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p120-catenin: past and present

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Abstract

p120-catenin was first described in 1989 as a Src substrate whose phosphorylation correlated with transformation. It was identified by cDNA cloning in 1992, and shown to interact with cadherins in 1994. Though enigmatic for some time, p120 has emerged as a master regulator of cadherin stability, and an important modulator of RhoGTPase activities. With the discovery of p120 family members and evidence for fundamental roles in cell biology and cancer, the field has expanded dramatically in recent years. As an introduction to this collection of reviews on p120 and its relatives, the editors have requested a personal commentary and historical perspective on the discovery of p120. The anecdotal parts have no particular purpose, but are mostly unpublished and perhaps of interest to some.

Keywords

p120-catenin; Src; RhoGTPases; cadherin; cell-cell adhesion; tumor suppressor; metastasis; contact inhibition; Kaiso; historical perspective

Introduction

p120-catenin (hereafter p120) was first reported in 1989 as a Src substrate whose phosphorylation correlated with transformation [1]. It was identified by cDNA cloning in 1992 [2], and shown to interact with cadherins in 1994 [3,4]. Though enigmatic for some time, p120 has emerged as a master regulator of cadherin stability [5–7], and an important modulator of RhoGTPase activities [8–10]. Reports of functional interactions with other Src substrates (eg, Cortactin), and transcription factors (eg, Kaiso) [11–15] indicate that like β-catenin, p120 is likely to have multiple roles in different cellular compartments. Indeed, p120 is physically or functionally linked to a wide variety of oncogenes and tumor suppressors, including Src kinases, receptor tyrosine kinases, receptor tyrosine phosphatases, E-cadherin, β-catenin, APC, RhoGTPases, Kaiso, and Wnt signaling effectors. These observations suggest prominent roles in cellular activities associated with cancer, including cell adhesion, motility, morphology, and growth. Interestingly, the extended p120 family might have in common the ability regulate RhoGTPases, but their individual roles are not necessarily limited to regulation of cell-cell adhesion. The focus of this BBA volume on p120 and it family members is indicative of the growing interest in these proteins, and suggests a bright future for the field as it endeavors to unravel underlying mechanisms and potential roles in disease and cancer. As requested by the

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editors of this volume, this introductory chapter is intended not as a review, but rather a personal commentary and historical perspective on the discovery of p120 and potential future directions.

An Historical Perspective

p120 was initially identified as part of a larger effort to determine the mechanism of cell transformation by v-Src [1]. At the time, it was one of many Src-substrates whose visualization was made possible for the first time by a technical advance, namely the advent of antibodies to phosphotyrosine (pTyr antibodies). There was substantial concern that p120 and the other substrates observed by this method might turn out to be irrelevant cytoskeletal proteins phosphorylated promiscuously because of their abundance, or due to an overexpressed kinase gone bad. On the other hand, p120 was unique among the substrates in that it was not phosphorylated by a transformation-defective Src variant, suggesting a possible role in oncogenic cell transformation. In any event, the substrates were purified *en masse* by pTyr-antibody affinity chromatography and monoclonal antibodies (mAbs) were generated [16]. The mAbs to individual Src substrates were then pooled, and used to screen cDNA expression libraries. Remarkably, the majority of the major substrates, known only as pTyr bands on a Western blot in 1989, were both identified and cloned by 1992 [2,17–19].

