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REVIEW

SUBJECT COLLECTION: CILIA AND FLAGELLA

Structure and function of distal and subdistal appendages of the mother centriole

Dandan Ma[1], Fulin Wang[1], Junlin Teng[1,*], Ning Huang[3,4,*] and Jianguo Chen[1,2,*]

ABSTRACT

Centrosomes are composed of centrioles surrounded by pericentriolar material. The two centrioles in G1 phase are distinguished by the localization of their appendages in the distal and subdistal regions; the centriole possessing both types of appendage is older and referred to as the mother centriole, whereas the other centriole lacking appendages is the daughter centriole. Both distal and subdistal appendages in vertebrate cells consist of multiple proteins assembled in a hierarchical manner. Distal appendages function mainly in the initial process of ciliogenesis, and subdistal appendages are involved in microtubule anchoring, mitotic spindle regulation and maintenance of ciliary signaling. Mutations in genes encoding components of both appendage types are implicated in ciliopathies and developmental defects. In this Review, we discuss recent advances in knowledge regarding the composition and assembly of centriolar appendages, as well as their roles in development and disease.

KEY WORDS: Centrosome, Distal appendages, Subdistal appendages, Microtubule anchoring, Ciliogenesis

Introduction

Centrosomes are non-membranous organelles consisting of centrioles and pericentriolar material (PCM). The two centrioles in G1 phase are referred to as the mother and daughter centrioles, and are structurally different; mother centrioles are decorated with distal appendages (DAs) and subdistal appendages (SDAs), whereas daughter centrioles lack appendages. The composition and cellular importance of centrioles has attracted attention following recent advances in microscopy and gene-editing techniques (Bowler et al., 2019; Chong et al., 2020; Huang et al., 2017; Mazo et al., 2016; Tanos et al., 2013). Centrosomes are well known as one of the main microtubule-organizing centers (MTOCs) (Rusan and Rogers, 2009; Wu et al., 2012) and the organizers of cilia, which are plasma membrane-bound antenna-like extensions (Joukov and De Nicolo, 2019), in mammalian cells. As the MTOC, the centrosome tethers the minus end of microtubules, in a manner primarily mediated by SDAs, which is required for their nucleation, stabilization and anchorage (Wu and Akhmanova, 2017). Defects in centrosome structure, number or function can result in aberrant cell proliferation, which eventually leads to tumorigenesis (Rivera-Rivera and Saavedra, 2016). As the cilia organizer, the mother centriole participates in the initial steps of ciliogenesis, the disruption of which is associated with a broad range of clinical diseases, including Joubert syndrome (Wang et al., 2020), airway disease (Legendre et al., 2021), retinal ciliopathies (Chen et al., 2021), obesity (Engle et al., 2021) and infertility (Aprea et al., 2021). Therefore, a deep understanding of centrosome structure and function will expand their potential as a target for the early diagnosis and subsequent treatment of related diseases. This Review discusses recent findings on the structure and functions of DAs and SDAs in the mother centriole, and highlights their significance in development and disease.

Architecture of DAs and SDAs

A centriole is considered mature when decorated with DAs and SDAs, and is thus called the mother centriole (Hall and Hehnly, 2021; Uzbekov and Alieva, 2018; Vasquez-Limeta and Loncarek, 2021). These two kinds of appendages differ in structure and molecular composition, which has been gradually characterized by electron microscopy (EM), super-resolution microscopy and advanced genetic and biochemical techniques (Bowler et al., 2019; Chong et al., 2020; Huang et al., 2017; Ma et al., 2022; Mazo et al., 2016; Tanos et al., 2013; Yang et al., 2018a). Two-dimensional EM shows that mammalian DAs present as trapezoidal sheets that attach to each microtubule triplet at the distal end of the mother centriole, together generating a nine-fold pinwheel-like structure with an opposite rotating direction to that of the centriolar microtubules (Anderson, 1972) (Fig. 1A). Super-resolution microscopy analysis uncovered a structure that extends into the gap between each pinwheel blade, named the distal appendage matrix (DAM) (Yang et al., 2018a). Correlation between super-resolution microscopy and EM revealed the DAs to be finger-like structures anchored to two adjacent centriolar microtubule triplets by fibrous bases (Bowler et al., 2019). DAs are composed of the centrosomal proteins (CEPs) CEP83, Fas binding factor 1 (FBF1) and sodium channel and clathrin linker 1 (SCLT1), which preferentially localize to the inner DAs (Bowler et al., 2019; Sillibourne et al., 2011; Tanos et al., 2013; Viol et al., 2020). Meanwhile, CEP89, leucine-rich repeats containing 45 (LRRC45), CEP164 and ankyrin repeat domain-containing protein 26 (ANKRD26) mainly occupy the outer DAs (Bowler et al., 2019; Kurtulmus et al., 2018; Schmidt et al., 2012; Viol et al., 2020) (Fig. 1A,B).

In addition to DAs, EM studies have also identified a number of cone-like structures that localize adjacent and at a proximal position to DAs, named SDAs (Bystrevskaya et al., 1988, 1992). In comparison with the nine-fold symmetry of DAs, the structure of SDAs is not conserved among different cell types (Hall and Hehnly, 2021; Uzbekov and Alieva, 2018; Tischer et al., 2021). Each cone-like structure of SDAs protrudes from two adjacent microtubule

[1]Key Laboratory of Cell Proliferation and Differentiation of the Ministry of Education, College of Life Sciences, Peking University, Beijing 100871, China. [2]Center for Quantitative Biology, Peking University, Beijing 100871, China. [3]Institute of Neuroscience, Translational Medicine Institute, Health Science Center, Xi'an Jiaotong University, Xi'an 710061, China. [4]Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Health Science Center, Xi'an Jiaotong University, Xi'an 710061, China.

*Authors for correspondence (junlinteng@pku.edu.cn; ning.huang@xjtu.edu.cn; chenjg@pku.edu.cn)

