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COMMENTARY

Plakoglobin and β-catenin: protein interactions, regulation and biological roles

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SUMMARY

β-Catenin can play different roles in the cell, including one as a structural protein at cell-cell adherens junctions and another as a transcriptional activator mediating Wnt signal transduction. Plakoglobin (γ-catenin), a close homolog of β-catenin, shares with β-catenin common protein partners and can fulfill some of the same functions. The complexing of catenins with various protein partners is regulated by phosphorylation and by intramolecular interactions. The competition between different catenin partners for binding to catenins mediates the cross-talk between cadherin-based adhesion, catenin-dependent transcription and Wnt signaling. Although plakoglobin differs from β-catenin in its functions and is unable to compensate for defects in Wnt signaling resulting from lack of β-catenin, recent evidence suggests that plakoglobin plays a unique role in Wnt signaling that is different from that of β-catenin. The functional difference between catenins is reflected in their differential involvement in embryonic development and cancer progression.

Key words: β-Catenin, Plakoglobin, Transactivation, Cell adhesion, Signal transduction

INTRODUCTION

A major lesson we have learned from gene knockout studies in mice is that the functions of many proteins significantly overlap, which enables the organism to carry out many physiological processes when a key component in a biological pathway is genetically eliminated. More recent studies have reported an increasing number of examples representing 'the other side of the coin', namely the multifunctionality characteristic of certain proteins that enables cells to coordinate the regulation of what sometimes appear to be unrelated biochemical processes. In these cases, the same protein participates in several different processes, which often are carried out at different locations in the cell and form an interdependent network of cellular events.

β-Catenin provides an intriguing example of such multifunctionality: it combines the features of a major structural protein at cell-cell junctions with those of a transcription factor (Barth et al., 1997; Behrens, 1999; Ben-Ze'ev and Geiger, 1998; Bullions and Levine, 1998; Seidensticker and Behrens, 2000). Whereas the great majority of β-catenin is engaged in a structural role at adherens junctions, linking adhesion receptors of the cadherin family to the actin cytoskeleton (Adams and Nelson, 1998; Yap et al., 1997), the non-junctional β-catenin is rapidly degraded by the ubiquitin-proteasome system (Fig. 1A). Stabilization of cytoplasmic β-catenin by Wnt signaling leads to its nuclear accumulation, complexing with LEF/TCF transcription factors and transactivation of LEF/TCF target genes (Eastman and Grosschedl, 1999; Nusse, 1999; Roose and Clevers, 1999). This nuclear signaling by β-catenin is involved in the regulation of cell fate during embryonic development (Wodarz and Nusse, 1998), and the aberrant activation of β-catenin-mediated transactivation might contribute to cancer progression by causing increased cell proliferation (Ben-Ze'ev, 1997; Ben-Ze'ev and Geiger, 1998; Morin, 1999; Polakis, 1999).

Plakoglobin (Cowin et al., 1986), also known as γ-catenin (Ozawa et al., 1989), another vertebrate catenin, is highly homologous to β-catenin (Butz et al., 1992; McCrea et al., 1991). Functions of plakoglobin in cell adhesion that are similar to (in adherens junctions) and different from (in desmosomes) those of β-catenin are well established (Cowin and Burke, 1996; Schmidt et al., 1994) (Fig. 1B). In contrast, the participation of plakoglobin in Wnt signaling is still under debate (Karnovsky and Klymkowsky, 1995; Kofron et al., 1997; Miller and Moon, 1997; Simcha et al., 1998). Recent studies, however, indicate that plakoglobin may play a unique role in the Wnt signaling pathway, one that is different from that of β-catenin (Charpentier et al., 2000; Simcha et al., 1996; Zhurinsky et al., 2000).

Here, we compare interactions that these two vertebrate catenins engage in and discuss recent advances in our understanding of the mechanisms regulating these interactions.

We also discuss the functional differences between plakoglobin and β-catenin in development and tumorigenesis.

CATENIN DEGRADATION AND THE WNT PATHWAY

Although β-catenin mediates cell-cell adhesion in most cell types and tissues, the transcriptional function of β-catenin is constitutively suppressed by the ubiquitin-proteasome-dependent degradation of non-junctional β-catenin (Aberle et al., 1997; Orford et al., 1997; Salomon et al., 1997; Fig. 1A). The targeting of β-catenin to the proteasome is achieved through its phosphorylation by a multiprotein complex consisting of the serine/threonine kinase glycogen synthase kinase 3β (GSK) and the scaffolding proteins adenomatous polyposis coli (APC) and axin (reviewed by Kikuchi, 2000). The phosphoserine motif in the N terminus of β-catenin (Yost et al., 1996) and plakoglobin (Sadot et al., 2000) is recognized by the ubiquitin ligase β-TrCP, which catalyzes the attachment of ubiquitin peptides to the catenin molecules (Hart et al., 1999; Kitagawa et al., 1999; Liu et al., 1999; Sadot et al., 2000; Winston et al., 1999; Fig. 1A).

The ability of this multiprotein complex to trigger β-catenin degradation is regulated by Wnt signaling. The binding of Wnt to its receptor, frizzled, activates the scaffolding protein dishevelled (Noordermeer et al., 1994), which then interacts with axin (Itoh et al., 2000; Kishida et al., 1999; Smalley et al., 1999) and recruits several other proteins, such as GSK-binding protein (GBP/FRAT) and protein phosphatase 2C (Li et al., 1999; Strovel et al., 2000; Fig. 1A). This leads to the disassembly of the complex (Jho et al., 1999; Li et al., 1999; Farr et al., 2000; Salic et al., 2000; Willert et al., 1999), degradation of axin (Yamamoto et al., 1999) and the accumulation of β-catenin in the cytoplasm and the nucleus. In the nucleus, β-catenin interacts with LEF/TCF transcription factors (Behrens et al., 1996; Brunner et al., 1997; Huber et al., 1996; Molenaar et al., 1996; Riese et al., 1997; van de Wetering et al., 1997) and activates β-catenin:LEF/TCF dependent transcription by providing the transactivation domain to the LEF/TCF complex (van de Wetering et al., 1997). Thus, activation of the Wnt signaling cascade results in β-catenin:LEF/TCF target gene expression.

