European Journal of Cell Biology 98 (2019) 74–80

Contents lists available at ScienceDirect

European Journal of Cell Biology

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

Review

Roles and mechanisms of Kinesin-6 KIF20A in spindle organization during cell division

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ARTICLE INFO

Keywords:
Kinesin-6
KIF20A
Microtubule
Anaphase
Spindle assembly
Mitosis

ABSTRACT

Mitotic kinesin is crucial for spindle assembly and chromosome segregation in cell division. KIF20A/MKlp2, a member of kinesin-6 subfamily, plays important roles in the central spindle organization at anaphase and cytokinesis. In this review, we briefly introduce the discovery and classification of kinesin-6 motors in model organisms, and summarize the biochemical features and mechanics of KIF20A proteins. We emphasize the complicated interactions of KIF20A with partner proteins, including MKlp1, Plk1 and Rab6. Particularly, we highlight the regulation of Cdk1 and chromosomal passenger complex on kinesin-6 KIF20A at late stage of mitosis. We summarized the multiple functions of KIF20A in central spindle assembly and the formation of cleavage furrow in both mitosis and meiosis. In addition, we conclude the expression patterns of KIF20A in tumorigenesis and its applications in tumor therapy.

1. Introduction

Kinesin superfamily proteins (KIFs) are molecular motors that mediate the transport of various cargos, including the newly synthesized protein complexes, vesicles and mRNAs along the microtubule filaments to their destinations. Kinesin motors bind to the microtubules and convert the chemical energy provided by the hydrolysis of ATP into a kinetic energy, finally move along the microtubules (Hirokawa and Takemura, 2004; Hirokawa and Noda, 2008; Hirokawa et al., 2009).

In 1998, Echard et al. discovered a kinesin-like protein associated with Rab6 in the GTP-bound active form, and named it Rabkinesin-6 (RB6K), and also described the localization of RB6K at the Golgi apparatus and on microtubules. Then in 2000, Hill et al. found that RB6K accumulates at mitotic cells, and the proteins localized at spindle midzone and cleavage furrow. In 2003, Neef et al. reclassified Rabkinesin-6 as MKlp2, because of the motor domain of Rabkinesin-6 shares a highly similarity with mitotic kinesin MKlp1 (Kif23) (Jordens et al., 2005). To date, the NCBI GenBank database classify *kinesin family member 20A* (*KIF20A*) as the official name for MKlp2 (Lawrence et al., 2004).

The number “6″ in Kinesin-6 is taken from Rab6Kinesin, and also from the last family name “N-6″ according to phylogenetic analyses of kinesin superfamily proteins (Miki et al., 2005). Kinesin-6 subfamily is comprised of KIF20A (Lawrence et al., 2004), KIF20B (MPP1) (Kamimoto et al., 2001; Matsumoto-Taniura et al., 1996; Westendorf et al., 1994) and MKlp1 (Lawrence et al., 2004; Nislow et al., 1990; Sellitto and Kuriyama, 1988). These three members are essential mitotic kinesins in anaphase and cytokinesis during cell division (Camlin et al., 2017; Hirokawa et al., 2009; Liu and Erikson, 2007).

There are many KIF20A homologs in other organisms, including *KIF20A* (also known as *MKlp2*) in *Homo sapiens* (Lai et al., 2000), Kif20*a* in *Mus musculus* (Vaid et al., 2007), *Kif20a* in *Rattus norvegicus*, *kif20a* in *Danio rerio* (Louw et al., 2018), subito in *Drosophila melanogaster* (Schüpbach and Wieschaus, 1989). The motor domain of kinesin-6 motors are highly conserved among different species, indicating the functions of kinesin-6 motors are partially conserved in diverse organisms.

In this review, we mainly introduce the interactions between KIF20A and partner proteins at late stage of mitosis. We summarized multiple functions of kinesin-6 motors in both mitosis and meiosis. Moreover, we summarize the discovery and applications of KIF20A as a potential target gene in tumor diagnose and therapy in recent years.

Abbreviations: KIF20A, kinesin family member 20A; Plk1, polo-like kinase 1; AAs, amino acids; CPC, chromosomal passenger complex; Cdk, cyclin-dependent kinase; INCENP, inner centromere protein; Aurora B, aurora kinase B; Mad2, mitotic arrest deficient 2; Rab, Ras-Associated Protein; FOXM1, Forkhead Box M1; Gli2, Glioma-associated oncogene 2

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https://doi.org/10.1016/j.ejcb.2018.12.002
Received 14 September 2018; Received in revised form 10 December 2018; Accepted 11 December 2018

