Journal of Cellular Biochemistry 102:820–828 (2007)

β-Catenin Signaling in Biological Control and Cancer

Nancy Gavert and Avri Ben-Ze'ev*

Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot 76100, Israel

Abstract A coordinated integration of cell–cell adhesion and the control of gene expression is essential for the development of multicellular, differentiated organisms. β-Catenin fulfils important regulatory functions in both cell–cell adhesion by linking cadherin adhesion receptors to the cytoskeleton, and also as a key element in the Wnt signaling pathway where it acts as cotranscriptional activator of target genes in the cell nucleus. Wnt signaling is involved in numerous aspects of embryonic development and in the control of tissue self-renewal in a variety of adult tissues. Hyperactivation of Wnt signaling, mostly by affecting β-catenin functions, is a hallmark of colon cancer and of many other human cancers. In this prospect, we discuss studies pointing to the molecular mechanisms that govern the integration between cell–cell adhesion and gene expression, as reflected in the switches between these two functions of β-catenin in colon cancer cells. J. Cell. Biochem. 102: 820–828, 2007.

Key words: β-catenin; cell adhesion; signal transduction; colon cancer

Cellular and tissue morphogenesis are determined, to a large extent, by the adhesive interactions of cells with their neighbors and with the extracellular environment. The coordination between changes in cell adhesion and the subsequent changes in the organization of the cytoskeleton and the regulation of gene expression are key elements in determining cell shape, cell proliferation, cell differentiation, and cell death. Unraveling the molecular basis of this coordination is central to our understanding of the principles underlying both normal cell behavior and the diseased cell state. In the past 10 years, a large number of studies pointed to the dual role played by β-catenin in cell adhesion, by its function in linking cadherin cell adhesion receptors to the cytoskeleton, and also in the regulation of gene transcription in normal cells in a variety of biological processes, including development and differentiation, the regulation of embryonic and adult stem cells, and also in the course of cancer development [for reviews see Conacci-Sorrell et al., 2002a; Logan and Nusse, 2004; Clevers, 2006; Polakis, 2007]. By studying the role of β-catenin in such diverse biological regulations, we could learn about the possible mechanisms that mediate the complex coordination between events that occur at the cell surface and the subsequent response in the regulation of gene expression in the cell nucleus.

A shift, by many researchers, toward studying β-catenin cell biology occurred with the discovery that in addition to its known role as a cytoplasmic plaque protein involved in linking cadherin family receptors to the actin cytoskeleton [Ozawa et al., 1989; McCrea et al., 1991; Peifer et al., 1992], β-catenin is also a cotranscriptional activator of genes in the nucleus together with lymphoid enhancer factor (LEF)/T-cell factor (TCF) [Behrens et al., 1996; Huber et al., 1996; Molenaar et al., 1996; van de Wetering et al., 1997], as a central component of the Wnt signaling pathway [Nusslein-Volhard and Wieschaus, 1980; Fig. 1]. Since β-catenin is an abundant protein expressed in every cell type, and is mostly localized at cell–cell adherens junctions fulfilling an essential role in cell adhesion, its additional function as coactivator of transcription and a key effector of the Wnt pathway, was initially considered a

Grant sponsor: Israel Science Foundation; Grant sponsor: The German-Israeli Foundation for Scientific Research and Development; Grant sponsor: The Yad Abraham Center for Cancer Diagnosis and Therapy; Grant sponsor: The Delores and Eugene M. Zemsky Weizmann-Johns Hopkins Research Program.

*Correspondence to: Avri Ben-Ze'ev, Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot 76100, Israel. E-mail: avri.ben-zeev@weizmann.ac.il

