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Beyond β -catenin: prospects for a larger catenin network in the nucleus

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Abstract

β -catenin is widely regarded as the primary transducer of canonical WNT signals to the nucleus. In most vertebrates, there are eight additional catenins that are structurally related to β -catenin, and three α -catenin genes encoding actin-binding proteins that are structurally related to vinculin. Although these catenins were initially identified in association with cadherins at cell–cell junctions, more recent evidence suggests that the majority of catenins also localize to the nucleus and regulate gene expression. Moreover, the number of catenins reported to be responsive to canonical WNT signals is increasing. Here, we posit that multiple catenins form a functional network in the nucleus, possibly engaging in conserved protein–protein interactions that are currently better characterized in the context of actin-based cell junctions.

Catenin proteins were initially identified in association with cadherins at cell–cell junctions, and most have been investigated predominantly in this setting (reviewed in REF. 1). However, β -catenin is also known to be a key signal transducer of the canonical WNT signalling pathway that is central in many developmental and pathologic contexts. Specifically, it enters the nucleus in response to WNT–receptor interactions and forms a complex with lymphoid enhancer-binding factor (LEF) or T cell factor (TCF) proteins to activate transcription. The other catenins are less studied outside the context of cell–cell junctions, but there is evidence that they modulate important gene expression programmes in vertebrates (reviewed in REFS 2–4).

Considerable work has focused on differences between catenin family members, resulting in their division into subfamilies on the basis of sequence homologies and their interacting partners (reviewed in REFS 1,3,5). However, catenins also have common properties. For example, all catenins associate with one or more types of cadherin complexes, in which they

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Competing interests statement

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FURTHER INFORMATION

WNT homepage:

<http://web.stanford.edu/group/nusselab/cgi-bin/wnt>

assist in stabilizing cadherins (reviewed in REFS 3,6,7) or forming physical linkages with the underlying actin or intermediate filament cytoskeletons at adherens junctions or at desmosomes, respectively^{1,5,8}, as well as with microtubules at adherens junctions^{9,10}. Thus, a core feature of catenins is their association with cadherins and, directly or indirectly, with the cytoskeleton, which enables them to be involved in cell–cell adhesion, motility and signalling at the cell surface. As mentioned above, a more recently discovered shared property is that each catenin can localize to the nucleus, where most are known or expected to control gene expression.

In this Opinion article, we discuss recent evidence indicating that most vertebrate catenins possess key nuclear roles, and that they possibly form a functional nuclear network that may be analogous to, or allow crosstalk with, catenins acting at cell–cell junctions. Given that recent comprehensive reviews on catenins are available^{2,3,5,11,12}, we focus here on a few most notable examples of vertebrate catenins and their nuclear functions. In general, we posit that catenins have coordinated roles in the nucleus, similar to their coordinated roles in the junctional cadherin complex where they functionally co-evolved. For example, in the case of α -catenin, we discuss how its essential actin-binding function at cadherin-based cell–cell contacts may be relevant to emerging roles of nuclear actin in gene expression. We also discuss p120 catenin family members in relation to WNT pathway responsiveness, RHO-family GTPase regulation and gene control. We further speculate on the possible relationship between nuclear catenin pools and catenins at cell–cell junctions. Using the p120 catenin subfamily members as an example, we propose that, in addition to β -catenin, which is well known to respond to canonical WNT signalling, several catenins might be involved in this pathway. We finally propose that this functional versatility of catenins, including their ability to regulate shared as well as unrelated target genes through interactions with distinct transcriptional regulators, may reflect the context- dependent diversity of outcomes seen in development and disease.

Basic features of catenins

All catenins, with the exception of the three α -catenin gene products (α E-catenin (epithelial), α N-catenin (neuronal) and α T-catenin (testes and heart))¹³ possess a central Armadillo domain consisting of repeating coiled-coils of α -helices that enable varied interactions in distinct intracellular compartments¹⁴. These catenins are capable of binding to cadherins directly and will be referred from now on as Armadillo catenins. β -catenin and plakoglobin (also known as γ -catenin) form the two-member β -catenin subfamily and associate in a competitive manner with the distal cytoplasmic tails of classic cadherins, which are single-pass transmembrane proteins that enable cell–cell adhesion, motility and communication at regions including the zonula adherens of epithelia (reviewed in REFS 15,16) (FIG. 1a). The three members of the α -catenin family bind to cadherins indirectly through β -catenin or plakoglobin. They are structurally similar to the actin-binding protein vinculin (reviewed in REFS 11,17) and assist in linking cadherins to the force-generating cortical actin cytoskeleton⁸ (FIG. 1b).

