Differentiation 83 (2012) S86–S90

Contents lists available at SciVerse ScienceDirect

Differentiation

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

Planar polarity of ependymal cilia

Norihito Kishimoto [a,b], Kazunobu Sawamoto [a,*]

[a] Department of Developmental and Regenerative Biology, Nagoya City University, Graduate School of Medical Sciences, Nagoya 467-8601, Japan
[b] Center for Integrated Medical Research, Keio University, Tokyo 160-8582, Japan

ARTICLE INFO

Available online 17 November 2011

Keywords:
Planar cell polarity
Ependymal cilia
Brain
Cerebrospinal fluid

ABSTRACT

Ependymal cells, epithelial cells that line the cerebral ventricles of the adult brain in various animals, extend multiple motile cilia from their apical surface into the ventricles. These cilia move rapidly, beating in a direction determined by the ependymal planar cell polarity (PCP). Ciliary dysfunction interferes with cerebrospinal fluid circulation and alters neuronal migration. In this review, we summarize recent studies on the cellular and molecular mechanisms underlying two distinct types of ependymal PCP. Ciliary beating in the direction of fluid flow is established by a combination of hydrodynamic forces and intracellular planar polarity signaling. The ciliary basal bodies' anterior position on the apical surface of the cell is determined in the embryonic radial glial cells, inherited by ependymal cells, and established by non-muscle myosin II in early postnatal development.

1. Introduction

Motile cilia are cellular protrusions that move rapidly, or beat, to generate extracellular fluid flow and to propel materials and cells. Unlike immotile single (primary) cilia, which are found in cells of almost all organs, motile multiple cilia are found in highly specific cell types, such as epithelial cells lining the airways (Knowles and Boucher, 2002) or oviduct (Lyons et al., 2006), and the ependymal cells lining brain ventricles (Worthington and Cathcart, 1963). In early development, motile single cilia are present in the embryonic node, a transient organ that contributes to establishing left–right (LR) patterning (Nonaka et al., 1998; Essner et al., 2002; Okada et al., 2005). Motile ciliary dysfunction leads to ciliopathies, a range of human disorders and syndromes that include respiratory diseases, infertility, defective LR-axis determination, and hydrocephalus (Afzelius, 2004; Huang et al., 2009).

In the brain ventricles, the beating of ependymal cell cilia is required to propel cerebrospinal fluid (CSF) flow (Del Bigio, 1995; Yamadori and Nara, 1979; Sawamoto et al., 2006). The direction of beating is defined by the ependymal planar cell polarity (PCP) (Sawamoto et al., 2006; Mirzadeh et al., 2010; Tissir et al., 2010; Guirao et al., 2010; Hirota et al., 2010). Here we summarize recent studies on the cellular and molecular mechanisms that establish ependymal PCP.

2. Planar polarity of multiciliated ependymal cells

Ependymal cells, multiciliated epithelial cells that line the cerebral ventricles of the adult brain, form an important part of the protective barrier between the brain and CSF (Del Bigio, 1995) and actively propel CSF flow (Yamadori and Nara, 1979). Studies in mice revealed that ependymal cells are derived from radial glial cells during embryonic development (Spassky et al., 2005). Ependymal cells are polarized within the plane of the epithelium; this is called PCP (Mirzadeh et al., 2010; Guirao et al., 2010). Multiciliated ependymal cells have been identified in the ventricular zone (VZ) of various vertebrates, including fish (Kishimoto et al., 2011), reptiles, birds (Garcia-Verdugo et al., 2002), and mammals that include rodents, rabbits, monkeys, and humans (Doetsch et al., 1997; Ponti et al., 2006; Quiñones-Hinojosa et al., 2006; Gil-Perotin et al., 2009; Sawamoto et al., 2011), indicating that ependymal cells are highly conserved in vertebrates.

Ependymal cell cilia have a 9+2 structure and project from the cell's apical surface into the ventricle (Bruni, 1998). Planar-polarized ciliary beating generates directional fluid flow (Worthington and Cathcart, 1963; Sawamoto et al., 2006; Tissir et al., 2010) and is believed to be involved in the circulation of CSF from the choroid plexuses, highly vascularized cauliflower-like masses of pia mater tissue in the ventricles, where it is produced, to the subarachnoid spaces, where it is absorbed. This directional flow helps to form a concentration gradient of molecules that guides the rostral migration of young neurons toward the olfactory bulb in the adult mammalian subventricular zone (Sawamoto et al., 2006). Hydrocephalus has been reported in animal models of ependymal ciliary dysfunction (Nakamura and Sato, 1993; Ibañez-Tallon et al., 2004; Banizs et al., 2005; Tissir et al., 2010) and in humans with primary

* Correspondence to: 1-Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan. Tel.: +81 52 851 8532; fax: +81 52 851 1898.
E-mail address: sawamoto@med.nagoya-cu.ac.jp (K. Sawamoto).