Received 27 June 2007; Accepted 28 June 2007

DOI 10.1002/jcb.21505

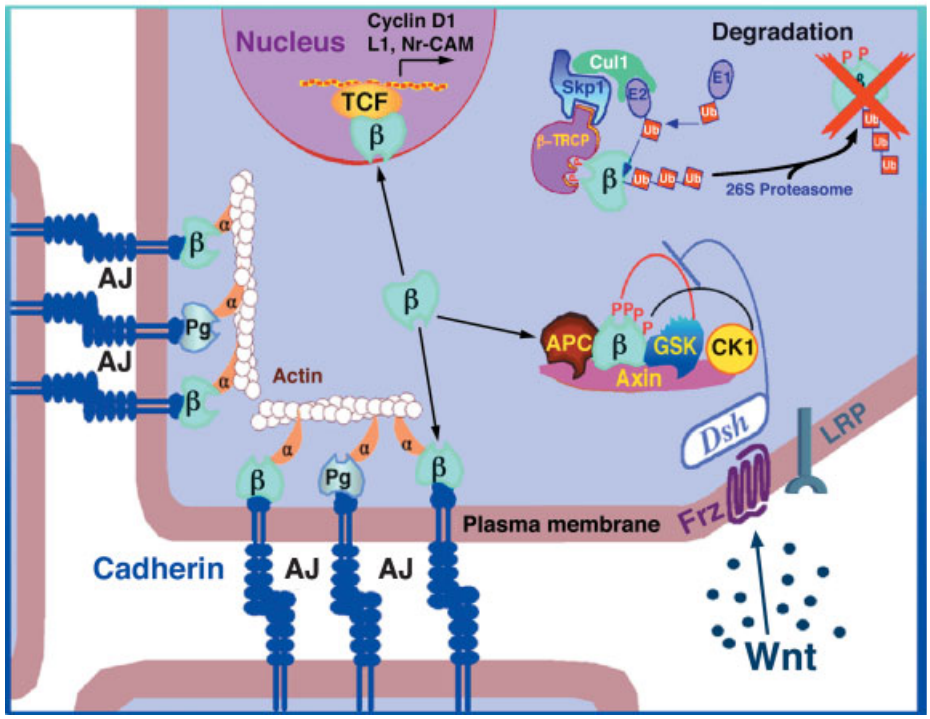

Fig. 1. The dual role of β-catenin in Wnt signaling and in cell–cell adhesion. β-catenin (β) and plakoglobin (Pg) bind to the cytoplasmic domain of cadherin transmembrane adhesion receptors and, via α-catenin (α), associate with the actin cytoskeleton to form adherens junctions (AJ). When the Wnt signaling pathway is inactive, the cytoplamsic pool of β-catenin is directed to degradation by a molecular complex including APC and Axin, and the kinases casein kinase 1 (CK1) and glycogen synthase kinase 3 (GSK), that phosphorylate β-catenin (PPPP) on N-terminal residues. Phosphorylated β-catenin is recognized by the E3 ubiquitin ligase component β-TrCP, which together with Skp1, Cul1, and the E1 and E2 ubiquitination complexes, mediates the ubiquitination of β-catenin (Ub) that directs β-catenin to degradation by the 26S proteasome. The binding of Wnt to Frizzled (Frz) and the coreceptor LRP activates Wnt signaling. This induces a disheveled (Dsh)-mediated inhibition of β-catenin phosphorylation by GSK thereby blocking β-catenin degradation, and its accumulation and complexing, in the nucleus, with T-cell factor (TCF). The β-catenin-TCF complex transactivates target genes such as *cyclin D1*, *L1-CAM* (L1), and *Nr-CAM* and many other genes [modified from Conacci-Sorrell et al., 2002a].

separate and unrelated function of β-catenin. The notion that these two seemingly different functions of β-catenin in the cell are in fact well coordinated is now a more widely accepted notion [Conacci-Sorrell et al., 2002a; Nelson and Nusse, 2004; Harris and Peifer, 2005; Brembeck et al., 2006]. In this prospect, we discuss studies pointing to the possible coordination between these different roles of β-catenin during invasive tumor development.

β-CATENIN SIGNALING IN COLON CANCER TISSUE

While the exact molecular mechanisms by which β-catenin is involved in various biological regulations are incompletely understood, these functions of β-catenin are most probably not controlled by regulating the transcriptional level of the *β-catenin* gene. Rather, a major regulatory mechanism of β-catenin consists of controlling the level of its cytoplasmic pool. In the cytoplasm, β-catenin binds to the adenomatous polyposis coli (APC) and axin proteins that is followed by the recruitment of two kinases, glycogen synthase kinase-3 (GSK) and casein kinase I, in a destruction complex that phosphorylates β-catenin on N-terminal serines and a threonine, leading to its targeting to polyubiquitination and degradation by the proteasome [Aberle et al., 1997; Fig. 1]. Mutations that cause aberrant interactions of β-catenin with the destruction complex, resulting in elevated cytoplasmic pools of β-catenin, are believed to play a key role in the development of a variety of tumors [Polakis, 2000, 2007]. Importantly, the key partners of β-catenin in the cell, including the cadherin receptor family, APC and TCF, all bind to overlapping sequences in the central repeat

domain of β-catenin (the Armadillo repeats) [Huber and Weis, 2001]. Competition between these various β-catenin partners for binding to this region could tilt the balance between the different roles played by β-catenin, thereby determining cell fate [Harris and Peifer, 2005]. Most notably, in the great majority of colon cancer patients, mutations in either the β-catenin binding site of APC [Kinzler and Vogelstein, 1996], or in the N-terminus of β-catenin that harbors the key phosphorylation sites that mark it for recognition by the ubiquitin-proteasome system (Fig. 1), lead to the accumulation of β-catenin in the cytoplasm and in the nucleus. More recent studies have shown that the tight regulation of Wnt/β-catenin signaling is essential for maintaining the balance between stem cells, proliferating cells and differentiated cells in normal intestinal tissue homeostasis [van de Wetering et al., 2002]. Disruption of this delicate balance in such a rapidly and constantly regenerating tissue is most probably responsible for development of colorectal cancer. In colon tumor cells, transactivation by the β-catenin-TCF/LEF complex of target genes is dramatically elevated [Korinek et al., 1997; Morin et al., 1997]. Identification of the aberrantly activated β-catenin-TCF/LEF target genes and understanding their contribution to cancer development is a very active area in cancer research.