The vertebrate p120 catenin subfamily has four members (p120 catenin, δ -catenin, ARVCF catenin and p0071 catenin), hereafter referred to as the p120 subfamily (FIG. 1a). Using

their respective Armadillo regions, they likewise bind in a competitive manner to classic cadherin cytoplasmic tails, but, importantly, their binding occurs at a more membrane-proximal region compared with β -catenin and plakoglobin^{18,19} (FIG. 2). When bound to cadherins, p120 subfamily members enhance the stability of cadherins by reducing their endocytosis (reviewed in REFS 6,7,20), locally modulate RHO-family small GTPases through means such as influencing the activity of guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs)^{21–23} and contribute to the actual physical linkages between cadherins and the underlying cytoskeleton^{8,9,10}. Vertebrate p120 subfamily members have also been shown to function when not bound to cadherins^{24–28}, potentially following their release from cadherins owing to changes in phosphorylation (reviewed in REFS 7,28,29).

Catenins of the three-member plakophilin subfamily (plakophilins 1 to 3) use their amino-terminal regions to competitively bind to specialized cadherins present within desmosomes, namely the desmoglein or desmocollin cadherins (plakoglobin is also found here) (reviewed in REFS 3,30,31) (FIG. 1a). The plakophilins have been implicated in a number of activities, including cadherin recycling in conjunction with the RAB11 small GTPase³² and likewise bridge cadherins to the cytoskeleton, although in this case the linkages are with intermediate filaments, safeguarding the integrity of tissues subject to mechanical strain.

All vertebrate catenins can enter the nucleus (reviewed in REFS 33–37). A few have defined nuclear localization signals (NLS) and/or nuclear export signals (NES), but for most catenins these signals have not been identified. Similarly to Armadillo catenins, the importin proteins that bind and deliver NLS-containing proteins to the nucleus or NES-containing proteins to the cytoplasm contain Armadillo-like regions³⁸. Such Armadillo-like regions in importins enable their nuclear transit (along with their cargo), through interactions with the nuclear pore complex machinery³⁹. Thus, the Armadillo catenins may likewise be inherently disposed for nuclear transit⁴⁰, whereas the α -catenins, which lack Armadillo domains, must use other transit mechanisms. NES sequences have been identified in certain catenins⁴¹, and findings indicate that some catenins may exit the nucleus in complex with transcriptional regulators to modulate gene targets^{42–46}.

Armadillo catenins in gene control

Nuclear functions of catenins have been extensively probed in the case of β -catenin and modestly investigated for plakoglobin^{37,47–55}. β -catenin is best known to function within the canonical WNT pathway, where it associates with TCF/LEF transcription factors, as well as with other gene modulators involved in developmental and pathological processes (reviewed in REFS 56–58). Despite the important roles of nuclear β -catenin, studies on the nuclear roles of other catenins in vertebrates have lagged behind. This may be because p120 catenin, and to some extent other members of the p120 catenin subfamily, first drew scientific interest for their roles in cadherin stabilization or the modulation of small GTPases^{59,60}. Indeed, these activities may be dominant in producing some of the gross phenotypes that are initially observed upon altering catenin expression. For example, gastrulation failures that appear in p120-catenin-knockdown *Xenopus laevis* embryos can be rescued in part using titrated dominant-negative RhoA, dominant-active Rac or C-cadherin (a cleavage-stage

cadherin that is present in early embryonic stages of *X. laevis* development)⁶¹. The earliest hints of roles for p120- and plakophilin subfamily members within the nucleus came from the immunolocalization of these catenins to nuclei^{42,62–71}, observations that tend to be very context-dependent, together with yeast two-hybrid screens that pointed to their associations with gene regulatory proteins (FIG. 2).

Nuclear roles of Kaiso and p120 catenin

The first report that p120 catenin could associate with a nuclear protein involved Kaiso⁴², which is a transcriptional regulator and a member of the BTB/POZ zinc-finger family. The consensus DNA-binding sequence of Kaiso (KBS; TCCTGCNA) was resolved *in vitro* using CAST (cyclic amplification and selection of targets) analysis⁷², which allowed part of the mechanism of action of p120 in the nucleus to be assessed *in vitro* and in cell lines. p120 catenin binds to Kaiso near its DNA-binding zinc-finger domain, and although alternative mechanisms have been proposed⁷³, evidence suggests that p120 catenin displaces Kaiso or prevents it from associating with its gene targets. This activates transcription through relief of Kaiso-mediated repression^{45,72} (FIG. 2). Multiple prior studies indicated that Kaiso promotes repression in an additional manner, independently of KBS, by binding to methylated CpG islands^{74,75}. This form of Kaiso-mediated repression may not be susceptible to modulation by p120 catenin, although this issue requires further investigation. Intriguingly, one recent genome-wide study indicated that Kaiso predominantly controls gene activation through binding to non-methylated CpG-rich DNA⁷⁶, although this is currently difficult to reconcile with the noted prior work from a variety of groups. Kaiso has also been implicated in the functions of gene insulator regions, as well as being associated with the transcription factor p53 (REFS 77,78). Together, these data suggest that Kaiso functions in multiple chromosomal contexts, but most are yet to be investigated for links to p120.

