Interplay of Cadherin-Mediated Cell Adhesion and Canonical Wnt Signaling

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The epithelial–mesenchymal transition is essential in both embryonic development and the progression of carcinomas. Wnt signaling and cadherin-mediated adhesion have been implicated in both processes; clarifying their role will depend on linking them to rearrangements of cellular structure and behavior. β-Catenin is an essential molecule both in cadherin-mediated cell adhesion and in canonical Wnt signaling. Numerous experiments have shown that the loss of cadherin-mediated cell adhesion can promote β-catenin release and signaling; this is accomplished by proteases, protein kinases and other molecules. Cadherin loss can also signal to several other regulatory pathways. Additionally, many target genes of Wnt signaling influence cadherin adhesion. The most conspicuous of these Wnt target genes encode the transcription factors Twist and Slug, which directly inhibit the E-cadherin gene promoter. Other Wnt/β-catenin target genes encode metalloproteases or the cell adhesion molecule L1, which favor the degradation of E-cadherin. These factors provide a mechanism whereby cadherin loss and increased Wnt signaling induce epithelial–mesenchymal transition in both carcinomas and development.

In both normal embryonic development and carcinomas, signals trigger epithelial–mesenchymal transitions (EMT). These biological programs convert polarized, rather immobile epithelial cells to fibroblastoid, highly motile mesenchymal cells (Fig. 1). EMT occurs over and over during embryonic development; for instance, it is crucial in the formation of mesoderm during gastrulation, which produces a three-layered embryo, and formation of the neural crest, the heart, and the craniofacial system (reviewed by Thiery 2002). EMT also occurs in carcinomas, where it promotes invasion and metastasis (reviewed by Thiery 2002; Yang and Weinberg 2008). A thorough understanding of these processes will require mechanistic explanations of how the signaling pathways implicated in EMTs trigger the rearrangements of cellular architecture and changes in behavior that permit it to happen. They should also explain how changes in healthy signaling lead to inappropriate EMTs in carcinomas. After three decades of work, an integrated picture of the connections between these processes is finally coming into focus. The present review centers on the role of cadherin-mediated cell adhesion and its interplay with Wnt/β-catenin signaling,

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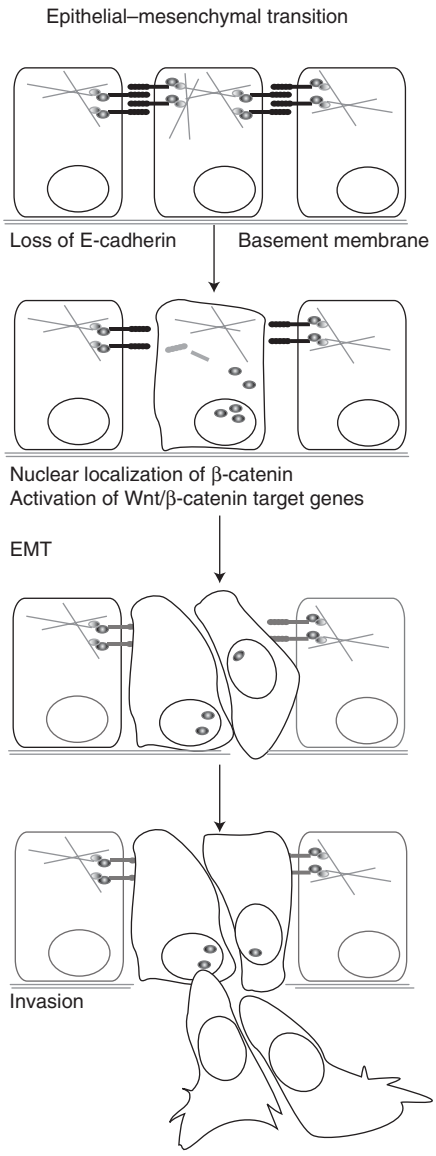

Figure 1. Epithelial–mesenchymal transition. EMT can be induced by the loss of E-cadherin and/or by the activation of canonical Wnt signaling. Epithelial cells become more motile and receive a mesenchymal character. The mesenchymal-like cells can pass the basement membrane and become invasive.

which are both crucial in the process of EMT (see also Nelson and Nusse 2004; Gavert and Ben-Ze'ev 2007).

In the late 1960s to early 1980s, Hay and collaborators recognized EMT as a distinct biological process in studies with embryos and three-dimensional cell cultures (Trelstad et al. 1967; Greenburg and Hay 1982). Soon afterwards, our group showed that Madin-Darby canine kidney (MDCK) epithelial cells are converted into fibroblastoid cells through the disruption of E-cadherin-mediated cell adhesion with specific antibodies (Imhof et al. 1983; Behrens et al. 1985). Stoker and Gherardi showed that MDCK epithelial cells could be converted into motile fibroblastoid cells by the addition of conditioned medium that contained scatter factor/hepatocyte growth factor, HGF/SF (Stoker et al. 1987; Weidner et al. 1991). Further work showed that MDCK epithelial cells acquired invasive properties, i.e., invaded collagen gels and embryonal heart tissue, following disturbed E-cadherin-mediated cell adhesion (Behrens et al. 1989), or by the addition of HGF/SF (Weidner et al. 1990; Weidner et al. 1991).

The process of EMT is reversible: Invasive human carcinoma cells that had lost E-cadherin expression and epithelial polarity could be made noninvasive by transfection with the E-cadherin cDNA (Frixen et al. 1991; Vleminckx et al. 1991). It could also be shown that poorly differentiated human breast and stomach carcinomas carried inactivating mutations in the E-cadherin gene (Becker et al. 1994; Berx et al. 1995), and inherited germline mutations of E-cadherin were found in early-onset, diffuse-type gastric cancer in human families (Guilford et al. 1998). The loss of E-cadherin expression coincided with the transition from well-differentiated adenoma to invasive carcinoma in a transgenic mouse model of pancreatic carcinogenesis (Perl et al. 1998). In other cases of human carcinomas, down-regulation of E-cadherin occurred by hypermethylation of the E-cadherin gene promoter (Hennig et al. 1995; Strathdee 2002). Beug and collaborators showed that activation of the c-Fos proto-oncogene in mammary gland epithelial cells also induced EMT, e.g., down-regulated E-cadherin, up-regulated several mesenchymal genes, and promoted invasion of the cells into collagen gels (Reichmann et al. 1992). Remarkably,

overexpression of stabilized β-catenin also scattered MDCK epithelial cells in tissue culture (Barth et al. 1997). In the last decade, groups have identified several more signaling pathways and specific transcription factors that induce EMT in development and in the invasion and metastasis of carcinomas. These include:

- TGFβ signaling (Oft et al. 1996; Mercado-Pimentel and Runyan 2007; Nguyen and Massague 2007).
- Wnt signaling (Kinzler and Vogelstein 1996; Huelsken et al. 2000; Fodde et al. 2001).
- Tyrosine kinase signaling (the ras pathway; Behrens et al. 1993; Oft et al. 1996; Meiners et al. 1998; Dietrich et al. 1999; Muller et al. 1999; Khoury et al. 2001).
- The transcription factors Snail, Slug, ZEB, E47, and Twist, which suppress E-cadherin expression (Batlle et al. 2000; Cano et al. 2000; Comijn et al. 2001; Peinado et al. 2004b; Yang et al. 2004).
- Tiam1/Rac1 signaling (Habets et al. 1994; Collard et al. 1996).
- Goosecoid and FOXC2 (Hartwell et al. 2006; Mani et al. 2007).

