



## Structure and function of vertebrate cilia, towards a new taxonomy

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### ABSTRACT

In this review, we propose a new classification of vertebrate cilia/flagella and discuss the evolution and prototype of cilia. Cilia/flagella are evolutionarily well-conserved membranous organelles in eukaryotes and serve a variety of functions, including motility and sensation. Vertebrate cilia have been traditionally classified into conventional motile cilia and sensory primary cilia. However, an avalanche of emerging evidence on the variations of cilia has made it almost impossible to classify them in a simple dichotomous manner. For example, conventional motile cilia are also involved in the sensation of bitter taste to facilitate the beating of cilia as a defense system of the respiratory system. On the other hand, the primary cilium, often regarded as a non-motile sensory organelle, has been revealed to be motile in vertebrate embryonic nodes, where they play a crucial role in the determination of left–right asymmetry of the body. Moreover, choroid plexus epithelial cells in the cerebral ventricular system exhibit multiple primary cilia on a single cell. Considering these lines of evidence on the diversity of cilia, we believe the classification of cilia should be based on their structure and function, and include more detailed criteria. Another intriguing issue is how in the evolution of cilia, their function and morphology are combined. For example, has motility been acquired from originally sensory cilia, or vice versa? Alternatively, were they originally hybrid in nature? These questions are inseparable from the classification of cilia *per se*. We would like to address these conundrums in this review article, principally from the standpoint of differentiation of the animal cell.

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### 1. Starting point—how were cilia and flagella classified in the past?

Until just a decade ago, motile cilia and flagella had dominated the conceptual classification of cilia. In those days, cilia and flagella used to be described as ‘minute motile processes’, and distinguished from each other based on their length, the pattern of movement, and the number per cell (Fawcett, 1981). However, having a common 9+2 axonemal configuration (Satir et al., 2008; Vincensini et al., 2011) and intraflagellar transport (IFT) machineries (Rosenbaum et al., 1999; Silverman and Leroux, 2009; Snow et al., 2004), they are now regarded as highly comparable organelles. Indeed, from the current point of view, the above classification criteria for motile cilia and flagella appear somewhat ambiguous, for example, flagella of *Chlamydomonas* are known to display effective and return strokes, which are similar to the breaststroke-like movement of most motile cilia and distinct from the sinusoidal wave-like movement of sperm flagella in mammals. Although the molecular mechanisms specifying motile cilia and flagella are not fully understood and are

interesting topics by themselves, we will not discuss them at length here. Nowadays, with the progress in our knowledge of primary and nodal cilia that take on 9+0 axonemal configuration, the term “cilia” has been used in a more broad sense, and often includes motile cilia and flagella as a subset (Satir et al., 2008; Silverman and Leroux, 2009; Vincensini et al., 2011). In this review, we use the term “flagella” to describe a subset of motile 9+2 cilia that occur only one or two per cell (Fig. 3, Class VI). Currently, textbooks of cell biology dedicate pages to the description of motile cilia and flagella, while only a brief description is devoted to the primary cilium (see e.g. Alberts et al., 2008). What position does primary cilium occupy in the category of cilia? How many ciliary subtypes have been reported, and how could cilia be classified? We focus on vertebrate cilia and discuss this issue in the next section.

### 2. Classifying cilia/flagella—what classification is applicable to vertebrate cilia and flagella?

Although we can date the history of primary cilia all the way back to the 19th century, when Zimmermann (1898) predicted the function of primary cilia as a sensory module, the concept of the “central flagellum” described by Zimmermann was not based

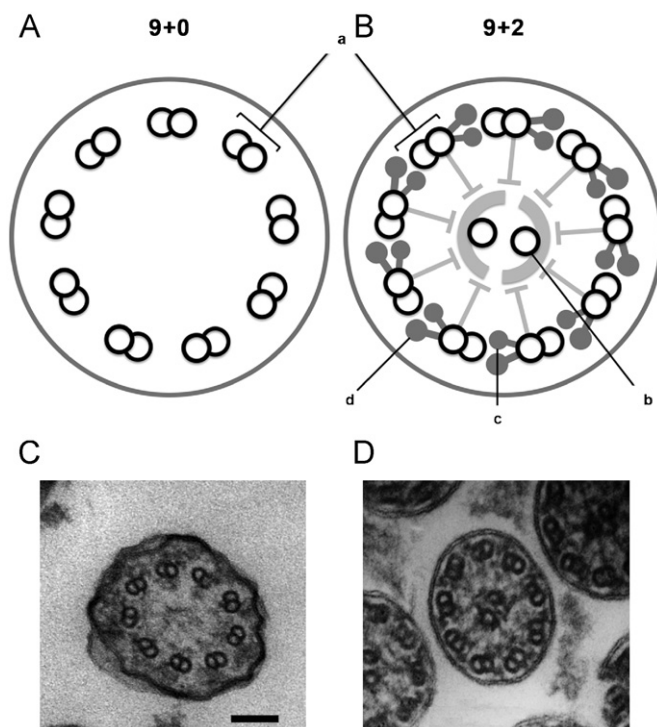
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on ultrastructural analyses. The introduction of transmission electron microscopy to cell biology in the 1950s (Bernhard and De Harven, 1956) resulted in the identification of the ultrastructure of primary cilia, which display a 9+0 axoneme configuration with diploid centrioles (diplosome) (Fig. 1A). Later, Barnes (1961) added the lack of motility to these criteria of primary cilia (Barnes, 1961). However, primary cilia were regarded as simple vestigial quiescent structures, whose functions were unknown (Wheatley, 2005). It was just about a decade ago when a category of primary cilia as a sensory organelle was experimentally established (Pazour and Witman, 2003; Praetorius and Spring, 2001, 2003). On the other hand, conventional cilia, represented by those in tracheal and oviduct epithelia, were recognized as motile components of the cell and were shown to have a 9+2 axonemal structure (Fig. 1B and D) emerging from the monoploid centriole, as well as axonemal dynein arms, which drive the motility of cilia/flagella (Gibbons, 1981). This dichotomic perspective, wherein the motile cilia assume a 9+2 configuration and formed multiple numbers in a single cell, while the sensory primary cilia take on a 9+0 configuration and are principally solitary in a single cell, prevailed until recent times when the primary cilia in the mouse node (Sulik et al., 1994) were re-evaluated using functional analysis of the *Kif3* knockout mice, which showed randomization of left–right asymmetry (Hirokawa et al., 2006; Nonaka et al., 1998; Takeda et al., 1999).

