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Review

The intriguing links between prominin-1 (CD133), cholesterol-based membrane microdomains, remodeling of apical plasma membrane protrusions, extracellular membrane particles, and (neuro)epithelial cell differentiation

Denis Corbeil [a], Anne-Marie Marzesco [b], Michaela Wilsch-Bräuninger [b], Wieland B. Huttner [b,*]

[a] Tissue Engineering Laboratories, BIOTEC, Technische Universität Dresden, Tatzberg 47–49, 01307 Dresden, Germany
[b] Max Planck Institute of Molecular Cell Biology and Genetics, Pfotenhauerstrasse 108, 01307 Dresden, Germany

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ABSTRACT

Prominin-1 (CD133) is a cholesterol-interacting pentaspan membrane protein concentrated in plasma membrane protrusions. In epithelial cells, notably neuroepithelial stem cells, prominin-1 is found in microvilli, the primary cilium and the midbody. These three types of apical membrane protrusions are subject to remodeling during (neuro)epithelial cell differentiation. The protrusion-specific localization of prominin involves its association with a distinct cholesterol-based membrane microdomain. Moreover, the three prominin-1-containing plasma membrane protrusions are the origin of at least two major subpopulations of prominin-1-containing extracellular membrane particles. Intriguingly, the release of these particles has been implicated in (neuro)epithelial cell differentiation.

1. Introduction

During development of the mammalian central nervous system (CNS), neurons, astrocytes and oligodendrocytes arise from a common pool of neuroepithelial (NE) cells, the primary neural stem cells, and their derivative progenitor cells [1,2]. Neural stem and progenitor cell proliferation and their generation of specific, differentiated cell types is a fundamental issue, and various aspects of the underlying cell biology have been in the focus of recent investigations, including cell–cell signalling, cell polarity and cell division. NE cells undergo mitosis at the ventricular (apical) surface while keeping contact to the basal lamina [3–6]. At early stages in development, i.e. before neurogenesis, NE cells found in the neural plate and neural tube proliferate to generate more NE cells. These proliferative divisions are symmetric in that one NE mother cell gives rise to two NE daughter cells, resulting in an exponential increase in NE cell number. Upon the onset of neurogenesis, a rising proportion of NE cells and their derivative radial glial cells (collectively referred to as apical progenitors) switch to differentiating divisions which are thought to be asymmetric in that one apical progenitor generates one apical progenitor and one post-mitotic neuron or neuronally committed basal (intermediate) progenitor [1,2].

From a cell biological perspective, the switch of apical progenitors from proliferative to neurogenic divisions is associated with (i) a change in the distribution of apical domain constituents (proteins of the apical cell cortex, apical junctional complexes and apical plasma membrane) from a symmetric to an asymmetric inheritance by the daughter cells [7–9], and (ii) the release of membrane particles derived from apically protruding structures such as microvilli, primary cilium and midbody [10,11]. Furthermore, concomitant with the switch, apical progenitors reduce the size of their apical domain [7]. These findings have raised the interest in apical domain constituents, notably those of the apical plasma membrane proper, in the context of apical progenitor cell division. Here, we review the characteristics of the apical plasma membrane of apical progenitors, concentrating on one of its key constituents, prominin-1/CD133, and discuss its membrane dynamics in light of the cell biology of physiological neural stem and progenitor cells as well as cancer stem cells.

2. Apical plasma membrane of neuroepithelial cells

2.1. Apical-basal polarity

A hallmark of the pseudostratified neuroepithelium is its apical-basal polarity. As is the case for other polarized epithelial cells, a characteristic feature of NE cells is the organization of their plasma membrane into two major domains, the apical and basolateral

* Corresponding author. Fax: +49 (0) 351 210 1600.
E-mail address: huttner@mpi-cbg.de (W.B. Huttner).

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domain, which exhibit a distinct protein and lipid composition [1,5,12]. Insight into the generation and maintenance of plasma membrane polarity has come from a large number of investigations, most of which have been carried out on classical epithelia such as those found in kidney and intestine, and with cell lines derived therefrom [13,14].

