Review

Developmental functions of the P120-catenin sub-family

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Abstract

For more than a decade, cell, developmental and cancer investigators have brought about a wide interest in the biology of catenin proteins, an attraction being their varied functions within differing cellular compartments. While the diversity of catenin localizations and roles has been intriguing, it has also posed a challenge to the clear interpretation of loss- or gain-of-function developmental phenotypes. The most deeply studied member of the larger catenin family is beta-catenin, whose contributions span areas including cell adhesion and intracellular signaling/ transcriptional control. More recently, attention has been directed towards p120-catenin, which in conjunction with the p120-catenin sub-family members ARVCF- and delta-catenins, are the subjects of this review. Although the requirement for vertebrate versus invertebrate p120-catenin are at variance, vertebrate p120-catenin sub-family members may each inter-link cadherin, cytoskeletal and gene regulatory functions in embryogenesis and disease.
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Keywords: p120-catenin; ARVCF-catenin; Delta-catenin; Development; Vertebrate; Invertebrate; Wnt signaling pathway; Kaiso repressor

1. Review

Catenin involvement in events encompassing the plasma membrane, cytoplasm and nuclear environments has made the mechanistic interpretation of cellular or developmental phenotypes challenging. Even in the face of such complexity, however, catenin investigators have witnessed an explosive growth in our understanding of β-catenin [1–6]. A more recent surge of interest has now been directed towards p120-catenin [7–10], which in conjunction with the p120-catenin sub-family members ARVCF- and δ-catenins, are the subjects of this review. In the coming pages and to varying extents, we will touch upon a number of points, which include: 1. Known distinctions/similarities between selected catenins; 2. β-catenin and Wnt signaling in the relatively new context of p120-catenin and the p120/Kaiso signaling pathway; and finally our main emphasis 3. Vertebrate and invertebrate evidence addressing the developmental functions of p120-catenin sub-family members.

Based upon protein and gene structure analysis, vertebrate catenins containing Armadillo domains (this excludes α-catenin) are most simply placed into three sub-families of the following compositions: p120-, ARVCF-, δ- and p0071-catenins (p120-catenin sub-family); plakophilins 1–3 (plako-philin sub-family); and β- and γ-catenins (β-catenin sub-family) [7,10] (Fig. 1). Depending upon factors including species, cell or developmental contexts, and physiologic versus pathologic states, particular catenins or catenin isoforms are present at greater or lesser levels [11–14]. We will not discuss the p120 sub-family member p0071-catenin, as it was included in an interesting recent review [10], and is more divergent from the remaining sub-family members under discussion. Less consideration will likewise be given plakophilin sub-family members reviewed elsewhere [15–19,10,20], or to the β-catenin sub-family member γ-catenin (plakoglobin), which plays essential but more restricted roles in vertebrate development [21–24,17, 10,25]. Some discussion of β-catenin will be made for comparative purposes, and because the developmental roles of p120-catenin intersect with those of the canonical (β-catenin mediated) and noncanonical Wnt signaling pathways [26–28].

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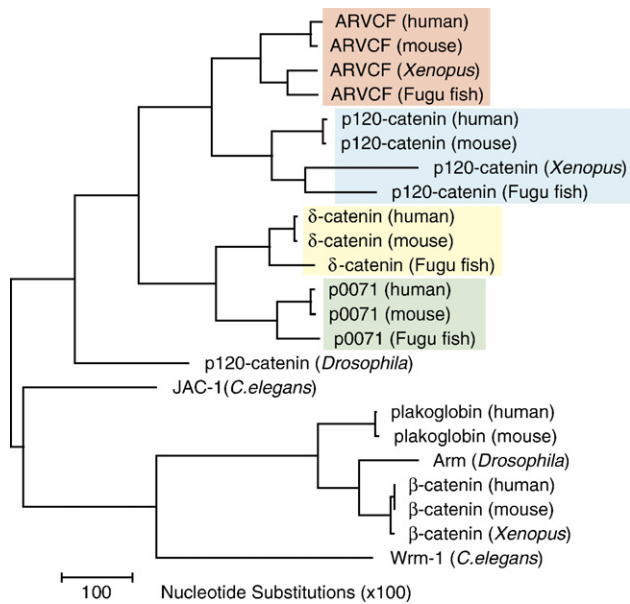E-mail address: pdmccrea@mdanderson.org (P.D. McCrea).

Fig. 1. Sequence comparison of catenin family proteins. Phylogenetic and molecular evolutionary analyses of the amino acid sequences of selected catenin family proteins (β-catenin, plakoglobin, p120-catenin, ARVCF, δ-catenin, p0071) from various species (human, mouse, *Xenopus laevis*, fugu fish, *Drosophila* and *C. elegans*) were conducted using MEGA version 3.1 (maximum parsimony option was adopted to construct a phyogenetic tree). Dp120 and JAC-1 are the respective p120-catenin sub-family homologues in *Drosophila* and *C.elegans*.

In invertebrates, few catenins are encoded at the gene level, with only β-catenin and a single p120-catenin sub-family member identified [29–31] (Fig. 1). An intriguing aspect of *C. elegans* is that prior duplications of the gene encoding β-catenin produced three related β-catenin-like products [32,33]. Each appears to execute separable sub-functions perhaps collectively ascribed to the single β-catenin gene product encoded in *Drosophila* and vertebrates, where the β-catenin polypeptide may be subject to a greater range of modulation. The Wnt-pathway signaling function of β-catenin in activating nuclear gene targets, for example, is responsive to regulation of its metabolic turn-over and possibly nuclear import/export [34–40,2,41,1]. Although less fully characterized, tyrosine kinase or other Wnt-independent phosphorylation events may also contribute to producing signaling pools of β-catenin [42–51].

Given interests in β-catenin, researchers have wondered if many or limited subsets of its functional properties are shared with structurally related p120-catenin sub-family members (Fig. 2). While similarities are apparent in a broad context, distinguishing features of p120-catenin family members have been indicated from findings that they are expressed in a variety of splice isoforms (β-catenin is expressed as a single splice isoform) [11–13]; their failure to associate directly with certain key protein partners of β-catenin (such as the TCF/LEF transcriptional repressors or APC or Axin) [52,53]; the binding of some members to desmosomal cadherins or to the membrane-proximal cytodomain of classical cadherins (as opposed to

the distal cytodomain to which β- or γ-catenin bind) [54,7,55,17,19,10]; and the interaction of some and perhaps all p120-catenin family members with small GTPases or their regulators [56–61,10] (Fig. 3).

Properties that are shared amongst catenins include their associations with the cytoplasmic tails of cadherin superfamily members (although to differing tail regions as pointed out above) [62–66,5]; their further localization and known or postulated functions in the nucleus; their demonstrated or presumed functional modulation through phosphorylation/de-phosphorylation; and at the structural level their possession of a central Armadillo domain composed of between 10-to-12 Armadillo repeats [67] (Figs. 2 and 3). This core region is likely in all cases to engage in multiple protein-protein interactions [68]. Additional associations occur through each catenins' more divergent amino- and carboxy-terminal sequences. Through intra-molecular interactions with the central Armadillo domain, such amino- and carboxy-terminal sequences have been indicated to modulate catenin associations with partner proteins [69].

2. Evolution and the p120-catenin sub-family

In considering the existence of varying p120-catenin family members across species, it is evident that increased diversity arose in vertebrates and especially mammals (Fig. 1). In *Drosophila* and *C. elegans*, for example, only one p120-catenin family member is apparent [29–31]. In most reports this member has been referred to as invertebrate p120-catenin, even though sequence analysis suggests that it more nearly resembles vertebrate δ-catenin. Thus, δ-catenin may be the most evolutionarily ancient p120-catenin sub-family member in vertebrates, with additional members (including p120-catenin itself) arising subsequently in response to vertebrate-specific selective pressures. To maintain continuity of nomenclature with earlier reports, we will refer to the single invertebrate member of the p120-catenin sub-family as p120-catenin.

