Published in final edited form as:

Prog Mol Biol Transl Sci. 2013 ; 116: 387–407. doi:10.1016/B978-0-12-394311-8.00017-0.

Beta-catenin versus the other catenins: assessing our current view of canonical Wnt signaling

Rachel K. Miller^{1,*}, Ji Yeon Hong^{2,#}, William A. Muñoz^{1,3,#}, and Pierre D. McCreas^{1,3,*}

¹Department of Biochemistry and Molecular Biology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030

²The Catholic University of Korea, Catholic High Performance Cell Therapy Center 505 Banpo-dong, Seocho-Ku, Seoul, Korea, 137-701

³Program in Genes and Development, The University of Texas Graduate School of Biomedical Sciences, Houston, TX 77030

Abstract

The prevailing view of canonical Wnt signaling emphasizes the role of beta-catenin acting downstream of Wnt activation to regulate transcriptional activity. However, emerging evidence indicates that other catenins in vertebrates, such as members of the p120 subfamily, convey parallel signals to the nucleus downstream of canonical Wnt pathway activation. Their study is thus needed to appreciate the networked mechanisms of canonical Wnt pathway transduction, especially as they may assist in generating the diversity of Wnt effects observed in development and disease. In this chapter, we outline evidence of direct canonical Wnt effects on p120-subfamily members in vertebrates, and speculate upon these catenins' roles in conjunction with or aside from beta-catenin.

Keywords

catenin; canonical; Wnt; beta-catenin; plakoglobin; gamma-catenin; p120-catenin; delta-catenin; ARVCF-catenin; p0071; Pkp1; Pkp2; Pkp3; Pkp4; cadherin; armadillo; plakophilin

I. Overview of catenins

The catenin proteins contribute to a number of fundamental processes in multicellular animals. Beta-catenin's best-known roles are in cell–cell adhesion and in canonical Wnt signaling. Vertebrate catenins were first isolated in association with cadherin proteins at cell–cell junctions [1]. Catenin proteins, which were named after the Latin word for chain, “catena,” provide an indirect link between cadherin proteins and the contractile cortical actin cytoskeleton [2]. Beta-catenin is also a central transducer of canonical Wnt signals, as it can enter the nucleus to modulate expression of gene targets, such as through the relief of TCF/LEF-mediated transcriptional repression [3]. Although the current Wnt literature focuses on beta-catenin's role, other evidence has begun to suggest that other catenins likewise act downstream of canonical Wnt or other signals to modulate gene activity (Fig. 1) [4–6].

*Corresponding Author: Pierre D. McCreas, Ph.D., The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1000, Houston, Texas 77030, pdmccrea@mdanderson.org, Office: (713) 834-6277, Fax: (713) 834-6273. *Co-corresponding Author: Rachel K. Miller, Ph.D., The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1000, Houston, Texas 77030, rkmliller@mdanderson.org, Lab: (713) 834-6307, Fax: (713) 834-6273.

#These authors contributed equally to this work.

II. Cadherin–catenin complexes

By definition catenins bind cadherins, generally but not exclusively at adherens or desmosomal cell-cell junctions. Most catenins are distinguished by a central domain composed of nine or twelve armadillo repeats [7, 8]. In vertebrates, there are three groups of armadillo-repeat catenins: namely, the beta-catenin, p120-catenin and plakophilin-catenin subfamilies (Fig. 2). Within adherens junctions, the cytoplasmic domains of classic cadherins, such as C-cadherin, E-cadherin and N-cadherin, contain two catenin binding sites [9]. Nearest to the membrane is the juxtamembrane or membrane-proximal domain of cadherins, where members of the p120-catenin subfamily (vertebrate p120-, ARVCF-, delta- or p0071-catenin) use their armadillo domains to bind in a mutually exclusive fashion (Fig. 3). In contrast, the beta-catenin subfamily in vertebrates has two members, beta- and gamma-catenin (plakoglobin), which employ their armadillo domains to bind in a mutually exclusive manner to the C-terminal, membrane-distal region of cadherins. Although the functions of catenins at adherens junctions remain under active investigation, as evident in chapters (A1, A4, C1 and D2), beta-catenin subfamily members indirectly link cadherins to the contractile actin–myosin cytoskeleton through their associations with proteins including alpha-catenin, vinculin and EPLIN [2, 10]. When bound, p120 subfamily members reduce cadherin endocytosis, promoting cadherin stabilization, association with the cortical actin cytoskeleton and the clustering of cadherins at adhesive sites [11, 12] (see chapter D2).

Related but distinct from the classic cadherins are the desmosomal cadherins (see chapter B3). For example, at desmosomal junctions, desmocollin- and desmoglein-cadherins associate with plakoglobin, a member of the beta-catenin subfamily, and further bind members of the plakophilin-catenin subfamily (plakophilins-1, -2 and -3) (Figs. 2 and 3) [13–16]. Within desmosomes, plakoglobin, plakophilins and additional proteins assist in linking desmosomes to the intermediate filament cytoskeleton. These catenin interactions appear roughly analogous to those of beta-catenin in complex with classic cadherins at adherens junction in that they bridge the desmosomal cadherin complex with the intermediate filament cytoskeleton [17, 18]. Also, the plakophilin subfamily functions within desmosomes may parallel those of p120 subfamily members at adherens junctions, in that they promote desmosomal cadherin stability and clustering [19, 20].

Despite its name and (indirect) association with cadherins, alpha-catenin lacks armadillo domains, and instead bears homology to the actin-binding protein vinculin [21]. Intriguingly, alpha-catenin has been implicated in mechanosensing within the cadherin complex [22] (see chapter A3) and has also been reported in the nucleus [23]. However, it will not be discussed further here, given its lack of homology with the other catenins.

III. The “canonical” view of canonical Wnt signaling

In addition to their roles in cell-cell interactions via the adherens and desmosomal junctions, catenins are essential to cellular communication via their function in Wnt signaling [24]. In fact, a recent study suggests that the Wnt-related functions of catenin proteins might have arisen earlier (are “more fundamental”) than their adhesive roles [25].

1. Discovery of Wnt signaling components

Wnt signaling has been investigated over the past 30 years [3], beginning with a genetic screen conducted by Nusslein-Volhard and Wieschaus to identify genes required for embryonic segment polarity in *Drosophila* [26]. The *wingless* (*Drosophila* Wnt ligand) gene was identified, and soon thereafter, Nusse and Varmus observed activation of the *int-1* gene upon nearby integration of mouse mammary tumor virus (MMTV) [27]. The *Drosophila* and

mammalian gene products were shown to be orthologous, and the gene names of *wingless* and *int-1* were combined to form Wnt1 [28].