Remarkably, upon transition from the neural plate to the neural tube stage, NE cells down-regulate occludin and lose functional tight junctions [15], which are known to prevent the lateral diffusion of membrane proteins between the apical and basolateral domains, but nonetheless maintain a polarized distribution of certain membrane constituents, notably prominin-1, an integral membrane protein expressed on their apical surface as described in detail below [16]. In contrast to occludin, expression of ZO-1, a peripheral membrane protein found on tight as well as adherens junctions, is up-regulated from the neural plate to the neural tube stage. Similarly, the expression of N-cadherin increases concomitant with the disappearance of occludin [15]. During the same transitional period, a down-regulation of the polarized delivery to apical plasma membrane proteins is observed [17]. This raises the question as to the mechanism that underlies the maintenance of the apical localization of certain membrane constituents such as prominin-1 upon down-regulation of tight junctions. An answer to this question appears to lie in the existence of plasma membrane subdomains.

2.2. Apical plasma membrane subdomains

A distinct feature of the apical plasma membrane of NE cells is the existence of protruding subdomains, notably microvilli, the primary cilium and the midbody (Fig. 1A). As in the case of absorptive epithelial cells such as those found in kidney proximal tubules and small intestine [18], NE cells show apical actin-based microvilli which are separated by planar domains [16]. The apical surface of NE cells also forms a primary cilium [11], a microtubule-based structure common to most eukaryotic cells that acts as a sensory organelle [19,20]. Remarkably, the abundance of apical microvilli and the length of the primary cilium decrease with the onset of neurogenesis [10,11]. In this context, it is interesting to note that two signaling pathways known to regulate the proliferation versus differentiation of progenitors have been linked to ciliary function, sonic hedgehog (shh) and wnt signaling [5,20]. In addition, a third membrane-enveloped structure protruding from the apical surface is the midbody – a thin cytoplasmic bridge connecting the nascent daughter cells that is formed at the late stage of cytokinesis as a result of cleavage furrow ingression and that contains the remnants of the central spindle and contractile ring (Fig. 1A) [21]. It is intriguing that on completion of cell division, the central cytoplasmic structure of the midbody, the so-called midbody ring, is inherited asymmetrically by one of the daughter cells [22,23].

Prominin-1 is concentrated at all these three apical protruding structures, a phenomenon observed even when NE cells have lost functional tight junctions [10,11,16]. This indicates that other fence mechanisms are operational in order to maintain the protrusion-specific localization of prominin-1 [24].

2.3. Apical plasma membrane microdomains

To gain further insight in this regard, and given that the apical plasma membrane is one key feature of epithelial cells and accordingly has been implicated in the proliferation versus differentiation of NE cells [7], we have dissected the biochemical and morphological properties of the prominin-1 in apical plasma membrane subdomains, notably microvilli and the primary cilium.

Prominin-1 is the first member of a novel evolutionarily conserved pentaspan membrane glycoprotein family [16,25,26]. Although broadly expressed in various tissues [16,27,28], several organ-specific somatic stem and cancer stem cells have been identified and isolated based on prominin-1 expression [29,30]. The physiological function of prominin-1 remains elusive.

How is prominin-1 selectively retained within apical plasma membrane protrusions of polarized epithelial cells? We have addressed this issue in two epithelial cell models, prominin-1-transfected MDCK cells [24] and the human colon-carcinoma-derived Caco-2 cells, which express prominin-1 endogenously [31], as these cell lines are easy to manipulate and, importantly, reproduce the morphological features of native epithelia expressing prominin-1 [16]. Applying new chemical tools to preserve and detect protein–lipid interactions, we have shown that the retention of prominin-1 in the microvillar membrane reflects its association with a novel cholesterol-based membrane microdomain in which prominin-1 directly interacts with plasma membrane cholesterol [32]. The latter interaction was demonstrated by photoaffinity labeling using a photoactivatable analogue of cholesterol [33].

