

Functions of p120ctn in development and disease

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1. ABSTRACT

p120 catenin (p120ctn), a component of the cadherin-catenin complex, was the first member to be identified in a most interesting subfamily of the Armadillo family. Several p120ctn isoforms are generated by alternative splicing. These isoforms fulfill pleiotropic functions according to their subcellular localization: modulating the turnover rate of membrane-bound cadherins, regulating the activation of small Rho GTPases in the cytoplasm, and modulating nuclear transcription. Over the last two decades, knowledge of p120ctn has grown remarkably, and this has been achieved in part by using different animal models. At least in frog and mammals, p120ctn is essential for normal development and homeostasis. Here we will discuss the effects of different p120ctn isoforms on cadherin turnover and on signaling in the cytoplasm and the nucleus. We will also elaborate on the structure and function of other members of the p120ctn subfamily: ARVCF, p0071 and delta-catenin. Finally, we will overview the respective roles of p120ctn family members in pathological processes, and particularly in cancer as p120ctn is frequently downregulated or mislocalized in various human tumors.

2. OVERVIEW OF p120CTN RESEARCH

The founder of the p120ctn family was identified in 1989 as a most efficient substrate for the oncogenic Src tyrosine kinase (1). A 120-kDa protein (hence the name p120) was detected by phosphotyrosine-specific antibodies in cells expressing pp60^{S27F}, an oncogenic c-Src mutant, but it was not detected in cells expressing a non-membrane-associated pp60^{2A/527F} double mutant. This protein was then found to associate with the cytoplasmic domains of cadherins, hence the descriptor 'catenin' and the protein name p120ctn. The mouse p120ctn cDNA was cloned in a labor-intensive manner in 1992 and the predicted protein was found to encode Armadillo repeats like those of beta-catenin (2). The Armadillo repeat domain of p120ctn, like that of beta-catenin, was found to interact with E-cadherin, a component of the adherens junction (3). The mouse gene *Ctnnd1* was localized on chromosome 2, whereas the human gene *CTNND1* was localized on chromosome 11q11 (4, 5). More recently, the relationship between p120ctn and E-cadherin was further elucidated by generating p120ctn-uncoupled E-cadherin mutants, as well as by knockdown and knockout studies (Sections 5 and 8). Using a very reliable monoclonal antibody (pp120), which recognizes an

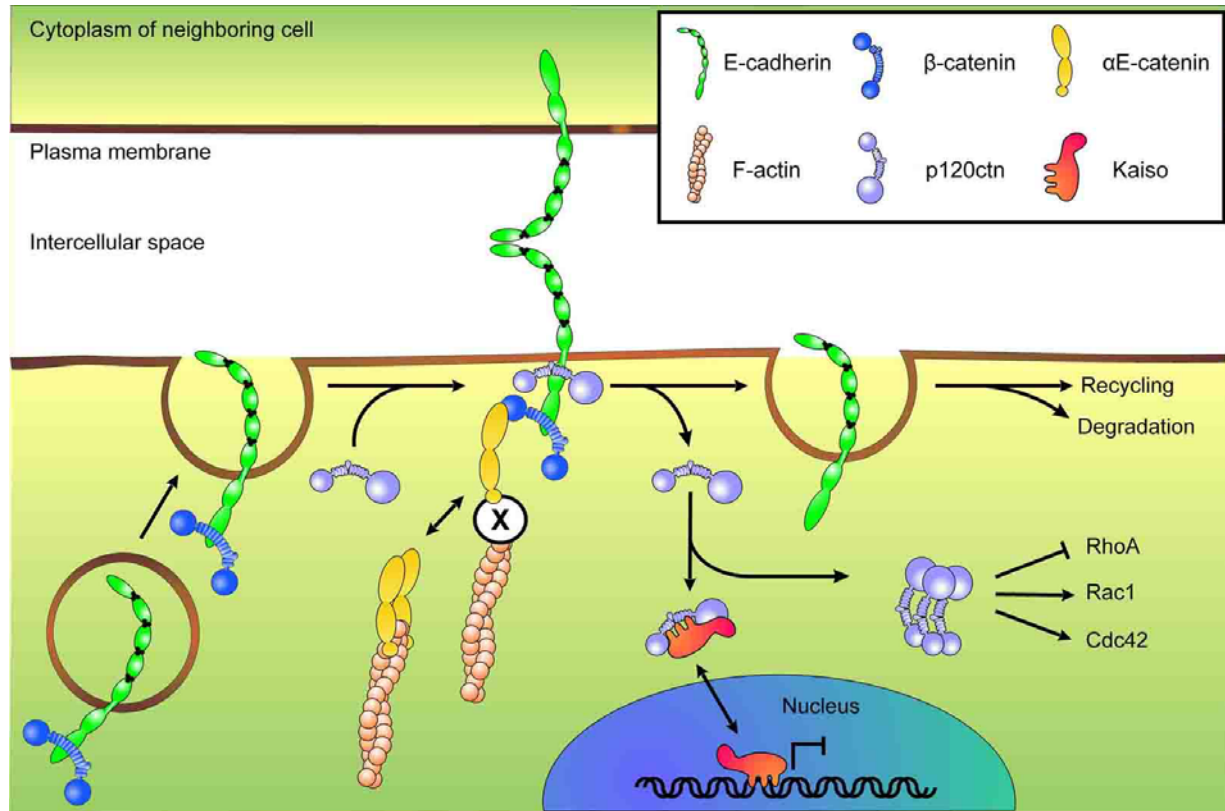


Figure 1. p120ctn performs different functions in different subcellular locations. Adherens junctions consist of transmembrane cadherins, which can bind *via* their cytoplasmic tails to beta-catenin and p120ctn. Beta-catenin binds to alpha-catenin, which can link to the actin cytoskeleton *via* an adaptor (*e.g.* Eplln) or as an unbound dimeric complex. p120ctn binds to the juxtamembrane domain of cadherins and prevents their endocytosis. Internalized cadherin molecules can be recycled or targeted for degradation. Cytoplasmic p120ctn can regulate RhoGTPase activity, whereas p120ctn shuttling between nucleus and cytoplasm can inhibit Kaiso-mediated transcriptional repression

epitope in the C-terminal part of p120ctn, four main protein isoforms differing from each other by the length of their N-termini and by alternative exon usage could be distinguished (3). Detailed analysis of human p120ctn transcripts revealed that an even larger diversity (48 predictable isoforms) of the p120ctn protein can be generated by alternative splicing (Section 3) (6). Further investigation of p120ctn isoforms showed that they are differentially expressed under several conditions, pointing to specific roles in development and disease, and particularly in cancer (Section 9). Along with the identification of p120ctn isoforms came the identification of p120cn family members, such as ARVCF (Armadillo repeat gene deleted in Velo-Cardio-Facial syndrome), p0071 and delta-catenin/NPRAP/neurojungin (neural plakophilin-related Armadillo protein), and the more distantly related plakophilins 1-3 (Section 4) (reviewed in 7, 8).

Besides binding to membrane-bound cadherins, p120ctn can also perform functions in the cytoplasm and in the nucleus by interacting with RhoGTPases and Kaiso, respectively (Figure 1). The first hint about the role of cytoplasmic p120ctn came from overexpression studies. Indeed, strong overexpression of p120ctn saturated the

cadherin-binding sites, and the excess p120ctn translocated to the cytoplasm, where it induced extensions that were neurite-like (9). Additional research revealed that p120ctn elicits a 'dendritic-like branching' phenotype by modulating RhoGTPase activity (10-12), and this was confirmed by genetic and RNAi-mediated ablation of p120ctn. Because p120ctn interacts physically with the transcription factor Kaiso (13), a nuclear function for p120ctn was envisioned. Indeed, p120ctn can tether away Kaiso from the nucleus, preventing its transcriptional repression activity (Section 7). During the last decade, all those research leads were further pursued to gain some mechanistic insight into p120ctn biology. These investigations, which also included the generation of different animal models, showed that p120ctn is indispensable for normal vertebrate development (Section 8), and that its deregulation is common in cancer (Section 9). Other members of the p120ctn family are also involved in various diseases.

3. A MULTITUDE OF p120CTN ISOFORMS

p120ctn is ubiquitously expressed during development and in adult organisms, except for several non-adherent hematopoietic cell lines and loosely organized