The discovery that cytoplasmic catenins are essential in cadherin-mediated cell adhesion was made in the late 1980s and early 1990s. Kemler's group reported that the conserved cytoplasmic carboxyl terminus of the cell adhesion molecule E-cadherin binds three proteins with mol.wts. of 102, 88, and 80 kDa, i.e., α-catenin, β-catenin, and plakoglobin (γ-catenin) (Vestweber and Kemler 1984; Ozawa et al. 1989; Nagafuchi and Takeichi 1989). Plakoglobin has been molecularly cloned by Franke and collaborators (Cowin et al. 1986), α-catenin by Takeichi and Tsukita and collaborators (Nagafuchi et al. 1991), and β-catenin by Gumbiner and collaborators (McCrea et al. 1991; Butz et al. 1992). β-Catenin forms a direct link between cadherins and α-catenin, whereas α-catenin also talks with the actin cytoskeleton (Rimm et al. 1995; Drees et al. 2005; Yamada et al. 2005; Abe and Takeichi 2008). This link is essential for strong cadherin-mediated cell adhesion (Nagafuchi and Takeichi 1988; reviewed by Takeichi 1991; Kemler 1993; Gates and Peifer 2005; see Meng and Takeichi 2009 and Shapiro and Weis 2009).

The Wnt/β-catenin signaling pathway has a crucial role in the embryonic development of all animal species, in the regeneration of tissues in adult organisms and in numerous other processes (reviewed by Cadigan and Nusse 1997; Clevers 2006; Klaus and Birchmeier 2008). Mutations or deregulated expression of components of the canonical Wnt pathway can induce disease, most importantly cancer (Bienz and Clevers 2000; Polakis 2000; Moon et al. 2004). Through the Wnt pathway, signals are exchanged between neighboring cells and tissues: Wnt proteins that are secreted from one type of cell interact with surface receptors of neighboring cells. There the signals are passed through the cytoplasm to the nucleus, where gene regulation is modulated. This process controls proliferation, survival, cell migration, differentiation, and patterning in the receiving cells and tissues.

The protein β-catenin plays a critical role in canonical Wnt signaling. Noncanonical Wnt signaling, which does not involve β-catenin, is not discussed here (Veeman et al. 2003). It had been known since the late 1980s that β-catenin (armadillo in *Drosophila*) is involved in Wnt signaling, but the way this molecule moves from the cytoplasm to the nucleus and interacts with the transcription machinery was unknown (Wieschaus and Riggleman 1987; Riggleman et al. 1990; Peifer et al. 1992). In 1995, an interaction was found between β-catenin and the lymphocyte enhancer binding factor 1 (LEF1). This observation precipitated feverish work, which firmly established that LEF1, and its closest relatives, T cell factors (TCF), are activated by signaling through the Wnt pathway (Behrens et al. 1996; Molenaar et al. 1996; Huber et al. 1996; Riese et al. 1997). LEF1 and TCFs are high mobility group (HMG) proteins and were discovered as DNA-binding proteins that bind to specific

sequences in lymphoid enhancers (Travis et al. 1991; van de Wetering et al. 1991; Waterman et al. 1991).

Canonical Wnt signaling works in the following fashion (for further detailed discussion of the Wnt pathway, see Cadigan and Pfeifer 2009; McCrea et al. 2009): In the absence of Wnt ligands, cytoplasmic β-catenin is recruited into a destruction complex, in which it interacts with APC and the axins, and is amino-terminally phosphorylated by axin-bound casein kinase 1α (CK1α) and GSK3β (Fig. 2A). Following phosphorylation, β-catenin is targeted for proteasome-dependent degradation involving an interaction with β-TrCP (β-transducin repeat-containing protein), a component of the E3 ubiquitin ligase complex. Therefore, in the absence of Wnt, cytoplasmic β-catenin levels remain low, and the transcription factors LEF1 and TCF interact with Grouchos in the nucleus to repress Wnt-specific target genes (Munemitsu et al. 1995; Aberle et al. 1997; Behrens et al. 1998; Roose et al. 1998; Liu et al. 2002). In the presence of Wnt ligands, LRP5–LRP6 surface receptors are phosphorylated by CK1γ and GSK3β (and possibly further kinases), and Dishevelled is recruited to the plasma membrane, where it interacts with Frizzled receptors and polymerizes with other Dishevelled molecules (Fig. 2B) (Davidson et al. 2005; Bilic et al. 2007; Schwarz-Romond et al. 2007). The inactivation of the destruction complex allows the cytoplasmic stabilization and translocation of β-catenin to the nucleus. Here, β-catenin forms a transcriptionally active complex with LEF1 and TCF transcription factors by displacing Grouchos and interacting with other coactivators (reviewed by Eastman and Grosschedl 1999; Stadeli et al. 2006; Klaus and Birchmeier 2008). This rounds out the picture of how Wnt's effects on genes are modulated by the activation and repression of β-catenin. What remains to be explained is how the different sets of target genes exert their influence on cell architecture and behavior, which is a major theme of this review.

CROSSTALK BETWEEN CADHERIN-MEDIATED CELL ADHESION AND CANONICAL Wnt SIGNALING THROUGH β-CATENIN

Wnt Signaling and Cadherins Compete for β-Catenin

The concept that canonical Wnt signaling and cadherin-mediated cell adhesion depend on the same pool of β-catenin is based on genetic and overexpression experiments in embryos and cultured cells. Heasman et al. showed in 1994 that overexpression of cadherins in *Xenopus* embryos inhibited dorsal axis formation, which is a clear function of canonical Wnt signaling (Heasman et al. 1994; see also Fagotto et al. 1996; Torres et al. 1996). Peifer and collaborators showed that armadillo (β-catenin) mutant embryos of *Drosophila*, which harbor only one E-cadherin allele, showed a less severe segment polarity phenotype than embryos with two cadherin alleles (Cox et al. 1996). Segment polarity is controlled by Wnt signaling (Nüsslein-Volhard et al. 1980; Rijsewijk et al. 1987). Similarly, cadherin overexpression mimicked the wingless (Wnt) phenotype in *Drosophila* embryos (Sanson et al. 1996). These data from the mid 1990s are thus consistent with a model in which there is crosstalk between β-catenin in two different compartments, the adhesion complex at the plasma membrane and a signaling complex in the nucleus.