Cholesterol-based membrane microdomains (also referred to as lipid rafts) are thought to reflect liquid-ordered domains that are more tightly packed than the surrounding phase of the membrane bilayer [34]. They are enriched in sphingolipids and sterols present in the exoplasmic membrane leaflet. Membrane cholesterol appears to be an essential structural player [35]. Such membrane microdomains have been suggested to play a role in signal transduction and a variety of membrane trafficking events (e.g. apical delivery, membrane budding and fission) [36,37]. The classical biochemical method used to determine the association of a given membrane protein with such membrane microdomains is based on its resistance to extraction with certain non-ionic detergents (e.g. Triton X-100) at 4 °C [38,39]. Proteins associated with detergent-resistant membrane complexes will float to low buoyant density fractions upon density gradient centrifugation in a cholesterol-dependent manner [40].

The novel characteristic of the apically restricted, prominin-1-containing membrane microdomains was revealed by our observation that this prominin-1 is solubilized in Triton X-100 but, remarkably, recovered as detergent-resistant membrane complexes upon extraction using another mild non-ionic detergent, Lubrol WX, in the cold [32]. Mild cholesterol depletion performed by adding methyl-β-cyclodextrin (mβCD) [41] was found to lead to the fragmentation of the Lubrol WX-resistant membrane complexes (as revealed by differential centrifugation) and to their loss of buoyancy [32].

Because the results obtained from detergent-based analyses may not necessarily reflect the native state of membrane microdomains [42], we have complemented our biochemical data by morphological investigations using light and transmission electron microscopy [24,32]. In vivo cholesterol depletion performed in the cold caused a striking redistribution of prominin-1 from an exclusively microvillar localization to a more homogeneous distribution over the entire apical plasma membrane. The effect of cholesterol depletion was reversible since the re-feeding of cells with cholesterol-loaded-mβCD restored the proper localization of prominin-1 [32].

These observations suggest that membrane cholesterol is an essential component of a distinct, prominin-1-containing membrane microdomain, which plays an important role in the retention of prominin-1 within plasma membrane protrusions [32]. This may explain why prominin-1 maintains its polarized distribution in NE cells at the neural tube stage, when tight junction function is down-regulated. The solubility of prominin-1 in Triton X-100 is not unique to this membrane protein since it was previously demonstrated for numerous microvillar-associated hydrolytic enzymes [43]. By contrast, certain apical membrane constituents such as