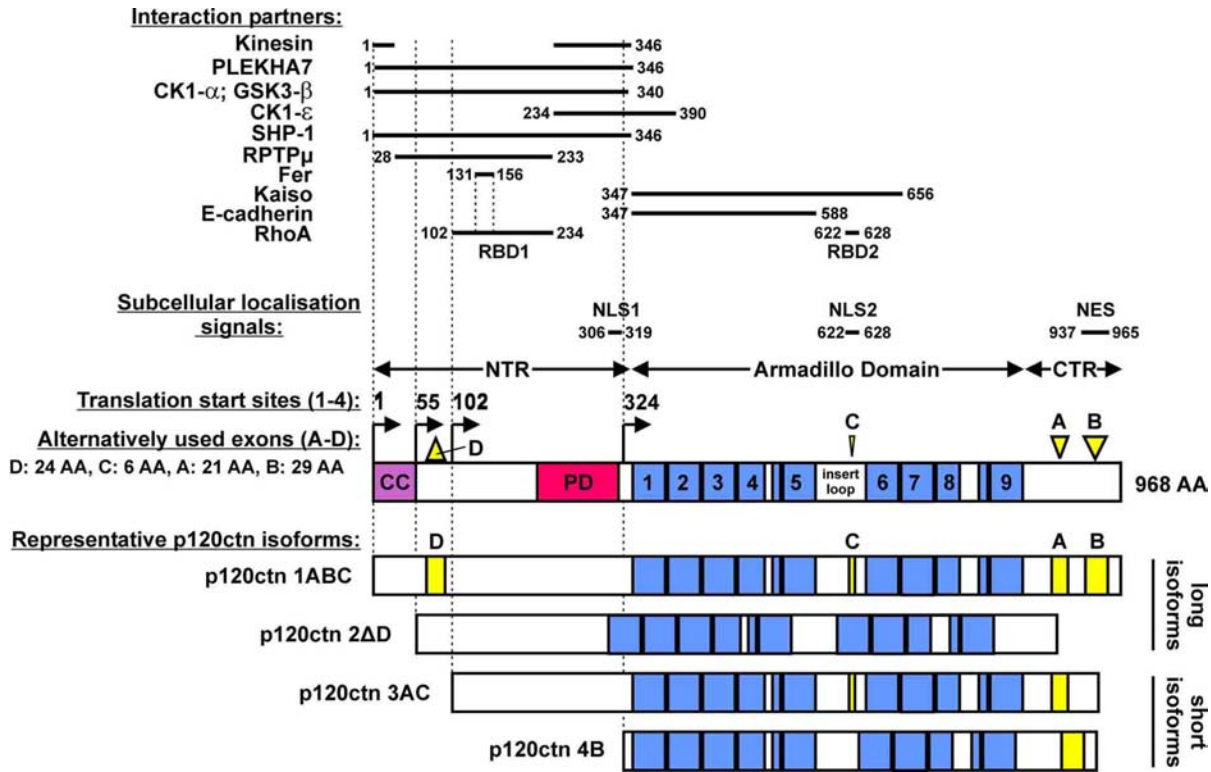


Figure 2. Overview of the p120ctn protein. Features include structural and functional domains, as well as a selection of alternative splice forms (see text for appropriate references). The p120ctn domains for binding different interaction partners are shown at the top. Some of these interactions will be reviewed elsewhere (Pieters *et al.*, in preparation). p120ctn contains two conventional nuclear localization signals (NLS) and a nuclear export sequence (NES), but Armadillo repeats (ARM) 3, 5 and 8 have also been implicated in nuclear trafficking. Due to alternative splicing, four translation start sites (1 to 4) can be used. Alternatively spliced internal exons A, B and C, encoding 21, 29 and 6 amino acid residues (AA), respectively, can be included, whereas exon D (encoding 24 AA) is rarely spliced out. p120ctn isoform 1ABC is the longest isoform, employs the first start codon, and contains all alternatively spliced exons. Numbered blue boxes refer to consecutive ARM repeats. CC, coiled coil domain; CTR, C-terminal (non-Armadillo) region; NTR, N-terminal (non-Armadillo) region; PD, phosphorylation domain, comprising many Ser, Thr and Tyr residues that are phosphorylated under particular conditions; RBD, RhoA-binding domain.

SW48 colon carcinoma cells, which exhibit very weak p120ctn expression (14, 15). Different p120ctn isoforms were expressed heterogeneously in normal cell lines and in tumor cell lines (3, 14, 16). In 1998, the human p120ctn gene (*CTNND1*), situated on chromosome 11q11, was cloned, and inter- and intra-exonic splicing events generated multiple p120ctn mRNA variants encoding different isoforms (6). Forty-eight putative p120ctn isoforms were generated by employing four different translation initiation sites (M1-4) combined with four alternatively spliced exons (A to D; Figure 2) (6, 17). p120ctn 1ABC is the longest isoform, with 968 amino acid residues (AA), contains all the alternatively spliced internal exons, and is translated from the first start codon to produce a protein with the longest N-terminal domain (Figure 2). p120ctn isoform 3 has a shorter N-terminal domain missing 100 AA that contain a coiled-coil domain, whereas p120ctn isoform 4 lacks almost the entire N-terminal domain in front of the Armadillo repeat domain, including the phosphorylation domain (PD) containing most phosphorylation sites of p120ctn. The central Armadillo repeat domain has nine Armadillo repeats (not

ten as was previously proposed), with each repeat consisting of three helices (18, 19). This Armadillo repeat domain is not much affected by alternative splicing. Only the six AA encoded by the alternatively spliced exon C are situated in the insert loop between Armadillo repeat ARM5 and ARM6, but this probably does not cause conformational changes in the overall structure of the Armadillo repeat domain (18, 19). In retrospect, the four p120ctn isoforms identified by Reynolds *et al.* (3) were the long isoforms 1N and 1A and the short isoforms 3N and 3A, with additional internal AA being encoded by the alternatively spliced exon A.

p120ctn isoform 1 (120 kDa or long isoform) and p120ctn isoform 3 (100 kDa or short isoform) display tissue-specific and cell-specific expression patterns. Long p120ctn isoform 1 is predominantly expressed in highly motile cells, such as fibroblasts and macrophages (3, 14, 20). In normal tissues, long p120ctn isoforms are predominantly expressed in the central and peripheral nervous systems, heart, spleen, testis, ovary and endothelial cells (17, 21, 22). In contrast, p120ctn isoform 3 is

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abundant in epithelial cell lines (3, 14, 20) and epithelial structures of the skin and the gastro-intestinal lining, which have a rapid turnover, as well as in kidney, liver, pancreas, mammary gland and prostate (6, 17, 21, 22). These cells and tissues show bias for expression of certain p120ctn isoforms, but most cells and tissues express both long and short isoforms. Interestingly, a switch from short to long p120ctn isoforms is seen during epithelial-to-mesenchymal transition (EMT), which is induced by expression of c-Fos (23), Snail (24), SIP1/ZEB2 (25, 26), E47 (26), Slug (26) or Twist (27) (see Section 9.2. for more details).

The transcript diversity of p120ctn is increased by alternative splicing of internal exons. Exon A encodes a 21-AA sequence that is ubiquitously expressed in various human and murine cell lines and tissues (Figure 2) (6). Exon B encodes a putative nuclear export signal (NES) with a characteristic leucine motif that counteracts the nuclear localization of p120ctn isoform 3A (28). Exon C encodes six AA that interrupt the second nuclear localization signal (NLS2) of p120ctn, which coincides with the second RhoA-binding domain (RBD2) (Figure 2). Expression of exon C blocks nuclear localization and inhibits 'dendritic-like branching' (Pieters *et al.*, in preparation). Exon C is strongly expressed in brain (6) (Pieters *et al.*, in preparation). A rare deletion of a fourth alternatively spliced internal exon, exon D, was reported in fetal and adult brain tissue (17). In conclusion, alternative exon usage regulates the subcellular localization of p120ctn isoforms and therefore directs their functionality.

4. THE p120CTN GENE FAMILY

The Armadillo catenin family consists of three subfamilies: the p120ctn subfamily (p120ctn, ARVCF, p0071 and delta-catenin), the plakophilin subfamily (plakophilins 1 to 3) and the beta-catenin subfamily (beta-catenin and plakoglobin) (7, 29) (Figure 3). The p120ctn subfamily members associate with cadherins to form proper adherens junctions, while members of the plakophilin subfamily support desmosomal adhesion. The beta-catenin and plakophilin subfamilies have been extensively reviewed elsewhere (30-32).

Invertebrates, such as *Caenorhabditis elegans* and *Drosophila melanogaster*, have only a few catenin genes. Only one beta-catenin and one p120ctn ancestor have been identified in *Drosophila*, whereas *C. elegans* contains four highly divergent beta-catenins and only one p120ctn subfamily member (33-36). Interestingly, sequence analysis revealed that invertebrate p120ctn resembles most the vertebrate delta-catenins but not p120ctn (8). In vertebrates and particularly in mammals, the diversity of the p120ctn family has increased throughout evolution. This has led to the emergence of two evolutionarily conserved clusters: the p120ctn and ARVCF branch, and the p0071 and delta-catenin branch (8) (Figure 3).

All p120ctn family members have similar overall structures, with a central domain containing nine Armadillo repeats (Figure 4) (18, 19). This Armadillo repeat domain enables all p120ctn subfamily members to bind the

juxtamembrane domain (JMD) of classical cadherins (37-42). When ARVCF and delta-catenin are overexpressed, they can compete with p120ctn for JMD binding (38, 43) and they can restore cadherin-based junctions in p120ctn-depleted cells (44). At endogenous levels, however, apparently none of them can substitute for p120ctn. Indeed, endogenous ARVCF and delta-catenin fail to stabilize classical cadherins in tissue-specific p120ctn knock-out mice (45-47).

ARVCF was identified as an Armadillo repeat gene that is consistently deleted in velo-cardio-facial syndrome patients with interstitial deletions in chromosome 22q11 (39). It encodes 962 AA and is most closely related to p120ctn (Figure 3). Like p120ctn, ARVCF is ubiquitously expressed in different tissues but is much less abundant (38). Also like p120ctn, ARVCF localizes to the nucleus in some cell types (38). Multiple isoforms of *Xenopus* ARVCF are generated by the use of two different translation initiation sites and three alternatively spliced inserts of 15, 18 and 117 bp (41) (Figure 4). An 18-bp insert is also found in human ARVCF (39) and corresponds to p120ctn exon C (6). Exon C of *Xenopus* ARVCF is expressed most strongly in brain (41). Human ARVCF too is expressed as multiple isoforms, which points to extensive alternative splicing like that observed for p120ctn (38).

The p0071 protein, encoded by the *PKP4/Pkp4* gene, is officially known as plakophilin-4, but this is a misnomer because it is more homologous to delta-catenin and p120ctn than to any of the genuine plakophilins (Pkp-1 to -3) (Figure 3). The p0071/Pkp4 protein is ubiquitously expressed and localizes in adherens junctions by means of its central Armadillo repeat domain, and in desmosomes by virtue of its N-terminus (37, 48). However, using novel antibodies, Hofmann *et al.* (49) localized p0071 in non-desmosomal adherens junctions but not in desmosomes of MCF-7 human breast carcinoma cells, human skeletal muscle and lung epithelium, and bovine pancreas, tongue, thymus and lymphatics. In addition, p0071 is targeted to the midbody by the kinesin-II family member, KIF3, but it is also located at the centrosomes and spindle bodies of mitotic cells, and at composite junctions (*areae compositae*) of the intercalated disks of cardiomyocytes (49-51). Two splice variants of p0071 have been reported (48). The long variant (encoding a protein of 1211 AA) was detected as a major isoform in brain. It is larger than p120ctn (981 AA) because of longer N- and C-terminal domains (Figure 4). A shorter variant was found to be predominant in A431 and HeLa cells (48), and lacks an internal stretch of 43 AA in the C-terminal domain.