As with many scientific endeavors, luck played an important role. For example, during generation of the substrate monoclonal antibodies, the lone p120-specific positive clone was very nearly lost. In a significant effort to rescue the unstable hybridoma, a single subclone out of over 200 screened remained positive, resulting in mAb 2B12 -- without which it would have been difficult or impossible to pursue p120. Persistence was also essential, however, as p120 was the only protein in the substrate collection whose cDNA could not be isolated by antibody-based expression cloning. Expression libraries at that time were generated by reverse transcribing mRNA using 3′ poly-A tails as cDNA primer templates. Thus, the 5′ ends of cDNA coding sequences were often underrepresented or absent. According to classic Murphy doctrine, mAb 2B12 recognized an epitope at the extreme 5′ end of the longest cDNA coding sequence. This chance occurrence also delayed the recognition of p120's multiple personalities. Antibodies to other p120 regions recognize all p120 isoforms, but mAb 2B12 interacted with an epitope found only in p120 isoform 1. Nonetheless, the antibody provided a specific handle for p120 purification, and the gene was eventually cloned by more labor-intensive methods [2](ie, large scale immunoprecipitation, extraction from SDS-polyacrylamide gels, digestion with cyanogen bromide, peptide microsequencing by Edman degradation, PCR from redundant oligonucleotides to generate exactly matched cDNA probes, and conventional screening of λgt10 libraries), that thankfully, have been made mostly irrelevant by the human genome project.

Interestingly, p120 and most of the other genes isolated in these screens (ie, Tensin, Focal Adhesion Kinase/FAK, p130CAS, p110AFAP, cortactin) turned out to be novel, and did indeed encode *bone fide* physiologically relevant Src substrates. With the exception of p120, each contained domains that were obviously relevant to protein tyrosine kinase (PTK) signaling (eg, PTK, SH2, or SH3 domains). p120, on the other hand, contained linked armadillo repeats with only 22% identity to β-catenin or plakoglobin. Nonetheless, an "Armadillo repeat" consensus pattern could be identified, suggesting for the first time that proteins other than β-catenin and plakoglobin might utilize this motif for a generalized purpose. The observation led to the recognition that linked Arm repeats form a functional domain (dubbed the Arm domain)[20] that has since been identified in numerous proteins. Importantly, the structural relationship to β-catenin also led to the idea that p120 might physically associate with cadherins [3]. In retrospect, however, the finding itself was at least partly a matter of luck -- despite the impeccable logic behind the experiment, the vast majority of Arm domain proteins discovered subsequently (p120 family members excepted) do not interact with cadherins.

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Although it is difficult to assign a single role to Src, an important lesson from the Src substrate project was the general recognition that Src-substrates have in common the ability to regulate the actin cytoskeleton. Thus, despite the number and complexity of its substrates, an overarching role of c-Src may be to coordinate actin-dependent cellular activities, such as adhesion and motility. Although p120 didn't initially seem to conform to the Src pattern (ie, lack of typical PTK-associated domains), both β-catenin and plakoglobin are excellent Src substrates, and are in fact well-established mediators of a functional connection to the underlying actin cytoskeleton. In retrospect, these observations provided the first clue that p120 would also participate in regulating actin dynamics. Indeed, it has become increasingly valuable to think about p120 in the context of a functional network of Src substrates (eg, FAK, cortactin) that coordinate actin-based events underlying cell morphology, motility, and adhesion.

The interaction between p120 and E-cadherin was formally reported in 1994 [3] and at the ASCB meeting of that year, where a prominent scientist remarked that p120 did indeed look like an interesting protein, but that it should have been given a better name (eg, integrins). At the summer Oncogene meetings, p120 had in fact been officially dubbed CAS (Cadherin-Associated Src Substrate), an unimaginative but appropriate moniker that described virtually everything known about p120 at the time. Incredibly, another Src substrate, p130, was also cloned that year, and the authors chose to name the protein CAS (Crk-Associated Substrate) [21]. The two posters appeared side by side at the Oncogene meeting, leading to considerable confusion. Thus, it was eventually resolved that p120CAS would become p120ctn (for catenin). For better or worse, the moniker is now irrevocably engrained in the literature.