Since the discovery of genes encoding Wnt ligands, numerous components within the signaling cascade have been identified and characterized (Fig. 1), such as *armadillo*, the *Drosophila* ortholog of vertebrate beta-catenin [29]. Experiments in *Xenopus laevis* (frog) embryos demonstrated a fundamental role for Wnt1 in body axis formation [30]. *Xenopus* beta-catenin was cloned based on its association with cadherins [31], and then, unexpectedly, found to participate in Wnt signaling/ body axis formation [32]. Key studies in *Drosophila* later examined the epistatic relationships of Wnt pathway components, including (among others) *porcupine*, *dishevelled*, *armadillo* (beta-catenin) and *zeste-white 3* (GSK3beta), followed later by discovery of the plasma-membrane associated Frizzled receptors [3]. LEF/TCF (HMG-box transcription factor) was discovered early-on, followed by characterization of its binding with and regulation by beta-catenin [33, 34]. Components of the canonical Wnt signaling pathway have continued to be discovered, such as the Wnt-ligand coreceptors LRP5/6 (*Drosophila* *arrow*), inhibitory secreted antagonists such as Dkk1, and the augmentation of low-level Wnt signaling via activation of LGR receptors by R-spondin ligand [3, 35].

2. The basics of canonical Wnt signaling

Canonical Wnt signaling has been extensively studied given its relationship to development and disease [24]. It is initiated when secreted Wnt ligands bind a Frizzled–LRP receptor–coreceptor complex (Fig. 1). Conversely, in the absence of appropriate Wnt ligands, the “signaling pool” of beta-catenin (*i.e.* non-cadherin bound), is diminished by its interaction with a “destruction complex” composed of the GSK3beta and CK1-alpha kinases, and the APC (adenomatous polyposis coli tumor suppressor) and axin scaffolds, among other components. The phosphorylation of beta-catenin by GSK3beta and CK1-alpha leads to ubiquitination by beta-TRCP (E3-ubiquitin ligase), followed by degradation in the proteasome. Since beta-catenin’s signaling pool is thereby lowered (in the absence of canonical Wnt signals), it is less likely that beta-catenin will enter the nucleus to relieve repression conferred by TCF/LEF, which reside in association with repressive factors such as Groucho [3].

Conversely, when secreted Wnt ligands bind the Frizzled–LRP receptor–coreceptor complex, LRP’s intracellular domain becomes phosphorylated by CK1-alpha. In one model, this leads to LRP-mediated sequestration of the axin-GSK3beta complex away from the destruction complex [36], promoting beta-catenin’s accumulation within a growing cytoplasmic “signaling pool.” This signaling pool is distinct from the usually much larger pool of beta-catenin bound to cadherins at cell–cell junctions, which is frequently viewed as being Wnt signaling-inactive. It should be pointed out, however, that evidence exists for beta-catenin’s dissociation from cadherins in response to other stimuli (*e.g.* RTKs or Src) [37], resulting in activation of canonical Wnt reporters. In any case, a portion of the cytoplasmic pool of beta-catenin that arises following canonical Wnt ligand activation translocates to the nucleus, where it binds TCF/LEF and relieves their repression of gene targets. Upon binding beta-catenin, the corepressors in association with TCF/LEF (*e.g.* Groucho and CtBP) [38] are shed in favor of coactivators/chromatin remodelers (*e.g.* p300 and Pygo) [39, 40] to promote gene target activation.

IV. The “other” catenins in the nucleus

To this point, research has largely focused on the adhesion-related roles of the catenin family, in addition to the transcriptional roles of beta-catenin in particular within the Wnt signaling pathway. However, catenins within all subfamilies localize to the nucleus (Fig. 3),

and a growing body of evidence suggests that they have transcriptional roles [41]. Thus, further assessment of the nuclear roles of the “other” is necessary.

1. The beta-catenin subfamily

Like beta-catenin, plakoglobin (gamma-catenin) utilizes its armadillo repeats to interact with binding partners (Fig. 2), including cadherins and nuclear transcription factors such as TCF/LEF [42]. Both plakoglobin and beta-catenin regulate transcription within the nucleus, and although they modulate some of the same genes, beta-catenin’s role in the canonical Wnt pathway appears more direct. For example, although plakoglobin activates some TCF/LEF-controlled gene targets [43] and shares with beta-catenin mechanisms regulating its protein stability, the means by which it executes transcriptional effects may be distinct from those of beta-catenin [42]. Surprisingly, for example, cytoplasmic more so than nuclear accumulation of plakoglobin appears to promote Wnt signaling [42], and its nuclear presence inhibits TCF/LEF gene-target activation in the co-presence of beta-catenin [44]. It has been proposed that the cytoplasmic sequestration of plakoglobin results in activation of Wnt targets by retention of TCF/LEF outside the nucleus, which contrasts with the mechanism generally noted for beta-catenin [42]. Noteworthy, however, is that in some developmental contexts, beta-catenin has likewise been found to derepress TCF by means that involve TCF dissociation from DNA [45].

2. The p120 subfamily

Increasing evidence shows that p120 subfamily members, like p120-, ARVCF-, delta-, and p0071-catenin (Fig. 2), regulate gene activity. In the late 1990s, p120 was found to bind the transcriptional repressor Kaiso [46, 47]. By competitively displacing Kaiso from its sequence-specific gene targets and/or sequestering Kaiso in the cytoplasm, p120 is thought to derepress (activate) transcription [46]. p120 also interacts with the transcriptional repressor GLIS2, facilitating GLIS2 cleavage and altering GLIS2’s selection of gene targets [48]. More recently, studies have uncovered nuclear activities of delta-catenin [49, 50].

In the context of the nucleus, some catenins appear to have partially overlapping transcriptional partners. For example, both p120 and delta-catenin bind and modulate Kaiso, albeit with different outcomes [46, 51], and beta-catenin and plakoglobin bind TCF/LEF. The shared *versus* exclusive transcription-factor associations of catenins may facilitate both networked and differential effects. One possibility, yet to be tested, is that different Wnt-ligand:Wnt-receptor pairings may preferentially stabilize certain catenins more than others, partially accounting for distinctive downstream nuclear outputs. Recent studies have identified components such as Frodo (presumed scaffold) and Dyrk1A (Ser/Thr kinase) as binding and facilitating the stabilization of p120-catenin, thus enhancing its signaling capacity. Since Frodo and Dyrk1A may preferentially bind and stabilize p120-catenin [4, 52], they serve as examples of the type of molecules that could facilitate selective catenin activity downstream of particular receptor–ligand pairings (*e.g.* canonical Wnt pathway).

3. The plakophilin subfamily

Plakophilin-1, -2 and -3 (Fig. 2) have further been reported in the nucleus (Fig. 3), and several nuclear functions are proposed. For example, plakophilin-2 has been reported to associate with beta-catenin and modulate Wnt gene activation [53]. Plakophilin-1 binds single-strand DNA, affecting cell survival following DNA damage [54]. Finally, our group has preliminarily resolved plakophilin-3’s association with two established transcription factors (unpublished results). Clearly, the continued study of plakophilin family members is required to broaden our perspective of their nuclear roles.