β-catenin has maintained a highly conserved sequence structure across species (67% sequence identity/77% conservation between *Drosophila melangaster* and humans), likely due to constraints imposed by its roles in intracellular signaling and cell-cell adhesion [33,70]. Earlier in evolution, gene duplication resulted in a product resembling β-catenin (and plakoglobin/γ-catenin), and the noted p120 sub-family precursor. The fact that p120 gene products were retained suggests they maintained or acquired functions advantageous to diverse phyla. It was thus mildly surprising that in all but one study where knock-out/knock-down approaches were applied in invertebrates [29], p120 appeared dispensable [30,31]. It is pertinent however that all such work indicated p120's relevance to functions of the cadherin-catenin complex, revealed upon evaluation of compound mutants. In vertebrates, p120-catenin's developmental requirement has been uniformly apparent [61,71,72], even though much remains
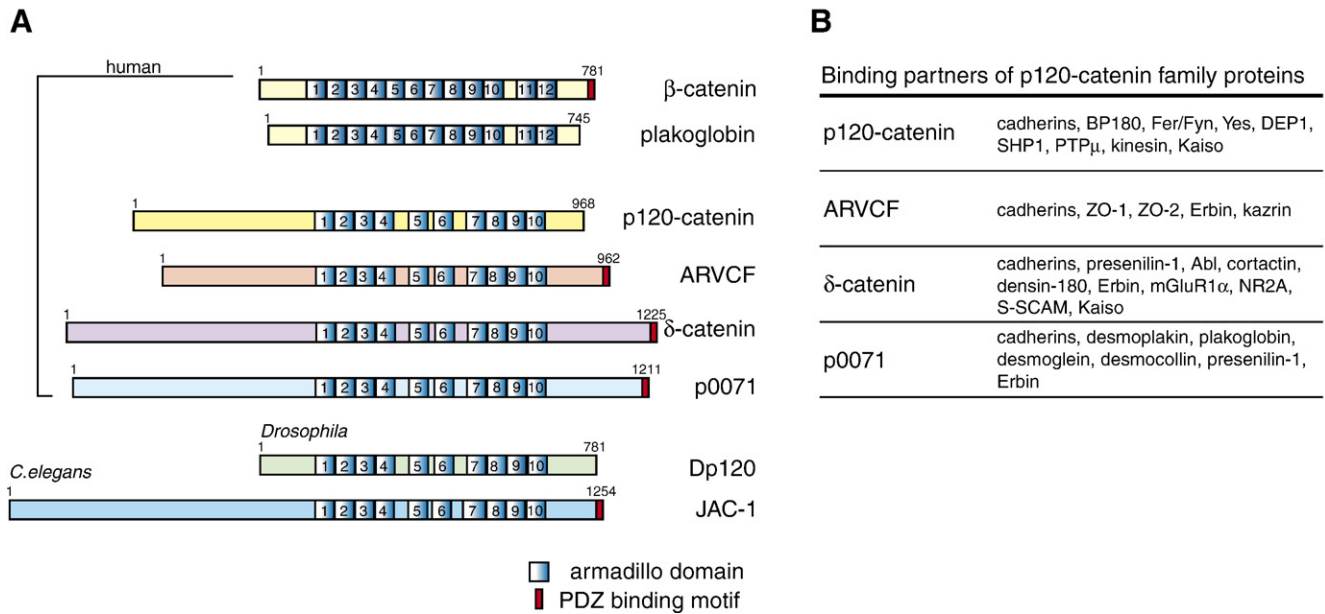
Fig. 2. Linear structural representation of catenin family proteins. (A) Aligned along their respective Armadillo repeat domains is a limited selection of human catenin proteins (β-catenin, p120-catenin, ARVCF, δ-catenin and p0071), along with invertebrate p120-catenin (*Drosophila* Dp120 and *C. elegans* JAC-1). Unlike β-catenin (or γ-catenin/plakoglobin) that contains 12 repeats within its Armadillo domain, members of the p120-catenin sub-family contain 10 Armadillo repeats and have more divergent amino- and carboxy terminal regions. Type I PDZ binding motifs (X-S/T-X-Φ where Φ represents hydrophobic amino acids), are present at the carboxytermini of some but not all p120 sub-family proteins. (B) A partial list of proteins thought to directly or indirectly associate with p120-catenin sub-family members. Most known associations occur through catenin Armadillo-domain or PDZ-motif interactions.

to be revealed concerning its mechanistic contributions as outlined in this review.

3. β-Catenin and cadherin basics

β-catenin is the prime intracellular signal transducer of the canonical Wnt signaling cascade [1–6,33] (Fig. 3). In this context, β-catenin becomes metabolically stabilized following extracellular Wnt association with transmembrane Frizzled and LRP receptors, resulting in downstream events including β-catenin's nuclear entry and association with members of the TCF/LEF (herafter TCF) repressor family. There upon, β-catenin's recruitment of co-activators leads to the activation (de-repression) of genes instrumental in embryogenesis, or in human disease such as human colon cancer or melanoma [37,41].

β-catenin further binds cadherins at the plasma membrane [73,74] (Fig. 3), and enables cadherin adhesion, motility or signaling in the context of associated proteins and dynamic cadherin-actin interactions [75–78,68,65,4,79–82,5]. Cadherins act together with nectin adhesion molecules [83,84], signaling molecules such as receptor-tyrosine and additional kinases [42–44,85,45,46,86,47–49,51], LAR-family and other phosphatases [87–90,50,82,91], Rho-family GTPaes [58,92,93,65], proteins involved in cell polarization and morphogenesis [94–98,2,99,5], as well as an array of associated cytoplasmic entities including catenins [75,68,4,79,80]. Cadherin contacts, are for example, instrumental in the strengthening of adhesive interactions between cells, the transduction of cell-cell signals and the

promotion or maintenance of cell polarization. In epithelia, the caherin-enriched zonula adherens is formed in an orchestrated manner that produces a circumferential band between contacting cells. Together with the tight junction, the zonula adherens acts as a gate-keeper for the passage of extra-cellular molecules or even entire cells traversing epithelial sheets. Other cadherin based junctions present in differing cell types likewise respond to outside-in and inside-out cues, including cues that result in the altered polarization or motility of cells in physiological or pathological contexts.

If we were to use β-catenin as as an example of developmental functions that might similarly involve members of the p120-catenin sub-family, points beyond β-catenin's involvement in cadherin or Wnt pathway function should be considered. This includes β-catenin's associations with receptor tyrosine kinases or other kinases or phosphatases [42–50], presenilins and mucins [100–105], with cytoskeletal components contributing to polarized cellular projections (associating in conjunction with APC to microtubule plus-ends) [106–109], and in the gene regulatory sphere, with transcriptional regulators beyond the well known association of β-catenin with TCF/LEF (canonical Wnt pathway), for example, with members of the Sox, nuclear hormone receptor and vitamin D families [110–113].

