Gene 547 (2014) 175–185

Contents lists available at ScienceDirect

Gene

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

Review

Primary cilium: an elaborate structure that blocks cell division?

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ARTICLE INFO

Article history:
Received 23 January 2014
Received in revised form 7 May 2014
Accepted 23 June 2014
Available online 24 June 2014

Keywords:
Primary cilia
Ciliogenesis
AurA
Plk1
Nek

ABSTRACT

A primary cilium is a microtubule-based membranous protrusion found in almost all cell types. A primary cilium has a "9 + 0" axoneme that distinguishes this ancient organelle from the canonical motile "9 + 2" cilium. A primary cilium is the sensory center of the cell that regulates cell proliferation and embryonic development. The primary ciliary pocket is a specialized endocytic membrane domain in the basal region. The basal body of a primary cilium exists as a form of the centriole during interphase of the cell cycle. Although conventional thinking suggests that the cell cycle regulates centrosomal changes, recent studies suggest the opposite, that is, centrosomal changes regulate the cell cycle. In this regard, centrosomal kinase Aurora kinase A (AurA), Polo-like kinase 1 (Plk1), and NIMA related Kinase (Nek or Nrk) propel cell cycle progression by promoting primary cilia disassembly which indicates a non-mitotic function. However, the persistence of primary cilia during spermatocyte division challenges the dominate idea of the incompatibility of primary cilia and cell division. In this review, we demonstrate the detailed structure of primary cilia and discuss the relationship between primary cilia disassembly and cell cycle progression on the background of various mitotic kinases.

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1. Introduction

Cilia are evolutionarily ancient organelles that protrude from the cell surface and can be divided into two categories, namely motile cilia and non-motile cilia (also called primary cilia). Despite their differences in axonemal structure and motility, motile cilia and primary cilia share a majority of ciliary components, possess the same intraflagellar transport system, and act as the antenna of the cell (Ishikawa et al., 2012; Rosenbaum and Witman, 2002). Present-day cilia may have descended from hybrid sensory-motile cilia and primary cilia may be a branch of these ancestral hybrid cilia that have gained specificity but lost motility during evolution (Takeda and Narita, 2012).

A solitary primary cilium is present on most human tissues including epithelium, connective, muscle, and nerve tissue (Arellano et al., 2012; de la Roche et al., 2013; Donnelly et al., 2010; Kumamoto et al., 2012; Lee and Gleeson, 2010; Morimoto et al., 2010; Shi and Tarbell, 2011; Sorokin, 1962; Wu et al., 2009; Zaghloul and Brugmann, 2011). Primary

Abbreviations: αTAT, α-tubulin acetyltransferase; AurA, Aurora kinase A; CaM, Calmodulin; Cas, Crk-associated substrate; CK1, Casein kinase 1; Cnk2p, *Chlamydomonas* NIMA-related kinase 2; Dvl, Dishevelled; HDAC 6, Histone deacetylase 6; HIF, Hypoxia-inducible factor; IFT, intraflagellar transport; Nek, NIMA-related expressed kinase; NIMA, never-in-mitosis A; NPHP, nephronophthisis; PDK, polycystic kidney disease; Plk1, Polo-like kinase 1; Shh, Sonic Hedgehog; SOFA, site of flagellar autotomy; VHL, von Hippel–Lindau.

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http://dx.doi.org/10.1016/j.gene.2014.06.050
0378-1119/