An additional, APC- and axin-independent pathway might also regulate β-catenin degradation, given that β-catenin (Murayama et al., 1998; Zhang et al., 1998) and GSK (Takashima et al., 1998) associate with presenilin. The role of presenilin in β-catenin degradation is still controversial, because presenilin could either stabilize (Zhang et al., 1998) or destabilize (Kang et al., 1999) β-catenin. The relative contributions of the presenilin and axin pathways to β-catenin stability, and the mechanism underlying presenilin-dependent degradation of β-catenin, are incompletely understood.

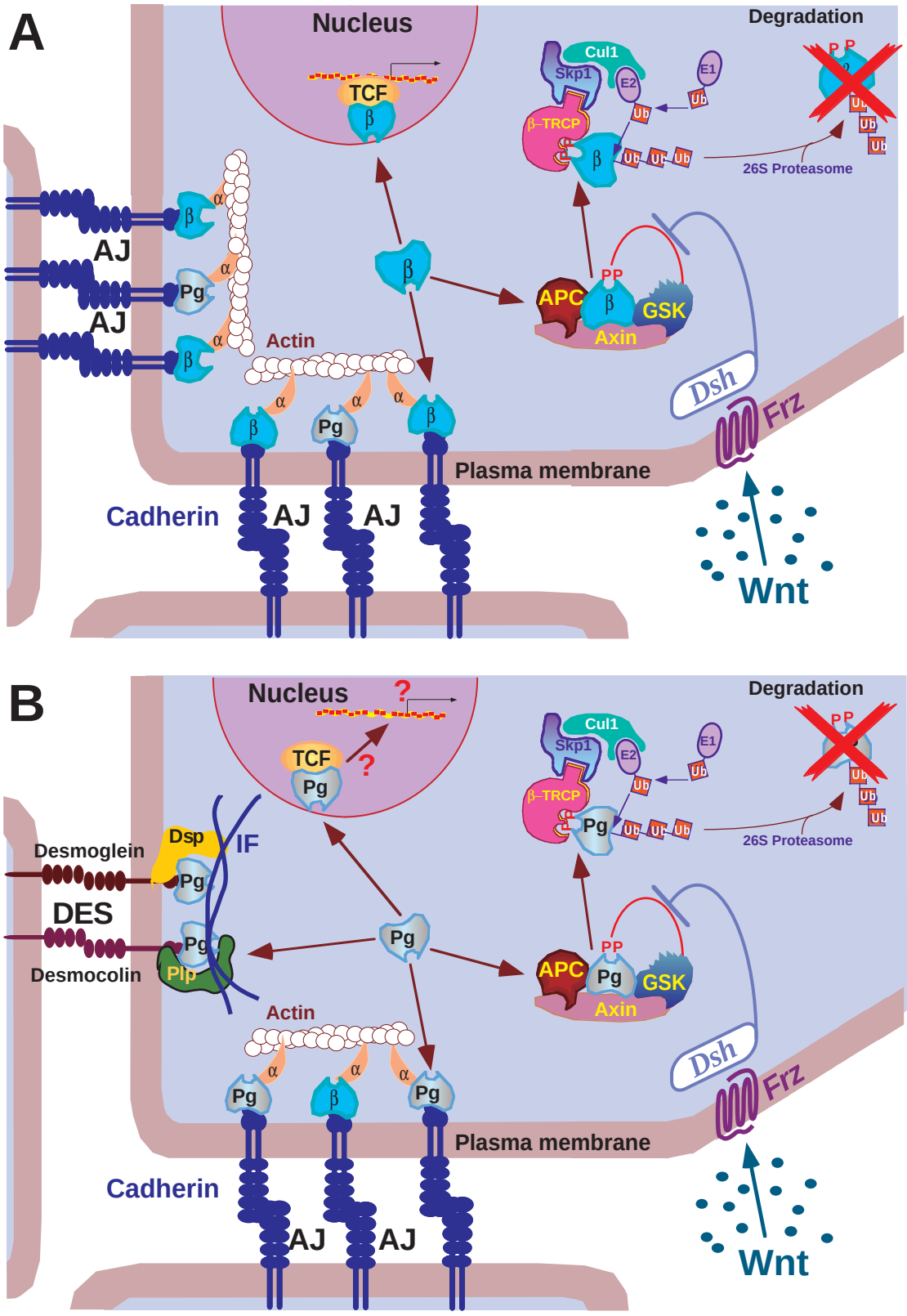
Plakoglobin, similarly to β-catenin, can bind to LEF/TCF factors (Hecht et al., 1999; Huber et al., 1996; Simcha et al., 1998; Zhurinsky et al., 2000), contains a transactivation domain in its C terminus (Hecht et al., 1999; Simcha et al., 1998) and is targeted for proteasomal degradation by the axin-APC complex (Kodama et al., 1999; Sadot et al., 2000; Fig. 1B). Although in certain cell types overexpression of Wnt results in the accumulation of plakoglobin (Bradley et al., 1993; Papkoff et al., 1996), the involvement of plakoglobin in Wnt signaling in vivo is still controversial, because plakoglobin cannot compensate for the absence of β-catenin in knockout mice (Bierkamp et al., 1996; Haegel et al., 1995; Huelsken et al., 2000; Ruiz et al., 1996). Interestingly, a recent study revealed that the expression of plakoglobin in the skin of transgenic mice (Charpentier et al., 2000) induces a phenotype very different from that conferred by β-catenin expression (Gat et al., 1998). This phenotype is more similar to that observed when upstream components of the Wnt pathway are overexpressed (Millar et al., 1999). We discuss the nature of these and other differences between the two catenins, and the possible involvement of plakoglobin in Wnt signaling, below.

