are exposed to mechanical stress. Transmembrane Cadherins, Desmoglein and Desmocollin are present in Desmosomes and physically interact with the Armadillo (Catenin) family proteins Plakoglobin (PG) and Plakophilins (PKPs). PG and PKPs interact with the cytoplasmic tail of Desmosomal Cadherins, which in turn anchor Plakin proteins. These protein interactions between complexes in the Desmosome function to mediate the anchorage of intermediate filaments to cell–cell and cell–matrix junctions and intracellular organelles (24, 25). PG also functions to regulate Src and Rho GTPase activity (26).

Gap junctions are present in many animal cell types and are located on the baso-lateral membrane basal to the TJs and AJs. In vertebrates, Gap junction channels are formed from a multigene family of proteins called Connexins. Their main role is to provide an intracellular connection between cells and a conduit for the transmission

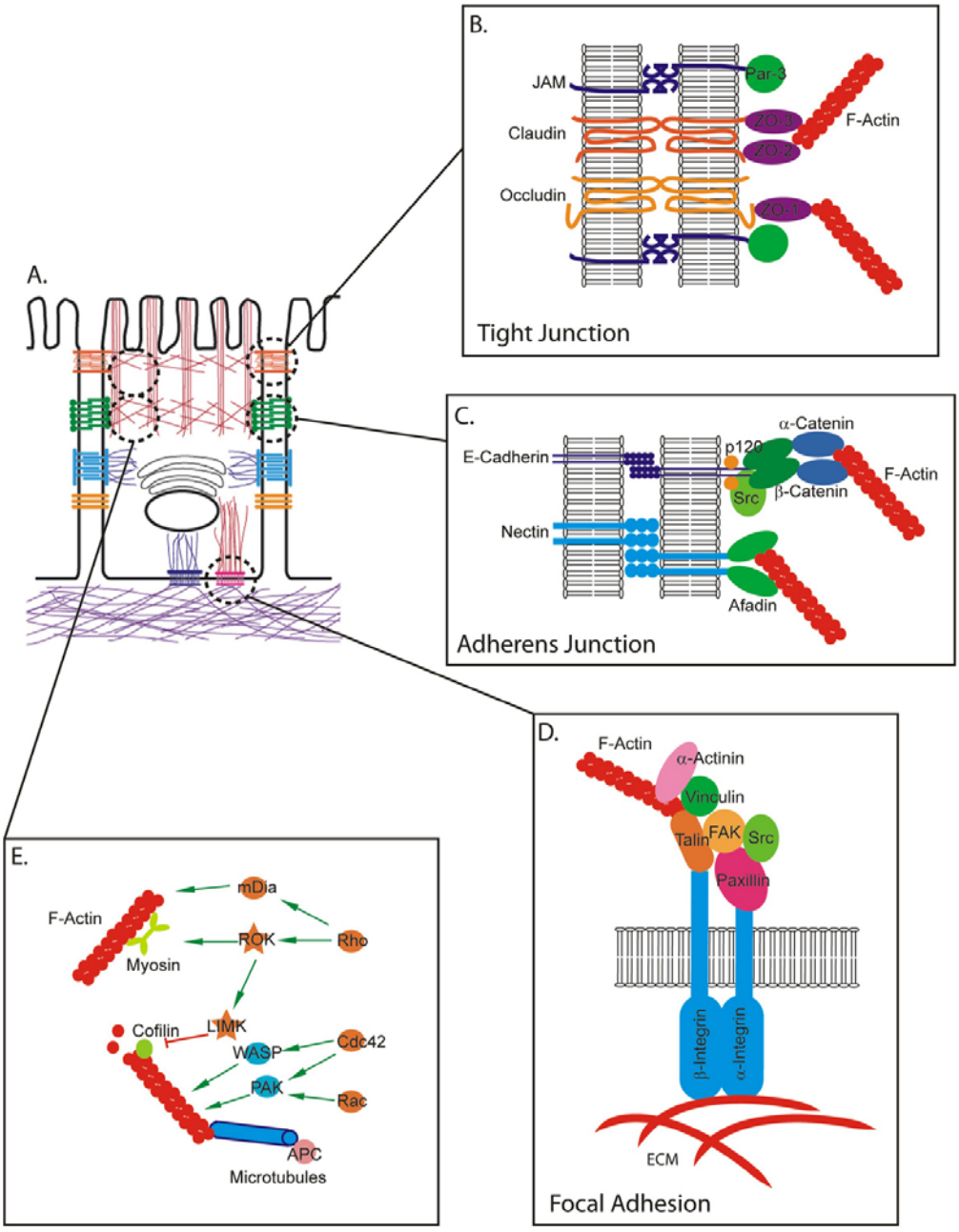


**Figure 1.** Epithelial polarity. (A) Epithelial cells are polarized along an apical-basal axis, with junctional complexes that bridge neighboring cells. Tight junctions (TJs) are localized to the most apical of the cell (orange), followed by the Adherens junction (AJ) (green). TJs and AJs are composed of transmembrane proteins which interact with intracellular proteins that link to the Actin/Microtubule Cytoskeleton (red). Basal to the AJ are desmosomes (cyan), which link to intermediate filaments (blue) and are followed by gap junctions (yellow). At the basal membrane are hemidesmosomes (dark blue), which link to intermediate filaments (blue) and Focal Adhesions (pink) that link to the Actin/Microtubule Cytoskeleton (red) and interact with the Extracellular Matrix (ECM) (purple). (B) TJs are composed of the transmembrane proteins such as JAM, Claudin and Occludin. These transmembrane proteins interact via their cytosolic domains to intracellular cell polarity proteins such as ZO-1, ZO-2, ZO-3, PAR-3 and to the Actin/Microtubule cytoskeleton. (C) AJs are composed of transmembrane proteins such as E-Cadherin and Nectin. Cadherins and Nectins are linked to the Actin/Microtubule Cytoskeleton via interactions with beta and alpha-Catenin or via Afadin, respectively. (D) Focal Adhesions are composed of transmembrane proteins such as Integrin which interact with the Actin/Microtubule network via an intracellular complex of Actin binding proteins. At the extracellular face, Integrins also interact with the ECM. (E) F-Actin interacts with Microtubules and with a variety of molecules which act to regulate filament polymerization/depolymerization and contractility.

of small molecules and ions between cells. They allow rapid signaling between electrically excitable cells and slower signaling by the spread of intercellular second messenger signals such as inositol triphosphate ($IP_3$) and $Ca^{2+}$ (27, 28). Gap junctions also have a structural role, as they function to tightly connect adjacent cells and contribute to cellular adhesion (29).