N.H., 0000-0002-8233-2572; J.C., 0000-0002-8406-011X

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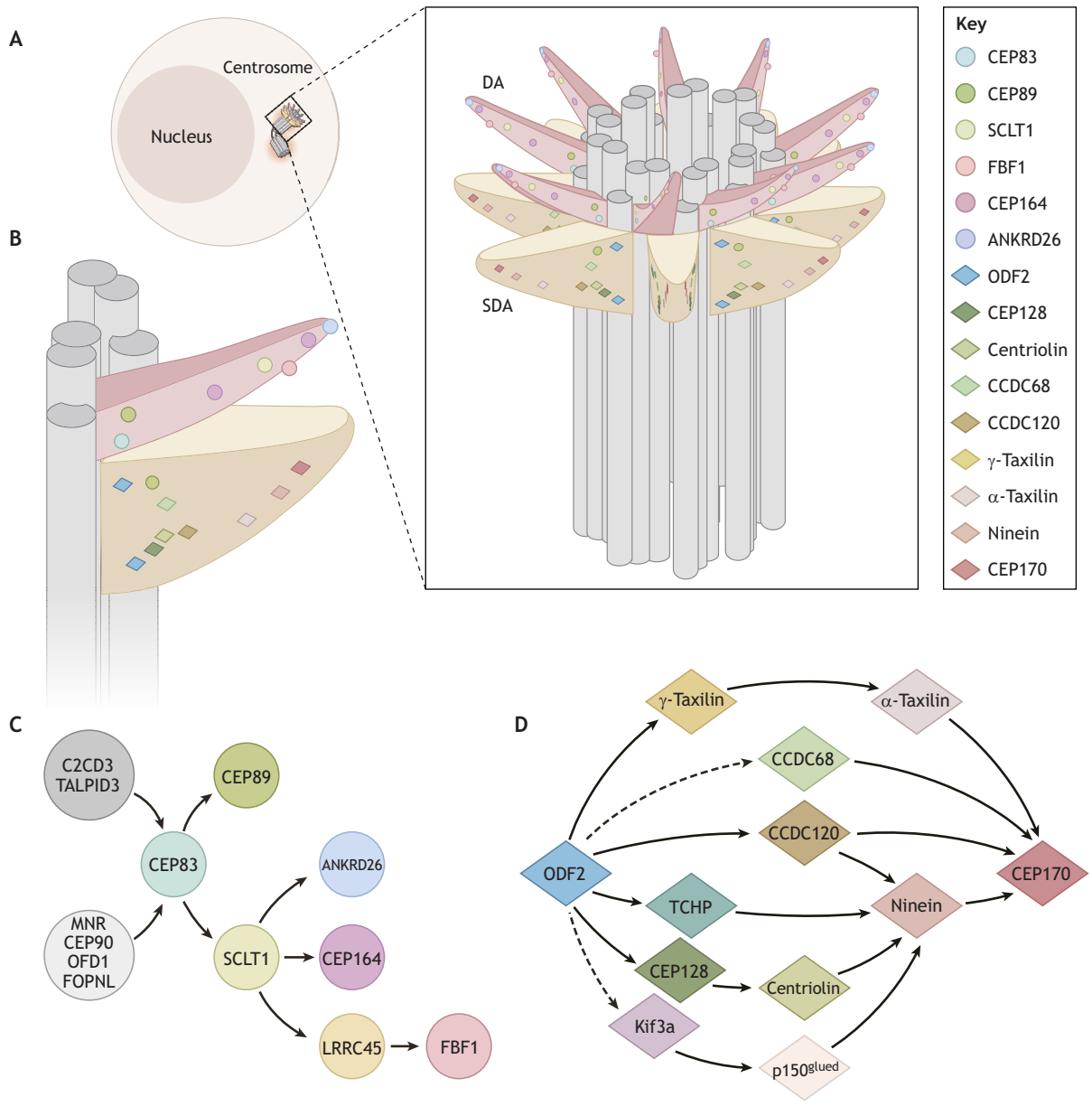

Fig. 1. Schematic illustrations of the localization and assembly of DA and SDA structures on mother centrioles. (A) Shown here is the architecture of centrioles and appendages within the cell in G1 phase. Centrosomes are composed of centrioles surrounded by pericentriolar material (left). The two centrioles in G1 phase are distinguished by their appendages, which localize in the distal and subdistal regions. The centriole possessing both types of appendage is older and is referred to as the mother centriole (magnified on the right), whereas the other centriole lacking appendages is the daughter centriole. In comparison with the nine-fold symmetry of DAs (pink), the structure of SDAs (yellow) is not conserved among different cell types. These two kinds of appendages differ in their molecular composition. The detailed distribution of DA proteins (circle) and SDA proteins (diamond) has been identified by various EM and super-resolution microscopy studies. (B) A close-up view of a single DA (pink) and SDA (yellow) from A. (C,D) Schematic representation of the various assembly pathways of DAs (C) and SDAs (D). Solid lines represent verified relationships between the two proteins determined using protein interaction techniques, whereas dotted lines indicate those that are unverified.

triplets of the mother centriole (Bystrevskaya et al., 1988; Paintrand et al., 1992). SDAs are composed of outer dense fiber of sperm tails 2 (ODF2), CEP128, centriolin, ninein and CEP170. ODF2 is located closest to the centriolar microtubule wall, whereas ninein and CEP170 reside at the SDA tips (Chong et al., 2020). Coiled-coil domain-containing 68 (CCDC68), CCDC120, α-taxilin and γ-taxilin have recently been identified as new components of SDAs, localized in the mid-zone between ODF2 and CEP170 (Fig. 1A,B; Huang et al., 2017; Ma et al., 2022). As characterized by super-resolution microscopy, SDA proteins can be classified into two groups; the first only occupies the SDA region (ODF2, CEP128 and centriolin), whereas the second occupies both the SDA region and the proximal ends of the centrioles (CCDC68, CCDC120, α-taxilin, γ-taxilin, ninein and CEP170) (Chong et al., 2020; Huang et al., 2017; Ma et al., 2022). Trichoplein (TCHP) is not a classical SDA protein given that it resides in the subdistal to medial zone of both the mother and daughter centrioles, and thus does not belong to either the DA or SDA group (Table 1; Ibi et al., 2011).

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Table 1. Main components of DA and SDA proteins