Shortly after these findings in model organisms, Geiger and Ben-Ze'ev and collaborators showed an interplay between cadherin-mediated cell adhesion and canonical Wnt signaling in cell culture experiments. In colon cancer cells, expression of N-cadherin or an interleukin receptor-cadherin hybrid (in which the β-catenin binding region of N-cadherin was maintained) triggered a relocation of β-catenin from the nucleus to the plasma membrane and inhibited LEF1-mediated transcription (Sadot et al. 1998; Shtutman et al. 1999; Gottardi et al. 2001; Stockinger et al. 2001). Inducible expression of the Fos proto-oncogene in mammary gland epithelial cells resulted in the loss of

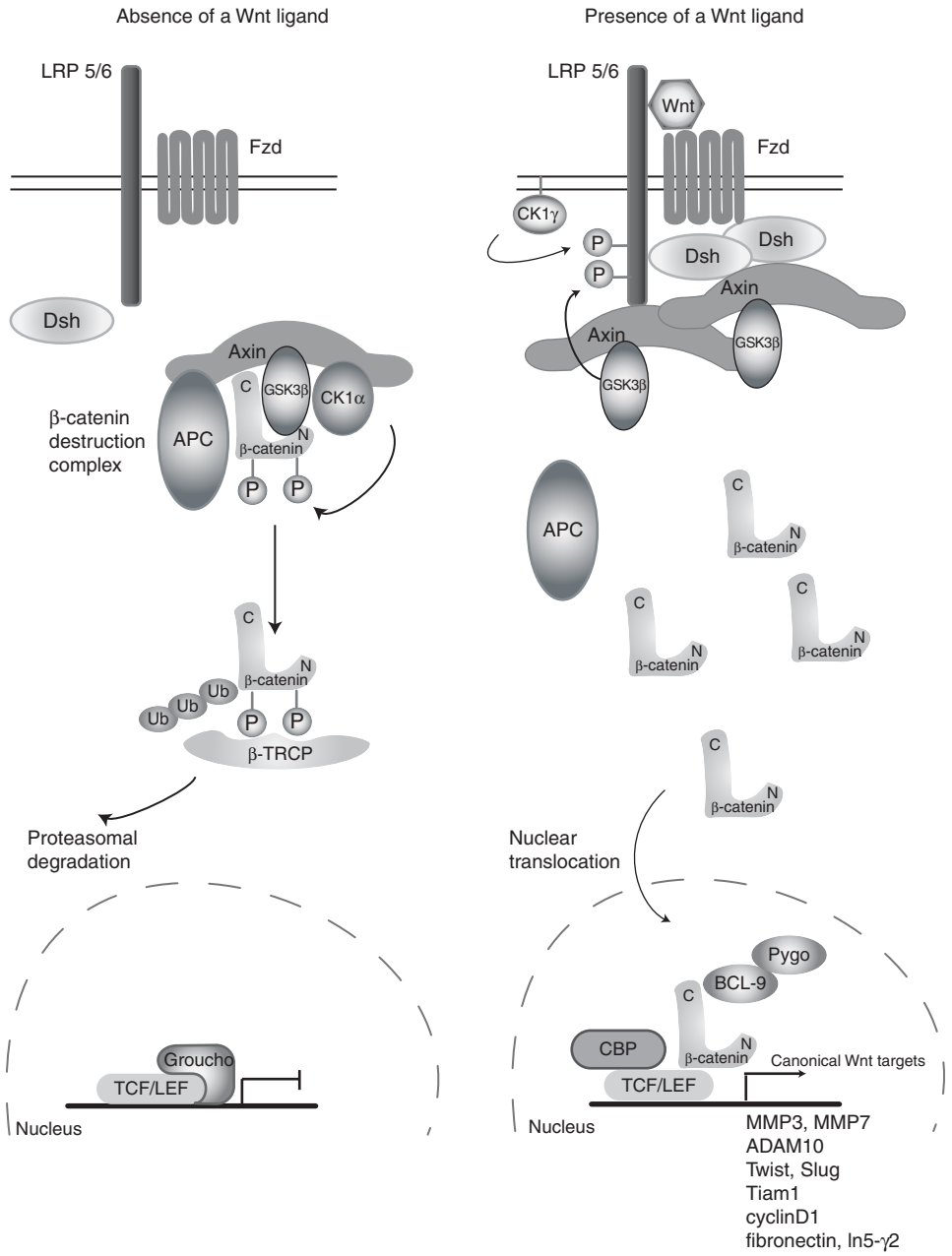

Figure 2. Canonical Wnt pathway. (*A*) In the absence of a Wnt ligand, β-catenin is sequentially phosphorylated in the destruction complex of axin and APC by the kinases CK1α and GSK3β, which results in ubiquitination by β-TRCP and, finally, in the degradation of β-catenin in the proteasom. (*B*) In the presence of a Wnt ligand, a Fzd/LRP5/6 complex is formed and is bound by Dishevelled, leading to the phosphorylation of the LRP5/6 receptor by GSK3β, CK1γ and other kinases. Phosphorylated LRP5/6 recruits axin to the plasma membrane, which leads to decay of the destruction complex, inhibited phosphorylation, and degradation of β-catenin. Stabilized β-catenin is then translocated to the nucleus, a process that can involve BCl9-2. β-Catenin interacts with TCF/LEF, and the recruitment of cofactors like BCL9, Pygopus, or CBP as well as the replacement of Groucho leads to the activation of target genes.

E-cadherin and cell polarization, the colocalization of β-catenin with LEF1 in the nucleus, and increased Wnt/β-catenin signaling (Eger et al. 2000). Moreover, the absence of E-cadherin in E-cadherin -/- embryonic stem (ES) cells led to an accumulation of β-catenin with LEF1 in the nucleus and activation of a Wnt reporter (Orsulic et al. 1999). This could be antagonized by expression of E-cadherin.

Behrens and collaborators have recently shown that siRNA-mediated knockdown of E-cadherin augments β-catenin-dependent transcription in colon cancer cells in which the Wnt pathway is active. On the other hand, the same procedure has no effect in nontransformed keratinocytes that do not display Wnt signaling (Kuphal and Behrens 2006). These data indicate that the mere loss of E-cadherin does not activate Wnt signaling—except in cases in which the β-catenin degradation machinery is compromised. These results are consistent with data from breast cell cancer lines showing that the absence of E-cadherin alone does not result in activation of Wnt signaling (van de Wetering et al. 2001). Nor does a loss of E-cadherin function in Rip1Tag2 transgenic mice contribute to Wnt/β-catenin signaling (Herzig et al. 2007). Weinberg and collaborators recently showed that in ras-transformed mammary gland cells (HMLER), shRNA down-regulation of E-cadherin results in translocation of β-catenin from cell–cell junctions to the cytoplasm and nucleus (Onder et al. 2008). This type of β-catenin was nonphosphorylated and thus was not targeted for ubiquitination and degradation. However, in this system, the loss of E-cadherin affected numerous other signaling pathways that have been implicated in metastasis formation.

Gottardi and Gumbiner have performed precise studies to determine what controls β-catenin targeting to cadherin adhesion or to TCF transcriptional complexes (Gottardi and Gumbiner 2004). They showed that Wnt signaling generates a monomeric, intramolecularly folded-back form of β-catenin that binds TCF but not cadherins. In contrast, the cadherin-binding form of β-catenin builds a dimer with α-catenin. X-ray crystallographic studies have shown that cadherin-binding involves all 12 armadillo repeats of β-catenin, whereas TCF-binding requires only the central eight repeats (Graham et al. 2000; Huber and Weis 2001). Thus it is possible that the carboxyl terminus of Wnt-produced β-catenin folds back over armadillo repeats, affecting binding to cadherin but not TCF. The selective binding of β-catenin induced by Wnt could also involve post-translational modifications or the activation of further proteins. Overall, these data suggest that β-catenin's selectivity between adhesion and transcription are not always coupled; in other words, they might be regulated independently.