COORDINATION BETWEEN CELL ADHESION AND β-CATENIN SIGNALING IN COLON CANCER CELLS

Since hyperactivation of β-catenin signaling, by mutations in APC or β-catenin, is considered one of the earliest events in the sequence of genetic changes that lead to colon cancer development [Kinzler and Vogelstein, 1996], one would expect to see an increase in the transcription of β-catenin-TCF target genes that contribute to uncontrolled cell proliferation characteristic to these early tumor stages. Identification of *c-myc* [He et al., 1998] and *cyclin D1* [Shtutman et al., 1999; Tetsu and McCormick, 1999] as targets of β-catenin-TCF signaling are in support of this notion. However, a dramatic elevation in the cytoplasmic and nuclear pools of β-catenin, at these initial stages of colon cancer development, is usually not observed in colon tumor tissue. Rather, the majority of well-differentiated areas of the tumor tissue only display membranal β-catenin, similar to its distribution in the normal colon epithelium [Brabletz et al., 1998]. β-catenin could only be detected in the nuclei of small clusters of invasive cancer cells that have already invaded the surrounding stroma. Such cells also often display a much-reduced level of the E-cadherin transmembrane adhesion receptor [Brabletz et al., 2001], and induce the expression of the mesenchymal marker fibronectin [Kirchner and Brabletz, 2000]. This behavior of tumor cells is considered similar to what is defined as an epithelial to mesenchymal transition (EMT), a property that cells display during embryonic development, when tightly adherent epithelial cells transform into single and motile mesenchymal cells, after dismantling their intercellular adhesive structures [Savagner, 2001; Thiery and Sleeman, 2006]. A challenge to our understanding of this process in colon cancer cells is further presented by the fact that in distant metastases, that develop from the primary tumor in patients (which often takes many years to occur), these two different morphological characteristics are again displayed [Brabletz et al., 2001]. This suggests that a reciprocal transition from mesenchymal to an epithelial phenotype (MET) also occurs in tumors. While during the very long time period required for the formation of such distal metastases numerous changes in gene expression obviously occur (including alterations in the expression of tumor suppressors and oncogenes), by studying the mechanisms that govern such plasticity in the colon cancer cell phenotype, it should be possible in the future to interfere with EMT and confer a more differentiated, non-invasive behavior by forcing tumor cells into MET.

To address the molecular mechanisms involved in this phenotypic plasticity of colon cancer cells, a model cell culture system was employed in which human colon cancer cells were grown either as sparse, or dense cultures. Sparse cell cultures displayed many of the characteristics of colon cancer cells at the invasive front of tumor tissue: they showed extensive nuclear accumulation of β-catenin and high levels of β-catenin-TCF signaling activity, but very low levels of E-cadherin expression [Conacci-Sorrell et al., 2003]. In contrast, dense cultures of such cells had mostly submembranal localization of β-catenin together with elevated E-cadherin in adherens junctions,

and showed very little nuclear β-catenin and much reduced β-catenin-TCF signaling (Fig. 2). This apparent link between E-cadherin organization and expression and β-catenin localization and signaling was further supported by experiments demonstrating that Slug, a major transcription factor regulating EMT by suppressing the promoter of the *E-cadherin* gene [Nieto, 2002], is also a target gene of β-catenin-TCF signaling [Conacci-Sorrell et al., 2003]. Slug expression is high in sparse cultures, but Slug is absent from dense cultures of colon cancer cells (Fig. 2). The switch between the sparse, more motile phenotype displaying high levels of nuclear β-catenin-TCF signaling and target gene expression, and low E-cadherin expression, to a more differentiated phenotype consisting of E-cadherin and β-catenin in adherens junctions, is suggested to involve an autoregulatory loop. When E-cadherin-mediated cell–cell contact formation is favored (when cell cultures become more dense), the initial low amount of cell surface localized E-cadherin is engaging in cell–cell contact adherens junction construction that results in a reduction in the nuclear β-catenin pool and consequently, also in β-catenin-TCF signaling. This leads to reduced transcription of *Slug* and Slug protein levels, a relief from transcriptional suppression of the *E-cadherin* gene, and further engaging of more E-cadherin in adherens junction formation and recruitment of β-catenin into cell–cell junctions. The end result of this autoregulatory loop in dense cultures of colon cancer cells is the acquisition of a more differentiated phenotype consisting of high E-cadherin levels and β-catenin in adherens junctions, and very low levels of nuclear β-catenin signaling (Fig. 2). Consistent with this view, disruption of adherens junctions in dense cultures of colon cancer cells by an antibody to the ectodomain of E-cadherin resulted in the release and nuclear localization of β-catenin, enhanced transactivation of β-catenin target genes, including Slug, followed by reduced E-cadherin levels [Conacci-Sorrell et al., 2003]. This, and similar cell model systems that partially mimic the EMT-like process at the invasive front of tumors, could be helpful in dissecting the molecular mechanisms that govern such regulatory loops, thereby providing means to interfere with their occurrence.

RECEPTOR TYROSINE KINASES AND β-CATENIN SIGNALING IN CANCER

The early activation of β-catenin signaling in the course of colon cancer development is often followed by activation of oncogenic mutations in *Ras* [Kinzler and Vogelstein, 1996; Zhang et al.,