Several putative KBS-containing genes have been identified^{45,79–81} (see below). Although this limited number does not indicate larger roles for Kaiso in conjunction with p120 catenin, surprising findings have arisen. In particular, the control regions of a number of mammalian or *X. laevis* Kaiso target genes (for example, those encoding matrilysin, cyclin D1, WNT11 and Siamois) are regulated not only by Kaiso^{45,79–85} but also by β -catenin and TCF^{86,87,88}. Indeed, although different underlying mechanisms have been proposed⁷³, the TCF and Kaiso repressors biochemically associate, their derepression is coordinated at gene control regions and their functional interrelationship has been shown *in vivo*^{45,79}. Thus, most evidence suggests that certain catenins, together with their respective associated transcription factors, may function together at a subset of gene promoters. Moving forward, it will be important to test whether other catenins beyond β -catenin and p120 catenin, as well as catenin pairs, participate in regulating more numerous gene control regions.

WNT response of Armadillo catenins

Catenins function in varied compartments and associate with entities such as junctions, small GTPases or nuclear complexes (reviewed in REFS 2,3,89,90). Seven of the nine Armadillo-domain catenins are subject to alternative translational start sites or alternative

RNA splicing, giving rise to different protein isoforms. While the β -catenin subfamily members do not normally exhibit such choices, p120- and plakophilin subfamily members each arise in distinct isoforms. Certain isoforms often appear at the same time in the same cells, but in other circumstances they may instead display spatially and temporally regulated expression patterns. For example, translational synthesis of human p120 catenin can be initiated from any of four alternative start sites and, additionally, p120 is subject to four alternative splicing events at the RNA level⁹¹ (FIG. 3) (reviewed in REF. 89). Although few have been characterized, some p120 isoforms display distinct biological activities (see, for example, REFS 92,93). Isoform 1 of p120 catenin contains a destruction box at its very N terminus, similar to that characterized in β -catenin⁹⁴ (FIG. 3). In the absence of WNT signals, p120 isoform 1 is more readily destroyed following phosphorylation of its destruction box. The negative regulatory machinery acting upon p120 is the same as that which acts upon β -catenin in the absence of WNT pathway activity (FIG. 4a). In the presence of an appropriate WNT ligand, the pathway becomes active through inhibition of the destruction machinery, which is composed of multiple components including intracellular kinases (casein kinase 1 α (CK1 α) and glycogen synthase kinase 3 β (GSK3 β)), a ubiquitin ligase (β TrCP) and scaffolds such as adenomatous polyposis coli (APC) and Axin (see the [WNT homepage](#)), and the signalling pool of p120 isoform 1 (as does that of β -catenin) increases. How p120 then transits into or exits the nucleus to modulate gene control relies on its Armadillo, NLS or NES regions (or unknown factors), as mentioned above. The destruction box is absent from p120 isoforms 2, 3 and 4, which are translated from points later in the coding sequence (FIG. 3). Thus, choice in the translational start site for p120 influences its sensitivity to WNT pathway activation. It is also interesting that p120 isoform 1 more readily inhibits the RhoA small GTPase⁹², as observed in cells undergoing epithelial mesenchymal transition (EMT). As mesenchymal cells often express reduced levels of E-cadherin relative to epithelial cells, catenins that do not immediately associate with other cadherins (for example, before increases in N-cadherin levels) may be more likely to directly transduce signals to the nucleus. Conceivably, therefore, the cytoplasmic or nuclear pools of catenins that are competent to respond to new or baseline signals would depend on the ratio between different p120 isoforms, with p120 isoform 1 being the most responsive to canonical WNT activity.

In contrast to p120 catenin, β -catenin (or plakoglobin) does not exhibit alternative primary sequence isoforms under normal circumstances. Therefore, we predict that changes in the relative abundance of the signalling pool of p120 isoform 1 (determined by the p120 translation start site used and the activity of the WNT pathway), contributes to selecting among possible outcomes to canonical WNT signals. Consequently, choices affecting the size of the signalling pool of p120 isoform 1 could potentially modulate WNT pathway gene output (by positively co-regulating a subset of genes that are targeted in parallel by β -catenin, and/or by regulating genes not shared with β -catenin and TCF), whereas β -catenin would be a more constant participant in canonical WNT signal transduction. Intriguingly, some evidence suggests that additional catenins of the p120 subfamily, namely ARVCF catenin and δ -catenin, respond to components of the canonical WNT pathway, although their involvement in WNT signalling is still being evaluated⁹⁴⁻⁹⁶. For example, although δ -catenin is phosphorylated by GSK3 and ubiquitylated⁹⁶, WNT-responsive destruction boxes

have not yet been definitively identified in any of δ -, ARVCF or p0071 catenin. It will be now important to delineate the catenins (and their isoforms) that respond to vertebrate canonical WNT signals. Another question is whether distinct WNT ligands or receptors might have preferential effects upon certain catenins, as such effects, if observed, could help to account for the large diversity of downstream outcomes that arise from upstream canonical WNT stimuli. Altogether, given the recent findings on p120 isoform 1, it might be necessary to consider redefining vertebrate canonical WNT signalling to involve a number of catenins as opposed to β -catenin alone.

