The nucleo-junctional interplay of the cellular prion protein: A new partner in cancer-related signaling pathways?

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ABSTRACT. The cellular prion protein PrPc plays important roles in proliferation, cell death and survival, differentiation and adhesion. The participation of PrPc in tumor growth and metastasis was pointed out, but the underlying mechanisms were not deciphered completely. In the constantly renewing intestinal epithelium, our group demonstrated a dual localization of PrPc, which is targeted to cell-cell junctions in interaction with Src kinase and desmosomal proteins in differentiated enterocytes, but is predominantly nuclear in dividing cells. While the role of PrPc in the dynamics of intercellular junctions was confirmed in other biological systems, we unraveled its function in the nucleus only recently. We identified several nuclear PrPc partners, which comprise &gamma;-catenin, one of its desmosomal partners, &beta;-catenin and TCF7L2, the main effectors of the canonical Wnt pathway, and YAP, one effector of the Hippo pathway. PrPc up-regulates the activity of the &beta;-catenin/TCF7L2 complex and its invalidation impairs the proliferation of intestinal progenitors. We discuss how PrPc could participate to oncogenic processes through its interaction with Wnt and Hippo pathway effectors, which are controlled by cell-cell junctions and Src family kinases and dysregulated during tumorigenesis. This highlights new potential mechanisms that connect PrPc expression and subcellular redistribution to cancer.

KEYWORDS. (10 max) Prion protein, &beta;-catenin, cancer, desmosomes, epithelial-mesenchymal transition, nucleus, Src kinase, nucleus, Wnt signaling, YAP, &gamma;-catenin

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INTRODUCTION

Beside its central role in transmissible spongiform encephalopathies, through a structural conversion into a pathogenic conformer, the cellular prion protein (PrPc), which is encoded by the Prnp gene and expressed in a wide range of tissues and cell types, was shown to contribute to the regulation of many basic biological processes, such as cell proliferation, differentiation, survival and adhesion. Despite absence of any severe phenotype, thorough analyses of Prnp knockout mice demonstrated that PrPc participates to several specific functions in specialized tissues, such as neuroprotection, synaptic activity, olfaction, immune response, epithelial and endothelial barriers. The molecular mechanisms underlying the large repertoire of PrPc functions is far from being totally elucidated but the identification of multiple interactors began to provide more comprehensive knowledge.

PrPc was described to be produced mostly as a glycosylphosphatidyl inositol (GPI)-anchored glycoprotein associated to lipid raft microdomains of the plasma membrane, where it forms a complex with several protein partners, i.e. secreted proteins, integral transmembrane proteins and peripheral membrane proteins including signaling proteins of the Src family kinases (SFK). Thus, the ability of PrPc to modulate cell signaling was proposed to mediate some of its biological effects.

Using the constantly renewing intestinal epithelium as a model, we demonstrated a dual localization of PrPc: i) in differentiated enterocytes, plasma membrane PrPc is addressed specifically toward sites of cell-cell contacts, and more precisely at desmosomes, whereas ii) in dividing cells, it is targeted to the nucleus. This junctional localization is also found in intestine in vivo, in epithelial cells of villi and at the top of crypts.

Desmosomes are known for their mechanoresistance properties. They have been studied mainly in skin and cardiac muscle and in pathologies of these tissues, but much less is known about desmosomes in intestine, which is highly subjected to mechanical stress. The molecular organization of these complexes is very similar to that of adherens junctions. They are composed of 2 cadherin family proteins with single transmembrane domains, desmosoglein and desmocollin, whose cytoplasmic domains bind 2 proteins of the catenin family, γ-catenin and plakophilin. The engagement of cell-cell contacts leads to the recruitment of a plakin family protein, desmoplakin, which links to intermediate filaments belonging to the

PrPc is a component of desmosomes in intestinal epithelium and is necessary for proper dynamic of cell-cell junctions in several epithelial cell types

Cell-cell junctions are multiprotein complexes. New components and partner proteins are being identified continually. Our team demonstrated the presence of PrPc in intercellular junctions of differentiated intestinal cells, in raft-like microdomains, within a protein complex including Src kinase, and components of desmosomes: desmosoglein 2, γ-catenin (also known as plakoglobin), plakophilin 2A and desmoplakin. This junctional localization is also found in intestine in vivo, in epithelial cells of villi and at the top of crypts.