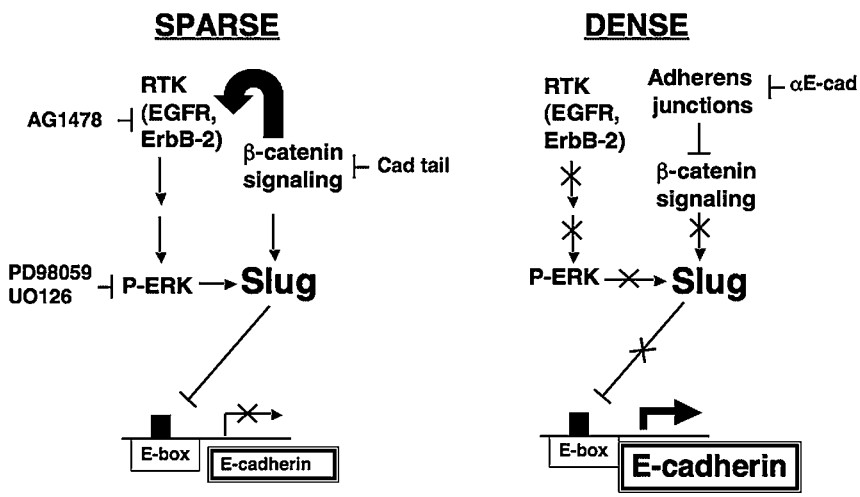

Fig. 2. Mechanisms of E-cadherin autoregulation in sparse and dense cultures of colon cancer cells. In sparse cultures, E-cadherin expression is suppressed by two different mechanisms: One involves activation of ERK (P-ERK) by tyrosine kinase receptors (RTK), such as ErbB-1 and ErbB-2. ERK activation induces *Slug* that inhibits E-cadherin expression by binding to the E-box of the *E-cadherin* gene promoter. Another pathway includes *Slug* gene induction by the β-catenin-TCF pathway. In addition, the β-catenin-TCF complex can also activate the *EGFR* gene promoter, thus further contributing to Slug induction. In dense cultures, the ERK pathway is inactive; the levels of ErbB-1, ErbB-2, and Slug are repressed, and E-cadherin expression increases. This leads to recruitment of nuclear β-catenin to adherens junctions, together with E-cadherin, and a reduction in β-catenin signaling thus inhibiting Slug expression. This relieves the inhibition on *E-cadherin* transcription resulting in elevated E-cadherin expression [modified from Conacci-Sorrell et al., 2003].

2003]. Activated Ras is responsible for inducing tyrosine phosphorylation of β-catenin that usually results in the release of β-catenin from its association with E-cadherin in adherens junctions. A variety of activated growth factor receptors were shown to mediate tyrosine phosphorylation of β-catenin in colon cancer and other tumor cells, including the EGF receptor [Roura et al., 1999], oncogenic RON, the hepatocyte growth factor receptor cMET [Wielenga et al., 2000; Danilkovitch-Miagkova et al., 2001], and the IGF type II receptor [Morali et al., 2001]. Such tyrosine phosphorylation brings about an increase in the cytoplasmic pool of β-catenin, often leading to enhanced β-catenin/TCF signaling in the nucleus. Moreover, among the β-catenin-TCF target genes activated in cancer cells, there are genes coding for growth factor receptors such as cMET [Boon et al., 2002] and the EGF receptor [Tan et al., 2005] that can further reinforce an autoregulatory loop to confer a more motile and invasive phenotype (Fig. 2).

The tyrosine kinase growth factor receptors FGFR and EGFR also promote the acquisition of a motile phenotype by inducing the expression of Slug/Snail family members of transcription factors [Ciruna and Rossant, 2001; Conacci-Sorrell et al., 2003] that repress the transcription of the *E-cadherin* gene [Batlle et al., 2000; Cano et al., 2000]. In the cell culture model of colon cancer cells (Fig. 2), sparse cultures displaying high levels of Slug and reduced E-cadherin also showed high levels of ErbB1 and ErbB2, unlike dense cultures where both Slug and ErbB receptor levels were reduced [Conacci-Sorrell et al., 2003]. β-catenin-TCF signaling that induces the transcription of both the *EGFR* and *Slug* genes in sparse cultures can therefore act cooperatively to confer the motile/invasive phenotype characteristic of carcinoma cells that invade the stroma.

Recent studies unraveled some of the molecular mechanisms that control the interactions of β-catenin with its various partners (mostly by affecting protein–protein interactions), thereby affecting cell fate. One study suggests that the cytoplasmic pool of β-catenin has preferential binding capacity with TCF in cells treated with Wnt factors. This specificity is apparently regulated by a conformational change in β-catenin that is localized in the cytoplasmic pool and involves an interaction of the C-terminus of the β-catenin molecule with its central repeat domain. This reduces its binding to cadherin receptors while allowing the selective binding of β-catenin to TCF [Gottardi and Gumbiner, 2004]. What controls such special interaction of the C-terminus with the central repeat domain of β-catenin [Cox et al., 1999; Zhurinsky et al., 2000; Piedra et al., 2001], which allows blocking of the cadherin-binding domain, remains to be determined. Another relevant aspect of this regulation is the preferential formation of a complex between β-catenin and cadherin, when β-catenin is already associated with α-catenin in a heterodimer, while the β-catenin monomer has a higher affinity to TCF binding [Gottardi and Gumbiner, 2004]. The mechanisms by which such specific associations are established and what regulates their specificity await further investigations.

