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Letter to the Editor

AC133 Antigen, CD133, Prominin-1, Prominin-2, Etc.: Prominin Family Gene Products in Need of a Rational Nomenclature

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The pentaspan membrane glycoprotein prominin was first characterized in 1997 in two independent studies [1, 2]. The interest in this molecule has grown exponentially, since it appears to be an important cell surface marker [3, 4] widely used to identify and isolate stem cells from various sources, including the hematopoietic and central nervous systems [5, 6]. Lately, several sequences related to prominin, including splice variants, have been reported, with sometimes confusing, if not whimsical, designations (Table 1). We therefore wish to contribute to the clarification of this issue by proposing a revised and simplified nomenclature for the members of the growing prominin family, including splice variants.

PROMININ/CD133

Prominin was originally identified in mouse neuroepithelial stem cells [1]. Its exact function being unknown, this glycoprotein was named prominin because of its notable subcellular localization in plasma membrane protrusions (from the Latin word *prominere*, to be prominent). In humans, this protein was originally identified as an antigenic marker expressed on hematopoietic stem and progenitor cells and referred to as AC133 antigen [2, 5]. Although this antigen displayed an identical membrane topology to mouse prominin (Fig. 1) [1, 2], there was uncertainty as to their relationship [7, 8] because of, among other reasons, the low level of amino acid identity and the unfaithful detection in certain tissues of the human gene products by the AC133 antibody (Miltenyi Biotech; Gladbach, Germany; http//www. miltenyibiotech.com), which binds to a glycosylation-dependent epitope [2]. Once it was demonstrated that both mouse prominin and the human AC133 antigen show similar cellular distribution and subcellular localization [9], it was proposed that the AC133 antigen be referred to as "prominin (mouse)-like 1" (PROML1) [9] until the completion of the sequencing of the human genome. It is now clear that the human genome does not contain any open reading frame more closely related to mouse prominin than PROML1. Hence in the meantime, human prominin was also assigned the designation "CD133" [10].

PROMININ-2

Recently, a second membrane protein structurally related to prominin and encoded by a distinct gene has been characterized in humans and rodents [4, 11, 12]. In the absence of information regarding its cellular localization, this prominin paralogue had been originally referred to as "prominin-related protein" (prom-rp) based on its structural similarity to the prominin [4] (Table 1). Immunocytochemical studies

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Table 1. Nomenclature for mammalian prominins

Orthologous group	Species (chromosomal location)	Splice variant (alternative name)	Former names (GenBank accession no.)
prominin-1	human (4p16.2-p12)	prominin-1.s1 (CD133.s1)	AC133-2 [13] (AF507034)
		prominin-1.s2 (CD133.s2)	AC133 antigen [2] (AF027208); PROML1 [9]; AC133-1 [13]
	mouse (5B3)	prominin-1.s1	prominin [1] (AF026269); prominin-2 [13]
		prominin-1.s2	mouse AC133 [8] (AF039663); prominin B1 [4]; prominin-1 [13]
		prominin-1.s3	prominin T1 [4] (AF305215)
		prominin-1.s4	prominin T2 [4] (AY223521)
		prominin-1.s5	prominin T3 [4] (AY223522)
		prominin-1.s6	prominin T4 (AY099088)
		prominin-1.s7	unnamed protein (AK029921)
		prominin-1.s8	unnamed protein (BC028286)
	rat (14q11)	prominin-1.s1	fudenine [14]* (AF263368) prominin [15] (AF386758)
prominin-2	human (2q11.1)	prominin-2.s1	prominin-related protein [4] (AF245303)
	mouse (2F1)	prominin-2.s1	prominin-related protein [4] (AF269062)
		prominin-2.s2	similar to prominin-related protein (BC039212)
	rat (3q35)	prominin-2.s1	prominin-like protein 2 (PROML2) [12]†, (AF486828); (AF508942) [11]

*Reported as a shorter form of prominin-1; this is due to several errors in the nucleotide sequence, one introducing a frameshift. In vivo evidence for the existence of this short form is lacking.