Our recent results, which identified the nuclear partners of PrPc, highlight its role in signaling complexes that contribute to a coordinated regulation of proliferation and cell-cell adhesion through a nucleo-junctional interplay, thus participating to epithelium homeostasis. We will discuss how these observations in tumoral and non-tumoral intestinal epithelial cells can shed a new light on recent data that identified PrPc as a potential important player in tumor biology in a large range of tissues.
FIGURE 1. Dual localization of PrP^C in intestinal epithelial cells and associated functions. In differentiated epithelial cells of the intestinal villi, as well as in confluent Caco-2/TC7 enterocytes, PrP^C is addressed to desmosomes, where it interacts with several desmosomal proteins and with Src tyrosine kinase. PrP^C, which contributes to the organization of desmosomes (D) and also of adherens junctions (AJ) and tight junctions (TJ) (black arrows), is involved in the global intestinal barrier function. The mechanisms underlying the dialog between desmosomes and the other cell-cell junctions through PrP^C and its molecular partners remain to be determined. The Src kinase, which is a well-known regulator of cell-cell junctions, could mediate PrP^C effects, as recently shown for adherens junctions in zebrafish embryos. In proliferative cells of the intestinal crypts and in proliferative Caco-2/TC7 cells, Src is present in the nucleus (N) along with PrP^C, which interacts with plakoglobin (γ-catenin, γ-cat), with the effectors of the canonical Wnt pathway β-catenin and TCF7L2 (previously known as TCF4) and with the effector of Hippo pathway YAP. PrP^C stimulates the transcriptional activity of the β-catenin/TCF7L2 complex (green arrow), which is decreased by γ-catenin (red arrow). Our experiments of co-immunoprecipitation and proximity ligation assay have suggested multiple combinations of protein complexes in both cytoplasmic and nuclear compartments, whose detailed compositions and outcome remain to be specified. YAP/β-catenin interaction was also shown to activate transcription through factors other than TCF, which are not represented on this scheme, and it is still unknown whether and how PrP^C modulate the activity of these complexes as well.
keratin family in epithelial cells (for review see ref. 13).

Invalidation of PrPc in enterocytes resulted in a notable alteration in the junctional targeting of its desmosomal partners and of Src kinase, which were more diffusely distributed in the cytoplasm. The length of desmosomes was shorter in the intestinal epithelium of PrPc knockout mice than in wild type mice, small desmosomes being considered less mature. In addition, in both cell and mouse models of PrPc invalidation, we showed global defects in the organization of cell-cell junctions and in intestinal barrier function. Mislocalization of components of adherens junctions, e.g. E-cadherin, and of tight junctions, e.g., occludin, ZO-1 and tricellulin, accompanied that of desmosomal proteins. There was no modification of the global levels of the different proteins, suggesting that PrPc contributes to mechanisms that control the targeting and/or the turnover of proteins at intercellular junctions and that it is required for the proper assembly or the stability not only of desmosomes, but also of adherens and tight junctions.

The role of PrPc in intercellular adhesion is not restricted to intestinal epithelial cells. A similar localization at cell-cell contacts can be observed in keratinocytes (unpublished data). PrPc implication in the regulation of cell-cell adhesion, including E-cadherin-mediated adhesion, which was demonstrated in other human epithelial cell lines, is evolutionarily conserved; this was shown by loss of embryonic cell adhesion upon PrP-1 knockdown in zebrafish, this phenotype being rescued by the zebrafish paralog PrP-2 and by mouse PrP. Moreover, PrP morphant embryos displayed deficient morphogenetic cell movements leading to gastrulation arrest, indicating that PrPc participates not only to junction stability, but also to their remodeling during dynamic rearrangements. Accordingly, PrP-2 was also shown necessary for the collective migration during lateral line sensory system development in zebrafish embryo; E-cadherin and β-catenin were mislocalized upon PrP-2 decreased expression. In endothelial cells of the hemat-encephalic barrier, PrPc seems to be involved in junction remodeling upon extravasation of leucocytes and in endothelial cell migration. PrPc-deficient mammary epithelial cells fail to address properly E-cadherin at cell-cell contacts, but, interestingly, they were at the same time unable to rearrange adherens junctions and to accomplish epithelial-mesenchymal transition in response to TGF-β.

Therefore, accumulating evidences in different biological systems and organisms converge to identify PrPc as an important regulator of the dynamic assembly/disassembly of several junctional complexes involved in cell-cell adhesion.

A POOL OF PrPc IS TARGETED TO THE NUCLEUS OF PROLIFERATIVE CELLS AND IS A PARTNER OF THE WNT PATHWAY IN INTESTINAL EPITHELIAL CELLS

In proliferating intestinal epithelial cells, i.e., in the intestinal crypts in vivo or in dividing human Caco-2/TC7 enterocytes in culture, we demonstrated that a PrPc pool was present in the nucleus. Although a nuclear localization of the prion protein had been reported in few studies, in particular in a human promyelocytic leukemia cell line and in neuronal cells for both the protease-resistant PrP form in prion infected cells and the normal PrP in non-infected cells, the role of this particular pool was not elucidated. An association of nuclear PrPc with histone H3 in neurones and β cells of the endocrine pancreas suggested a possible role of PrPc in transcriptional regulation, but this hypothesis was not demonstrated definitely until our recent study in enterocytes.