Protein	Localization	Cellular functions	Implications in development and disease	References
CEP83 (also known as CCDC41)	DA	Ciliary vesicle docking to the mother centriole; mother centriole docking to the membrane; Rabin8 and GTPase Rab8 vesicular accumulation at the centrosome	Nephronophthisis; intellectual disability; retinal dystrophy	Joo et al., 2013; Tanos et al., 2013; Cuenca et al., 2019; Failler et al., 2014; Veldman et al., 2021
CEP89/ CEP123	DA; SDA	Ciliary vesicle formation	Autosomal dominant polycystic kidney disease	Sillibourne et al., 2013; Skalická et al., 2018
SCLT1	DA	Ciliogenesis	Bardet–Biedl syndrome; orofaciodigital syndrome type IX	Tanos et al., 2013; Morisada et al., 2020; Adly et al., 2014
FBF1	DA; DAM	Rabin8 and GTPase Rab8 vesicular accumulation at the centrosome		Cuenca et al., 2019; Yang et al., 2018a
LRRC45	DA; PE	Ciliary axoneme extension; centrosome cohesion; recruitment of FBF1		Kurtulmus et al., 2018; He et al., 2013
CEP164	DA	TTBK2 recruitment to DA; maintenance of DAM integrity and FBF1 radial distribution; control of the GLI2–cyclin D–CDK6 axis and DNA damage response pathway	Nephronophthisis	Čajánek and Nigg, 2014; Rosa et al., 2022; Yang et al., 2018a; Slaats et al., 2014; Kobayashi et al., 2020; Airik et al., 2019; Chaki et al., 2012
Chibby	DA	Ciliary vesicle formation; basal body docking		Steere et al., 2012; Burke et al., 2014
ANKRD26	DA	PIDDosome activation		Burigotto et al., 2021; Evans et al., 2021
CC2D2A	SDA	Cilia biogenesis		Veleri et al., 2014
ODF2 (also known as cenexin)	DA; SDA	SDA structural integrity; transition fiber and basal foot assembly; spindle orientation; centrosome cohesion		Tateishi et al., 2013; Hung et al., 2016; Yang et al., 2018b
CEP128	SDA	Microtubule anchoring; regulators of TGF-β and BMP signaling at the primary cilium	Dorsalization and organ development in zebrafish	Kashihara et al., 2019; Mönnich et al., 2018
Centriolin	SDA	Cytokinesis		Seronick et al., 2022
TCHP	Subdistal to medial zone of both centrioles	Microtubule anchoring; negative regulator of ciliogenesis		Ibi et al., 2011; Inoko et al., 2012
Ndell	SDA	Negative regulator of ciliogenesis		Inaba et al., 2016
CCDC68	SDA, PE	Microtubule anchoring		Huang et al., 2017
CCDC120	SDA, PE	Microtubule anchoring		Huang et al., 2017; Ma et al., 2022
γ-Taxilin	SDA, PE	SDA structural integrity; microtubule anchoring; spindle orientation; centrosome cohesion		Ma et al., 2022; Makiyama et al., 2018
α-Taxilin	SDA, PE	SDA structural integrity; microtubule anchoring; spindle orientation; centrosome cohesion		Ma et al., 2022
HVFL3 (also known as CCDC61)	SDA	Centrosome cohesion and positioning		Pizon et al., 2020
Ninein	SDA, PE	Microtubule anchoring and nucleation; basal foot assembly	Microcephalic primordial dwarfism; spondyloepimetaphyseal dysplasia with joint laxity (leptodactylic type)	Delgehyr et al., 2005; Dauber et al., 2012; Grosch et al., 2013
Kif2a	SDA	Ciliary length control; ciliary spatial localization	Primary microcephaly	Mazo et al., 2016; Zhang et al., 2019
CEP170	SDA, PE	Microtubule anchoring; basal foot assembly		Huang et al., 2017; Ma et al., 2022
Kif3a	SDA	Centriole cohesion; SDA organization; microtubule anchoring; ciliary basal foot assembly		Kodani et al., 2013;
$p150^{glued}$	SDA	Centriole cohesion; SDA organization		Kodani et al., 2013
AKNA	SDA	Microtubule organization; NSC delamination in forebrain development	Brain development	Camargo Ortega et al., 2019

PE, proximal end.

During ciliogenesis, the mother centrioles undergo several changes to become basal bodies, the base structures for both primary and motile cilial elongation (Ishikawa and Marshall, 2011). Here, SDAs in cells possessing primary cilia are thought to transform into a structure named the basal foot, which links basal bodies to microtubules, as has been confirmed by both EM and super-resolution microscopy studies (Nguyen et al., 2020; Paintrand et al., 1992). The basal foot structure of motile cilia displays unique

patterns, including a cone-like structure composed of three electron-dense areas that bind to three adjacent microtubule triplets (Nguyen et al., 2020) and orient towards the direction of ciliary beating (Boisvieux-Ulrich et al., 1985). Importantly, the basal feet of both primary and motile cilia share scaffold components with SDAs, such as ODF2, CEP128, ninein and CEP170 (Nguyen et al., 2020; Ryu et al., 2021), further indicating their similarity in structure and function.

Although the DAs and SDAs possess different functions and appear to be two independent structures (Uzbekov and Alieva, 2018; Vasquez-Limeta and Loncarek, 2021), several recent studies have revealed crosstalk between these two structures (Chong et al., 2020; Tateishi et al., 2013). Super-resolution microscopy studies have revealed that DAs and SDAs are structurally coupled, given that ODF2 and CEP89 are part of both structures (Chong et al., 2020; Ma et al., 2022). The CEP89 signal at DAs is reduced following SDA depletion by CEP128 knockout, implying interplay between these two structures (Chong et al., 2020). A rescue analysis of ODF2 deletion mutants in murine embryonic F9 cells by EM suggested that amino acids 188–806 are required for DA formation, whereas amino acids 1–59 and 188–806 are involved in SDA integrity (Ishikawa et al., 2005; Tateishi et al., 2013). However, other studies have reported that ODF2 is only responsible for SDA assembly (Kuhns et al., 2013; Tanos et al., 2013; Viol et al., 2020), given that ODF2 depletion hardly affects the localization of DA components in retinal pigment epithelial 1 (RPE1) cells, indicating cell type-dependent roles of ODF2 in DA assembly.

Assembly and dynamics of centriole appendages

Hierarchical assembly of DAs and SDAs

DA and SDA proteins are assembled in a hierarchical manner. The DA assembly pathway was first uncovered by characterizing CEP83, SCLT1 and FBF1 as DA components (Tanos et al., 2013). A series of siRNA-mediated knockdown experiments revealed that CEP83 acts upstream of DA assembly by recruiting both CEP89 and SCLT1, whereas CEP89, but not SCLT1, is required for the DA localization of CEP164 and FBF1 (Tanos et al., 2013). The identification of LRRC45 at DAs further enriched the hierarchy of the DA network, given that LRRC45 is recruited by both CEP83 and SCLT1 and is required for FBF1 localization (Kurtulmus et al., 2018). C2CD3 and its binding partner TALPID3, found at the distal end of both centrioles, has been reported to remove daughter centriole-specific proteins (i.e. CEP120, centrobin and NEURL4) from the mother centriole, which in turn recruits Oral-facial-digital syndrome 1 (OFD1) to the DA periphery, promoting DA assembly (Wang et al., 2018; Ye et al., 2014). CEP83, recruited by the distal end protein complex moonraker (MNR)–CEP90–FOPNL–OFD1 (MNR is also known as KIAA0753, and FOPNL as CEP20), localizes to the root of the DA structure to initiate structural assembly (Kumar et al., 2021; Le Borgne et al., 2022), further recruiting CEP89 and SCLT1 (Tanos et al., 2013). SCLT1 is required for the localization of LRRC45 and CEP164, which are responsible for recruiting FBF1 to DA regions (Fig. 1C) (Kurtulmus et al., 2018; Yang et al., 2018a). ANKRD26 is recruited to the DA by SCLT1 but not by CEP164 (Burigotto et al., 2021; Evans et al., 2021).