Tyrosine phosphorylation of β-catenin as a mechanism controlling the release of β-catenin from adherens junctions has been suggested by numerous early studies [Behrens et al., 1993; Roura et al., 1999], but the underlying mechanisms are largely unknown. In a recent study aimed to identify novel partners of tyrosine phosphorylated β-catenin, by a yeast two hybrid screening, BCL9-2 was identified as a preferred binding partner of β-catenin when it is phosphorylated on tyrosine 142 (Y142) [Brembeck et al., 2004]. This tyrosine residue appears to be very important for the binding of α-catenin to β-catenin [Aberle et al., 1996], while Y142 phosphorylation weakens the interaction of β-catenin with the adherens junction complex and apparently, also with the destruction complex [Danilkovitch-Miagkova et al., 2001; Piedra et al., 2003; Rasola et al., 2007]. The studies by Brembeck et al. [2004] confirmed that BCL9-2 overexpression enhances tyrosine phosphorylation of β-catenin on Y142, causes the release of β-catenin from cell–cell junctions and enhances its nuclear transcriptional activity. Moreover, activation of the tyrosine kinase receptor MET, together with BCL9-2 overexpression, brings about the shift in β-catenin localization from its function in adherens junctions to the nucleus, where it acts together with LEF/TCF in transactivation. The importance of BCL9-2 in the aberrant activation of β-catenin-TCF signaling in colon cancer cells is suggested by the findings that BCL9-2 is overexpressed in human colon cancer cells and also in human colon cancer tissue [Adachi et al., 2004]. Suppression of

BCL9-2 levels resulted in relocalization of β-catenin to adherens junctions and a reversion of the more mesenchymal phenotype to an epithelial morphology. In contrast, overexpression of BCL9-2 in normal epithelial cells caused scattering and an EMT-like behavior in MDCK cells [Brembeck et al., 2004]. These studies demonstrate the therapeutic potential of regulating β-catenin by unraveling the molecular basis of the decisions leading to the shifts between β-catenin's different functions.

β-CATENIN SIGNALING AT THE INVASIVE FRONT OF TUMORS

As mentioned above, aberrant β-catenin signaling is considered a very early step in colon cancer development, but significant nuclear accumulation of β-catenin is only observed in colon cancer cells that already invaded into the stroma, which is a more advanced stage in cancer progression. This raised the question of whether β-catenin-TCF signaling is also involved in transactivation of target genes that contribute to latter stages of tumorigenesis. β-catenin-TCF target genes characteristic of these stages, promoting tumor cell motility and invasion, have been identified and include metalloproteases [Brabletz et al., 1999; Crawford et al., 1999; Takahashi et al., 2002], ECM components [Gradl et al., 1999; Hlubek et al., 2001, 2004], and cell adhesion receptors such as CD44 [Wielenga et al., 1999] and uPAR [Mann et al., 1999]. Recently, members of the immunoglobulin-like cell adhesion receptors of the L1-CAM family (Nr-CAM and L1-CAM) were also identified as target genes of β-catenin-TCF signaling [Conacci-Sorrell et al., 2002b; Gavert et al., 2005]. The expression of these proteins (previously detected only in nerve cells) in cultured fibroblasts, or in colon cancer cells, induced cell motility and enhanced tumorigenesis. Moreover, L1-CAM was detected exclusively at the invasive front of colon cancer tissue, in a subpopulation of invasive cells also displaying extensive nuclear β-catenin staining [Gavert et al., 2005]. ADAM10, a metalloprotease that cleaves the ectodomain of L1-CAM [Mechtersheimer et al., 2001], and of other cell adhesion receptors, including E-cadherin [Maretzky et al., 2005], was also identified recently as a β-catenin-TCF target gene [Gavert et al., 2007]. In colon cancer tissue ADAM10 is colocalized at the invasive front of the cancer tissue together with L1-CAM [Gavert et al., 2005]. Furthermore, forced expression of L1-CAM in colon cancer cells conferred metastasis to the liver, in a mouse model for liver metastasis, and ADAM10 overexpression enhanced this metastatic capacity induced by L1-CAM [Gavert et al., 2007]. This implies that ectodomain shedding of these cell adhesion receptors may play an important role in colon cancer cell invasion [Conacci-Sorrell et al., 2005]. Interestingly, the expression of several β-catenin-TCF target genes that can promote tumor cell motility and invasion is only detected in the invasive areas of the primary tumor, but not in distal metastases that develop several years later. These genes include, in addition to L1-CAM, also the recently discovered β-catenin-TCF target gene *fascin*, that induces filopodia formation [Vignjevic et al., 2007], and the EphB/EphrinB cell sorting receptors and their ligands [Batlle et al., 2005]. Expression of these β-catenin-TCF target genes is clearly absent from distal metastases of colon cancer cells, while they are abundantly expressed in the primary tumor. It remains to be determined how their expression is preferentially silenced in colon cancer cells displaying extensive nuclear β-catenin localization and signaling.

SUMMARY AND CONCLUSIONS

β-Catenin-mediated regulation of various embryonic developmental stages, EMT, embryonal and adult stem cell biology, and the formation of malignant tumors, is executed, in most cases, through the dual function of β-catenin in cell adhesion and transcriptional activation of target genes. In recent years, this close link between the role of β-catenin in cadherin-mediated adhesion and its function in gene transcription is gaining increasing appreciation and recognition. The β-catenin network of protein interactions remains a highly regulated and complex network at the center of key decision points, by its capacity to integrate signals from the extracellular environment, by regulating the adhesive interactions of cells, with programs of gene regulation via its capacity to regulate target gene transcription. How these programs that control cell and tissue specific biological processes (involving β-catenin-TCF target gene regulation) are executed, remains to be determined.

The dissection of such gene programs using gene array technologies in cells and tissues will undoubtedly shed more light on the molecular details governing these processes, and the causes for their disruption in the diseased state. Insights into the molecular details will also provide the basis for developing therapies, via small molecules and other means, especially against malignant cancer development.

REFERENCES

Aberle H, Schwartz H, Hoschuetzky H, Kemler R. 1996. Single amino acid substitutions in proteins of the armadillo gene family abolish their binding to alpha-catenin. J Biol Chem 271:1520–1526.