Through a proteomic approach, we identified γ-catenin, a component of desmosomes in differentiated cells, as a nuclear PrPc partner in proliferating intestinal epithelial cells. γ-catenin is a protein of the catenin family displaying a dual junctional and nuclear localization, as its counterpart β-catenin. Whereas junctional γ-catenin is mainly associated with desmosomal cadherins, junctional β-catenin is exclusively localized at adherens junctions where it interacts with E-cadherin cytodomain.
β-catenin was extensively studied because it is the central effector of the canonical Wnt pathway. In the absence of Wnt stimulation, a cytoplasmic pool of β-catenin is phosphorylated by a destruction complex and addressed to the proteasome for degradation. In response to Wnt activation, the destruction complex is disrupted, and the stabilized cytoplasmic β-catenin is targeted to the nucleus where it acts as a co-activator of the transcription factors of the TCF/LEF family to regulate the expression of many target genes, which drive cell proliferation in intestinal crypts. We showed that PrPc interacts, in cytoplasm and nucleus, not only with γ-catenin but also with β-catenin and TCF7L2 (previously known as TCF4), the main member of the TCF/LEF family in intestine. Furthermore, we demonstrated that PrPc stimulates the transcriptional activity of the β-catenin /TCF7L2 complex, whereas γ-catenin, which is known to interact with TCF/LEF as well, decreases it (Fig. 1). Dysregulation of Wnt signaling was proposed to contribute to the pathogenesis of several neurodegenerative disorders and it must be noticed that Wnt/β-catenin signaling was shown impaired in the brain of mice infected with scrapie agents. This raises the question of the respective impacts of the physiological and pathogenic forms of the prion protein on this pathway.

We showed that nuclear PrPc interacts also with YAP (Yes-associated protein), which is a regulator of organ size and of progenitor cell proliferation. YAP and TAZ (transcriptional co-activator with PDZ-binding motif) are the major downstream effectors of the Hippo pathway (For review see ref. 28). YAP abundance and nuclear localization are negatively regulated by the Hippo kinase cascade, which is activated by the integration of multiple upstream signals including cell-cell contacts. The Hippo pathway is closely inter-linked with the Wnt pathway through multiple and complex mechanisms: cytoplasmic YAP and TAZ could function as inhibitors of Wnt signaling, whereas nuclear YAP and TAZ cooperate with β-catenin for the transcriptional activation of several target genes. Interaction of PrPc with YAP in the cytoplasm and the nucleus is another mechanism through which PrPc may modulate the activity of Wnt effectors and the expression of their target genes. The outcome of the multiple combinations of protein complexes involving PrPc and components of the Wnt and Hippo pathways, whose composition probably differs between cytoplasm and nucleus, remain to be deciphered, but clearly, the role of PrPc in transcriptional regulation is not restrained to its interaction with the β-catenin/TCF7L2 complex and may involve other co-regulators (Fig. 1).

PrPc interaction with junctional and nuclear partners: a role in epithelium homeostasis and cancer?

PrPc levels are increased in several cancer types including gastric and colorectal cancers; its augmented expression has been associated with adenoma-to-carcinoma progression and with high-grade tumors and poor prognosis of patients. Based on such observations, PrPc was proposed to play a role on cancer development, tumor progression and response to therapy. The mechanisms by which PrPc mediated these effects have been unraveled in only few studies, which focused exclusively on its interaction with partners on the plasma membrane. We propose that PrPc must now be considered as an actor in oncogenic processes also through its role in the dynamic of cell-cell junctions and its dual junctional and nuclear localization leading to its capability to modulate the transcriptional activity of Wnt and potentially Hippo effectors. Both pathways are modulated by cell contacts and are deregulated at high frequency in many human cancers. Proliferation of constantly renewing intestinal epithelial cells depends on the activation of the Wnt pathway. Moreover, activating Wnt pathway mutations are frequent and early events in colorectal cancer and have been described in a variety of other tumors. In agreement with a role of PrPc in the activation of the Wnt effectors, we observed an alteration...
of nuclear β-catenin localization in intestinal crypts from PrPe knockout mice and an impairment of growth and survival of intestinal organoids derived from these mice. This could explain the shortening of the villi that we described previously in PrPe knockout mice. It must be determined whether the stimulation of proliferation by PrPe, which was described in gastric cancer cells, or in colorectal cancer stem cells, is linked to an increased nuclear localization of PrPe combined with an enhanced activity of Wnt effectors.