The hierarchical assembly of SDA components was first identified using a CRISPR/Cas9 approach; depletion of ODF2 or CEP128 weakens centriolin localization at SDAs, whereas loss of centriolin specifically disrupts the SDA, but not the proximal end, localization of ninein, CEP170, Kif2a and p150^{glued} (also known as DCTN1) (Mazo et al., 2016). Subsequently, the assembly rules of SDA were further expanded, and CCDC68 and CCDC120 were identified as two SDA components (Fig. 1D) (Huang et al., 2017). SDA proteins are characterized by coiled-coil domains, which are important for their localization and interaction with one another (Fig. 2). ODF2 acts upstream of other SDA proteins and provides structural integrity, given that siRNA-mediated knockdown of ODF2 causes decreased fluorescence intensity related to the centrosomal localization of SDA proteins, such as CCDC68, CCDC120, α-taxilin and γ-taxilin (Huang et al., 2017; Ma et al., 2022). Removal of amino acids 1–59 at the N-terminus of ODF2 results in loss of interactions with other SDA components or reduces their SDA localization (Huang et al., 2017; Ma et al., 2022). CCDC120 further recruits ninein to SDA via amino acids 91–320 of its N-terminus, and *in vitro* binding assays suggest a direct interaction (Huang et al., 2017). ODF2 also recruits TCHP to the subdistal-to-medial zone of the mother centriole, which in turn recruits ninein to SDAs (Ibi et al., 2011). Kif3a localizes to SDAs and recruits the dynactin subunit p150^{glued}, which is required for the localization of ninein to SDAs (Kodani et al., 2013) (Fig. 1D). The SDA midzone group proteins, including CCDC68, CCDC120 and α-taxilin, have been suggested to bind directly to CEP170 to facilitate its recruitment to SDAs, as their depletion results in loss of CEP170 from the centrosome (Huang et al., 2017; Ma et al., 2022). Moreover, the SDA localization of CEP170 is also dependent on ninein (Graser et al., 2007).

Dynamics of DAs and SDAs throughout the cell cycle

The composition and structure of DAs is not static and dynamically changes throughout the cell cycle. Several studies have shown that DA outer components, such as CEP164, FBF1 and CEP89, lose their DA localization in G2 phase and re-associate on mature centrioles (Bowler et al., 2019; Schmidt et al., 2012; Viol et al., 2020). Accordingly, EM studies have revealed that DA structure densities robustly decline during late G2 phase and mitosis but are restored in the early G1 phase of the subsequent cell cycle (Bowler et al., 2019; Kong et al., 2014). However, the DA inner proteins SCLT1 and CEP83 appear to be permanently recruited to the mature centriole, maintaining the nine-fold structure of the DA during the cell cycle (Bowler et al., 2019; Viol et al., 2020). Several mitosis-related kinases, such as NimA-related protein kinase 2 (NEK2) (Viol et al., 2020), Polo-like kinase 1 (PLK1) and Aurora A kinase (AurA or AURKA) (Bowler et al., 2019; Kong et al., 2014) have been implicated in the disassociation of DA outer components in late G2 phase, indicating that DA inner proteins might serve as a platform for the association of other DA proteins that are regulated by the cell cycle.

Although EM studies have revealed that the SDA structure also disappears in G2 phase and re-appears after mitosis (Kong et al., 2014; Vorobjev and Chentsov Yu, 1982), SDA components display different dynamics during the G2–mitosis transition. ODF2 remains localized to the centrioles during the cell cycle, and its centrosomal localization is even enhanced in late G2 phase (Bowler et al., 2019; Viol et al., 2020), whereas ninein (Chen et al., 2003) and CEP170 (Guarguaglini et al., 2005) translocate from SDAs to the PCM. Whether SDAs contain a platform that persistently associates with the centrioles throughout the entire cell cycle remains to be investigated. Interestingly, both DA and SDA structures still exist on mature centrioles during mitosis (Hung et al., 2016), indicating the diverse control mechanisms of centriole appendages among different cell types.

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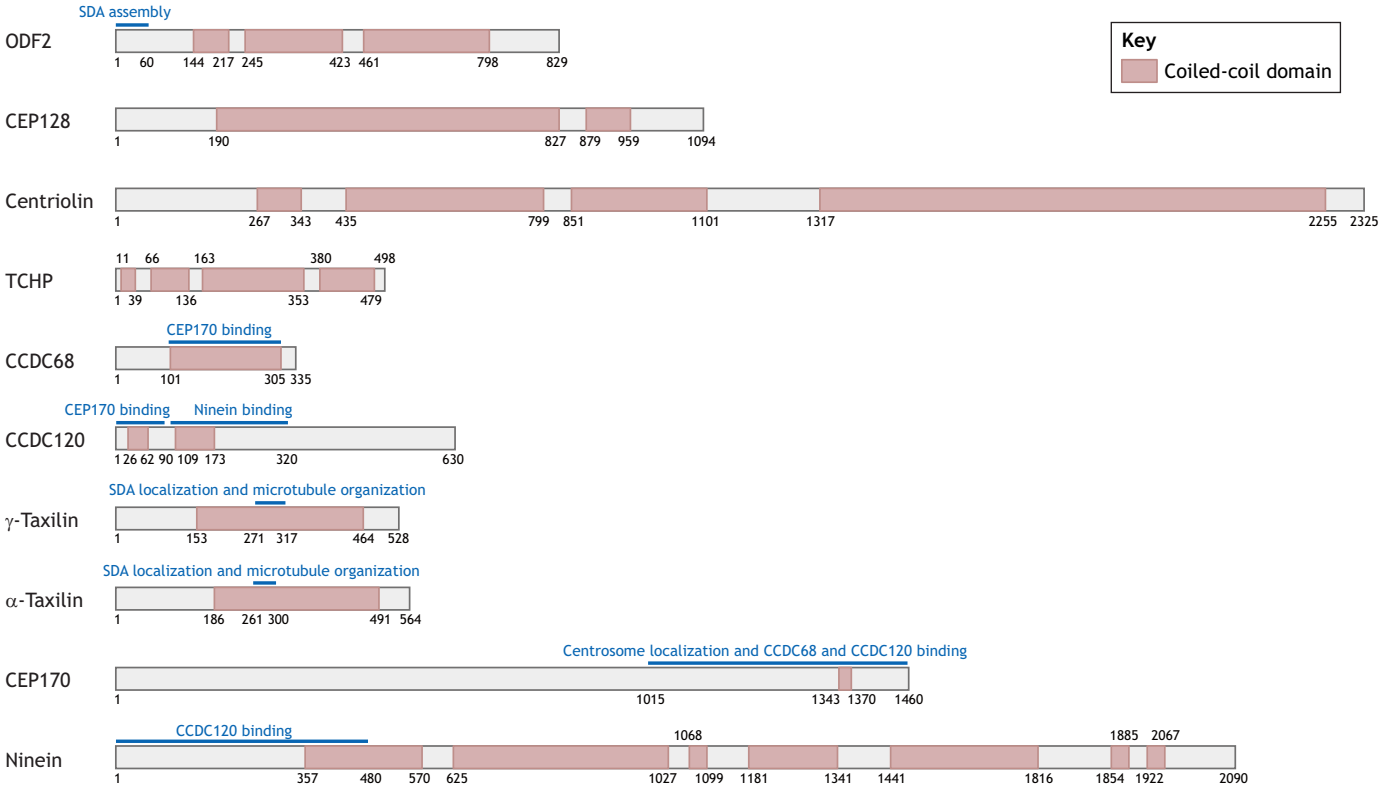

Fig. 2. Domain organization of SDA proteins. Schematic showing the secondary structures of SDA proteins and their interaction domains. The coiled-coil domains are marked in pink; the blue lines indicate the interaction and functional regions in each protein.