Aberle H, Bauer A, Stappert J, Kispert A, Kemler R. 1997. Beta-catenin is a target for the ubiquitin-proteasome pathway. EMBO J 16:3797–3804.

Adachi S, Jigami T, Yasui T, Nakano T, Ohwada S, Omori Y, Sugano S, Ohkawara B, Shibuya H, Nakamura T, Akiyama T. 2004. Role of a BCL9-related beta-catenin-binding protein, B9L, in tumorigenesis induced by aberrant activation of Wnt signaling. Cancer Res 64: 8496–8501.

Batlle E, Sancho E, Franci C, Dominguez D, Monfar M, Baulida J, Garcia De Herreros A. 2000. The transcription factor snail is a repressor of E-cadherin gene expression in epithelial tumour cells. Nat Cell Biol 2:84–89.

Batlle E, Bacani J, Begthel H, Jonkheer S, Gregorieff A, van de Born M, Malats N, Sancho E, Boon E, Pawson T, Gallinger S, Pals S, Clevers H. 2005. EphB receptor activity suppresses colorectal cancer progression. Nature 435:1126–1130.

Behrens J, Vakaet L, Friis R, Winterhager E, Van Roy F, Mareel MM, Birchmeier W. 1993. Loss of epithelial differentiation and gain of invasiveness correlates with tyrosine phosphorylation of the E-cadherin/beta-catenin complex in cells transformed with a temperature-sensitive v-SRC gene. J Cell Biol 120:757–766.

Behrens J, von Kries JP, Kuhl M, Bruhn L, Wedlich D, Grosschedl R, Birchmeier W. 1996. Functional interaction of beta-catenin with the transcription factor LEF-1. Nature 382:638–642.

Boon EM, van der Neut R, van de Wetering M, Clevers H, Pals ST. 2002. Wnt signaling regulates expression of the receptor tyrosine kinase met in colorectal cancer. Cancer Res 62:5126–5128.

Brabletz T, Jung A, Hermann K, Gunther K, Hohenberger W, Kirchner T. 1998. Nuclear overexpression of the oncoprotein beta-catenin in colorectal cancer is localized predominantly at the invasion front. Pathol Res Pract 194:701–704.

Brabletz T, Jung A, Dag S, Hlubek F, Kirchner T. 1999. Beta-catenin regulates the expression of the matrix metalloproteinase-7 in human colorectal cancer. Am J Path 155:1033–1038.

Brabletz T, Jung A, Reu S, Porzner M, Hlubek F, Kunz-Schughart LA, Knuechel R, Kirchner T. 2001. Variable beta-catenin expression in colorectal cancers indicates tumor progression driven by the tumor environment. Proc Natl Acad Sci USA 98:10356–103561.

Brembeck FH, Schwarz-Romond T, Bakkers J, Wilhelm S, Hammerschmidt M, Birchmeier W. 2004. Essential role of BCL 9-2in the switch between beta-catenin's adhesive and transcriptional functions. Genes Dev 18:2225–2230.

Brembeck FH, Rosario M, Birchmeier W. 2006. Balancing cell adhesion and Wnt signaling, the key role of beta-catenin. Curr Opin Genet Dev 16:51–59.

Cano A, Perez-Moreno MA, Rodrigo I, Locascio A, Blanco MJ, del Barrio MG, Portillo F, Nieto MA. 2000. The transcription factor snail controls epithelial-mesenchymal transitions by repressing E-cadherin expression. Nat Cell Biol 2:76–83.

Ciruna B, Rossant J. 2001. FGF signaling regulates mesoderm cell fate specification and morphogenetic movement at the primitive streak. Dev Cell 1:37–49.

Clevers H. 2006. Wnt/beta-catenin signaling in development and disease. Cell 127:469–480.

Conacci-Sorrell M, Zhurinsky J, Ben-Ze'ev A. 2002a. The cadherin-catenin adhesion system in signaling and cancer. J Clin Invest 109:987–991.

Conacci-Sorrell ME, Ben-Yedidia T, Shtutman M, Feinstein E, Einat P, Ben-Ze'ev A. 2002b. Nr-CAM is a target gene of the beta-catenin/LEF-1 pathway in melanoma and colon cancer and its expression enhances motility and confers tumorigenesis. Genes Dev 16:2058–2072.

Conacci-Sorrell M, Simcha I, Ben-Yedidia T, Blechman J, Savagner P, Ben-Ze'ev A. 2003. Autoregulation of E-cadherin expression by cadherin-cadherin interactions: The roles of beta-catenin signaling, Slug, and MAPK. J Cell Biol 163:847–857.

Conacci-Sorrell M, Kaplan A, Raveh S, Gavert N, Sakurai T, Ben-Ze'ev A. 2005. The shed ectodomain of Nr-CAM stimulates cell proliferation and motility, and confers cell transformation. Cancer Res 65:11605–11612.

Cox RT, Pai LM, Kirkpatrick C, Stein J, Peifer M. 1999. Roles of the C terminus of Armadillo in Wingless signaling in Drosophila. Genetics 153:319–332.

Crawford HC, Fingleton BM, Rudolph-Owen LA, Goss KJ, Rubinfeld B, Polakis P, Matrisian LM. 1999. The metalloproteinase matrilysin is a target of beta-catenin transactivation in intestinal tumors. Oncogene 18:2883–2891.