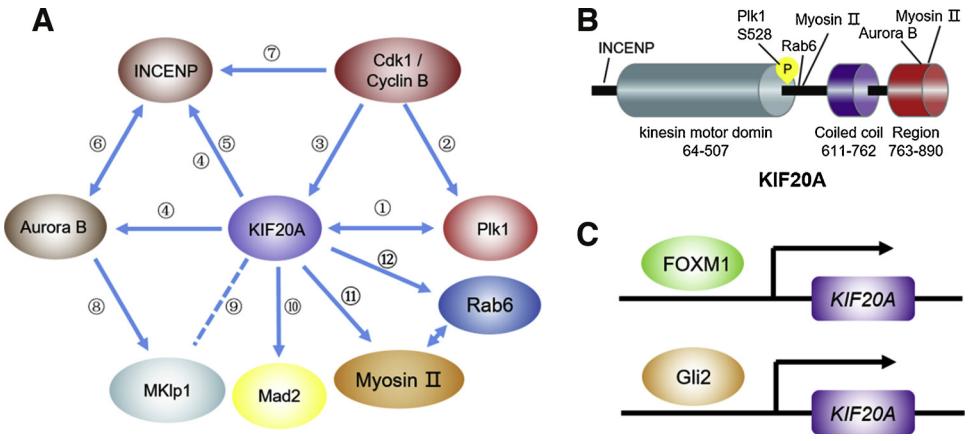

Fig. 1. The regulations of KIF20A during cell division. (A) ① Plk1 phosphorylates KIF20A and regulates the binding activity of KIF20A to microtubules. KIF20A regulates Plk1 to spindle midzone at anaphase. ② Localization of Plk1 regulated by activation of Cdk1. ③ The active state of Cdk1/cyclin B regulates the activity and localization of KIF20A from early stage to late stage of mitosis. ④ Recruitment of the CPC to the spindle is depend on KIF20A. ⑤KIF20A interacts with Aurora B to regulate INCENP. ⑥ Aurora B and INCENP form a complex, the recruitment of Aurora B-INCENP complex from centromeres to the central spindle is regulated by KIF20A. ⑦ Cdk1 phosphorylates INCENP, and inhibits the translocation of CPC to the spindle midzone. ⑧ Aurora B regulates MKlp1 by phosphorylation, and this process requires KIF20A ⑨KIF20A and MKlp1 have a similar positioning and functions, but there is no direct interaction. ⑩ Mad2 negatively regulates the binding of KIF20A to microtubules and its localization. ⑪ and ⑫ Both Rab6 and Myosin II is required for the fission of Rab6-positive vesicles, and KIF20A is involved in this fission process. Rab6 recruit KIF20A to fission site at the Golgi complex and then KIF20A recruit Myosin II. (B) The functional domains of KIF20A protein. KIF20A contains a Rab6 binding domain (529–665 AAs), two Myosin II binding domain (529–665 AAs, and 831–890 AAs), a Plk1 phosphorylation site (Ser-528), an Aurora B phosphorylation site (Ser-878) and an INCENP binding site (Thr-59). (C) FOXM1 direct regulates the expression level of KIF20A. Gli2 regulates KIF20A in response to Hh signaling, increases the expression of KIF20A gene through the activation of FOXM1.

2. The molecular and mechanistic properties of kinesin-6 KIF20A

Human *KIF20A* gene maps to chromosome 5, band q31.2, spans 8.988 kb of genomic DNA, and is comprised of 19 exons (Lai et al., 2000). Human *KIF20A* cDNA encodes an 890-amino acid protein called KIF20A, which is involved in intracellular transport in cells (Hirokawa, 1998) and microtubule organization in cell division (Lawrence et al., 2004). In addition, the nucleotide sequence spanning -1253 to +96 provides the promoter activity of KIF20A transcription start (Fontijn et al., 2001).

Kinesin-6 KIF20A is composed of three functional domain: a globular N-terminal motor domain which mediates the motor activity (Lai et al., 2000), a central coiled coil domain containing Rab6 and MyosinII binding domains, which is essential for dimerization and interactions with partner proteins, and a C-terminal tail domain which contributes to vesicle transport and interactions with partner proteins (Echard et al., 1998; Kitagawa et al., 2013 Miserey-Lenkei et al., 2017) (Fig. 1). The N-terminal motor domain consists of five conserved motifs, including N1 (P-loop), N2 (Switch I), N3 (Switch II), N4 and L2 (KVD finger) according to GeneCards: The Human Gene Database (https://www.genecards.org/). But compared with conventional kinesin-1, the relative conserved nucleotide binding motif shares only 35% identical in amino acid sequence (Atherton et al., 2017).

KIF20A is a first kinesin determined, in which a monomeric motor domain can bridge two microtubule protofilaments. Due to its motor domains is located at the N-terminal, KIF20A was classified as N-kinesin (Lawrence et al., 2004). The ATP cycle and walking mode of KIF20A is similar to kinesin-1 KIF1A, however, the detailed mechanism of KIF20A remains to be elucidated (Atherton et al., 2017). KIF1A binds tightly to microtubules in a state of binding to ATP. After ATP is hydrolyzed to ADP, KIF1A is released from the binding site. The ADP-bound form of KIF1A moves along the microtubules by one-dimensional Brownian motion. When ADP is released, KIF1A combines with the microtubules again (Hirokawa and Takemura, 2004). Kinesin-6 KIF20A moves directly toward the microtubule plus ends (Hirokawa and Takemura, 2004). The mechanical force energy is provided by ATP hydrolysis of the motor domain of KIF20A (Atherton et al., 2017).