P120-catenin family members, being lesser studied than β-catenin, may thus prove to have multiple plasma membrane, cytoplasmic and nuclear roles. Some of these roles will be relevant to understanding the molecular mechanisms underpinning developmental phenotypes discussed below. In this regard, while considerable cell line
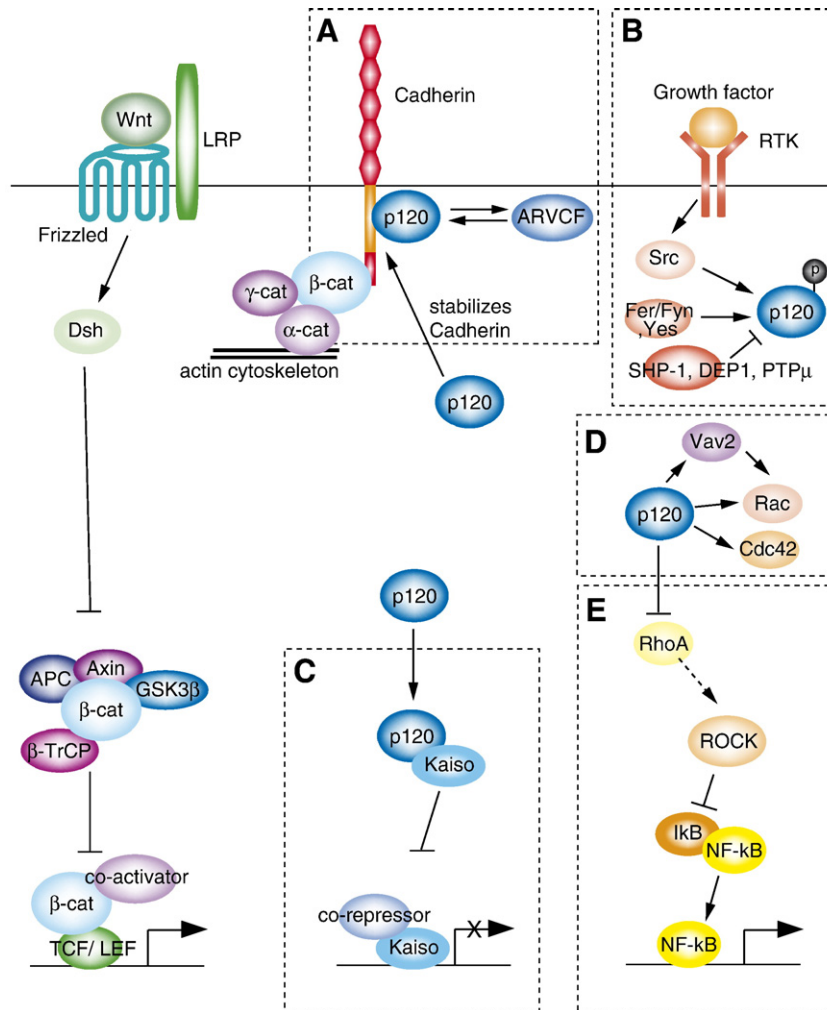
Fig. 3. Signaling pathways and interactions involving p120-catenin. (A) The association of p120-catenin with cadherin. P120-catenin binds to the juxta-membrane region of cadherin intracellular domains and contributes to metabolic stabilization of the cadherin-catenin complex. (B) P120-catenin is directly or indirectly acted upon by protein kinases and phosphatases, some of which are depicted. While mechanistically unresolved in most cases, phosphorylation/de-phosphorylation events are believed to modulate the protein:protein interactions and intracellular localizations of p120 sub-family members. (C) P120-catenin modulates small GTPase functions. P120-catenin is thought to indirectly activate Rac1 (and perhaps Cdc42) through Vav2, while p120 inhibits RhoA. (D) P120-catenin is an upstream regulator of the Kaiso transcriptional repressor. P120-catenin directly interacts with Kaiso, relieving Kaiso-mediated transcriptional repressor by interfering with Kaiso:DNA promoter association and sequestering Kaiso to the cytoplasm. (E) P120-catenin in NF-κB signal transduction. Inhibition of RhoA activity by p120-catenin is followed by inactivation of the NF-κB signaling pathway in epithelial tissues. (Not Boxed) Running down the left margin of this schematic is a simplified view of the Wnt/ β-catenin signaling cascade, which is comprised of a large array of signaling mediators and modulators. In brief, the association of Wnt ligand with a co-receptor complex comprised of Frizzled/LRP results in β-catenin's metabolic stabilization, nuclear entry and association with TCF/LEF to relieve target gene repression.

and embryo work initially highlighted distinguishing features of p120-catenin and its sub-family members relative to β-catenin, recent findings have indicated that p120- and β-catenin functions are closely inter-related in certain developmental processes, such as the transduction or down-stream execution of canonical (β-catenin mediated) or non-canonical Wnt signals [26–28].

4. p120-Catenin sub-family members in development

In vertebrates, some p120-catenin family members, including p120-catenin itself, have essential roles in development. This has been indicated both in amphibian systems in which the levels of selected catenin proteins were knocked-

down [61,114], and in mammalian systems in which total or conditional knock-outs of targeted catenins took place [71,72]. On the other hand, absent or subtle effects followed the removal or depletion of other family members. For example, although the depletion of ARVCF in *Xenopus* was embryonic lethal (producing failures in gastrulation similar to those following p120-catenin knock-down) [61], its knock-out in mice produced no obvious effects (R. Kucherlapti, personal communication). Further, in the mouse system where δ-catenin expression is predominantly restricted to neural tissues, whole-animal knock-outs produced significant cognitive deficits and altered synaptic function but no phenotypes elsewhere [115]. Perhaps due to δ-catenin's wider temporal and tissue expression in amphibians, δ-catenin knock-down in

Xenopus produces gastrulation failures in a proportion of animals (D. Gu and P. McCrea, unpublished results).

When contrasting findings from vertebrate and invertebrate systems, the reported distinctions in developmental outcomes appears to be even more pronounced than those between amphibians and mammals. As noted when considering invertebrates, only a single p120 sub-family member has been identified [29–31], with its knock-down or knock-out surprisingly resulting in mild effects (see below). If anything, few effects might instead have been expected in vertebrates due to the existence of multiple sub-family members [7,10] (Fig. 1). However, because the relative levels of p120, ARVCF and δ-catenin have not been established within most cells or tissues, it is difficult to even arrive at an expectation for functional compensation.

5. Developmental indications from human disease

Findings concerning the functions of catenin proteins come from a diversity of research areas including those addressing human genetic disease. Best characterized are specific mutations arising in the human β-catenin gene, or in other genes whose products likewise promote or modulate the canonical Wnt pathway, such as APC and Axin [38]. In these cases, established linkages exist between genetic aberrations and the progression of colon [116,117], thyroid [118], ovary, breast [37,119], prostate [111,112,120,113], liver [121], and cervical carcinomas and melanoma [122–124], as well as the promotion of bone and additional pathologies [125,40].

The linkage of genetic mutations in p120-catenin sub-family members to human disease is in contrast less well elucidated, although indications are already that such contributions exist and may be significant [122]. For example, regarding p120-catenin itself (human CTNND; 11q11) [126], good correlations are present between its loss or reduced activity and increased incidences of inflammatory bowel disease, particularly ulcerative colitis and active Crohn's pathologies [127]. Additional studies have focused upon altered p120-catenin intracellular localization and function in cancer [8,28,128], as addressed in one of this issue's accompanying reviews. Regarding other p120 sub-family members, deletions in δ-catenin (human CTNND2; 5p15) correlate with the severity of mental deficits in Cri-du-Chat syndrome (CDCS), which is associated with as much as 1% of all mental retardation [129]. Recently, an objective genetic screen for tumor suppressors identified δ-catenin as a prominent candidate [130]. In addition to cadherins, δ-catenin binds presenilin-1 [131–133], the molecule most often mutated in Alzheimers [134,135]. Further, δ-catenin associates with scaffolding and polarity proteins [136–140], small GTPases and signaling proteins [141–143,59], and the Kaiso transcriptional repressor [144]. Thus, it is possible that reduced δ-catenin levels alters multiple physiological outputs, although in mice, apparently within a limited tissue (neural) context. The ARVCF gene in turn resides within a chromosomal region (22q11) that when deleted results in craniofacial defects associated with mental retardation [145,126]. In summary, there is presently suggestive evidence that each p120 sub-family

member participates in normal human development or adult physiology. It is obvious, however, that much additional work is required. This is especially true in cases where human chromosomal deletions have removed the function of multiple gene products.

6. Knock-out and depletion studies

6.1. Introductory summary of p120 mouse knock-outs

Given the advantages of targeted gene knock-outs, recent work from three laboratories has assessed p120-catenin's developmental function in mice and supported its requirement in embryogenesis or tissue maintenance [71,72]. As might be anticipated, global p120-catenin ablation produced more profound embryonic lethal effects (A. Reynolds, personal communication; W. Birchmeier, personal communication). Work in mice has further indicated δ-catenin's developmental requirement [115], while an ARVCF knock-out study has revealed few if any developmental effects (R. Kucherlapati, personal communication).

6.2. Salivary gland knock out

Interest in p120's regulation of small GTPases as well as cadherin turn-over were among incentives leading the group of A. Reynolds' (Vanderbilt U.) to assess p120 ablation in the mouse [71]. Using the MMTV-Cre/lox system, the salivary (submandibular) gland was targeted and examined. While less emphasis was placed upon further MMTV-Cre effects in the lachrymal gland and epidermis, lachrymal phenotypes were consistent with those of the salivary gland, while p120 loss in skin had lesser effects at early developmental stages. Coincident with MMTV-Cre activity (e13.5–e14.5), the phenotypes observed in salivary gland were graphic and included the loss of acinar differentiation, and deficiencies in cell adhesion, polarity and adhesion. Such effects were noted to phenocopy high-grade intraepithelial neoplasias, that in humans progress in a significant proportion of cases to become invasive cancers. Immediately following p120's conditional knock out (e14), embryos exhibited tumor like protrusions in the lumens of salivary ducts. These protrusions grew to become largely unpolarized epithelial masses, with ducts also enclosing a large number of non-adhesive cells. Most mice died soon after birth with occluded ducts and absent acini, indicating the developmental requirement for p120-catenin in mammals.