Centriole appendages in ciliary function

Given that cilia originate from basal bodies, centriole appendages are considered prerequisites for ciliogenesis. During this process, DA proteins are required for the attachment of pre-ciliary vesicles to the mother centriole to initiate ciliogenesis (Kumar and Reiter, 2021), whereas SDA components are responsible for the spatial positioning and signaling of primary cilia (Galati et al., 2016) (Fig. 3A,B; Table 1) and the beating direction of motile cilia (Boisvieux-Ulrich et al., 1985).

Distal appendages

DA proteins are indispensable for the early steps of primary ciliogenesis. During this process, DA components [i.e. CEP83, CEP89, FBF1, CEP164 and Chibby (also known as CBY1)] are required for the accumulation of Rabin8 (also known as RAB3IP), the Rab8 family GTPases and vesicular transport machinery at the centrosome to form a ciliary vesicle (Cuenca et al., 2019; Schmidt et al., 2012; Sillibourne et al., 2011; Burke et al., 2014), after which CEP83 mediates its migration to the mother centriole and subsequent centriole-to-membrane docking (Joo et al., 2013; Tanos et al., 2013). Centriole migration to the membrane during initial ciliogenesis is also driven by CEP164-mediated cytoskeletal remodeling as the mechanical force causing centriole movement (Pitaval et al., 2017). FBF1, the ciliary gating protein, is required for ciliary entry of assembled intraflagellar transport (IFT) machinery (Wei et al., 2013; Hodge et al., 2021). Dye-filling 19 (DYF-19), the *C. elegans* homolog of the FBF1 protein, has been shown to assist in IFT transport via a direct interaction with the IFT component DYF-11 (Wei et al., 2013). Twitchy, the FBF1 ortholog in *Drosophila*, functions similarly in sensory neurons (Hodge et al., 2021). Loss of Twitchy results in uncoordinated locomotion and an adult-lethal phenotype. Moreover, Twitchy mutant male flies fail to produce motile sperm, and thus display male infertility via an unknown mechanism (Hodge et al., 2021).

Tau tubulin kinase 2 (TTBK2), a key kinase that phosphorylates various substrates during cilia initiation, is recruited to DAs by CEP164 following cilia initiation (Oda et al., 2014; Bernatik et al., 2020). This recruitment is mediated by the CEP164 N-terminal WW domain (amino acids 56–89) and the TTBK2 C-terminal proline-rich region (amino acids 1074–1085) (Čajánek and Nigg, 2014; Rosa et al., 2022). Once in position, TTBK2 promotes ciliogenesis by phosphorylating the centriolar distal end ciliary negative factor, M-phase phosphoprotein 9 (MPP9; also known as MPHOSPH9), followed by its ubiquitin proteasome-mediated degradation and removal of its associated proteins, such as CEP97 and CP110 (Huang et al., 2018). TTBK2 also phosphorylates CEP83, which is necessary for ciliary vesicle docking at the membrane and removal of CP110 (Lo et al., 2019). Following removal of CEP97 and CP110 from the distal end of the mother centriole, LRRC45 promotes the early steps of ciliary axoneme extension (Kurtulmus et al., 2018). In addition, NEK2 has also been reported to overlap with DAs (Viol et al., 2020) and facilitate primary cilia disassembly by activating Kif24, a microtubule-depolarizing kinesin (Kim et al., 2015).

Subdistal appendages

Given that depletion of the SDA base component ODF2 does not impair ciliogenesis in RPE1 cells (Mazo et al., 2016; Viol et al., 2020), it appears that the SDA structure might not be essential during the early steps of cilia formation. However, several recent studies have uncovered the various roles of SDA proteins in the regulation of ciliary signaling and positioning. CEP128, which is localized close to and binds ODF2 (Kashihara et al., 2019), has been

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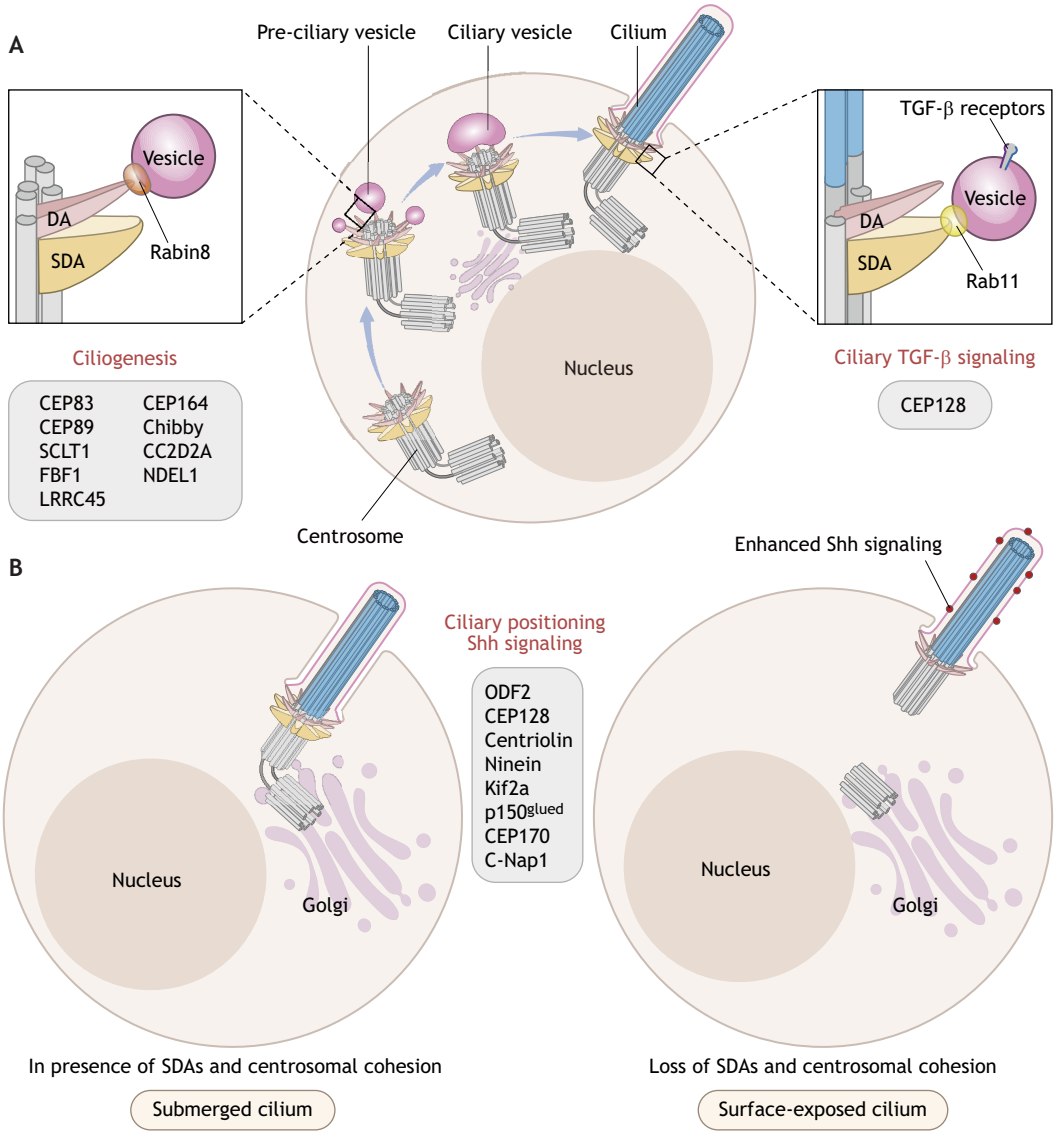