V. Isoform diversity in the “other” catenins

As described, catenins other than beta-catenin modulate different aspects of cellular behavior, including cell adhesion, transcription and GTPase activity (described below) (Fig. 3). Regulation of these processes may be influenced through specific isoform usage within different contexts. For example, p120-catenin exists as multiple isoforms that arise due to alternative translational initiation and/ or RNA splicing (Fig. 2) [5]. The same cell can express greater than one isoform. Isoform 1 (longest) has been associated somewhat more with motile cell states, and isoform 3 (shorter) with sessile behaviors [55, 56]. Such associations are thought to result in part from differential p120 isoform effects on small-GTPases [57], as addressed below and in Chapter D2. Alternative isoform usage by p120 subfamily members has repeatedly been observed across tissues and developmental or disease stages, but its basis and functional distinctions require further study [58]. As the organization of exons within the p120 subfamily is conserved [13], it is expected that at least some of the alternative splice isoforms of p120 may additionally exist in other subfamily members, including ARVCF-, delta-, and p0071-catenin (Fig. 2). The exon organizations of plakophilins resemble each other, as well as the organization of p120 subfamily members, but are not similar to those of beta-catenin subfamily members [13]. However, whereas p120 subfamily members appear to have multiple isoforms, only two have been identified for plakophilin-1 and -2 (Fig. 2) [59–61]. Differential usage and regulation of catenin isoforms may achieve specificity of cellular responses within the contexts of cell adhesion, small-GTPase activity and transcription.

VI. Wnt signaling and “the other” catenins

As noted earlier, canonical Wnt signaling is currently defined as the pathway in which signal transduction occurs *via* beta-catenin, overlooking the potential roles of multiple similarly structured catenins in vertebrates (Fig. 1). This is understandable because beta-catenin is the dominant player, with its loss or gain often resulting in graphic phenotypic and molecular effects. When manipulating members of the p120 subfamily, the effects on Wnt signaling are more modest. For example, to resolve external Wnt phenotypes in *Xenopus* embryos, p120 effects are best tested in the context of a sensitized background, such as in conjunction with altered beta-catenin levels [62]. Thus, in contrast to beta-catenin, p120 cannot induce duplicate axis formation in *Xenopus* when expressed alone in the ventral region, a commonly used readout of ectopic canonical Wnt signaling. Yet if the derepression of TCF/LEF is made coordinate with the depletion of Kaiso (the transcriptional repressor that p120-catenin analogously relieves), partial duplicate axes are observed [62]. The p120 subfamily effects on Wnt signaling may further be masked by known p120-subfamily effects on small GTPases [4], which regulate cytoskeletal structures and cell junctions. Finally, unlike beta-catenin, each p120 subfamily member has multiple isoforms generated from alternative translational start sites and/ or by RNA splicing (Fig. 2). Thus, as discussed below, owing to the resulting presence or absence of a “destruction box” targeted by the destruction components (*e.g.* GSK3beta, CK1-alpha, APC, axin and beta-TRCP), different isoforms of the same catenin are not equally responsive to canonical Wnt signals [6].

In conclusion, the greater focus on beta-catenin is justified because given its dominant role within the canonical Wnt pathway. However, the fact that some isoforms of other catenins, such as p120 isoform1, likewise respond to canonical Wnt signals, and thereupon enter the nucleus to modulate transcription factors distinct from LEF/TCF, suggests that there is a networked canonical response that requires attention (Fig. 1). An especially pertinent point is that canonical Wnt signals generate numerous distinct outcomes depending on the organism, tissue or temporal or disease setting. While this is well known to be accounted for in part by the contributions of other distinct signals, some of which cross talk with the Wnt

pathway (*e.g.* Notch, FGF, TGF-beta) [63], it is equally interesting to consider that the effects on other catenins may contribute to context-specific outcomes.

1. Crosstalk between cell adhesions and Wnt signaling

Similar to beta- and gamma-catenin/plakoglobin (both members of the beta-catenin subfamily), most catenins of the p120-catenin and plakophilin subfamilies have been observed in the nucleus (Fig. 1). While evidence is still being accumulated, one possibility is that the repertoire of catenin components within adherens junctions and desmosomes facilitates crosstalk between these adhesive structures and the nucleus (Fig. 3). In addition to highly polarized, mature junctions participating in contact inhibition (modulation of hippo signaling, etc.) [64–66], such catenin transit or crosstalk between cell junctions and the nucleus might be relevant to regulating dynamic cadherin contacts, such as those observed during morphogenesis or wound healing.

In common with beta-catenin, the nuclear localization of p120-catenin and plakophilin subfamily members is context dependent. In most instances their junctional localization is much more prominent, to the extent that their presence in the nucleus might understandably be overlooked. Relative to beta-catenin, which is often likewise difficult to visualize in the nucleus, there has been relatively scant attention paid to the nuclear roles of p120 and plakophilin family members, despite the potential or known relevance of the p120 and plakophilin subfamilies in development and disease (see chapter C6) [67].

Under some conditions, release of catenins from adherens junctions may precede their nuclear translocation to engage in gene regulation. For example, even though it is not the generally discussed route, beta-catenin's dissociation from cadherin in response to RTK or Src activity has been associated in certain contexts with higher Wnt-reporter activity [37]. Kinases and phosphatases are enriched at cell junctions, and some modulate the retention *versus* release of catenins from cadherins [68, 69]. Likewise, cadherin absence has been associated in certain studies with higher canonical Wnt/ beta-catenin signaling. This might be ascribed to beta-catenin no longer being sequestered by cadherin, enhancing its potential signaling pool (especially in cells with a less than fully active destruction complex) [70]. Additionally, cadherin-associated p120 has recently been tied to the assembly of the canonical Wnt signalosome, resulting in greater beta-catenin signaling activity [71]. However, cell adhesion has also been implicated in destabilizing the signaling pool of beta-catenin by promoting destruction complex activity [72].

As for many complexes, it is accepted that catenin protein associations and localizations respond to secondary protein modifications. For example, upon Wnt pathway activation, not only is beta-catenin stability enhanced (its destruction box remains unphosphorylated), but the active signaling pool of beta-catenin is modified such that it binds TCF but not cadherin [73]. Likewise, findings suggest that the localization of catenins to junctions, cytoplasm or nucleus is responsive to their modification, or modifications upon their direct binding partners [37]. In addition to responsiveness of the cadherin–catenin complex to RTKs, Src or Wnt signals, the complex has further been implicated in functional interactions with the Hippo and other pathways [64–66] (see chapter B8). Concerning the roles of catenins in particular, considerably more work remains to address the extent to which catenins that are cadherin-bound represent a latent signaling pool, which upon release in response to an appropriate stimulus allows them to fulfill a nuclear function.

Further relationships indicate links of the canonical Wnt pathway with the cadherin–catenin complex [74]. Two recent papers, for example, reported biochemical and/or functional associations of Wnt pathway components with the cadherin–catenin complex [71, 72]. Additionally, beta-catenin's transcriptional targets include Twist, Snail and Slug [75, 76],

which repress the expression of E-cadherin (see chapter C4) [77, 78]. Interestingly, the destruction complex regulating the stability of beta-catenin (and those other catenin isoforms encoding destruction boxes) additionally acts upon Snail, which is likewise a GSK3beta target and is degraded by the proteasome. Indeed, Wnt1 has been shown to stabilize Snail [79, 80]. Thus, as a consequence of the nuclear entry of beta-catenin (perhaps in concert with other catenins), canonical Wnt pathway activity may lead to reduced cadherin levels and enhanced cell migration in some morphogenic or wound-healing contexts. A reduced level of E-cadherin may also favor the formation of larger cytoplasmic/signaling pools of p120-subfamily catenins to more fully modulate small-GTPases, or to enhance the catenins' nuclear impact.