BCL9 protein, the product of a human proto-oncogene, also acts in the switch between cadherin cell adhesion and β-catenin signaling. This story has been worked out through work on BCL9 and its ortholog legless, a *Drosophila* segment polarity gene. Legless, which was isolated in 2002 by the group of Konrad Basler, is required for Wnt signaling in the fly (Kramps et al. 2002). It acts by binding directly to β-catenin. Human BCL9 was discovered in a B-cell lymphoma because of a translocation to the immunoglobulin locus, which caused BCL9 overexpression in the tumors (Willis et al. 1998). Remarkably, human BCL9 could rescue the segment polarity phenotype of the legless mutation (Kramps et al. 2002), indicating functional identity. Vertebrates have a second homolog BCL9-2 (Brembeck et al. 2004; Adachi et al. 2004), which also binds to β-catenin like BCL9. BCL9-2 promotes nuclear location of β-catenin, increased β-catenin signaling, and triggers EMT in vertebrate cells and Zebra fish embryos (Brembeck et al. 2004). BCL9-2 cannot colocalize with the E-cadherin/β-catenin/α-catenin complex at the plasma membrane, but following tyrosine phosphorylation of β-catenin, it is translocated to the nucleus and promotes β-catenin signaling. Thus BCL9 proteins may act in the switch between cadherin-mediated cell adhesion and Wnt signaling (Brembeck et al. 2004; Sampietro et al. 2006; Hoffmans and Basler 2007; de la Roche et al. 2008).

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Proteolysis of Cadherins Affects Wnt Signaling

Competition for β-catenin is one mechanism by which cells can modulate Wnt signals. Another is the cleavage of E- and N-cadherin by proteases, which can lead to the release of β-catenin and to up-regulated β-catenin signaling. This occurs in normal development but also in processes such as wound healing, Ca^{2+}-influx, and apoptosis. Cadherins are cleaved intracellularly by proteases like caspase 3 or presenilin, or extracellularily by ADAM10 (Ito et al. 1999; Steinhusen et al. 2001; Marambaud et al. 2002; Maretzky et al. 2005; Shoval et al. 2007). Intracellular cleavage of cadherins releases nearly the entire cytoplasmic domain, whereas extracellular cleavage releases the adhesion domain (Fig. 3). ADAM10 belongs to the family of disintegrins and metalloproteases (ADAM), type I transmembrane proteins that combine cell–cell adhesion and proteinase activity (reviewed by Primakoff and Myles 2000; Seals and Courtneidge 2003). ADAM10 was recently identified as a β-catenin/TFC target gene (Gavert et al. 2007). The group of Saftig has shown that cleavage of E- and N-cadherin by ADAM10 in keratinocytes and neuronal cells, respectively, reduced cell adhesion, increased cell migration and led to translocation of β-catenin to the nucleus. Translocated β-catenin activated Wnt/β-catenin target genes like c-Myc and cyclinD1 (Maretzky et al. 2005; Reiss et al. 2005). These are clear examples of an immediate crosstalk between a loss of cadherin-mediated cell adhesion and Wnt/β-catenin signaling.

Presenilin1 (PS1) is an integral membrane protein and a component of the γ-secretase complex, which mediates an ε-cleavage of type I membrane proteins such as the amyloid precursor protein (APP). A mutant form of PS1 (PS1 FAD, familial Alzheimer's disease) is known to process APP, leading to increased production of the β-amyloid peptide (Aβ42), which is responsible for Alzheimer's disease (reviewed by Marambaud and Robakis 2005; Selkoe and Wolfe 2007). Mechanistically, PS1 acts in several ways to influence cell adhesion

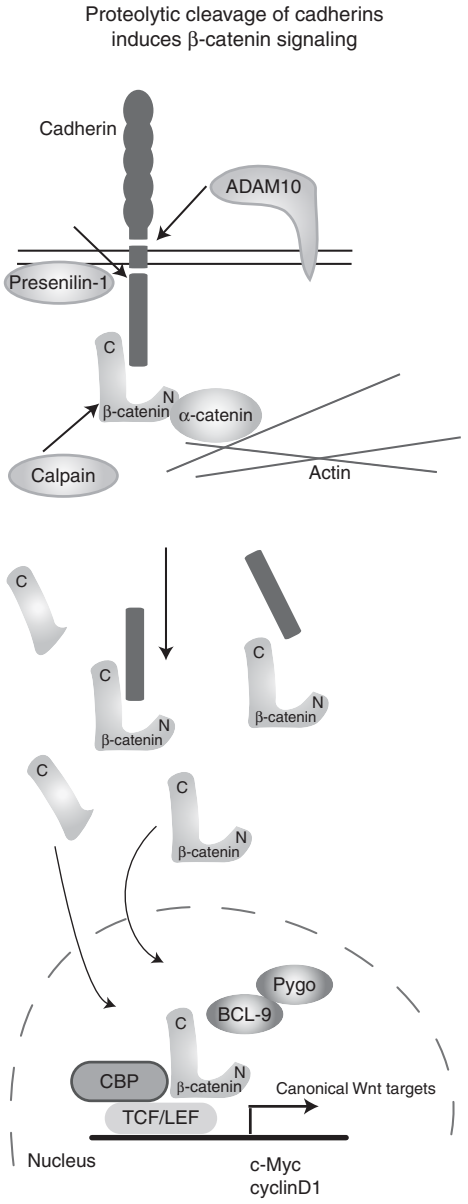

Figure 3. Proteolytic cleavage of cadherin can release β-catenin and induce canonical Wnt signaling. Under certain cellular conditions, cadherins can be cleaved by proteases like ADAM10 and Presenilin-1. This cleavage leads to loosening of cell adhesion, but also to the release of β-catenin, which is translocated into the nucleus and as a result, activates Wnt/β-catenin target genes. Another protease, calpain, is interfering with the adhesion complex by the amino-terminal cleavage of β-catenin. β-Catenin cleaved by calpain is stabilized and can enter the nucleus and activate target genes.

and transcription. PS1 can bind to E-cadherin and β-catenin and promotes their association to the cytoskeleton, and the overexpression of PS1 results in enhanced cadherin-mediated cell adhesion (Georgakopoulos et al. 1999; Baki et al. 2001). Under imbalanced calcium conditions or apoptosis, PS1 does not stabilize cell–cell adhesion but cleaves E-cadherin, which leads to the disassembly of adherens junctions, to the release of a cytoplasmic E-cadherin fragment, and to an increase of soluble β-catenin (Marambaud et al. 2002). It is possible that the release of β-catenin from adherens junctions caused by PS-1 modulates gene expression. It has been shown that the released N-cadherin fragments generated by PS1 favor nuclear localization of β-catenin and promote β-catenin signaling (Uemura et al. 2006). The released fragments of E-cadherin also translocate to the nucleus and affect transcriptional activity (Ferber et al. 2008). In contrast, PS1 can facilitate GSK3β-mediated phosphorylation of β-catenin, thereby favoring the degradation of β-catenin and negatively regulating β-catenin/LEF signaling (Zhang et al. 1998; Kang et al. 1999; Soriano et al. 2001; Kang et al. 2002). This latter type of cross-talk between PS-1 and β-catenin signaling has also been shown by genetic means; tumors with elevated β-catenin signaling developed in the skin of mice with PS-1 deficiency (Xia et al. 2001; Kang et al. 2002). Taken together, this indicates that PS-1 modulates junctional signaling (1) by cleaving cadherins, leading to increased β-catenin signaling and alterations in gene activity, and (2) by stabilizing cell-adhesion and promoting the degradation of β-catenin, thereby decreasing β-catenin mediated transcription.