Other nuclear partners of p120 catenin

Just as β -catenin associates indirectly with DNA through transcriptional regulators other than TCF/LEF (reviewed in REF. 55), p120 catenin has nuclear binding partners other than Kaiso, providing further evidence for p120 having important nuclear roles. For example, p120 catenin binds to zinc-finger protein GLIS2 (REF. 97), which is a Kruppel-like transcriptional repressor that, in cooperation with SRC, favours the nuclear translocation of p120 catenin. In turn, p120 catenin promotes cleavage within the carboxy-terminal zinc-finger domain of GLIS2, presumably via an associated protease. This cleavage has been shown to reduce the ability of GLIS2 to drive neural differentiation *in vivo*⁹⁷. Regulators of GLIS2 thus include p120 catenin and SRC; however, it is not clear which factors operate upstream of p120 in this pathway. Since cadherin expression sequesters p120 catenin away from GLIS2, the cadherin–catenin complex is a conceivable upstream modulator of p120 catenin-mediated signals to GLIS2 (FIG. 4b).

Further recent evidence that p120 catenin has nuclear roles comes from findings that it binds to the transcriptional regulators RE1-silencing transcription factor (REST) and CoREST (also known as RCoR1)⁴⁶. The larger REST–CoREST complex is usually repressive, with recent findings indicating that p120 can displace REST–CoREST from DNA to enable gene activation (FIG. 2). REST–CoREST binds to numerous gene targets, the best characterized of which are those associated with neuronal differentiation^{98,99}. Indeed, the neural differentiation of mouse embryonic stem cells is enhanced upon p120 expression and diminished upon p120 depletion. In this context, cadherin levels rather than canonical WNT signals seem to determine the nuclear activity of p120 catenin. For example, E-cadherin depletion led to the activation of known REST gene targets, and p120 depletion significantly rescued this effect. Because E-cadherin levels drop as embryonic stem cells begin to differentiate, the current model is that E-cadherin loss leads to an observed increase in free p120 that then enters the nucleus to act upon REST–CoREST or other gene regulators. Although the presence of distinct but co-expressed cadherin types suggests that the model might be more complex, it is possible that the same mechanism applies to p120 or to β -catenin subfamily and α -catenin family members. Thus, in addition to canonical WNT or other pathways acting upon select catenin isoforms for nuclear signalling (for example, p120 isoform 1), we speculate that even transient reductions in the levels or catenin-binding competence of cadherin complexes^{40,55,100–105} may enhance the robustness and variety of catenins that are available for gene regulation (FIG. 4).

In the case of cadherin-bound p120 locally modulating small GTPases^{21–23}, the above model is analogous to previous models in which crosstalk between small GTPases located at cadherin junctions or other subcellular regions may occur through competition for p120 catenin, with consequent effects on cell adhesion and motility (reviewed in REFS 27,106). Here, we suggest that changes in cadherin abundance or activity may be communicated to the nucleus through several catenin subtypes. We also suggest that the diversity of vertebrate catenins arose to share signals between cell compartments, to enable crosstalk between adhesive (cadherins), motility (small GTPases) and gene regulatory (transcription factor) functions. Distinctions between specific catenins (for example, p120 catenin versus plakophilin 3 catenin), combinations of catenins, or splice-isoforms of the same catenin (for example, p120 isoform 1 versus isoform 3) would enable greater dimensionality in modulating such crosstalk. Within the nucleus, such catenin diversity would enable a range of gene regulatory outputs.

Other Armadillo catenins in the nucleus

Recent studies have shown that other catenins of the p120 family, as well as plakophilins, have important functions in the regulation of gene expression.

Other p120 family members in gene expression

The p120 catenin subfamily member δ -catenin can bind to and modulate the activity of the WNT pathway transcriptional factor LEF¹⁰⁷ and the repressor Kaiso¹⁰⁸, as well as the novel Krab-domain zinc-finger transcriptional repressor ZIFCAT¹⁰⁹, the gene targets and biological roles of which are not yet established. As δ -catenin binds to ZIFCAT in its zinc-finger domain, it might compete ZIFCAT away from DNA and thereby enable gene activation through derepression. Intriguingly, and perhaps under both non-apoptotic and apoptotic conditions, δ -catenin is cleaved into two large fragments by caspase 3, which exposes an NLS that more effectively directs the carboxyl-fragment of δ -catenin to the nucleus, where it presumably modulates ZIFCAT and other nuclear targets (FIG. 2).

Plakophilins in the nucleus

Catenins of the plakophilin catenin subfamily more closely resemble those of the p120 than the β -catenin subfamily^{1,3,110}. Intriguingly, plakophilin 3 binds to the transcription factor ETS translocation variant 1 (ETV1; also known as ER81)¹¹¹, which is an ETS family member that has crucial roles in dopaminergic neural development. Plakophilin 3 also associates with the closely related ETV5. Gene fusions of ETV1 are instrumental in human disease (reviewed in REF. 112). Although it is not known whether plakophilin 3 has a role in ETV1-related cancers, increased or reduced levels of plakophilin 3 are found in human tumours, depending on the carcinoma or cell line examined, with further reports of its upregulation in cancer cells (reviewed in REF. 3). When plakophilin 3 associates with ETV1, ETV1 gene targets are more highly activated, with phenotypic studies in *X. laevis* supporting their functional interaction. While the exact mechanism is unclear, plakophilin 3 might enhance the association of ETV1 with DNA through binding to a putative inhibitory region on ETV1 (REF. 113) (FIG. 2). Thus, catenins of the p120 and plakophilin subfamilies seem to negatively or positively affect the association of their respective transcription factor

partners with DNA. This is consistent with the theme, promoted by this Opinion article but not yet broadly validated, that multiple catenins direct transcriptional output by modulating the activities of various DNA-binding partners.