Delta-catenin was discovered as a presenilin-1-binding protein (52). It is expressed almost exclusively in the nervous system (52-55). The human and mouse delta-catenins encompass 1225 and 1247 AA, respectively, and the mouse delta-catenin has a 25-AA insert in Armadillo repeat 7 (new nomenclature based on 18, 19) possibly due to alternative splicing (Figure 4) (40, 56). The insert loop of delta-catenin contains a polylysine stretch similar to the NLS2 of p120ctn (Figure 2) (40). Four translation initiation sites have been identified in *Xenopus* delta-catenin in

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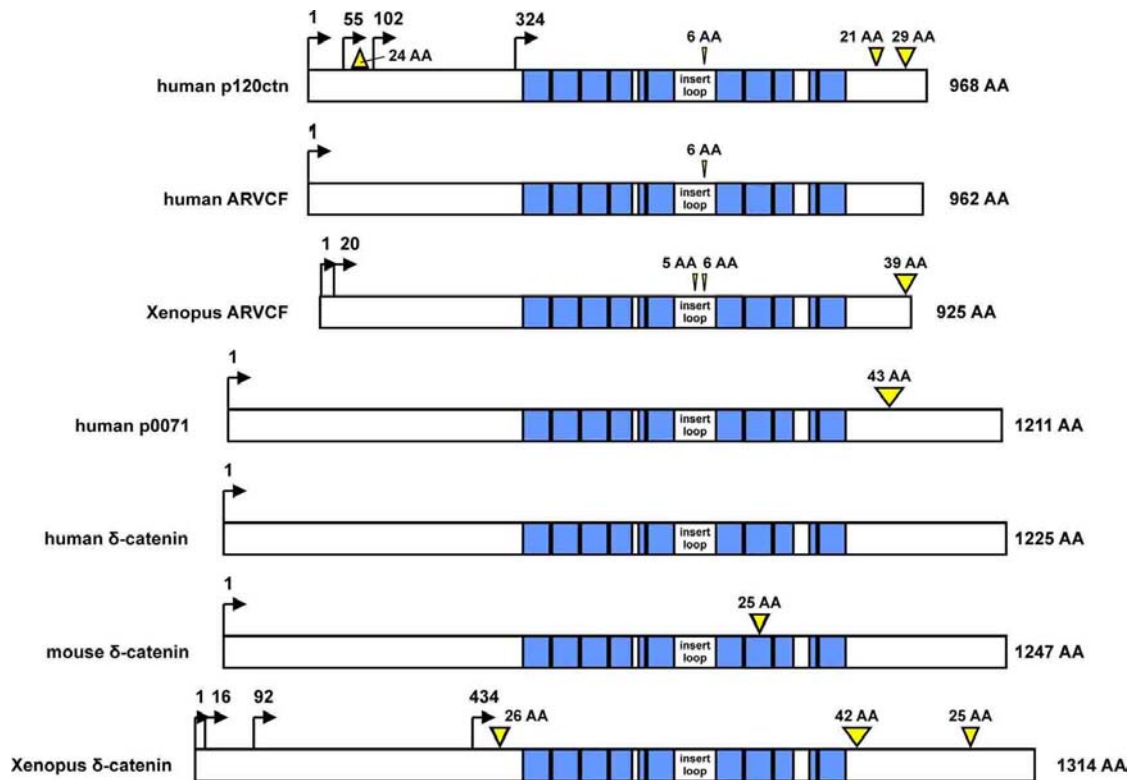


Figure 4. Overview of isoforms of p120ctn subfamily members. Yellow triangles indicate sequences encoded by alternatively spliced internal exons. For alternatively used 5' exons, the multiple possible translation start sites are indicated. Armadillo repeats are represented by blue boxes. The sizes of the longest protein isoforms of each family member are indicated on the right. AA: amino acid residues.

mutations in the JMD selectively uncoupled p120ctn from E-cadherin, disabled p120ctn phosphorylation, and interfered with cell-cell adhesion (66).

In contrast to this evidence for a p120ctn supportive role in cadherin-mediated adhesion (see also Sections 5.2 and 5.3), two reports postulated p120ctn as a negative regulator of cadherin function (67, 68). Although differential phosphorylation or another biochemical modification was proposed as a probable explanation for this discrepancy (67, 68), differential expression of p120ctn isoforms might also explain why p120ctn can act both as a positive and a negative regulator. In both instances in which p120ctn acted as a negative regulator, the authors used a 'mesenchymal' p120ctn isoform 1 construct, which is predominantly expressed in non-epithelial cell types, in order to induce cell-cell adhesion. Colo-205 cells express only p120ctn isoform 1 (67). A better option would have been to co-transfect a construct encoding the 'epithelial' p120ctn isoform 3 with E-cadherin cDNA. Expressing p120ctn isoform 1 in E-cadherin-deficient mouse fibroblastic L-cells probably stabilizes their mesenchymal phenotype rather than transforming it to an adherent one.

5.2. p120ctn regulates cadherin turnover: evidence from genetic and knockdown studies

The positive regulatory effect of p120ctn on cadherin expression levels was further underscored in

several studies using RNAi-mediated depletion of p120ctn in cells or genetic depletion in mice. The first clue that p120ctn is critical for cadherin function emerged from analysis of SW48 colon carcinoma cells bearing mutations in the p120ctn gene (15). Due to p120ctn insufficiency, these poorly differentiated cells failed to form compact colonies and displayed less E-cadherin protein but not reduced E-cadherin mRNA (15). The epithelial morphology and the cadherin levels could be restored by expressing p120ctn isoform 1, 3 or 4, or by using a RhoA-uncoupled variant of p120ctn isoform 1 (*delta622-628*), but not by using an E-cadherin-uncoupled p120ctn mutant. Pulse-chase experiments revealed that p120ctn expression increased the E-cadherin half-life (15).

Stable RNAi-mediated knockdown of p120ctn in mammalian cells resulted in a drastic and dose-dependent decrease in classical cadherins, such as E-, P-, and VE-cadherin (44, 69, 70), and including mesenchymal cadherins, such as N-cadherin and cadherin-11 (71). Furthermore, the absence of p120ctn also resulted in decreased expression of beta- and alpha-E-catenin due to decreased cadherin levels (44, 69). Human cells depleted of p120ctn became dispersed, but introduction of a murine p120ctn cDNA rescued both morphology and cadherin levels (44). Cadherin chimeras, consisting of the extracellular domain of interleukin-2 receptor and a cytoplasmic tail of VE-cadherin that still binds p120ctn,

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reduce endogenous VE-cadherin levels due to increased internalization of cell surface VE-cadherin, whereas p120ctn-uncoupled variants of such chimeras do not have such an effect (70).

In *Drosophila melanogaster* and *Caenorhabditis elegans*, p120ctn is dispensable for the formation of cadherin-based junctions and exerts a merely supportive role (34, 35, 72). In contrast, p120ctn has been shown to stabilize cadherin levels *in vivo* both in amphibians and in mammals. Knockdown of p120ctn (73, 74) or of its family members ARVCF (74) or delta-catenin (57) in *Xenopus* embryos reduces the levels of classical cadherins. Moreover, gastrulation defects seen upon depletion of p120ctn or delta-catenin in *Xenopus* could be rescued by ectopic expression of C-cadherin (57, 74). Tissue-specific p120ctn depletion in mice decreases levels of E-cadherin (45-47, 75), N-cadherin (75-77), P-cadherin (46) and VE-cadherin (77). In conclusion, p120ctn regulates cadherin turnover at the cell membrane both *in vitro* and *in vivo*.

5.3. p120ctn and cadherin biogenesis, endocytosis and degradation

How does p120ctn regulate cadherin trafficking? Cadherin-based junctions are highly dynamic, and cadherin complexes are constantly assembled and disassembled. The process of cadherin trafficking involves cadherin synthesis in the Golgi, transport to the cell surface, stabilization at the cell surface, or internalization followed by recycling or degradation (Figure 1) (78, 79). When newly synthesized E-cadherin is transported from the Golgi complex to the plasma membrane, its basolateral targeting depends on a membrane-proximal dileucine motif in the cadherin tail and on its association with beta-catenin (80, 81). Unlike beta-catenin, p120ctn does not interact with E-cadherin during its biogenesis (82), and p120ctn-uncoupled E-cadherin is indeed properly targeted to the plasma membrane (66). In contrast, p120ctn has been reported to associate with N-cadherin early during its biogenesis (83), and both N-cadherin and p120ctn move along microtubule tracks towards cell-cell contacts (84, 85). p120ctn isoform 1 colocalizes and interacts with microtubules and the motor protein kinesin, which transports cargos towards the plus ends of microtubules nearby the plasma membrane (85-87). The N-terminus of p120ctn binds to the heavy chain of kinesin, but an N-terminal deletion mutant and native p120ctn isoform 4 do not bind kinesin (85, 86, 88). p120ctn isoform 1, which contains the entire N-terminal domain, binds to kinesin with a higher affinity than p120ctn isoform 3, which lacks 100 AA of the N-terminus (86). p120ctn might therefore play a role in delivering N-cadherins to the plasma membrane, and disassembly of the N-cadherin/p120ctn/kinesin complex indeed delayed the delivery of N-cadherin to cell-cell contacts (85). In contrast, delivery of newly synthesized E-cadherin to the plasma membrane was not delayed by depletion p120ctn (44).

Interestingly, a recent study revealed the interaction of the N-terminal domain of p120ctn with PLEKHA7 (pleckstrin homology domain-containing, family A member 7) (89). In the zonula adherens of

polarized epithelial cells, a p120ctn-*PLEKHA7*-*Nezha* chain forms a bridge between the cadherin-catenin complex and the minus ends of microtubuli. The integrity of the zonula adherens is clearly dependent on this macromolecular complex and a possible underlying mechanism is the recruitment *via* this complex of the minus-end directed motor KIFC3 (89). As the cell surface expression of E-cadherin was not reduced by depletion of *PLEKHA7*, *Nezha* or *KIFC3*, this could indicate that p120ctn and associated proteins stabilize the minus ends of noncentrosomal microtubules, in line with previously reported stabilization of these ends by cadherin-mediated junctions (90).