Recently it has been proposed that the NMDA (*N*-methyl-D-aspartate) receptor in synapses links cadherin-mediated adhesion and β-catenin signaling (Abe and Takeichi 2007). The NMDA receptor is a glutamate-gated ion channel, which signals through the influx of Ca^{2+} and induces long-term synaptic plasticity in the nervous system (Carroll and Zukin 2002). N-cadherin has an important function in this process (Arikkath and Reichardt 2008). Triggering the NMDA receptor in neuronal cells activates the proteases ADAM10 and PS-1, which are able to process cadherins (Marambaud et al. 2003; Reiss et al. 2005). Another protease, calpain, has been shown to be critically involved in synaptic plasticity (Staubli et al. 1988). Abe and Takeichi have now shown that the NMDA-dependent activation of calpain cleaves β-catenin at its amino terminus (Fig. 3). As a result, β-catenin is stabilized, accumulates in the nucleus, and induces TCF/LEF1-dependent gene expression (Abe and Takeichi 2007). If it proves to be true that calpain cleaves β-catenin bound to cadherin and that this is essential in synaptic processes, this would establish a direct link between neuronal activity, adhesion between cells at the synapse, and β-catenin signaling.

Phosphorylation and the Control of β-Catenin in Signaling and Adhesion

Yet another link between adhesion and Wnt signaling can be found in the phosphorylation of components of the cadherin adhesion system, of the β-catenin degradation complex, or of the TCF transcription system, which regulate the strength of interactions. The action of various serine/threonine and tyrosine kinases therefore influences the function of β-catenin in adhesion and in signaling (reviewed by Daugherty and Gottardi 2007). For instance, the carboxy-terminal phosphorylation of cadherins can strengthen or weaken interactions with β-catenin, depending on the sites of phosphorylation (Choi et al. 2006; Qi et al. 2006). Tyrosine 654 phosphorylation of β-catenin reduces cadherin binding and adhesion function (Fig. 4) (Roura et al. 1999). The phosphorylation of β-catenin at tyrosine 489 or 142 strengthens Wnt signaling (Brembeck et al. 2004; Rhee et al. 2007). The phosphorylation of axin or APC, respectively, on serine or threonine residues can strengthen or weaken interactions with β-catenin, and the phosphorylation of TCFs also influences their binding to β-catenin (Rubinfeld et al. 1996; Willert et al. 1999; Lee et al. 2001; Ha et al. 2004).

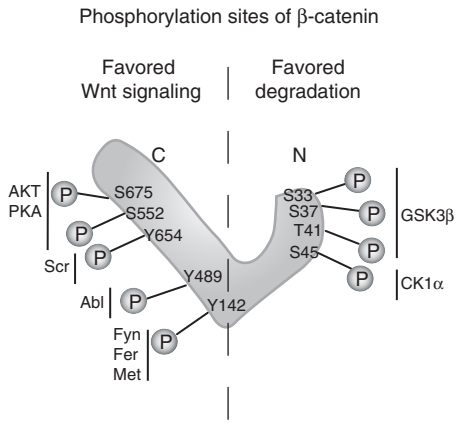

Figure 4. Phosphorylation sites of β-catenin. β-Catenin can be sequentially phosphorylated by different kinases, either promoting the degradation or the signaling activity of β-catenin. Phosphorylation at the amino terminus favors degradation, whereas phosphorylation in the armadillo domain changes the adhesiveness to cadherins and promotes nuclear localization.

Tyrosine kinases and tyrosine phosphatases have been shown to regulate the switch between cadherin-mediated cell adhesion and β-catenin signaling (Warren and Nelson 1987; Behrens et al. 1993; Muller et al. 1999; Roura et al. 1999; reviewed by Daugherty and Gottardi 2007). Insulin-like growth factor II leads to the internalization of E-cadherin/β-catenin and to E-cadherin degradation (Morali et al. 2001). β-Catenin then becomes nuclear, and β-catenin/TCF target genes are activated. HGF/SF action on Met can result in tyrosine 142 phosphorylation of β-catenin and induction of EMT in epithelial cells and axonal growth and branching of neuronal cells (Brembeck et al. 2004; David et al. 2008). A dominant-negative TCF4 can inhibit neural branching. The tyrosine kinase Met is itself a Wnt/β-catenin target gene (Boon et al. 2002). FGF and FGF receptor signaling also affects E-cadherin/β-catenin interaction and β-catenin/TCF signaling (Pai et al. 2008). Hunter and collaborators have shown that EGF receptor signaling induces EMT and caveolin-mediated endocytosis of E-cadherin (Lu et al. 2003). As a result, β-catenin localizes to the nucleus and activates Wnt/β-catenin target genes. EGF treatment also down-regulates caveolin-1, which enhances the transcriptional activity of β-catenin. Caveolin-1 negatively affects canonical Wnt signaling through the recruitment of β-catenin to caveolar membranes (Galbiati et al. 2000). E-cadherin can also be internalized by a different mechanism: Tyrosine phosphorylation of E-cadherin by Src kinase induces the recruitment of the E3 ubiquitin ligase Hakai and favors cell scattering (Fujita et al. 2002). Hakai ubiquitinates E-cadherin and mediates the clathrin-dependent internalization and lysosomal degradation of E-cadherin (Bonazzi et al. 2008; Shen et al. 2008). It is not yet clear whether the action of Hakai influences β-catenin signaling. Recently, the tyrosine phosphatases PTPRK and PCP-2 have been shown to inhibit β-catenin signaling and increase E-cadherin-dependent adhesion (Yan et al. 2006; Novellino et al. 2008). The cumulative evidence suggests that tyrosine phosphorylation-dependent destabilization of cadherin/β-catenin complexes and tyrosine-phosphorylation-dependent activation of β-catenin can both activate signaling and induce EMT.

A novel type of interplay between the loss of N-cadherin-mediated adhesion and transcriptional activity following tyrosine-phosphorylation of β-catenin has recently been discovered in Slit-activated neural retina cells (Rhee et al. 2007). Slit is a secreted axon guidance cue that binds and activates the Robo receptor, and this leads to the inactivation of N-cadherin (Brose et al. 1999). Balsamo and collaborators have shown that a population of N-cadherin-associated β-catenin, which is phosphorylated on tyrosine 489 in response to Slit-activation of the Robo-associated tyrosine kinase abl, is mobilized to the nucleus and becomes transcriptionally active (Rhee et al. 2007). This provides an example in which the down-regulation of cadherin-mediated adhesion in neuronal cells is coordinated with long-term effects on transcription.

The L1 adhesion system has recently also been shown to affect cadherin-mediated cell adhesion and β-catenin signaling (Shtutman

et al. 2006). L1 is a transmembrane adhesion molecule with extracellular immunoglobulin-like domains and fibronectin type III repeats. It is up-regulated by Wnt/β-catenin signaling, it is expressed exclusively at the invasive front of colon cancer tissue, and its expression is correlated with tumor progression and metastasis (see also section B; Haspel and Grumet 2003; Gavert et al. 2005; Gavert et al. 2007). It has now been shown that L1 disrupts the formation of adherens junctions by releasing E-cadherin, that it promotes EMT-like transition, and that it induces β-catenin signals (Shtutman et al. 2006).