Fig. 1. The various interactions involving β-catenin and plakoglobin. (A) β-Catenin (β) and plakoglobin (Pg) can bind, independently, to the cytoplasmic tail of cadherin adhesion receptors in adherens junctions (AJ). Via α-catenin (α), they mediate cadherin association with the actin cytoskeleton. When Wnt signaling is inactive, free β-catenin is degraded by a multimolecular complex including the tumor suppressor APC, axin and glycogen synthase kinase (GSK), which phosphorylates β-catenin (PP). This complex associates with the ubiquitin-proteasome system via the ubiquitin lygase β-TrCP, which, together with Cul1 and Skp1, mediates the ubiquitination (Ub) of β-catenin and targets it for degradation by the proteasome. The binding of Wnt to the Frizzled (Frz) receptor activates Wnt signaling, and disheveled (Dsh) inhibits β-catenin turnover by suppressing GSK activity. This results in the accumulation of β-catenin in the nucleus, its complexing with TCF family transcription factors, and activation of target gene expression. (B) Plakoglobin can interact with the same proteins as β-catenin but, in addition, binds to the desmosomal cadherins desmocollin and desmogelin in desmosomes (DES), mediating their interaction, via desmoplakin (Dsp) and plakophilin (Plp), with intermediate filaments (IF). The ability of plakoglobin to transactivate target genes in complex with TCF is still controversial (?).

CATENIN STRUCTURE AND BINDING SITES FOR PROTEIN PARTNERS

Many molecules interact with β-catenin and plakoglobin (for examples, see Table 1). The functional consequences of some of these interactions are well established (e.g. those involving cadherins, LEF/TCF, or the APC/axin degradation machinery; see Fig. 1), whereas the significance of some other interactions is still incompletely understood.

A characteristic structural feature of catenins is a central armadillo (arm) repeat domain flanked by the C- and N-terminal domains (Hatzfeld, 1999). Although all three catenin domains can mediate protein-protein interactions, the great majority of partners bind to the arm repeat region (Table 1). The arm repeat motif folds into a single structural unit, whose tertiary structure (determined by crystallographic analysis) revealed an array of densely packed α-helices that form a superhelix that has a positively charged groove that spans the entire arm repeat region (Huber et al., 1997). This groove might constitute the binding surface for the various catenin partners, which would explain the observation that at least five arm repeats are needed to maintain protein-protein interactions. No consensus sequence, however, has been detected in the arm-binding domains of the different catenin partners, although they each possess many negatively charged residues, which



could dock into the positively charged groove formed by the arm repeats (Hsu et al., 1998; Huber et al., 1997; Omer et al., 1999). Although the nature of the binding site on the arm repeat dictates mutually exclusive binding of the various partners to this region (Hulsken et al., 1994; Kishida et al., 1998; Orsulic et al., 1999; Rubinfeld et al., 1995; Sadot et al., 1998), the molecular interactions formed by each protein partner are unique. Thus, it is possible selectively to disrupt the binding of

Table 1. Protein partners of β-catenin and plakoglobin

Protein partner	β-Catenin binding	Plakoglobin binding	Binding site on catenins	Function of the interaction	References
Classical cadherins	+	+	Arm repeats	Adhesion	Kemler, 1993
Desmocollin	–	+	Arm repeats	Adhesion	Troyanovsky et al., 1994b
Desmoglein	–	+	Arm repeats	Adhesion	Troyanovsky et al., 1994a
Desmoplakin	–	+	Arm repeats	Adhesion	Kowalczyk et al., 1997
Fascin	+	ND*	Arm repeats	Adhesion	Tao et al., 1996
IQGAP	+	ND	N terminus and the 1st arm repeat	Adhesion	Fukata M et al., 1999; Kuroda et al., 1998
Keratin 5	–	+	ND	Adhesion	Smith and Fuchs, 1998
MAGI	+	ND	C terminus	Adhesion	Dobrosotskaya and James, 2000
p35-Cdk5 kinase	+	ND	Arm repeats	Adhesion	Kwon et al., 2000
Protein-tyrosine phosphatase LAR	+	+	ND	Adhesion	Muller et al., 1999
α-Catenin	+	+	N terminus and the 1st arm repeat	Adhesion	Aberle et al., 1996
FAM	+	ND	ND	Catenin de-ubiquitination	Taya et al., 1999
EGFR	+	ND	Arm repeats	Catenin phosphorylation	Hoschuetzky et al., 1994; Takahashi et al., 1997
APC	+	+	Arm repeats	Degradation	Rubinfeld et al., 1993; Shibata et al., 1994
Axin/conductin	+	+	Arm repeats	Degradation	Behrens et al., 1998; Ikeda et al., 1998; Kodama et al., 1999
β-TrCP	+	+	N terminus	Degradation	Hart et al., 1999; Sadot et al., 2000; Winston et al., 1999
Presenilin	+	ND	ND	Degradation (?)	Murayama et al., 1998; Yu et al., 1998; Zhang et al., 1998
NLK	+	ND	N terminus	LEF/TCF phosphorylation	Ishitani et al., 1999
Caveolin-1	+	+	ND	Membrane localization (?)	Galbiati et al., 2000
Nup1	+	ND	ND	Nuclear import	Fagotto et al., 1998
PI3 kinase	+	ND	ND	Regulation of catenin stability	Espada et al., 1999
CBP/P300	+	ND	N and C terminus	Transactivation	Hecht et al., 2000; Takemaru and Moon, 2000
LEF-1	+	+	Arm repeats	Transactivation	Behrens et al., 1996; Huber et al., 1996
Pontin	+	ND	N terminus and arm repeats	Transactivation	Bauer et al., 1998
RAR	+	ND	Arm repeats	Transactivation	Easwaran et al., 1999
SMAD4	+	ND	ND	Transactivation	Nishita et al., 2000
SOX17	+	ND	Arm repeats	Transactivation	Zorn et al., 1999
TBP	+	+	N and C terminus (in plakoglobin – C terminus only)	Transactivation	Hecht et al., 1999
TCFs	+	ND	Arm repeats	Transactivation	Korinek et al., 1997; Molenaar et al., 1996

*ND, not determined.

certain proteins to the arm repeats by mutations within the arm domain, but maintain the binding of other partners (Prieve and Waterman, 1999).