The remaining two plakophilin catenins are also thought to function in the nucleus. For example, plakophilin 2 associates in some contexts with β -catenin⁶³, α T-catenin¹¹⁴ and the largest subunit of the RNA polymerase III holoenzyme (RPC155)¹¹⁵. Plakophilin 1 can bind to single-stranded DNA¹¹⁶. Much of the biological significance of these associations, as well as how plakophilins enter the nucleus in the absence of an obvious NLS, remains to be clarified. Plakophilin 1 and/or plakophilin 3 have also been found in association with components of mRNA ribonuclear protein particles, cytoplasmic stress granules and ribosomal complexes, such that the plakophilin catenins might further modulate mRNA localization, stability or translation^{117–119}. The nuclear presence of the plakophilin catenins is most apparent in cells that are devoid of desmosomal cadherins or at developmental stages before full junction formation. This suggests that desmosomal junctions and cell nuclei may engage in crosstalk via the plakophilin catenins in a manner analogous to that proposed for the catenins that interact with cadherins at adherens junctions. Once in the nucleus, the plakophilin 2-RPC155 interaction may enable plakophilin 2 to modulate rRNA or tRNA synthesis. Additionally, since plakophilin 2 is also found in large complexes that are devoid of RPC155, it may potentially have other functions in the nucleus¹¹⁵. Indeed, evidence that plakophilin 2 can associate with β -catenin may be relevant to the involvement of plakophilin 2 in positive modulation of canonical WNT signalling⁶³. Such associations are consistent with the idea that catenins potentially form a signalling network in the nucleus, as was indicated in our earlier example of p120 catenin–Kaiso and β -catenin – TCF functioning at shared gene targets, and as will be addressed below in contexts involving α -catenin.

Nuclear functions of α -catenins

α -catenins are filamentous actin (F-actin) binding proteins, which are best known for their role in mechanically linking the cadherin– β -catenin complex to the underlying actin–myosin cytoskeleton during cell–cell adhesion (reviewed in REF. 120). Curiously, epithelial cells contain a substantial amount of cadherin-free α E-catenin (the epithelial form of α -catenin)^{121,122}, and there has been much interest in the potential signalling functions of this pool. As β -catenin is the major stoichiometric binding partner of cytosolic α E-catenin¹²³, there has been particular interest in the ability of α -catenin to affect the nuclear functions of β -catenin. Although a number of forced-expression studies showed that α E-catenin could inhibit nuclear accumulation of¹²⁴ and signalling by β -catenin^{125–128}, it was only recently that two independent α E-catenin-silencing studies revealed its role as a *bona fide* negative regulator of β -catenin signalling in the nucleus^{129,130}. The latter study not only confirmed earlier suggestions that endogenous α E-catenin partly localizes to the nucleus^{125,131}, but also showed that the nuclear accumulation of α E-catenin depends on the presence of nuclear β -catenin¹³⁰. Although both studies revealed that α E-catenin can be found in a complex with β -catenin and TCF on WNT-responsive promoters, and that it negatively regulates mRNA expression from these promoters^{129,130}, each suggested a distinct mechanism. In the first study, α E-catenin was found to limit WNT signalling by promoting the ubiquitylation and proteolysis of β -catenin through binding to the APC scaffolding component of the

destruction complex¹²⁹ (FIG. 5a). Additionally, α E-catenin seemed to destabilize β -catenin present at promoters in complex with TCF, as part of a histone H3 Lys4 demethylase transcriptional repressor complex that contains APC, C-terminal binding protein (CtBP), CoREST and Lys-specific demethylase 1 (LSD1) (FIG. 5b). Thus, although p120 catenin derepresses REST-CoREST repressor complexes to activate gene targets⁴⁶, as discussed above (FIGS 2,4), α E-catenin might facilitate target gene repression through this complex.

By contrast, the second study found that the C-terminal actin-binding region of α E-catenin was needed to inhibit β -catenin-TCF-mediated gene transcription, suggesting that the ability of α -catenin to affect actin organization might be related to its function as a transcriptional inhibitor⁷⁹. Indeed, cell nuclei contain substantial pools of globular actin (G-actin), and β -actin is incorporated into all three RNA polymerase complexes, as well as some chromatin remodelling complexes that are needed for gene activity^{132–135}. This raises the possibility that nuclear proteins with a capacity to bind to and stabilize short nuclear actin filaments may limit gene expression by locally depleting G-actin from transcription complexes (FIG. 5c). Supporting this idea, a nuclear-targeted form of α E-catenin induced the formation of nuclear F-actin filaments. This correlated with reduced RNA synthesis and a more compact chromatin organization, suggesting that actin filament formation might function alongside the CtBP–CoREST–LSD1 complex in α E-catenin-driven gene repression. Thus, different models of transcriptional inhibition by α E-catenin have been suggested^{78,79}, and each might contribute to distinct aspects of a multi-step inhibitory mechanism.