Consistent with the observation that MMTV-Cre conditional-null mice exhibit salivary duct epithelial masses and reduced cell adhesion and polarity, expression of E-cadherin was lowered. Lesser effects were seen upon the stability of P-cadherin, or upon components of other junction types. Relative to the abnormal epithelial masses within ducts, the ducts themselves exhibited more modest changes in response to p120-catenin loss, but included abnormal mixing of luminal and basal cell layers, more tortuous tubular morphology, cell shedding and reductions in cell polarity. The causative basis was proposed to be the reduced levels of E-cadherin, with additional

consideration given to possible effects of p120 absence upon canonical (β-catenin mediated) and non-canonical Wnt signaling (suggested from studies in *Xenopus*, see below) [26–28], as well as effects upon Rho-GTPases [146,58,61] (Fig. 3).

6.3. Skin knock-out

In undertaking p120-catenin ablation in skin, the laboratory of E. Fuchs (Rockefeller U.) employed K14-Cre mediated recombination [72]. Although the expected reduction in E-cadherin and associated components occurred (β-catenin and α-catenin), the skin of neonatal p120 deficient mice maintained barrier functions and appeared normal at histologic and ultrastructrual levels. Other junctional types (desomsomal and tight junctions) remained unperturbed, and the standard markers of terminal differentiation were retained. In vitro, however, p120-null keratinocytes displayed partial lessenings in radial actin organization, as well as a reduced efficiency in generating epithelial sheets and undergoing stratification. Even if these latter effects were not apparent in vivo, they are consistent with p120's accepted role in promoting adherens junction stability and function [147–151,9]. In vivo, it was proposed that greater cell densities and surface areas available between contacting cells provided more opportunity to overcome p120-catenin deficiency, as did proportionately less cytoskeletal activity arising from cell-substrate interactions. An interesting response to p120 loss in both salivary gland and skin was increased cell proliferation. In the case of neonatal keratinocytes, hyperproliferation of the epidermis was almost two-fold when assessed using bromodeoxyuridine or other assays.

As the mice aged, pronounced phenotypes arose such as hair loss, skin hyperplasia, increased subdermal immune cell infiltration, increased dermal blood vessel density and reductions in subcutaneous fat (wasting). These observations together appeared consistent with a progressive inflammatory response. By employing skin grafts to nude mice and anti-inflammatory drugs, it was demonstrated that the phenotypes observed were not likely due to reductions in adherens junction components, as was proposed to contribute to phenotypes observed in the salivary gland [71]. Instead, both in vivo and in vitro, p120-null skin cells exhibited an activated NF-κB pathway, with nuclear localization of phosphorlated p65 and expression of NF-κB target genes furthering the pro-inflammatory cascade. As opposed to being an extrinsic consequence of inflammation, NF-κB activation was found to be an intrinsic response to p120-catenin loss. The means by which p120-catenin loss activates NF-κB was not revealed in full, although indications were that activated RhoA and Rho-kinase (ROCK) are involved (Fig. 3E). Knock-outs conducted in salivary gland or skin thus support p120's requirement in modulating cadherin or Rho GTPase functions, with a new link having been established between p120 and the NF-κB signaling pathway [72].

6.4. Dorsal forebrain knock-out

Dendritic actin-rich spines or protrusions are key elements comprising postsynaptic sites of excitatory input, and synaptic function is dependent upon their morphological plasticity. The dynamic involvement of cadherin, catenin and actin function in synapse formation, maintenance and remodeling has been well supported [66]. The recent targeted knock-out of p120-catenin in dorsal forebrain, in turn, produced a number of interesting phenotypes in pyramidal neurons that reflect p120-catenin's roles in dendritic spine and synapse formation [152]. Consistent with observations from other tissues and experimental systems, p120 loss resulted in reduced cadherin levels as well as consequent effects upon Rho GTPase activities. Specifically, while the larger organization of dendritic trees remained relatively normal, the loss of p120 dramatically reduced spine density along dendrites and altered the neck length and head width of spines. A reduced number of hippocampal synapse densities was also observed. *In vitro* analyses indicated that the spine density effects arose largely from altered regulation of Rho (increase Rho and reduced Rac activity), whereas spine head-width alterations appeared to result from the reduced presence of N-cadherin following p120 deletion. Reduced N-cadherin levels, possibly inclusive of lowered cadherin-mediated Rac activation, was further associated with perturbed maturation of dendritic spines *in vitro* [152]. Overall, this work supports the existence of cadherin and small GTPase functional interactions with p120-catenin *in vivo*, consistent with relationships noted in salivary gland and skin (above), as well as p120 studies in *Xenopus* (see below).

6.5. Mouse knock-outs of δ-catenin and ARVCF-catenin

In addition to p120-catenin, three other p120 sub-family members include δ-catenin, ARVCF-catenin and p0071-catenin (not discussed) [7,10] (Figs. 1 and 2). The knock-out of δ-catenin in mice produced no obvious morphological or early developmental effects, although consistent with δ-catenin's predominant expression in mouse neural tissues [153], cognitive deficits included spatial and conditioning impairments, as well as short falls in some aspects of motor coordination [115]. Other proteins that bind δ-catenin and contribute to synapse formation and function, N-cadherin (not E-cadherin) and PSD-95, were lowered, possibly through mechanisms analogous to C- or E-cadherin reductions following in vivo knock-down/knock-out of p120- or ARVCF-catenins [61,71,72], or following p120 depletion in cell line contexts [147–151,9]. While δ-catenin's overexpression in normal mammalian kidney epithelial cells correspondingly results in increased E-cadherin expression [154], in human cancers greater (as opposed to lesser) δ-catenin levels have interestingly been associated with decreased and redistributed E-cadherin and p120-catenin [155,156]. Finally, since δ-catenin (in common with p120- and ARVCF-catenins) has further been shown to modulate Rho GTPases and thereby the cytoskeleton [154,157,59], this may be an additional-factor in generating the observed cognitive dysfunctions.

The ARVCF-catenin knock-out in mice interestingly produced no obvious phenotypes (R. Kucherlapti, personal communication). However, genetic crosses with mice bearing

an over-active canonical (β-catenin/TCF) Wnt pathway resulted in progeny (ARVCF−/−; APC1638N−/+) that exhibited a somewhat higher incidence of gastro-intestinal tumors and with a subtle shift in their spectrum to the upper gastro-intestinal tract. It is expected that genetic crosses of ARVCF null animals with other mice, including those lacking distinct p120 sub-family members (such as δ-catenin), will prove informative.

7. Most but not all invertebrate studies point to a modulatory as opposed to essential role of p120-catenin in development

It is notable that the preponderance of published reports from the *Drosophila* and *C. elegans* systems contrast with those from vertebrates in indicating that p120-catenin is not essential for development.

7.1. P120-catenin knock-down in C. elegans

In *C. elegans*, work from the laboratories of J. Pettit (U. Aberdeen) and J. Hardin (U. Wisconsin) showed that the single p120-catenin sub-family member (JAC-1) is not required for nematode development [30,158–160]. Following p120/JAC-1 knock-down *via* RNAi (>90% reduction in transcript levels; JAC-1 antibodies not available), no obvious defects appeared in embryonic or post-embryonic development. However, crosses with animals homomorphic for α-catenin (hmp-1) resulted in phenotypes resembling stronger alleles of α-catenin (HMP-1). Embryos developed normally until the 1.25 fold stage, whereupon a large dorsal bulge arose followed by failures in dorsal flexure and elongation. Normally, such elongation involves the coordinated circumferential contraction of epidermal cells. In embryos having reduced p120/JAC-1 (RNAi) and α-catenin (homomorphic allele) functions, circumferential actin bundles were thicker than normal and became detached from adherens junctions that displayed reduced levels of cadherin (HMR-1). These phenotypes were again similar to strong or null α-catenin/HMP-1 mutants, suggesting that p120/JAC-1 has a role in anchoring actin filaments to the adherens junction and maintaining cadherin localization. P120's role in microfilament:junctional association has also been supported in mammalian cell line studies [161]. Work in *C. elegans* therefore suggests that p120-catenin is dispensable for development, while more detailed assays reveal positive contributions to cadherin and cytoskeletal functions [30,158–160].

