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The Developmental Biology of Kinesins

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Abstract

Kinesins are microtubule-based motor proteins that are well known for their key roles in cell biological processes ranging from cell division, to intracellular transport of mRNAs, proteins, vesicles, and organelles, and microtubule disassembly. Interestingly, many of the ~45 distinct kinesin genes in vertebrate genomes have also been associated with specific phenotypes in embryonic development. In this review, we highlight the specific developmental roles of kinesins, link these to cellular roles reported *in vitro*, and highlight remaining gaps in our understanding of how this large and important family of proteins contributes to the development and morphogenesis of animals.

Introduction:

Microtubules are cytoskeletal elements comprised of tubulin and act as scaffolds for intracellular transport of a wide variety of cargoes, including individual proteins, vesicles, mRNAs, and even organelles. Microtubule-based transport is orchestrated by motor proteins, namely kinesins and dynein, and is integral to differentiation, morphogenesis, and cell survival. Dyneins function exclusively in minus-end directed transport and have been reviewed extensively elsewhere (Hou and Witman, 2015; Reck-Peterson et al., 2018; Viswanadha et al., 2017). By contrast, Kinesins are a large superfamily of proteins that are responsible not only for trafficking cellular cargoes along microtubules but also for controlling microtubule growth and stability. To date, ~45 different vertebrate kinesins have been placed into 15 different subfamilies, generating a wide diversity and specificity of function within kinesins (Supp. Table 1)(Miki et al., 2001).

Most kinesins follow a generalized structure: a highly conserved motor domain that facilitates binding and release of microtubules through ATP hydrolysis, a long neck sequence that allows homo- or heterodimerization, and finally, highly divergent cargo binding domains (Hirokawa and Noda, 2008). The 15 different subfamilies have been further categorized into three broad categories based on the location of the motor domain: N-kinesins, C-Kinesins, and M-Kinesins (Figure 1) (Lawrence et al., 2004; Miki et al., 2001). N-Kinesins contain a N-terminal motor and are plus-end directed in their movement along microtubules (Figure 1A, D). C-Kinesins have a C-terminally located motor domain and are minus-end directed microtubule motors (Figure 1B, D). And finally, M-Kinesins contain a

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"middle" motor that is more centrally located in the peptide and are described generally as microtubule depolymerizers (Figure 1C, E). Different motor domains are important for the specific microtubule-based functions each kinesin has adopted within the cell (Fig. 2).

How each kinesin interacts with microtubules, and what functions it may display *in vitro* have been relatively well defined (Supp. Table 1; Cellular roles), and the atomic structures and biophysical properties of kinesins have been reviewed extensively elsewhere (Endow et al., 2010; Verhey and Hammond, 2009; Wang et al., 2015). By contrast, the ways in which kinesins contribute to overall organismal development remain far less well defined, so in this review, we aim to highlight the specific functions of kinesins in embryonic development. Generally, these fall within five broad categories, which we address in turn below: (i) kinesins required for early axis specification by transporting maternal determinants prior to or as the result of fertilization; (ii) mitotic kinesins necessary for successful mitosis and meiosis (Fig. 2A); (iii) ciliary kinesins necessary for the formation, function, and regulation of cilia (Fig. 2B); (iv) kinesins essential for axonal and dendrite formation and function in neuronal tissues (Fig. 2C); and (v) kinesins required for development of specific organs and tissues.

In Supplemental Table 1, we provide a full accounting of all mammalian kinesins, their cell biological roles as established by *in vitro* studies, and *in vivo* phenotypes in animal models or humans. In the main text of this review, we will highlight the links between different kinesins' cellular functions and specific processes in embryogenesis, we note gaps that remain in understanding, and highlight the most exciting questions left to answer in kinesin developmental biology.

Transport of polarizing maternal determinants:

In a variety of different organisms, the embryonic axes are established prior to or as the result of fertilization. Interestingly, the establishment of these embryonic axes are often dependent upon microtubule-based transport. Most notably, axis specification is dependent upon specific members of the N-type kinesins for transport of maternally deposited mRNAs and proteins (Supp. Table 1). N-type kinesins regularly partake in transporting maternal determinants through a variety of different mechanisms that highlight an evolutionarily conserved function. Here, we will review the contribution of kinesins in early axis specification in *D. melanogaster*, *X. laevis*, and *D. rerio*.

Prior to fertilization, the *D. melanogaster* oocyte establishes an anterior/posterior axis by polarizing maternally deposited mRNAs and proteins. How maternal determinants are polarized in the oocyte has been the subject of much debate for years, however, live imaging revealed *oskar* mRNA was actively transported along microtubules (Zimyanin et al., 2008). Though microtubules are oriented in every direction in the embryo, there is a slight biased orienting of plus-ends towards the posterior pole (Zimyanin et al., 2008). More detailed analysis later showed that *oskar* mRNA and Staufen protein are posteriorly localized via multiple modes of activity of the N-terminal plus-end directed Kinesin-1 motor (Brendza et al., 2002, 2000; Clark et al., 1994). In order to properly localize *oskar* mRNA and Staufen protein, Kinesin-1 transports *oskar* and Staufen in a two part mechanism:

(i) by directly transporting the mRNA and protein as cargo and (ii) by participating in “microtubule sliding” where Kinesin-1 binds microtubules as cargo and walks along neighboring microtubules to produce a “sliding” effect (Lu et al., 2016; Métivier et al., 2019). This microtubule sliding activity of Kinesin-1 in flies is critical for cytoplasmic streaming in *Drosophila* oocytes that further reinforces *oskar* and Staufen localization at the posterior pole of the oocyte (Lu et al., 2016).

Interestingly, while Kinesin-1 contributes to overall posterior localization of Staufen and *oskar* mRNA via these mechanisms, an interesting dynamic occurs between Kinesin-1 and Myosin-V at the posterior pole (Lu et al., 2020). Kinesin-1 actively continues to transport Staufen and *oskar* mRNA moving them away from the posterior cortex, however, Myosin-V actively works to anchor *oskar* and Staufen to the posterior cortex (Lu et al., 2020). Eventually Myosin-V wins this battle-of-motor proteins due to the low microtubule density at the posterior pole, anchoring Staufen and *oskar* mRNA to the posterior cell cortex (Lu et al., 2020). Altogether the activity of Kinesin-1 posteriorly localizes *oskar* mRNA and Staufen protein in the *D. melanogaster* oocyte which are each separately critical for axis specification prior to fertilization.