†Reported as a form of prominin-2 that contains an alternative C-terminus; this is due to an error in the nucleotide sequence that introduces a frameshift. In vivo evidence for the existence of prominin-2 with an alternative C-terminus is lacking.

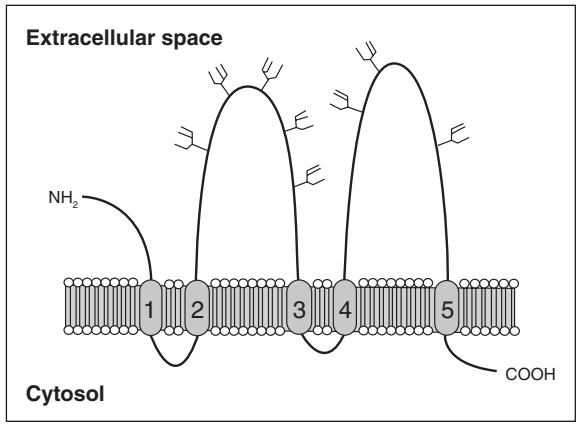

Figure 1. Membrane topology of mouse prominin-1. *After the cleavage of the signal peptide, prominin-1 is predicted to consist of an extracellular N-terminal domain, five transmembrane segments (1-5) separating two small cytoplasmic loops and two large glycosylated extracellular loops containing more than 250 amino acid residues, and a cytoplasmic C-terminal domain. Potential N-glycosylation sites are indicated by forks.*

have shown since that prom-rp does associate with plasma membrane protusions and therefore constitutes a second prominin molecule [11]. Moreover, phylogenetic analyses have clearly established that human and rodent prominins constitute a first orthologous group of genes (prominin-1), while the recently characterized paralogues constitute a second orthologous group (prominin-2) [11]. The exon-intron organization is very similar between prominin-1 and prominin-2, and is identical across species within each orthologous group [11].

A Unifying Nomenclature

In view of the above developments in the field, and given the existence of yet other designations for certain prominins (Table 1), we wish to suggest a nomenclature for prominin family gene products, including splice variants, that is simple and consistent.

First, we propose to refer to these molecules according to the orthologous group of genes from which they are produced, i.e., prominin-1 or prominin-2 (Table 1). It is conceivable that additional prominin genes will be found, as defined by the presence of features characteristic of the prominins such as A) five transmembrane domains; B) two large loops (>200 residues), and C) a specific localization in high-curvature membrane subdomains. In this case, these gene products should be referred to as prominin-3, prominin-4, and so on. CD133 is an alternative name for prominin-1, whereas the term AC133 antigen should only be used to refer to the human prominin-1/CD133 form bearing the glycosylation-dependent

AC133 epitope [2, 4] (see below). All other names (Table 1) should be abandoned.

Second, the principal name prominin-1 or prominin-2 should be followed, whenever relevant, by a suffix (s) indicating the splice variant, numbered according to the chronology of publication (including database submissions in which the sequence is designated as a distinct splice variant) and irrespective of the species, e.g., prominin-1.s1 (Table 1).

Third, with regard to glycosylation, in the case of human prominin-1 evidence exists that cells in certain states of differentiation [9] and certain tissues such as kidney (*Mareike Florek* and *Denis Corbeil*, unpublished observations) express a polypeptide that does not bear the glycosylation-dependent [2] AC133 epitope. In anticipation that this will not only reflect alternative splicing but also differential glycosylation of a given splice variant, we propose to use the suffix (g) followed by a number that defines the glycosylation in the chronology of characterization, e.g., prominin-1.g1 for the forms bearing the AC133 epitope and prominin-1.g2 for those lacking it.

Fourth, whenever the orthologous versus paralogous relationship of a given prominin-related sequence cannot (yet) be established, as is presently the case for the nonmammalian vertebrates and invertebrates [11], for the time being, it should be referred to as prominin-like and numbered chronologically.

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