Cell surface cadherins can be internalized *via* different pathways, including clathrin-dependent endocytosis (91-95), caveola-mediated endocytosis (96, 97), lipid-raft-mediated endocytosis (98, 99) and micropinocytosis (100, 101). The decision to enter a certain endocytotic pathway is highly cell-specific and depends on the microenvironment. Once internalized, cadherins can be recycled back to the plasma membrane or targeted for proteasomal or lysosomal degradation. p120ctn blocks clathrin-mediated endocytosis of VE-cadherin, and this inhibition depends on the binding of p120ctn to the JMD of VE-cadherin (93). On the other hand, increased E-cadherin endocytosis was observed in cells expressing a p120ctn-uncoupled E-cadherin mutant as well as in cells in which p120ctn was depleted by RNAi (102). It is not clear how p120ctn prevents endocytosis, but several possibilities have been proposed. First, a dileucine motif in the cytoplasmic tail of E-cadherin (close to the JMD) is responsible for clathrin-mediated internalization of E-cadherin (102). If the dileucine motif is mutated or if the cadherin tail is completely deleted, E-cadherin fails to undergo endocytosis (102, 103). p120ctn might regulate E-cadherin endocytosis by masking the dileucine motif to prevent its interaction with adaptor proteins, such as AP-2, which are required for clathrin-mediated endocytosis (104). Second, p120ctn seems to compete with presenilin-1 and Hakai for binding to the JMD of classic cadherins. Presenilin-1 favors E-cadherin degradation by proteolytic cleavage of the cadherin cytoplasmic tail (105, 106). Although, during synapse maturation, p120ctn dissociates from another classical cadherin, N-cadherin, and is replaced by presenilin-1 (107). Hakai is an E3 ubiquitin ligase and binds to the phosphorylated tyrosine motifs in the JMD of E-cadherin (but it does not bind other classical cadherins). (108, 109) This leads to ubiquitination and endocytosis of E-cadherin (Figure 1) (see also Section 6). To conclude, p120ctn seems to act as a cap that binds cadherin and prevents its endocytosis. In the light of this, one may expect p120ctn defects to have major pathological effects.

6. p120CTN AND SIGNALING IN THE CYTOPLASM

The early hints about the role of cytoplasmic p120ctn came from p120ctn overexpression studies. Expressing large amounts of exogenous p120ctn protein saturated cadherin-binding sites, and the excess of p120ctn translocated to the cytoplasm and caused a neuron-like cellular morphology, *i.e.* outgrowth of extensions similar to

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dendritic branching (9). This phenotype was due to p120ctn-mediated RhoA inhibition, as the phenotype could be mimicked by adding a RhoA inhibitor (C3 exotransferase) or by expressing p190RhoGAP (10, 110). Also, this dendritic-like branching could be blocked by coexpressing a constitutively active (CA) RhoA variant (10-12). An N-terminal deletion that includes RBD1 diminishes p120ctn-induced branching (111), but branching is completely blocked by deleting a second RBD (containing AA 622-628; Figure 2) (10). Is this branching phenotype RhoA-specific? Or are there other RhoGTPases involved? Also, activation of Rac1 and Cdc42 might influence p120ctn-mediated branching because in two studies branching was blocked by dominant negative forms of Rac1 and Cdc42 (11, 12). Moreover, p120ctn binds to Vav2, a specific guanine nucleotide exchange factor for RhoGTPases, and overexpression of a dominant-negative Vav2 construct decreased p120ctn-induced 'dendritic-like branching' (12). Overall, p120ctn regulates RhoGTPase activity by inhibiting RhoA and by activating Rac1 and Cdc42, and this alters cytoskeletal dynamics and increases cell migration (12). However, this 'simple' hypothesis was not confirmed in all other studies and the current idea is that Rho-GTPase family members are differentially regulated by various p120ctn isoforms in a complex and sometimes antagonistic way that depends much on the micro- and macro-environments (69, 110, 112) (Patrick Derksen, personal communication) (Pieters *et al.*, in preparation). The contextual signals involved are diverse and include growth factor signaling, cell-cell interactions, cell-matrix interactions, and surface tension.

Do cadherins modulate p120ctn-mediated cytoplasmic signaling? Dendritic-like branching could be blocked by sequestering overexpressed p120ctn by co-expression of E- or C-cadherin (10, 12). Such inhibition was possible by either the complete transmembrane domain of E- or C-cadherin or by its JMD only, but not by its beta-catenin binding domain CBD only (10, 12). On the other hand, E-cadherin binding is dispensable for this p120ctn-induced branching because E-cadherin-uncoupled p120ctn mutants lacking either Armadillo repeat 1 (ARM1) or Armadillo repeats 1-3 (ARM1-3) can still elicit a branched morphology (9, 71). Like cadherins, microtubules can tether p120ctn away from cytoplasmic pools and thereby prevent p120ctn-induced dendritic-like branching. Coexpression of the kinesin heavy chain reduced the branching elicited by p120ctn isoform 1 but not that elicited by p120ctn isoform 3, which means that isoform 1 has a higher affinity for kinesin (86).

Also phosphorylation of p120ctn turned out to be important for cytoplasmic signaling, including the dendritic-like branching induced by p120 overexpression. The majority of phosphorylation sites, as well Ser as Thr and Tyr residues, are located in the phosphorylation domain (PD), which is situated in the N-terminus of p120ctn (Figure 2). Deleting either the entire N-terminus of p120ctn (mimicking p120ctn isoform 4) or only its embedded phosphorylation domain prevents dendritic-like branching, whereas p120ctn mutants lacking only part of the phosphorylation domain can still elicit branching (9, 11,

111). Further, several Tyr residues in the first RBD of p120ctn have been shown to affect the affinity between p120ctn and RhoA (113). The following questions therefore emerge: how does protein phosphorylation affect cadherin-based adhesion in general? Which kinases and phosphatases are involved, either directly or indirectly? Which phosphorylation sites in p120ctn play which roles? These issues will be reviewed in depth elsewhere (Pieters *et al.*, in preparation). Generally speaking, most studies on posttranslational modifications of cadherin-catenin complexes deal with tyrosine-specific phosphorylation executed by either receptor tyrosine kinases (RTKs) or non-receptor tyrosine kinases (nRTK). On the other hand, protein tyrosine phosphatases (PTPs) reverse this phosphorylation and allow dynamic protein modification in response to internal and external cues (reviewed in 114). The presence of multiple phosphorylation sites in cadherins and catenins and the multitude of different kinases and phosphatases located at the membrane increase the potential for modulating cell-cell adhesive strength. The underlying mechanisms are, however, not fully clear, and there is evidence for both a positive role and a negative role for tyrosine phosphorylation. One way to investigate the phosphorylation of cadherin-catenin structures is by using Src-mediated cellular transformation, which leads to constitutive phosphorylation on Tyr of all membrane-bound Src substrates, including cadherins and catenins.

Indeed, the p120ctn protein was originally identified as a most efficient substrate for the nRTK Src and for several RTKs (1, 2). How does tyrosine phosphorylation of p120ctn affect cadherin-based adhesion? In Src-transformed MDCK and L-cells, constitutive tyrosine phosphorylation of p120ctn and beta-catenin is associated with weakening of the cadherin-based junctions (115, 116). This p120ctn phosphorylation is dependent on E-cadherin association. In contrast, the presence of cadherin-bound beta-catenin is not essential for Tyr phosphorylation of p120ctn, as an E-cadherin-alpha-catenin fusion is equally potent in phosphorylating p120ctn junctions (115, 116). Also inducible expression of the nRTK Fer in embryonic fibroblasts disrupts their adherens junctions, apparently due to diminished levels of cadherin-bound alpha- and beta-catenins (117). Treatment of SKOV3 ovarian cancer cells with lysophosphatidic acid (LPA) increases the association of nRTK Fyn with p120ctn at cell-cell junctions, activation of Fyn, and intercellular junction dispersal (118). Knockdown of Fyn prevented this LPA-induced cell dispersal. So, forced tyrosine phosphorylation of mature confluent cell layers causes cell dispersal. The reverse is also true, because in human endothelial cells, p120 is transiently Tyr-phosphorylated in nascent cell-cell contacts, but this phosphorylation is lost in stable confluent layers (119). Loose cells might be more accessible for growth factors and therefore show an increased phosphotyrosine status. Nonetheless, it is not clear how Tyr phosphorylation of p120ctn affects its binding to E-cadherin. Several groups reported that tyrosine phosphorylation of p120ctn increases its binding affinity for E-cadherin (117, 120-123), while others found no change in binding affinity between E-cadherin and p120ctn upon Src-mediated phosphorylation (3, 116). Finally, an

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acidic extracellular pH activated c-Src and Fyn kinases in HepG2 cells, resulting in Tyr phosphorylation of p120ctn and E-cadherin, and apparently a decreased association between p120ctn and E-cadherin (124). Because the binding domain of p120ctn in the E-cadherin cytoplasmic tail encompass Tyr residues, which upon phosphorylation recruit the E3 ubiquitin ligase Hakai, decreased p120ctn binding facilitates the action of Hakai and results in ubiquitination and endocytosis of E-cadherin.

A phosphorylation-dependent electrophoretic mobility shift of p120ctn is seen in the case of E-cadherin induction in transduced MDA-MB231 cells, and this shift was ascribed to Ser/Thr phosphorylation (66). Interestingly, induction of p120ctn-uncoupled E-cadherin mutants was unable to induce this shift, which indicates that E-cadherin binding is necessary also for Ser/Thr phosphorylation of p120ctn. On the other hand, Ser/Thr phosphorylation of p120ctn does not affect the p120ctn-cadherin binding affinity or the cadherin complex stability. Indeed, mutating either individual Ser or Thr phosphorylation sites to Ala or mutating six major Ser/Thr sites together to Ala does not interfere with the capacity of mutated p120ctn to rescue the phenotypes of p120ctn-deficient cells (125). In conclusion, increased Tyr phosphorylation of p120ctn disrupts adherens junctions, while constitutive Ser/Thr phosphorylation of p120ctn does not affect their integrity.

