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Focus on Molecules: Prominin-1 (CD133)

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1. Structure

Prominin-1 (alias CD133, PROML1; NCBI accession number: NM_006017, human; NM_008935, mouse; NM_021751, rat) is a membrane glycoprotein specifically associated with plasma membrane protrusions. It displays a unique membrane topology with five membrane-spanning domains and two large N-glycosylated extracellular loops (over 250 residues each). After the cleavage of the signal peptide, the N-terminal domain is exposed to the extracellular space whereas the C-terminal domain resides in the cytoplasm (Fig. 1A) (Corbeil et al., 2001). Prominin-1 has been found in any metazoan species analyzed. Relatives have been found in other vertebrate classes such as birds and fish and in various invertebrates including insects and worms. Although a low percentage of amino acid identity is observed among vertebrate and invertebrate prominin-1, multiple sequence analysis revealed a conserved cysteine-rich domain located in the transition of the first transmembrane segment and the first cytoplasmic loop and leucine zipper-like motifs in the extracellular loops. The physiological relevance of these domains remains to be defined.

The *PROMININ-1* gene is located on chromosome 4p15.32 in human (NCBI gene 8842), 5B3 in mouse (NCBI gene 19126) and 14q21 in rat (NCBI gene 60357). The genomic organization is strikingly similar in all three species. The *PROMININ-1* gene is composed of at least of 37 exons that span more than 150 kb, and is under the control of five alternative promoters (Fargeas et al., 2006). To date, eight prominin-1 splice variants affecting the open reading frame have been identified, and several of them exhibit distinct C-terminal domains. A typical prominin-1 molecule comprises ≈850 amino acid residues with an apparent molecular mass of ≈115–120 kDa including glycosylation.

2. Function

In spite of an ever growing interest in prominin-1 as it defines a broad population of somatic stem and progenitor cells including those derived from the nervous and hematopoietic systems and is expressed in various developing epithelia and differentiated cells (Corbeil et al., 2001; Fargeas et al., 2006), its precise physiological function is still unknown. Yet, it is on the visual system that the loss of its function seems to have the most conspicuous effect as it results in retinal degeneration. In this respect, the main characteristics of prominin-1 can be recapitulated as follows. First, prominin-1 exhibits a profound preference for membrane curvature, which is illustrated by its concentration in various types of plasma membrane protrusions. Second, prominin-1 is associated with membrane particles (prominosomes) that are found in various body fluids including saliva and lacrimal fluid. Third, prominin-1 is associated with a cholesterol-based membrane microdomain in which prominin-1 interacts directly and specifically with plasma membrane cholesterol (Corbeil et al., 2001). No other prominin-1-interacting partner or natural ligand have been identified so far.

The original cloning of prominin-1 cDNAs included two human retinoblastoma cell lines (WERI-Rb-1 and Y79) as source. It is expressed in vivo in the retina throughout life. In developing mouse retina, prominin-1 is found in the outer cell layer, corresponding to the prospective photoreceptors (Maw et al., 2000), which is in line with its expression in various progenitors. Similar observations have recently been made in chick (J.J. and D.C., unpublished data) and lower vertebrates such as the urodele amphibian axolotl (*Ambystoma mexicanum*) (Fig. 1B), suggesting that the role of prominin-1 in retinal development may be conserved throughout the evolution. In postnatal retina, prominin-1 is enriched in the few membrane evaginations at the base of the rod outer segment (Fig. 1C) (Maw et al., 2000), which are closest to the inner segment and represent the early stages in disk biogenesis, in mice and humans (Maw et al., 2000; M.F. and D.C., unpublished data) as well as in transgenic frog (*Xenopus laevis*) (E-Abstract 2867 by Han et al. (2003); http://abstracts.iovs.org). Prominin-1 (human) can also be detected in cones, but in contrast to the rods, it appears to be distributed throughout the entire outer segment (M.F. and D.C., unpublished data).

Is this specific sub-cellular localization of prominin-1 in photoreceptors related to disk formation in which complex changes in

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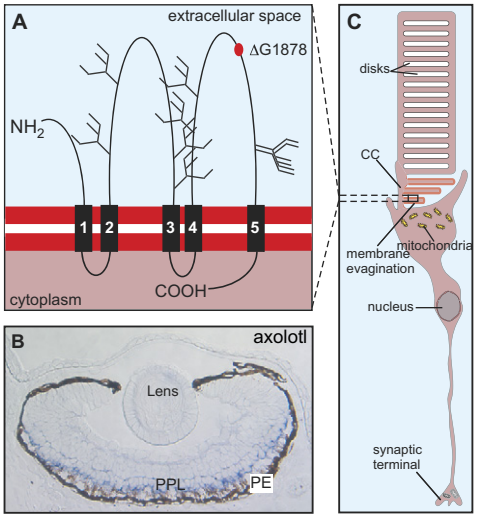