3. The “other” catenins roles in Wnt signaling

As was noted, a potentially significant but understudied role of the p120-subfamily catenins is in canonical Wnt signaling (Fig. 1). While certain work has drawn into question the extent to which gene control exercised by Kaiso (and by inference p120) is pertinent to Wnt signaling [81], growing evidence indicates that p120 subfamily members act in parallel with beta-catenin in Wnt-mediated transcriptional regulation. Initial clues came from findings that p120 relieves Kaiso-mediated repression of *Xenopus siamois* [62] and *wnt11* [82], both established canonical Wnt target genes and thus responsive to beta-catenin relief of TCF-mediated repression. It was found that the combined and respective p120 and beta-catenin relief of Kaiso and TCF is additive in activating target gene promoters, and has the predicted developmental consequences [62]. This was evident in both molecular assays (*e.g.* endogenous gene or luciferase reporter readouts), and in gross phenotypes, such as the formation of ectopic dorsal axes in early *Xenopus* embryos [62]. Further, as predicted, exogenously expressed Kaiso inhibits beta-catenin mediated axis duplication in embryos [62]. Together these data support the role of p120/Kaiso, acting together with beta-catenin/TCF, in some canonical-Wnt developmental contexts.

Thus far, the regulation of Wnt target genes has been reported for beta-catenin, plakoglobin (gamma-catenin), p120-catenin and plakophilin-2 [43, 53, 62]. We expect that additional p120 and plakophilin subfamily members are involved. For example, delta-catenin has also been reported to bind and modulate Kaiso [51]. Also quite suggestive is that axin lowers the levels not only of beta-catenin, plakoglobin and p120-catenin, but also of delta-catenin and ARVCF-catenin (Fig. 1) [6]. Further, work from our group has shown that isoform-1 of p120 (longest) possesses a conserved destruction box at its amino-terminus and responds as predicted to both Wnt signals and the pathway's destruction machinery (Fig. 2) [6]. Independent results indicate the sensitivity of delta-catenin to GSK3-beta, likewise leading to ubiquitin/ proteasome-mediated destruction [83]. Together these data suggest that Wnt signaling initiates multiple responses through various catenins, likely modulating specific cellular responses within different biological contexts.

VII. Canonical Wnt signaling in the context of catenin–small-GTPase effects

All three catenin subfamilies act at cell junctions, but the p120 and plakophilin subfamily members additionally regulate small-GTPases within the cytoplasmic space (Fig. 3). As addressed in Chapter D2, through their association with GEFs and GAPs [84] or via direct small-GTPase interactions [85], catenins modulate the activity of RhoA, Rac1 and Cdc42 to modulate cytoskeletal dynamics [56]. For example, in a context-dependent manner, both p120 and plakophilin subfamily members can activate Rac1 and inhibit RhoA [56]. Thus, upon release from cadherin, these catenins regulate small-GTPases, either those distal (*e.g.* cell-free edge) or in the immediate junctional region. Catenin–small-GTPase communication is likewise predicted to arise upon canonical Wnt pathway stabilization of p120 isoform1, and/or Wnt-mediated stabilization of other p120 subfamily or plakophilin-catenins.

Consistent with this possibility are initial findings that a little understood component of the Wnt pathway, Frodo, enhances p120 stabilization to produce an increased modulatory effect on small-GTPases [86]. It is also intriguing that catenins further associate with the microtubule cytoskeleton, kinesins and centrosomes [87–89]. Since p120 and plakophilin subfamily catenins bind and regulate classic and/or desmosomal cadherins, as well as small-GTPases, these proteins appear well positioned to contribute to outcomes including motile versus sessile cell behaviors (Fig. 3) [90, 91]. Indeed, full-length and shorter p120 isoforms have distinguishable effects on RhoA [57, 90], such that the stabilization of certain p120 isoforms would be expected to alter cell behavior (Fig. 2). As the field progresses forward, the role of catenin stabilization in response to canonical Wnt signals will need to take into consideration catenin relationships with small-GTPases (cell architecture, trafficking and motility), in addition to effects on nuclear gene activity. Thus, while requiring further study, the p120- and plakophilin catenins potentially assist in coordinating cellular outcomes involving the canonical Wnt pathway, cadherin–catenin and cytoskeletal complexes, and gene regulation.

VIII. Redefining “canonical” Wnt signaling

As evidence for cross-talk between Wnt signaling and adherens and desmosomal junctions increases, it may become more difficult to define the boundaries of “canonical” Wnt signaling. An underdeveloped area of study focuses on whether Wnt signaling affects cell adhesion via direct mechanisms independent of downstream transcription. Wnts have been connected with endosomal internalization of cadherins in gastrulation [92]. Further, studies in *Drosophila* have shown that Wnt signaling induces reduction of membrane associated beta-catenin and concomitant destabilization of cadherins, thereby reducing cell adhesion [93]. Reduction in cell adhesion is then followed by Wnt-induced expression of E-cadherin [93, 94]. In other contexts, Wnt signaling is also associated with increased transcription of Twist, Slug and Snail, which has been reported to repress E-cadherin (see chapter C4) [77]. Additionally, Wnt pathway components physically interact with cadherins and protocadherins within adherens junctions [95]. Given that members of the p120- and plakophilin-subfamilies stabilize cadherins when bound to them within cell-cell junctions [11, 12], Wnt signaling effects upon catenin levels may also modulate cell adhesion. Additionally, such “other” catenins, namely the p120- and plakophilin- catenin family members, may regulate small-GTPases differentially as a consequence of canonical Wnt signaling. Thus, as more is learned in the years ahead, the boundaries between “non-canonical” Wnt trajectories, which also regulate these small-GTPases, and “canonical” Wnt signaling may not appear as separable in many contexts.

IX. Conclusion and Gaps in Knowledge

Following its stabilization, beta-catenin is the central signal transducer of the canonical Wnt pathway, entering the nucleus to relieve repression conferred by TCF/ LEF. However, evidence is beginning to suggest a broader effect of canonical signals through additional stabilizing effects on p120 isoform 1, and likely additional p120 or plakophilin subfamily members. Given that p120-catenin family members regulate small-GTPases and the stability of cadherins, canonical Wnt signals may produce a number of rather direct catenin-mediated effects beyond those that catenins are known or conjectured to execute in the nucleus.

Numerous questions remain regarding the role of these “other” catenins in Wnt signaling. First, it will be interesting to identify the transcription factor partners and the genes that are directly regulated by each catenin. This will help us understand each catenin’s distinct *versus* overlapping functions in response to Wnt or other signals. Further, if multiple catenins respond to Wnt signals, are they differentially regulated in accordance with a

particular Wnt-ligand:Frizzled-receptor pairing? What factors might then assist in transducing such differential effects? One possibility is the involvement of scaffolding proteins with preferences for particular catenins. In all cases, to understand the larger catenin network, we will need to identify and functionally characterize many more selective and shared protein partners within junctions and the cytoplasm/ cytoskeleton. Likewise, we must resolve direct catenin gene targets and regulatory factors within the nucleus, perhaps using the well- developed model of beta-catenin as a guide. In all cases, there is much that the cadherin–catenin field looks forward to in the coming years, with a primary interest in establishing a deeper understanding of the roles of catenins in promoting and coordinating cellular processes within varied cellular compartments.