7. p120CTN AND TRANSCRIPTION FACTOR SIGNALING

Like beta-catenin, p120ctn acts both as a component of adherens junctions and as a transcriptional regulator in the nucleus. p120ctn in the nucleus (28, 87, 111, 126, 127) interacts with transcription factors Kaiso (13) and Glis2 (128). Interestingly, Kaiso coprecipitates efficiently with p120ctn isoform 3 in epithelial lines, but not with p120ctn isoform 1 in fibroblasts (13). Nuclear trafficking of p120ctn depends on conventional NLS and NES signals (Figure 2) (28, 111, 126), as well as on its Armadillo repeat domain (87) and on the microenvironment (129). Kaiso also contains a functional NLS for its nuclear import (130). In addition, recent reports point at interesting interactions between the Wnt signaling pathway and p120ctn in the cell junctions or the cytoplasm (131-133).

p120ctn and its relation to the transcription factor Kaiso have been studied extensively (134-136). The Armadillo repeat domain of p120ctn binds to the C-terminal zinc finger domain of Kaiso and thereby inhibits the interaction between this zinc finger domain and DNA (13). Kaiso has a dual specificity for DNA: it can bind to sequence-specific Kaiso binding sites (KBS) and to methylated CpG-dinucleotides (137, 138). Remarkably, the function of Kaiso that involves binding to sequence-specific KBSs is dispensable *in vivo* (139). The binding of Kaiso to methylated DNA is evolutionarily conserved (139) and allows histone-deacetylase-dependent transcriptional repression. This involves the recruitment of chromatin co-repressor components, such as nuclear co-repressor 1 (NCOR) (140), to the N-terminal poxvirus and zinc finger

(POZ) domain of Kaiso. The POZ domain also enables Kaiso to homodimerize (13, 141). Kaiso acts as a transcriptional repressor and p120ctn can bind to Kaiso and block its repressor activity, resulting in activation of the target genes of Kaiso, such as *Siamois*, *c-Fos*, *Myc*, *Ccnd1* (encodes Cyclin D1) (142), *xWnt11* (143), and *Mmp7* (encodes Matrilysin) (144). There is significant overlap between the target genes of p120ctn/Kaiso and the beta-catenin/TCF signaling pathways. The synergism between these pathways was observed both in cell lines (144) and in *Xenopus* embryos (142). The promoter of the matrilysin gene contains two KBSs, and Kaiso can repress beta-catenin-induced activation of the *Mmp7* gene, but this Kaiso-mediated transcriptional repression of *Mmp7* can be reversed by p120ctn expression (144). Several other beta-catenin target genes contain KBSs, and in *Xenopus* embryos they can be either repressed by Kaiso or activated by either beta-catenin activity or Kaiso depletion (142). The strongest transcriptional activation of *Siamois* was obtained by beta-catenin expression in Kaiso-depleted *Xenopus* embryos (142). p120ctn relieves the Kaiso-mediated repression of beta-catenin target genes, and its ablation in *Xenopus* embryos increases the repression of these genes (142). Frodo physically links the p120ctn/Kaiso and beta-catenin/TCF pathways by binding to both p120ctn and Dishevelled (131). Frodo acts upstream of both signaling pathways and stabilizes p120ctn, which relieves Kaiso-mediated transcriptional repression of beta-catenin target genes (131). An additional link between p120ctn/Kaiso and the beta-catenin/TCF pathways is provided by the interaction between Kaiso and TCF3 in *Xenopus* (145). Although Kaiso acts as a genome wide transcriptional repressor in *Xenopus* embryos (146), no increased gene expression was observed in Kaiso-deficient mice (147). Morpholino-mediated depletion of Kaiso in *Xenopus* embryos results in severe defects in gastrulation and in convergent extension, and these phenotypes can be rescued by re-expression of Kaiso (142, 143). In contrast, Kaiso-deficient mice are viable (147). The discrepancy between the findings in mice and in *Xenopus* concerning the developmental requirement for Kaiso and its gene regulatory activity might be explained by functional redundancy of Kaiso-like family members (134). Indeed, Kaiso is part of a small protein family that contains two other Kaiso-like proteins, namely ZBTB4 (Kaiso-like 1) and ZBTB38 (ZENON). Like Kaiso, these proteins bind methylated DNA and act as transcriptional repressors (148). Like Kaiso, ZBTB4 exerts bimodal DNA binding, whereas ZBTB38 binds only methylated DNA (148). ZBTB4 has been implicated in p53 activation (149). Interestingly, no ZBTB4 homolog could be identified in *Xenopus*, which indicates that ZBTB4 might substitute for Kaiso in mouse but not in frog.

It was generally assumed that the stability of the ubiquitously expressed p120ctn was regulated differently from that of cytoplasmic beta-catenin. Beta-catenin is well known to be subject to association with axin and APC proteins, to phosphorylation by kinases of the CK1 family and by GSK3-beta, eventually followed by ubiquitination and proteasomal degradation. The McCrea group recently reported that specifically the long isoform-1 of p120ctn can

associate with CK1-alpha and GSK3-beta, and that it is prone to phosphorylation by these kinases, as well as to axin binding, ubiquitination and proteasomal degradation (133). A quadruple point mutation, converting four Ser residues at the N-terminus of *Xenopus* p120ctn into Ala residues, protects against this molecular destruction complex and efficiently relieves Kaiso-mediated repression of the Wnt target genes, *Wnt11* and *xSiamois*. Moreover, the related Armadillo subfamily members ARVCF and delta-catenin of *Xenopus* bind likewise to axin and are responsive to the axin-containing destruction complex (133), in line with a previous report on vulnerability of human delta-catenin to GSK3-beta-triggered degradation (150).

In another recent report, p120ctn was shown to bind to CK1-epsilon *via* an N-terminal domain (Figure 2) (132). This interaction domain is also contained in the shorter isoform 3, which is the most abundant isoform in epithelial cells. Whereas CK1-alpha is an inhibitor of canonical Wnt signaling by virtue of its destabilizing effect on cytoplasmic beta-catenin, CK1-epsilon is activated upon Wnt triggering and contributes to stabilizing beta-catenin. The authors provide evidence that activated CK1-epsilon phosphorylates several proteins in a pre-signalosome complex comprising p120ctn, E-cadherin, the Wnt coreceptor LRP5/6, and the Wnt receptor Fz. This event results in recruitment of Dvl, axin and GSK3-beta to the signalosome, leading to inactivation of the beta-catenin destruction complex, but at the same time, beta-catenin and p120ctn/CK1-epsilon dissociate from E-cadherin. Dissociated and stabilized beta-catenin promotes TCF-mediated transcription, whereas dissociation of p120ctn/CK1-epsilon might act as a negative feedback to halt further Wnt signaling at the receptor level (132). In this model, p120ctn functions as an essential but subtle regulator of Wnt signaling by recruiting CK1-epsilon to the E-cadherin/LRP/Fz receptor complex, and by counteracting this phenomenon upon Wnt-induced activation of CK1-epsilon.

8. THE P120CTN FAMILY IN ANIMAL MODELS

8.1. Animal models for p120ctn

The knockout and depletion of p120ctn in invertebrates (*C. elegans* and *Drosophila*), amphibians (*Xenopus*) and mammals (mouse) was recently reviewed (8). The only p120ctn subfamily members in *C. elegans* and *Drosophila* are CeJAC-1 and Dmp120ctn, respectively (Figure 3), yet their genetic deletion or RNAi-mediated reduction did not affect normal development (Table 1) (34, 35, 151). In contrast, RNAi depletion of both zygotic and maternal p120ctn in *Drosophila* embryos resulted in severe morphogenetic defects, particularly in head involution (33). *Drosophila* p120ctn interacts with DRho1 (the *Drosophila* RhoA homolog) (33), but DRho1 maintains proper localization of DE-cadherin and catenins in the absence of Dmp120ctn (151). In addition, mutants of *Drosophila* DE-cadherin could be rescued by p120ctn-uncoupled DE-cadherin mutants but not by beta-catenin-uncoupled mutants, indicating that p120ctn in invertebrates is not a core component of adherens junctions and that it has only a

supportive role (34, 72).

In contrast, morpholino-mediated p120ctn knockdown in *Xenopus* resulted in severe developmental defects; the nature of the defects depended on which cells of early cleavage embryos were injected with morpholinos (Table 1) (73, 74). On the other hand, induced expression of murine p120ctn isoform 1A or 1N during amphibian development leads to gastrulation defects and head malformation, respectively, in contrast to the secondary body axis abnormality caused by overexpression of beta-catenin (152, 153). So, normal development is contingent on maintenance of p120ctn expression levels within a physiological range. Total knockout of p120ctn results in early death of embryos (mentioned in refs. 45, 76). According to a personal communication from Walter Birchmeier (Berlin), embryonic death is seen at E10. Despite seemingly normal mesoderm formation, embryos do not turn at E8.5 to E9. The notochord is interrupted, and cell-cell adhesion within the notochord and to the endoderm is weakened. Embryos stop growing at the 10-somite stage and closure of the neural tube is not completed. Several tissue-specific p120ctn knockouts have been generated by using the Cre/LoxP system. Two types of floxed p120ctn alleles were generated. In one of them, p120ctn exons 3 to 8, encoding all four possible start codons (M1-4), were flanked by LoxP sites to prevent any natural initiation of translation after Cre-mediated recombination (45). In the other approach, exon 7 of p120ctn was floxed, and Cre-mediated recombination resulted in a frameshift leading to degradation of mRNA by non-sense mediated decay (76). The importance of p120ctn during development is further demonstrated by Cre-mediated ablation of p120ctn in endothelial tissues at 7.5 dpc, which caused death at 11.5 dpc (77). In other studies, developmental defects in tissue-specific p120ctn knockouts are mostly avoided by employing mouse lines expressing Cre near the end of embryonic development. Nevertheless, ablating p120ctn after midgestation in salivary gland and intestine can still result in perinatal death (45, 47), whereas its ablation in the skin, teeth or dorsal forebrain does not affect viability (46, 75, 76). Though these conditional p120ctn knockout mice show a wide range of tissue-specific phenotypes (listed in Table 1) (8), reduction of cadherin levels seems to be a common underlying mechanism (Section 5.2).