It is worth noting that the loss of α E-catenin has also been linked to the activation of a variety of nuclear signalling pathways, such as RAS¹³⁶, nuclear factor- κ B (NF- κ B)^{137,138}, Hedgehog^{139,140} and Hippo–Warts^{141,142}. Although α E-catenin can be co-immunoprecipitated with various components of these pathways (for example, the NF- κ B negative regulator I κ B α ¹³⁸, the Hippo–Warts effector YAP^{141,142} and the Hedgehog nuclear effector GLI3 (REF. 140)), the molecular details of these interactions remain unclear. Given the fundamental role of α E-catenin in tissue organization¹¹, along with recent studies revealing that cytosolic α E-catenin can alter actin dynamics by limiting actin-related protein 2/3 (ARP2/3)-based actin polymerization or filament-severing by cofilin^{122,143,144}, it may be useful to consider the pleiotropic effects of α E-catenin loss in the context of its broader roles in cell–cell adhesion and the regulation of cytoplasmic, as well as possibly nuclear, F-actin.

We find it intriguing that some gene promoters are positively co-regulated by β -catenin and p120 catenin, whereas the nuclear accumulation of α E-catenin depends on β -catenin and antagonizes transcription. This suggests the possibility that the proximal relationship of these catenins may be conserved at both adherens junctions and gene promoters. What are these proximal relationships? One possible contribution is that the catenin network controls the organization of actin in both spaces. Broadly speaking, cadherin-associated catenins control the coordination of cadherin adhesion receptors with the cortical cytoskeleton, although we typically view the roles of p120 catenin, β -catenin and α E-catenin at cadherin contacts individually (for example, p120 catenin and β -catenin bind to and stabilize cadherin proteins, p120 subfamily members regulate RHO–RAC signalling to modulate junction formation, and α E-catenin binds to, bundles and stabilizes F-actin filaments). Perhaps analogously, nuclear catenins control gene expression, in part, by modulating nuclear actin

organization at transcriptional promoters. Indeed, evidence that myosins, ARP2/3, cofilin and WASP can be localized to nuclear subdomains and are involved in various aspects of gene expression¹⁴⁵ supports our need to conceptualize the shared versus distinct functions of these actin-regulating proteins in both nuclear and cytoplasmic compartments. Moreover, evidence for nuclear myosins in transcription raises the possibility that the function of α E-catenin as a force-sensitive protein¹⁴⁶ may also be relevant to its role in transcription. Lastly, it is important to note that the nuclear functions of α -catenins are not likely to be restricted to α E-catenin, as α N-catenin can interact with a Kruppel-like zinc-finger transcriptional repressor protein, ZASC1 (also known as ZNF639)⁷⁰. Indeed, evidence that α E-, α N- and α T-catenin knockouts produce distinct phenotypes¹³ suggests the possibility that functional diversification in the α -catenin family may be equally related to differences in nuclear signalling and structural differences at cell–cell junctions.

Conclusions and perspectives

In summary, we have discussed here the emerging nuclear roles of catenin proteins that extend beyond the β -catenin signalling paradigm. With α -catenin as an exception, these catenins each possess a central Armadillo domain, a structural interface that is well-suited to nuclear–cytoplasmic shuttling and protein–protein interactions. Multiple catenins are sensitive to shared upstream regulatory inputs such as cadherin levels and WNT pathway activity, whereas shared downstream catenin roles in gene regulation involve the modulation of protein–DNA or protein–protein interactions. Indeed, some genes seem to be regulated by multiple catenins that have common or antagonistic regulatory roles.

Lastly, growing recognition that actin and actin-binding proteins contribute to various aspects of gene expression, such as in association with RNA polymerases or other transcriptional effectors, raises the possibility that catenins control cell–cell adhesion and gene expression through shared relationships with actin. We anticipate that the examination of catenin interactions in the nucleus, both at the protein and the whole-genome expression levels, will lead to exciting findings that relate to processes such as cellular differentiation and reprogramming, and the contributions of nuclear actin to these processes.

In this regard, it is intriguing that a number of catenin nuclear partners have strong functional connections to the regulation of chromatin. For example, REST and CoREST scaffold a sizeable array of repressive histone modifying activities^{98,99,147}, with p120 relieving such repression at some gene targets. Likewise, on the basis of many, if not all, available studies⁷⁶, Kaiso recruits a number of repressive chromatin modifiers^{148–151}. In several contexts, Kaiso is negatively modulated by p120 or is positively modulated by δ -catenin¹⁰⁸ (which was recently implicated in the modulation of chromatin in severe autism¹⁵²). Kaiso is also reported to associate with the p53–p300 complex⁷⁸, and both α -catenin and β -catenin seem to associate with CtBP, CoREST and LSD1. Thus, it seems that the larger biology of nuclear catenins is well integrated with that of chromatin regulation.