KIF20A motor domain has several specific characteristics, including an approximately 60-amino acid N-terminus extension, an 18-amino acid insertions in loop 2, a 99-amino acid loop 6. Loop 6 is a largest specific insertion (99 AAs) of KIF20A, and its density region exists in all nucleotide states, forming a distinct subdomain (Atherton et al., 2017). The catalytic core insert loop 6 is a major characteristic of kinesin-6 family members, which locates at the opposite side of the microtubule-binding surface (Miki et al., 2005; Atherton et al., 2017). In addition, there is a 40-amino acid insert between KIF20A neck linker and coiled-coil domain (Atherton et al., 2017). There is a microtubule-binding domain in the C-terminal neck and stalk region of KIF20A protein (Echard et al., 1998; Neef et al., 2003). The stalk domain and C-terminal tail domain of KIF20A are required for microtubule binding, higher-order complex formation and chromosome binding sites in KIF20A (Kitagawa et al., 2014) (Fig. 1).

KIF20A's microtubule-stimulated ATPase $K_{0.5,\ MT\ (\mu M)} \approx 1.07 \pm 0.18$, $K_{cat\ (S)}^{-1} \approx 4.39 \pm 0.20$ (Atherton et al., 2014, 2017). KIF20A's microtubule-stimulated ATPase is about 10 times slower than kinesin-1 motor (Cochran et al., 2004; Atherton et al., 2017).

3. The regulation of kinesin-6 KIF20A and partner proteins during cell division

3.1. The co-dependence between KIF20A and MKlp1

In interphase, kinesin-6 KIF20A proteins are mainly located at the Golgi complex and interacts with GTP-bound forms of Rab6 to mediate the membrane transport and dynamics of the Golgi apparatus (Echard et al., 1998) (Fig. 2A). KIF20A proteins are sequestered in the nucleus in G2 phase thereby preventing cytoplasmic microtubules from cross-linking activities and depolymerizing (Fontijn et al., 2001) (Fig. 2B). At early stages of mitosis, nuclear envelope breakdown, KIF20A is released into the cytoplasm and also Cyclin-dependent kinase Cdk1/cyclin B is activated (Fig. 2C). A Cdk1/cyclin B phosphorylated kinesin-5 motor mediates spindle pole separation and bipolar spindle formation by crosslinking and sliding overlapping antiparallel microtubules from opposite spindle poles (Verhey and Hammond, 2009). Cdk1/cyclin B phosphorylation of kinesin-6 KIF20A preventing premature central spindle formation (Fig. 2D). After Cdk1/cyclin B degradation at anaphase, kinesin-6 KIF20A is dephosphorylated and localizes to the central spindle (Verhey and Hammond, 2009) (Fig. 2E). As the chromosomes move to spindle poles, the formation of spindle is mediated by kinesin-6 motors (Fig. 2E). During telophase, kinesin-6 motors accumulate at the midbody and continue to function in cytokinesis (Verhey and Hammond, 2009) (Fig. 2F).

MKlp1 is identified as a mitotic motor (Sellitto and Kuriyama, 1988). MKlp1 is a microtubule-associated kinesin motor that regulates