X. laevis, on the other hand, offers an example of post-fertilization axis specification that also requires kinesin activities. In *Xenopus*, sperm entry triggers the assembly of maternally-deposited cortically-located microtubules to position and anchor their plus ends to the future dorsal cell cortex (Elinson and Rowning, 1988; Olson et al., 2015). These parallel microtubule arrays are essential for the transport of maternally deposited factors to the future dorsal side of the embryo in a process termed “cortical rotation.” Specifically, these microtubules are thought to act as tracks for the dorsal translocation of several regulatory factors, including the Frat1/GBP and Dishevelled proteins, as well as β-catenin, Vg1 and Wnt11 mRNAs (Miller et al., 1999; Schroeder et al., 1999; Tao et al., 2005; Weaver et al., 2003). Strikingly, two sets kinesins transport different mRNA and protein cargoes during these translocation events. Specifically Kinesin light chain (Klc4) was shown to both bind, and be required for transport of Frat1/GBP(Weaver et al., 2003), while the Kinesin-2 complex, Klp3A/3B (the homolog of mammalian Kif3A/3B), specifically transports Vg1 mRNA (Betley et al., 2004). The transport of these maternal mRNAs and proteins by two separate kinesins in *X. laevis* highlights how kinesins have evolved highly specific interactions with their cargoes. The dorsal translocation activities of these kinesins and the determinants they carry as cargo is central to the establishing the dorsal/ventral axis of the embryo and initiating the program for formation of the Nieuwkoop center and later the Spemann-Mangold organizer (Gerhart et al., 1991; Weaver and Kimelman, 2004; White and Heasman, 2008). In the absence of cortical rotation, the embryo becomes ventralized and fails to form any dorsal structures essential for survival.

Interestingly, Kinesin-1 family members in *D. rerio* serve similar functions to *D. melanogaster* and *X. laevis* in early embryo axis specification. Specifically, Kif5Ba has similar dorsalizing activity to that of Xlc4 and Kif3A/B in *X. laevis*, while also participating in microtubule organizing activities that have been described with Kinesin-1 in *D. melanogaster*. Kif5Ba promotes formation of parallel microtubule arrays and delivers *wnt8a* and Syntabulin to the future dorsal side of the zebrafish embryo (Campbell et al.,

2015). This dual function for kinesins in early embryo axis specification is both essential and conserved at some level in vertebrate axis specification. However, how kinesin family members may contribute to early mammalian embryonic axis specification remains an interesting area for future work.

Early embryonic cell cycle progression:

The earliest phase of development in most animals involves a period of remarkably rapid cell division. In order to execute mitosis, cell division is highly dependent upon a complex set of microtubule movements, alignments, and attachments that requires a diverse set of kinesins. Though such cleavage divisions in most embryos lack many of the cell cycle controls in place in adult cells, they nonetheless still require the proper microtubule dynamics, alignment, and attachment to cargoes or adaptors to ensure faithful segregation of chromosomes. A huge number of distinct kinesins have been implicated in diverse aspects of cell division *in vitro* (Fig. 2), so it is interesting that Kif11, Kif22, and Kif10 (Fig. 2A, 3A) have also been shown to play specific roles in embryonic cleavage and knockout of any one leads to cell cycle arrest and early embryonic death in mice (Supp. Table 1).

Kif11 has been shown *in vitro* to be required for spindle bipolarity/poleward flux at metaphase (Fig. 2A) (Heck et al., 1993; Sawin et al., 1992). Kif10 is required at the kinetochore to ensure proper chromosome alignment during mitosis (Fig. 2A) (Brown et al., 1996; Putkey et al., 2002; Wood et al., 1997; Yao et al., 2000; Yen et al., 1992). Finally, Kif22 is classified as a chromokinesin, meaning its cargo binding domain is capable of binding chromosomes. As such Kif22 is required for chromosome movements during prometaphase and metaphase (Fig. 2A) (Antonio et al., 2000; Levesque and Compton, 2001; Ohsugi et al., 2008; Tokai et al., 1996; Tokai-Nishizumi et al., 2005; Zhu et al., 2005). In addition to mammalian kinesins, the microtubule depolymerizing kinesin, KLP10A, related to the Kinesin-13 family in mammals, has dual roles in cell cycle progression in *D. melanogaster.* In females, KLP10A has been shown to control acentrosomal spindle organization and dynamics in oocytes (Radford et al., 2012), while also controlling centrosomal length in *D. melanogaster* male germline stem cells (GSCs) (Chen et al., 2016). Given the myriad functions of kinesins in mitosis, these studies highlight the power of intersecting cell biology *in vitro* with genetics *in vivo* for understanding kinesin function during development.

Cilia formation and function during development:

Cilia are microtubule-based projections of the cell that function in signaling and fluid flow in many developing organisms. During development, two types of cilia are integral for the organism: primary cilia are essential organelles for processing signaling events that govern embryonic patterning, while motile cilia generate polarized fluid flows essential to both patterning and homeostasis in tubular organs. Cilia rely heavily upon kinesins for their formation, function, and regulation in a variety of different manners. Although ciliary kinesins have been extensively reviewed relatively recently (Lechtreck, 2015; Reilly and Benmerah, 2019; Scholey, 2008), we will briefly review them here with an emphasis on developmental contexts.