cilium has been long-regarded as a vestigial structure mainly because primary ciliary function was enigmatic although they undoubtedly play a role in sensory transduction (Wheatley, 1995). In addition, primary cilia play a role in hereditary cystic kidney disease since a majority of the proteins encoded by the disease-related genes are present in primary cilia (Pazour et al., 2000). The wealth of accumulated data draws a clear picture of primary cilia as either optical, chemical, osmotic, or mechanical sensory devices that transduce signals to intracellular signaling cascades (Delling et al., 2013; Rich and Clark, 2012). Hedgehog, Wnt, Platelet-derived growth factor aa (PDGFaa), and Hippo are specific intracellular signaling cascades that are coordinated at the primary cilium (Breunig et al., 2008; Lancaster et al., 2011; Ohazama et al., 2009; Schneider et al., 2010; Spassky and Aguilar, 2008; Steere et al., 2012). Defects of primary cilia and their related proteins cause the dysregulation of cell proliferation and embryonic development that leads to genetic disorders, including polycystic kidney diseases (PKD) (Nonaka et al., 1998), randomization of left-right asymmetry (Eley et al., 2005), sensorineural deafness (Eley et al., 2005), nephronophthisis (NPHP) (Sang et al., 2011), Joubert syndrome (JBTS) (Davis and Katsanis, 2012), and Meckel–Gruber syndrome (MKS) (Sang et al., 2011). These heterogeneous diseases can be grouped together and referred to as ciliopathies. Ciliopathies exhibit a broad spectrum of clinical phenotypes and sometimes share phenotypic overlap with each other. Alzheimer's disease has also been recently linked to primary ciliary defects and may therefore be considered a ciliopathy (Armato et al., 2013).

Primary cilia may be regarded as post-mitotic structures since a solitary primary cilium appears after a cell has undergone differentiation. A normal, differentiated cell has a pair of centrioles within the centrosome that differ functionally and morphologically (Pierce and Nachury, 2013). A normal centriole number is maintained by duplication and segregation mechanisms synchronized to the cell cycle. However, extra centrioles within the centrosome result in extra cilia on the cell surface so that the cell then exhibits a cilia-diluted phenotype with reduced signaling molecules leading to a variety of cancers (Mahjoub and Stearns, 2012). When a cell is in the G0 and G1 phases of the cell cycle, the mother centriole within the centrosome moves to the cell membrane and then differentiates into the basal body of the primary cilium (Tang et al., 2013). The presence of a primary cilium on the cell surface may be incompatible with cell division because the basal body must detach from the cell membrane in order to function as the microtubule organizing center and form the mitotic spindles (Kobayashi and Dynlacht, 2011; Santos and Reiter, 2008). Although the dominate thinking suggests that the cell cycle regulates changes in centrosomal proteins, recent evidence suggests the reverse in that changes in centrosomal proteins regulate the cell cycle. In this regard, various canonical regulators of the cell cycle also engage in non-mitotic functions of primary cilia (Pan and Snell, 2007). The major centrosomal mitotic kinase Aurora kinase A (AurA), Polo-like kinase 1 (Plk1), and NIMA related Kinase (Nek or Nrk) promote primary cilia disassembly and release of the captured centriole thereby allowing the centrosome to form a mitotic spindle (Pugacheva et al., 2007; Seeger-Nukpezah et al., 2012). In addition, partner proteins including Ca^{2+}/CaM (Plotnikova et al., 2012), Pitchfork (PIFO) (Kinzel et al., 2010), Hypoxia-inducible factors (HIF) (Xu et al., 2010), Trichoplein (Short, 2012) activate AurA through the HEF-1-dependent or independent cascade and the Dishevelled2–Plk1 complex supplements the missing link between Wnt5-induced steps and the HEF1–AurA cascade during primary cilia disassembly (Lee et al., 2012). An increasing number of mitotic kinases have been implicated in the kinase-dependent disassembly of primary cilia and these mitotic kinases interconnect with each other to construct a network similar to the cell cycle regulation system. Consequently, a mechanistic view emerges whereby cell cycle regulators promote the liberation of the basal body in order to form the centrosome during cell division. One can legitimately draw the conclusion that the presence of a primary cilium on the cell surface is incompatible with cell division. However, a caveat to this statement rests in the observation that dividing *Drosophila* spermatocytes during meiosis possess a primary cilium beneath their cell surface (Riparbelli et al., 2012). This leads us to ponder why primary cilia disassembly occurs during cell division in most cell types but does not occur in *Drosophila* spermatocytes. An exploration of what factors are common to both (i.e., most cell types versus *Drosophila* spermatocytes) may shed light on what factors are directly involved in primary cilia disassembly only and what factors are directly involved in cell division only.