References Cited

1. Ozawa M, Baribault H, Kemler R. The cytoplasmic domain of the cell adhesion molecule uvomorulin associates with three independent proteins structurally related in different species. *EMBO J.* 1989; 8:1711–1717. [PubMed: 2788574]
2. Abe K, Takeichi M. EPLIN mediates linkage of the cadherin catenin complex to F-actin and stabilizes the circumferential actin belt. *Proc Natl Acad Sci USA.* 2008; 105:13–19. [PubMed: 18093941]
3. Clevers H, Nusse R. Wnt/beta-Catenin Signaling and Disease. *Cell.* 2012; 149:1192–1205. [PubMed: 22682243]
4. McCrea PD, Gu D, Balda MS. Junctional music that the nucleus hears: cell-cell contact signaling and the modulation of gene activity. *Cold Spring Harb Perspect Biol.* 2009; 1:a002923. [PubMed: 20066098]
5. Pieters T, van Roy F, van Hengel J. Functions of p120ctn isoforms in cell-cell adhesion and intracellular signaling. *Front Biosci.* 2012; 17:1669–1694.
6. Hong JY, Park JI, Cho K, Gu D, Ji H, Artandi SE, McCrea PD. Shared molecular mechanisms regulate multiple catenin proteins: canonical Wnt signals and components modulate p120-catenin isoform-1 and additional p120 subfamily members. *J Cell Sci.* 2010; 123:4351–4365. [PubMed: 21098636]
7. Huber AH, Nelson WJ, Weis WI. Three-dimensional structure of the armadillo repeat region of beta-catenin. *Cell.* 1997; 90:871–882. [PubMed: 9298899]
8. Shapiro L, Weis WI. Structure and biochemistry of cadherins and catenins. *Cold Spring Harb Perspect Biol.* 2009; 1:a003053. [PubMed: 20066110]
9. Yap AS, Crampton MS, Hardin J. Making and breaking contacts: the cellular biology of cadherin regulation. *Curr Opin Cell Biol.* 2007; 19:508–514. [PubMed: 17935963]
10. Kwiatkowski AV, Maiden SL, Pokutta S, Choi HJ, Benjamin JM, Lynch AM, Nelson WJ, Weis WI, Hardin J. In vitro and in vivo reconstitution of the cadherin-catenin-actin complex from *Caenorhabditis elegans*. *Proc Natl Acad Sci USA.* 2010; 107:14591–14596. [PubMed: 20689042]
11. Reynolds AB, Carnahan RH. Regulation of cadherin stability and turnover by p120ctn: implications in disease and cancer. *Semin Cell Dev Biol.* 2004; 15:657–663. [PubMed: 15561585]
12. Nelson WJ. Regulation of cell-cell adhesion by the cadherin-catenin complex. *Biochem Soc Trans.* 2008; 36:149–155. [PubMed: 18363555]
13. Hatzfeld M. Plakophilins: Multifunctional proteins or just regulators of desmosomal adhesion? *Biochim Biophys Acta.* 2007; 1773:69–77. [PubMed: 16765467]
14. Bass-Zubek AE, Godsel LM, Delmar M, Green KJ. Plakophilins: multifunctional scaffolds for adhesion and signaling. *Curr Opin Cell Biol.* 2009; 21:708–716. [PubMed: 19674883]
15. Garrod D, Chidgey M. Desmosome structure, composition and function. *Biochim Biophys Acta.* 2008; 1778:572–587. [PubMed: 17854763]
16. Franke WW, Rickelt S, Barth M, Pieperhoff S. The junctions that don't fit the scheme: special symmetrical cell-cell junctions of their own kind. *Cell Tissue Res.* 2009; 338:1–17. [PubMed: 19680692]

17. Delva E, Tucker DK, Kowalczyk AP. The desmosome. *Cold Spring Harb Perspect Biol.* 2009; 1:a002543. [PubMed: 20066089]
18. Saito M, Tucker DK, Kohlhorst D, Niessen CM, Kowalczyk AP. Classical and desmosomal cadherins at a glance. *J Cell Sci.* 2012; 125:2547–2552. [PubMed: 22833291]
19. Bornslaeger EA, Godsel LM, Corcoran CM, Park JK, Hatzfeld M, Kowalczyk AP, Green KJ. Plakophilin 1 interferes with plakoglobin binding to desmoplakin, yet together with plakoglobin promotes clustering of desmosomal plaque complexes at cell-cell borders. *J Cell Sci.* 2001; 114:727–738. [PubMed: 11171378]
20. South AP, Wan H, Stone MG, Dopping-Hepenstal PJ, Purkis PE, Marshall JF, Leigh IM, Eady RA, Hart IR, McGrath JA. Lack of plakophilin 1 increases keratinocyte migration and reduces desmosome stability. *J Cell Sci.* 2003; 116:3303–3314. [PubMed: 12840072]
21. Pokutta S, Drees F, Yamada S, Nelson WJ, Weis WI. Biochemical and structural analysis of alpha-catenin in cell-cell contacts. *Biochem Soc Trans.* 2008; 36:141–147. [PubMed: 18363554]
22. Lecuit T. alpha-catenin mechanosensing for adherens junctions. *Nat Cell Biol.* 2010; 12:522–524. [PubMed: 20453846]
23. Scott JA, Yap AS. Cinderella no longer: alpha-catenin steps out of cadherin's shadow. *J Cell Sci.* 2006; 119:4599–4605. [PubMed: 17093264]
24. Nusse R. Wnt signaling. *Cold Spring Harb Perspect Biol.* 2012; 4
25. Dickinson DJ, Nelson WJ, Weis WI. A polarized epithelium organized by beta- and alpha-catenin predates cadherin and metazoan origins. *Science.* 2011; 331:1336–1339. [PubMed: 21393547]
26. Nusslein-Volhard C, Wieschaus E. Mutations affecting segment number and polarity in *Drosophila*. *Nature.* 1980; 287:795–801. [PubMed: 6776413]
27. Nusse R, Varmus HE. Many tumors induced by the mouse mammary tumor virus contain a provirus integrated in the same region of the host genome. *Cell.* 1982; 31:99–109. [PubMed: 6297757]
28. Rijsewijk F, van Deemter L, Wagenaar E, Sonnenberg A, Nusse R. Transfection of the *int-1* mammary oncogene in cuboidal RAC mammary cell line results in morphological transformation and tumorigenicity. *EMBO J.* 1987; 6:127–131. [PubMed: 3034569]
29. Wieschaus E, Riggelman R. Autonomous requirements for the segment polarity gene *armadillo* during *Drosophila* embryogenesis. *Cell.* 1987; 49:177–184. [PubMed: 3105892]
30. McMahon AP, Moon RT. Ectopic expression of the proto-oncogene *int-1* in *Xenopus* embryos leads to duplication of the embryonic axis. *Cell.* 1989; 58:1075–1084. [PubMed: 2673541]
31. McCrear PD, Turck CW, Gumbiner B. A homolog of the armadillo protein in *Drosophila* (plakoglobin) associated with E-cadherin. *Science.* 1991; 254:1359–1361. [PubMed: 1962194]
32. McCrear PD, Briehar WM, Gumbiner BM. Induction of a secondary body axis in *Xenopus* by antibodies to beta-catenin. *J Cell Biol.* 1993; 123:477–484. [PubMed: 8408227]
33. Nusse R. A versatile transcriptional effector of Wntless signaling. *Cell.* 1997; 89:321–323. [PubMed: 9150130]
34. Porfiri E, Rubinfeld B, Albert I, Hovanes K, Waterman M, Polakis P. Induction of a beta-catenin-LEF-1 complex by wnt-1 and transforming mutants of beta-catenin. *Oncogene.* 1997; 15:2833–2839. [PubMed: 9419974]
35. Haegebarth A, Clevers H. Wnt signaling, *lgr5*, and stem cells in the intestine and skin. *Am J Pathol.* 2009; 174:715–721. [PubMed: 19197002]
36. Zeng X, Huang H, Tamai K, Zhang X, Harada Y, Yokota C, Almeida K, Wang J, Doble B, Woodgett J, Wynshaw-Boris A, Hsieh JC, He X. Initiation of Wnt signaling: control of Wnt coreceptor Lrp6 phosphorylation/activation via frizzled, dishevelled and axin functions. *Development.* 2008; 135:367–375. [PubMed: 18077588]
37. Nelson WJ, Nusse R. Convergence of Wnt, beta-catenin, and cadherin pathways. *Science.* 2004; 303:1483–1487. [PubMed: 15001769]
38. Polakis P. Wnt signaling in cancer. *Cold Spring Harb Perspect Biol.* 2012; 4
39. Miyagishi M, Fujii R, Hatta M, Yoshida E, Araya N, Nagafuchi A, Ishihara S, Nakajima T, Fukamizu A. Regulation of Lef-mediated transcription and p53-dependent pathway by associating beta-catenin with CBP/p300. *J Biol Chem.* 2000; 275:35170–35175. [PubMed: 10906119]