Why is the re-discovery of primary cilia in the mouse primitive node in the context of left–right asymmetry a milestone for the new classification of cilia (Wheatley, 2005)? Nodal cilia are monocilia and assume a 9+0 axonemal configuration (Hirokawa

et al., 2006; Takeda et al., 1999), therefore fulfilling two out of three criteria of authentic primary cilia (Barnes, 1961). However, they were motile and the mode of motility was completely different (Okada et al., 2005) from that of conventional motile cilia (Afzelius, 1959; Teunis and Machemer, 1994). While conventional motile cilia exhibit planar beating, nodal cilia (Fig. 1C) show rotational movement, where the axis is tilted posteriorly 40 degrees towards the surface of the nodal pit to generate a leftward flow of extraembryonic fluid. This extraordinary property resulted in this group of cilia being classified as an independent third group, “nodal cilia” (Satir and Christensen, 2007). Therefore, the discovery of nodal cilia as a motile entity with 9+0 axonemes was a breakthrough that challenged the long-lasting authentic classification of mammalian cilia into two categories. Moreover, the nodal cilia of different vertebrates in the structural orthologs of nodes share a common axonemal structure unique to primary cilia (9+0) in the mouse; rabbit posterior notochord (PNC) (Feistel and Blum, 2006; Okada et al., 2005) and Medaka fish (*Oryzias latipes*) Kupffer’s vesicle (Kupffer, 1868; Okada et al., 2005). These findings reinforced the view that this group constitutes a novel third category that could be distinguished from classic primary cilia (Okada et al., 2005). The question of whether or not nodal cilia have a sensory function remains to be elucidated.

A recent study has reported the existence of a 9+2 configuration in mouse nodal cilia (Caspary et al., 2007), which challenges the prevailing idea that the nodal cilia assume 9+0 configuration. Although the authors speculated that the condition of fixation is a major determinant for conserving the relatively labile central pair (CP) of tubules, they did not deny the existence of some cilia with a 9+0 configuration (Caspary et al., 2007). On the other hand, from a functional standpoint, the manner of ciliary movement identified in nodes is definitively rotational but not planar beating (Nonaka et al., 1998; Okada et al., 2005; Takeda et al., 1999). As the presence of a CP of tubules is believed to be responsible for the “beating” movement of cilia under physiological conditions (Yagi and Kamiya, 2000), the presence of motile 9+2 cilia appears to be contradictory to the extensive observation of mouse nodes that do not show a beating movement at all. Therefore, we believe that most of the nodal cilia actually take on a 9+0 configuration, as reported previously (Takeda et al., 1999). Then how can we account for the seemingly incoherent story on the node? One plausible explanation to reconcile the ultrastructural description by Caspary et al. (2007) with those by Takeda et al. (1999) is a modified version of the two cilia hypothesis (Fig. 2), originally proposed by McGrath et al. (2003). In the original two cilia hypothesis, the authors suggested the presence of two distinct populations of nodal epithelium: nodal pit cells with motile cilia (possessing both left–right dynein and polycystin-2 [PC2]) located centrally, and the perinodal crown cells with sensory cilia (possessing PC2 but not left–right dynein) located circumferentially. In our modified model, non-motile 9+2 cilia are speculated to be installed in the circumferential area of the node, where McGrath et al. (2003) found non-motile cilia that sense nodal flow and increase intracellular  $Ca^{2+}$  concentrations, in what are named perinodal crown cells (Lee and Anderson, 2008). Although we cannot draw a definitive conclusion on the detailed alignment of cilia in the node before scrutinizing the ultrastructure of nodal cilia, it is reasonable that 9+2 non-motile cilia, comparable to kinocilia of the inner ear and frog olfactory cilia (Reese, 1965), exist on the border of nodes, namely on nodal crown cells (Fig. 2A), rather than randomly distributed on nodal pit cells (Fig. 2B and C), as the latter alignment would make the non-motile cilia interfere with the rotation of motile primary cilia, which would be an inefficient system for the organism. Therefore, cilia installed on nodal crown cells could correspond to the 9+2



**Fig. 1.** Overview of the structure of cilia with reference to axonemal architecture. (A) Classic primary cilia show a 9+0 configuration, in which the central pair (CP, b) of microtubules (MTs) is absent. This type of cilium usually lacks dynein arms that generate a shearing force for the motility of cilia. (B) In contrast, conventional motile cilia take on a more complex cytoarchitecture. In addition to the CP and peripheral 9 microtubule doublets (a), they express many components responsible for motility, such as inner (c) and outer (d) dynein arms. Transmission electron microscopy of (C) the nodal cilium of mouse and (D) conventional motile cilia from mouse tracheal epithelium. Bar, 100 nm.

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