The mutually exclusive binding of catenins to different partners, and the different localizations of various catenin complexes in the cell, contributes to their distinct molecular compositions (Fig. 1). The binding sites for partners in the N- and C-terminal domains of catenins, in addition to the arm domain, enable the catenins to act as scaffolds for multiprotein assemblies. For example, the N-termini of β-catenin and plakoglobin can recruit α-catenin to ternary complexes containing cadherin family adhesion receptors (Aberle et al., 1994; Nagafuchi et al., 1994), thus bridging adherens junctions to the actin cytoskeleton (Fig. 1). In the nucleus, both the N- and C-termini of β-catenin link the β-catenin:LEF/TCF complex to the basal transcription machinery (Hsu et al., 1998; van de Wetering et al., 1997) via interactions with TATA-box-binding protein (TBP) (Hecht et al., 1999) and CREB-binding protein (CBP) (Hecht et al., 2000; Takemaru and Moon, 2000). In the degradation complex, β-catenin is recruited via its arm repeat domain by APC (Hulsken et al., 1994; Rubinfeld et al., 1993; Su et al., 1993) and axin (Behrens et al., 1998; Kishida et al., 1998), and is ubiquitinated after interaction between the phosphorylated serines on its N terminus (by GSK) and the β-TrCP ubiquitin ligase (Hart et al., 1999; Jiang and Struhl, 1998; Kitagawa et al., 1999; Latres et al., 1999; Liu et al., 1999; Sadot et al., 2000; Winston et al., 1999). This scaffolding function of β-catenin (and probably also of plakoglobin) in the assembly of mutually exclusive complexes (Fig. 1) is essential for cell adhesion and Wnt signaling and provides a mechanism for cross-talk between these processes.

REGULATION OF CATENIN INTERACTIONS

The different catenin complexes described above co-exist simultaneously in the cell (Fig. 1A). The recruitment of β-catenin into each of these complexes is regulated by the relative abundance of β-catenin and the various factors that bind β-catenin (Fagotto et al., 1996; Heasman et al., 1994; Hulsken et al., 1994; Orsulic et al., 1999; Sadot et al., 1998; Sanson et al., 1996; Simcha et al., 1998) and by phosphorylation-dependent changes in the affinity of interactions between catenins and

their partners (Behrens et al., 1993; Kinch et al., 1995; Roura et al., 1999; Willert et al., 1999).

Competition between catenin partners for binding to β-catenin

Competition between different catenin partners for a limited pool of catenins can regulate the function of catenins. For example, overexpression of cadherins results in the recruitment of the majority of β-catenin into adherens junctions, thus reducing its availability for complexing with LEF/TCF factors and thereby inhibiting β-catenin-mediated transcription (Orsulic et al., 1999; Sadot et al., 1998; Simcha et al., 1998). Such cadherin overexpression leads to severe aberrations in the development of *Xenopus* (Fagotto et al., 1996; Heasman et al., 1994) and *Drosophila* (Sanson et al., 1996), which requires signaling by β-catenin. In contrast, the decrease in cell-cell adhesion during the epithelial-mesenchymal transition might lead to the release of some cadherin-associated β-catenin, which could contribute to activation of LEF/TCF-dependent transcription (Eger et al., 2000; Espada et al., 1999). The interaction between cadherins and β-catenin, in addition to sequestering the potential signaling pool of β-catenin, also competes with the APC-axin β-catenin degradation machinery, thereby protecting the pool of catenins that is involved in adhesion from degradation (Hulsken et al., 1994; Rubinfeld et al., 1995).

Whereas overexpression of cadherins results in the sequestering of β-catenin away from the nucleus and inhibition of its signaling function, overexpression of LEF-1, in contrast, leads to translocation of β-catenin to the nucleus in MDCK cells (Simcha et al., 1998) and induces double axis formation in *Xenopus* (Behrens et al., 1996), through the β-catenin:LEF/TCF pathway (Fagotto et al., 1996; Heasman et al., 1994; Molenaar et al., 1996).

In addition to competition between the cytoplasmic and nuclear partners for β-catenin binding, there might be competition between several transcription factors that interact with β-catenin in a mutually exclusive fashion. For example, the binding of β-catenin to LEF/TCF family members (Behrens et al., 1996; Huber et al., 1996; van de Wetering et al., 1997), members of the SOX subfamily of HMG domain-containing transcription factors (Zorn et al., 1999) and to retinoic acid receptor (RARα) (Easwaran et al., 1999) is mediated by an interaction with the arm domain of β-catenin.

The various members of the LEF/TCF family differ in their abilities to interact with regulatory (co-repressor) proteins such as groucho (Levanon et al., 1998; Roose et al., 1998), CtBP (Brannon et al., 1999) and with β-catenin (Roose et al., 1999). Thus, competition between different LEF/TCF factors for β-catenin binding might affect the regulation of β-catenin-dependent transactivation by these proteins. Transcription factors such as SOX17 and RARα also compete with LEF/TCF for β-catenin binding, and inhibit LEF/TCF-dependent transcription (Zorn et al., 1999). In addition to suppressing LEF/TCF signaling, the association between β-catenin and RAR is suggested to mediate the co-activation of RAR-regulated target genes by β-catenin (Easwaran et al., 1999). The role played by these interactions of β-catenin with SOX17 and RAR in vivo remains, however, to be determined.

Since the interaction of β-catenin with transcription factors is mediated mostly by the arm domain of the molecule, which is highly homologous to that of plakoglobin (Cowin and Burke, 1996), plakoglobin might also interact with the same nuclear partners (Fig. 1B). Plakoglobin forms a complex with LEF-1 when the two molecules are co-transfected into cells (Huber et al., 1996; Simcha et al., 1998), but its ability to bind to other nuclear proteins will have to be investigated.

Cell-cell contacts of both the adherens junction and desmosome types contain plakoglobin (Cowin et al., 1986; Fig. 1B). A competition between classical and desmosomal cadherins for plakoglobin binding is involved in the regulation of the assembly of these junctions (Ben-Ze'ev and Geiger, 1998; Cowin and Burke, 1996; Lewis et al., 1997). In adherens junctions, plakoglobin binds to α-catenin and anchors adherens junctions to actin (Knudsen et al., 1995; Fig. 1A), whereas, in desmosomes, plakoglobin binds to the desmosomal cadherins desmocollin and desmoglein (Troyanovsky et al., 1994a,b) and to desmoplakin (Kowalczyk et al., 1997) and keratins (Smith and Fuchs, 1998), providing a link to the intermediate filament cytoskeleton (Schmidt et al., 1994; Fig. 1B). Interestingly, although plakoglobin can anchor classical cadherins via α-catenin to actin in adherens junctions, it loses this ability when incorporated into desmosomes. This specificity is achieved by mutually exclusive interactions of plakoglobin with α-catenin and desmosomal cadherins (Chitaev et al., 1998).

