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Review

Phosphorylation and isoform use in p120-catenin during development and tumorigenesis

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ABSTRACT

P120-catenin is essential to vertebrate development, modulating cadherin and small-GTPase functions, and growing evidence points also to roles in the nucleus. A complexity in addressing p120-catenin's functions is its many isoforms, including optional splicing events, alternative points of translational initiation, and secondary modifications. In this review, we focus upon how choices in the initiation of protein translation, or the earlier splicing of the RNA transcript, relates to primary sequences that harbor established or putative regulatory phosphorylation sites. While certain p120 phosphorylation events arise via known kinases/phosphatases and have defined outcomes, in most cases the functional consequences are still to be established.
In this review, we provide examples of p120-isoforms as they relate to phosphorylation events, and thereby to isoform dependent protein–protein associations and downstream functions. We also provide a view of upstream pathways that determine p120's phosphorylation state, and that have an impact upon development and disease. Because other members of the p120 subfamily undergo similar processing and phosphorylation, as well as related catenins of the plakophilin subfamily, what is learned regarding p120 will by extension have wide relevance in vertebrates.

1. Introduction

Together with cell interactions taking place with the extracellular matrix (e.g. integrin-mediated), varied cell–cell adhesion complexes contribute to development and tissue homeostasis. In vertebrate epithelial cells, three major types of cell–cell contacts tend to be discussed, including adherens, tight and desmosomal junctions. Given our focus upon p120-catenin, we note that it was initially characterized as a substrate of the Src kinase [113], and shortly thereafter was found in association with one of the principal transmembrane components of epithelial adherens junctions, E-cadherin [1,100,111]. Adherens junctions are complex both with respect to the number of components involved, and the kinds of outside-in and inside-out (etc.) signals transduced or facilitated. Two of an assortment of proteins able to bind to the cytoplasmic carboxyl-tails of classic cadherins include p120-catenin and β-catenin. Within the p120 subfamily of catenins are ARVCF-, δ- and p0071-catenin; each competes with the other as well as with p120-catenin itself to bind a membrane-proximal site on the cadherin tail [17,54,86]. β-catenin (or the related γ-catenin/plakoglobin) binds to a more membrane-distal site on the tail, indirectly linking the cadherin complex to the contractile cortical-actin cytoskeleton, an interaction that contributes to cell adhesion and motility [91,135].

As noted, p120-catenin was originally described as a Src kinase substrate, and then as a component of the cadherin–catenin complex. P120-catenin promotes cadherin stability, lowering the complex's susceptibility to endocytosis, ubiquitination, and proteosomal destruction [25,33,56,92,149,150]. With the exception of αE-, αN- and αT-catenin, which are structurally related to vinculin, all catenins including p120 contain a central Armadillo-repeat domain that facilitates protein–protein interactions. The Armadillo domain is only modestly homologous between p120 subfamily catenins (45–55% primary sequence identity), and the amino- and carboxyl-terminal regions are yet more divergent. In addition to binding and modulating E- or other classic-cadherins, p120-catenin regulates small-GTPases (e.g. Rac1 and RhoA). This can occur while p120 is associated with or dissociated from the larger cadherin–catenin complex [6,69–71,144]. P120 can bind small-GTPases as a guanine-nucleotide dissociation inhibitor/GDI (e.g. for RhoA), or associate indirectly via GEFs, GAPs or other small-GTPase effector proteins. P120-catenin further associates with microtubules and motor proteins [23,43,155]. A final intriguing property of p120-catenin relates to its nuclear entry and association with transcriptional regulators such as Kaiso [30,31,108], Glis2 [51] and REST/CoREST [77]. In particular,

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p120-isoform 1 appears to participate in vertebrate canonical Wnt signaling [49]. In summary, p120 binds and regulates the cadherin–catenin complex (cell–cell junctions), small-GTPases and cytoskeletal factors (cell–cell junctions and elsewhere), and transcription factors (nucleus). Thus, we will address in this review how p120's phosphorylation and isoform status is relevant to an array of cellular processes.

P120-catenin's phosphorylation, isoform status and intracellular localization vary with the cell type and tissue (reviewed in [70,107,114]. With respect to nuclear localization, p120 was initially suggested to contain two nuclear localization signals (NLS) [2,7], and three potential nuclear-export (NES) regions (Fig. 1) [137]. The NLS sequence between Armadillo repeats 5 and 6 modulates p120's (isoform 1) nuclear localization [63], although other findings have instead pointed to p120's (isoform 3) Armadillo region in nuclear entry (repeats 3 and 5) or export (repeat 8) [114]. For example, the Armadillo domain of p120 appears needed for it to shuttle into the nucleus in response to Rac1 [76]. Also favoring p120 nuclear entry is the transcription factor Glis2, especially in combination with Src phosphorylation of p120 [51]. At cell–cell contacts such as adherens junctions, p120 interacts with E- and other cadherins, with either's phosphorylation affecting their association [36,38,44,104,138]. Thus, as we will discuss in the context of p120's isoform-specificity, its phosphorylation and protein–protein interactions help to determine p120's intracellular localizations and functions.