40. Thompson B, Townsley F, Rosin-Arbesfeld R, Musisi H, Bienz M. A new nuclear component of the Wnt signalling pathway. *Nat Cell Biol.* 2002; 4:367–373. [PubMed: 11988739]
41. McCrea PD, Gu D. The catenin family at a glance. *J Cell Sci.* 2010; 123:637–642. [PubMed: 20164302]
42. Zhurinsky J, Shutman M, Ben-Ze'ev A. Plakoglobin and beta-catenin: protein interactions, regulation and biological roles. *J Cell Sci.* 2000; 113 (Pt 18):3127–3139. [PubMed: 10954412]
43. Maeda O, Usami N, Kondo M, Takahashi M, Goto H, Shimokata K, Kusugami K, Sekido Y. Plakoglobin (gamma-catenin) has TCF/LEF family-dependent transcriptional activity in beta-catenin-deficient cell line. *Oncogene.* 2004; 23:964–972. [PubMed: 14661054]
44. Garcia-Gras E, Lombardi R, Giocondo MJ, Willerson JT, Schneider MD, Khoury DS, Marian AJ. Suppression of canonical Wnt/beta-catenin signaling by nuclear plakoglobin recapitulates phenotype of arrhythmogenic right ventricular cardiomyopathy. *J Clin Invest.* 2006; 116:2012–2021. [PubMed: 16823493]
45. Hikasa H, Ezan J, Itoh K, Li X, Klymkowsky MW, Sokol SY. Regulation of TCF3 by Wnt-dependent phosphorylation during vertebrate axis specification. *Dev Cell.* 2010; 19:521–532. [PubMed: 20951344]
46. Daniel JM. Dancing in and out of the nucleus: p120(ctn) and the transcription factor Kaiso. *Biochim Biophys Acta.* 2007; 1773:59–68. [PubMed: 17050009]
47. Daniel JM, Reynolds AB. The catenin p120(ctn) interacts with Kaiso, a novel BTB/POZ domain zinc finger transcription factor. *Mol Cell Biol.* 1999; 19:3614–3623. [PubMed: 10207085]
48. Hosking CR, Ulloa F, Hogan C, Ferber EC, Figueroa A, Gevaert K, Birchmeier W, Briscoe J, Fujita Y. The transcriptional repressor Glis2 is a novel binding partner for p120 catenin. *Mol Biol Cell.* 2007; 18:1918–1927. [PubMed: 17344476]
49. Gu D, Tonthat NK, Lee M, Ji H, Bhat KP, Hollingsworth F, Aldape KD, Schumacher MA, Zwaka TP, McCrea PD. Caspase-3 cleavage links delta-catenin to the novel nuclear protein ZIFCAT. *J Biol Chem.* 2011; 286:23178–23188. [PubMed: 21561870]
50. Koutras C, Lessard CB, Levesque G. A nuclear function for the presenilin 1 neuronal partner NPRAP/delta-catenin. *J Alzheimers Dis.* 2011; 27:307–316. [PubMed: 21811021]
51. Rodova M, Kelly KF, VanSaun M, Daniel JM, Werle MJ. Regulation of the Rapsyn Promoter by Kaiso and {delta}-Catenin. *Mol Cell Biol.* 2004; 24:7188–7196. [PubMed: 15282317]
52. Hong JY, Park JI, Lee M, Munoz WA, Miller RK, Ji H, Gu D, Sokol SY, McCrea PD. Down's-syndrome-related kinase Dyrk1A modulates the p120-catenin-Kaiso trajectory of the Wnt signaling pathway. *J Cell Sci.* 2012; 125:561–569. [PubMed: 22389395]
53. Chen X, Bonne S, Hatzfeld M, van Roy F, Green KJ. Protein binding and functional characterization of plakophilin 2. Evidence for its diverse roles in desmosomes and beta -catenin signaling. *J Biol Chem.* 2002; 277:10512–10522. [PubMed: 11790773]
54. Sobolik-Delmaire T, Reddy R, Pashaj A, Roberts BJ, Wahl JK 3rd. Plakophilin-1 localizes to the nucleus and interacts with single-stranded DNA. *J Invest Dermatol.* 2010; 130:2638–2646. [PubMed: 20613778]
55. Slorach EM, Chou J, Werb Z. Zeppol is a novel metastasis promoter that represses E-cadherin expression and regulates p120-catenin isoform expression and localization. *Genes Dev.* 2011; 25:471–484. [PubMed: 21317240]
56. Anastasiadis PZ. p120-ctn: A nexus for contextual signaling via Rho GTPases. *Biochim Biophys Acta.* 2007; 1773:34–46. [PubMed: 17028013]
57. Yanagisawa M, Huvelde D, Kreinest P, Lohse CM, Cheville JC, Parker AS, Copland JA, Anastasiadis PZ. A p120 catenin isoform switch affects Rho activity, induces tumor cell invasion, and predicts metastatic disease. *J Biol Chem.* 2008; 283:18344–18354. [PubMed: 18407999]
58. Pieters T, van Hengel J, van Roy F. Functions of p120ctn in development and disease. *Front Biosci.* 2012; 17:760–783.
59. Bonne S, Gilbert B, Hatzfeld M, Chen X, Green KJ, van Roy F. Defining desmosomal plakophilin-3 interactions. *J Cell Biol.* 2003; 161:403–416. [PubMed: 12707304]
60. Gandjbakhch E, Charron P, Fressart V, Lorin de la Grandmaison G, Simon F, Gary F, Vite A, Hainque B, Hidden-Lucet F, Komajda M, Villard E. Plakophilin 2A is the dominant isoform in

human heart tissue: consequences for the genetic screening of arrhythmogenic right ventricular cardiomyopathy. *Heart*. 2011; 97:844–849. [PubMed: 21378009]