Intraflagellar Transport (IFT):

Intraflagellar Transport (IFT) is the process by which ciliary components are actively transported from the basal body, a modified mother centriole, into the cilium and out again. IFT is essential for the proper assembly and maintenance of each and every cilium and it, too, has been reviewed extensively elsewhere (Prevo et al., 2017; Reilly and Benmerah, 2019; Scholey, 2008). The Kinesin-2 family is indispensable for IFT, with Kif3A and Kif3B serving as motors required for anterograde movement of IFT in all cilia types (Fig. 2B, Supp. Table 1). In multiple animal models, loss of Kif3A/B function leads to global ciliogenesis defects in every ciliated cell type (Supp. Table 1). *Kif3A* and *Kif3B* mutant mice are embryonic lethal due to exencephaly and laterality defects associated with ciliogenesis defects (Marszalek et al., 1999; Nonaka et al., 1998; Takeda et al., 1999). Interestingly, the two other kinesins of the Kinesin-2 family, Kif17 and Kif3C, have been implicated in IFT in specific tissues in *C. elegans* and zebrafish (Supp. Table 1), however their roles in IFT in mammals remains unclear (Jiang et al., 2015). Kif17 (osm-3 in *C. elegans*) has been well-described as an "accessory" IFT motor that aids in assembly of distal segments in specialized cilia types both in *C. elegans* and in *D. rerio* (Insinna et al., 2008, 2008; Zhao et al., 2012). Most interestingly, Kif17 is homodimeric and walks at a slower rate than the Kif3A/3B kinesin complex. When bound to an IFT train with Kif3A/3B, a recent study found that the two kinesin complexes find a walking rate between the rate of the faster and slower kinesins (Milic et al., 2017). This unique cooperation between the two sets of motors highlights the complex molecular interactions that can occur between kinesins.

Primary cilia:

Primary cilia act as signaling antenna, transmitting signals like Sonic Hedgehog (Shh) that are vital for proliferation, cell survival, and specification during development (Bangs and Anderson, 2017). Primary cilia are present on mitotically active cells and are continually assembled and disassembled when entering and exiting the cell cycle. Here, we will discuss the kinesins important for Shh signaling and ciliary disassembly.

How the cilium transmits Shh signals detected within the cilium to the rest of the cell still remains an active area of research, but myriad studies have demonstrated that activation requires the localization of Shh signaling components to the ciliary tip. Interestingly, the atypical kinesin Kif7 organizes this compartment of primary cilia by regulating the length of ciliary microtubules at the tip and binding Gli proteins, the transcription factors responsible for downstream Shh signaling (Cheung et al., 2009; He et al., 2014; Liem et al., 2009). Consistent with this cell biological function, *Kif7* mutant mice phenocopy mice with mutations in the *Shh* pathway, dying at the end of gestation with polydactyly and expanded motor neuron fates (Liem et al., 2009).

Both assembly and disassembly of primary cilia are closely linked with the cell cycle, and accordingly, both processes are essential for normal signaling. Cycling cells assemble primary cilia during interphase and disassemble cilia when entering mitosis (Wang and Dynlacht, 2018). For disassembly, two Kinesin-13 family members are essential: Kif2A and Kif24 (Fig. 2B). In general, the Kinesin-13 subfamily acts as M-type depolymerizing kinesins. Kif2A interacts with Polo Like Kinase 1 (PLK1) upon entry into the cell cycle

and mediates primary cilia disassembly (Broix et al., 2018; Miyamoto et al., 2015). This kinesin has also been shown to depolymerize axonal microtubules (Homma et al., 2003). Kif2A mutant mice are embryonic lethal with severe brain defects partially due to cell death of neural progenitors due to improper disassembly of cilia upon cell cycle entry (Broix et al., 2018; Homma et al., 2003). Interestingly, the other Kinesin-13 member Kif24, which is mammalian specific, is suggested to play a similar role in ciliary disassembly in cell culture, though no *in vivo* validation has been reported (Supp. Table 1, Fig. 2B) (Kim et al., 2015; Kobayashi et al., 2011).

Motile cilia and multiciliated cells:

Motile cilia play diverse roles in embryonic development. Single motile cilia are required to move fluid and signals that break the left/right symmetry of the embryo (Little and Norris, 2020). On the other hand, multiciliated cells have dozens of motile cilia located in the brain (i.e. ependymal cells), the trachea, and male/female reproductive tracts where they move fluids to ensure the development and health of those tissues (Brooks and Wallingford, 2014). Additionally, sperm have motile flagella that are essential for sperm movement. A variety of kinesins, including the IFT kinesins, are important for the formation, function, and regulation of motile cilia. In addition, several non-IFT kinesins have been linked to motile cilia specific roles. This set of kinesins are often identified as being direct targets of the master motile cilia transcription factor FoxJ1 (Choksi et al., 2014a, 2014b; Jacquet et al., 2009); these include: Kif6, Kif9, Kif27, Kif19A and Kif18B (Fig. 2B).

Kif6 and Kif9 are the only two members of the Kinesin-9 super family and both have been linked to motile cilia function, albeit through separate and specific functions. This family is thought to consist of N-type motors, although the precise walking and molecular capabilities of these two kinesins remains unexplored. We recently reported that Kif6 is expressed in a highly tissue-specific manner and is specifically required for ciliogenesis of multiciliated ependymal cells in the brain (Fig. 3), while deleterious mutations in *Kif6* does not affect other multiciliated tissues in mice or zebrafish (Buchan et al., 2014; Konjikusic et al., 2018). In contrast, Kif9 is not required for ciliogenesis, but rather is necessary for ciliary beating. Klp1 is the Kif9 homologue in the ciliated algae *Chlamydomonas*, and it localizes to the central apparatus of motile flagella, and its loss leads to structural disruption of the central pair and defective flagellar beating (Bernstein et al., 1994; Yokoyama et al., 2004). Moreover, a recent study reported that *Kif9* mutant mice have impaired sperm flagellar motility (Miyata et al., 2020). Intriguingly, this study observed no hydrocephaly in their *Kif9* mutant mice, suggesting that Kif9 is dispensable for ependymal cell cilia motility, while analysis of the multiciliated cells of the trachea or oviduct was not reported.