The Catenin p120 Relieves Kaiso-Mediated Repression of Wnt Target Genes

The turnover of cadherins is another crucial element of cell adhesion. It is critically dependent on the catenin p120, which binds to the highly conserved juxtamembrane domain of cadherins and increases their stability at the cell membrane. Depletion of p120 leads to an immediate turnover of E-cadherin and to a weakening of cell–cell adhesion (reviewed by Reynolds and Roczniak-Ferguson 2004). McCrea and collaborators have shown that p120 also influences the Wnt pathway through an interaction with the transcription factor Kaiso (Kim et al. 2004; Park et al. 2005; see also McCrea et al. 2009). Kaiso belongs to the BTB/POZ (zinc finger and broad-complex, tramtrack and bric-a-brac/poxvirus) protein family. The zinc-finger of Kaiso binds both CpG methylated sequences and a defined promoter consensus motif (Daniel et al. 2002; Kim et al. 2004). The association of Kaiso to promoters has been shown to repress Wnt target genes in *Xenopus* embryos and in mammalian cell lines by interfering with the binding of β-catenin to TCF/LEF (Kim et al. 2004; Park et al. 2005; Spring et al. 2005). It was recently suggested that Kaiso function may be mediated by its interaction with the DNA binding domain of TCF, leading to the displacement of TCF from promoters (Ruzov et al. 2009). The interaction of p120 with Kaiso influences the repressor function of Kaiso either by sequestrating Kaiso in the cytoplasm or by replacing it from the promoter (Park et al. 2005). It is likely that p120 affects the nuclear shuttle of Kaiso, since the NLS of p120 is crucial to the inhibition of Kaiso-mediated transcriptional repression (Kelly et al. 2004a; Kelly et al. 2004b). A functional interplay between p120, Kaiso, and Wnt target genes has also been observed in human cancer (reviewed by van Roy and McCrea 2005). The Wnt pathway also converges with the p120/Kaiso pathway further upstream, since p120 is stabilized by Frodo, a Dsh interacting partner. The interaction of Dsh with Frodo leads to stabilization of p120, which in turn enhances the displacement of Kaiso from target genes (Park et al. 2006). This means that the cell adhesion-modulating catenin p120 enables a further cross talk of cell junctions and the Wnt pathway in a β-catenin-independent fashion.

Adhesion and Wnt/β-Catenin Signaling in Cardiomyopathy

Mutations in genes that encode desmosomal proteins, including desmosomal cadherins, are the cause of arrhythmogenic right ventricular cardiomyopathies (ARVC) in humans. In this disease, muscle tissue of the right ventricle of the heart is replaced by fibrofatty tissue, resulting in arrhythmias and sudden death (reviewed by Sen-Chowdhry et al. 2004; MacRae et al. 2006). The mutated genes include all types of components of desmosomes: The cadherins desmocollins and desmogleins, the catenins plakoglobin and plakophilin2, and the linker protein to intermediate filaments, desmoplakin (MacRae et al. 2006; see also Heuser et al. 2006). Genetic experiments in mice have corroborated the essential role of desmosomal proteins in heart structure and function (see for instance Ruiz et al. 1996; Grossmann et al. 2004). Previously it had been firmly believed that the primary cause of ARVC is the weakening of desmosomal adhesion between cardiomyocytes in the diseased heart. However, the work of Garcia-Gras et al. has introduced a new twist in concepts: The cardiac-specific ablation of desmoplakin in mice is sufficient to

cause nuclear translocation of plakoglobin (γ-catenin), which then inhibits Wnt/β-catenin signaling (Zhurinsky et al. 2000; Garcia-Gras et al. 2006). It is known that Wnt/β-catenin signals supports cardiomyogenesis, whereas inhibition promotes adipogenesis (Ross et al. 2000). This could explain the reduced production of cardiomyocytes and the increased production of adipocytes, which is observed in ARVC. These data nicely show how a switch from cadherin-mediated cell-adhesion to modulated Wnt signaling might result in the complex properties of a human disease.

General Remarks

The studies described above show how a loss of E-cadherin-mediated cell adhesion induces β-catenin release and signaling. These functions cause biological responses such as EMT, invasion and metastasis (Fig. 1). In other cases, loss of E-cadherin induces EMT without promoting β-catenin mobilization, but it affects other signaling pathways (see also Perrais et al. 2007; Onder et al. 2008). A compromised β-catenin degradation machinery appears to be the prerequisite for β-catenin signaling, which follows the loss of cadherins. β-Catenin occupies different functional niches in the cells, and the flow between these niches and the subsequent effects on cell adhesion and signaling are regulated by further events such as phosphorylation. Taken together, the data show intricate networks of both interacting and separate pathways that control cell adhesion and signaling, and their contribution to EMT needs to be unraveled in each case.

CANONICAL Wnt SIGNALING AFFECTS CADHERIN-MEDIATED CELL-ADHESION

So far, our focus has mainly been on events within the cytoplasm that affect the cell by modulating β-catenin's functions in cell adhesion and its availability as a transcription factor in combination with other molecules. This section summarizes the effects of Wnt signaling at the gene level, showing its impact on cell–cell adhesion through the regulation of the expression of diverse cell adhesion-modulating molecules. For a frequently updated overview of Wnt target genes see Roel Nusse's webpage (www.stanford.edu/~rnusse/wntwindow.html).

Some Wnt target genes encode for components of cell junctions such as L1-CAM (Gavert et al. 2005), Nr-CAM (Conacci-Sorrell et al. 2002) and connexin 43 (van der Heyden et al. 1998). E-cadherin is negatively regulated by Wnt signaling (Huber et al. 1996; Jamora et al. 2003). Other Wnt targets encode transcription factors that negatively control the expression of cadherins like Twist (Howe et al. 2003) and Slug (Vallin et al. 2001; Conacci-Sorrell et al. 2003). Additionally, Wnt targets also encode enzymes that are involved in regulating the stability of cell adhesions, such as Tiam1 (Malliri et al. 2006), Matrilysin (Brabletz et al. 1999; Crawford et al. 1999) and Stromelysin (Prieve and Moon 2003). Wnt/β-catenin signaling also directly controls the expression of the mesenchymal genes fibronectin and laminin-5γ2 (Gradl et al. 1999; Hlubek et al. 2004). Wnt target genes that affect cell motility also include fascin (Vignjevic et al. 2007), EphB/Ephrin (Batlle et al. 2005), CD44 (Wielenga et al. 1999), and S100/A4-metastasin (Stein et al. 2006). Overall, Wnt signaling appears to modulate target genes that cause a switch from primarily epithelial to more mesenchymal cells (Fig. 5).