2. Isoforms of p120-catenin

Considering combinatorial possibilities that result from four distinct translation-initiation sites and four alternatively spliced exons, human p120-catenin possess in theory 64 primary-sequence isoforms (Fig. 1) [62]. P120-isoform 1 is the product of the most upstream translational initiation. It contains an amino-terminal coiled-coil domain, absent from isoforms 2 to 4. Isoform 4 is missing almost the entire amino-terminus of p120-catenin, thus lacking the coiled-coil as well as a regulatory region harboring many potential or confirmed phosphorylation sites [147]. P120-isoform 2 and -isoform 3 lack smaller regions, perhaps most noteworthy being the amino-terminal coiled-coil region that enables some of p120's interactions (Fig. 1). The differential functions of p120's isoforms are just beginning to be revealed, such as in the regulation of RhoA activity [154]. As noted, varying p120-isoforms are expressed in different ratios among varying cell types or contexts [94]. With the exception of macrophages [156], non-adherent (e.g. B- and T-)

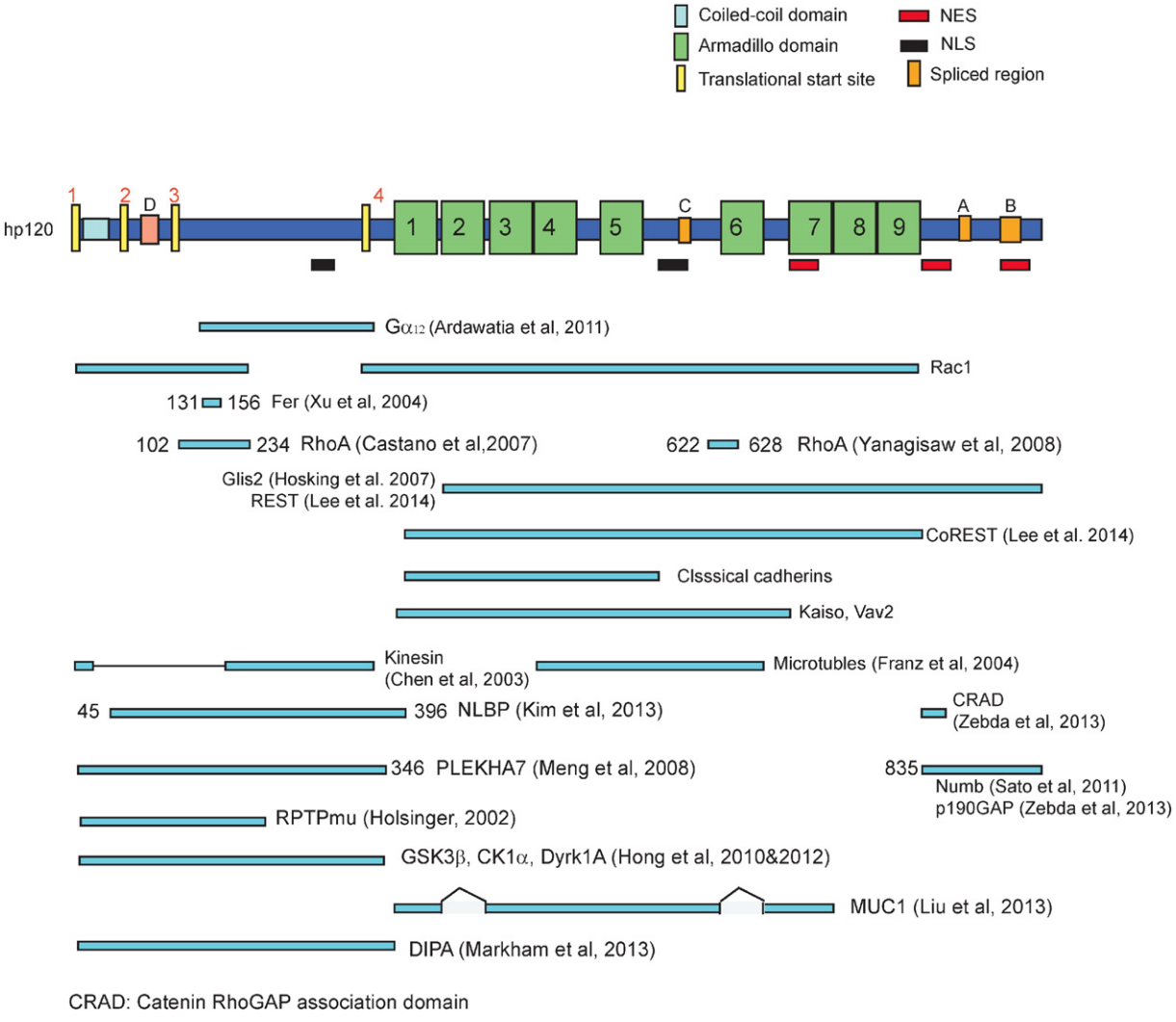

Fig. 1. P120-catenin structural features. Structural features of human p120-catenin in relation to its direct interaction partners, alternative translational start sites (yellow boxes 1–4), alternatively spliced regions (tan boxes A-D), and subcellular localization signals (NLS black boxes; NES red boxes). An alternatively spliced region D is rarely excluded. The Armadillo domain is depicted in green; and in the case of p120-catenin and related sub-family members, it has nine repeat units each of about forty-two amino acids. Indicated are a number of putative nuclear localization sequences (NLS) [2,63,114], and nuclear export sequences (NES) [137]. An amino-terminal coiled-coil region is shown in light blue and exists solely in p120-isoform 1. Additional information on the functional differences between p120-catenin isoforms is included in the review text, while representative references relating to the indicated protein interactions of p120-catenin are included within the figure itself.