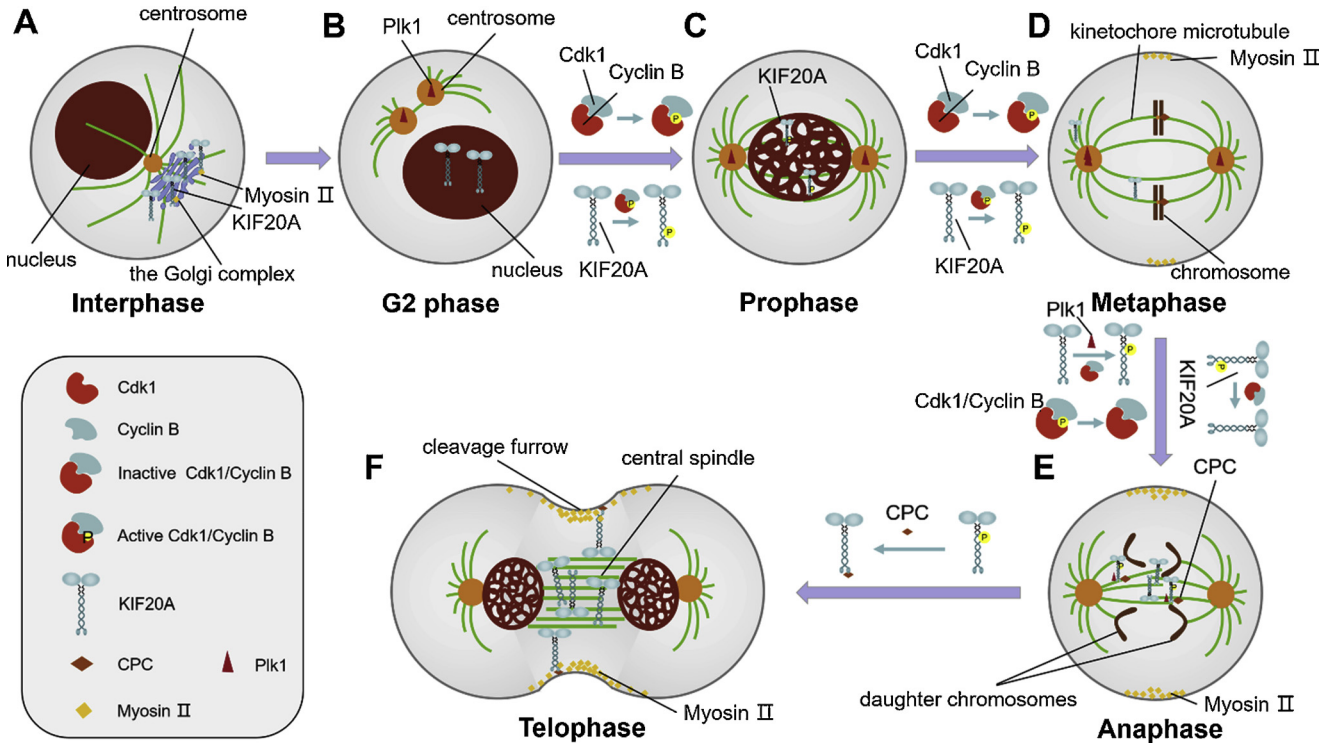

Fig. 2. The multiple roles of kinesin-6 KIF20A in different stages of mitosis. (A) In interphase, KIF20A, Myosin II and Rab6 co-localized at the Golgi fission hotspots to regulate the fission process of Rab6-positive vesicles. (B) In G2 phase, KIF20A accumulates at the nucleus. (C–D) At early stage of mitosis, Cdk1/Cyclin B complex is activated. Phosphorylation prevents premature release of KIF20A and advanced complex formation, which ensures normal cell cycle progression. Myosin II recruits KIF20A to the equatorial cortex prior to furrow ingression in metaphase. (E) At the late stage of mitosis, Cdk1/cyclin B1 activity is decreased, and KIF20A is dephosphorylated and released. Plk1 phosphorylates and forms a complex with KIF20A. KIF20A recruits Plk1 form centrosome to the spindle midzone during the metaphase to anaphase transition. (F) In anaphase, CPC is dephosphorylated, which is inhibited by Cdk1 phosphorylation, and is regulated by KIF20A from centromere localization to central spindle. Myosin II regulates the cleavage furrow ingression and constriction of actomyosin ring. Aurora B phosphorylates KIF20A in late anaphase. CPC and KIF20A form a complex to locate at the cleavage furrow, and promote cleavage furrow formation.

microtubule sliding, microtubule movement and organelle transport (Del Castillo et al., 2015; Hirokawa and Noda, 2008). The formation of central spindle is reduced in *KIF20A*-deleted HeLa S3 cell and U2OS cell compared with wild-type cells, but MKlp1 remained in the middle of central spindle (Gruneberg et al., 2004). Meanwhile, in the *MKlp1*-deleted cells, KIF20A proteins still localize at the central spindle and exhibit no dependence on MKlp1 (Gruneberg et al., 2004). Taken together, there is no correlation between the localization of KIF20A and MKlp1 proteins at the central spindle or midbody.

In mammalian cells, the ingressing furrow at cytokinesis is mainly dependent on KIF20A rather than MKlp1. Co-depletion of KIF20A and MKlp1 inhibit cleavage furrow ingression. Whereas the duration of furrow ingression in KIF20A -depleted cells increased compared with the MKlp1-depleted cells. KIF20A is more important in the maintenance of the ingressing furrow at late stage of cytokinesis. (Kitagawa et al., 2013).

3.2. The interactions between Plk1 and KIF20A

Polo-like kinase 1 (Plk1) is a serine/threonine-protein kinase, which regulates chromosome segregation and stimulates anaphase B spindle elongation (Brennan et al., 2007). Plk1 forms a complex with KIF20A in mitotic cells, and its localization to central spindle is KIF20A -dependent. The binding of KIF20A to Plk1 is regulated by its phosphorylation at EHS528LQV (Lowery et al., 2004; Neef et al., 2003), and Plk1 binds to phosphorylated KIF20A through its polo-box domain (Neef et al., 2003) (Fig. 1B). Plk1 mainly phosphorylates KIF20A rather than MKlp1. On the other hand, Plk1 regulates the activity of KIF20A binding to microtubules by the phosphorylation. Interestingly, microtubules in turn regulate Plk1 activity toward KIF20A (Neef et al., 2003).

3.3. The associations of Cdk1, CPC and KIF20A

During the process of mitosis, the structure and physiological characteristics of the cells are undergoing a series of significant changes. A key factor in regulating the accuracy of the mitotic process is chromosomal passenger complex (CPC) (Carmena et al., 2012; Sampath et al., 2004), which is composed of Aurora B (Aurora kinase B), INCENP (inner centromere protein), Survivin and Borealin (Kitagawa and Lee, 2016). Cyclin-dependent kinases (Cdks), as a kind of central components of the cell-cycle control system, regulate cell-cycle though the rise or fall of cyclins-Cdks (Satyanarayana and Kaldis, 2009). Cyclin and Cdks form a complex to fulfill their functions. Without cyclin, Cdk is inactive. M-Cdk, one of the Cyclin-Cdk complexes, is made up of cyclin-B and Cdk1, which specifically drive cell to entry into mitosis (Malumbres, 2014).

Anaphase onset triggers the interactions of the CPC with KIF20A. KIF20A is required for the recruitment of the CPC to the spindle, and stabilization of microtubules is necessary for the recruitment of the CPC and KIF20A (Hümmer and Mayer, 2009). CPC and KIF20A are interdependent on the combination with central spindles. KIF20A regulates the interactions between KIF20A and CPC through C-terminal cargo-binding domain (Hümmer and Mayer, 2009). siRNA mediated *KIF20A* inhibition blocks CPC relocation from separating chromosomes at anaphase (Gruneberg et al., 2004).