Kif27 is a mammalian-specific paralog of the Kinesin-4 protein Kif7 and has been found to function specifically in motile cilia (Fig. 2B). Mouse *Kif27* knockout results in situs inversus, hydrocephaly, and otitis media, all phenotypes linked to motile cilia dysfunction (Vogel et al., 2012). Kif27 thought to be required for assembly of the central pair of microtubules and localizes to basal bodies of trachea multiciliated cells (Wilson et al., 2009; Yue et al., 2018). The precise function of Kif27 remains to be determined, but *in vitro*, this

kinesin is slowly processive and can inhibit microtubule growth (Wilson et al., 2009; Yue et al., 2018)

Finally, the two other kinesins with suggested roles in motile cilia, Kif19A and Kif18B, are part of the Kinesin-8 family, motors that primarily function in microtubule depolymerization. Kif19A localizes to the tip of these multiciliated cells where it depolymerizes microtubules to regulate ciliary length (Niwa et al., 2012; Wang et al., 2016, p. 19). In fact, *Kif19A* knockout mice present with hydrocephalus and display longer cilia on their ependymal and tracheal/oviductal multiciliated cells, presumably causing disrupted fluid flow in these tissues (Niwa et al., 2012). The other Kinesin-8 family member, Kif18B can promote microtubule catastrophe of the mitotic spindle in cell culture but has also been reported to be a target of FoxJ1 and loss of function in zebrafish showed shorter motile cilia in the pronephros (Choksi et al., 2014a). To date there is no mammalian *Kif18B* mutant reported to validate a role in mammalian multiciliated cells.

Development of the brain and central nervous system (CNS):

The development of the central nervous system is a complex process requiring proliferation of neural progenitors, extension of long polarized microtubule-based axonal/dendritic processes, transport of support factors along these microtubule-based extensions, and later transport of neurotransmitters/ signals to/from nearby cells. It is no surprise, then, that many of the 45 kinesins have been linked to the CNS in one way or another (Fig. 3C, Supp. Table 1). Although the function of kinesins in the CNS has been reviewed at length (Hirokawa et al., 2010), we will briefly review their roles with a focus on developmental contexts.

Mitosis and Proliferation in the Brain and CNS:

As described above (see early embryonic cleavages), successful completion of mitosis and proliferation/differentiation of cells is critical for the development of any given tissue in the embryo. Cells must not only replicate themselves to form more progenitor cells (a term called “symmetric divisions”), but ultimately divide to replicate two daughter cells with two separate states: progenitor and non-progenitor-like states (“asymmetric divisions”). The development and homeostasis of the brain and CNS is no different. Interestingly, two Kinesin-6 family members play separate and specific roles in mitotic events and proliferation decisions in the CNS. Kif20A is required for the control of symmetric vs. asymmetric cell divisions in the developing CNS, so *Kif20A* knockout mice are embryonic lethal, displaying smaller brain and body size due to increased apoptosis in the brain caused by improper cell division decisions (Geng et al., 2018). In contrast, Kif20B controls midbody organization during cytokinesis in polarized cortical stem cells. Knockout in mouse leads to perinatal lethality and microcephaly caused by loss of midbody organization (Janisch et al., 2018, 2013). These examples highlight the fact that despite close homology, kinesins have frequently evolved highly divergent roles in mitosis in distinct tissues in the developing brain and CNS.

Axonal outgrowth:

Axons are long, polarized, microtubule-based neuronal projections that send signals from the neuronal cell body to other cells. Axons extend from the cell body, orienting their minus ends towards the cell body, and the plus-ends/growing ends of microtubules towards the tip of an axon (Figure 2C). While the generation and dynamics of the axonal growth cone is heavily dependent upon the actin cytoskeleton and its dynamics (Dent et al., 2011), axons still rely on kinesins for axonal outgrowth in a variety of ways (Hirokawa et al., 2010). Two mammalian kinesins, Kif21A and Kif5A (Fig 2C), that have been linked to the control of axon outgrowth by separate and specific functions. First, Kif21A, a member of the Kinesin-4 family, acts via microtubule growth inhibition at the cell cortex, allowing microtubules to accumulate within the axon rather than at the cortex (van der Vaart et al., 2013). Mutations in *Kif21A* in human and mouse are associated with Congenital Fibrosis of the Extraocular Muscles Type 1 (CFEOM1) resulting from aberrant axon morphology and reduced responsiveness to inhibitory cues (van der Vaart et al., 2013; Yamada et al., 2003). On the other hand, Kif5A is required for axonal outgrowth through the transport of neurofilaments (Xia et al., 2003, p. 200). Loss of *Kif5A* in mouse leads to loss of large caliber axons and neurofilament accumulation in neuronal cell bodies (Brenner et al., 2018; Nicolas et al., 2018; Reid et al., 2002). Interesting, in *D. melanogaster* Kinesin-2 also contributes to axonal outgrowth and microtubule polarity by guiding plus-ends towards axonal outgrowths and actively excluding them from dendrites via the existing microtubule network (Mukherjee et al., 2020). The plus-end directed motion of Kinesin-2 guides growing microtubules as cargo towards existing plus ends, further elongating axons, while preferential excluding them from dendrites where microtubule polarity is minus-ends outward (Mukherjee et al., 2020). Additional kinesins have been linked to axonal outgrowth, but further analysis is warranted (see Supp. Table 1).

Axonal Transport:

Once axonal outgrowth is completed, plus-/minus-end directed transport along fully developed axons is also highly dependent upon kinesins. Several kinesins have evolved specific roles in axonal transport, but unlike Kif5a, are not required for axon outgrowth (Fig 2C). For example, Kif1A and KifC2 are required for bidirectional vesicular transport along axons: Kif1A is a neuronal-specific kinesin required for plus-end directed transport of presynaptic vesicles from the cell body to the axon, and knockout mice die shortly after birth due to motor and sensory neuron deficiencies (Hall and Hedgecock, 1991; Okada et al., n.d.; Otsuka et al., 1991; Stavoe et al., 2016; Yonekawa et al., 1998). Conversely, KifC2, a C-type kinesin in the Kinesin-14B family, is thought to contribute to minus-end directed vesicular transport from the axon back to the cell body, however validation in mice showed no obvious phenotypes as mutants were viable and fertile (Hanlon et al., 1997; Saito et al., 1997). This effect may be due to genetic compensation (see below). Rather than vesicles, Kif13A can directly bind and transport specific proteins within axons (Zhou et al., 2013). *Kif13A* mutant mice develop normally and are adult-viable but display high-level anxiety phenotypes caused by loss of serotonin receptor transport (Delevoye et al., 2009; Nakagawa et al., 2000; Sagona et al., 2010; Zhou et al., 2013). Finally, the Kinesin-1 family member Kif5C has been exhaustively studied *in vitro* for its role in intracellular cargo transport, yet Kif5C knockout mice are viable. They do, however, develop with smaller brain sizes due

to an overall loss of motor neurons (Kanai et al., 2000). It is not understood how Kif5C contributes to maintenance of motor neurons through axonal transport (Kanai et al., 2000), and a more in-depth analysis is warranted.