### 3.4. Focal adhesions and hemidesmosomes

While the apical-basal junctions are important for communication between neighboring cells, anchoring of cells to the extracellular matrix (ECM)/basal lamina is also crucial for correct cellular morphology, adhesion and polarity. This interaction with the ECM is achieved via focal adhesions and hemidesmosomes, which contain Integrins, a family of integral transmembrane proteins that bind to the ECM on the extracellular side and interact with the cytoskeleton inside the cell (Figure 1D). Cell-matrix adhesions act as anchoring sites for the Actin cytoskeleton, causing tension and shape changes that can affect nuclear shape and chromatin structure and thus gene expression. Integrins also mediate cell-cell adhesion via connections to receptors on neighboring cells. Integrins lead to the activation of signal transduction pathways at the level of phosphorylation or by physically bringing kinases into close proximity to their substrates (reviewed in 30, 31, 32). Signaling from the ECM to the Actin cytoskeletion is regulated by FAK and Rho GTPases thereby controlling the formation and remodeling of cell contacts (33).

The Syndecan family of transmembrane receptors, with a role functionally similar to Integrins, is also required for the formations of focal adhesions and acts to link the cytoskeleton to the plasma membrane. Syndcans also similarly direct the organization and deposition of the ECM and thus function to tether the ECM to the cytoskeleton (34, 35).

### 3.5. The Actin cytoskeleton and Microtubule network

The Actin cytoskeleton and the Microtubule network serve as structural components of the cell and allow cell motility via the regulation of Actin polymerization and vesicular transport. Actin is physically associated with Integrins by linkages mediated by several proteins (Figure 1D). One of the best studied examples is Talin which binds and activates Integrins to form a complex with Filamentous Actin (F-Actin) and Vinculin through interactions with its 'tail domain'. This association with Vinculin which also binds F-Actin directly, facilitates the association with the Actin cross-linking protein alpha-Actinin (36). Integrins are also capable of indirectly recruiting scaffold and signaling proteins such as Paxillin and the protein Tyrosine kinase focal adhesion kinase (FAK), which in turn associates with additional molecules to regulate the activation state of the Rho family of small guanine nucleotide (GTP)ases (e.g. Rac, Rho and CDC42) by the recruitment of guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs) to the adhesion complexes.

Rho GTPases act to regulate the driving force for cell movement by regulating the dynamic reorganization of the Actin cytoskeleton that directs protrusion at the leading edge and retraction at the rear of the cell. Other mechanisms include directed secretion, which provides new membrane components and turnover of cell–matrix interactions to control adhesion.

Migrating cells attach to the ECM via Integrins and Syndecans that link to polymerized Actin within the cell. During cell translocation there is constant formation and sequential disruption of adhesive contacts. At the leading edge of the cell are two types of protrusive structures called lamellipodia (protrusive sheet-like structures consisting of a cross-linked meshwork of Actin-Myosin filaments (Actomyosin)) and filopodia (fingerlike structures consisting of thin parallel bundles of Actin filaments oriented in the direction of protrusion) that form weak sites of attachment called focal complexes. In addition, just behind the leading edge, Actomyosin filament bundles form and insert into large focal adhesion complexes which provide robust anchorage. Focal adhesions can become fibrillar adhesions, which are major sites of Fibronectin matrix deposition and remodeling (35). Movement is possible via the contractile activity of these filaments and the polymerization of Actin filaments at the leading edge (37).

The regulation of cell motility also involves Microtubule's function as tracks for the transport of cellular components and vesicles. Microtubules are composed of alpha- and beta-tubulin dimers and are orientated in the cell with the minus ends directed to apical pole and the fast growing plus ends oriented basally. Motor proteins such as Kinesins and Dyneins track along Microtubles to direct proteins from the Golgi complex to the apical plasma membrane and by targeting the transport vesicles between the basolateral and apical membrane domains (38). Microtubules can also regulate adhesion complex disassembly by promoting Integrin endocytosis (35). Directional cell migration requires the polarization of Microtubule cytoskeleton and the reorientation of the centrosome and Golgi to face the front of the cell (39). This involves the association of microtubule plus-end tips with plasma membrane complexes at the leading edge as well as movement of the nucleus to the back of the cell (40-42).

### 3.6. Regulation of the cytoskeleton by the Rho and Rab families of small GTPases

The establishment of epithelial polarity and coordinated cell movements are essential during embryogenesis for morphogenetic processes ranging from gastrulation to development of the nervous system. In adult tissues, migration of fibroblasts and vascular endothelial cells is essential for wound healing. These mechanisms are also hijacked during metastasis, where tumor cells migrate from the initial tumor mass into the circulatory system and subsequently migrate into new sites. Animal cells move by crawling and this motion is primarily regulated by the members of the Rho family of GTPases, Rho, Rac, and Cdc42 that coordinate assembly and disassembly of Actin filaments in response to extracellular signals (39). The process of migration also requires the remodeling of adhesive contacts and this is achieved by the regulation of

vesicular trafficking by Rab GTPases (43). Rab GTPases control endocytosis and are responsible for targeting lipids and proteins to their correct domains and the recycling of adhesion molecules such as E-Cadherin and thus control the disassembly of AJs (44-46).

Rho and Rab belong to the Ras superfamily of small GTPases. Most GTPases exist in an inactive (GDP-bound) and an active (GTP-bound) conformation. Guanine nucleotide exchange factors (GEFs) catalyze the release of GDP, allowing GTP to bind. In their active, GTP-bound state, Ras and Rho GTPases interact with target proteins to promote a cellular response. Their inactivation is brought about by GTPase activating proteins (GAPs) which act to catalyze the GTPase's intrinsic GTPase activity and return it to its inactive, GDP-bound state (47, 48).

Rho GTPases regulate cytoskeletal organization via a variety of mechanisms, including the regulation of Actin polymerization, Actomyosin contractility, vesicular transport, the regulation of Matrix metalloproteinases (MMPs) and the turnover of junctional components. Cdc42 regulates filopodia formation by controlling Actin polymerization via the regulation of downstream effectors such as Cdc42 effector protein (CEP)2/3, Actin related protein (ARP)2/3 and Wiskott-Aldrich syndrome protein (WASP) (49, 50). Cdc42 also functions to restrict Rac activity to the leading edge of moving cells (39, 51). Rac in turn regulates the formation of lamellipodia, focal complexes and Rho activity. Rho regulates the formation and maintenance of focal adhesions and the contractile forces of Actomyosin filaments to form stress fibers (39, 51, 52). Cdc42 also controls the polarized reorientation of the Microtubule cytoskeleton by controlling the association of APC (refer to section 4.1) to the plus ends of Microtubules and by controlling the localization of Dlg to the plasma membrane (53). Rho GTPases are also capable of regulating the production or secretion of MMPs, thus affecting matrix remodeling and invasiveness (54).