In the absence of Wnt signaling, when the level of free β-catenin is relatively low, there is probably strong competition for the limiting amount of β-catenin (and most probably plakoglobin) among various partners. When β-catenin accumulates, in response to activation of the Wnt pathway, this competition is relieved and β-catenin can function in both Wnt signaling and cell adhesion (Hinck et al., 1994; Shibamoto et al., 1998; Yanagawa et al., 1997).

Competition between β-catenin and plakoglobin

The binding of the two catenins to common protein partners (Fig. 1) raises the possibility of competition between these two proteins for their various partners. For example, the expression of high levels of exogenous plakoglobin can efficiently displace the endogenous β-catenin from adherens junctions, leading to its degradation by the proteasome (Salomon et al., 1997). Similarly, in plakoglobin-knockout mice, β-catenin is incorporated into desmosomes, which are normally devoid of this protein (Bierkamp et al., 1999; Ruiz et al., 1996). The competition for binding to the degradation machinery between β-catenin and overexpressed plakoglobin (Miller et al., 1999; Simcha et al., 1998) or membrane-anchored forms of both catenins (Klymkowsky et al., 1999; Miller and Moon, 1997) might compromise degradation, cause accumulation of the endogenous β-catenin (Miller et al., 1999; Simcha et al., 1998) and therefore actiate LEF/TCF-mediated transcription (Klymkowsky et al., 1999; Simcha et al., 1998; Zhurinsky et al., 2000; Fig. 2A). This type of competition, however, was demonstrated only in cells overexpressing plakoglobin, and it is not known whether the endogenous plakoglobin competes at sites other than adherens junctions, or whether plakoglobin can regulate β-catenin signaling in vivo.

Nucleocytoplasmic shuttling of catenins

Regulation of catenin levels by the Wnt pathway is considered to be the major mechanism by which catenins are driven into the nucleus. However, the balance between catenin functions in the cytoplasm and the nucleus might also be regulated by

mechanisms controlling their import into and export from the nucleus. Catenins lack classical nuclear localization signal sequences (NLSs) and probably accumulate in the nucleus by two mechanisms. Two groups have demonstrated direct, importin-independent nuclear import of β-catenin in a semi-permeabilized cell model for nuclear import (Fagotto et al., 1998; Yokoya et al., 1999), which could be mediated by the interaction between β-catenin and the Nup1 nucleoporin (Fagotto et al., 1998). Alternatively, since overexpression of LEF/TCF leads to β-catenin accumulation in the nucleus (Behrens et al., 1996; Molenaar et al., 1996; Simcha et al., 1998), it was suggested that the nuclear import of the β-catenin/LEF (or plakoglobin/LEF) complex is mediated by the classical NLS provided by LEF/TCF proteins. It is also possible that if β-catenin normally shuttles between the cytoplasm and the nucleus, overexpression of LEF/TCF leads to a more efficient sequestration of catenins by LEF/TCF in the nucleus. Since the elevation in the levels of either β-catenin or plakoglobin leads to their nuclear accumulation when the levels of LEF/TCF are very low (Simcha et al., 1996, 1998), LEF/TCF-independent mechanisms are likely to be important for regulating the nuclear import of catenins in vivo.

Interestingly, the *Drosophila* β-catenin homolog, Armadillo, is excluded from the nuclei of some cells that display high levels of this protein in the cytoplasm (Cox et al., 1999b). This implies that there might be a regulation of catenin nuclear import/export, or a specific anchoring of the protein in the cytoplasm, when its levels increase, which would prevent its nuclear localization. Such anchoring might occur, for example, in cells expressing mutant presenilin, since the inhibition of β-catenin degradation by LiCl (an inhibitor of GSK activity) in such cells results in accumulation of β-catenin in the cytoplasm and not, as expected, in the nucleus (Nishimura et al., 1999).

Since the arm repeat domain implicated in the nuclear import of catenins is very similar in β-catenin and plakoglobin (Cowin and Burke, 1996), it is conceivable that plakoglobin, when overexpressed, can enter the nucleus by a mechanism similar to that used by β-catenin. However, the soluble pool of endogenous plakoglobin in epithelial cells is much smaller than that of β-catenin (Sadot et al., 2000; Simcha et al., 1998). This probably explains the observation that plakoglobin, in contrast to β-catenin, is not translocated into the nucleus following LEF-1 overexpression in MDCK cells (Simcha et al., 1998), or transfection of dominant negative β-TrCP, both of which result in β-catenin localization to the nucleus (Sadot et al., 2000; Simcha et al., 1998).

Phosphorylation of catenins and their partners

Catenins undergo serine/threonine and tyrosine phosphorylation that regulates their interactions with other proteins. The N-termini of β-catenin and plakoglobin contain the GSK consensus phosphorylation site (Aberle et al., 1997; Yost et al., 1996). However, GSK does not efficiently phosphorylate mammalian β-catenin in vitro and needs to be linked to β-catenin by axin, which contains binding sites for both proteins (Kitagawa et al., 1999). The phosphorylation of the N-terminal serine residues of catenins is required for their interaction with the ubiquitin ligase β-TrCP and their subsequent degradation by the proteasome (Hart et al., 1999; Kitagawa et al., 1999; Latres et al., 1999; Liu et al., 1999; Sadot et al., 2000; Winston et al., 1999; Fig. 1). Point mutations in these phosphorylation sites lead to stabilization of β-catenin and activation of β-catenin-dependent transactivation in a variety of tumors (Ben-Ze'ev and Geiger, 1998; Morin, 1999; Polakis, 1999). In addition to enhancing catenin degradation, the phosphorylation of catenins by GSK increases their binding in vitro to the cytoplasmic domain of cadherin (Miller and Moon, 1997), but the significance of this observation to catenin function in cells is unclear.