Active Cdk1/cyclin B separates KIF20A from INCENP and AuroraB, namely, Cdk1 negatively regulates the interactions between CPC and KIF20A through phosphorylation (Hümmer and Mayer, 2009). The expression of non-degradable cyclin B does not influence the distribution of CPC and KIF20A in metaphase (Hümmer and Mayer, 2009). Plk1 localizes at centrosomes and kinetochores, and switches to the central

spindle during metaphase to anaphase. And this process is controlled by the activation state of Cdk1 (Neef et al., 2007). KIF20A is also essential for the localization of CPC to the equatorial cortex (Kitagawa et al., 2013).

In early mitosis, Cdk1/cyclin B1 activity is increased, and KIF20A is inhibited by phosphorylation. The stalk and C-terminal tail domains of KIF20A are phosphorylated by Cdk1/Cyclin B1 to control the localization of KIF20A in the cytoplasm during mitosis (Kitagawa et al., 2014). The C-terminal tail domain of KIF20A mediates microtubule binding *in vivo*, but Cdk1/ cyclin B1-dependent phosphorylation inhibits this activity and inhibits C-terminal tail domain from interacting with the motor domain. This phosphorylation also inhibits the formation of higher-order complex and promotes the dissolution of KIF20A (Kitagawa et al., 2014). Cdk1/cyclin B1 phosphorylation controls the solubility of KIF20A oligomerization/clustering and timely recruitment to chromosome. Cdk1/cyclin B1 phosphorylation also inhibits oligomerization/aggregation and microtubule-bundling of KIF20A in early mitosis (Kitagawa et al., 2014).

In contrast, at late stage of mitosis, Cdk1/cyclin B1 activity is decreased, and KIF20A is dephosphorylated and released. Activation of KIF20A and its functions are fulfilled through the reversal of Cdk1/cyclin B1-mediated inhibitory phosphorylation. Reversing Cdk1/Cyclin B1-dependent phosphorylation of KIF20A is essential for the formation of a CPC- KIF20A complex and relocating the CPC from chromosomes to the cell equator at cytokinesis (Kitagawa et al., 2014) (Fig.1A). It is also crucial for relocating INCENP independent of dephosphorylation at its Thr-59 residue (Kitagawa et al., 2014).

3.4. The regulation of Aurora b, Cdc14, INCENP on KIF20A

The Aurora family is a key regulator of chromosome segregation and cytokinesis (Bischoff and Plowman, 1999; Glotzer, 2009). The N-terminal motor and C-terminal tail domain of KIF20A is required for the positioning of Aurora B to the central spindle region. Aurora B co-localizes with KIF20A at anaphase during mitosis (Gruneberg et al., 2004). The recruitment of Aurora B-INCENP complex from centromeres to the central spindle is KIF20A -dependent (Hümmer and Mayer, 2009). KIF20A and MKlp1 show a similar pattern of localization at central spindle, and both have overlapping regions with Aurora B. Aurora B is a binding partner protein for KIF20A but not MKlp1 (Gruneberg et al., 2004). Aurora B phosphorylates KIF20A at S878 (Fung et al., 2017) at anaphase, and phosphorylates MKlp1 at S911 (Neef et al., 2006).

The inner centromere protein (INCENP), a first passenger protein (Cooke et al., 1987), functions as a scaffold protein in activating and targeting the Aurora-B kinase (Kaitna et al., 2000; Adams et al., 2000; Honda et al., 2003). INCENP protein separate from chromosomes at anaphase and localize at the spindle midzone (Cooke et al., 1987) Aurora B and INCENP formed a complex at spindle midzone (Gruneberg et al., 2004), and Aurora B interacts with the C-terminal domain of INCENP, and activates the kinase activity of Aurora B (Glotzer, 2009). Inhibition of INCENP leads to the simultaneous destabilization of Aurora-B, whereas the protein level of KIF20A is not affected in *INCENP*-depleted cells (Hümmer and Mayer, 2009). Simultaneously, KIF20A proteins can not localize at the tips of microtubules, but localize to the taxol-stabilized microtubule lattices (Hümmer and Mayer, 2009). Cdk1 phosphorylates INCENP and KIF20A (Kitagawa and Lee, 2016). Phosphorylation of INCENP at T59 inhibits the translocation of CPC to the spindle midzone (Hümmer and Mayer, 2009).

Cdc14 is a dual-specificity phosphatase, which has the activity to dephosphorylate serine/threonine and tyrosine *in vitro* (Hartwell et al., 1974). Cdc14 dephosphorylates Cdk1 substrates and also antagonizes Cdk1 by promoting proteolysis of cyclin B, which is fulfilled through the dephosphorylation of the APC activator Cdh1 (Stegmeier and Amon, 2004). Cdc14 also dephosphorylates Swi5 to enhance the Cdk1 inhibitor Sic1 (Visintin et al., 1998). The localization of Cdc14 to the central spindle is mediated by KIF20A through the site of stalk and tail region. KIF20A and Cdc14 show a similar localization pattern. The dephosphorylation of INCENP by Cdc14 leads to the release of INCENP from centromeres at the metaphase to anaphase transition (Gruneberg et al., 2004). KIF20A directly interacts with Aurora B and Cdc14 A to regulate INCENP, and dually control the recruitment of Aurora B-INCENP complex from centromeres to the central spindle (Gruneberg et al., 2004).