The role of Rho, Rac and Cdc42 on the regulation of the cytoskeleton can be attributed to various downstream targets. One downstream effector of Rho that contributes to Actin stability is Rho-Kinase (ROK), a serine–threonine kinase which directly phosphorylates Myosin light chain, and phosphorylates and inactivates Myosin phosphatases to result in an increase in bundle formation and contraction of Actomyosin filaments, which leads to AJ disruption. ROK also activates LIM-kinase which subsequently inactivates the Actin-severing factor Cofilin. Another Rho effector, Dia leads to the promotion of Actin polymerization and the stabilization of AJs (55-57) (Figure 1E). Cdc42 and Rac1 regulate AJ adhesion by regulating their downstream effector, IQ motif containing GTPase activating protein (IQGAP1). IQGAP1 interacts with E-Cadherin and beta-Catenin and competes with alpha-Catenin for an overlapping binding site in beta-Catenin. IQGAP1 can thus lead to the dissociation of alpha-Catenin from the AJ and thereby affect cell adhesion (58).

Actin stress fiber turnover and focal adhesion formation is regulated by Ras activity (51). Contraction of Actin stress fibers is regulated via the downstream effector of Cdc42 and Rac, p21-activated kinase (PAK1) (59). Myosins also control the rearrangement of the Actin cytoskeleton by using the force generated by ATP hydrolysis to move antiparallel Actin filaments past each as well as mediating Actin directed vesicular transport (60).

Collective cell migration is controlled by the coordinated suppression of Actomyosin contractility at cell-cell contacts, whilst remaining high around the edge. This is regulated by Par3/Par6/aPKC which control the localization of RhoE to cell contacts where it acts to antagonize ROK driven Actomyosin contractility (61).

### 3.7. Regulation of cell-adhesion by Src

Src accumulates at Cadherin based cell adhesions where it is responsible for reforming and maintaining the strength and integrity of established cell-cell contacts (62-64) (Figure 1C). The modulation of Src activity by both upstream protein tyrosine kinases and phosphatases is required for its role in the dynamic regulation of the Actin cytoskeleton (65). Src transduces E-Cadherin signaling by regulating the activity of several Actin regulators. Src phosphorylates Coractin which regulates the Actin cytoskeleton by binding directly to Actin filaments or by associating with Actin regulatory proteins such Arp2/3 (66-68). Src activity also leads to the activation of the Arp2/3 complex via its ability to phosphorylate and activate WASP (69). Src also supports apical junctional tension by targeting non-muscle Myosin IIB (65). Moreover, Src in concert with FAK signaling has been shown to be critical for the regulation of adhesion turnover at the leading edge of migrating cells (70). Src-FAK signaling achieves this by regulating Actomyosin contractility through Extracellular signal related kinase (ERK) and Myosin light chain kinase (MLCK) (70).

### 3.8. The mesenchymal to epithelial transition and the epithelial to mesenchymal transition

The establishment of polarized epithelial cells is generated through specific interactions with their surroundings such as the ECM or intercellular contacts and this process is termed the mesenchymal to epithelial transition (MET). Mesenchymal cells are not polarized, possessing only weak focal contacts with other cells. They generally do not associate with the basal lamina and migrate as individual cells or in chains. The filopodia and/or lamellipodia at the leading edge of migrating cells penetrate into neighboring cells and form small focal contacts at the points of cell-cell contact; a process that is initiated by the recruitment and activation of Cdc42 and Rac to Cadherin–Cadherin contact sites. This process leads to the formation of mature AJs which in turn triggers the establishment of the TJ (71, reviewed in 72).

The reverse process is called the epithelial to mesenchymal transition (EMT). While the epithelial properties of cells allow them the ability to differentiate into new structures; the mesenchymal properties of cells allow them to move and settle at new sites or to play a supporting role, thus allowing the body to form complex tissues and organs and to orchestrate wound repair.

Mechanisms that control EMT considerably overlap with those that control adhesion, invasive motility and production of ECM components, and are controlled by patterning signaling pathways (73, 74).

EMT is initiated by extracellular signals such as those from components of the ECM or soluble growth factors. This signaling leads to the activation of small GTPases and Src families of proteins that promote the disassembly of junctional complexes and changes in cytoskeletal organization. The downstream consequence of such signals leads to the activation of transcriptional regulators likes Snail and Slug and the repression of E-Cadherin. Down regulation of E-Cadherin abolishes the E-Cadherin-beta-Catenin interaction at the AJs and allows the entry of beta-Catenin in the nucleus where it can participate in canonical Wnt signaling. These processes translate into the loss of apical-basal polarity and cell-cell contacts, allowing detachment from surrounding cells. Cells undergoing EMT also digest the basal membrane via the action of MMPs to further facilitate migration (72, 75-77).

Potent inducers of EMT include Wnt (reviewed in 78, 79), PI3K, Ras, TGF-beta (77, 80) and Notch (81) pathway activation. These pathways have also been implicated in metastasis, a process where the epithelial characteristics of cells are lost while the cell gains migratory and invasive properties (77, 80, 82).

Disruption of epithelial polarity is expected to displace signaling molecules from their correct cellular localization, and thus disrupt the transduction of patterning signals. One signaling pathway that is critical in this process, both during development and in cancer, is the Wnt signaling pathway. The Wnt signaling pathway has several branches and each branch has been linked to orchestrating aspects of morphogenesis during development and in cancer.

## 4. WNT SIGNALLING

The Wnt family of signaling molecules have important roles in the regulation of cell adhesion as well as the morphogenetic movements that occur during embryogenesis and wound healing (83-85). Wnt pathway misregulation also has a role in many human pathologies, including cancer (86, 87). Indeed, the Wnt-1 gene was initially identified as a proto-oncogene when it was discovered as the insertion site of the mouse mammary tumor virus (MMTV) (88). In humans, deregulation of the Wnt pathway is observed in over 90% of colorectal cancers as well as in a large number of sporadic tumor types (89, 90).

The Wnt family of genes is conserved in all phyla of the animal kingdom and is comprised of 19 members in humans (91, 92). Wnt genes encode secreted glycoproteins that act as short or long range signaling molecules and act to specify different cell fates in a concentration dependent manner (reviewed in 93, 94). The Wnt signal is interpreted by at least three downstream pathways. The canonical pathway involves the accumulation of beta-Catenin in the cytoplasm and its localization to the nucleus where it regulates transcription. Whereas, the non canonical pathways such as the planar cell polarity (PCP) pathway and the $Ca^{2+}$ pathway do not directly regulate beta-Catenin's transcriptional role in the nucleus. In vertebrates, most Wnts have roles in both canonical and non-canonical signaling. However, studies in *Xenopus* have lead to the classification of Wnts 1, -3a, -8, and -8b as canonical since they act to direct cell fate. Whereas, Wnts 4, -5a and -11 are classified as non-canonical because they act to induce morphological movements during gastrulation (5, 95-97). In addition, studies utilizing mammalian cells lines have shown that only a subset of the Wnt proteins is capable of inducing transformation. Wnts 1, -2, -3 and -3a are capable of inducing strong transformation of mammary cell lines and induce the cytosolic accumulation of beta-Catenin (canonical). Whereas, Wnts 4, -5a, -5b and -7b did not lead to transformation and were not capable of elevating the levels of beta-Catenin (non-canonical) (98, 99).