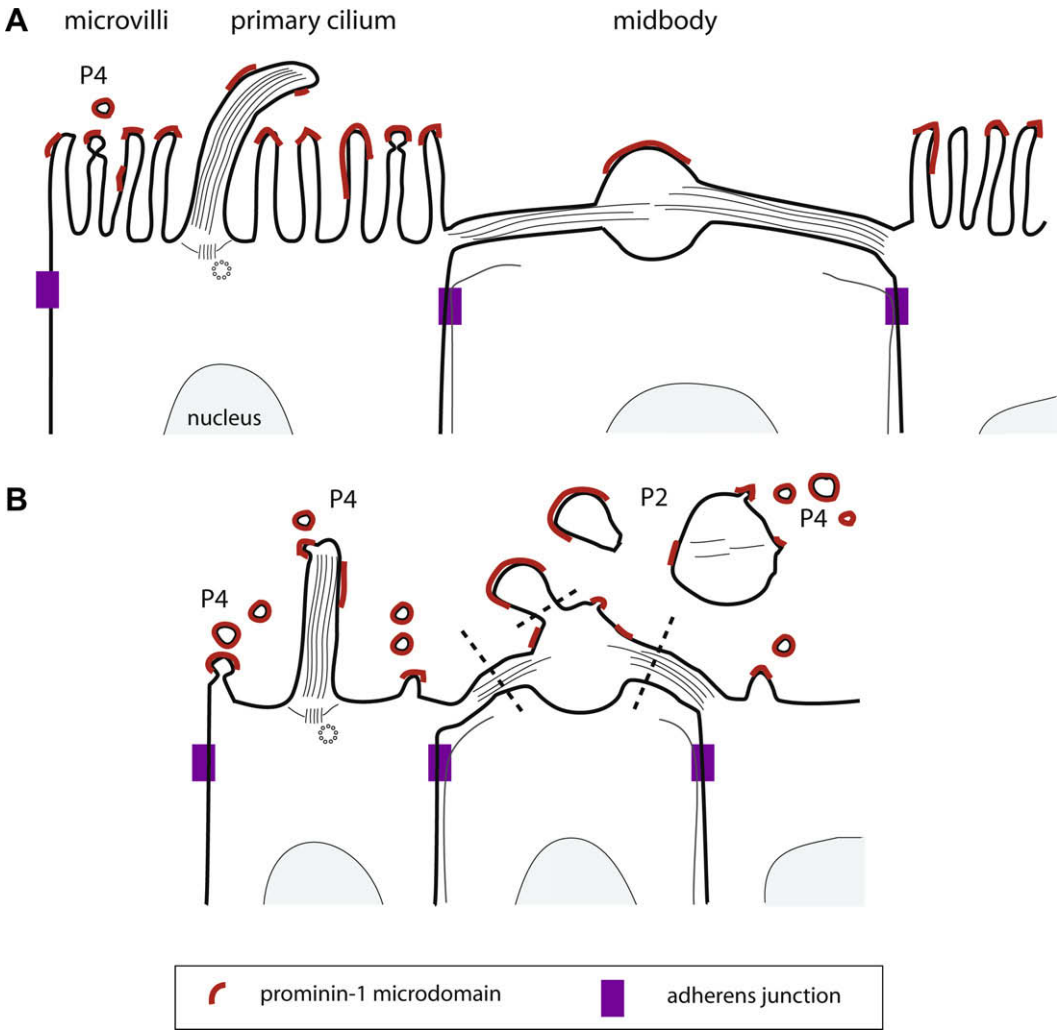

Fig. 1. Schematic representation of the current view on the apical plasma membrane of neuroepithelial cells and its remodelling during the process of cell differentiation. Apical plasma membrane is depicted before (A) and after (B) the onset of neurogenesis. Three types of membrane protrusions (microvilli, primary cilium, midbody) and possible pathways of formation of prominin-1-containing P2 and P4 membrane particles are indicated. Dashed lines in (B) indicate the site of membrane fission. Red indicates prominin-1-containing membrane microdomains. Purple indicates adherens junctions.

placental alkaline phosphatase, a glycosylphosphatidylinositol (GPI)-anchored protein [44], are insoluble in Triton X-100 [32], indicating that certain apical membrane microdomains are preserved in this detergent. In MDCK cells expressing both prominin-1 and placental alkaline phosphatase, their morphological segregation from each other was observed, with the latter protein being excluded from the prominin-1-containing microvillar subdomains and concentrated in the planar portions of plasma membrane [32]. Thus, the differential biochemical behaviour of these membrane proteins has its morphological counterpart in their segregation within the apical plasma membrane.

How many subtypes of membrane microdomains co-exist within the apical plasma membrane? Our hypothesis that the plasma membrane of protrusions contains a specific subtype of cholesterol-based membrane microdomains distinct from those in its planar portions has recently been substantiated by analyzing the co-distribution of prominin-1 with two membrane microdomain-associated gangliosides, GM_1 and GM_3, [43,45,46]. Specifically, GM_1 (as probed with cholera-toxin B subunit), but not GM_3, co-localized with prominin-1 on microvilli [47]. The exclusion of GM_3 from the prominin-1-containing microvillar subdomain suggests its localization in the planar areas of the plasma membrane, as described above for placental alkaline phosphatase [47]. In agreement with this notion, an earlier report demonstrated by immunolabelling electron microscopy that GM_3 is found in the planar regions of the MDCK plasma membrane [48]. Strikingly, and in contrast to the microvillar membrane, the analysis of the primary cilium indicated that both, GM_1 and GM_3, are present in the latter protrusion [47]. Thus, GM_3 appears to be enriched in the primary cilium, but not in microvilli, whereas both membrane protrusions contain prominin-1 [11,49]. The co-localization of prominin-1 and GM_1 in microvilli and the primary cilium suggests that they may physically interact. The presence in the first extracellular domain of prominin-1 of a potential ganglioside-binding motif is consistent with this hypothesis [50].