Dendrite formation and transport:

Dendrites are the site for receiving neuronal signals. Interestingly, unlike axons, dendrites have a mixed polarity of microtubules, leading to minus ends and plus ends pointing towards and away from the cell bodies. This means that while axons are very polarized, dendrites do not have the stringent traffic patterns observed in axons. Interestingly, though we will not expand on this here, actin also has a role in dendrite formation and maintenance (Konietzny et al., 2017). Dendrites are typically not as long and large as axons, but they are microtubule based and do require kinesins for their formation and function.

Several kinesins have implicated dendritic functions: Kif3B, Kif21B and KifC2 (Fig. 2C). Interestingly, a recent report found human patients with schizophrenia associated with Kif3B mutations (Alsabban et al., 2020). This study further showed *Kif3B* heterozygous mice displayed schizophrenic phenotypes and abnormal dendritic spine morphology due to loss of specific NMDAR receptor transport (Alsabban et al., 2020). On the other hand, a recent study expressed human missense variants of Kif21B in mouse and found that the mice developed microcephaly and suggested a role for Kif21B in axonal transport (Asselin et al., 2020) (see below in kinesins in human diseases). However, Kif21B has also been shown to be responsible for branching of the dendritic arbor and spine formation (Supp. Table 1; (Joseph R. Marszalek et al., 1999; Muhia et al., 2016). Cell culture experiments support the necessity of KifC2 for dendritic transport, however as discussed above, KifC2 mouse mutants are viable and fertile.

Organogenesis:

The development of each organ in the vertebrate body requires fine regulation of cell division, complex organizations, and specific polarization of multiple cells within the tissue. These processes are heavily reliant on microtubules, so it is not surprising that some kinesins display specific roles in organogenesis (Fig. 3). Here, we will review these roles on an organ by organ basis.

Kidney development:

Several kinesins have associations with development of the kidney in mouse, zebrafish and human (Fig. 3C), and these fall into two separate categories: (i) the necessity for cilia in proper renal function and (ii) the general development of the tissue.

The first category is closely linked to roles in the cilium. Cilia-mediated signaling is essential for mechano-sensation of fluid flow through renal ducts, and ciliary dysfunction leads to Polycystic Kidney Disease (PKD) (Veland et al., 2009). The IFT kinesins have been linked to PKD but we will not discuss their roles here as they are described above (see ciliary kinesins section). Interestingly, Kif12 is a non-IFT kinesin that has a potential link to ciliary function in the mammalian kidney (Fig. 2B, Fig. 3C). *Kif12* has been transcriptionally linked to PKD through mouse models (Gong et al., 2009). Additionally,

localization of Kif12 has been found at the primary cilia in the mouse kidney though its developmental function has yet to be defined in an animal model (Gong et al., 2009; Mrug et al., 2015).

Two kinesins have discreet non-ciliary functions in kidney development (Fig. 3C). Kif26B is required for migration and polarization of the mesenchyme that surrounds the ureteric bud during development (Guillabert-Gourgues et al., 2016; Uchiyama et al., 2010). *Kif26B* mutant mice die 24 hours post birth due to kidney agenesis (Uchiyama et al., 2010). On the other hand, human mutations in *Kif14* and analysis in developing zebrafish suggest a role for this kinesin in renal hypodysplasia stemming from improper cytokinesis (Carleton et al., 2006; Filges et al., 2014; Gruneberg et al., 2006; Makrythanasis et al., 2018; Moawia et al., 2017; Reilly et al., 2019).

Enteric nervous system (ENS) development:

While many kinesins are required for the development of the CNS in a variety of different manners (see above), one has a particular role in the development of the enteric nervous system (ENS) (Supp. Table 1, Fig. 3D). The ENS is a separate neuronal system which innervates the gut to control the digestive system (Rao and Gershon, 2016). Kif26A is an atypical kinesin in that it lacks the typical ATPase activity of the motor domain. It has been shown to negatively regulate GDNF/Ret signaling important for ENS development but has also been proposed to stably bind microtubules and regulate the length of neurites in the ENS, although this has not been shown in depth (Zhou et al., 2009). *Kif26A* mutant mice are born at normal mendelian ratios but die at 5 weeks of age with megacolon due to failure of neurite overgrowth in the ENS (Zhou et al., 2009). The mechanism to which Kif26A controls ENS neurite outgrowth may not be fully defined, but it offers another clear example of tissue-specific roles adopted by certain kinesins.

Female/male fertility:

Intriguingly, some kinesins show a specific role in mammalian fertility (Supp. Table 1, Fig. 3F). Among these, Kif18A is the most interesting, as it is required in both female and male fertility. Interestingly, *Kif18A* male and female mutant mice are born and develop normally, but are infertile (Czechanski et al., 2015) because Kif18A is specifically required for cell cycle progression of germ cells during gonad development (Czechanski et al., 2015; Liu et al., 2010; Mayr et al., 2007; Stumpff et al., 2012, 2008). How this kinesin has evolved such a specific role in gonadal development remains to be explored.

Primitive endoderm/Epiblast:

Kinesins are classically known as microtubule-based transport motors, required for transport of signals, organelles, and cargos across the cell. One kinesin is required for intracellular transport of a specific receptor during early embryonic development, Kif16B (Fig. 2D, 3A). Prior to creation of a mouse knockout, Kif16B was well-described to participate in endosome trafficking and recycling *in vitro* and in cell culture (Blatner et al., 2007; Hoepfner et al., 2005). However *Kif16B* knockout in mouse revealed that Kif16B is specifically required for endosomal trafficking of FGFR in the early embryo (Ueno et al., 2011). Upon loss of function, Kif16B mutant embryos fail to form epiblast and primitive

endodermal cell lineages due to the loss of FGFR transport, leading to embryonic lethality prior to implantation (Ueno et al., 2011). This phenotype closely mimics phenotypes associated with FGFR mutant mice (Arman et al., 1998). It is the combined *in vitro* cell culture and *in vivo* work that defined the developmental role Kif16B plays in the mouse embryo.