Danilkovitch-Miagkova A, Miagkov A, Skeel A, Nakaigawa N, Zbar B, Leonard EJ. 2001. Oncogenic mutants of RON and MET receptor tyrosine kinases cause activation of the beta-catenin pathway. Mol Cell Biol 21:5857–5868.

Gavert N, Conacci-Sorrell M, Gast D, Schneider A, Altevogt P, Brabletz T, Ben-Ze'ev A. 2005. L1, a novel target of beta-catenin signaling, transforms cells and is expressed at the invasive front of colon cancers. J Cell Biol 168:633–642.

Gavert N, Sheffer M, Raveh S, Spaderna S, Shtutman M, Brabletz T, Barany F, Paty P, Notterman D, Domany E, Ben-Ze'ev A. 2007. Expression of L1-CAM and ADAM10 in human colon cancer cells induces metastasis. Cancer Res (in press).

Gottardi CJ, Gumbiner BM. 2004. Distinct molecular forms of beta-catenin are targeted to adhesive or transcriptional complexes. J Cell Biol 167:339–349.

Gradl D, Kuhl M, Wedlich D. 1999. The Wnt/Wg signal transducer beta-catenin controls fibronectin expression. Mol Cell Biol 19:5576–5587.

Harris TJ, Peifer M. 2005. Decisions, decisions: Beta-catenin chooses between adhesion and transcription. Trends Cell Biol 15:234–237.

He TC, Sparks AB, Rago C, Hermeking H, Zawel L, da Costa LT, Morin PJ, Vogelstein B, Kinzler KW. 1998. Identification of c-MYC as a target of the APC pathway. Science 281:1509–1512.

Hlubek F, Jung A, Kotzor N, Kirchner T, Brabletz T. 2001. Expression of the invasion factor laminin gamma2 in colorectal carcinomas is regulated by beta-catenin. Cancer Res 61:8089–8093.

Hlubek F, Spaderna S, Jung A, Kirchner T, Brabletz T. 2004. Beta-catenin activates a coordinated expression of the proinvasive factors laminin-5 gamma2 chain and MT1-MMP in colorectal carcinomas. Int J Cancer 108: 321–326.

Huber AH, Weis WI. 2001. The structure of the beta-catenin/E-cadherin complex and the molecular basis of diverse ligand recognition by beta-catenin. Cell 105:391–402.

Huber O, Korn R, McLaughlin J, Ohsugi M, Herrmann BG, Kemler R. 1996. Nuclear localization of beta-catenin by interaction with transcription factor LEF-1. Mech Dev 59:3–10.

Kinzler KW, Vogelstein B. 1996. Lessons from hereditary colorectal cancer. Cell 87:159–170.

Kirchner T, Brabletz T. 2000. Patterning and nuclear beta-catenin expression in the colonic adenoma-carcinoma sequence. Analogies with embryonic gastrulation. Am J Pathol 157:1113–1121.

Korinek V, Barker N, Morin PJ, van Wichen D, de Weger R, Kinzler KW, Vogelstein B, Clevers H. 1997. Constitutive transcriptional activation by a beta-catenin-Tcf complex in APC−/− colon carcinoma. Science 275:1784–1787.

Logan CY, Nusse R. 2004. The Wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol 20: 781–810.

Mann B, Gelos M, Siedow A, Hanski ML, Gratchev A, Ilyas M, Bodmer WF, Moyer MP, Riecken EO, Buhr HJ, Hanski C. 1999. Target genes of beta-catenin-T cell-factor/lymphoid-enhancer-factor signaling in human colorectal carcinomas. Proc Natl Acad Sci USA 96:1603–1608.

Maretzky T, Reiss K, Ludwig A, Buchholz J, Scholz F, Proksch E, de Strooper B, Hartmann D, Saftig P. 2005. ADAM10 mediates E-cadherin shedding and regulates epithelial cell-cell adhesion, migration, and beta-catenin translocation. Proc Natl Acad Sci USA 102: 9182–9187.

McCrea PD, Turck CW, Gumbiner B. 1991. A homolog of the armadillo protein in Drosophila (plakoglobin) associated with E-cadherin. Science 254:1359–1361.

Mechtersheimer S, Gutwein P, Agmon-Levin N, Stoeck A, Oleszewski M, Riedle S, Postina R, Fahrenholz F, Fogel M, Lemmon V, Altevogt P. 2001. Ectodomain shedding of L1 adhesion molecule promotes cell migration by autocrine binding to integrins. J Cell Biol 155: 661–673.

Molenaar M, van de Wetering M, Oosterwegel M, Peterson-Maduro J, Godsave S, Korinek V, Roose J, Destree O, Clevers H. 1996. XTcf-3 transcription factor mediates beta-catenin-induced axis formation in Xenopus embryos. Cell 86:391–399.

Morali OG, Delmas V, Moore R, Jeanney C, Thiery JP, Larue L. 2001. IGF-II induces rapid beta-catenin relocation to the nucleus during epithelium to mesenchyme transition. Oncogene 20:4942–4950.

Morin PJ, Sparks AB, Korinek V, Barker N, Clevers H, Vogelstein B, Kinzler KW. 1997. Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC. Science 275:1787–1790.

Nelson WJ, Nusse R. 2004. Convergence of Wnt, beta-catenin, and cadherin pathways. Science 303:1483–1487.