0301-4681/$ - see front matter © 2011 International Society of Differentiation. Published by Elsevier B.V. All rights reserved.
Join the International Society for Differentiation (www.isdifferentiation.org)
doi:10.1016/j.diff.2011.10.007

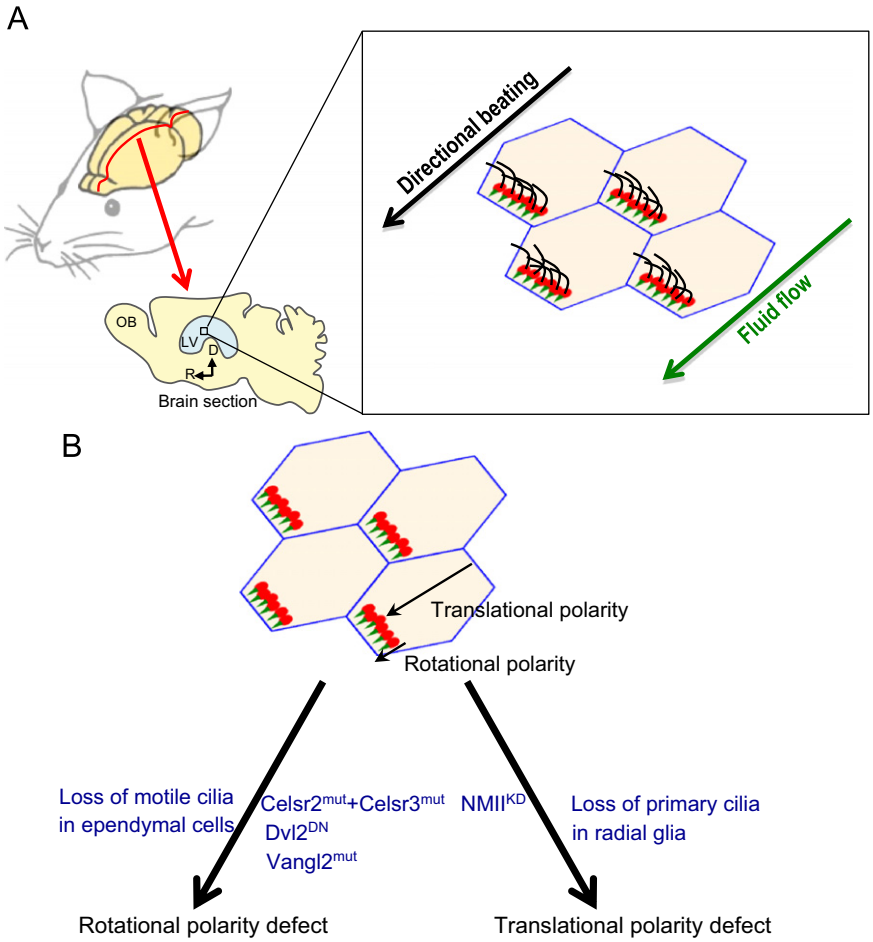

Fig. 1. Planar polarity in ependymal cells. A: Basal foot orientation (green triangles) aligns with the direction of CSF flow (green arrow) and ciliary beating (black arrow). OB, olfactory bulb; LV, lateral ventricle; D, dorsal; R, right. B: Normal ependymal translational and rotational planar polarities. Deficiencies in PCP components (Celsr2/3, Vangl2, or Dvl2) or a loss of motile cilia in ependymal cells causes defective rotational polarity. It remains unclear whether mutations in *Celsr2/3* or *Vangl2* also disturb the translational polarity. NMII disruption or loss of primary cilia in radial glial cells during embryonic development causes defective translational polarity. It remains unverified whether the loss of primary cilia in radial glial cells causes defective rotational polarity. DN, dominant negative; mut, mutation; KD, knockdown. Red circles: basal bodies; green triangles: basal feet. (Modified from Wallingford, 2010). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ciliary dyskinesia (Jabourian et al., 1986; De Santi et al., 1990; al-Shroof et al., 2001), a disorder in which ciliary motility is impaired. Thus, the directional beating of planar-polarized ependymal cilia is important for maintaining proper brain function (Fig. 1A).

Mirzadeh et al. (2010) proposed the terms *rotational* and *translational* to describe two distinct types of ependymal cilia planar polarities, based on the orientation and positioning of the basal body clusters on the cell's apical surface. Rotational polarity refers to the basal body's direction, which is defined by the position of the basal foot, an electron-dense conical structure attached laterally to the basal body barrel, relative to the cell's long axis; the basal foot points in the direction of fluid flow (Fig. 1B). Translational polarity refers to the basal body's anterior position on the cell's apical surface. In contrast to the rotational polarity, the functional significance of translational polarity is unknown.

3. Cellular and molecular mechanisms underlying ependymal planar cell polarity

3.1. Rotational polarity mechanisms

Epithelial cells in *Xenopus* larval skin are an excellent model for studying ciliary orientation mechanisms. After gastrulation, directional fluid flow on the skin surface, generated by the movement of roughly oriented cilia, fine-tunes the ciliary orientation through positive feedback (Mitchell et al., 2007). Similarly, *in vitro* cell culture experiments have demonstrated that cilia can be oriented by hydrodynamic forces generated by artificial fluid flow applied over ependymal cells (Guirao et al., 2010). Even before cilia mature, CSF produced by the choroid plexus may flow through lateral ventricles into the foramina of Monro, the interventricular openings leading to the third ventricle, and eventually become reabsorbed into the venous blood via the arachnoid granulations (Warwick and Williams, 1973; Fishman, 1992; Miyan et al., 2003; Redzic et al., 2005; Grzybowski et al., 2006). The CSF pulsatile flow may also contribute to the CSF absorption (Greitz, 2004; Lee and Yoon, 2009). The passive CSF flow may help shape the rotational polarity. Interestingly, the ciliary polarity in *Xenopus* skin can be re-oriented by external fluid flow (Mitchell et al., 2007), in contrast to mouse ependymal cilia, which are locked into one direction after differentiation (Guirao et al., 2010).

Recent studies indicate that the PCP signaling pathway, well known for its roles in planar cell polarization in several organs of various animals (Klein and Mlodzik, 2005), is also crucial for the proper rotational polarity of ependymal cilia (Tissir et al., 2010; Guirao et al., 2010; Hirota et al., 2010; reviewed by Bayly and Axelrod, 2011; Gray et al., 2011; Wallingford 2010). Core PCP