Genetic compensation:

Genetic compensation is common in gene families with high sequence homologies (El-Brolosy et al., 2019), as is the case for kinesins. Moreover, recent studies have revealed that genetic compensation plays a significant role in dictating phenotype severity in mutant analysis *in vivo* (El-Brolosy et al., 2019). We suggest that more in depth investigation of genetic compensation between kinesins could provide important insights into previously undefined developmental roles, so we offer two examples here:

The kinesin-3 family contains two highly homologous kinesins, Kif13A and Kif13B (Hirokawa et al., 2009). *Kif13B* knockout mice develop completely normally and are viable (Kanai et al., 2014). Knockout of *Kif13A* alone also produces no severe developmental phenotype, although these mice do display high level anxiety phenotypes (Zhou et al., 2013). Work in cell culture suggested a role of Kif13B in controlling the structure and signaling functions of cilia (Schou et al., 2017), so it was striking that when *Kif13A* and *Kif13B* double knockout mice were generated, they displayed perinatal lethality with craniofacial abnormalities but *did not* display other ciliary related phenotypes such as polydactyly or exencephaly. Because cilia mediated Shh signaling is integral to craniofacial development (Schock and Brugmann, 2017), this genetic experiment suggest the possibility of a highly tissue-specific role for Kif13A/B in craniofacial ciliogenesis.

Within the Kinesin-2 family, studies in zebrafish also reveal a specific genetic compensation between Kif3B and Kif3C (Zhao et al., 2012). Kif3A can dimerize with either Kif3B or Kif3C (Muresan et al., 1998; Nonaka et al., 1998; Yamazaki et al., 1996). However, the role of Kif3C in animal development remains largely unclear. Double knockout of *kif3B* and *kif3C* in zebrafish shows a complete loss of photoreceptor and hair cell cilia that is not present in either *kif3B* or *kif3C* knockout zebrafish alone (Zhao et al., 2012). In either case, the clear genetic compensation between Kif3 proteins demonstrates that highly homologous kinesins can serve redundant roles. Many other kinesins display high levels of homology within families and could easily function redundantly during development. More in-depth genetic studies of homologous kinesins *in vivo* should reveal previously undetected roles in animal development.

Kinesins in human genetic disorders:

Given the diversity of kinesin function during developmental and physiology described here, it is no surprise that kinesins are also implicated in human disorders and disease, as was recently reviewed elsewhere (Kalantari and Filges, 2020). In addition to many roles in cancer progression (Rath and Kozielski, 2012), many so-called “Kinesinopathies” are effectively modeled by mouse/zebrafish developmental mutant phenotypes (Supp. Table 1).

On the other hand, some kinesins display discrepancies between human disease phenotypes and those reported in animal models (Supp. Table 1), though more detailed analysis is now clarifying these discrepancies and offering insights into previously overlooked kinesin functions.

One recent example involved expression of human missense variants of Kif21B in mouse confirming human microcephaly associations (Asselin et al., 2020). In addition to humanized mutational analysis in vertebrate models, kinesin biologists should not ignore the power of mouse conditional genetics when it comes to *in vivo* analysis. A recent study used conditional knockout out *Kif11* specifically in vascular endothelial cells to overcome early embryonic necessity, which revealed vascular defects in the retina and slower proliferation of the cerebellum, mimicking several symptoms associated with *Kif11* mutations in human that were previously overlooked (Wang et al., 2020). While it remains possible that several kinesins have evolved differential functionality in humans in comparison to roles shown in other vertebrates, it is likely that more in depth *in vivo* studies via humanized mutational analysis or conditional genetic approaches in animal models will continue to offer insights into human disease phenotypes.

Conclusions:

Here, we have outlined the central roles of kinesins during embryonic development. These include regulating cell division and cargo transport in a variety of different tissues and/or cellular compartments, as well as in regulating the length and stability of microtubules in the same or different cell types and tissues. Within subfamilies of kinesins, we observe both redundant roles between family members, and extremely divergent roles. Some kinesin family members play specific roles in specific tissues during development (e.g. Kif6, Kif18A, Kif26B, and Kif26A), while others play multiple roles in several different tissues (Supp. Table 1, Fig. 2). How certain kinesins have evolved such specific roles in tissue development remains to be explored and will elucidate links between kinesin evolution and the evolution of their cargos, transport, and microtubule interactions. Several kinesins clearly are understudied *in vivo*, and demand our attention (e.g. KifC2, Kif2B, Kif24, Kif25, Kif12, Kif19B, and Kif16A; Supp. Table 1). Additionally, some kinesins have been reported in human disease and disorders yet their etiology remains only poorly defined (e.g. Kif16A, Kif16B, Kif1B, and Kif21B;Supp.Table 1, (Asselin et al., 2020).