61. Schmidt A, Langbein L, Rode M, Pratzel S, Zimbelmann R, Franke WW. Plakophilins 1a and 1b: widespread nuclear proteins recruited in specific epithelial cells as desmosomal plaque components. *Cell Tissue Res*. 1997; 290:481–499. [PubMed: 9369526]
62. Park JI, Kim SW, Lyons JP, Ji H, Nguyen TT, Cho K, Barton MC, Deroo T, Vleminckx K, Moon RT, McCrea PD. Kaiso/p120-catenin and TCF/beta-catenin complexes coordinately regulate canonical Wnt gene targets. *Dev Cell*. 2005; 8:843–854. [PubMed: 15935774]
63. Katoh M. Networking of WNT, FGF, Notch, BMP, and Hedgehog signaling pathways during carcinogenesis. *Stem Cell Rev*. 2007; 3:30–38. [PubMed: 17873379]
64. Kim NG, Koh E, Chen X, Gumbiner BM. E-cadherin mediates contact inhibition of proliferation through Hippo signaling-pathway components. *Proc Natl Acad Sci USA*. 2011; 108:11930–11935. [PubMed: 21730131]
65. Cordenonsi M, Zanconato F, Azzolin L, Forcato M, Rosato A, Frasson C, Inui M, Montagner M, Parenti AR, Poletti A, Daidone MG, Dupont S, Basso G, Bicciato S, Piccolo S. The Hippo transducer TAZ confers cancer stem cell-related traits on breast cancer cells. *Cell*. 2011; 147:759–772. [PubMed: 22078877]
66. Varelas X, Miller BW, Sopko R, Song S, Gregorieff A, Fellouse FA, Sakuma R, Pawson T, Hunziker W, McNeill H, Wrana JL, Attisano L. The Hippo pathway regulates Wnt/beta-catenin signaling. *Dev Cell*. 2010; 18:579–591. [PubMed: 20412773]
67. McCrea PD, Park JI. Developmental functions of the P120-catenin sub-family. *Biochim Biophys Acta*. 2007; 1773:17–33. [PubMed: 16942809]
68. Andl CD, Rustgi AK. No one-way street: cross-talk between e-cadherin and receptor tyrosine kinase (RTK) signaling: a mechanism to regulate RTK activity. *Cancer Biol Ther*. 2005; 4:28–31. [PubMed: 15662113]
69. Lilien J, Balsamo J. The regulation of cadherin-mediated adhesion by tyrosine phosphorylation/dephosphorylation of beta-catenin. *Curr Opin Cell Biol*. 2005; 17:459–465. [PubMed: 16099633]
70. Jeanes A, Gottardi CJ, Yap AS. Cadherins and cancer: how does cadherin dysfunction promote tumor progression? *Oncogene*. 2008; 27:6920–6929. [PubMed: 19029934]
71. Casagolda D, Del Valle-Perez B, Valls G, Lugalde E, Vinyoles M, Casado-Vela J, Solanas G, Batlle E, Reynolds AB, Casal JI, de Herreros AG, Dunach M. A p120-catenin-CK1epsilon complex regulates Wnt signaling. *J Cell Sci*. 2010; 123:2621–2631. [PubMed: 20940130]
72. Maher MT, Flozak AS, Stocker AM, Chenn A, Gottardi CJ. Activity of the beta-catenin phosphodestruction complex at cell-cell contacts is enhanced by cadherin-based adhesion. *J Cell Biol*. 2009; 186:219–228. [PubMed: 19620634]
73. Gottardi CJ, Gumbiner BM. Distinct molecular forms of beta-catenin are targeted to adhesive or transcriptional complexes. *J Cell Biol*. 2004; 167:339–349. [PubMed: 15492040]
74. Janssens S, Crabbe E, Vleminckx K. The role of Wnt in cell signaling and cell adhesion during early vertebrate development. *Front Biosci*. 2012; 17:2352–2366.
75. Vallin J, Thuret R, Giacomello E, Faraldo MM, Thiery JP, Broders F. Cloning and characterization of three *Xenopus* slug promoters reveal direct regulation by Lef/beta-catenin signaling. *J Biol Chem*. 2001; 276:30350–30358. [PubMed: 11402039]
76. Tan C, Costello P, Sanghera J, Dominguez D, Baulida J, de Herreros AG, Dedhar S. Inhibition of integrin linked kinase (ILK) suppresses beta-catenin-Lef/Tcf-dependent transcription and expression of the E-cadherin repressor, snail, in APC^{-/-} human colon carcinoma cells. *Oncogene*. 2001; 20:133–140. [PubMed: 11244511]
77. Heuberger J, Birchmeier W. Interplay of cadherin-mediated cell adhesion and canonical Wnt signaling. *Cold Spring Harb Perspect Biol*. 2010; 2:a002915. [PubMed: 20182623]
78. Foubert E, De Craene B, Berx G. Key signalling nodes in mammary gland development and cancer. The Snail1-Twist1 conspiracy in malignant breast cancer progression. *Breast Cancer Res*. 2010; 12:206. [PubMed: 20594364]
79. Yook JI, Li XY, Ota I, Fearon ER, Weiss SJ. Wnt-dependent regulation of the E-cadherin repressor snail. *J Biol Chem*. 2005; 280:11740–11748. [PubMed: 15647282]