β-Catenin and plakoglobin are also phosphorylated on tyrosine residues by receptor and non-receptor tyrosine kinases (Hamaguchi et al., 1993; Matsuyoshi et al., 1992), and the EGF receptor directly interacts with β-catenin and plakoglobin (Hoschuetzky et al., 1994; Muller et al., 1999). The decrease in affinity of β-catenin for cadherin upon phosphorylation by SRC (Roura et al., 1999) is consistent with the observation that the non-junctional catenin pool is preferentially phosphorylated on tyrosine (Kinch et al., 1995) and might represent a mechanism for regulation of cell adhesion by tyrosine kinases and phosphatases. Whether tyrosine phosphorylation of catenins affects their interaction with partners in the degradation complex or with transcription factors in the nucleus remains to be determined.

The interactions of catenins with their junctional partners and with the degradation machinery are affected by phosphorylation of the catenin partners. Since the binding site for catenin partners in the arm repeat domains of catenins is enriched in positively charged residues, the interactions mediated by this catenin domain are enhanced by the phosphorylation of the binding sites of catenin partners. Thus, the phosphorylated forms of APC and axin display markedly enhanced binding to β-catenin (Rubinfeld et al., 1996; Willert et al., 1999), and dephosphorylation of axin, in response to Wnt signaling, results in the release of β-catenin from the degradation complex (Jho et al., 1999; Willert et al., 1999). The phosphorylation of cadherin by GSK and casein kinase II also increases the affinity of β-catenin for the cadherin cytoplasmic domain (Lickert et al., 2000).

Regulation of catenin function by their terminal domains

In contrast to their arm domains, the N- and C-terminal domains of β-catenin and plakoglobin share little sequence similarity (Cowin and Burke, 1996). Recent studies have indicated that the terminal domains of both catenins might also be involved in regulating the interaction of the arm repeats with various protein partners (Chitaev et al., 1996; Palka and Green, 1997; Wahl et al., 2000; Zhurinsky et al., 2000). For example, the binding of catenins to cadherins through the arm repeats is enhanced by deletion of the C terminus in plakoglobin (Chitaev et al., 1996). Such a deletion can also markedly stimulate the assembly of plakoglobin-containing desmosomes (Palka and Green, 1997). The exclusion of β-catenin from desmosomes involves the terminal domains of the molecule, since the arm domain of β-catenin can efficiently bind to desmosomal cadherins (Wahl et al., 2000). Comparison of the abilities of β-catenin–plakoglobin chimeras to bind to desmoglein 2 demonstrated that the N- and C-terminal domains of β-catenin cooperate to abolish this binding, and when these domains of plakoglobin are replaced by those of β-catenin the resulting chimeric molecule cannot bind to desmoglein 2 (Wahl et al., 2000).

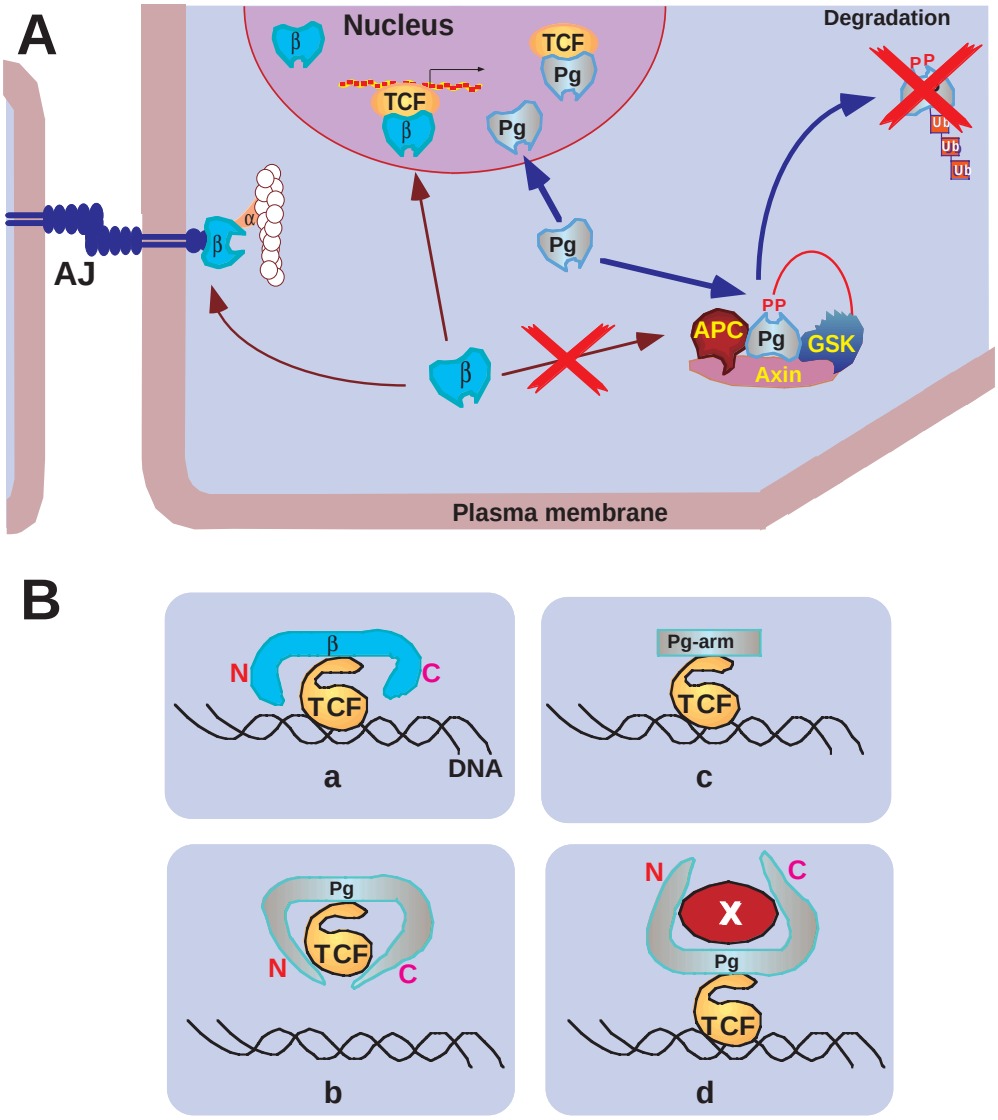


Fig. 2. Differential effects of β-catenin and plakoglobin on TCF-mediated transactivation. (A) In cells overexpressing plakoglobin, the sequestration (by plakoglobin) of components in the degradation machinery, which regulates β-catenin turnover, leads to β-catenin accumulation and activation of β-catenin–TCF-mediated gene expression. Plakoglobin-TCF complexes in the nucleus inefficiently form ternary complexes containing DNA (see Zhurinsky et al., 2000). (B) Although the armadillo repeats (arm) of both β-catenin (a) and plakoglobin (c) can effectively form a ternary complex with TCF, the N- and C-terminal domains of plakoglobin inhibit DNA-containing ternary-complex formation (b). A mechanism that might promote transactivation by plakoglobin may involve a hypothetical protein (X) (d) whose binding to plakoglobin results in a conformational change allowing complexing between plakoglobin, TCF and the DNA.