Fig. 1. Expression of prominin-1 in rod photoreceptor cells. (A) Topological model of human prominin-1. The five transmembrane segments (1–5) passing through a cholesterol-enriched plasma membrane (red) are represented by black rectangles. Forks indicate potential N-glycosylation sites. A frameshift mutation (solid red circle) due to deletion of guanine 1878 causes a recessive form of retinal degeneration. (B) Expression of prominin-like 1 transcripts (dark blue) in the prospective photoreceptor layer (PPL) of axolotl (1.5-cm long juvenile) revealed by in situ hybridization. PE, pigmented epithelial cells. (C) Schematic representation of a rod photoreceptor cell. Plasma membrane evaginations at the base of the outer segment appear in red. CC, connecting cilium.

membrane curvature (both negative and positive) are observed? Nascent disks develop from the connecting cilium as flattened plasma membrane evaginations enriched in cholesterol. Further plasma membrane outgrowths between the rims of two adjacent evaginations lead to their merging, and finally, their sealing allows the release of the newly disk membrane into the rod outer segment cytoplasm. In cones, the disks retain the topology of lamellar evaginations in continuity with the plasmalemma. These orchestrated processes occur during the entire life of the photoreceptor cell. Various not mutually exclusive scenarios that involve prominin-1 in these processes, particularly those common to rods and cones, can be envisioned. As prominin-1 is associated with a membrane microdomain, it may provide the newly synthesized plasma membrane protrusions with the adequate set of proteins and/or lipids (e.g. cholesterol) to create the proper membrane curvature for which prominin-1 has its own affinity. Prominin-1 alone however cannot be viewed as the unique driving-force underlying the biogenesis of plasma membrane protrusions since its over-expression in heterologous systems does not appear to result in an increase in plasmalemma protrusions. On the other hand, prominin-1 may also be involved in the alignment of two adjacent newly synthesized disk precursors, an essential step in their biogenesis. A trans-dimerization of prominin-1 molecules mediated by their large extracellular loops may occur. The presence of leucine zipper-like motifs in these domains is consistent with such a scaffold role.

The importance of prominin-1 in the maintenance of photoreceptors is demonstrated by human disease.

3. Disease involvement

The *PROMININ-1* gene is the site of a single-nucleotide deletion (Fig. 1A, ΔG1878) that causes an autosomal recessive retinal degeneration (OMIN 604365; Maw et al., 2000). Clinically, the affected individuals, who originate from a consanguineous Indian pedigree, have reported night blindness, loss of peripheral vision from childhood with progression to profound visual impairment, and extinguished electroretinograms by their third decade. The alteration results in a frameshift that causes a premature termination of translation at codon 627. Mouse prominin-1 showing a similar truncation does not reach the cell surface but is degraded in the endoplasmic reticulum (Maw et al., 2000). Other mutations in the *PROMININ-1* gene, which generate for instance autosomal dominant macular dystrophies, have been reported (Michaelides et al., 2003). (The dominant nature of these mutations supports the hypothesis that prominin-1 molecules undergo a dimerization process.) Finally, it is important to note that the role of prominin-1 for photoreceptor maintenance is substantiated by recent data from a murine model, where prominin-1 deficiency leads to progressive retinal degeneration (E-Abstract B421 by Oh et al. (2005); http://abstracts.iovs.org). Overall, these observations support strongly the hypothesis that prominin-1 may provide a new scaffolding mechanism in disk morphogenesis.

4. Future studies

The significance of prominin-1 in the visual system is now emerging. From basic research to clinical application several directions can be envisioned. As a first step, it will be essential to obtain a structural model of the extracellular loops of prominin-1. Such information, together with further biochemical analyses, may provide clues regarding its potential dimerization, which may be relevant for disk morphogenesis. The identification of the prominin-1 splice variant(s) specifically expressed in mature photoreceptors and their progenitors will also be useful, particularly in the context of the identification of potential cytoplasmic interacting proteins. On a more general note, the morphological and biochemical characterization of prominin-1 in various animal models including invertebrates may help to understand its precise role in the biogenesis of photoreceptive membranes. Clinically, it will be important to determine if prominin-1 as a stem and progenitor marker can be used to identify stem cells in the eye, such as those derived from the limbus. Likewise, prominin-1 as a marker of endothelial progenitors might be considered as a molecular target in retinal neovascularization. Indeed, there is suggestive evidence for its expression in ocular hemangioblastomas associated with von Hipple-Lindau disease. Finally, PROMININ-1 may also be regarded as a candidate gene in vector-mediated gene transfer/replacement for retinal disease.

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