In our view, key remaining questions include the extent and diversity of the nuclear functions of catenins, and the degree to which they are networked or act independently. Although our perspective offers a taste of what may be in store, a comprehensive picture of

nuclear catenin functions is lacking. In some cases, helpful technologies are already available. For instance, chromatin immunoprecipitation followed by sequencing (ChIP-seq) can be applied to compare catenin residency at gene control regions on the whole-genome level, whereas RNA sequencing (RNA-seq) can reveal overlapping versus non-overlapping patterns of target gene expression following catenin depletion versus expression. Such an analysis could be combined with the analysis of active and inactive chromatin states, as well as of catenin protein-protein interactions in the nucleus. Collectively, this will shed more light on distinguishing separable versus collective catenin roles in regulating gene activity or chromatin states. More complete resolution of catenin NLS or NES motifs will allow for the generation of catenin constructs that are incapable of entering or exiting the nucleus, which will be necessary to determine the nuclear contributions of catenins independently of their roles in the cytoplasm and at cell-cell junctions. Given that catenins modulate adhesive and cytoskeletal activities at junctions, but also participate in more distal cytoskeletal or gene control functions, an even greater challenge will be to understand how catenins functioning in distinct intracellular compartments during development or homeostasis coordinate their activities. Ultimately, reliable technologies will be required that, together in real time, permit multiple known or suspected catenin interaction nodes to be investigated in living cells or animal systems. In conjunction with the controlled perturbation of selected catenins, this will enable the assembly of predictive and testable models of catenin functional contributions at the systems level.

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a Vertebrate Armadillo-domain proteins of the p120, plakophilin and β -catenin subfamilies

b α -catenin family of F-actin-binding proteins

Figure 1. An overview of vertebrate catenins

Most vertebrates have twelve genes that encode different types of catenins, with the genomes of some teleost fishes having certain catenins duplicated^{1,3,5}. **a** | Vertebrate catenins containing Armadillo domains were first identified at cell–cell contacts in association with classic cadherins (β -catenin and p120 catenin subfamily members), or with desmosomal cadherins (plakophilin catenin subfamily members and γ -catenin (plakoglobin)). Subsequently, catenins were found to have key roles in the cytoplasm and the nucleus. The large Armadillo domain of each catenin is shown in grossly simplified form (different shades of blue). It varies from 9–12 Armadillo repeats, depending on the catenin (each repeat is ~42 amino acids in length), with limited unique sequences interspersed. As the different repeat units within the same larger Armadillo domain are only weakly homologous to one another, different protein–protein interactions are supported, depending on the domain region in question. Additional features on certain catenins include phosphorylation domains, alternative translation start sites, alternative splicing events at the RNA level, nuclear localization signals (NLS), nuclear export signals (NES) and PDZ motifs, and amino-terminal ‘destruction boxes’ that are responsive to canonical WNT signals. Shading reflects the relatedness of protein families; for example, β -catenin is more closely related to plakoglobin than to the p120 or plakophilin catenin families. An Armadillo catenin (p120) depicted with additional features is presented in FIG. 3; the reader is also referred to more comprehensive reviews noted in the text. **b** | α -catenins are filamentous

actin (F-actin)-binding proteins that are structurally related to vinculin. The N-terminal dimerization domain engages in mutually exclusive β -catenin (heteromeric) or α -catenin (homomeric) binding, whereas the central mechanosensitive and carboxy-terminal F-actin-binding domains are together composed of four to five α -helical bundles.

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Figure 2. Conditions that promote catenin nuclear signalling

a | When WNT signalling through the Frizzled–low-density lipoprotein receptor-related protein 5 (LRP5) or Frizzled–LRP6 receptor is low or absent and/or cadherin expression levels are high, catenins typically do not enter the nucleus owing to their inhibition via the Axin–adenomatous polyposis coli (APC)–casein kinase 1 α (CK1 α)–glycogen synthase kinase 3 β (GSK3 β) destruction complex and their associations with cadherins, respectively. Plakophilin 1 (PKP1), PKP2 or PKP3 interact with desmosomal cadherins indirectly through γ -catenin (plakoglobin) and desmoplakin (grey circles), whereas β -catenin and p120