Finally, most kinesins have been studied in some capacity with regard to *in vivo* analysis, but some have no observable phenotype in vertebrate models. Although it remains a possibility that they are dispensable for development, the high homology between certain members of kinesin families leads us to hypothesize that they may function redundantly. As we have outlined, several kinesins have already been subject to such analysis and have redundant roles. We suggest then a more detailed phenotypic analysis for the compensation between kinesins family members may lead to exciting and previously undefined developmental roles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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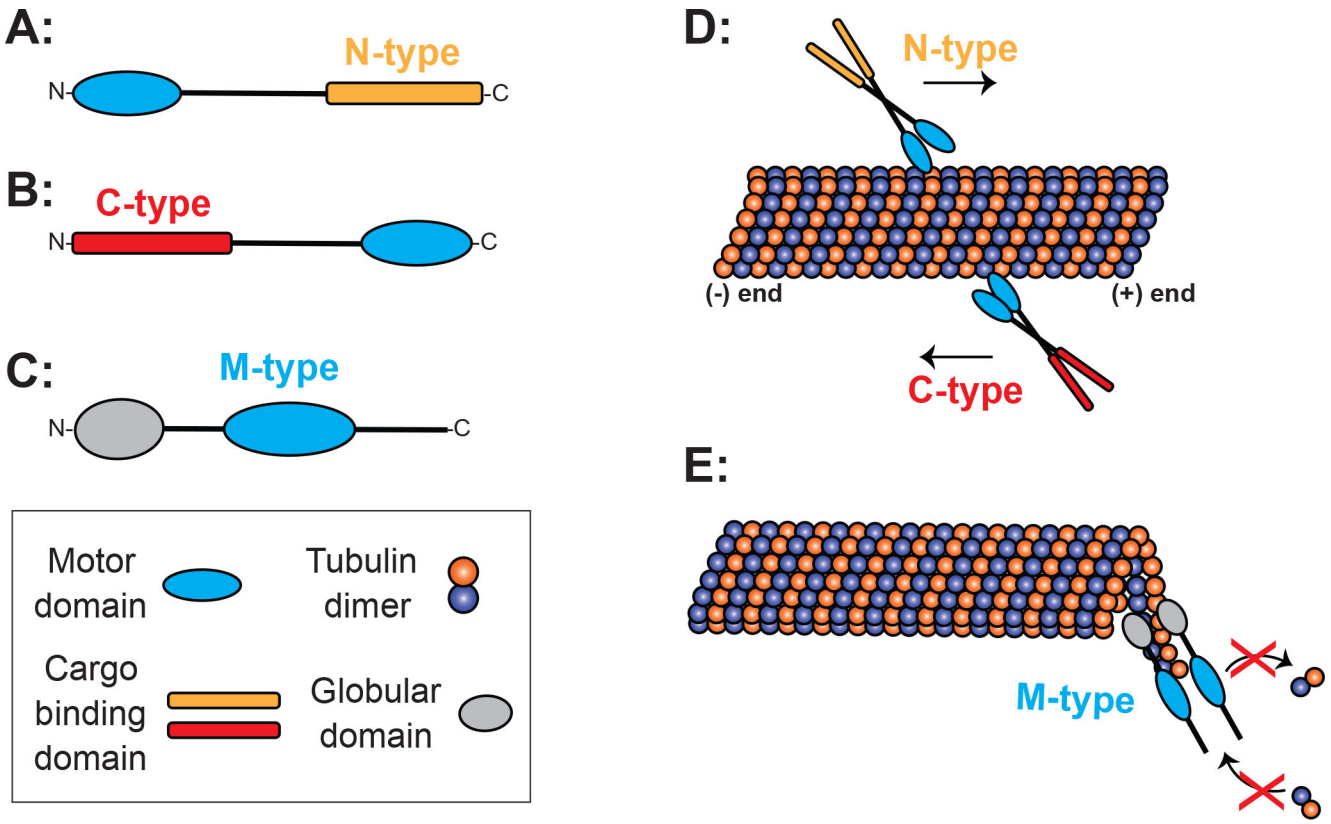

Figure 1. Schematic representing motor domain locations in N-, C-, and M-type kinesins.

Figure 1A. Schematic of N-type kinesins with N-terminal motor domains. Figure 1B. Schematic of C-type kinesins with C-terminal motor domains. Figure 1C. Schematic of M-type kinesins with motor domains located in the middle of the polypeptide. Figure 1D. Schematic depicting general direction of movement along microtubules of N- and C-type kinesins. N-type are plus end directed, while C-type are minus end directed. Figure1E. Schematic depicting M-type kinesins as microtubule depolymerizing kinesins, regulating plus end growth by depolymerizing microtubules at these locations. Inset acts as legend for figure.