The terminal domains of both β-catenin and plakoglobin are also involved in the downregulation of catenin:LEF:DNA ternary complex formation (Zhurinsky et al., 2000; Fig. 2B). Although full-length plakoglobin interacts with LEF-1 almost as efficiently as does β-catenin (Fig. 2A,B), its ability to form a ternary complex with LEF-1 and DNA is very weak (Zhurinsky et al., 2000). In contrast, a construct containing the arm domain of plakoglobin alone very efficiently assembles into ternary complexes (Fig. 2B,c). An inhibitory action of the terminal domains is apparently common to both catenins, since the arm repeats of β-catenin also form ternary complexes more efficiently than does the full-length protein (Zhurinsky et al., 2000).

Given that the C-termini of β-catenin and plakoglobin contain the acidic transactivation domain, and the arm repeats form the positively charged binding site, the C-termini of catenins might interact with the arm domain and thus regulate the interactions with proteins that bind to this site (Fig. 2B,b). This notion is supported by the finding that the C terminus of *Drosophila* Armadillo can bind to its arm repeat domain in a two-hybrid screen (Cox et al., 1999a). An alternative possibility is that the N- and C-termini interact, which Wahl et al., have demonstrated by a modified two-hybrid assay (Wahl et al., 2000; Fig. 2B,b). Although the exact nature of these intramolecular interactions in catenins remains to be unraveled, they propose the intriguing possibility that interactions between catenins and their partners are modulated by such intramolecular interactions. For example, the binding of transcription factors (e.g. CBP, TBP) to the catenin terminal domains may promote binding of the LEF-catenin complex to DNA (Zhurinsky et al., 2000; Fig. 2B,d). Moreover, one can speculate that the decrease in the affinity of catenins for cadherin, upon catenin tyrosine phosphorylation of the last arm repeat (Roura et al., 1999), might involve negative regulation of cadherin-catenin interaction by the catenin's C terminus (Chitaev et al., 1996). These intriguing possibilities remain to be addressed experimentally.

In conclusion, the regulation of interactions between catenins and their partners is achieved through several mechanisms, including competition between different

partners, phosphorylation and intramolecular interactions. The understanding of the cooperation and cross-talk between these mechanisms in the fine tuning of the numerous functions catenins perform in development and cancer remains the challenge for future investigation.

THE FUNCTION OF CATENINS IN DEVELOPMENT AND CANCER

Catenins and development

Catenin-mediated cell adhesion and Wnt signaling both play multiple roles in various developmental processes and also in the adult organism. Adherens junctions define tissue integrity, mediate specific cell-cell recognition, participate in determining epithelial cell polarity and sequester many signaling molecules to cell adhesion sites, thereby regulating signal transduction (Barth et al., 1997; Behrens, 1999; Ben-Ze'ev, 1999; Gumbiner, 1996; Steinberg and McNutt, 1999). Wnt signaling elicits a very broad range of catenin-dependent and -independent responses (Peifer and Polakis, 2000), including specification of cell fate at different stages of development (Wodarz and Nusse, 1998), regulation of cell proliferation (Gat et al., 1998; Kolligs et al., 1999; Orford et al., 1999; Young et al., 1998) and survival (Orford et al., 1999), cytoskeletal remodeling to define cell polarity (Peifer and Polakis, 2000; Thorpe et al., 2000) and cell motility (Heisenberg et al., 2000; Wallingford et al., 2000).

The requirements for β-catenin and plakoglobin in cell adhesion and Wnt signaling have been compared by genetic analysis in *Drosophila*, *Xenopus* and mice. In *Drosophila*, mutations that disrupt Armadillo functions lead to defects in both cell adhesion and Wnt signaling. Although both β-catenin and plakoglobin can complement the adhesion defects, β-catenin demonstrated only partial signaling activity, and plakoglobin was completely inactive in signaling (White et al., 1998).

In *Xenopus*, maternal β-catenin establishes the dorso-ventral asymmetry (Funayama et al., 1995; Heasman et al., 1994) and specifies formation of axial structures by acting as part of the Wnt signaling pathway (Sumanas et al., 2000). Although *Xenopus* plakoglobin is also expressed at this stage of development, it cannot compensate for β-catenin removal, and depletion of maternal plakoglobin RNA does not affect axis specification, which indicates that β-catenin has a specific role in this process (Kofron et al., 1997). Initial studies showing that the ventral microinjection of plakoglobin in *Xenopus* embryos induces dorsalization of the embryos (similarly to β-catenin) were thus unexpected (Karnovsky and Klymkowsky, 1995). However, later studies have shown that cells expressing high levels of exogenous plakoglobin display increased levels of endogenous β-catenin (probably resulting from sequestration of key components in β-catenin degradation), thus suggesting that there is an indirect action via β-catenin (Miller and Moon, 1997). This issue is still under debate, because Klymkowsky et al., have suggested that additional mechanisms of action of membrane-tethered catenins involve recruitment of LEF/TCF factors in the cytoplasm (Klymkowsky et al., 1999).