### 4.1. Canonical Wnt signaling

Activation of the canonical Wnt pathway involves the binding of Wnt to members of the Frizzled (Fzd) family of cell surface receptors (of which there are 10 members in mammals) and the co-receptor lipoprotein receptor–related protein (LRP)-5/6. The signal is then relayed in the cytoplasm through Dishevelled (Dsh, three family members in mammals) and leads to inhibition of the destruction complex. The destruction complex comprised of Glycogen Synthase Kinase 3-beta (GSK3-beta), Casein Kinase I (CKI) and the scaffolding proteins Axin and Adenomatous Polyposis Coli (APC), normally phosphorylate beta-Catenin in the absence of the Wnt signal, thereby targeting it for proteasomal degradation (Figure 2). T-Cell Factor (TCF)/ Lymphoid Enhancer Factor (LEF) in conjunction with Groucho/TLE normally act as co-repressors in the absence of Wnt stimulation. However, in the presence of the Wnt signal, inhibition of the destruction complex leads to the accumulation of unphosphorylated beta-Catenin that escapes degradation and is free to enter the nucleus where it displaces Groucho/TLE from TCF/LEF binding sites and acts as a transactivator to activate transcription through the recruitment of various cofactors (reviewed in 100, 101, 102). Transcriptional targets of beta-Catenin/Tcf/Lef include *c-myc*, *cyclin D*, *axin-2* and *BMP4* (103-106). Colorectal cancers have a prevalence of APC truncation mutants which diminish or abolish beta-Catenin and Axin binding sites and lead to aberrant stabilization of beta-Catenin and consequent unchecked Wnt signaling (107, 108).

### 4.2. PCP pathway

The PCP pathway was first described in *Drosophila* where it was found to be responsible for the correct segmental and spatial organization of the body plan (reviewed in 109). In vertebrates, PCP signaling is crucial for neural tube closure and wound healing (110-112). PCP signaling in vertebrate systems involves the binding of non-canonical Wnts (such as Wnt5a and Wnt11) to the Fzd receptor, and thereby activating the recruitment of cytoplasmic Dsh to the plasma membrane. Transmembrane

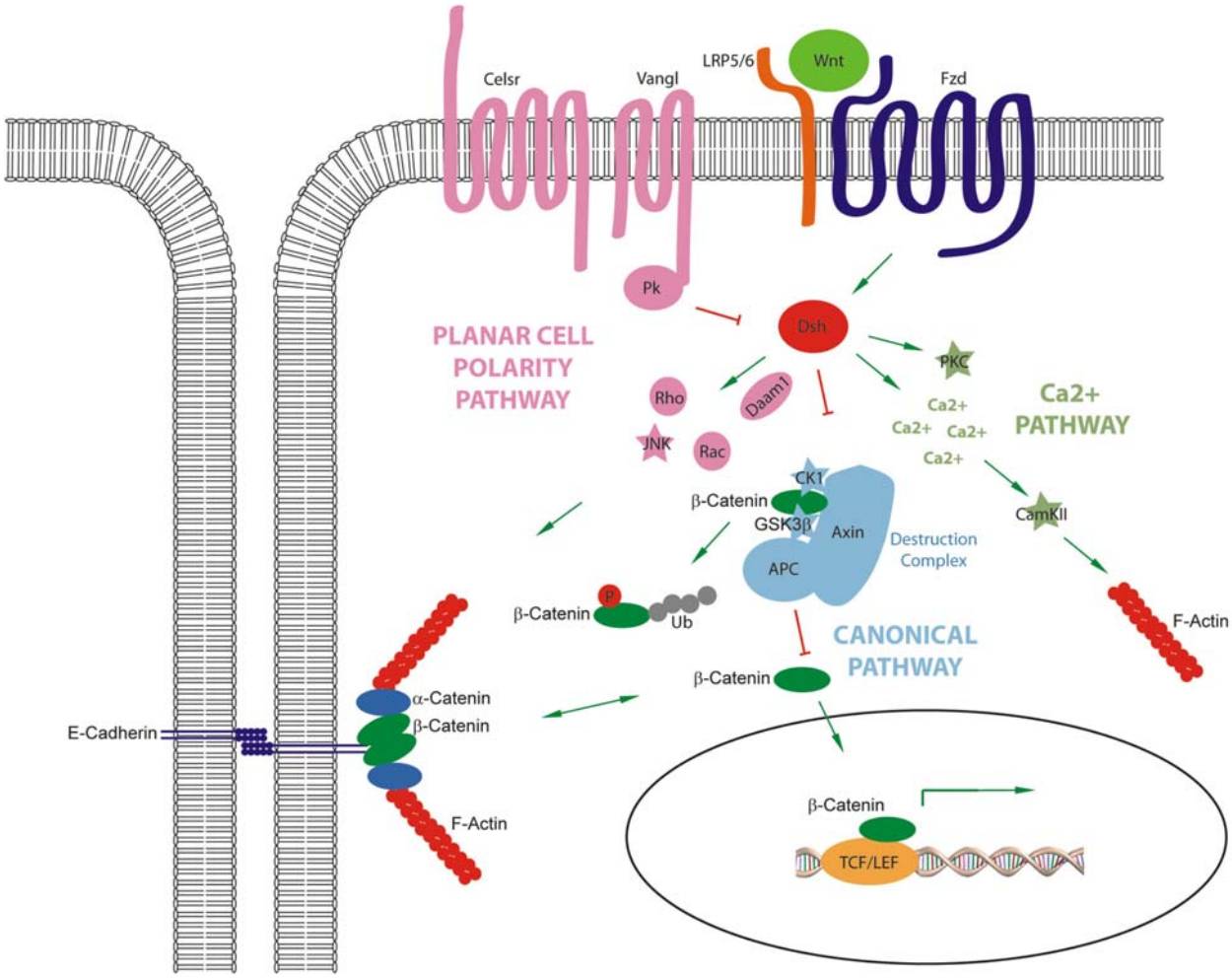


**Figure 2.** Wnt signaling. Activation of the canonical Wnt pathway involves the binding of canonical Wnts to Frizzled (Fzd) cell surface receptors and the LRP5/6 co-receptor. The signal is relayed in the cytoplasm through Dishevelled (Dsh), which leads to the inhibition of the destruction complex. The destruction complex is composed of the scaffolding proteins Axin and APC and the kinases GSK3-beta and CKI. In the absence of Wnt signal the destruction complex leads to the phosphorylation and ubiquitylation of beta-Catenin and its subsequent targeting for proteasomal degradation. The majority of beta-Catenin in a cell is present at the AJ in a complex with E-Cadherin. However, inhibition of the destruction complex leads to the stabilization and accumulation of beta-Catenin in the cytoplasm, where it is then free to enter the nucleus. In the nucleus, beta-Catenin binds to TCF/LEF binding sites and functions to transactivate transcription of Wnt target genes. The Planar cell polarity pathway activation involves the binding of non-canonical Wnts to the Fzd receptor and the subsequent activation and recruitment of Dsh. Transmembrane proteins such as Celsr and Vangl interpret this signal and Vangl in association with Prickle (Pk) can antagonize Dsh recruitment and activation. Signaling through this pathway is mediated by Daam1 and leads to the activation of JNK and small GTPases such as Rac and Rho, which act to regulate the Actin/Microtubule cytoskeleton. In the Ca2+ pathway, binding of non-canonical Wnts to the Fzd reporter leads to the stimulation of intracellular Ca2+ and the activation of PKC and CamKII, which in turn regulate the Actin/Microtubule cytoskeleton.