7.2. P120-catenin knock-down or elimination in Drosophila

In *Drosophila* as in *C. elegans*, studies using targeted knock-downs or genetic nulls point largely to the non-essential developmental role of p120-catenin. The group of M. Peifer (U. North Carolia) employed both genetic and RNAi methods to reduce p120-catenin function, finding that each yielded viable and fertile flies that retained normal distributions of adherens junction components [31]. Even flies that lacked maternal contributions of p120-catenin exhibited normal development. The level of adherens junction components such as DE-cadherin also appeared similar to controls, although less than two-fold differences would have been difficult to resolve. Flies mutant for p120-catenin were not completely normal, however, since a proportion exhibited aberrations in the regularity of cell fronts participating in dorsal closure. Dorsal closure is a morphogenic process that involves the elongation of lateral sheets of epithelial cells and their dorsal migration to enclose the embryo. Further, more detailed examinations revealed alterations in cell shape and actin organization at the front, which correlated with the closure process being slowed in affected embryos. Ultimately, dorsal closure became fully resolved (normal phenotype) even in those p120 mutants that experienced delays.

An interesting observation from normal (wild-type) flies was that the protein levels of junctional p120-catenin varied relative to those of DE-cadherin, β-catenin and α-catenin, and that junctional p120 localization tended to be greatest in tissues undergoing morphogenic movements [31]. This suggested that p120-catenin may not be a core adherens junction component in flies, but may play a positive modulatory function especially in tissues subject to movement or mechanical stress. While p120's contribution to adherens junction function and morphogenesis was not made apparent when its function was removed in isolation, p120 null mutants placed in conjunction with weak DE-cadherin (or β-catenin) alleles resulted in enhanced phenotypes. For example, cuticle defects became more pronounced and resembled strong DE-cadherin alleles, including the appearance of ventral holes. The specificity of these observations was suggested when weak allele phenotypes were rescued by transgenic expression of p120 catenin. Thus, while p120 was not essential in these studies (based upon its removal in isolation), p120 was clearly a positive modulator of cadherin complex functions.

Another *Drosophila* study did not reveal alterations to Rho1 GTPase localization in p120 mutants [162]. While p120 removal subtly altered the phenotype of Rho1 mutant embryos, generating a greater number of embryos with elongated cuticles, embryonic processes generally did not point to a genetic interaction between p120-catenin and Rho1. This proved to be the case even when employing Rho mutants earlier shown to display an interaction (see below) [29]. These results indicate that the relationship of p120 with Rho GTPases resolved in vertebrates may not be conserved in flies, or that redundant Rho1 regulators act in parallel to p120 in *Drosophila*.

7.3. A differing view on Drosophila p120-catenin

Independent work upon p120-catenin function in flies was conducted by the group of S. Parkhurst (Fred Hutchinson Can. Res. Ctr.) [29]. In common with vertebrate studies, p120 was shown to associate with Rho1 with a preference for GDP-bound Rho1. Interestingly, α-catenin was also found to bind Rho1 (either GDP- or GTP bound), raising the possibility that α-

catenin may assist in recruiting Rho1 to the cadherin-catenin complex or tether it once present. Contrasting with above noted findings, RNAi mediated depletion of p120-catenin resulted in the relocalization of Rho1, as well as in morphogenic failures including head involution. Transgenic p120 over-expression enhanced Rho1 mutant phenotypes as would be anticipated from vertebrate work, although it was again an effect not seen in the other *Drosophila* study. While the dissimilar *Drosophila* observations are not yet explained, they conceivably might have resulted from different experimental environments (stresses) to which the flies were exposed. For example, the delayed but none-the-less completed dorsal closure phenotypes observed in the Peifer lab may not have resolved themselves as fully under slightly different laboratory conditions. Another *Drosophila* study addressing this issue was focused upon dendritic morphogenesis and completed by the group of FB Gao (Gladstone Inst.) [163]. While p120-dependent phenotypes were indeed resolved using genetic, RNAi and over-expression approaches, they were only seen in a sub-set of neurons, with no detection of larger effects. It remains interesting, however, that although the possible impact upon small GTPases or cadherins was not pursued in this latter work, the phenotypes of dendrites deficient for *Drosophila* p120 bore resemblances to those described above in mouse hippocampal pyramidal neurons lacking p120 [152], with both types of actin-rich spine (or spine-like) structures exhibiting altered morphologies.

7.4. Finally, more evidence that the cadherin:p120 association is dispensable to Drosophila development

Finally, supportive of the view that cadherin:p120 association is not essential in *Drosophila* are results from the group of P. Rorth (EMBL) [164]. In flies with zygotic or clonal absence of DE-catenin it was found that phenotypes such as aberrations in border cell migration within the egg chamber could be rescued not only by reintroduction of wild type DE-cadherin, but also by a mutant form of DE-cadherin that lacked the capacity to bind p120-catenin. Likewise, both native and p120-uncoupled DE-cadherin rescued DE-cadherin deficiencies in germline and follicular cell clones. Comparable rescues were further seen in embryos. For example, normal head and ventral cuticle phenotypes were recovered with partial rescue of zygotic lethality. The larger body of evidence from invertebrates therefore indicates that p120-catenin plays a supportive but not an essential role in development, with one *Drosophila* study differing in this view.

7.5. Amphibians

In amphibian systems, researchers have largely employed knock-down (as opposed to knock-out) or over-expression approaches [165]. The knock-down of p120-catenin in *Xenopus* results in failed gastrulation and is thus embryonic lethal [61]. Because a large number of early embryonic perturbations can result in gastrulation effects, assessment of the underlying basis of the phenotype was initially based upon candidate possibilities suggested from earlier mammalian cell line studies. This

included the role of p120-catenin in enhancing cadherin metabolic stability [147–151,9], as well as in regulating Rho GTPase activity [146,56–58]. Remarkably, carefully titrated doses of dominant-active Rac (DA-Rac) or dominant-negative Rho (DN-Rho) completely rescued p120-catenin knock-down phenotypes in *Xenopus* [61]. Significant rescue also followed expression of C-cadherin, presumably as a result of restoring C-cadherin's cell-cell adhesive activity and/or of restoring cadherin-dependent Rho GTPase activities. Because p120-catenin has additional roles in the nucleus as indicated below, a question arose as to why DA-Rac, DN-Rho or C-cadherin rescued the p120-catenin knock-down phenotype to such a significant extent. One possibility is that a sufficient fraction of p120-catenin protein survived depletion (knock-down) to conduct its roles within the p120/Kaiso signaling pathway [26–28]. This includes the relief of repression conferred by Kaiso upon its target genes. The p120-catenin knock-down, therefore, was likely to have created a sensitized background that facilitated the in vivo resolution of p120:GTPase and p120:cadherin functional interdependencies, but not p120's role in p120/Kaiso developmental signaling [26–28].

Because the *Xenopus laevis* fate map is known, it is possible to inject chosen cells in early clevage-stage embryos to approximate spatial control over morpholino or cDNA/mRNA effects at later developmental stages. Such an approach was used to test the impact of depleting p120-catenin in the anterior neural plate, including regions that specify cranial neural crest [114]. Consistent with *Drosophila* studies, p120-catenin was shown to be most highly expressed in embryonic regions undergoing extensive morphogenic movements. However, in *Xenopus*, the knock-down of p120 in anterior neural regions produced dramatic effects that included abberant evagination of the optic vesicles as well as reduced migration of neural crest cells from the neural tube to populate the branchial arches. Rescue analysis of p120 depleted embryos indicated that the knock-down effects likely arose from changes in p120-dependent Rho-family GTPase and/or cadherin function, consistent with broader p120 depletions producing gastrulation failures (see above). However, a perplexing question that remains in comparing results from gastrula *versus* later-stage embryos [61,114], is why converse forms of Rho (or Rac) proved effective in rescuing p120 knock-down. While speculative, possibilities include the presence of distinct cadherin repertoires at early versus later embryonic stages, potentially modulating small GTPases (or vice versa) in distinctive manners. In summary, *Xenopus* work upon neurula and later embryonic stages demonstrated that p120-catenin is essential beyond its early requirement in gastrulation, heightening attention upon p120 dependent processes that are morphogenic in nature.