In this review, we will characterize primary cilia including the long-neglected ciliary pocket and discuss the relationship between primary cilia and the centrosome during cell division.

2. Structure of primary cilia

The morphology of ciliary structure in general has been obtained from ultrastructural studies of motile cilia/flagella. These traditional ultrastructural studies are now being extended to molecular studies to elucidate the molecular architecture of canonical primary cilia. In this regard, proteomic analysis of mammalian primary cilia versus sensory cilia and motile cilia have provided insights into primary ciliary function (Gilliam et al., 2012; Ishikawa et al., 2012; Mayer et al., 2008; Ostrowski et al., 2002; Pazour et al., 2005). Ishikawa and colleagues identified 195 candidate primary ciliary proteins of which 25% were primary cilia-

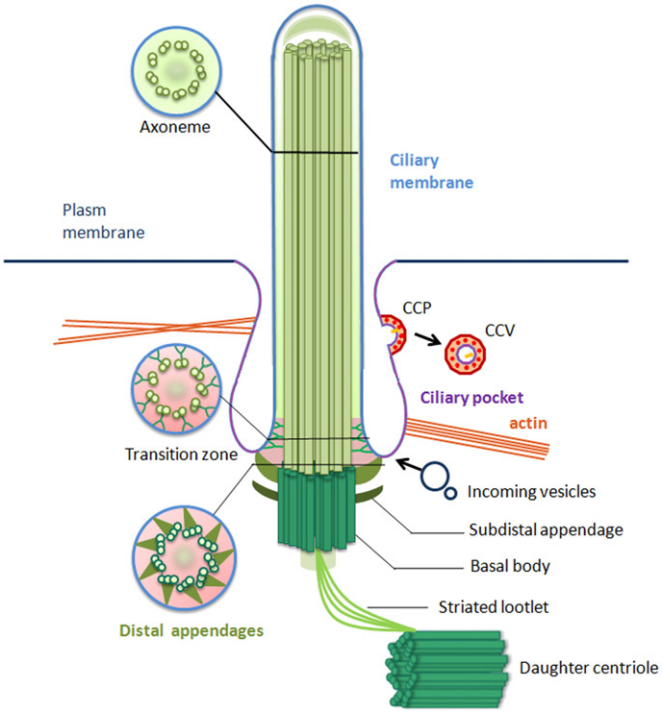

Fig. 1. Structure of primary cilia. We divided primary ciliary structure to be ciliary skeleton and ciliary membrane (Hoerner and Stearns, 2013; Paintrand et al., 1992). The ciliary skeleton is composed of "9 + 0" axoneme and basal body complex (Gluenz et al., 2010; Scherft and Daems, 1967). During the transition between microtubule doublets and triplets is transition zone, indicated by Y-shaped bridges extending from microtubule doublets to ciliary membrane and distal appendages (Aubusson-Fleury et al., 2012; Gluenz et al., 2010; Torikata, 1988). Mother centriole and daughter centriole are interconnected by striated lootlets, stretched from the central transparent materials of mother centriole to lateral face of daughter centriole (Broekhuis et al., 2013; Uzbekov and Prigent, 2007; Uzbekov et al., 2012). Primary ciliary pocket is defined to be membrane domain starting from distal appendages to the region where ciliary sheath emerges to extracellular environment (purple) (Barnes, 1961; Molla-Herman et al., 2010; Rattner et al., 2010; Sorokin, 1962, 1968). Anchoring of CCP and formation of CCV at ciliary pocket region is indicative of ciliary pocket's role of endocytosis (Molla-Herman et al., 2010; Rich and Clark, 2012). Actin-based network is connected to ciliary pocket and facilitates proper orientation of primary cilia (Benmerah, 2012). Incoming vesicles derived from Golgi complex seem to dock at membrane junction at distal appendages and keep balances between ciliary membrane addiction and removal (Molla-Herman et al., 2010).