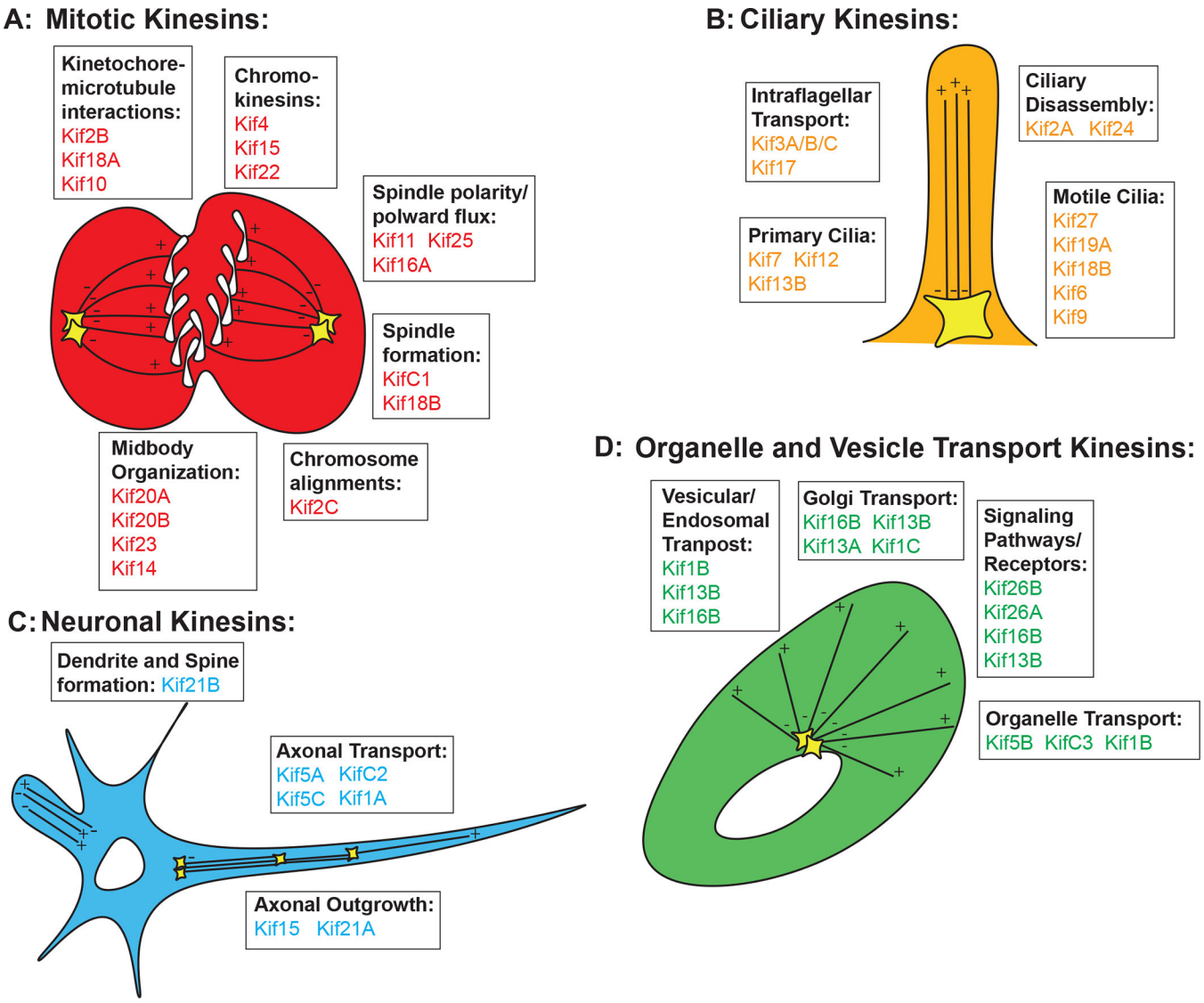

Figure 2. Cellular functions associated with kinesin. Figure 2A.

The kinesins found to have a role in mitosis either *in vivo* and/or in cell culture categorized by the exact functions they have in mitosis. Figure 2B. Kinesins found to have functions in cilia, categorized by the type of cilia and functions they have within cilia. Figure 2C. Kinesins who have a neuronal role categorized by the functions they have in dendrite and axon outgrowth or axonal transport. Figure 2D. Kinesins associated with organelle and vesicle intracellular transport categorized by the type of cargo they transport. Names of kinesins are color coded to match the subcellular functions associated with each kinesin.

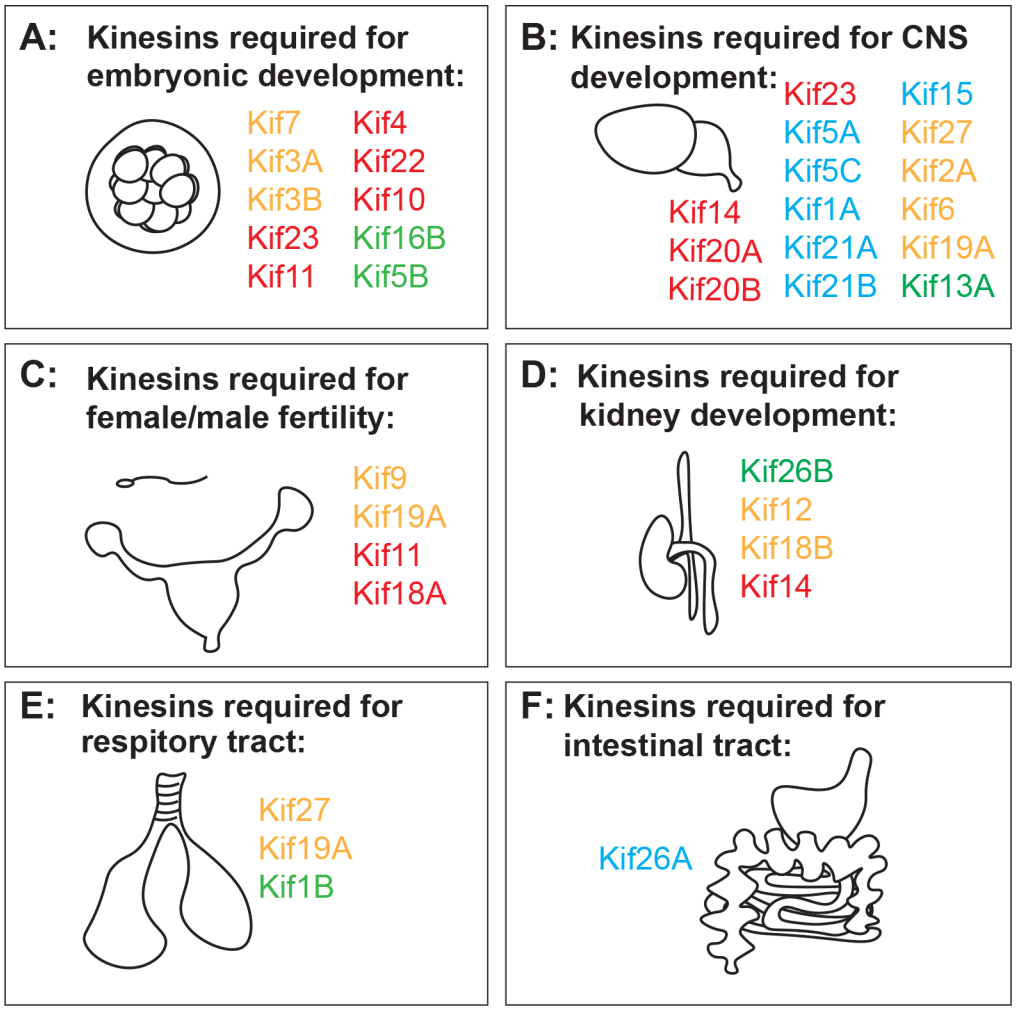

Figure 3. Developmental functions of each kinesin with confirmed *in vivo* studies categorized by organ and tissue.

All kinesin names are color coded to match cellular roles defined in Figure1. Red for mitosis, yellow for cilia, blue for neuronal functions, and green for vesicle/endosome transport. Figure 3A. Kinesins required for embryonic development. Figure 3B. Kinesins required for development of brain and central nervous system. Figure 3C. Kinesins required for male and female fertility. Figure 3D. Kinesins required for kidney development. Figure 3E. Kinesins required for respiratory tract development. Figure 3F. Kinesins required for the development of the intestinal tract.