It was shown recently that Prnp transcription increased considerably during epithelial-mesenchymal transition (EMT). EMT is a key regulator of metastasis in some cancers, during which cells change their epithelial properties to adopt a more mesenchymal and invasive phenotype (for review see ref. 35). PrPe contributes to metastatic capacity of colorectal cancer stem cells positive for the membrane glycoprotein receptor for hyaluronan CD44. Moreover, PrPe interacts with CD44 and both proteins enhance the ability of migration and invasion of breast cancer cells. Surprisingly, in this latter study, a predominant nuclear localization of PrPe in the breast tumor samples was observed, which, as emphasized by the authors, needed further investigations. In that context, it is interesting to note that CD44 is a target gene of Wnt effectors, the β-catenin/TCF complex, that we demonstrated activated by nuclear PrPe. Mehraban and colleagues showed that stable PrPe-deficient mammary epithelial cells failed to complete EMT in response to TGF-β. This was linked to a lack of polysialylation of neural cell adhesion molecule 1 (NCAM1) caused by a perturbed transcription of the polysialyltransferase ST8SIA2 gene. Interestingly, they demonstrated that PrPe regulates the transcription of the polysialyltransferase ST8SIA2 gene through a β-catenin-dependent mechanism. It thus appears that the links between PrPe and EMT could implicate not only PrPe capability to modulate the dynamics of cell-cell junctions but also a role of its nuclear pool in the regulation of Wnt target genes.

Mechanisms leading to increased levels of PrPe in tumoral cells and the impact of nucleo-junctional PrPe interplay in cancer process remain to be characterized. Comparing several intestinal cell lines, we found no correlation between global PrPe levels and Wnt pathway status. Moreover, the impact of Wnt activation on PrPe nuclear accumulation remains to be clarified. The nuclear targeting of PrPe could rely on cell-cell junction remodeling in the course of cell transformation and could involve Src kinase. Indeed, we showed that dismantling of calcium-dependent junctions in Caco-2/TC7 cells was sufficient to impair PrPe targeting at cell-cell contacts and to observe its nuclear localization (Fig. 2A). Src kinase, the junctional partner of PrPe, accumulated in the cytoplasm after junction disassembly (Fig. 2A) and colocalized with PrPe in nucleus or perinuclear compartments of proliferative epithelial intestinal cells (Fig. 2B). Although the roles of intracellular and nuclear pools of Src kinase in cancer cells are not clear yet, activated Src is known to phosphorylate β-catenin, leading to an impairment of its binding to E-cadherin and to an augmentation of its intracellular levels (for review see ref. 38). In the context of SFK-dependent junction remodeling leading to EMT, PrPe would not be targeted to the cell membrane, and we speculate that the resulting increased levels of cytoplasmic PrPe and β-catenin favor the interactions between both proteins, leading to their nuclear translocation. SFK activity (Src and Yes) has been shown recently to favor YAP nuclear translocation. It would be important to determine how, upon cancer-associated dismantling of cell-cell junction, PrPe, which interacts with YAP, could modulate its activation as well. In order to determine how the mechanisms that involve PrPe in cancer process and EMT are integrated, the analysis of the respective proportions and subcellular localizations of PrPe, Src,
β-catenin, TCF, γ-catenin, YAP and TAZ in a large-scale study of human tumors would be of great interest.

In conclusion, the mechanisms of PrP<sup>c</sup> contribution in cancer biology must be further explored. In a recent extra views report, Santos and colleagues pointed out, as good candidate for therapeutic interventions, the PrP<sup>c</sup> role as a scaffold protein organizing membrane platforms and the search for specific partners within tumor cells, extracellular matrix, and soluble factors secreted from tumor cells.<sup>12</sup> Based on our recent
findings, we propose that studies on tumors must integrate the PrPc partners located not only within membrane complexes, including cell-cell junctions, but also within the nucleus. In particular, the interaction of PrPc in nucleus of dividing cells with effectors of Wnt and Hippo pathways, which are both clearly involved in cancer, opens a new field of research on the mechanisms that link PrPc expression and subcellular localization to cancers.

**ABBREVIATIONS**

- PrPc: cellular prion protein
- ZO-1: zonula occludens-1
- NLS: nuclear localization signal
- TCF7/LEF: T cell factor/lymphoid enhancing factor
- EMT: epithelial–mesenchymal transition
- YAP: Yes-associated protein
- SFK: Src family kinases
- TAZ: transcriptional co-activator with PDZ-binding motif
- N-CAM: Neural cell adhesion molecule
- EGTA: ethylene glycol tetraacetic acid

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

No potential conflicts of interest were disclosed.

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