Seminars in Cell & Developmental Biology 69 (2017) 102–110

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Seven pass Cadherins CELSR1-3

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ARTICLE INFO

Article history:
Received 18 April 2017
Received in revised form 12 July 2017
Accepted 13 July 2017
Available online 15 July 2017

Keywords:
Tissue polarity
Axon guidance
Neuronal migration
Ciliogenesis
Neural tube defects
Brain wiring

ABSTRACT

Cadherin EGF LAG seven-pass G-type receptors 1, 2 and 3 (CELSR1-3) form a family of three atypical cadherins with multiple functions in epithelia and in the nervous system. During the past decade, evidence has accumulated for a key role of CELSR1 in epithelial planar cell polarity (PCP), and for CELSR2 and CELSR3 in ciliogenesis and neural development, especially neuron migration and axon guidance in the central, peripheral and enteric nervous systems. Phenotypes in mutant mice indicate that CELSR proteins work in concert with FZD3 and FZD6, but several questions remain. Apart from PCP signaling pathways implicating CELSR1 that begin to be unraveled, little is known about other signals generated by CELSR2 and CELSR3. A crucial question concerns the putative ligands that trigger signaling, in particular what is the role of WNT factors. Another critical issue is the identification of novel intracellular pathways and effectors that relay and transmit signals in receptive cells? Answers to those questions should further our understanding of the role of those important molecules not only in development but also in regeneration and disease.

Contents

1. Introduction

Among the large cadherin superfamily, vertebrate CELSR1-3 proteins ("cadherin, EGF LAG seven-pass G-type receptor 1, 2 and 3") and their orthologs Flamingo (Fmi)/Starry night (Stan) in *Drosophila*, and FMI-1 in *C. elegans*, form a small group character-

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http://dx.doi.org/10.1016/j.semcdb.2017.07.014
1084-9521/

ized by the presence of seven transmembrane segments, whereas classic cadherins are type I membrane proteins. This specific feature is at the origin of the recent terminology ADGRC1-3 for "Adhesion G protein-coupled receptors, subfamily C" [1]. Mammalian *CELSR1-3* genes have similar genomic organizations, with 35 (*CELSR1* & *CELSR3*) or 34 exons (*CELSR2*). There is 3′ alternative exon splicing in *CELSR2* [2] and developmentally regulated neuronal inclusion of a 15nt micro-exon 16b in the mouse *CELSR3* (unpublished).

CELSR proteins have a large ectodomain (~2700 amino acids) composed of nine N-terminal cadherin repeats (typical cadherins have five repeats), several epidermal growth factor (EGF)-like domains, two laminin G-type repeats, one hormone receptor (HRM) motif, and a G-protein-coupled receptor (GPCR) proteolytic site (GPS) embedded in a GAIN (GPCR Autoproteolysis INducing) domain [3]. This is followed by seven transmembrane segments and a cytoplasmic tail that varies in size from 300 to 600 residues which, in contrast to the ectodomain, is poorly conserved between the three members. Cadherin, EGF-like and laminin repeats presumably confer adhesive properties and facilitate cell–cell communication, and the GAIN and laminin domains might bind unidentified ligands. Contrary to what the term ADGRC conveys, no coupling with G-proteins has been demonstrated thus far. Whether autoproteolytic cleavage at the GPS occurs in CELSR1-3 proteins also remains unclear. Antibodies to CELSR1 allowed detection of full length (400 kD) and cleaved (85 kD) forms generated by as yet unidentified proteolysis events not involving the GPS [4].

CELSR1 and its invertebrate orthologs regulate epithelial planar cell polarity (PCP) in several organs and species, and is thus a "core PCP" gene/protein [5–8]. In contrast, in most cases, CELSR2-3 interact closely with FRIZZLED (FZD), especially FZD3, but not with VANGL and other PCP members, and therefore do not qualify as bona fide PCP genes.

2. Expression of CELSR1-3

In the nervous system, *CELSR1-3* expression is regulated spatially and temporally, in complementary patterns [9–11]. *CELSR1* mRNA is heavily expressed in zones of neural stem cell (NSC) proliferation and abates postnatally in parallel to decreasing numbers of NSC. *CELSR3* mRNA is absent from NSC, but expressed at low levels in intermediate progenitors (IP) and very highly in neurons. It is sharply downregulated at the end of neuron maturation and persists only in the adult cerebellar granular layer, the hilus of the dentate gyrus and the rostral migratory stream (RMS). *CELSR2* mRNA is found in NSC, IP and postmitotic cells and remains stable in the adult. This hints at roles of *CELSR1* in NSC, of *CELSR3* in neuronal maturation, and of *CELSR2* in development and maintenance of the nervous system. *CELSR1-3* mRNAs are also variably expressed in non-neural epithelia, such as the skin [12,13], lungs [14], kidney [15], endothelial cells [16], gastrointestinal [17] and reproductive systems [18].