3.5. The interactions between KIF20A and other proteins

Ras-Associated Protein (Rab) proteins are involved in motor protein-mediated transport in different cellular compartments (Zerial and McBride, 2001). Rab6 directly interacts with KIF20A coiled-coil domain (529–665 AAs) and is required for recruitment and stabilization of KIF20A at the Golgi complex (Miserey-Lenkei et al., 2017). KIF20A has been shown to regulate intra-Golgi transport (Echard et al., 1998) and fission process from Golgi membranes (Miserey-Lenkei et al., 2017). KIF20A directly interacts with Myosin II and Rab6 to mediate the spatial coordination between Rab6-positive transport vesicles formation at fission hotspots and their dissociation from Golgi/TGN membranes along microtubules (Miserey-Lenkei et al., 2017). KIF20A directly interacts with Myosin II through two Myosin II binding sites (KIF20A 529–665 AAs and 831–890 AAs) to recruit and stabilize Myosin II in interphase at Rab6 vesicle fission site on the Golgi (Miserey-Lenkei et al., 2017), and then regulates Golgi vesicle formation (Majeed et al., 2014). In mitosis, Myosin II recruits KIF20A to the equatorial cortex prior to furrow ingression in metaphase, and then targets Aurora B to the growing equatorial cortex during furrow formation (Kitagawa et al., 2013). The cortical localization of KIF20A -Aurora B is mediated by the interactions between KIF20A and Myosin II on actomyosin filament (Kitagawa et al., 2013).

KIF20A has a consensus mitotic arrest deficient 2 (Mad2) binding motif, which is a mitotic target of Mad2. The C-terminal domain (871–880 AAs) of KIF20A is crucial for its interaction with Mad2 (Hardwick, 2005; Li and Murray, 1991). Endogenous KIF20A does not compete with other binding partners of Mad2 protein (Lee et al., 2010). Mad2 inhibits KIF20A binding to microtubules, and when mitotic checkpoints are active, endogenous Mad2 prevents KIF20A from loading onto the mitotic spindle. The level of KIF20A proteins located at the mitotic spindle is increased after the ablation of Mad2 (Lee et al., 2010).

At early stage of mitosis, Mad2 negatively regulates the load of KIF20A onto the mitotic spindle. At late stage of mitosis, the localization of KIF20A at the cytokinesis of CPC is also reduced by Mad2. Moreover, this regulatory relationship and the Cdk1-mediated regulation of KIF20A on relocating the CPCs are temporally separated during mitosis (Lee et al., 2010).

Forkhead Box M1 (FOXM1), a direct upstream transcriptional regulator of KIF20A, regulates the expression level of *KIF20A*. FOXM1 can trans-activate the *KIF20A* gene after binding to the FHRE located at position 80 bp (Khongkow et al., 2016) (Fig.1C).

Glioma-associated oncogene 2 (Gli2), an essential transcriptional regulator of Hedgehog (Hh) signaling, is crucial for hepatocellular carcinoma proliferation and survival. *KIF20A* is a downstream target gene of Hh signaling pathway (Fig.1C). Gli2 positively regulates *KIF20A* in response to Hh signaling in hepatocellular carcinoma cells. In addition, Gli2 also increases the expression of *KIF20A* gene through the activation of *FOXM1* (Shi et al., 2016).

4. The multiple functions of kinesin-6 KIF20A in mitosis

KIF20A proteins are widely expressed in fetal tissues, and highly expressed in adult thymus, bone marrow and male reproduction system, but are expressed in heart, placenta and spleen at relative low levels (Lai et al., 2000; Taniuchi et al., 2005). Expression of KIF20A is

regulated at both mRNA and protein level during cell cycle, and reaches a maximum level during G2/M stage (Fontijn et al., 2001; Gasnereau et al., 2012; Hill et al., 2000). overexpression leads to defects in cell division and evenly leads to cell death (Hill et al., 2000). *KIF20A* overexpression can stimulate cell proliferation and invasion, and *KIF20A* inhibition also suppress cell viability and invasion (Duan et al., 2016). *KIF20A* -depleted cells can not complete cytokinesis and cleavage furrow formation as usual in time and extent during anaphase, but the chromosomes arrange and separate normally (Neef et al., 2003). Simultaneously, in *KIF20A* -depleted cells, the Aurora B-INCENP complex and Plk1 can not correctly localize at spindle midzone (Gruneberg et al., 2004). KIF20A is localized to the spindle midzone anaphase and to the cleavage furrow and midbody during telophase in mitotic cells (Fontijn et al., 2001; Hill et al., 2000). The localization of KIF20A to the central spindle is dependent on its C-terminus tail and N-terminal motor domain (Gruneberg et al., 2004).

KIF20A has a plasma membrane targeting function. A 20-AAs basic stretch in the KIF20A C-terminal tail (refer to as lipid association motif) through a reversible between phosphorylation or dephosphorylation reaction functions as a molecular switch for the plasma membrane target function of KIF20A. Aurora B delays intercellular bridge resolution by phosphorylating KIF20A S878 in the lipid association motif, which inhibits cytokinetic abscission (Fung et al., 2017).