Wnt Targeted Transcription Factors Regulate Cadherin Expression—Twist, Snail and Slug

Twist is a bHLH transcription factor that was first identified in *Drosophila* as an inducer of mesoderm formation (Nüsslein-Volhard et al. 1984; Simpson 1983; Thisse et al. 1988). Twist is also expressed in mesodermal cells of vertebrates (Wolf et al. 1991; Fuchtbauer 1995; Wang et al. 1997). Wnt1 regulates Twist expression in *Drosophila* and murine cells (Bate and Rushton 1993; Howe et al. 2003), and Wnt/β-catenin signaling regulates Twist expression in migrating cells in *Xenopus* (Borchers et al. 2001). Gene ablation experiments in the mouse show that Twist is

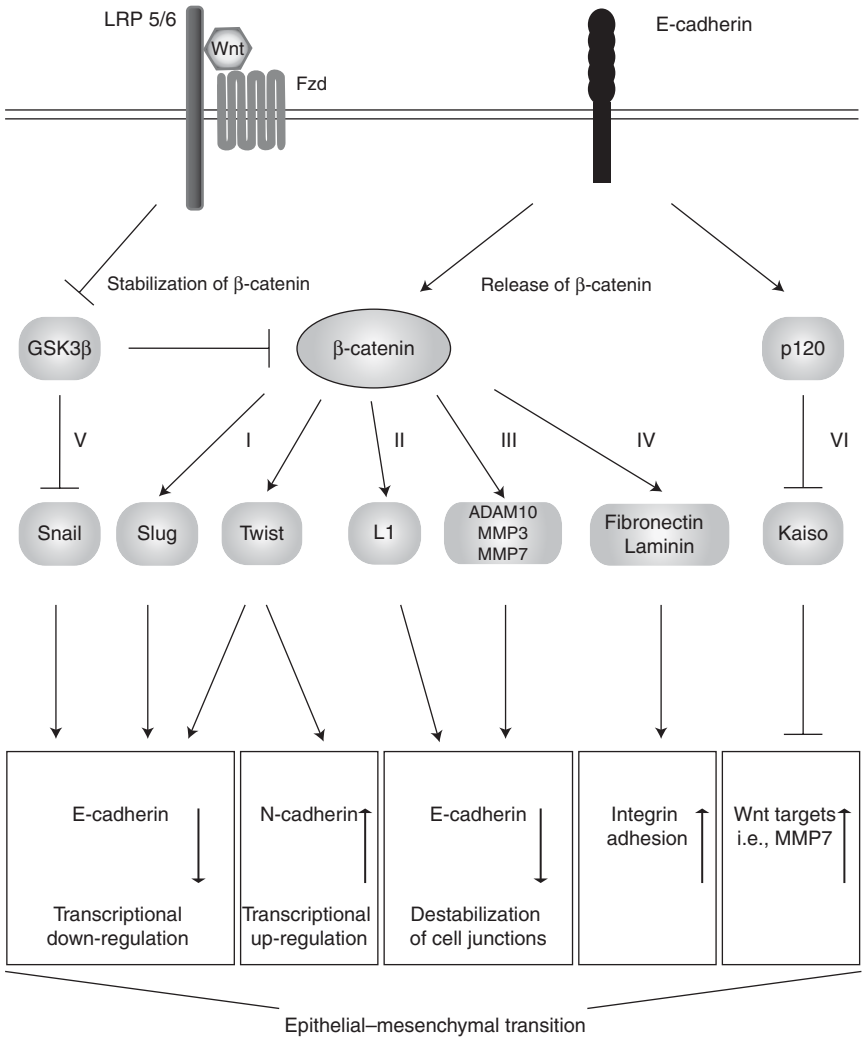

Figure 5. Canonical Wnt signaling modulates cell adhesions. Activated Wnt signaling leads to stabilization and nuclear localization of β-catenin, which induces the expression of Wnt target genes: I) The transcription factors Slug and Twist both repress the expression of E-cadherin, and Twist activates the expression of N-cadherin. II) The cell adhesion molecule L1 interferes with E-cadherin-mediated cell adhesion. III) The proteases MMP3 and MMP7 modulate the extracellular matrix, and MMP3, MMP7, and ADAM10 cleave E-cadherin. IV) The cell matrix molecules fibronectin and laminin favor cell-substrate adhesion. V) Wnt signaling inactivates GSK3β, leading to stabilization of Snail, which also inhibits the expression of E-cadherin. VI) p120 relieves the repressor Kaiso from Wnt target genes.

important for cell migration and cell localization during cranial neural tube morphogenesis (Chen and Behringer 1995; Soo et al. 2002). Twist down-regulates the expression of E-cadherin by binding to E-box elements of the promotor (Ip et al. 1992; Rohwedel et al. 1995; Lee et al. 1997; Yin et al. 1997; Kophengnavong et al. 2000), and it induces EMT and invasion and metastasis of mammary gland cells (Yang et al. 2004). In contrast, Twist is also involved in the up-regulation of N-cadherin (Oda et al. 1998; Yang et al. 2004; Alexander et al. 2006). N-cadherin can act as a proinvasive adhesion molecule that is produced

in carcinomas following a so-called cadherin switch (Wheelock and Johnson 2003; Hazan et al. 2004). In spite of its opposing regulatory functions on the promoters of E- and N-cadherin, both of these functions of Twist promote EMT. The same type of duality has been observed in tumors and cancer cell lines (Hsu et al. 1996; Hazan et al. 1997; Sandig et al. 1997; Tomita et al. 2000; Rosivatz et al. 2002; Gravdal et al. 2007). Because transfections of E-cadherin cannot fully correct EMT in mammary gland cells, it is suggested that Twist affects additional EMT-inducing genes (Yang et al. 2004). These data reveal a mechanism by which Wnt signaling can promote EMT, tumor progression, and metastasis via the regulation of Twist.

Like Twist, the transcription repressors Snail and Slug are involved in the regulation of EMT (Nieto et al. 1994; Sefton et al. 1998; Batlle et al. 2000; Cano et al. 2000; Veltmaat et al. 2000; ten Berge et al. 2008). Snail was first identified in *Drosophila* (Nüsslein-Volhard et al. 1984; Grau et al. 1984) and its homolog Slug in the chick (Nieto et al. 1994). Both Snail and Slug bind to the E-box motive of the E-cadherin promoter through a carboxy-terminal zink-finger domain and suppress the expression of E-cadherin (Batlle et al. 2000; Cano et al. 2000; Hajra et al. 2002; Bolos et al. 2003). This is mediated by the amino-terminal SNAG domain of Snail, which recruits a histone deacetylase (Batlle et al. 2000; Peinado et al. 2004a). Slug is not able to repress the expression of E-cadherin in rat bladder carcinoma cells, but disrupts desmosomes (Savagner et al. 1997).

Snail and Slug not only play a role in cell adhesion, but also their functions are affected by the Wnt pathway. The Slug promoter harbors a LEF binding site and is responsive to β-catenin/TCF signaling, which leads to the expression of Slug and in turn to the down-regulation of E-cadherin (Vallin et al. 2001; Conacci-Sorrell et al. 2003). The Snail promoter is not directly responsive to β-catenin/TCF signaling (Conacci-Sorrell et al. 2003), but Wnt signaling leads to increased levels of Snail by inhibiting GSK3β. Blocking GSK3β activity increases the transcriptional level of Snail (Bachelder et al. 2005) and also increases its stability; Snail is a substrate of GSK3β, and phosphorylation marks Snail for degradation (Zhou et al. 2004; Yook et al. 2005). Additionally, Snail interacts directly with β-catenin and enhances Wnt target gene expression, and is believed to stimulate the Wnt pathway in a positive feedback loop (Stemmer et al. 2008). These data indicate that Slug and Snail are important regulators of cadherin-mediated cell adhesion and that the Wnt pathway affects cell–cell adhesion via regulation of these transcriptional regulators (Fig. 5).