proteins such as Celsr and Van gogh-like (Vangl) in association with Prickle (Pk) interpret this signal, triggering the asymmetric localization of PCP pathway components such as Fzd, Dsh, Vangl and Pk. Signaling through this pathway is mediated by the formin homology protein Daam1 and leads to the activation of small GTPases such as Rac and Rho and the c-Jun N-terminal Kinase (JNK) (Figure 2). Rho GTPases and JNK act in concert to regulate the reorganization of the Actin cytoskeleton and Microtubule dynamics to result in coordinate cell movements and planar and epithelial cell polarity (reviewed in 113, 114-117).

### 4.3. Wnt/$Ca^{2+}$ pathway

The Wnt/$Ca^{2+}$ pathway involves the binding of non-canonical Wnts (such as Wnt11) to the Fzd receptor. Signaling through this pathway stimulates the release of intracellular $Ca^{2+}$ and the activation of PKC and Calmodulin-dependent kinase II (CaMKII), which in turn,

regulate the organization of the Actin-cytoskeleton and cell adhesion (reviewed in 118, 119) (Figure 2).

### 4.4. Wnt pathway cross talk

Non-canonical Wnt signaling is capable of negative feedback to regulate the canonical pathway. Elevated $Ca^{2+}$, which results from the activation of the Wnt/$Ca^{2+}$ pathway, can activate the phosphatase Calcineurin. Activated Calcineurin dephosphorylates the NF-AT transcription factor which allows it to accumulate in the nucleus where it acts to suppresses canonical Wnt signaling (120). Furthermore, non-Canonical Wnt-5a activity leads to the degradation of beta-Catenin via a Siah2 and APC dependent, but GSK3-beta independent mechanism (121). Conversely, Rac1 and JNK2 kinase activity is required for the nuclear accumulation of beta-Catenin during canonical signaling (122).

## 5. CROSS-TALK BETWEEN CELL ADHESION AND WNT SIGNALLING PATHWAYS

Pathways that control epithelial polarity/cell-adhesion and morphogenesis have been classically viewed as distinct pathways. However, new work has exposed multiple levels of cross-talk between cell adhesion and pathways that regulate morphogenesis. Disruption of epithelial polarity is expected to displace signaling molecules from their correct cellular localization, and thus disrupt the transduction of patterning signals. Conversely, any corruption to morphogenetic signaling will lead to defects in cell-adhesion and the co-ordination of cell movements.

### 5.1. Links between canonical Wnt signaling and epithelial polarity.

Canonical Wnt pathway activation and the resultant activation of beta-Catenin/TCF/LEF transcription complexes have been shown to target genes involved in EMT programs and cell migration (78). As described above, E-Cadherin is a component of the AJ and the loss of E-Cadherin expression is a hallmark of EMT. The downregulation of E-Cadherin is required for morphogenetic processes where cellular rearrangement occurs by changing polarity and cell-cell contacts. Jamora *et al.*, used hair follicle development as a model system to show that downregulation of E-Cadherin is required during follicular morphogenesis, a process where stem cells form a bud structure. Moreover, they show that this downregulation of E-Cadherin is mediated by beta-Catenin and LEF-1 binding to and inhibiting the E-Cadherin promoter (123). Wnt signaling has been shown to downregulate E-Cadherin during brain development in mice (124) and a correlation between reduced E-Cadherin and elevated nuclear beta-Catenin have also been observed in human cancers (125). Furthermore, canonical Wnt signaling directly affects EMT as it leads to the accumulation of the EMT transcriptional regulators Snail and Slug. Canonical Wnt signaling prevents GSK3-beta from phosphorylating Snail, which allows it to accumulate and participate in the inhibition of E-carherin transcription (102). LEF-1 and beta-Catenin also upregulate *slug* transcription (126), which leads to the repression of E-Cadherin (127).

In addition to the down-regulation of E-Cadherin, Wnt/beta-Catenin signaling is capable of regulating many other aspects of EMT. During EMT, MMPs act to dismantle the local basement membrane (72). Activation of beta-Catenin/TCF-4 leads to upregulation of MT1-MMP/MMP-14, MMP-7 and MMP-26 in a variety of cancer cell types (128-131). Similarly, the degradation of the ECM is mediated by Urokinase, which has been shown to be under the control of beta-Catenin and is expressed at high levels at the invasive front of carcinomas (132). Wnt target gene activation following APC loss (the key early event in the development of sporadic colorectal cancers (133, 134)) leads to the activation of Integrin and Rho pathway clusters in mice (135). In colon cancer cells, the over-expression of Fzd7 induces TCF-reporter transcriptional activity (136) whilst Fzd7 knockdown leads to the inhibition of canonical Wnt signaling-mediated epithelial patterning (137). Interestingly, Fzd7 is itself a beta-Catenin/TCF target gene (138, 139). Notably, these studies suggest a possible role for Fzd7 in canonical upregulation of invasion factors via the canonical Wnt pathway (140). Indeed, Fzd7 upregulates EMT transcription factor such as Slug via the canonical Wnt pathway. Furthermore, beta-Catenin/TCF-4 activation in colon cancers has been shown to regulate molecules involved in migration and invasion such as CD44 (141-143), S100A4 (144), Laminin gamma2 (145, 146), L1 (147) and in *Xenopus* fibroblasts beta-Catenin activity upregulates Fibronectin (148). Fzd7 in particular appears to have opposing roles in morphogenesis. For example, Wnt6 and Fzd7 mediate neural crest cell induction via canonical Wnt signaling (149-151), while Wnt11 and Fzd7 mediate neural crest cell migration via the non-canonical Wnt signaling pathway (152) (discussed further below). Presumably the Wnt branch of the Wnt pathway activated by Fzd7 is dependent on the tissue and cellular context. Indeed, recent evidence suggests regulation by the ECM in colorectal cancer (138) (Figure 3).