KIF20A stimulates the polarized accumulation of RhoA (Ras homolog gene family, member A), which is required for furrow formation and stable ingression at the equatorial cortex (Kitagawa et al., 2013). KIF20A can functions during furrow ingression in the absence of MKlp1. KIF20A can form a complex with the actomyosin filaments. KIF20A binds actomyosin filaments and myosin-II to maintain the ingressing furrow (Kitagawa et al., 2013). Recruitment of Aurora B to the equatorial cortex is mediated by KIF20A, and this process is vital for the maintenance of the ingressing furrow (Kitagawa et al., 2013).

KIF20A recruits Plk1 to the spindle midzone in anaphase. KIF20A promotes Plk1 binding to microtubules through phosphorylation to ensure normal cell cycle (Cesario et al., 2006; Neef et al., 2003) (Fig. 2). The C-terminal cargo-binding domain of KIF20A mediates the interactions between KIF20A and CPC (Hümmer and Mayer, 2009). Aurora B is a specific mitotic cargo of KIF20A (Kitagawa et al., 2013). In *KIF20A* -deleted cells, Aurora B, Survivin and INCENP still locates at centromere in anaphase A and can not relocate to the central spindle (Gruneberg et al., 2004; Hümmer and Mayer, 2009; Tcherniuk et al., 2010). Deletion mutants of KIF20A, which lack cargo binding to the tail region, can not rescue Aurora B relocation to the central spindle (Gruneberg et al., 2004; Neef et al., 2006). KIF20A -Aurora B complex stimulates cell polarization and furrow formation, and Aurora B kinase stimulates the furrow propagation and completion (Kitagawa et al., 2013). KIF20A has a key role in Aurora B-dependent abscission and its relocation to the intercellular bridge (Fung et al., 2017). The dephosphorylation of KIF20A is essential for the relocation of CPC from anaphase separating chromosomes to the cell equator (Kitagawa et al., 2014; Kitagawa and Lee, 2016). Namely, CPC relocation to the spindle midzone requires KIF20A (Kitagawa and Lee, 2016) (Fig. 2). Moreover, in mice, KIF20A interacts with RGS3, a regulator of G protein signaling, in the intercellular bridges of neural progenitor cells and regulates the division modes of these cells during cortical neurogenesis (Geng et al., 2018). KIF20A knockout causes a thinner cortex and the absence of progenitor cells and neurons due to early cell cycle exit and a transition from proliferative to differentiatve divisions (Geng et al., 2018). In addition, the germline knockout of *kif20a* in mice results in obvious developmental abnormalities, smaller body and brain, and embryonic lethality (Geng et al., 2018).

The Cdk1-mediated phosphorylation of KIF20A maintains the mitotic spindle dynamics, which is crucial for chromosome congression during prophase and metaphase (Kitagawa et al., 2014; Kitagawa and Lee, 2016). Taken together, these results indicate that KIF20A protein regulates the localization and movement of Plk1, Aurora B, INCENP and Cdc14, and are regulated by Cdk1 and others, but the exact mechanisms have not been fully explained.

5. The role of kinesin-6 KIF20A proteins in meiosis

In oocytes, KIF20A proteins are positioned in the germinal vesicle (Liu et al., 2013). After germinal vesicle breakdown (GVBD), KIF20A is localized at centromeres and accumulated at the chromosomes (Liu et al., 2013; Zhang et al., 2014) and also localized at spindle microtubules (Liu et al., 2013). KIF20A transfers to the midbody at telophase I, and re-localizes to centromeres at metaphase II. KIF20A proteins are also located at the cytoplasm (Liu et al., 2013).

In mouse oocytes (Liu et al., 2013) and porcine oocytes (Zhang et al., 2014), KIF20A protein has been demonstrated to be essential for the extrusion of the first polar body (Zhang et al., 2014). The specific inhibitor Paprotrain mediated KIF20A inhibition influences the divisions of zygotes and results in the failure of early development of porcine embryos (Zhang et al., 2014).

After KIF20A disruption by Paprotrain treatment, oocytes failed to extrude polar body (Liu et al., 2013; Zhang et al., 2014). The control oocytes reached the MII stage, but most of the paprotrain-treated oocytes remained at metaphase I stage. KIF20A inhibition blocks mouse oocyte maturation in cell cycle progression (Zhang et al., 2014). But the spindle structure and chromosome alignment is normal after KIF20A inhibition (Liu et al., 2013; Zhang et al., 2014).

6. Progress and implications of kinesin-6 KIF20A in cancer diagnose and therapy

KIF20A expression is significantly increased in glioma (Duan et al., 2016), nasopharyngeal carcinoma (Liu et al., 2017), breast cancer (Khongkow et al., 2016), nonsmall cell lung cancers (Kikuchi et al., 2003; Zhao et al., 2018), gastric cancer (Claerhout et al., 2011; Hasegawa et al., 2002; Yan et al., 2012), colorectal cancer (Kitahara et al., 2001), hepatoma (Gasnereau et al., 2012), hepatocellular carcinoma (Lu et al., 2018; Shi et al., 2016), intrahepatic cholangiocarcinoma (Obama et al., 2005), pancreatic cancer (Imai et al., 2011; Nakamura et al., 2004; Stangel et al.,2015; Taniuchi et al., 2005; Taniuchi et al., 2014), cervical cancer (Zhang et al., 2016), and malignant melanoma (Yamashita et al., 2012).