8.2. Animal models for p120ctn family members

Like p120ctn, ARVCF and delta-catenin are essential during *Xenopus* development. For instance, gastrulation defects are caused by generalized or localized knockdown of delta-catenin (Table 1) (57, 74). However, ARVCF and delta-catenin seem to be dispensable in mice, because both ARVCF and delta-catenin knockout mice are viable (personal communication by Raju Kucherlapati, Boston, MA, and ref. 154). Nevertheless, delta-catenin-deficient mice display cognitive dysfunctions, including severe learning defects, and abnormal synaptic plasticity (154). This is in line with the observed hemizygous loss of delta-catenin in humans suffering from the Cri du Chat syndrome, which is featured by severe mental retardation (155).

Table 1. Knockout and knockdown of p120ctn family members in different species

Catenin	Organism	Tissue/cell type	Knockout (KO) or knock down (KD)	Phenotype	References
JAC-1	<i>C. elegans</i>	whole animal	KD (RNAi)	No obvious developmental defects	(35)
p120ctn	<i>Drosophila</i>	whole animal	zygotic and maternal KO	No obvious developmental defects; except delayed dorsal closure	(34)
		whole animal	KD (RNAi)	No obvious developmental defects	(151)
		whole animal	KO (includes several genes)	Severe dorsal open phenotype	(33)
		whole animal	KD (RNAi)	Severe morphogenic effects, including head involution	(33)
		whole animal	KO and KD (RNAi)	Reduced numbers and density of spine-like neuronal protrusions	(191)
p120ctn	<i>Xenopus</i>	whole animal	KD (Morpholino)	Disrupted gastrulation and axial elongation; reduced C-cadherin levels	(74)
		anterior neural ectoderm	KD (Morpholino)	Impaired evagination of optic vesicles and defective eye formation; perturbed cranial neural crest cell; migration and malformations in craniofacial cartilage	(73)
p120ctn	mouse	whole animal	KO	Early embryonic death	(45, 76); W.B.
		salivary gland	KO (MMTV-Cre)	Die shortly after birth; blocked acinar differentiation; reduced E-cadherin levels; formation of neoplasias; abnormal epithelial polarity and morphology	(45)
		skin	KO (K14-Cre)	Viable; reduced adherens junction components; increased RhoA activity; epidermal hyperplasia and chronic inflammation in aged mice; NFκB activation; skin neoplasias; mitotic defects	(46, 165)
		teeth	KO (K14-Cre)	Viable; reduced E- and N-cadherin; dysplastic hypo-mineralized enamel; disrupted ameloblast polarity and morphology	(75)
		vascular endothelium	KO (Tie2-Cre)	Die at 11.5 dpc; disorganized embryonic and extraembryonic vasculature; decreased microvascular density and hemorrhage; defective proliferation; reduced VE- and N-cadherin	(77)
		dorsal forebrain	KO (Emx1-Cre)	Viable; reduced spine and synapse densities; decreased N-cadherin levels; increased RhoA activity	(76)
		small intestine; colon	KO (Villin-Cre)	Die within 3 weeks; disruption of epithelial barrier; mucosal erosion; reduced adherens junction components; increased inflammation and neutrophil binding	(47)
		liver	KO (Albumin-Cre)	Viable; severely impaired intrahepatic bile duct development; normal hepatocyte differentiation; unaltered cell-cell adhesion; accelerated initiation of hepatocarcinogenesis by diethylnitrosamine	van Hengel <i>et al.</i> , unpublished
ARVCF	<i>Xenopus</i>	whole animal	KD (Morpholino)	Disrupted gastrulation and axial elongation; reduced C-cadherin levels	(74)
		anterior neural ectoderm	KD (Morpholino)	Perturbed cranial neural crest cell migration; malformations in craniofacial cartilage	K.V. & M.D.
	mouse	whole animal		Viable; no obvious abnormality	R.K.
delta-catenin	<i>Xenopus</i>	whole animal; anterior neural ectoderm	KD (Morpholino)	Defects in gastrulation and axial elongation; reduced cadherin levels; RhoA activation; malformations in eye and craniofacial skeleton	(57)
		mouse	whole animal	KO	Impaired cognitive functions; abnormal synaptic plasticity; reduced N-cadherin and PSD-95 levels

W.B.: Walter Birchmeier, personal communication; K.V. & M.D.: Kris Vleminckx and Mieke Delvaeye, personal communication; R.K.: Raju Kucherlapati, personal communication.

p120ctn can probably substitute for ARVCF and delta-catenin in knockout mice, whereas p120ctn family members ARVCF, p0071 and delta-catenin cannot rescue the lethal phenotypes in p120ctn knock-out mice. This further illustrates that ARVCF, p0071 and delta-catenin are functionally not fully redundant. Alternatively, ARVCF, p0071 and delta-catenin might be intrinsically redundant, although they have restricted spatial and temporal expression patterns.

9. p120CTN AND CANCER

9.1. Altered expression of p120ctn in tumors

The role of p120ctn in tumors has been reviewed (156, 157). In general, p120ctn is either absent or altered in most human tumors, and its derangement is often correlated with poor prognosis. Alterations in p120ctn expression include decreased levels and translocation to the cytoplasm, and occasionally to the nucleus. These alterations remove p120ctn from the cell membrane and disable p120ctn-mediated stabilization of E-cadherin. p120ctn can act as a

proto-oncogene or as an invasion-suppressor, depending on the order in which p120ctn and E-cadherin are down-regulated. Loss of p120ctn results in decreased E-cadherin levels, and E-cadherin is indeed frequently down-regulated in epithelial cancers in which it acts as a tumor-suppressor (158, 159). On the other hand, E-cadherin loss results in translocation of p120ctn to the cytoplasm, where p120ctn modulates RhoGTPases in a way that favors cell motility (see Sections 6 and 9.5). Like overexpression of dominant active Rac1, p120ctn-mediated Rac1 activation might promote cellular transformation. p120ctn also acts as a proto-oncogene by relieving the Kaiso-mediated repression of beta-catenin target genes, such as *c-Fos*, *Myc*, *Ccnd1* (encodes Cyclin D1) and *Mmp7* (encodes Matrylisin) (142, 144), and this favors tumor formation and invasion. In addition, Kaiso-deficient mice are more resistant to intestinal tumorigenesis when bred into an APC^{Min/+} genetic background (147). Heterozygous APC^{Min} mice are used as a model for human familial adenomatous polyposis caused by a mutation of the *Apc* gene (adenomatous polyposis coli) that leads to nuclear localization of beta-catenin and

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activation of the canonical Wnt pathway. In contrast to tumor-associated nuclear beta-catenin, nuclear localization of p120ctn is observed only rarely in human tumors (127, 160).

Only a few mutations in the *CTNND1* gene have been reported, in breast cancer (161) and in SW48 colon carcinoma cells (15). It is noteworthy that p120ctn expression might be compromised by mutating a single p120ctn allele. Indeed, expression of p120ctn can be monoallelic in some cell types (162). Perhaps other mechanisms are involved in p120ctn downregulation in tumors, such as transcriptional downregulation, epigenetic modification or microRNA-mediated silencing, but this is poorly documented. p120ctn is transcriptionally downregulated by FOXC2 in non-small cell lung cancer cells (NSCLC) (163). FOXC2 binds to the p120ctn promoter and reduces its activity. On the other hand, RNAi-mediated silencing of FOXC2 increases p120ctn promoter activity as well as p120ctn mRNA and protein levels. p120ctn stabilizes cadherins at the cell membrane and RNAi-mediated depletion of its transcriptional repressor, FoxC2, enhances E-cadherin levels in NSCLC cells (163). Another intriguing finding is the upregulation of non-junctional delta-catenin expression in advanced human prostate cancers, which correlates with reduced levels or cytoplasmic relocation of both E-cadherin and p120ctn (164). The reduced expression of E-cadherin and p120ctn at the cell–cell junctions could be reproduced by transfecting a prostate cancer cell line with a plasmid expressing delta-catenin.

The role of p120ctn in cancer was further investigated in animal models. Ablation of p120ctn in salivary gland resulted in morphological abnormalities closely resembling high-grade intraepithelial neoplasia, a precancerous condition in humans that typically progresses to invasive cancer (45). Ablation of p120ctn in skin caused hyperproliferation (46) and p120ctn-deficient skin grafts displayed signs of epidermal hyperkeratosis and dysplastic keratinocytes (165). In addition, p120ctn regulates several processes involved in tumorigenesis, such as RhoGTPase activity, cell proliferation, motility, invasion, anchorage-independent growth (AIG), and inflammatory conditions (see below).

9.2. p120ctn isoforms in EMT and cancer

Epithelial-to-mesenchymal transition (EMT) is an orchestrated series of events that allows epithelial sheets to dissociate, lose cell-cell interactions and cell-extracellular matrix interactions, and reorganize the cytoskeleton and transcriptional program in order to induce a mesenchymal phenotype (166). During EMT, E-cadherin downregulation in epithelial cells is accompanied by upregulation of mesenchymal cadherins (e.g. N-cadherin or cadherin-11), a phenomenon called cadherin switching (167). Cadherin switching has been observed during normal development, such as primitive streak formation and neural crest delamination, and also during tumorigenesis (167, 168). Interestingly, a switch from short to long p120ctn isoforms has been observed during EMT induced by expression of c-Fos (23), Snail (24), SIP1/ZEB2 (25, 26), E47 (26), Slug

(26) or Twist (27). The downregulation of short ‘epithelial’ p120ctn isoforms during EMT is due to decreased expression of epithelial splicing regulatory proteins 1 and 2 (ESRP1 and ESRP2), which favors skipping of exon 3 (encoding the first two translation initiation sites) and initiation of translation from the third start codon (encoded by exon 5) (27). Also Src transformation of MDCK cells induces an EMT-like process (169) associated with a switch from short to long p120ctn isoforms (14). This switch during EMT is consistent with the expression pattern of long and short p120ctn isoforms in fibroblasts and epithelial cell types, respectively (Section 3). Re-expression of E-cadherin in Snail-induced mesenchymal cells failed to restore the epithelial morphology and expression of ‘epithelial’ short p120ctn isoforms (24). This confirms that the abundance of the different p120ctn isoforms is regulated by cell-type-specific splice factors but not necessarily by the expression of certain cadherin types (27). In contrast, the p120ctn isoform switch was not observed during EMT induced in highly differentiated colon cancer cells by TGF-beta and TNF-alpha (170). This discrepancy might be explained by the expression of long p120ctn isoforms in non-induced cells at levels that cannot be augmented even further during EMT. Increased RhoA inhibition is observed during EMT induced by TGF-beta and TNF-alpha, which coincides with increased binding of p120ctn to RhoA (170).