3. Roles of CELSR1-3

3.1. CELSR1 and epithelial PCP

CELSR1 mutant mice have a complex phenotype, with looping tail, defective neural tube closure (craniorachischisis), head shaking behavior, abnormal body hair whorls. Mutant inner ear cells have defective organization of stereocilia bundles. Normally, the apical surface of receptor cells is decorated with a "V" of stereocilia centered on a kinocilium, pointing to the external aspect of the cochlear canal. This orientation is a classical hallmark of PCP and parallels the polarized distribution of PCP proteins such as FZD3, FZD6, VANGL2, and PRICKLE2 [19–21]. PCP proteins localize asymmetrically to one edge of the apical cell cortex, presumably by selective targeting and protein stabilization or degradation, and this is thought to be crucial for vectorial PCP signaling [22].

Remarkably, PCP phenotypes similar to those in *CELSR1* mutants are found in mice with mutations in other PCP genes. The inner ear phenotype was reported in mice with mutated *VANGL2* [19,23], and *FZD3* and *FZD6* [20]. Neural tube closure defects were observed in *VANGL2*, double Disheveled *DVL1* and *2*, and *FZD3* and *−6* [20,24,25]. Skin hair patterning defects were described in *FZD6* and *VANGL2* mutants [12,26,27]. This provides strong evidence that CELSR1 is involved in classical epithelial PCP, together with FZD3 and 6, DVL1 and 2, and VANGL2 (Fig. 1).

3.2. CELSR1 and ectoderm patterning

Inactivation of CELSR1 in embryonic ectoderm generates striking skin hair patterning defects [13,27], and a similar phenotype results from inactivation of FZD6 [28]. Prior to hair growth, CELSR1 becomes asymmetrically localized along the anterior/posterior (A/P) axis in basal epidermal cells, and this is essential for A/P orientation of skin hairs. In *CELSR1* mutant embryos, the membrane recruitment of FZD6 and the asymmetric localization of VANGL2 along the A/P axis are compromised. Thus, CELSR1 plays a critical role for PCP establishment in the developing skin and hair follicles. Like that of skin hairs, the orientation of ectodermal lingual papillae is under the control of PCP genes VANGL1, VANGL2, and CELSR1 [29].

3.3. CELSR1 in the reproductive system

Homozygous male and female *CELSR1* mutant mice are sterile. In males, sterility is due to anatomical defects and obstructions of the rete testis, which blocks sperm entry in the epididymus (Fig. 2A–E). Similar defects result from inactivation of FZD3 and FZD6, further indicating that a PCP-like mechanism is involved. Females have anomalies of the oviduct with abnormal cilia orientation and beats [18,30], as well as spectacular cystic dilatations of the oviduct or uterus (Fig. 2F). Mutant females also have defective oocyte maturation (Fig. 2G, H). CELSR1 is not detected at the oocyte surface but is highly expressed at junction between granulosa cells, suggesting that the oocyte maturation defect is non cell autonomous.

3.4. CELSR1 and neural tube closure

The implication of PCP in convergent extension and neural tube closure was initially demonstrated in *Xenopus* and zebrafish [31–35]. In mice, inactivation of *VANGL2*, *DVL1&2*, *CELSR1, FZD3* or *FZD3&6* leads to craniorachischisis, the most severe neural tube closure defect [20,22,24,25,36–40]. In humans, craniorachischisis is associated with mutations in *VANGL2* and *CELSR1* [41–43], and myelomeningocele with mutations in *VANGL1*, *VANGL2*, *FZD6*, *PRICKLE1* and *CELSR1* [41–46]. Neural tube closure defects are attributed to defective cell intercalation at the midline, leading to broadening of the floor plate that prevents the dorsal fusion of neural folds. In the bending neural plate, CELSR1 is concentrated in adherens junctions oriented toward the midline and this may explain its role during neural tube closure [47]. In line with this, mutations associated with human craniorachischisis impair the trafficking of CELSR1, reducing its membrane localization *in vitro* [43]. Interestingly, craniorachischisis is also found in humans and mice with mutations in gene SEC24b, which encodes a component of the COPII complex implicated in trafficking of the PCP gene VANGL2 [48–50].