The field was slow to bring p120 into its models of the cadherin complex. Interestingly, our seminal manuscript reporting the p120-cadherin interaction was editorially rejected (lack of functional significance) by the Journal of Cell Biology and had to be resubmitted elsewhere [3]. p120-cadherin coimmunoprecipitation experiments were difficult to repeat because the interaction is of relatively low affinity in detergent lysates. Moreover, in a particularly powerful demonstration of Murphy's law, the main p120 isoforms comigrated exactly with α- and β-catenins in many cell types [3]. Methods used frequently at that time to detect α- and β-catenins in cadherin immunoprecipitates (eg, 35S-methionine labeling and autoradiography) were virtually useless because p120 bands were masked by α- and β-catenins. Thus, it was necessary to prove that the coprecipitating bands recognized by p120 mAbs on Western blots were not cross reacting with the exactly comigrating α- and β-catenins. Nonetheless, p120 colocalized precisely with cadherins in most cell types, and localized aberrantly to the cytoplasm in metastatic cell lines that had lost E-cadherin. Eventually, direct mapping experiments, and the uncoupling of p120 binding by minimal mutations in the cadherin juxtamembrane offered indisputable proof [22,23]. Cadherins are in fact both necessary and sufficient for recruitment of p120 to membranes/junctions [22]. It is as yet unclear whether the apparent low affinity of the interaction is functionally important in cells, as suggested by mechanistic models where cytoplasmic p120 and/or shuttling between a bound and cytoplasmic state might be functionally relevant [24](eg, see review by Anastasiadis in this volume).

The discovery of Kaiso in 1999 as a novel p120 binding partner provided the first tangible evidence that p120 might have additional roles in the nucleus [11]. The possibility was implied by analogy to β-catenin, and later supported by localization studies in cadherin-deficient cells [25]. It is now clear that these proteins interact functionally at the level of transcription [15, 26]. Moreover, recent studies in Xenopus have revealed novel interactions with Wnt signaling pathways [13,14](see the reviews by Daniel, and by McCrea and Park in this volume). Interestingly, in the context of APC(Min/+) mice, Kaiso-deficiency results in a partial resistance to intestinal cancer [27]. An interesting possibility is that p120 and β-catenin may

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collaborate functionally to control cell-cell adhesion at the level of cadherin complex, and then again in the nucleus as their signaling pathways converge on Wnt effectors.

Functional interactions between p120 and RhoGTPases were reported in 2000 [8–10], providing the first convincing evidence that p120 might play a major role in controlling the interplay between cadherins and the underlying actin cytoskeleton. The mechanism(s) are now front and center in the field, in part because it is clear that RhoGTPases control cadherin function, and vis versa [28]. It has been known for some time that p120 overexpression in fibroblasts induces a striking branching morphology [29]. The series of papers in 2000 connected this phenotype to the suppression of Rho, and to some extent activation of Rac. Such activities are likely shared by most or all members of the p120 family, because most, including at least some of the more distantly related plakophillins, can induce branching phenotypes when overexpressed. Because p120 can interact directly with Rho *in vivo* [30], and can keep Rho in an inactive GDP-bound form *in vitro* [8], it was suggested that it might act by sequestering Rho in its inactive state - as described previously for Guanine Nucleotide Dissociation Inhibitors (GDIs). Co-overexpression of a cadherin cytoplasmic domain reverses the p120-induced branching phenotype, implying that interaction of p120 with cadherins and Rho might be mutually exclusive [8]. These observations suggest a RhoGDI-like model, and a role for p120 in suppression of Rho in the cytoplasm, but are based almost entirely on overexpression studies and are thus subject to interpretation. While roles for p120 in controlling RhoGTPases have been confirmed in many studies, including *in vivo* work in developmental systems [30–32], the current models do not adequately account for the central role played by RhoGTPases in membrane associated cadherin complexes. Our unpublished data implies that p120 can target suppression of Rho to cadherin complexes via transient recruitment of p190RhoGAP (Wildenberg/Reynolds, submitted). Other observations suggest that p120 might be essential for cadherin-mediated activation of Rac [33]. These ideas are not mutually exclusive, and may reflect a diversity of binding partners and functions (eg, β-catenin) as well as cell type specific mechanisms. Indeed, differences in how Rac and Rho are used from one cell type to another are well established and represent a major complication for the RhoGTPase field, and now the p120 field as well.