EMT-like processes have been observed during progression of prostate carcinoma and in anaplastic thyroid carcinomas. These changes coincide with a switch from short to long p120ctn isoforms and from E- to N-cadherin (171, 172). Forced expression of E-cadherin in the pancreatic carcinoma cell line MIA PaCa-2 restored the epithelial phenotype and suppressed cell migration and invasion, but forced expression of N-cadherin did not have the same effect (173). Interestingly, E-cadherin bound predominantly to unphosphorylated p120ctn isoform 3 whereas tyrosine-phosphorylated p120ctn isoform 1 interacted exclusively with N-cadherin (173). In skin cancer, p120ctn actions and isoform switching are more controversial. One RT-PCR study reported predominant expression of short p120ctn isoforms both in normal skin tissue and in benign and malignant skin cancer cells (160). In squamous cell carcinomas (SCCs), the p120ctn levels were consistently reduced but E-cadherin levels were not. Any remaining p120ctn was detected in the cytoplasm and sometimes in the nucleus but not at the cell–cell boundaries (160). Another study (111), which used antibodies specific for different p120ctn isoforms, revealed that neonatal human keratinocytes and HaCaT cells (immortalized but non-tumorigenic keratinocytes) expressed p120ctn isoforms 2, 3 and 4, whereas SCCs expressed predominantly p120ctn isoform 2 but not isoforms 3 or 4. Thus, both studies indicate that there is no striking difference in expression of p120ctn isoforms between benign (immortalized human keratinocytes) and malignant epithelial skin tumors (SCCs). On the other hand, it was reported that expression of exogenous R-cadherin in squamous carcinoma cells sequesters p120ctn away from endogenous E- and P-cadherin and thereby causes downregulation of these cadherins (174).

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Melanocytes are quite interesting because, unlike most epithelial cells, they express the mesenchyme-associated long p120ctn isoforms in combination with E-cadherin. This shows that specific p120ctn isoforms are not invariably restricted to a certain cadherin type. As both keratinocytes and melanocytes express E-cadherin, heterotypic interaction by a homophilic adhesion mechanism is possible. However, melanomas switch to N-cadherin during tumorigenesis, and this enables them to dissociate from the keratinocyte layers and to interact heterotypically with stromal cells, including fibroblasts and endothelial cells (175). This tumorigenic conversion is not associated with a p120ctn isoform switch as both normal melanocytes and melanomas express primarily p120ctn isoform 1 (111). In melanomas, p120ctn can compete with RhoA for binding to p190RhoGAP, which leads to RhoA activation. Reintroducing E-cadherin in melanomas blocked chemokine-induced invasion and sequestered p120ctn away from p190RhoGAP, leading to RhoA inactivation (176).

In lung SCCs and adenocarcinomas, abnormal expression of p120ctn, including downregulation of both long and short isoforms, is associated with tumor progression and poor prognosis (177). Abnormal p120ctn expression, including complete loss, downregulation or mislocalization of p120ctn, correlated with abnormal E-cadherin expression (including reduced or absent membrane expression of E-cadherin besides increased cytoplasmic expression of E-cadherin) and overexpression of RhoGTPases. Abnormal expression of p120ctn and E-cadherin and overexpression of RhoGTPases were associated with malignant human lung cancer *in vitro* and *in vivo* (178). E-cadherin and p120ctn isoform 3 are expressed in normal bronchial epithelium, but p120ctn isoform 1 is upregulated and localized in the cytoplasm of squamous cell lung cancers and lung adenocarcinomas (179). Further analysis revealed that overexpression of p120ctn isoform 1 mRNA correlates significantly with abnormal E-cadherin expression, lymph node metastasis and poor differentiation (179). Another study confirmed a significant reduction of both long and short p120ctn isoforms in lung carcinomas compared to normal lung tissues (180). Somewhat surprisingly, expression of p120ctn isoform 3 mRNA and protein was found to positively correlate with lymph node metastasis (180). More recently, these investigators reported that expression of p120ctn isoform 3 in lung cancer cells inhibited *in vivo* tumor growth in nude mice but failed to block invasion (181). On the other hand, p120ctn isoform 1 effectively blocked invasion but not tumor growth. All together, p120ctn isoforms 1 and 3 appear to have opposing effects on invasion and proliferation in lung cancer cells due to differential regulation of RhoGTPase activity (see also Section 9.3.) and differential stabilization of cadherin-based junctions (181, 182).

Little is known about the effects of the alternatively spliced internal exons of p120ctn on tumorigenesis. Exon B encodes a NES and is expressed in some human tissues, such as kidney, pancreas, colon, small intestine and prostate. Interestingly, expression of exon B is lost in the corresponding tumorigenic tissues (111),

suggesting that during tumor progression p120ctn is shifted towards the nucleus, which relieves the repression of oncogenic target genes of Kaiso.

9.3. Differential regulation of RhoGTPases by p120ctn in cancer

In contrast to the dogma stating that p120ctn isoform 1 inhibits RhoA activity and activates Rac1 and Cdc42 (see Section 6), in lung cancer cells p120ctn isoform 1 blocks Rac1 activity whereas p120ctn isoform 3 activates RhoA and inhibits Cdc42 activity (181). Knockdown of p120ctn in lung cancer cell lines results in inhibition of RhoA and activation of Rac1 and Cdc42 (182). Activated RhoA has also been observed in a mouse model of invasive lobular carcinoma (Patrick Derksen, Utrecht, personal communication). Treatment of these mice with the clinically approved Rock inhibitor Fasudil inhibited tumor growth *in vivo*. Activation of the RhoA/Rock pathway in cells derived from primary mouse invasive lobular carcinomas results in phosphorylation of cofilin. Phosphorylated cofilin was also found in human invasive lobular carcinoma samples (Patrick Derksen, personal communication). The explanation for the discrepancy between the dogma and RhoGTPase regulation in lung and breast cancer might be related to the presence or absence of E-cadherin. Indeed, the effect of p120ctn on Rac1 activity depends on E-cadherin expression: knockdown of p120ctn results in Rac1 inhibition in E-cadherin-negative cells, but in Rac1 activation in E-cadherin-positive cells (183). The lung cancer cells used in the study of Liu *et al.* (181) were still expressing E-cadherin, and this might explain the inhibition of Rac1 induced by p120ctn isoform 1. However, since the mouse model for invasive lobular carcinoma involves genetic inactivation of E-cadherin, the deviant RhoA activity in these tumors cannot be explained by E-cadherin expression but must have been caused by an unidentified mechanism.

9.4. p120ctn isoforms: effects on proliferation and tumor growth

p120ctn can regulate cell proliferation in different ways. Several lines of evidence show that p120ctn, and in particular high levels of cytoplasmic p120ctn, promotes cell proliferation and tumor growth. Such high cytoplasmic expression promotes transformed growth of both E-cadherin-negative and -positive cells, and knockdown of p120ctn reduces the growth rate, as evidenced by a reduction in the proportion of cells in the S-phase (69, 183). Ras/MAPK signaling is important for the p120ctn-mediated growth effect, because RNAi-mediated depletion of p120ctn inactivates MAPK signaling in E-cadherin-negative cells (183). Both p120ctn isoforms 1 and 4 as well as constitutively active Rac can reactivate MAPK signaling (183). On the other hand, AIG mediated by p120ctn isoform 1 could be blocked by a MEK inhibitor (183). In addition, primary keratinocytes deficient in p120ctn grow more slowly than their wild-type counterparts due to defects in mitosis and cytokinesis, including the generation of binucleate cells (165). A similar phenotype was observed upon knockdown of p0071 (50). The defects seen in cells devoid of either p0071 or p120ctn could be rescued by constitutively active RhoA and dominant negative RhoA, respectively (50, 165).

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On the other hand, p120ctn can also block proliferation. p120 knockdown in NIH3T3 cells promotes serum-free cell proliferation and partial cell transformation (112). In E-cadherin-positive breast cancer cells, p120ctn depletion results in increased proliferation and activation of Ras-MAPK signaling (183). Expression of p120ctn isoform 3 in E-cadherin-positive cells blocks cell proliferation, DNA synthesis and *in vivo* tumor growth (181, 184). Cells expressing p120ctn isoform 3 are arrested in the G1-S phase, and the transition from G1 to S phase depends on the cyclin-dependent kinase 2/Cyclin E complex. p120ctn isoform 3 associates with this complex and prevents its proteasomal degradation. This leads to S-phase lengthening, centrosome overduplication, and genomic instability (184). In contrast to p120ctn-deficient keratinocytes in culture (see above), genetic ablation of p120ctn in skin results in hyperproliferation and increased MAPK signaling (46). Cell proliferation is also increased in p120ctn-deficient colon and small intestine (47). These observations indicate that p120ctn might have different effects on cell growth *in vitro* and *in vivo*, and that the effects also depend on the cell type and the microenvironment.