80. Zhou BP, Deng J, Xia W, Xu J, Li YM, Gunduz M, Hung MC. Dual regulation of Snail by GSK-3 β -mediated phosphorylation in control of epithelial-mesenchymal transition. *Nat Cell Biol.* 2004; 6:931–940. [PubMed: 15448698]
81. Ruzov A, Savitskaya E, Hackett JA, Reddington JP, Prokhortchouk A, Madej MJ, Chekanov N, Li M, Dunican DS, Prokhortchouk E, Pennings S, Meehan RR. The non-methylated DNA-binding function of Kaiso is not required in early *Xenopus laevis* development. *Development.* 2009; 136:729–738. [PubMed: 19158185]
82. Kim SW, Park JI, Spring CM, Sater AK, Ji H, Otchere AA, Daniel JM, McCrea PD. Non-canonical Wnt signals are modulated by the Kaiso transcriptional repressor and p120-catenin. *Nat Cell Biol.* 2004; 6:1212–1220. [PubMed: 15543138]
83. Oh M, Kim H, Yang I, Park JH, Cong WT, Baek MC, Bareiss S, Ki H, Lu Q, No J, Kwon I, Choi JK, Kim K. GSK-3 phosphorylates delta-catenin and negatively regulates its stability via ubiquitination/proteasome-mediated proteolysis. *J Biol Chem.* 2009; 284:28579–28589. [PubMed: 19706605]
84. Niessen CM, Yap AS. Another job for the talented p120-catenin. *Cell.* 2006; 127:875–877. [PubMed: 17129772]
85. Anastasiadis PZ, Moon SY, Thoreson MA, Mariner DJ, Crawford HC, Zheng Y, Reynolds AB. Inhibition of RhoA by p120 catenin. *Nat Cell Biol.* 2000; 2:637–644. [PubMed: 10980705]
86. Park JI, Ji H, Jun S, Gu D, Hikasa H, Li L, Sokol SY, McCrea PD. Frd1 links Dishevelled to the p120-catenin/Kaiso pathway: distinct catenin subfamilies promote Wnt signals. *Dev Cell.* 2006; 11:683–695. [PubMed: 17084360]
87. Bahmanyar S, Kaplan DD, Deluca JG, Giddings TH Jr, O'Toole ET, Winey M, Salmon ED, Casey PJ, Nelson WJ, Barth AI. beta-Catenin is a Nek2 substrate involved in centrosome separation. *Genes Dev.* 2008; 22:91–105. [PubMed: 18086858]
88. Chen X, Kojima S, Borisy GG, Green KJ. p120 catenin associates with kinesin and facilitates the transport of cadherin-catenin complexes to intercellular junctions. *J Cell Biol.* 2003; 163:547–557. [PubMed: 14610057]
89. Ichii T, Takeichi M. p120-catenin regulates microtubule dynamics and cell migration in a cadherin-independent manner. *Genes Cells.* 2007; 12:827–839. [PubMed: 17584295]
90. Reynolds AB, Rocznik-Ferguson A. Emerging roles for p120-catenin in cell adhesion and cancer. *Oncogene.* 2004; 23:7947–7956. [PubMed: 15489912]
91. Yanagisawa M, Anastasiadis PZ. p120 catenin is essential for mesenchymal cadherin-mediated regulation of cell motility and invasiveness. *J Cell Biol.* 2006; 174:1087–1096. [PubMed: 16982802]
92. Ulrich F, Krieg M, Schotz EM, Link V, Castanon I, Schnabel V, Taubenberger A, Mueller D, Puech PH, Heisenberg CP. Wnt11 functions in gastrulation by controlling cell cohesion through Rab5c and E-cadherin. *Dev Cell.* 2005; 9:555–564. [PubMed: 16198297]
93. Wodarz A, Stewart DB, Nelson WJ, Nusse R. Wingless signaling modulates cadherin-mediated cell adhesion in *Drosophila* imaginal disc cells. *J Cell Sci.* 2006; 119:2425–2434. [PubMed: 16720643]
94. Yanagawa S, Lee JS, Haruna T, Oda H, Uemura T, Takeichi M, Ishimoto A. Accumulation of Armadillo induced by Wingless, Dishevelled, and dominant-negative Zeste-White 3 leads to elevated DE-cadherin in *Drosophila* clone 8 wing disc cells. *J Biol Chem.* 1997; 272:25243–25251. [PubMed: 9312140]
95. Hay E, Buczkowski T, Marty C, Da Nascimento S, Sonnet P, Marie PJ. Peptide-based mediated disruption of N-cadherin-LRP5/6 interaction promotes Wnt signalling and bone formation. *J Bone Miner Res.* 2012
96. Logan CY, Miller JR, Ferkowicz MJ, McClay DR. Nuclear beta-catenin is required to specify vegetal cell fates in the sea urchin embryo. *Development.* 1999; 126:345–357. [PubMed: 9847248]
97. Bonne S, van Hengel J, Nollet F, Kools P, van Roy F. Plakophilin-3, a novel armadillo-like protein present in nuclei and desmosomes of epithelial cells. *J Cell Sci.* 1999; 112 (Pt 14):2265–2276. [PubMed: 10381383]

Figure 1. Catenins and canonical Wnt signaling. (color)

A. Canonical Wnt signaling inhibits the destruction complex (purple), preventing degradation of catenin proteins (red). Upon stabilization, catenin proteins may enter the nucleus to bind transcription factors (blue), regulating downstream gene expression. Canonical regulation of the p120- and plakophilin- catenin subfamilies is distinct from the non-canonical Wnt signaling trajectories (not shown). Dotted lines represent relationships that are currently uncertain.

B. In *Xenopus* embryos, overexpression of Axin, a destruction complex component, reduces the levels of p120-catenin subfamily members. Beta-catenin is also destabilized by Axin (positive control) [6].¹

C. Members of all subfamilies of catenins localize to the nucleus in certain contexts [41].²

¹6. Hong, J. Y., Park, J. I., Cho, K., Gu, D., Ji, H., Artandi, S. E. and McCrea, P. D. (2010) Shared molecular mechanisms regulate multiple catenin proteins: canonical Wnt signals and components modulate p120-catenin isoform-1 and additional p120 subfamily members. *J. Cell Sci.* **123**, 4351–4365 (reproduced with permission)

Figure 2. The catenin superfamily and isoforms. (color)

A. Catenin proteins are characterized by an armadillo domain comprising 9 or 12 armadillo repeats. They are classified into three distinct subfamilies, the beta-catenin subfamily, the p120-catenin subfamily, and the plakophilin subfamily.

B. The best characterized member of the p120 subfamily, p120-catenin, has numerous isoforms. These isoforms are generated by a combination of differential translational starts sites (e.g. Isoforms 1–4) and differential splice exons (e.g. exons A, B, and C in black). The isoforms vary in their regulation. For example, only the longest isoform of p120-catenin (Isoform 1) possesses a “destruction box” with conserved GSK3-beta (and CK1-alpha) phosphorylation sites at its N-terminus (*). Plakophilin isoforms arise through alternatively spliced exons. For example, plakophilin 2B has one additional exon (green) as compared with plakophilin 2A.

²⁴¹. McCrea, P. D. and Gu, D. Ibid. The catenin family at a glance. 637–642 (reproduced with permission)

96. Logan, C. Y., Miller, J. R., Ferkowicz, M. J. and McClay, D. R. (1999) Nuclear beta-catenin is required to specify vegetal cell fates in the sea urchin embryo. *Development*. **126**, 345–357

51. Rodova, M., Kelly, K. F., VanSaun, M., Daniel, J. M. and Werle, M. J. (2004) Regulation of the Rapsyn Promoter by Kaiso and δ -Catenin. *Mol. Cell Biol.* **24**, 7188–7196

61. Schmidt, A., Langbein, L., Rode, M., Pratzel, S., Zimbelmann, R. and Franke, W. W. (1997) Plakophilins 1a and 1b: widespread nuclear proteins recruited in specific epithelial cells as desmosomal plaque components. *Cell Tissue Res.* **290**, 481–499

97. Bonne, S., van Hengel, J., Nollet, F., Kools, P. and van Roy, F. (1999) Plakophilin-3, a novel armadillo-like protein present in nuclei and desmosomes of epithelial cells. *J. Cell Sci.* **112** (Pt 14), 2265–2276

Figure 3. Cellular roles of catenins. (color)

Beta-catenin and p120-catenin have confirmed roles in Wnt signaling, although certain isoforms of all catenins (red) localize to the nucleus and may interact with transcription factors (blue). p120-catenin and plakophilin subfamily members (red) also regulate small-GTPases (Rac1, RhoA, Cdc42- yellow). All catenins associate with cadherins at junctional complexes (orange), with beta-catenin and p120 subfamily members residing exclusively at adherens junctions and plakophilins residing exclusively at desmosomes. Plakoglobin is present at both adherens and desmosomal junctions.