7.6. ARVCF- and δ-catenins in Xenopus

Vertebrate p120-catenin is most closely related to the p120 sub-family member ARVCF-catenin. In specificity tests, p120-catenin depletion phenotypes were rescued by a properly titrated dose of p120-catenin as expected, but interestingly, also

by ARVCF [61]. Further, the depletion of ARVCF, which resulted in similar phenotypes to p120 knock-down, was rescued by exogenous p120-catenin. These results suggest that p120-catenin and ARVCF-catenin exhibit in vivo functional overlap. Indeed on the biochemical level, ARVCF was shown in common with p120-catenin to associate with cadherin, RhoA and the Rac GEF, Vav2. In binding the membrane proximal domain of cadherin, ARVCF associates in a mutually exclusive manner relative to p120-catenin [166], suggesting that each occupies the same or an overlapping cadherin site. Further, ARVCF in common with p120 appears to facilitate cadherin stabilization, likely by reducing the extent of cadherin internalization [61]. While exhibiting shared functions, it is notable that the p120- and ARVCF-catenins are not functionally redundant in amphibians, since the depletion of either catenin in isolation is embryonic lethal. Presumably this results in part because each catenin is not present at endogenous levels adequate to compensate for loss of the other. In mice, ARVCF may be dispensable owing to a lesser role or greater capacity of p120-catenin to compensate. Over all, in vivo vertebrate evidence indicates that both p120- and ARVCF-catenins (as well as δ-catenin) modulate cadherin metabolic stability and small GTPase activities [61,115,71,72]. The distinct knock out phenotypes of p120, ARVCF and δ-catenin in mice presumably results from each catenin having at least certain differing but required functions, or that quite similar functional profiles are executed but in dissimilar cell/tissue contexts.

δ-Catenin is a p120 sub-family member that both binds cadherin membrane-proximal regions and modulates Rho-family GTPases [154,157,59]. δ-catenin's depletion or rescue analysis in *Xenopus* has not yet been fully assessed, although preliminary work suggests that δ-catenin is expressed more widely in *Xenopus* than in mice and is essential in early amphibian development (D. Gu and P. McCrea, unpublished results). In summary, amphibian together with mammalian results indicate that p120-catenin is required for early as well as later aspects of development. The p120 knock-down in *Xenopus* appears to produce its principal impact upon Rho GTPase and/or cadherin functions. Additional requirements for p120-catenin may have been masked by the proportion of p120-catenin surviving depletion, possibly including p120's role within the p120/Kaiso signaling pathway [26–28]. In amphibians, ARVCF is also essential to development, while the knock-down of δ-catenin will require further evalutaion.

8. Over-expression studies

8.1. Exogenous-expression studies in vertebrates suggest p120-catenin levels must be maintained within a physiological range for normal development to proceed

Prior to knock-out or depletion studies of p120 sub-family members, the over-expression of cadherin constructs in varying systems had already suggested p120 sub-family involvement in embryogenesis. These studies employed cadherin deletion or point mutants that were incapable of binding p120 sub-family members. Complicating matters somewhat is that such cadherin

constructs may have further been deficient for interactions with other known or unknown protein partners. For example, in addition to p120 sub-family members, proteins that indirectly or directly associate with cadherin juxta-membrane domains include presenilin [103], Fer tyrosine kinase [167,168], PTP1b phosphatase [169], and PTP1u phosphatase [170,171,82]. Thus, the over-expression of cadherin juxta-membrane mutants has been informative, although results must be viewed within the potentially larger context of juxta-membrane interactions and functions.

8.2. Chicken over-expression of N-cadherin mutants

In large measure, indications from mammalian cell line work have been that the larger cadherin juxta-membrane domain, representing perhaps one-third to one-half of cadherin cytoplasmic tails (roughly 30-70 amino acids), modulates functions including cadherin lateral dimerization/clustering and adhesive strengthening [172–175], cell motility [176,177], and cell organization/orientation and morphogenic movements [178]. Interestingly, in a number of in vivo over-expression contexts, lesser effects arose than might have been expected if the association of p120-catenin sub-family members in particular were required. For example, while exogenous expression of a juxta-membrane deletion mutant of N-cadherin interfered with myotomal cell organization in developing chick embryos, a more restricted triple-point mutant incapable of binding p120-catenin sub-family members produced no effect [178]. In this latter case, since over-expression of native full-length N-cadherin did not perturb development in the chick myotome (cadherin over-expression can be disruptive in other systems/contexts), an uncoupled N-cadherin point-mutant might likewise have been less apt to produce a phenotype. Even with this consideration, such exogenous expression work in conjunction with other studies (see invertebrates below) suggests that cadherin association with p120-catenin sub-family members is not crucial in all developmental contexts.

8.3. Over-expression in Xenopus of cadherin mutants

In *Xenopus*, the over-expression of deletion mutants of N-cadherin has pointed to the relevance of protein interactions taking place within the juxta-membrane region [179,180] . In these experiments, exogenous segments of the cadherin juxta-membrane domain appear to act in a dominant-negative manner by sequestering known/unknown protein factors away from endogenous cadherins. For instance, the over-expression of both limited and longer juxta-membrane segments of N-cadherin produce strong embryonic phenotypes. Since such phenotypes were generated using even limited peptide regions unable to bind p120 sub-family members (or β-catenin/γ-catenin), other juxta-membrane associations are of interest when evaluating cadherin developmental inputs.

The over-expression of larger constructs of cadherin, most recently that of E-cadherin, has further pointed to the relevance of the juxta-membrane region in development [114]. In this case, targeted injections of E-cadherin triple-point or deletion

mutants incapable of binding p120 sub-family members resulted in aberrant eye formation and neural crest migration. These effects were rescued if the mutants were co-injected with native E-cadherin, and were not seen upon the isolated expression of equivalent amounts of native E-cadherin. Differing with some aspects of the above study in chicken, including the cadherin and tissue under study [178], it appears that proper E-cadherin:p120 sub-family associations are required for vertebrate craniofacial morphogenesis/anterior neural development in amphibians.

8.4. Over-expression in Xenopus of p120-catenin/ ARVCF-catenin

The exogenous expression of p120 or ARVCF-catenin in *Xenopus* results in obvious embryonic defects in gastrulation [181,182,61]. As noted in the chick myotome, p120 over-expression generated strong effects upon the anterior-posterior elongation of myofibers, although no impact was seen upon myotomal expansion [178]. In both vertebrate animal systems, a number of underlying mechanism may contribute to the observed effects. The most prominent possibilities include over-expression effects upon cadherins or Rho GTPases (and thereby NF-κB?), or perhaps also upon the p120/Kaiso developmental pathway. In any case, it is apparent that normal development requires p120-catenin levels to be maintained within a set physiological range.

9. Nuclear roles of the p120-catenin sub-family

Each of the p120-catenin sub-family members has been observed in nuclei of cell-culture or tissue cells, yet with the exception of p120-catenin itself, little is know about their actions in this compartment. ARVCF-catenin was recently found to interact with Kazrin (T. Vaught and P. McCrea, unpublished results), a protein first reported to associate with desmosomal or inter-desmosomal components [183]. Since ARVCF [166,184], as well as Kazrin shuttle between cytoplasmic and nuclear spaces (T. Vaught and P. McCrea, unpublished results), and ARVCF is structurally related to the transcriptional modulators β-catenin and p120, it is reasonable to conjecture that ARVCF has nuclear functions. Finally, one report has indicated that δ-catenin forms a complex with the transcriptional repressor Kaiso [144], described below in the context of its better understood interaction with p120.