catenins, as well as (indirectly) α -catenin, interact with classic cadherins. In the absence of nuclear catenins, the DNA-binding factors shown repress gene targets in a number of cases, although some transcription factors are activators even in the absence of catenins (for example, ETS translocation variant 1 (ETV1)). Likewise, a recent genome-wide study suggests the association of Kaiso with gene activation (not shown)⁷⁶. **b** | WNT signalling or cadherin loss promotes nuclear accumulation of β -catenin, p120 catenin (isoform 1) and possibly other catenin isoforms. p120 catenin derepresses Kaiso to activate genes. p120 catenin also dissociates the RE1-silencing transcription factor (REST)–CoREST complex from genes, resulting in target derepression (activation). Also, other p120 catenin family members (for example, δ -catenin or PKP3) have been shown to enter the nucleus and regulate transcription, but which pathways impact their nuclear residence has been less explored. In the case of δ -catenin, caspase 3 (CASP3)-mediated cleavage seems to promote the nuclear accumulation of its carboxyl fragment, followed by zinc-finger transcriptional repressor ZIFCAT association and unknown gene regulatory effects. δ -catenin can also enter the nucleus in the uncleaved form and has been demonstrated to bind to and modulate the Kaiso repressor (not shown)¹⁰⁸. Nuclear PKP3 has been shown to bind to ETV1 and enhance its activity. Additionally, α -catenin accumulates in the nucleus and negatively modulates β -catenin-driven transcription (see FIG. 5). X, Y and Z indicate additional nuclear binding partners of β -catenin, such as SOX proteins, nuclear hormone receptors and FOXO⁵⁵. X,Y,Z also reflects the concept that each catenin probably binds to multiple gene regulatory proteins. TCF, T cell factor.

Figure 3. p120 catenin isoform 1 is responsive to canonical WNT signals

p120 catenin isoform 1, but not the shorter p120 catenin isoforms 2–4, contains an amino-terminal destruction box (shown in black within the coiled-coil (CC) domain); this is subject to phosphorylation by casein kinase 1 α (CK1 α) and glycogen synthase kinase 3 β (GSK3 β), leading to the ubiquitylation and proteasome-mediated destruction of p120 catenin isoform 1 when canonical WNT ligands are not bound to their Frizzled–low-density lipoprotein receptor-related protein 5 (LRP5) or Frizzled–LRP6 receptor pairs. The WNT receptors and destruction complex are shown in simplified form. As with β -catenin (not shown), WNT activity results in the stabilization of p120 catenin isoform 1 through inhibition of the Axin–adenomatous polyposis coli (APC)–CK1 α –GSK3 β destruction complex, leading to increased p120 catenin isoform 1 function in the nucleus through association with regulators of gene activity. p120 catenin is involved in additional cellular processes (not depicted) such as the regulation of cadherins and small GTPases; although conjectural, this may enable the regulation by WNT of p120 catenin isoform 1 to affect a number of cellular compartments coordinately. Arrows with digits 1–4 indicate alternative protein translation start sites; digits 1–9 indicate Armadillo repeats; green underlining indicates areas in the Armadillo repeat domain containing primary sequence stretches distinct from the typical Armadillo repeat; capital letters A to D indicate regions where optional splicing events occur at the RNA level. PD, phosphorylation domain.

Figure 4. p120 catenin modulates gene transcription via various zinc-finger domain transcriptional repressors

a | Analogous to the case for β -catenin, p120 catenin isoform 1 is stabilized in response to WNT signalling. This enables the signalling pool of p120 catenin isoform 1 to increase and relieve Kaiso-mediated repression, thereby activating transcription. Alternative, shorter p120 catenin isoforms (that is, isoforms 2–4; see FIG. 3) may also relieve Kaiso-mediated repression, but they are not as sensitive to canonical WNT regulation. A number of genes seem to be co-regulated by β -catenin–T cell factor (TCF) and p120 catenin–Kaiso. An alternative model of p120 catenin function in regulating Kaiso and TCF-mediated gene expression is referenced in the text. **b** | p120 catenin can be released into the cytoplasm by E-cadherin loss or E-cadherin downregulation, or via changes in cadherin or p120 catenin phosphorylation states. Nuclear p120 displaces the RE1-silencing transcription factor (REST)–CoREST repressive complex from REST target genes to activate transcription (pathway labelled 1 in the scheme). Additionally, GLIS2 enhances nuclear entry of p120 catenin, which in turn enhances the cleavage of GLIS2 within its DNA-binding zinc-finger domain by an unknown mechanism. This may reduce GLIS2 repressor function, resulting in gene activation mediated by GLIS2 (pathway labelled 2 in the scheme). APC, adenomatous polyposis coli; CK1 α , casein kinase 1 α ; GSK3 β , glycogen synthase kinase 3 β ; LEF, lymphoid enhancer-binding factor; LRP, low-density lipoprotein receptor-related protein.

Figure 5. Models for transcription inhibition by αE-catenin

αE-catenin might inhibit WNT target gene expression by directly binding to adenomatous polyposis coli (APC) to promote the turnover of β-catenin via the destruction complex, which enables its ubiquitination and proteasome-mediated degradation (**a**) or the recruitment of transcriptional co-repressors such as C-terminal binding protein (CtBP), CoREST and Lys-specific demethylase 1 (LSD1), thereby inhibiting β-catenin-mediated transcription (**b**)¹²⁹. Alternatively, αE-catenin might inhibit β-catenin–T cell factor (TCF)-mediated transcription by promoting the polymerization of globular actin (G-actin) in the nucleus, leading to the formation of filamentous actin (F-actin) and local depletion of nuclear actin monomers (or short polymers) that are needed for the full functionality of RNA polymerase II (Pol II) and chromatin remodelling complexes involved in transcriptional activity (**c**)¹³⁰. LEF, lymphoid enhancer-binding factor.