Nieto MA. 2002. The snail superfamily of zinc-finger transcription factors. Nat Rev Mol Cell Biol 3:155–166.

Nusslein-Volhard C, Wieschaus E. 1980. Mutations affecting segment number and polarity in Drosophila. Nature 287:795–801.

Ozawa M, Baribault H, Kemler R. 1989. The cytoplasmic domain of the cell adhesion molecule uvomorulin associates with three independent proteins structurally related in different species. EMBO J 6:1711–1717.

Peifer M, McCrea PD, Green KJ, Wieschaus E, Gumbiner BM. 1992. The vertebrate adhesive junction proteins beta-catenin and plakoglobin and the Drosophila segment polarity gene armadillo form a multigene family with similar properties. J Cell Biol 118:681–691.

Piedra J, Martinez D, Castano J, Miravet S, Dunach M, de Herreros AG. 2001. Regulation of beta-catenin structure and activity by tyrosine phosphorylation. J Biol Chem 276:20436–20443.

Piedra J, Miravet S, Castano J, Palmer HG, Heisterkamp N, Garcia de Herreros A, Dunach M. 2003. p120 Catenin-associated Fer and Fyn tyrosine kinases regulate beta-catenin Tyr-142 phosphorylation and beta-catenin-alpha-catenin interaction. Mol Cell Biol 23:2287–2297.

Polakis P. 2000. Wnt signaling and cancer. Genes Dev 14:1837–1851.

Polakis P. 2007. The many ways of Wnt in cancer. Curr Opin Genet Dev 17:45–51.

Rasola A, Fassetta M, De Bacco F, D'Alessandro L, Gramaglia D, Di Renzo MF, Comoglio PM. 2007. A positive feedback loop between hepatocyte growth factor receptor and beta-catenin sustains colorectal cancer cell invasive growth. Oncogene 26:1078–1087.

Roura S, Miravet S, Piedra J, Garcia de Herreros A, Dunach M. 1999. Regulation of E-cadherin/Catenin association by tyrosine phosphorylation. J Biol Chem 274:36734–36740.

Savagner P. 2001. Leaving the neighborhood: Molecular mechanisms involved during epithelial-mesenchymal transition. Bioessays 23:912–923.

Shtutman M, Zhurinsky J, Simcha I, Albanese C, D'Amico M, Pestell R, Ben-Ze'ev A. 1999. The cyclin D1 gene is a target of the beta-catenin/LEF-1 pathway. Proc Natl Acad Sci USA 96:5522–5527.

Takahashi M, Tsunoda T, Seiki M, Nakamura Y, Furukawa Y. 2002. Identification of membrane-type matrix metalloproteinase-1 as a target of the beta-catenin/Tcf4 complex in human colorectal cancers. Oncogene 21:5861–5867.

Tan X, Apte U, Micsenyi A, Kotsagrelos E, Luo JH, Ranganathan S, Monga DK, Bell A, Michalopoulos GK, Monga SP. 2005. Epidermal growth factor receptor: A novel target of the Wnt/beta-catenin pathway in liver. Gastroenterology 129:285–302.

Tetsu O, McCormick F. 1999. Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells. Nature 398:422–426.

Thiery JP, Sleeman JP. 2006. Complex networks orchestrate epithelial-mesenchymal transitions. Nat Rev Mol Cell Biol 2:131–142.

van de Wetering M, Cavallo R, Dooijes D, van Beest M, van Es J, Loureiro J, Ypma A, Hursh D, Jones T, Bejsovec A, Peifer M, Mortin M, Clevers H. 1997. Armadillo coactivates transcription driven by the product of the Drosophila segment polarity gene dTCF. Cell 88:789–799.

van de Wetering M, Sancho E, Verweij C, de Lau W, Oving I, Hurlstone A, van der Horn K, Batlle E, Coudreuse D, Haramis AP, Tjon-Pon-Fong M, Moerer P, van den Born M, Soete G, Pals S, Eilers M, Medema R, Clevers H. 2002. The beta-catenin/TCF-4 complex imposes a crypt progenitor phenotype on colorectal cancer cells. Cell 111: 241–250.

Vignjevic D, Schoumacher M, Gavert N, Janssen K-P, Jih G, Lae M, Louvard D, Ben-Ze'ev A, Robine S. 2007. Fascin, a novel target of beta-catenin-Tcf signaling, is expressed at the invasive front of human colon cancer. Cancer Res 67:6844–6850.

Wielenga VJ, Smits R, Korinek V, Smit L, Kielman M, Fodde R, Clevers H, Pals ST. 1999. Expression of CD44 in Apc and Tcf mutant mice implies regulation by the WNT pathway. Am J Pathol 154:515–523.

Wielenga VJ, van der Voort R, Taher TE, Smit L, Beuling EA, van Krimpen C, Spaargaren M, Pals ST. 2000. Expression of c-Met and heparan-sulfate proteoglycan forms of CD44 in colorectal cancer. Am J Pathol 157: 1563–1573.

Zhang B, Ougolkov A, Yamashita K, Takahashi Y, Mai M, Minamoto T. 2003. Beta-Catenin and ras oncogenes detect most human colorectal cancers. Clin Cancer Res 9:3073–3079.

Zhurinsky J, Shtutman M, Ben-Ze'ev A. 2000. Plakoglobin and beta-catenin: Protein interactions, regulation and biological roles. J Cell Sci 113:3127–3139.