9.5. p120ctn isoforms: effects on motility and invasion

RhoGTPases are key mediators of the dynamic rearrangements of the actin cytoskeleton (185), which are crucial for cell motility. The activity of several RhoGTPases is modulated by p120ctn (10-12). p120ctn-mediated inhibition of RhoA activity decreases the number of stress fibers and focal adhesions, whereas p120ctn-mediated activation of Rac1 and Cdc42 increases formation of, respectively, lamellipodia and filopodia. Overall, p120ctn expression is expected to alter cytoskeletal dynamics to favor cell motility and to enhance migration (11, 12). Several p120ctn knockdown studies have indeed revealed that p120ctn is important for cell migration and invasion. Cells devoid of p120ctn fail to repopulate the wounded area in a scratch assay (112). On the other hand, stable knockdown of p120ctn in E-cadherin-deficient cells resulted in decreased migration and invasiveness. These deficiencies could be rescued by reexpression of p120ctn isoform 1, but not by reexpression of cadherin-uncoupled p120ctn isoform 1 (71). Moreover, p120ctn induces invasiveness by its association with mesenchymal cadherins, such as N-cadherin or cadherin 11, whereas knockdown of these mesenchymal cadherins and the use of p120ctn-uncoupled mutants blocks invasiveness (71). Migration and invasion of E-cadherin-deficient cells is blocked by ectopic expression of E-cadherin (71). E-cadherin might sequester p120ctn away from the mesenchymal cadherins, resulting in their endocytosis and degradation. Invasiveness can also be blocked by constitutively active RhoA and dominant negative Rac1 expression, but is enhanced by inhibition of ROCK, a downstream effector of RhoA (71). The p120ctn-depleted cells have been employed for testing the potential of different p120ctn isoforms to induce invasion. Invasiveness is strongest upon expression of p120ctn isoform 1A, it is unaffected by p120ctn isoform 3A, and is blocked by p120ctn isoform 4 (186). In clear renal cell carcinomas, E-cadherin is downregulated and p120ctn is translocated to

the cytoplasm. Furthermore, p120ctn undergoes an isoform switch from predominantly short to long p120ctn isoforms. This switch is correlated with micrometastasis, which indicates that, at least for this cancer type, p120ctn isoform 1 simulates invasiveness *in vivo* (186). p120ctn can also block invasion because p120ctn depletion in lung cancer cell lines enhances invasion and metastasis due to differential regulation of RhoGTPase activity (see Section 9.3.) (182). To conclude, p120ctn isoforms affect migration and invasion in different ways by inducing RhoGTPase-mediated rearrangements of the actin cytoskeleton.

9.6. p120ctn and anchorage-independent growth

Anchorage-independent growth (AIG) is a hallmark of tumor formation and is dependent on endogenous p120ctn. Stable knockdown of p120ctn in E-cadherin-negative MDA-MB-231 cells abolished their ability to grow anchorage-independently *in vitro* (colony formation in soft agar) and *in vivo* (xenografts), but this effect could be rescued by re-expression of p120ctn isoform 1 (183). Endogenous p120ctn is also required for anchorage-independent survival of E-cadherin-negative mouse breast cancer cell lines; its depletion makes them more susceptible to anoikis. (Patrick Derksen, personal communication). Oncogenes, such as activated variants of Src and Rac1, can circumvent anoikis by activation of downstream survival and proliferation signals. In an E-cadherin-negative setting, p120ctn attains oncogenic characteristics and might bypass anchorage dependence by activating the MAPK pathway (183). In addition, p120ctn promotes tumor growth *via* Rac1 activation, and expression of a constitutively active Rac1 mutant reverses the cell cycle defect and can rescue AIG *in vitro* and xenograft growth *in vivo* (183). E-cadherin, but not p120ctn-uncoupled cadherin, can block both AIG and activation of Rac1 and Ras in the presence of p120ctn (183). Stable knockdown of p120ctn in E-cadherin-positive MCF7 cells results in reciprocal effects on AIG, Rac1 activity and MAPK signaling (183). However, the molecular mechanism is not clear because p120ctn knockdown also affects the E-cadherin expression levels. Depletion of endogenous E-cadherin in MCF7 cells phenocopies the effect of p120ctn knockdown, indicating that under normal conditions E-cadherin blocks AIG by inhibiting both Rac and Ras-mediated signaling (183).

p120ctn ablation blocked AIG in cells transformed with Rac1 or Src, but not in cells transformed with H-Ras (69). AIG in cells transformed with Rac1 or Src is dependent on p120ctn-mediated RhoA inhibition because ablation of p120ctn in these transformed cells is rescued by inhibition of ROCK, a downstream RhoA effector (69). Activating the RhoA pathway by adding LIMK1, which is downstream of ROCK, also blocks AIG in transformed cells (69). RhoA activation results in phosphorylation and inactivation of cofilin at serine residue 3 (S3), whereas p120ctn-mediated RhoA inhibition results in cofilin activation. Strangely, in contrast to ROCK inhibition, AIG is not rescued by a dominant active S3A cofilin mutant that cannot be phosphorylated. So, other RhoA effectors might be involved in the regulation of AIG (69). The dependence of AIG on either Rac1 activation or RhoA inhibition might

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be explained by the 'Bar-Sagi' pathway, in which Rac1 activation results in RhoA inhibition (112). In conclusion, p120ctn is involved in AIG. The exact mechanism remains unclear but it might depend on the type of cellular transformation.

9.7. p120ctn and the inflammation–cancer interaction

A strong connection exists between inflammation and tumor progression (187). p120ctn depletion in mouse skin caused hyperproliferation and chronic inflammation due to increased NF- κ B activation (46). Both general immunosuppressive drugs (Dexamethasone) and a NF- κ B inhibitor (IKK2 inhibitor) reduced the hyperproliferation in p120ctn-deficient skin grafts (46, 165). The NF- κ B activation in p120ctn-depleted keratinocytes is dependent on RhoA activity. Constitutively active RhoA and ROCK mutants result in nuclear translocation of NF- κ B in wild-type keratinocytes, whereas nuclear NF- κ B expression can be reverted in p120ctn-deficient keratinocytes by expression of dominant-negative RhoA or by treatment with ROCK inhibitor (46). Moreover, nuclear NF- κ B can also be reverted by introducing a cadherin-uncoupled p120ctn mutant, but not by a RhoA-uncoupled mutant (*delta622-628*) (46). So, NF- κ B activation depends on RhoA activity, which in turn might be influenced by expression of the alternatively spliced exon C. Poorly differentiated human SCCs also showed nuclear NF- κ B as well as perturbed expression and/or localization of p120ctn (165). Finally, genetic ablation of intestinal p120ctn also results in increased infiltration of COX-2-positive neutrophils, which is commonly seen in inflammatory bowel disease (47). This disease predisposes intestinal tissue to cancer (188).

10. CONCLUSIONS AND PERSPECTIVES

For a long time, p120ctn has stood in the shadow of its famous relative, beta-catenin, which has exceptional features as both junctional component and tumorigenic transcriptional activator. However, it has now become clear that p120ctn has many characteristics that make it stand out from beta-catenin as a unique intracellular regulator, at least in vertebrates.

What p120ctn shares with other members of the Armadillo protein family is, of course, the central Armadillo repeat domain, which nevertheless exhibits differences in structure and function among the family members. What makes p120ctn unique in relation to beta-catenin is its binding to an evolutionarily conserved juxtamembrane domain of cadherins, the occurrence of multiple isoforms generated by alternative splicing, its tight regulation by multiple phosphorylation events, and its binding to various unique interaction partners, including kinases and linkers to the microtubular cytoskeleton. This translates into several site-specific intracellular functions: cadherin stabilization at intercellular junctions, Rho family member modulation in the cytoplasm, control over the transcriptional repressor Kaiso, and modulation of the canonical Wnt signaling pathway. These findings imply that the ubiquitously expressed p120ctn may turn out to be a key

regulator of intracellular signaling and tissue organization. Indeed, in the embryos of frog and mouse, p120ctn is indispensable for early development, and studies of conditional knock-out mice point to important roles in morphogenesis and homeostasis.

p120ctn represents the prototype of a small Armadillo protein subfamily that includes ARVCF, delta-catenin and p0071. Much less is known about the specific functions of the other members, but a few mouse models indicate that they cannot compensate for the loss of p120ctn, whereas p120ctn can at least in part compensate for loss of the others. Nonetheless, the other subfamily members deserve further analysis because of their possible involvement in some human diseases. The next steps in their study could include generation of mice with more complex genotypes, combining knock-outs of one Armadillo subfamily member with knockout of the most related family member, or triggering knock-outs by various predisposing conditions.

Regarding p120ctn itself, numerous associations have been reported between p120ctn dysregulation on the one hand and tumorigenesis and tumor progression on the other hand. However, as might be expected from the pleiotropic roles of p120ctn under physiological conditions, these interactions are complex. Often seen is either the loss of p120ctn or its cytoplasmic accumulation. Another recurrent observation is the switch to longer isoforms during epithelial-to-mesenchymal transition (EMT), which leads to increased tumor malignancy. How such changes in p120ctn expression modify intra- and intercellular signaling and cause complex pathological cellular behavior is under investigation.

Some suggestions to further scrutinize the regulatory roles of p120ctn family members can be made. Instead of deleting large parts of protein domains, one may zero in with point mutations affecting specific posttranslational modifications or the binding to any of the many interaction partners of p120ctn, including cadherins, RhoGTPases, kinases and phosphatases, cytoskeleton-associated proteins, and transcriptional regulators. That all this can be achieved is exemplified by recent studies targeting phosphorylation sites in p120ctn (132, 133), the generation of p120ctn-uncoupled mutations in classic cadherins (66), and the generation of a short deletion affecting one particular RhoA binding site in p120ctn (10). Generation of constitutive or conditional knock-in mice for these very particular mutations may reveal more clearly the multiple and context-dependent *in vivo* roles of p120ctn. For instance, our laboratory generates mice in which particular isoforms of p120ctn are either excluded or constitutively expressed. As for the link of p120ctn to cancer, it is intriguing that so few somatic p120ctn mutations have been reported in human tumors. The molecular mechanisms by which p120ctn is inactivated or otherwise modulated in cancer needs to be addressed in detail. Also, more informative animal models need to be generated in order to elucidate the role of changes in p120ctn in various diseases, and particularly in cancer.

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