Taken together, these studies indicate that two plasma membrane protrusions with distinct cytoskeletal bases (actin for microvilli and tubulin for the primary cilium) appear to be composed of distinct subtypes of membrane microdomains. Physiologically, these observations suggest a critical function of the assemblies containing prominin-1 and certain membrane lipids, notably cholesterol and certain gangliosides, in maintaining a membrane-based polarity of NE cells in the absence of functional tight junctions.

3. NE cell division and the symmetric versus asymmetric distribution of apical membrane constituents

Although a possible direct contribution of prominin-1 to the proliferation versus differentiation of stem cells remains to be investigated, it has been shown that NE cells can symmetrically or asymmetrically distribute specific apical constituents upon cell division [7]. Specifically, the switch of NE cells from proliferative to neurogenic divisions was found to be associated with a change in the distribution of apical membrane from a symmetric to an asymmetric inheritance by the daughter cells, rather than a rotation of the cleavage plane from parallel to perpendicular relative to their apical-basal axis [7]. The correlation between the switch of NE cells to neurogenic divisions and the unequal distribution of the apical membrane to only one daughter cell is amazing, particularly if one considers the minute proportion that the apical membrane constitutes relative to the entire plasma membrane, which amounts to only 1–2% [7]. It was considered improbable that this correlation is accidental, that is, that an equal versus unequal distribution of the apical membrane makes no difference for daughter cell fate. Instead, in agreement with the distinct nature of the apical versus basolateral membrane of polarized epithelial cells in terms of constituents (protein and lipid) [51], these observation raise the possibility that certain membrane constituents with a critical role for cell fate are concentrated within the apical domain of NE cells. Given the specific association of prominin-1 with a distinct membrane microdomain [32], we have therefore hypothesized the existence of "*stem cell-characteristic membrane microdomains*" containing molecular determinants that maintain stem cell properties [10]. Thus, a comprehensive characterization of prominin-1-containing membrane microdomains, including their proteome and lipidome, may reveal novel facets of stem cell biology.

4. Release of membrane particles containing prominin-1

Having noticed that NE cells reduce the size of their apical plasma membrane concomitant with their switch from proliferative to neurogenic divisions [7], our groups made an unexpected observation as to the possible mechanism underlying this reduction. Specifically, we found that in the developing embryonic mouse brain, the fluid in the lumen of the neural tube contains membrane particles carrying certain apical constituents including prominin-1, with the latter remaining associated with membrane microdomains [10,52]. Little is known about the molecular mechanism underlying the release of these membrane particles. However, obtaining insight in this regard is not only of importance for basic cell biology, but also for developmental biology and medicine, as several lines of evidence suggest a link between the release of prominin-1-containing membrane particles and cell differentiation. Specifically, the release of prominin-1-containing membrane particles may contribute to cell differentiation by reducing and/or modifying the composition of stem and progenitor cell-characteristic membrane microdomains within the apical plasma membrane [10,11]. In addition, it cannot be excluded that these vesicles may play a role in intercellular communication as well [30].