Two other aspects of these transcription factors need to be mentioned here. First, Snail, Slug, and Twist are regulated by many signaling pathways, of which Wnt is only one. It has been shown that the cellular context determines which pathways crosstalk to Snail, Slug, and Twist and regulate the expression of E-cadherin (reviewed by Nieto 2002; Huber et al. 2005). Next to the E-boxes, the E-cadherin promoter harbors other regulatory elements, such as cis-regulatory elements (Stemmler et al. 2005), and can be regulated by other transcription factors like δEF1/ZEB1, Sip-1/ZEB2, and E12/E47 (Grooteclaes and Frisch 2000; Comijn et al. 2001; Perez-Moreno et al. 2001).

Second, EMT plays a crucial role in gastrulation, a process in which the regulation of E-cadherin has an important function (Burdsal et al. 1993). During gastrulation, epiblast cells form the primitive streak from which endoderm and mesoderm are generated. The importance of canonical Wnt signaling can be seen from the fact that Wnt3, β-catenin, and LRP5/LRP6-deficient mouse epiblasts fail to form the primitive streak (Liu et al. 1999; Huelsken et al. 2000; Kelly et al. 2004c). The down-regulation of E-cadherin in mouse gastrulation is not controlled by Twist, as Twist is not expressed in the primitive streak (Chen and Behringer 1995). However, Snail is expressed in the primitive streak in the mouse (Smith et al. 1992), and ablation of Snail leads to the continued expression of E-cadherin transcripts in the mesoderm. It also causes defects in the generated mesoderm cell layer (Carver et al. 2001). FGF signaling has an important role during mouse gastrulation, and a deficiency in

FGFR1 prevents the expression of Snail, in turn disturbing the down-regulation of E-cadherin and EMT (Deng et al. 1994; Yamaguchi et al. 1994; Ciruna et al. 1997; Deng et al. 1997; Ciruna and Rossant 2001). So the down-regulation of E-cadherin does not seem to be controlled by the Wnt pathway in mouse gastrulation, but further data indicate a cross talk of Wnt and FGF signaling. In FGFR1-deficient epiblasts, the expression of the Wnt target Brachyury is negatively affected, but lowering E-cadherin levels rescues Brachyury expression in the primitive streak (Ciruna and Rossant 2001). Therefore, increased E-cadherin levels are thought to sequester β-catenin and negatively affect canonical Wnt signaling.

Wnt Signaling Induces Expression of Proteases that Decrease Cell–Cell Adhesion

EMT and metastasis depend on modifications of the extracellular matrix and cell–cell adhesion through the cleavage of E-cadherin. This is achieved by proteases, which are regulated by Wnt signaling. A direct canonical Wnt target is the metalloproteinase Matrilysin (MMP7; Crawford et al. 1999). Stromelysin-1 (MMP3) expression is regulated by Wnt5a in a β-catenin-independent manner, indicating that Stromelysin-1 expression is controlled by the noncanonical Wnt pathway (Prieve and Moon 2003). Both Stromelysin-1 and Matrilysin degrade components of the extracellular matrix and are up-regulated in colorectal cancers, and MMP7 has been shown to promote metastasis (reviewed by Wagenaar-Miller et al. 2004). Both proteases also cleave E-cadherin, which results in the shedding of the E-cadherin ectodomain and causes cells to become motile and invasive (Fig. 5) (Lochter et al. 1997; Noe et al. 2001).

The Wnt Target Gene Tiam1 and IQGAP1 Modulate Cell–Cell Adhesion

Wnt has additional effects on cell–cell adhesion through its regulation of target genes. Tiam1 (T-cell lymphoma invasion and metastasis 1) is a nucleotide exchange factor that selectively activates Rac1 (Michiels et al. 1995) and is required for cadherin-based cell adhesions and suppression of epithelial motility (Hordijk et al. 1997; Malliri et al. 2004). Tiam1 modulates the dynamics of cell–cell adhesion by regulating tight junction assembly via activation of the Par complex (reviewed by Mertens et al. 2006) and by stabilizing the β-catenin/E-cadherin complex (Fukata et al. 1999). Tiam1 is a Wnt target gene, as shown by the fact that its expression can be induced by Wnt1 and correlates with active Wnt signaling in human colon adenoma, adenomatous polyps of Min/+ mice, and in the crypts of the small intestine (Liu et al. 2005; Malliri et al. 2006; Minard et al. 2006). Min/+ mice deficient in Tiam1 develop a reduced number of intestinal tumors and an impaired formation of mammary tumors. The developing tumors are however more aggressive and invade the submucosa in larger fractions (Malliri et al. 2006). These data indicate that Wnt signaling interferes with Tiam1 activity, which regulates cell growth, cell migration, and adherens junction formation.

A further mechanism is seen in the case of IQGAP1 (IQ motif containing GTPase-activating protein 1), which is involved in cytoskeletal dynamics and other cellular functions (reviewed by Briggs and Sacks 2003; Brandt and Grosse 2007). IQGAP1 regulates the dynamics of E-cadherin-based adherens junctions (Izumi et al. 2004) and interferes with β-catenin–α-catenin complex formation by binding the amino terminus of β-catenin, leading to reduced E-cadherin-mediated cell adhesion (Kuroda et al. 1998). It has recently been shown that IQGAP1 is up-regulated in colorectal carcinomas and promotes the invasiveness of colon cancer cells (Hayashi et al. 2009). GTP-bound Rac1 inhibits the interaction between IQGAP1 and β-catenin and stabilizes cell–cell adhesion (Fukata et al. 1999). As IQGAP1 acts downstream of Rac1, one likely possibility is that Tiam1/Rac1 positively regulates cell adhesion by inhibiting IQGAP1. Therefore, it is plausible that Wnt signaling affects cell adhesion via Tiam1/Rac1, which balances the activity of IQGAP1. Alongside its

function in cell adhesion, IQGAP1 influences Wnt signaling, because in cells with stabilized β-catenin, IQGAP1 enhances the transcriptional coactivator function of β-catenin (Briggs et al. 2002). These results are an example of a cross-talk of canonical Wnt and Rac signaling including Tiam1 and IQGAP1 in the regulation of cell–cell adhesion.

General Remarks

The work described in this section shows several ways in which canonical Wnt signaling affects cadherin-mediated cell adhesion: (1) it down-regulates E-cadherin expression via the transcription factors Twist and Slug, (2) it up-regulates adhesion molecules that favor cell motility, such as N-cadherin and L1, and (3) it induces proteases and other EMT promoters. Wnt signaling can therefore induce a cadherin switch and weaken cell–cell adhesion (Fig. 5). Wnt/β-catenin signaling is up-regulated in many developmental processes and by mutations in the progression of tumors (reviewed by Clevers 2006; Grigoryan et al. 2008). Overall, cadherin loss and Wnt/β-catenin signaling can thus cooperate to promote EMT, invasion and metastasis.

Until recently there have been considerable gaps in our ability to link signals to the architectural and behavioral changes in cells which lead to EMT and metastases. But as this review shows, the Wnt pathway and the regulation of cell adhesion are strongly linked by a number of complementary mechanisms. This suggests a model that integrates a number of fundamental processes that underlie development and disease.

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