A key advance in 2002 was the discovery that p120 is essentially a master regulator of cadherin stability [5–7]. This is likely its core function at the level of the cadherin complex -- in the absence of p120, most cadherins are internalized and often degraded, suggesting that p120 controls cadherin turnover at the cell surface. The mechanism is post-translational and requires direct physical interaction between p120 and the cadherin complex [5]. It has been known for some time that the stability of α-catenin and β-catenin is directly dependent on physical interaction with cadherins [34]. The amount of cadherin present is therefore rate limiting at the protein-protein interaction level for stabilizing α- and β-catenins. In contrast, cadherin stability is directly dependent on p120. Thus, in the hierarchy of who controls what, p120 is at the top of the pyramid, and in fact, the entire cadherin complex is degraded if p120 is selectively removed (eg, by RNAi methods, etc).

The implications of this novel arrangement are deceptive, and have yet to be fully appreciated. For example, it strongly implies that cadherins compete for an essentially limiting pool of p120, and are removed from the cell surface if p120 is unavailable. Thus, overexpression of any classical cadherin cytoplasmic domain (ie, DN-cadherin constructs) sequesters the apparently limiting amounts of p120 such that the endogenous cadherins are internalized and either degraded or recycled, along with their dependant partners, α- and β-catenin. An extensive preexisting literature based on *in vitro* and *in vivo* use of dominant negative (DN) cadherins provides multiple examples of this phenomenon, but does not attribute the adhesive defects to loss of p120 function. Though other events could contribute, it is now clear that the p120-based mechanism described above is central. Thus, it might be constructive to reexamine prior *in*

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vitro and *in vivo* DN-cadherin studies in the context that they in fact reflect consequences of physically removing p120. Of particular interest are *in vivo* transgenic studies in the intestine and the pancreas, where DN-cadherin expression induced adenomas, and dramatically increased metastasis, respectively [35,36]. Studies using direct p120-ablation in mice are underway to determine whether p120-loss by itself will indeed recapitulated these observations.

Interestingly, the above phenomenon is also relevant when one overexpresses full length classical or type II cadherins (eg, N-cadherin) in cells that already express other p120-dependant cadherins (eg, E-cadherin). The predicted (and actual) consequence based on the above data is not simply co-expression of N-cadherin with E-cadherin. Instead, the ectopic N-cadherin sequesters the available p120, and endogenous E-cadherin is efficiently internalized. The end result is essentially the replacement of one cadherin by another via a largely post-transcriptional mechanism. In cells that naturally express more than one cadherin, it is evident that they somehow share and/or compete for a limiting amount p120. Conversely, if a particular cadherin is artificially eliminated (eg, by knockout or knockdown), levels of the remaining cadherin(s) often increase. For example, targeted knockout of E-cadherin in the mouse epidermis increases P-cadherin levels [37]. How cells monitor and regulate p120 levels to accommodate these needs is currently unknown, but it is clear that p120 expression levels in cells are critical, and act as a master regulator or rheostat for overall cadherin levels. These observations highlight the importance of better understanding the status of p120 in human tumors: there are numerous reports of p120 downregulation in cancer, but the cause(s) are unknown and the relative importance of the phenomenon in tumor progression has not been determined [38].

This year (2006) marks the culmination of a great deal of effort aimed at directly addressing some of these issues *in vivo* by examining controlled p120 ablation in mice. Conventional p120 KO in mice is embryonic lethal but two conditional p120 KO mouse models have now been generated and three manuscripts detail for the first time the consequences of targeted p120 KO in mammalian tissues [39–41]. As predicted from *in vitro* studies, endogenous cadherins (eg, E-, N-, and P-cadherins) are significantly downregulated in all cell systems targeted to date, including neurons and the epithelial linings of the gut, prostate, epidermis, and salivary gland. In many cases, cell-cell adhesion and cell morphology is significantly impaired, but the severity of p120 KO with respect to cell adhesion and morphology differs markedly from one system to the next. A likely explanation is the variable presence of p120 family members with at least partially redundant functions. To accelerate progress, the conditional p120 KO animals have been widely distributed to interested laboratories with the goal of more rapidly examining and comparing consequences of p120-loss in diverse organ systems.