The elimination of either β-catenin or plakoglobin by gene knockout in mice results in embryonic lethality (Bierkamp et al., 1996; Haegel et al., 1995; Huelsken et al., 2000; Ruiz et al., 1996). The phenotypes that lead to embryonal death are, however, very different for the two catenins. Whereas the lack of plakoglobin leads to defects in desmosome assembly that result in compromised heart development (Bierkamp et al., 1996; Ruiz et al., 1996), mice lacking β-catenin are characterized by an inability to form dorsal structures in the developing embryos (Huelsken et al., 2000). These defects reflect the importance of β-catenin in Wnt-mediated axis formation. In contrast, adherens junctions are well developed in β-catenin-null embryos, and elevated plakoglobin levels compensate for the adhesive role of β-catenin (Haegel et al., 1995; Huelsken et al., 2000). Owing to the early embryonal lethality in plakoglobin-knockout mice, one cannot rule out the possibility that plakoglobin-mediated Wnt signaling is needed at later stages of development. Future studies employing conditional, tissue-specific, knockouts might reveal the requirements for plakoglobin in development and in the adult organism.

Intriguing studies of transgenic mice expressing either β-catenin or plakoglobin under a skin-specific keratin 14 promoter recently implicated plakoglobin in signaling (Charpentier et al., 2000; Gat et al., 1998). β-Catenin expressed under this promoter stimulated de novo hair follicle proliferation and, at a later stage, caused hair tumors in adult mice (Gat et al., 1998). In contrast, plakoglobin expression driven by the same promoter resulted in an opposite phenotype displaying hair growth that was slower in comparison with that of wild-type mice and a decrease in the period of the hair growth phase (Charpentier et al., 2000). It is not known whether this phenotype resulted from attenuation of β-catenin nuclear signaling, since immunofluorescence studies revealed no change in β-catenin levels or localization in the skin of these mice. Such effects could still be related to subtle changes in endogenous β-catenin (due to plakoglobin overexpression) that were below the detection limit of immunofluorescence.

Other studies suggest that plakoglobin recruits LEF/TCF proteins into a plakoglobin-containing complex that binds to DNA very inefficiently (Zhurinsky et al., 2000; Fig. 2B), which can potentially antagonize β-catenin:LEF/TCF signaling. Alternatively, plakoglobin might form a transcriptional complex that has a different specificity of DNA recognition and induces plakoglobin-specific target genes (Fig. 2B,d). This notion is supported by the observation that expression of WNT-3 or DVL-2 (an isoform of dishevelled, Fig. 1) in the skin of transgenic mice (Millar et al., 1999) results in phenotypes that are similar to those observed when plakoglobin is overexpressed (Charpentier et al., 2000) and very different from those displayed in mice overexpressing β-catenin. This may indicate the involvement of plakoglobin in Wnt signaling downstream of Wnt-3 and Dvl-2 (Millar et al., 1999). Note, however, that both Wnt-3 and Dvl-2 are very efficient at elevating β-catenin levels in cultured cells (Lee et al., 1999). By examining the effects of Wnt-3 and Dvl-2 on plakoglobin and β-catenin and comparing them with the effects of other components of the Wnt pathway (and of other Wnt isoforms), we should learn more about the possible involvement of plakoglobin in Wnt signal transduction and whether this role is different from that played by β-catenin.

Differential involvement of β-catenin and plakoglobin in cancer progression

β-Catenin levels are elevated in cancers of various origins and

in different organs (Ben-Ze'ev, 1997; Ben-Ze'ev and Geiger, 1998; Morin, 1999; Polakis, 1999). These increases in β-catenin levels result mostly from mutations in β-catenin itself that affect residues in the GSK-phosphorylation sites critical for β-catenin degradation. In addition, mutations in key components of the degradation machinery, such as APC or axin, have also been detected in some tumors (Morin et al., 1997; Satoh et al., 2000). The result of such mutations is an elevation in β-catenin content and activation of β-catenin:LEF/TCF-dependent transcription. This could contribute to uncontrolled cell proliferation and tumor progression (Gumbiner, 1997; Korinek et al., 1997; Peifer, 1997). Several target genes of the β-catenin:LEF/TCF complex have been implicated in the oncogenic effect conferred by β-catenin signaling. Induction of the genes that encode MYC and cyclin D1, whose promoters contain LEF/TCF-binding sites, might provide the molecular basis for growth regulation by β-catenin signaling (He et al., 1998; Shtutman et al., 1999; Tetsu and McCormick, 1999), whereas the induction of matrilysin expression could promote cell invasion (Crawford et al., 1999). In addition, PPARδ, a transcription factor involved in colon cancer, is also a target for the β-catenin-TCF complex (He et al., 1999).

In contrast to frequent mutations in β-catenin in tumors of different origin (Morin, 1999; Polakis, 1999), only one case of plakoglobin mutation has been reported in gastric cancer (Caca et al., 1999). Moreover, plakoglobin expression is often lost during cancer progression (Aberle et al., 1995) and restoration of plakoglobin expression in several highly tumorigenic cells lacking plakoglobin can suppress their tumorigenicity (Ben-Ze'ev 1997; Simcha et al., 1996). However, a transforming activity of plakoglobin has also been recently reported (Kolligs et al., 2000). Kolligs and co-authors observed a higher efficiency of *MYC* induction by plakoglobin compared with β-catenin (Kolligs et al., 2000). Although plakoglobin forms a complex with LEF/TCF and DNA inefficiently in human 293T cells (Zhurinsky et al., 2000; Fig. 2A), the possibility that cell-type-specific factors allow signaling by plakoglobin, either in complex with LEF/TCF (Fig. 2B,d) or with other transcription factors, remains to be investigated.

CONCLUSIONS

The studies discussed above reveal a complex network of interactions involving the catenins, which cooperate to regulate the many functions attributed to β-catenin and plakoglobin. The emerging mechanisms regulating binding of catenins to their partners involve phosphorylation and intramolecular interactions, and accumulating evidence suggests that plakoglobin also has a role in signaling. Whether plakoglobin participates in Wnt signal transduction, and how the various functions of plakoglobin, which differ from those of β-catenin, are regulated remains to be determined. Comparing the effects of plakoglobin and β-catenin on transcription, defining new potential target genes for β-catenin and plakoglobin by DNA-chip technology and studies with transgenic mice employing tissue-specific elimination of β-catenin and plakoglobin will provide some answers to these intriguing questions about the functions of catenins in development and cancer.

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