In contrast to the role of beta-Catenin/TCF in the induction of EMT, as mentioned above, Wnt canonical signaling also has a role in tubular patterning and epithelialization (MET). Tubulogenesis during various developmental processes including kidney, gut, cardiovascular, mammary and respiratory morphogenesis and is a process that requires the repeated epithelization of mesenchymal cells to form complex tubules (153). Wnt-4 triggers kidney tubulogenesis in a process that requires cell contact (154, 155), whereas Wnt-7b and Wnt-1 have been shown to be required in respiratory and mammary tubulogenesis respectively (153). Tubulogenesis has been shown to generally require beta-Catenin signaling for the initiation of epithelialization but must also be switched off to complete MET and perhaps a switch to non-canonical Wnt signaling (153). beta-Catenin activation in epithelial progenitors induces TCF/LEF dependent transcripts associated with epithelialization including *Pax8*, *cyclin D1* and *Emx2* (156). Wnt-1 expression in a mammary epithelial cell line led to the upregulation of the gap junction protein

Connexin43 (157), which has been shown to reduce cell migration (158, 159). Similarly, in *Xenopus*, Wnt-3a activity results in the upregulation of the gap junction protein Connexin30 (160), which appears to function in the regulation of cell fate (161).

In addition to the role of canonical Wnt signaling in the transcriptional control of epithelial cell polarity, adhesion and migration, other components of the pathway have molecular connections with the cells cytoskeletal architecture. APC has a role in migration and its loss results in the reduction of directional cell migration and Microtubule stability (162-165) and contributes to tumor formation (164, 166). APC interacts with the cytoskeleton by a variety of mechanisms; it localizes to lamellipodia and cell-cell junctions (164, 167) and binds to the plus ends of Microtubules in a Cdc42 and aPKC dependent manner (168). APC also organizes the Actin and Microtubule networks (169, 170) via its interactions with junctional regulators beta-Catenin, Axin (regulator of PG (171)) and IQGAP1 (172); Microtubule regulators CtBP and EB1; and Actin cytoskeletal regulators Asefs (Rac1-Cdc42 GEFs) (173-175).

Microtuble function is also regulated by the effect of Wnt signaling on Par1 activity. Wnt-3a activation leads to the upregulation in Par1 activity (176, 177), and GSK3-beta directly phosphorylates and activates Par1 (178). The AJ regulator Src can also be activated by binding to Dsh2 in a Wnt-3a dependent manner (179).

### 5.2. Non canonical Wnt pathways regulate cell adhesion

Non-canonical Wnt signaling regulates the cytoskeleton, adhesion and migration by signaling through the Wnt/$Ca^{2+}$ and Wnt/PCP pathways. In addition, non-canonical Wnt pathway components have direct regulatory effects on the ECM and junctional complexes.

Members of the Wnt/$Ca^{2+}$ signaling pathway have been demonstrated to be regulators of cell-migration during normal development and in mammalian cancer cell lines. Numerous studies have noted that Wnt-5a expression increases cell motility and adhesion during vertebrate development (180, 181) and in mammalian cancer cell lines (182-185). The role for Wnt-5a in migration appears to require the Ror-2 co-receptor (186, 187) and to signal through, Dsh2 (182, 186), PKC (184, 185, 188), CaMK-II (183), FAK, Src (185) and Rho GTPases (182, 189, 190). The morphogenetic cell movements that occur during mammalian palate development can only occur in the presence of Wnt-5a and Ror-2 (187). Similarly in mammalian fibroblast and melanoma cells lines, Ror-2 is required for Wnt-5a induced cell migration and Ror-2 is capable of mediating filopodia formation (186). In a gastric cancer cell line, Wnt-5a over-expression caused an increase in cell-substrate adhesion, cell migration and adhesion-dependent FAK activation. This effect on the cytoskeleton was mediated through Src and PKC, as migration in these cells was reversed upon treatment with Src or PKC inhibitors (185). Similarly, a study utilizing melanoma cell lines, showed that Wnt-5a triggers membrane contractility, Golgi polarization, endosome trafficking and cell movement. Wnt-5a treatment leads to PKC autophosporylation and a redistribution of cell adhesion molecules including Actin and Myson IIB (182, 184). This Wnt-5a induced effect required Fzd5, Dsh2, and PKC, as antibodies against Fzd5, depletion of Dsh2 or inhibition of PKC blocked Wnt-5a induced redistribution of cytoskeletal proteins and cell invasion (182, 184). Endosomal trafficking was also shown to be involved as blocking Rab4 and RhoB function abolished the cytoskeletal redistribution (182). A similar pathway involving Wnt-11, Fzd7 and PKC appears to function during cell movements during vertebrate gastrulation (191-193). One study also showed that the cell cohesion during gastrulation was controlled by Wnt-11 induction of Rab5, which functioned to regulate the endocytosis of E-Cadherin (193).

Several lines of evidence also point to a role for CaMK-II in migration. Wnt-5a stimulation of prostate cells led to increased CaMK-II activity and a threefold increase in intracellular $Ca^{2+}$. CaMK-II activity stimulated Actin remodeling and improved wound healing capacity, whereas CaMK-II inhibition induced Actin remodeling to decrease cell motility and hindered wound healing (183). A role for CaMK-II vascular smooth muscle cell migration and the movement, extension and branching of filopodia in hippocampal neurons has been demonstrated via its ability to promote Gogli polarization, Rac activation and F-Actin reorganization (189, 190). CaMK-II can also promote focal adhesion turnover and cell motility by inducing tyrosine dephosphorylation of FAK and Paxillin (194). In addition to CaMK-II activation, intracellular $Ca^{2+}$ can regulate cell-adhesion and motility by a variety of additional mechanisms. Proteins that are involved in Actin polymerization (including those involved in filament severing, capping, nucleation, bundling, and linkage to cell membranes, organelles, or other proteins) require $Ca^{2+}$ for their activity. Myosin's motor activity is regulated by $Ca^{2+}$ dependent phosphorylation (195) and the process of endocytosis is also $Ca^{2+}$ dependent (196, 197). Cadherins ($Ca^{2+}$-dependent adhesion molecules) are also regulated by intracellular $Ca^{2+}$ levels. Under conditions of low intracellular $Ca^{2+}$, IQGAP1interacts with active CDC42/Rac1 that is anchored to the cell membrane at sites of cell-cell interaction. This allows stabilization of the Cadherin-Catenin-Actin microfilament complexes and strong intercellular adhesion. When intracellular $Ca^{2+}$ levels are elevated, $Ca^{2+}$ binds directly to IQGAP1 and Calmodulin, and leads to the dissociation of IQGAP1 from CDC42/RAC1, making IQGAP1 available to bind to E-Cadherin and beta-Catenin, and by out competing alpha-Catenin binding, leads to reduced Cadherin mediated cell-cell adhesion (58).