9.1. P120-catenin and the p120/Kaiso signaling pathway

While much p120 work has focused upon its roles at the plasma membrane or in the cytoplasm (cadherin complex; Rho GTPases), accruing information from *Xenopus* has heightened attention upon p120-catenin's gene regulatory roles. The principal focus has been upon the p120:Kaiso complex which was first resolved and characterized in mammalian cell lines [53], followed by studies in *Xenopus* that placed its functions within a new developmental signaling pathway [26–28]. In vivo and in vitro studies agree that in response to upstream signals

that have yet to be resolved, p120-catenin enters the nucleus where it binds Kaiso and displaces it along with associated co-repressors from gene control regions, resulting in gene activation [26–28,185].

Intriguingly, p120 and Kaiso were recently revealed to modulate genes known also to be regulated by the canonical Wnt (β-catenin/TCF-mediated) pathway [27,28]. The promoter of one of these targets, *Siamois*, was shown to contain functional binding sites for Kaiso as well as those known for TCF, and the resolution of a TCF:Kaiso complex suggested that these repressors act cooperatively. Indeed, a close functional inter-relationship between the p120/Kaiso and β-catenin/TCF pathways was indicated, with for example, coordinate de-repression of Kaiso and TCF (respectively via p120 and β-catenin) producing greater Siamois gene activity than de-repression of Kaiso or TCF in isolation.

10. Discussion

In evaluating p120-catenin's developmental roles, a primary theme spanning both invertebrate and vertebrate systems is that p120 modulates cadherin-catenin complex functions. This assessment resides in part upon reductions in cadherin levels as a consequence of p120 loss in vertebrates, and invertebrate genetic crosses wherein mild or non-apparent p120 phenotypes become severe when compounded with mutants in cadherin-catenin components such as DE-cadherin, α- or β-catenin.

10.1. p120 and cadherin function

Many possibilities emerge when considering how cadherin-catenin complex function might be altered upon loss of p120 (Fig. 3). This is because cadherins and catenins are integrated into a web of other functional components many of which are in direct physical association [64,65,186,187,5,66]. For example, work from vertebrate and invertebrate systems suggests that p120 modulates actin organization at cell-cell junctions as well as at non-junctional regions [146,58,188]. Cadherins promote cell-cell adhesion, and importantly also provide focal points where contractile microfilaments exert force (traction) during morphogenic processes. In *C. elegans*, for example, elongation of the embryo is much more severely perturbed when a mutation in α-catenin (HMP-1), a component of the complex, is compounded with one in p120 (JAC-1) [30]. This correlates with reduced actin attachment at cell-cell junctions as well as anomolous cadherin (HMR-1) distributions in the mutant embryos. In *Drosophila*, mutations in other junctional complex components (DE-cadherin or β-catenin) also produce more severe phenotypes in conjunction with mutations in p120, and are likewise associated with greater cytoskeletal disorganization [31]. Analogously, mammalian cell-line work has shown that p120-uncoupled forms of E-cadherin are incapable of promoting cell compaction, correlating with an inability of these cells to form properly associated circumferential actin rings [161].

In vertebrate systems, the cadherin juxta-membrane region binds p120 sub-family members and additional proteins, and has been implicated in modulating processes including cadherin

dimerization, cadherin-mediated adhesive strengthening and cadherin endocytosis/stability. Supportive of p120's impact upon cadherin and cytoskeletal functions, keratinocytes obtained from p120-null mice exhibit lowered cadherin levels when plated in vitro, as well as partial defects in cell-cell associations and actin-based structures involved in cell interactions [72]. The targeted p120 knock-out in mouse salivary gland likewise lowered cadherin levels and disrupted tissue organization and cell polarization [71], while in *Xenopus*, p120 knockdown perturbed cadherin-dependent directed cell movements and likewise lowered cadherin levels [61]. These results provide backing to the view that p120-catenin assists in modulating the structure and function of adherens junctions through direct or indirect effects upon cadherin as well as upon the actin cytoskeleton. Some of the observed in vivo effects following p120-catenin loss are likely to involve increased cadherin endocytosis (degradation/recycling), which is the primary subject of an accompanying review in this issue [186,9]. Indeed, in addition to cadherin mis-localization, increased intracellular vesicular stores of E-cadherin appeared in p120 null keratinocytes plated in vitro [72], suggesting altered cadherin trafficking following p120-catenin loss.

10.2. P120 and its developmental requirement

The question of p120-catenin's role at the organismal level has as noted distinguished work undertaken in vertebrate versus invertebrate systems. In vertebrates, it is accepted that p120 depletion or complete loss results in severe or observable developmental defects during or following removal [61,71,72,152]. Conversely, invertebrate studies in *Drosophila* and *C. elegans* have led most investigators to believe that the isolated depletion or loss of p120-catenin has little if any obvious effects upon development [31,30,162,163]. One *Drosophila* study however has differed in two regards, first pointing to p120's essential role in development and secondly supporting p120's functional interaction with Rho [29], each accepted points in vertebrate circles. What might be the basis of such opposing experimental results and conclusions in *Drosophila* is not clear. If basal lab conditions imparted slightly different stresses one can imagine that a tipping point could be reached whereby lesser or greater effects were observed. Indeed, even in cases where p120-deficient *Drosophila* embryos ultimately proceeded on a normal developmental course, delays in dorsal closure and alterations in cell shapes and actin organization at the closing front were reported [31].

Whatever the explanation, it remains that most invertebrate work indicates that p120-catenin is not developmentally required, distinguishing invertebrate from vertebrate outcomes. While p120-catenin may have similar roles in vertebrates and invertebrates, it equally possible that p120 executes vertebrate- or invertebrate-specific embryonic roles. For example, one *Drosophila* study indicates that p120 lacks any clear functional interactions with Rho1 [162], whereas in *Xenopus*, mice and mammalian cell lines, small GTPase interactions are prominent. It is relevant to consider in this regard that invertebrate and vertebrate p120-catenins bear regions of structural divergence.

For example, although similar in the Armadillo domain (43–51% identical) [31], *Drosophila* p120 lacks regions of sequence similarity that are conserved across vertebrate p120-catenins. Further noteworthy is that even when comparing *Drosophila* and *C. elegans* p120-catenin, discrete differences are suggested based upon dissimilar sequence regions that potentially engage in distinctive protein:protein interactions. Within vertebrate p120-catenin, regions that are divergent from invertebrates may likewise play important and even essential roles. Assuming that other p120 sub-family members lack equivalent regions or are not expressed within the same cells, then functional compensation would be unlikely to occur following p120 loss in vertebrates.

Conversely, it is possible to propose that p120-catenin executes predominantly similar roles in both invertebrates and vertebrates, but that greater demands are placed upon p120 function in vertebrate contexts. This might arise if cell-cell adhesion in larger animals requires more exacting regulation relative to *Drosophila* and *C. elegans*, or if the mechanical stresses upon junctional regions are more pronounced. In a number of vertebrate contexts, cadherin endocytosis/stability is sensitive to p120-catenin levels [147–151,9,61,71,72,152], while in *Drosophila*, embryogenesis has appeared more resistant to partial reductions in cadherin levels/ functions [189–191], likely contributing to the increased difficulty in resolving phenotypic effects following p120 depletion or loss [31].

10.3. P120 effects upon cell proliferation and polarity: Rho GTPase and NF-κB fuctions

A key aspect of p120-catenin biology was recently revealed by groups using mice as their developmental system. Effects from the targeted removal of p120 in the salivary gland included a subtle increase in cell proliferation [71], while its removal from skin produced very significant growth effects [72]. The knock out of p120 in the salivary gland (E14) eliminated formation of the epithelial secretory compartment (acini) while the luminal areas within secretory ducts exhibited pronounced epitheloid tumor-like masses. Given that these masses grew despite increased apoptotic rates, proliferation may have been heightened beyond what was apparent from BrDU measurements. In any case, p120-catenin's knock-out in skin keratinocytes produced an obvious (approaching two-fold) proliferation response. Further analysis of the skin phenotype revealed the unexpected finding that NF-κB signaling had become activated and was instrumental in generating the growth response [72].