Fig. 3. The multiple functions of DA and SDA proteins in ciliary regulation. (A) Schematic overview of the early steps of ciliogenesis. DA proteins (e.g. CEP83, CEP89, FBF1, CEP164 and Chibby) are essential for pre-ciliary vesicle docking and ciliary vesicle formation at the cell membrane to initiate ciliogenesis. Rabin8 has been reported to mediate the association between DA proteins and pre-ciliary vesicles. The SDA protein CEP128 is required for recruiting Rab11-containing vesicles that transport TGF-β receptors into the cilium, thus facilitating ciliary TGF-β and BMP signaling. (B) The SDA structure, together with the proximal-end proteins, is required for the submerged ciliary localization close to the Golgi in the cell. Double loss of an SDA protein (e.g. ODF2, ninein or CEP170) and the C-Nap1 protein at the proximal ends results in translocation of the submerged cilium to the cell surface, away from daughter centriole next to Golgi, causing increased mechanical sensitivity and ectopic Shh signaling.

reported to regulate cell signaling and Rab11-containing vesicle trafficking in primary cilia (Fig. 3A) (Mönnich et al., 2018). Depletion of CEP128 in zebrafish causes impaired transforming growth factor-β/bone morphogenetic protein (TGF-β/BMP) signaling, resulting in severe developmental defects, such as a dorsalized phenotype of morphants (Mönnich et al., 2018). NudE neurodevelopment protein 1-like 1 (NDEL1) and TCHP, for example, inhibit cilia assembly via the AurA activation pathway in growing cells (Inaba et al., 2016; Inoko et al., 2012). Depletion of NDEL1 results in decreased TCHP at the mother centriole (Inaba et al., 2016), which is required for AurA activation, predominantly in G1 phase (Inoko et al., 2012). TCHP or AurA depletion induces G0/G1 arrest and untimely primary cilia formation (Inoko et al., 2012). Moreover, SDA proteins cooperate with the centriole proximal end protein C-Nap1 (also known as CEP250), which is the centrosome cohesion factor, to determine the spatial location and sensory properties of cilia (Fig. 3B) (Mazo et al., 2016). Single- or double-knockout of DA proteins and C-Nap1, via a CRISPR/Cas9 approach, does not affect the assembly of cilia; however, loss of both DAs and C-Nap1 causes the translocation of the submerged cilium to the cell surface away from the daughter centriole next to Golgi (Mazo et al., 2016). The surface-exposed cilium can respond to mechanical stimuli and cell signaling molecules, causing increased mechanical sensitivity and ectopic Shh signaling (Mazo et al., 2016) (Fig. 3B). Interestingly, siRNA-mediated depletion of the SDA components ninein or Kif3a reduces CEP290 localization to centriolar satellites and subsequently inhibits ciliary transition zone formation (Tu et al., 2018), indicating the potential link between the maintenance of microtubule anchoring and ciliogenesis.

Not only are primary ciliary functions affected by depletion of SDA proteins, but multi-ciliated cell functions are also dysregulated (Herawati et al., 2016; Kunimoto et al., 2012). For example, loss of *Odf2* exons 6 and 7 causes depleted basal feet from the basal bodies of multi-ciliated tracheal cells and uncoordinated ciliary movement (Herawati et al., 2016; Kunimoto et al., 2012), resulting in a coughing/sneezing-like phenotype in mice (Kunimoto et al., 2012).

Centriole appendages in microtubule organization

During interphase, cytoplasmic microtubules are nucleated by the γ-tubulin ring complexes (γTuRCs) at the centrosome, some of which are then released and anchored at the SDA tips (Doxsey, 2001). Ninein and CEP170 are components of the microtubule-anchoring complex at SDAs (Pizon et al., 2020). Other SDA proteins, such as CCDC68, CCDC120, α-taxilin and γ-taxilin, participate in this complex through direct or indirect interactions with ninein and CEP170 (Fig. 4A; Table 1) (Huang et al., 2017; Ma et al., 2022). Ninein also acts as a scaffold for γ-TuRCs and thus indirectly participates in microtubule nucleation (Delgehyr et al., 2005). In addition, some centrosomal proteins, such as TCHP, end-binding protein 1 (EB1; also known as MAPRE1), fibronectin type III and SPRY domain-containing 1 (FSD1), the CEP350-FGFR oncogene partner (FOP; also known as CEP43)–CEP19 complex and SSX family member 2 interacting protein (SSX2IP), localize close to SDAs and also play critical roles in microtubule anchoring through directly binding to microtubules or interacting with SDA components (Hori et al., 2014; Ibi et al., 2011; Mojarad et al., 2017; Schrøder et al., 2011; Tu et al., 2018; Yan et al., 2006).

During mitosis, SDA proteins (such as ODF2, α-taxilin, γ-taxilin and CEP170) are required for proper spindle orientation, most likely coordinating astral microtubule organization (Fig. 4B; Table 1) (Hung et al., 2016; Ma et al., 2022). The SDA components CEP170 and ninein translocate to the PCM during mitosis (Chen et al., 2003; Guarguaglini et al., 2005; Hung et al., 2016) and might maintain astral microtubule integrity via their microtubule-binding ability. Given that the densities of SDA structures during mitosis are different among EM studies (Hung et al., 2016; Kong et al., 2014; Vorobjev and Chentsov Yu, 1982), monitoring the detailed mitotic localization of SDA components will improve our understanding of SDA dynamics and component functions.