Non-canonical Wnt pathway activation can also exert an effect on the ECM via the regulation of Integrin and Syndecan function. A recent co-expression study showed that Wnt-5, Fzd2, Dsh and APC localize to the leading edge in migrating cells. Furthermore the authors found that Fzd2 exists in a complex with alpha2-Integrin and that Dsh and APC are complexed with PAK and Paxillin (198). Dsh was demonstrated to have a role in the signaling that occurs after Integrin engagement with the ECM. Loss of Dsh (Dsh1, Dsh2 and Dsh3 shRNAi) leads

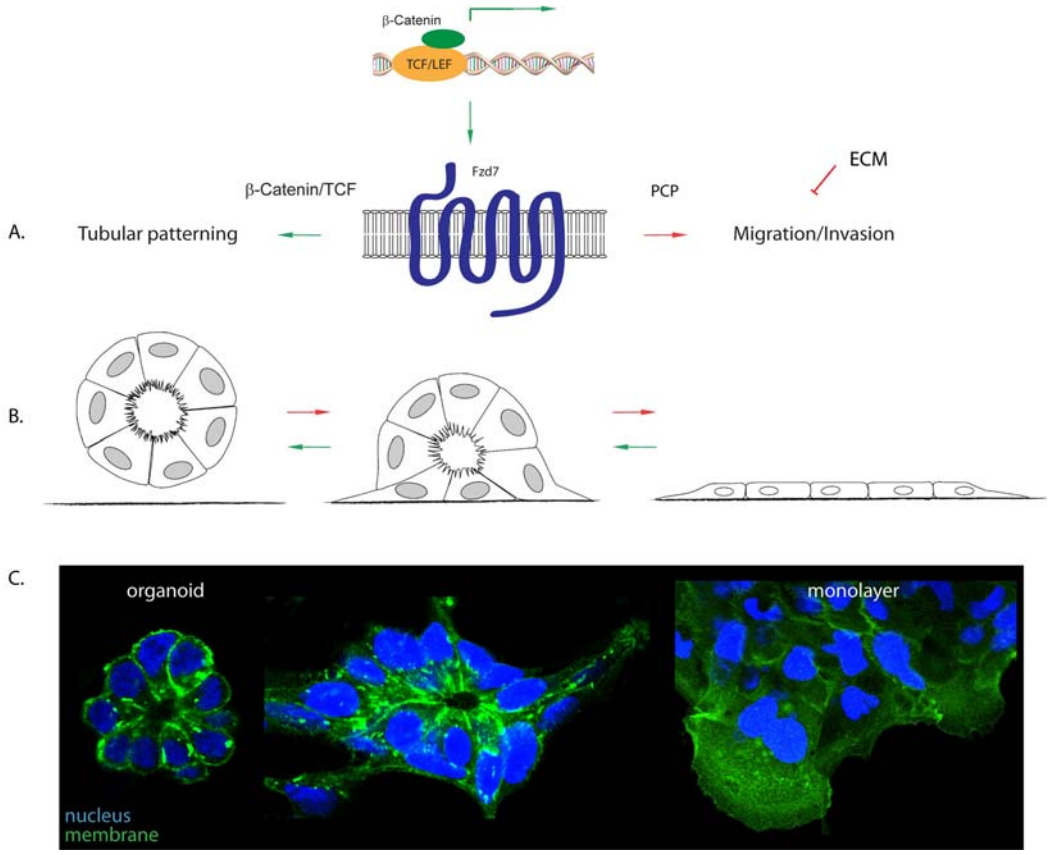


**Figure 3.** Fzd7 has a role in tubular patterning and migration. (A) Fzd7 is a target of beta-Catenin/TCF in colorectal cancer (CRC). Fzd7 activity is required for the transition from the migratory state (mesenchymal) to the tubular patterning state (epithelial) in CRC. Fzd7's role in migration appears to be via non-canonical pathways, this is in part down regulated by the ECM in some contexts e.g. in CRC. (B) A diagrammatical representation of transition between organoid (tubular) and monolayer (mesenchymal) that occurs in CRC cells. (C) Confocal images of the transitions between organoid and monolayer states. Red arrows denote EMT and green arrows denote MET.

to an impairment in cell-substrate adhesion, migration; a reduction in cell adhesion dependant activation of FAK and impairment of both focal-adhesion turnover and stabilization of Microtubules at the cell periphery (198). Integrin function is also required for cytoskeletal reorganization in a previously uncharacterized non-canonical Wnt pathway composed of secreted Frizzled Related Protein sFRP-1, Fzd4, Fzd7, GSK3-beta and Rac1 (199). sRFP-1 over-expression induced ECM dependent cell spreading and formation of Actin stress fibers and focal contacts in endothelial cells. This sFRP-1-induced spreading could be blocked by addition of blocking antibody against beta1- or alpha2-beta1-Integrin, showing a requirement for Integrin function in SRFP-1 induced cell spreading. Depletion of Fzd4 and Fzd7 dramatically increased cell spreading and were demonstrated to bind and co-localize with sFRP-1 at the plasma membrane. Rac1 activation is also involved, as a dominant negative Rac1 abolished sRFP-1 induced cell spreading. Inhibition of GSK3-beta also blocked the ability of sFRP-1 to activate Rac1 but depletion of beta-Catenin did not affect sFRP-1 spreading enhancement (199). Furthermore, crosstalk between the Wnt and Integrin (via FAK) signaling pathways is required for both intestinal homeostasis and cancer (200). Similarly Syndecan levels are regulated by non-canonical Wnt signaling in cell lines and dorsal mesodermal cells from *Xenopus* gastrulae. Wnt-5a and Wnt-11 activity leads to the reduction of cell surface levels and promotes the degradation of Syndecan 4 (SDC4). The mechanism appears to work through Fzd7 and Dsh, as expression of Fzd7 lead to an increase in SDC4, and a SDC4 deletion construct that can only weakly interact with Dsh, is rendered resistant to Wnt-5a induced degradation (201, 202). Wnt-5a expression induces migration and invasion in gastric cancer cells, which requires the induction of the ECM component Laminin gamma2 expression which was induced through the activation of PKC and c-Jun-N-terminal kinase (JNK) (203). Similarly a role for Fzd7 in the regulation of the MET and cell motility was uncovered in colon cancer cells (136, 137). Fdz7 loss of function led to a persistent mesenchymal state (as indicated by upregulation of *slug* and downregulation of *E-cadherin* transcripts) (Figure 3) in a colorectal cell line that is normally able to transition into a 3D epithelial state that resembles enclosed carcinoma tubules. Fzd7 was shown to be required for the upregulation of Laminin-5 alpha3 and

gamma2 chains that normally occurs during EMT and is required for cell migration (137).

