Available online at www.sciencedirect.com
ScienceDirect
Biochimica et Biophysica Acta 1773 (2007) 78–88
Biochimica et Biophysica Acta BBA
www.elsevier.com/locate/bbamcr

Review

Diverse functions of p120ctn in tumors

Jolanda van Hengel, Frans van Roy *

Molecular Cell Biology Unit, Department for Molecular Biomedical Research, VIB-Ghent University, Technologiepark 927, B-9052 Gent (Zwijnaarde), Belgium

Received 31 May 2006; received in revised form 22 August 2006; accepted 23 August 2006
Available online 30 August 2006

Abstract

p120ctn is a member of the Armadillo protein family. It stabilizes the cadherin–catenin adhesion complex at the plasma membrane, but also has additional roles in the cytoplasm and nucleus. Extensive alternative mRNA splicing and multiple phosphorylation sites generate additional complexity. Evidence is emerging that complete loss, downregulation or mislocalization of p120ctn correlates with progression of different types of human tumors. It remains to be determined whether a causal relationship exists between specific isoform expression, subcellular localization or selective phosphorylation of p120ctn on the one hand and tumor prognosis on the other.

Keywords: Cancer progression; EMT; Cell–cell adhesion; Armadillo; Catenin; Cadherin; Rho GTPase

1. Introduction: cadherins and catenins in cancer

Cell–cell interactions, which are mediated by adhesion molecules, play vital roles in developmental morphogenesis, tissue remodeling and carcinogenesis. One of the major epithelial cell–cell adhesion molecules, E-cadherin, is frequently lost or down-regulated in various human cancers. Reduction of its expression correlates with the emergence of malignant characteristics, such as loss of epithelial morphology, and gain of invasiveness and metastatic potential [1,2]. Both reversible and irreversible mechanisms are at play. E-cadherin is somatically inactivated in diffuse-type gastric cancer and invasive lobular breast cancer [3–5]. On the other hand, down-regulation of E-cadherin gene expression by transcriptional silencing (promoter hypermethylation or expression of specific transcriptional repressors) increases cell motility and morphological epithelial to mesenchymal transition (EMT) (reviewed in: [2,6–8]). For instance, the transcriptional repressors Snail1 and SIP1 are key EMT regulators [8,9] that downregulate numerous epithelial target genes, including E-cadherin and many other junctional proteins [10,11].

The histological similarity of secondary, metastasis-derived tumors to the primary tumor indicates that EMT-mediated metastatic development must be followed by a reverse process, MET, at the site of secondary sites [12]. For instance, E-cadherin expression is dynamically and reversibly modulated during progression of ductal breast carcinoma [13]. Reduced E-cadherin expression favors dissemination, but regaining expression favors survival and reattachment of metastasizing cells [13–15]. Brabletz et al. [14] reported that colorectal carcinomas, which show E-cadherin downregulation and nuclear β-catenin at the invasive front, reexpress E-cadherin in their metastases whereas β-catenin localizes to the PM and the cytoplasm. This is indicative of a MET process. Recently, the term 'metastable phenotype', was introduced at a recent EMT meeting in Vancouver [16]. Cells with this phenotype express both mesenchymal markers (e.g. matrix metalloproteinases and vimentin) and epithelial markers (keratins) and show some residual E-cadherin expression.

Although it is well known that E-cadherin is an invasion suppressor in many cancers [2], the molecular basis of this property is poorly understood. In the past, it had been thought that E-cadherin acts like molecular glue to inhibit cell movements. The E-cadherin complex contains many cytoplasmic signaling molecules, including α-catenin and the Armadillo (Arm) proteins β-catenin, plakoglobin and p120ctn. This complex has been implicated not only in cell–cell adhesion, but also in epithelial cell polarity, migration, growth and survival. Recent studies demonstrated that the E-cadherin–β-

* Correspondence author. Tel.: +32 9 33 13 601; fax: +32 9 33 13 609.
E-mail address: F.Vanroy@dmbr.UGent.be (F. van Roy).

0167-4889/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamcr.2006.08.033

catenin–α-catenin complex at the adherens junctions forms a dynamic rather than a stable link to the cytoskeleton [17,18]. The diverse signals emanating from the E-cadherin complex are therefore likely to be altered by tumor-associated inactivation of E-cadherin, resulting in the various cancer phenotypes.

In the last two decades, the adhesive and transcriptional functions of β-catenin in human malignancies have become clear [19,20]. Tumor genetics revealed that mutations in members of the Wnt–β-catenin pathway occur in approximately 90% of colorectal cancers, as well as in other cancer types, such as hepatocellular carcinomas [21,22]. Mutations that activate the Wnt–β-catenin pathway promote stabilization of β-catenin and induce its nuclear accumulation. This results in activation of gene transcription, and alteration of cell migration and polarity. Other mutations, e.g. in conductin or in the adenomatous polyposis coli (APC) gene product, also affect the degradation of β-catenin. Activating mutations in the β-catenin gene itself have been reported in approximately 10% of colorectal cancer and in up to 40% of hepatocellular carcinomas [23,24]. The role of the Arm protein p120ctn in malignancies is less clear.