Centriole appendages in development and disease

Ciliopathies

Given that the DA structure mainly participates in the initial steps of ciliogenesis, mutations in DA proteins cause cilia defects and ciliopathies in humans (Table 1). Several mutations in CEP83 have been identified in individuals with nephronophthisis (NPHP), an autosomal recessive chronic renal failure that develops in childhood (Failler et al., 2014). CEP83 mutations in two different individuals lead to it having an abnormal DA localization and weakened interaction with CEP164, which in turn causes CEP164 mislocalization at centrosomes (Failler et al., 2014). Fibroblasts from individuals harboring CEP83 mutations display a slightly decreased ciliary rate but longer ciliary length after serum deprivation (Failler et al., 2014). Other clinical studies have also reported that individuals harboring CEP83 mutants present with intellectual disability and retinal dystrophy, two symptoms defined as NPHP-related ciliopathies (Failler et al., 2014; Veldman et al., 2021).

CEP164 has been reported to recruit Chibby to DAs to promote ciliary vesicle formation and basal body docking during multi-ciliogenesis (Burke et al., 2014). Loss of CEP164 in multi-ciliated cells severely affects the centrosomal localization of Chibby and the transition zone component FAM92A and FAM92B (also known as CIBAR1 and CIBAR2), leading to the failure of small pre-ciliary vesicle recruitment at basal bodies (Siller et al., 2017). Conditional knockout of *Cep164* in mice results in a severe loss of multi-cilia from the airway, ependyma, oviduct and efferent duct. These mice display hydrocephalus and male infertility, which mimics the symptoms presented by patients with primary ciliary dyskinesia (Siller et al., 2017; Hoque et al., 2021). In humans, CEP164 mutations have been found in individuals with NPHP-related ciliopathies (Chaki et al., 2012). These CEP164 mutants lose their DA localization, which leads to almost complete loss of ciliogenesis in renal epithelial cells (Chaki et al., 2012).

SCLT1 deficiency in mice causes ciliopathy-specific phenotypes, such as cystic kidney, cleft palate and polydactyly (Li et al., 2017).

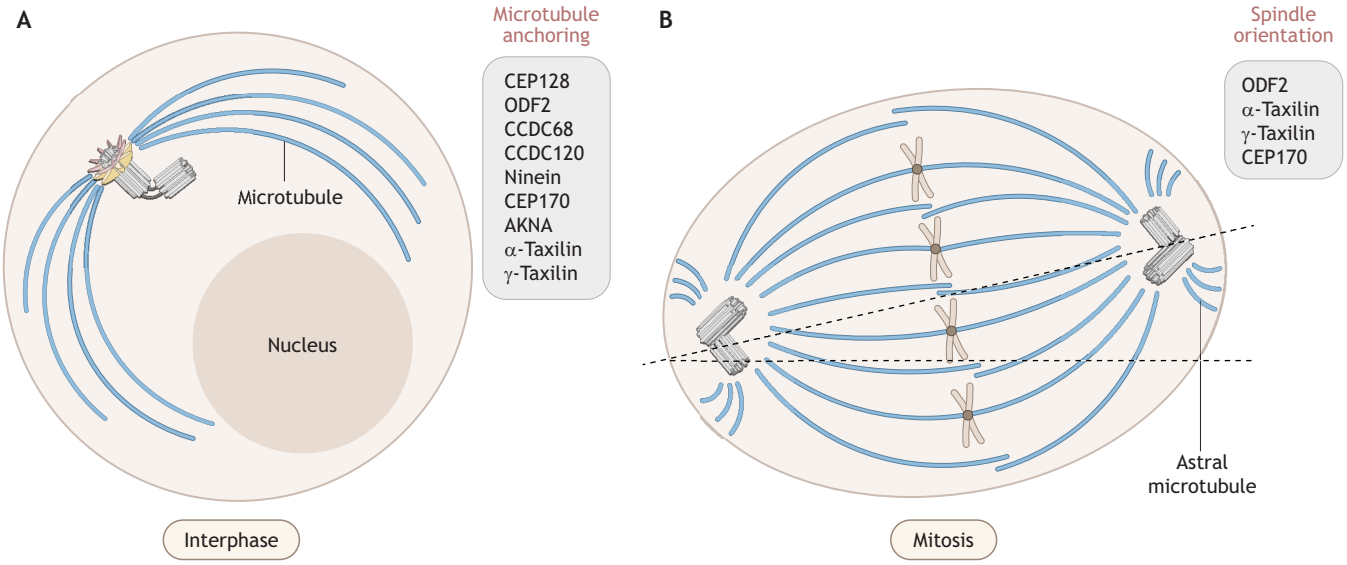

Fig. 4. Roles of SDA proteins in microtubule organization. (A) In interphase, SDAs are required for microtubule anchoring at the centrosome, and several SDA components, such as ODF2, ninein and CEP170, are involved this process. (B) During mitosis, SDA structures disappear from centrosomes in some cell types (e.g. RPE1 cells), whereas certain SDA proteins, including ODF2, α-taxilin, β-taxilin and CEP170, are required for correct spindle orientation.

Loss of SCLT1 inhibits ciliogenesis in the kidney, increases the proliferation of renal epithelial cells and also activates signal transducer and activator of transcription 3 (STAT3) signaling (Li et al., 2017). In humans, SCLT1 mutations cause Bardet–Biedl syndrome (BBS), a rare autosomal recessive ciliopathy characterized by polydactyly, renal dysfunction and obesity (Morisada et al., 2020). Moreover, the *SCLT1* gene is mutated in patients with midline cleft, microcephaly, microphthalmia or anophthalmia, abnormal genitalia and congenital heart disease, which is diagnosed as orofaciodigital (OFD) syndrome type IX (Adly et al., 2014). In addition, *CEP89* gene defects are frequently identified in patients with autosomal dominant polycystic kidney disease (ADPKD) (Skalická et al., 2018).

Owing to their strong association with ciliopathies, DA proteins are considered potential therapeutic targets for clinical cases. CRISPR/Cas9-based genetic therapies have been introduced to clinical practice with a view to meeting the medical needs of ciliopathies with renal and retinal phenotypes (Molinari and Sayer, 2021). CEP290, which is essential for ciliary transition zone assembly, is frequently mutated in human ciliopathies (Wu et al., 2020). Leber congenital amaurosis type 10 (LCA10), for example, is a severe retinal dystrophy caused by CEP290 mutation (Maeder et al., 2019). EDIT-101, a gene editing system designed to remove CEP290 mutations, has been developed and delivered directly into the eye of a LCA10 patient to restore function (Maeder et al., 2019; Ledford, 2020). This trial encourages the development of other CRISPR-based medicines for inherited DA mutation-induced ciliopathies.