An unanticipated consequence of p120 loss in multiple organ systems is inflammation. In the intestines and colon, severe defects in cell-cell adhesion contributed to obvious breakdown of the epithelial barrier function and exposure to bacteria and other gut contents (A. Reynolds, unpublished). In the epidermis, however, cell-cell adhesion was not obviously compromised, and the barrier function appeared intact. Here, inflammation was attributed to constitutive cell autonomous activation of RhoA and downstream NFkB activity [40]. p120-ablation by siRNA treatment does, in fact, dramatically increase Rho activity in a wide variety of cell lines. Interestingly, severe inflammation (ie, neutrophil infiltration) was observed in the developing salivary glands by embryonic day 16.5, despite the sterile environment (M. Davis, unpublished). Thus, inflammation in some cases may be the result of cell autonomous activation of Rho/NFkB signaling and could be an important general consequence of p120 downregulation. These observations highlight the importance of targeting and comparing multiple systems and reveal the potential of these mouse models for advancing the study of p120 in development and disease. While the long-term effects of p120-loss *in vivo* are not yet

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clear, the early data -- Rho activation, cadherin deficiency, defects in cell-cell adhesion and morphology, and inflammation -- are obvious hallmarks of human cancer, and further highlight the need to better understand p120-deficiency in human cancers.

The great historical irony with respect to p120 is that the role of tyrosine phosphorylation remains unknown (see review by Alema and Salvatore in this volume). The first publication on p120 featured a strong correlation between p120 phosphorylation and transformation by Src. A role for p120 in transformation has not been ruled out, but p120 knockdown does not obviously block cell-transformation by Src. On the other hand, p120 is required in MDCK cells for Src-induced growth in soft agar (A. Reynolds, unpublished), and much of what we know to date about p120 is indeed consistent with a role in transformation, including its association with cadherins, its role in regulating RhoGTPases, and its functional link to p190RhoGAP. Advances in other aspects of p120 biology may provide important clues for reexamining these issues. For example, the observation that p120 is essential for stabilizing and retaining cadherins at the cell surface is a critical finding and provides a solid basis for modeling positive and negative p120 effects at the mechanistic level. p120 binding partners described in recent years include the kinases Fer, Yes, and Fyn, as well as several tyrosine phosphatases (DEP-1, PTPu, SHP-2, etc.)(reviewed in [42], which can now be incorporated into these models. Moreover, most of the tyrosine and serine/threonine phosphorylation sites have been mapped and mutated [43,44], and there are now elegant p120 knockdown and addback systems to facilitate structure/function analyses [6]. Phosphospecific p120 antibodies have also been generated to many of the sites and made widely available [45,46]. These reagents provide necessary and powerful tools that will vastly accelerate studies going forward. Though elusive, there is little doubt that p120 phosphorylation will play a critical role in regulating p120 and cadherin function.

Back to the Future

Publication rates on p120 and its family members have accelerated from 5 in 2000 to over 55 in 2005. The practically exponential increase in interest will ensure rapid progress over the next decade. The field has reached a critical mass in terms of the number of labs involved and the generation of a wide variety of outstanding reagents. While many interesting questions remain, it is worth mentioning here a few issues of particular relevance in the near future.