P120 loss-of-function effects upon NF-κB were shown to be cell-autonomous at initial stages, and may have been independent of above-noted alterations in cadherin complex functions. For example, an exogenous p120-catenin mutant incapable of binding cadherins retained the capacity to restore cytoplasmic NF-κB localization and to lessen pathway activity within p120-null keratinocytes. This exogenous p120 mutant also reestablished physoiolgic levels of actin-based stress fibers, that presumably had become overly dense due to heightening Rho activity upon p120 removal. Indeed, Rho and its effector ROCK proved to be required intermediaries between p120-catenin loss

and NF-κB effects. Thus, p120-catenin loss is proposed to heighten NF-κB activity, cell proliferation and stress fiber formation as a consequence of increased Rho activity (Fig. 3). Raised Rho activity following p120 loss might further be expected to produce cytoskeletal effects at cell-contact sites, adding to the direct (but still largely undefined) consequences of p120-catenin loss within the cadherin complex itself. Finally, beyond NF-κB in particular, additional cell cycle effectors reside down-stream of Rho, and could contribute to increased proliferation responses observed in p120 null tissues.

As might have been expected given perturbations in cell proliferation, cytoskeletal and likely cadherin function, targeted p120 loss was also correlated with reductions in cell polarity and cell organization in mouse salivary gland and skin [71,72]. Targeted p120 loss to the dorsal forebrain in turn produced alterations in the morphology of actin-rich dendritic spines as well as reduced synaptic density [152]. While not as closely evaluated at the cellular level in *Xenopus*, p120 knock-down also produced developmental phenotypes that were consistent with alterations in such cell properties. For example, the generalized (morpholino-directed) knock-down of p120-catenin resulted in early gastrulation defects [61], while targeted p120 knock-down in the anterior neural plate produced migratory and related defects in the neural crest [114]. Such phenotypes were likely to have resulted from altered cytoskeletal, cell-polarization and cadherin functions, given that phenotypic rescues of p120-depleted embryos were obtained upon the exogenous expression of appropriate forms of Rho (or Rac) or cadherin. Work from *Xenopus* embryos have thus agreed reasonably well with findings from mammalian cell line and mouse animal systems, and support the relevance of p120-catenin in modulating Rho and cadherin developmental functions.

10.4. P120 in the context of the p120/Kaiso developmental signaling pathway

In addition to effects of p120-catenin upon Rho-dependent functions such as cell proliferation and cytoskeletal control, work in *Xenopus* has further implicated p120 as a signal transducer within the novel p120/Kaiso developmental pathway [26–28] (Fig. 3D). The p120/Kaiso pathway is not fully delineated but in a number of respects appears analogous to the canonical Wnt/β-catenin pathway. The first point is that similar to β-catenin's relief of TCF (or LEF) mediated transcriptional repression of canonical Wnt target genes, p120-catenin mediates relief of transcriptional repression conferred by Kaiso, a POZ/zinc-finger family member. More meaningful were findings that the promoters of developmentally important genes possessed functional Kaiso consensus binding sites adjoining established TCF/LEF sites [27,192].

While the upstream activation of Wnt/β-catenin signaling is accepted to involve extra-cellular Wnt ligands and a plasma-membrane receptor complex composed of Frizzled and LRP5/6 (additionally numerous intracellular components including Dishevelled and various kinases) [193] (see also www.stanford.edu/~rnusse/wntwindow.html), the upstream regulators of the p120/Kaiso pathway have yet to be revealed. Given

that p120 binds cadherin juxtamembrane domains, the cadherin-catenin complex itself constitutes a potential receptor complex that upon (kinase or conformational?) activation releases p120 and thereby enables it to function in nuclear or cytosolic Rho GTPase capacities. Another possibility, supported by evidence being gathered in *Xenopus*, is that upstream components of the canonical Wnt pathway (Dishevelled, Frodo) associate with and regulate p120-catenin levels/activity (J. Park and P. McCrea, unpublished results). If this proves correct, then the p120/Kaiso pathway might be viewed as acting in parallel with the β-catenin/TCF pathway at both upstream and down-stream points in Wnt signal transduction [26–28].

While the p120/Kaiso pathway would be predicted to be evolutionarily conserved between amphibians and mammals (Kaiso does not appear to exist in invertebrates), it is interesting that the genetic knock-out of Kaiso in mice does not produce an observable phenotype [194], whereas Kaiso knock-down in *Xenopus* is embryonic lethal [26,195,27]. One explanation being considered is that mammals contain an additional Kaiso-like molecule (lacking in amphibians) that might compensate for Kaiso loss and thus mask the pathway's developmental relevance in mice. A further twist is that some work in *Xenopus* suggests Kaiso removal in mammals might promote cancer [27,28,128]. This possibility is based upon the accepted role of the Wnt/β-catenin pathway in tumor progression [196,41,1], combined with *Xenopus* and mammalian cell line work showing greater activation (de-repression) of Wnt target genes following coordinate Kaiso and TCF de-repression [27]. From this perspective it was therefore again surprising that a Kaiso knock-out produced a subtle protective effect countering tumor formation in mice [194].

Here, a plausible explanation stems from the fact that Kaiso is a dual-specificity repressor that also recognizes methylated CpG islands [197,198]. In this scenario, loss of Kaiso-mediated repression results in enhanced expression of tumor suppressor genes that had acquired pathologically methylated promoters, leading to a protective effect [194]. In any case, more work will be required to determine the impact of Kaiso and the p120/Kaiso pathway upon development in mammals. Interestingly, Kaiso's intracellular localization appears to be subject to complex environmental cues that are expected to have an impact upon its function in both physiological and pathological contexts [128]. Thus far, the described phenotypes following p120-catenin tissue-specific knock out in mouse salivary gland and skin might be expected to result from "direct" effects upon cadherin, Rho GTPases or cytoskeletal functions. However, it is noteworthy that one of Kaiso's direct gene targets is Wnt-11 [26], a non-canonical Wnt ligand that effects Rho GTPase activities in contexts such as morphogenesis. Thus, it remains possible that partial cadherin or actin-based effects following p120 loss may result indirectly from enhanced Kaiso-mediated repression of genes involved in cytoskeletal (etc.) control.

11. Perspectives

For researchers in the field, a fulfilling aspect of studying p120-catenin has been witnessing its impressive biological

reach, apparent most from vertebrate studies, wherein cadherin adhesive and metabolic functions as well as cytoskeletal control and nuclear gene regulation are each involved. As was noted at the beginning of this review, the multi-faceted biological capacity of Armadillo-domain proteins in general was presaged from work upon β-catenin, the most-studied member of the larger catenin family. While similarities exist between β-catenin and p120, including their association with cadherins (although to different regions) and unexpected parallels in gene control, functional differences are equally apparent and include p120 sub-family modulation of Rho GTPases and cadherin stability.

As we move forward, vertebrate studies are likely to be focused upon the developmental contributions of p120-catenin sub-family members in more varied tissue contexts. For example, work is presently on-going to address p120-catenin knock-out effects in liver and colon. A further area that should prove informative is the genetic crossing of mouse lines in which catenin knock-out phenotypes were not graphic or lethal. For example, the mating of ARVCF knock-out mice (no apparent phenotype in isolation), with mice null for δ-catenin (cognitive dysfunctions but otherwise normal). One approach to assess the extent of functional overlaps amongst p120 sub-family members will be to evaluate the consequence of knocking-in one catenin's coding region into the genetic locus of another. To address the particular contributions of p120 sub-family members to cadherin function, genetic knock-ins of cadherin point mutants uncoupled from the p120-sub-family (or vice versa) should be revealing. Workers will undoubtedly also attempt to return to issues that were raised during earlier studies of p120-catenin but that remain largely unanswered. These include the developmental role of phosphorylation in modulating p120 sub-family function [44], as well as of the varied splice (or translation-initiation) isoforms. While not yet proven, it is presumed that such distinctions have an impact upon the intracellular localization [28,128], metabolic stability and protein-protein interactions of p120 sub-family members or their protein partners [151]. Finally, from a bio-medical perspective, it is thought that p120 sub-family members will prove to have important roles in disease progression given their direct association with cadherins, Rho GTPase signaling pathways and gene control. Thus, for example, mice with altered catenin function will be crossed into genetic models of tumor or metastasis progression. For p120 sub-family members enriched in neural tissues, such as δ-catenin and ARVCF-catenin, additional crosses may include assessments of cognitive or behavioral outcomes. As proposed for β-catenin [1–3], vertebrate p120-catenin sub-family members, even while distinctive, are likely to inter-link cadherin, cytoskeletal and gene regulatory functions in development.

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