Beyond ciliogenesis

DA proteins also possess important functions outside of ciliogenesis in homeostasis and development. In cytotoxic T lymphocytes (CTLs), CEP83 is required for the docking of the transient mother centriole at the plasma membrane, favoring the delivery of secretory lysosomes to the immunological synapse and thus functioning to support the destruction of virally infected or cancerous targets by CTLs (Stinchcombe et al., 2015). Anchorage of the mother centriole at the apical membrane of radial glial progenitors (RGPs) by DAs is also essential during the early stages of cortical development, given that loss of CEP83 in RGPs results in centrosome detachment from the apical membrane, disorganized microtubule structures, overproduction of RGPs and an enlarged cortex (Shao et al., 2020). As well as performing structural functions, DA proteins can also initiate cell signaling cascades and determine cell fate irrespective of ciliogenesis. p53-induced death domain protein 1 (PIDD1) forms a molecular platform, named the PIDDosome, to activate caspase-2 and induce apoptosis in response to DNA damage (Burigotto et al., 2021; Evans et al., 2021). ANKRD26, the DA localization of which is dependent on SCLT1, can recruit PIDD1 to DAs to mediate PIDDosome activation in the presence of supernumerary centrosomes or DNA damage, as a way to limit cell proliferation (Burigotto et al., 2021; Evans et al., 2021). The DA tip protein CEP164 has been reported to bind to GLI family zinc finger 2 (GLI2) and control its activation. GLI2 is released from the mother centriole following loss of CEP164, which activates the GLI2–cyclin D–CDK6 axis and promotes cell hyperproliferation in both cancer cells (e.g. pancreatic ductal adenocarcinoma cells) and non-cancer cells (e.g. collecting duct epithelial cells) (Kobayashi et al., 2020; Airik et al., 2019). Ectopic CEP164 expression restores DA localization of GLI2 and normal expression levels of cyclin D–CDK6 (Kobayashi et al., 2020). CEP164 loss also activates the DNA damage response (DDR) pathway in renal inner medullary collecting duct (IMCD3) cells, causing apoptosis and epithelial-to-mesenchymal transition (Chaki et al., 2012; Slaats et al., 2014). Overexpression of wild-type, but not disease-related mutants, of CEP164, can rescue the proliferation deficits in CEP164-depleted IMCD3 cells (Chaki et al., 2012). Therefore, CEP164 might become a promising therapeutic target for cancer and polycystic kidney disease.

The multiple functions of SDA proteins in microtubule organization and ciliary regulation raise questions regarding their roles in development. ODF2 is critical for the establishment of apical–basal polarity during lumen formation of 3D-cultured Madin–Darby canine kidney (MDCK) acini (Hung et al., 2016). AT-hook transcription factor (AKNA), an SDA component, is responsible for microtubule organization and neural stem cell (NSC) delamination during forebrain development (Camargo Ortega et al., 2019). shRNA-induced *AKNA* knockdown in mouse causes retention of a greater number of NSCs in the ventricular zone (VZ), whereas overexpression of AKNA induces fast delamination with fewer NSCs and more basal progenitors (Camargo Ortega et al., 2019). The roles of AKNA in microtubule nucleation and growth are essential for delamination, as disruption of microtubule dynamics by Taxol treatment prevents AKNA-induced delamination (Camargo Ortega et al., 2019). Moreover, a recent proteome study has revealed that interactors of the SDA proteins CEP170 and ODF2 decline during differentiation from human NSCs to neurons (O'Neill et al., 2022), further indicating multiple roles for centriolar SDA in brain development.

SDA components are also pivotal to the self-renewal and differentiation of neural progenitors. Since centrosome duplication and maturation produce two differently aged mother centrioles, the division of RGPs is thought to be asymmetric; the daughter cell with the older mother centriole mostly stays in the VZ and retains its stemness, while the one with the younger mother centriole is likely to exit the VZ and differentiate into the cortical plate (Wang et al., 2009). Ninein, an SDA-specific protein that marks centrosome maturation (Ou et al., 2002), has been implicated in this process (Wang et al., 2009). shRNA-induced ninein knockdown in mouse disrupts asymmetric division and causes premature exit of cells from the VZ, which can be rescued by ninein overexpression (Wang et al., 2009). Given that ninein relocates from SDAs to the PCM during mitosis (Chen et al., 2003), the impaired asymmetric division in ninein-depleted RGPs might be caused by spindle pole misorientation. α-Taxilin and γ-taxilin, as partners of ninein at SDAs, are also required for SDA structural integrity (Ma et al., 2022); however, their involvement in neural progenitor differentiation remains unknown.

Clinical surveys have demonstrated a relationship between ninein mutations and microcephalic primordial dwarfism (MPD); such patients suffer from growth delays, microcephaly and developmental retardation (Dauber et al., 2012). Ninein mutations are also involved in spondyloepimetaphyseal dysplasia with joint laxity, leptodactylic type (SEMDJL2), which is characterized by disproportionate short stature, midface hypoplasia, joint laxity and deformities of the legs and feet (Grosch et al., 2013).

Conclusion and perspectives

As an increasing number of DA and SDA components have been identified and their functions recognized, the appendages of the mother centriole have attracted attention in recent years. These appendages have been shown to play a role in various intracellular events, including ciliary functions and microtubule organization,

and their mutation has been correlated with several clinical developmental disorders.

Although several appendage proteins have been defined using super-resolution microscopy and biochemical and genetic tools, it is highly likely that there remain other proteins to be discovered. For example, ODF2 is considered the most upstream protein at SDAs; however, the direct recruitment relationship between ODF2 and the other SDA components has not been validated. Therefore, proteins that bridge ODF2 and other SDA proteins must exist, which requires further investigation. Some SDA components show various localization patterns during mitosis (Chen et al., 2003; Guarguaglini et al., 2005), hence, characterizing the mechanisms that facilitate SDA protein translocation during G2-M phase transition will expand our understanding of SDA protein functions. Recent studies have shown that some centrosomal proteins near SDAs can facilitate both microtubule anchoring and cilia formation (Hori et al., 2014; Ibi et al., 2011; Mojarad et al., 2017; Schrøder et al., 2011; Tu et al., 2018), and it would be interesting to elucidate whether microtubule aster anchoring and ciliogenesis are cooperatively controlled. In addition, most studies concerning SDA proteins concentrate on their impact on cellular behavior, such as microtubule dynamics and ciliogenesis, but their function in individual developmental contexts and homeostasis remains elusive. Future studies are expected to provide additional insights into the role of SDAs in development and disease and uncover the underlying mechanisms, a deeper understanding of which will provide clues for the early diagnosis and treatment in clinical cases.

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