2. Structure of p120ctn isoforms

The human *CTNND1* gene comprises 21 exons and encodes potentially up to 48 protein isoforms due to many inter- and intra-exonic splicing events [25]. Human isoforms, designated 1 to 4, differ from each other in the start codon used. Alternative combinations with or without internal exons A–D generate additional isoforms [25,26]. Typical examples are isoforms 1ABC and 3AB. Several domains have been identified in p120ctn, including the coiled coil domain found only in isoform 1, and the phosphorylation domain found in all isoforms except type 4 (see Fig. 1). Isoform 1 (120-kDa or long isoform) and isoform 3 (100-kDa or short isoform) are expressed predominantly in highly motile fibroblastoid cells and epithelial cells, respectively [25,27]. The Arm domain of β-catenin consists of a series of 12 linked repeats of ~42 amino acids (aa) folded in helical conformation [28]. The proteins p120ctn, δ-catenin, ARVCF, p0071, and plakophilins (PKP)-1 to -3 belong to a separate subfamily of Arm proteins. The three-dimensional structure of the Arm domain of plakophilin-1 reveals nine instead of the originally predicted ten Arm repeats [29].

3. Expression of p120ctn in various cell compartments and in tumors

p120ctn associates with most if not all classical (type I) and nonclassical (type II) cadherins [30]. p120ctn may promote cell surface trafficking of cadherins through its ability to complex with kinesin and move vesicles along microtubules [31–33]. However, other studies indicate that p120ctn does not bind to the E-cadherin–catenin complex until p120ctn is located near or at the basolateral membrane [34]. Further, p120ctn promotes lateral clustering of cadherins [35,36], and regulates cadherin stability and turnover at the plasma membrane (PM) [37–39]. It regulates the membrane trafficking route followed by E-cadherin [40]. On arrival at the plasma membrane (PM), E-cadherin is rapidly degraded in cells that express low amounts of p120ctn [39]. Treatment of cells with lysosomal inhibitors prevents cadherin degradation in cells in which p120ctn expression is knocked down [37,38]. These studies indicate that p120ctn is required for retaining and stabilizing E-cadherin molecules at the PM. The precise role of p120ctn in this process remains unclear. p120ctn also facilitates the recycling of cadherin back to the cell surface. Calcium switch experiments have shown that p120ctn accelerates the delivery of cadherins to the PM via an interaction with kinesin motors [31,33]. Coupled with the growing literature on p120ctn down-regulation in tumors of all types, these data indicate that E-cadherin loss in at least a subset of cancers is due to prior down-regulation of p120ctn, in addition to other well-described mechanisms causing E-cadherin deficiency. Nonetheless, direct evidence is lacking, and very little is known about the timing, mechanism, or consequences of p120ctn down-regulation during tumor progression.

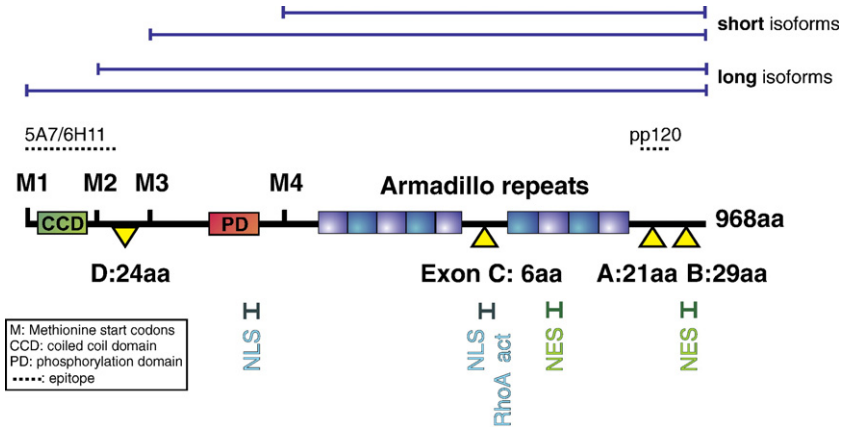

Fig. 1. Schematic diagram of the human p120ctn protein. Multiple isoforms of p120ctn result from the use of alternative start codons (M) and alternative splicing of exons A (exon 18), B (exon 20), C (exon 11) and D (exon 4); sizes are indicated in amino acid residues (aa). p120ctn has two consensus NLS sequences and two leptomycin-B sensitive NES sequences, as indicated. The hinge region containing a NLS is also important in regulating Rho function. Approximate locations of mAb epitopes are indicated. Armadillo repeats (1 to 9) are depicted by shaded boxes.