4.1. Two major classes of membrane particles containing prominin-1

Two major size classes of prominin-1-containing membrane particles were observed in the ventricular fluid, relative large (0.5–1 μm) electron-dense particles with a ring-like appearance, referred to as P2 particles, and small (50–80 nm) electron-translucent vesicles, referred to as P4 particles [10]. The latter membrane vesicles were found to be distinct from the similar-size exosomes [53]. P2 and P4 particles appear in the ventricular fluid at the very onset and during the early phase of neurogenesis, respectively [10]. P4 particles have a widespread distribution, being found not only in the embryonic [10] and adult [54] cerebrospinal fluid, but also in various external body fluids [10,49]. Until now, studies on the release of P2 particles have been confined to NE cells [10,11]. In the Caco-2 cell culture model, the P4-type vesicles were found to be released into the conditioned medium – a phenomenon that occurred, interestingly, upon cell differentiation [10].

P4 vesicles appear to originate from microvilli, the primary cilium and the midbody of NE cells, as suggested by the presence of membrane buds containing prominin-1 (Fig. 1B) [10,11]. P2 particles arise from the midbody and, accordingly, contain tubulin and anillin (Fig. 1B) [11].

The release of the prominin-1-containing membrane particles is likely to contribute to the morphological remodelling of the apical plasma membrane of NE cells observed during the onset of neurogenesis, i.e. the reduction in the number of the apical microvilli, the decrease in the length of the primary cilium, and the appearance of large pleiomorphic protuberances that turn out to be cross-sectioned midbodies (Fig. 1B) [10,11]. A notable exception with regard to the lack of apical microvilli after the onset of neurogenesis is the floorplate [10]. It may be more than a coincidence that the floorplate acts as signaling center [55,56]. Finally, the release of these membrane particles may well contribute to the reduction in the apical surface of NE cells that occurs concomitant with their switch from proliferative to neurogenic divisions [7].

4.2. Membrane microdomains and the release of extracellular membrane vesicles

Because prominin-1 is endogenously expressed by Caco-2 cells [31], we used these cells as a model to study the mechanism underlying the release of the small, P4 type prominin-1-containing vesicles from their presumptive donor membrane, the microvilli, which are highly abundant in these cells ([52]). Given the cholesterol-binding capacity of prominin-1 and its association with a distinct cholesterol-based membrane microdomain, it was of obvious interest to explore the possibility that the release of P4 vesicles from microvilli is affected by the plasma membrane cholesterol level. Indeed, cholesterol reduction (performed at physiological temperature using lovastatin and mβCD), which was previously shown to reduce the size of the Lubrol WX-resistant membrane complexes containing prominin-1 [32], was found to significantly enhance P4 vesicle release from differentiated Caco-2 cells [52].

At the level of the donor membrane, the morphological correlate of this increased vesicle release was a transition in the structure of the microvilli from a tubular shape to a pearling state, with multiple membrane constrictions all along their length [52]. The latter were found at an equal distance from one another (≈50–100 nm) that matched the size of the resulting P4 vesicles. When a microvillus showed only a single membrane constriction, it was typically found near its tip, indicating that this was the site where pearling was initiated [52]. These data suggest that changes in membrane microdomain organization may be (part of) the mechanism underlying P4 vesicle release. In agreement with this model, the biochemical properties of prominin-1 within the P4 vesicles were found to be identical to those in microvilli, i.e. exhibiting (i) the same differential solubility/insolubility in Triton X-100 versus Lubrol WX and (ii) a specific interaction with membrane cholesterol [52].

5. Perspectives

Our observations on the cholesterol-binding membrane protein prominin-1 and the membrane microdomains it is associated with

suggest significant roles of these molecular units in the organization of apical plasma membrane protrusions of epithelial cells and, in particular, NE stem cells. These results set the stage for a more detailed dissection of the molecular biology of prominin-1/membrane lipid assemblies. Moreover, there are several open questions, to be addressed in the future, that are related to the prominin-1-containing membrane particles. What is their fate (are they subject to endocytosis)? What is their protein and lipid composition? And, more importantly, what is their function? Our hypothesis that the release of prominin-1-containing membrane particles is somehow linked to cell differentiation may have significant biomedical implications, e.g. with regard to human disease linked to epithelial cell de-differentiation such as cancer, and with regard to the control of neural stem cell proliferation versus differentiation, the study of which led to their discovery.

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