Junctional complexes are also regulated by non-canonical Wnt activity. Wnt-5a was shown to be required for hippocampal axon differentiation which was attenuated by downregulating Dsh or inhibiting aPKC. Wnt-5a activation led to the stabilization and activation of aPKC and this occurred via the activity of Dsh1 which participates in the Par3/Par6/aPKC complex (204). In the *Xenopus* ectoderm, Fzd8 and Dsh have also been shown regulate the localization and activity of the aPKC target Lgl (205). Wnt-3a and Wnt-5a signaling can also regulate the stability of Cadherin-beta-Catenin juntional complexes. In a study utilizing rat cardiac myocytes cultured with Wnt-3a and Wnt-5a containing medium showed that Wnt signaling induced cell aggregation which was caused by increased levels of complexed N-Cadherin-beta-Catenin. This stabilization of complexed Cadherin–beta-Catenin required the activity of Fzd2 as the over-expression of a dominant negative Fzd2 construct in the rat cardiac myocytes cultured with Wnt-3a and Wnt-5a failed to induce cell aggregation (206).

The Wnt/PCP pathway also has a role in the regulation of cell motility and AJs. Wnt-5a regulates podocyte morphogenesis in a process that results in the redistribution of Dsh and Daam1 and results in increased numbers of stress fibres and cell motility. This process required Vangl2, as depletion of Vangl2 caused a reduction in cell projections, decreased stress fibres and a reduction in cell motility (207). A study utilizing mammalian cell lines showed that Vangl2 is also required for AJ function. Depletion of Vangl2 led to the impairment of cell adhesion and cytoskeletal integrity in cell lines, and impaired AJs and defects in neural tube closure in loss of function mice. Vangl2 is required to bind Rac1 and controls its distribution. Vangl2 loss of function results in the mislocalization of Rac1 to the nucleus or cytoplasm instead of the AJs, where it is required for its role in promoting Actin polymerization (208).

### 5.3. Components of the Wnt signaling cascade are regulated by polarity molecules

Wnt signaling is in turn regulated by components of the cells adhesion and migration machinery, namely regulators of the ECM, junctions, cytoskeleton and the endocytic pathway. Components of the ECM such as Collagen, Laminin and Integrins can affect Wnt signaling. Type I Collagen promotes EMT via the Integrin linked kinase (ILK)-dependent activation of NF-kappaB which leads to increased levels of Snail and LEF-1. ILK signaling also acts to inhibit GSK3-beta which normally acts to inhibit Snail, LEF-1(209) and enhances the formation of the beta-Catenin/LEF-1 complex (210). A pathway that includes Laminin-5, alpha-6 beta-4 Integrin and Rac1 acts to sense and transduce shear stress regulates beta-Catenin levels and signaling in colon cancer cells (211) and Integrin alpha(v)beta(3) regulates PKC activity in mammalian cell lines (212).

Junctional components and regulators N-Cadherin, PG, Src, Merlin and the Cdc42/Par6/aPKC complex also have a role in the regulation of Wnt signaling. In osteoblasts, N-Cadherin participates in a complex with Axin and the Wnt co-receptor LRP5 and results in increased beta-Catenin degradation and a reduction in TCF/LEF function in response to Wnt-3a (213). The Desmosomal component PG interacts with LEF-1 and TCF-4 to induce transcription and affects the levels of beta-Catenin in the nucleus by interaction with its degradation machinery (214, 215). Src regulates the phosphorylation of beta-Catenin in colorectal cancer cells and inhibition of Src disrupts beta-Catenin/TCF4 nuclear association and activation (216). Activation of the focal adhesion and stress fiber regulator, Ras in keratinocytes leads to the stabilization of beta-Catenin for nuclear import (217). The AJ regulator Merlin has an inhibitory effect on canonical Wnt signaling. Loss of Merlin leads to the upregulation of TCF4 activity, upregulation in nuclear beta-Catenin and target gene expression (*cyclin D*) whilst junctional beta-Catenin was downregulated. The ability of Merlin to modulate beta-Catenin/TCF4 depends on Rac1, as RNAi of Rac1 in Merlin deficient cells suppresses TCF4 activity (218). The apical membrane regulators Cdc42/Par6/aPKC function in a pathway that is activated upon the disruption of cell-cell contacts and leads to the activation of non-canonical Wnt signaling and the polarized reorganization of the Microtubule cytoskeleton (219). Cdc42/Par-6/aPKC inhibits GSK3-beta at the leading edge of migrating cells, leading to the accumulation of APC at the plus ends of Microtubules which is essential for the establishment of cell polarity (168). In *Drosophila*, aPKC and Patj can participate in a complex with Fzd1 and inhibit its function (220).

The cytoskeletal regulators LKB1 and Par1 are also regulators of Wnt signaling. LKB1 associates with aPKC and is capable of phosphorylating and inhibiting GSK3-beta, which leads to the upregulation of active beta-Catenin in the presence of Wnt or Dsh (221, 222). Par1 regulates Dsh and leads to the activation of canonical Wnt/beta-Catenin pathway and the down regulation of the Wnt/PCP pathway. Par1 binds and phosphorylates Dsh at sites that are essential for its translocation from cytoplasmic vesicles to the cell cortex (176, 223). The phosphorylation of Dsh by Par1 is however not crucial for Par1's role in regulating Dsh, as a Dsh mutant where the Par1 phosphorylation sites are abolished can still be rescued by Par1 over-expression. Instead it appears that Par1 and Dsh both function to antagonistically regulate the association of E-Cadherin with the Actin cytoskeleton which may occur via the regulation of Rho GTPases. This was demonstrated by the ability of Par1 expression to promote the resistance of E-Cadherin to extraction with non-ionic detergents (assay for cytoskeletal association). However, when Par1 was depleted, Dsh expression led to the reduction in the association of E-Cadherin with the Actin cytoskeleton and the reintroduction of Par1 was able to attenuate the effect of Dsh on E-Cadherin (224).

The endocytic pathway which controls the trafficking of specific molecules to their correct localization in the cell also has a role in the regulation of Wnt signaling. beta-Arrestin2 controls the internalization of Fzd4 in a process that is induced by Wnt-5a and PKC

activity. beta-Arrestin2 is able to recruit Fzd4 into Clathrin coated pits by binding to phosphorylated Dsh2 (225).

## 6. SUMMARY AND PERSPECTIVE

This review has highlighted recent work which has revealed that canonical and non-canonical Wnt signaling pathways are intimately linked at many different points with the mechanisms that are involved in the regulation of cell-adhesion and cell communication. During normal morphogenesis, both Wnt signaling and the modulation of adhesion are required to act in concert; however any defects in these processes can lead to cancer. Work identifying the points of crosstalk between Wnt signaling and cell-adhesion pathways may lead to novel avenues for targeted cancer therapy. We anticipate that drugs designed to target molecules at the points of intersection between the Wnt and epithelial cell polarity pathways will be a 'double hit' in the fight to control carcinogenesis. For example, drugs targeted at preventing the mislocalization of polarity molecules that interact with Wnt pathway components are expected to inhibit cancer formation via two distinguishable mechanisms. However, caution must be exercised as the precise regulation of both Wnt signaling and cell adhesion/communication is required for the normal processes of development, organogenesis and repair.

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