KIF20A is found overexpressed in pancreatic tumor cells in pancreatic ductal adenocarcinoma (PDAC). Inhibition of the expression of KIF20A inhibits the growth of pancreatic cancer cells. Discs Large Homologue 5 (DLG5), a scaffolding protein in cell-cell contact, is a cargo protein of KIF20A. DLG5 plays an important role in pancreatic cancer, associated with the occurrence and cell growth of pancreatic cancer (Taniuchi et al., 2005). KIF20A promotes cell motility and invasiveness of pancreatic cells by transport the RNA-binding protein IGF2BP3 and IGF2BP3-bound transcripts, including ARF6 and ARHGEF4 to cell protrusions along microtubules, which further increase the formation of membrane protrusions (Taniuchi et al., 2014). A KIF20A -derived peptide vaccine is effective in clinical application of pancreatic cancer (Asahara et al., 2013; Miyazawa et al.,2017; Suzuki et al., 2014), and confirmed that KIF20A -depleted pancreatic cancer cells exhibit a significant growth inhibition (Stangel et al.,2015).

KIF20A is required for the normal and pathologic hepatocyte proliferation, and associated with human hepatocellular carcinomas (Gasnereau et al., 2012). KIF20A is overexpressed in human cervical cancer, and is correlated with carcinogenesis and aggressiveness of cervical cancer (Zhang et al., 2016).

In breast cancer, KIF20A regulates mitotic spindle assembly and mitotic catastrophe, which are essential in paclitaxel-induced cell senescence and cell death (Khongkow et al., 2016). KIF20A binds with the papillomavirus E2 during mitosis, suggesting a correlation with papilloma tumor (Yu et al., 2007). In dividing glioma cells, KIF20A is significantly overexpressed and is correlated with the pathological

grade of gliomas. KIF20A is involved in the spindle formation and cytokinesis. *KIF20A* knockdown inhibits glioma cell proliferation because of the cytokinesis failure and formation of binucleate cells (Saito et al., 2017).

In gastric cancer, the ablation of KIF20A inhibits cell viability and induces G2/M arrest, increasing the sensitivity of cancer cells to genistein inhibition. In addition, KIF20A overexpression significantly attenuates genistein-induced cell viability inhibition and G2/M arrest (Yan et al., 2012). After the inhibition of KIF20A, the cell cycle is arrested in G1 phase and apoptosis increased in lung cancer (Zhao et al., 2018).

KIF20A is related to paclitaxel resistance (Khongkow et al., 2016) and radioresistance (Xiu et al., 2018), and both are related to FOXM1. Inhibition of either Gli2 or KIF20A can inhibit hepatocellular carcinoma growth *in vivo* (Shi et al., 2016). KIF20A also positively regulates the expression of Ki67 in glioma cell lines (Duan et al., 2016).

7. Conclusion and future perspectives

The motor and biochemical properties of KIF20A have not been fully elucidated, though it is similar to the kinesin-1 motor. Compared to MKLP1 and KIF20B, KIF20A has several unique properties in the kinesin-6 subfamily. Many studies have shown that KIF20A plays important roles in mitosis: microtubule assembly, spindle formation, cytokinesis, and also plays a role in meiosis. However, the molecular kinetics of kinesin-6 KIF20A on antiparallel microtubules of central spindle in cells remain to be discovered, which will be helpful to explore the roles of KIF20A in cell division.

KIF20A has a coordinated relationship or interaction with many proteins, and these proteins also have complex relationships between each other. These complicated relationships contribute to the normal progression of the cell cycle, but are not elaborated in this article. There are still many issues remained to be studied. For example, KIF20A has a clear interaction with members of the CPC family Aurora B and INCENP, but the relationship with Borealin and Survivin has not been reported. The interactions between KIF20A and other partner proteins in anaphase central spindle remains largely unknown and are fascinating research areas to uncover the mechanisms of central spindle assembly.

In recent years, kinesin-6 KIF20A has been found to be significant in the field of oncology, and effective applications have been found in pancreatic cancer. KIF20A overexpression is highly correlated with tumor cell proliferation, tumor progression and invasion, poor clinical outcome and poor overall survival. KIF20A is a prognostic indicator and might be a novel target for tumor therapy to treat a variety of tumors.

Author contributions

Wen-Da Wu, Kai-Wei Yu, Ning Zhong and Yu Xiao wrote the manuscript. Zhen-Yu She modified and authored the manuscript.

Acknowledgements

This study was supported by the following grants: the Health and Family Planning Commission of Fujian Province (Grant No. 2018-1-69), Startup Fund for scientific research, Fujian Medical University (Grant No. 2017XQ1001), Fujian Medical University high level talents scientific research start-up funding project (Grant No. XRCZX2017025) and College Students' innovation and entrepreneurship training program (Grant No. 201810392035). We sincerely thank all members of the Cytoskeleton Laboratory at Fujian Medical University for their discussions. The author declares no competing or financial interests.

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