More emphasis on other p120 family members is essential. Although p120 is ubiquitous, and likely the most abundant in mammals, there is growing evidence that some p120 family members are more widely expressed than previously thought. Moreover, it appears that this family may have in common the ability to regulate Rho. Although δ-catenin and ARVCF can functionally substitute for p120 with respect to binding and stabilization of E-cadherin [5], it is likely that the core function inherited and retained by all of these proteins is the ability to somehow regulate and coordinate RhoGTPases. It is possible that the cadherin stabilizing function of p120 and the ability to regulate Rho is one and the same, but evidence to date is inconclusive. As demonstrated recently for p0071 (Hatzfeld, personal communication, NCB/In Press), these proteins have probably found creative uses for this potentially powerful activity (ie, binding/coordinating Rho), and it will be important to independently assess the roles of each family member. As part of this effort, it is now critical to develop better mAbs to each family member and make them widely available, as the paucity and availability of such reagents has limited progress on these proteins. In p120 KO studies, for example, it has been very difficult to determine the extent to which the consequences of p120-loss might be masked in some tissues by redundant roles of family members because immunohistochemistry-competent antibodies are scarce or unavailable.

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The role of p120 itself in modulating RhoGTPase activities needs to be resolved at the mechanistic level, as it is likely to account for the fact that cadherins are central regulators of RhoGTPases and vis versa. Although p120 can clearly act in GDI-like fashion to directly inhibit Rho, the location and significance of this activity under conditions where p120 is not overexpressed is not yet understood. New evidence suggests that p120 may also inhibit Rho via recruitment of p190RhoGAP to cadherin complexes (Wildenberg/Reynolds, submitted), and other observations suggest a role for p120 in activation of Rac [33]. Also, p0071 interacts directly with the RhoGEF, Ect2 (Hatzfeld, NCB: In Press), providing an example of Rho activation by a p120 family member. Differences between how various cell types use Rac and Rho may account for much of the confusion, but different cell types also express different cadherins, which in turn are coupled to different receptor tyrosine kinases. A potential solution to this underlying complexity is to focus on a few representative cell lines/types that are already well characterized in the literature with respect to oncogenic signaling and roles for Rac and Rho. As the individual characteristics of defined systems emerge, they can then be more accurately compared and contrasted.

Understanding the role(s) of p120 phosphorylation, both tyrosine and serine/threonine, will be essential for deciphering mechanisms underlying the regulation of cadherin-based cell-cell adhesion and how they relate to other cellular functions (eg, cell growth, contact inhibition, endothelial permeability). A great deal of effort has been invested in developing the *in vitro* and *in vivo* tools necessary for more efficient exploration of these events. Cadherins in all tissues are physically and functionally coupled to receptor tyrosine kinases (RTK's), and p120 in particular with its relationship to RhoGTPases may play central roles in modulating these interactions. One possibility is that receptor signaling controls dynamic cell-cell adhesion by modification of p120, which in turn regulates rapid addition or removal of cadherins from the cell surface. As implied above, these relationships are probably highly interdependent and broadly relevant to multiple areas of cell biology, development and cancer.

Although great progress has been made with respect to p120 function in the nucleus (eg, Kaiso), the overall and relative significance of such activities are as yet unclear. The critical relationships to Wnt signaling observed in Xenopus should be reexamined in mammalian models. Interestingly, several novel nuclear p120-binding partners have been described recently at conferences and will undoubtedly lead to exciting new areas of research. Given the critical role(s) of β-catenin in the nucleus and the overall importance of cadherins in cancer, the potential for p120 and its relatives in the nucleus remains an important frontier.

Finally, the emerging data justify more emphasis on discriminating studies aimed at clarifying the role(s) of p120 in human cancer. The pathology data is consistent with p120 downregulation in many human cancers [38], but these observations represent snapshots in time and do not address cause and effect. Direct analysis of targeted p120 ablation in mice will reveal whether p120-ablation has the potential (by itself or in combination with other oncogenic events) to promote cancer, but cannot definitively determine whether p120 downregulation or mutation does in fact contribute to initiation or progression of particular human cancers. Given that much of the evidence summarized above is consistent with such a role, it may be time to place more emphasis on determining whether the pathology data reflects genuine alterations in genetic or epigenetic events and whether they are relevant in some cancers to human tumor progression. Perhaps over the next decade, p120 and its family members will emerge as important players in a variety of human diseases.

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