The role of TACC3 in mitotic spindle organization

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Abstract
TACC3 regulates spindle organization during mitosis and also regulates centrosome-mediated microtubule nucleation by affecting γ-Tubulin ring complexes. In addition, it interacts with different proteins (such as ch-TOG, clathrin and Aurora-A) to function in mitotic spindle assembly and stability. By forming the TACC3/ch-TOG complex, TACC3 acts as a plus end-tracking protein to promote microtubule elongation. The TACC3/ch-TOG/clathrin complex is formed to stabilize kinetochore fibers by crosslinking adjacent microtubules. Furthermore, the phosphorylation of TACC3 by Aurora-A is important for the formation of TACC3/ch-TOG/clathrin and its recruitment to kinetochore fibers. Recently, the aberrant expression of TACC3 in a variety of human cancers has been linked with mitotic defects. Thus, in this review, we will discuss our current understanding of the biological roles of TACC3 in mitotic spindle organization.

KEYWORDS
cancer, centrosome, microtubule, spindle, TACC3

1 | INTRODUCTION

Cell division is a process that is prone to errors, which result in changes in genetic inheritance, increasing the probability of cancer. It is therefore crucial to ensure the accuracy of genetic inheritance. Mitosis is the last phase of cell division, leading to the formation of two daughter cells with the same genetic information. This process occurs in a very precise way to ensure the accurate allocation of genetic material among the progeny cells. The centrosome is the primary microtubule-organizing center (MTOC) with a pair of centrioles, which plays an important role in the formation of the bipolar spindle and mitotic entry, and spindle assembly is initiated when the centrosomes are separated. In mitosis, one crucial step is the correct chromosome congression and segregation of sister chromatids. The mitotic spindle is responsible for the accurate segregation of chromosomes into two daughter cells during cell division. The kinetochores of the chromosome are attached to the spindle by the kinetochore fibers (k-fibers), which are discrete bundles of parallel microtubules emanated from the centrosome. Each microtubule, formed by α and β tubulin polymers, has a fast-growing plus end and a minus end that grows more slowly. The spindle is a self-organized and dynamic macromolecular structure (O’Connell & Khodjakov, 2007), and its assembly is controlled spatially and temporally by motor and nonmotor microtubule-associated proteins. One of these well-known proteins is TACC3 which has gained widespread attention in recent years due to its high up-regulated expression in some cancers.

TACC proteins are a family that is identified by a conserved motif called the TACC domain. The TACC domain is required for TACC proteins to associate with the spindle. As in Xenopus laevis and other examined vertebrates, the TACC family in human cells contains three members, including TACC1, TACC2, and TACC3. All three TACC proteins in humans concentrate at the centrosomes and mitotic spindles (Gergely et al., 2000). However, in mammals, TACC1 appears to have a wider expression than TACC3 (Sadek et al., 2003). The different distribution characteristics imply that these proteins have different roles, but the conserved TACC domain suggests overlapping functions. All three of the TACC proteins function as microtubule plus-end tracking proteins that regulate microtubule dynamics (Lucaj et al., 2015; Nwagbara et al., 2014; Rutherford et al., 2016).

The aberrant expression of TACC proteins in humans is usually associated with cancers (Ha, Kim, & Breuer, 2013a). For some cancers, like breast carcinoma, the three proteins are all expressed abnormally (Fish et al., 2016; Song et al., 2016; Yoshiaki et al., 2016). TACC1 and TACC2 are related to several human cancers, such as breast cancer (Fish et al., 2016; Yoshiaki et al., 2016) and gastric carcinoma (Lv et al., 2014), while TACC3 is associated with a number of cancers. TACC3 is highly expressed in most cancers tissues, such as prostate cancer (Li et al., 2017), glioma (Sun et al., 2017), cholangiocarcinoma (He et al., 2017).
2016), and colorectal cancer (Du et al., 2016), lung cancer (Jiang et al., 2016), gastric cancer (Yun et al., 2015). However, the expression of TACC3 is down-regulated in thyroid cancer and ovarian carcinoma and preeclampsia (Peters et al., 2005; Ulisse et al., 2007; Zhu, Cao, Li, & Wang, 2016). Extensive and abnormal expression patterns of TACC3 in cancers make it more attractive than the other two proteins. In view of the anomalies of TACC3 expression, especially its up-regulated expression in most cancers, it is of importance to clarify the precise mechanism of TACC3 in cancer development.

While the knowledge of the function of TACC3 in cancer is still obscure, its clinical significance is becoming clear. The knockdown of TACC3 inhibits cell proliferation in human renal cell carcinoma (Guo & Liu, 2017) and induces G2/M cycle arrest in cholangiocarcinoma (He et al., 2016). Furthermore, perturbing the function of TACC3 selectively inhibits the nucleation of centrosome microtubules in ovarian cancer cells (Yao et al., 2014). In mouse thymic lymphoma cells, TACC3 depletion induces multipolar spindle formation, leading to mitotic arrest (Yao et al., 2012). These observations indicate that the depletion of TACC3 is highly relevant to spindle defects in cancer cells. Thus, a novel opinion is proposed that TACC3 works as a therapeutic target for anticancer drugs precisely designed to inhibit the mitotic function of cancer with aberrant TACC3. The phenomenon that TACC3 disruption leads to tumor regression in vivo strongly indicates that TACC3 is a promising target for the treatment of human cancers (Yao et al., 2012). Understanding the underlying mechanisms of TACC3 in mitotic spindle helps to develop anticancer drugs for mitotic processes without interfering with the microtubule activity in nondividing cells, and subsequently inhibit cancer cell proliferation to treat cancers. In this review, we describe the current understanding of the roles and regulatory mechanisms of TACC3 in mitotic spindle organization.

2 | THE REGULATION OF TACC3 IN CENTROSOME-MEDIATED MICROTUBULE NUCLEATION

TACC3 is identified as a centrosomal protein that interacts with microtubules (Gergely et al., 2000). Silencing of TACC3 affects centrosome integrity and results in partially destabilized microtubules, spindles with reduced microtubule content and defects in chromosome alignment (Gergely, Draviam, & Raff, 2003; Schneider et al., 2007; Suhail, Singh, & Manna, 2015). In contrast, the overexpression of TACC3 increases the length and number of microtubules (Peset et al., 2005; Lee, Gergely, Jeffers, Peakchew, & Raff, 2001). These phenotypes suggest that TACC3 directly regulates microtubule stability. However, these defective phenotypes may also arise from centrosome defects caused by the aberrant expression of TACC3. Centrosomes have three important roles in mitosis, including nucleating, anchoring, and organizing microtubules. Thus, exploring the precise process affected by TACC3 helps to understand the regulatory function of TACC3 in the spindle.

The γ-tubulin ring complex (γTuRC) plays a key role in the spatial and temporal control of microtubule nucleation (JM et al., 2011; Kollman, Polka, Zelter, Davis, & Agard, 2010). Previous studies show that maskin (a homologue of TACC3 in Xenopus) is not required for centrosome-mediated microtubule nucleation (Albee & Wiese, 2008; Kinoshita et al., 2005; Peset et al., 2005) and the centrosomal levels of γ-tubulin are not affected by the disruption of maskin (Lee et al., 2001; O’Brien et al., 2005). However, emerging evidence suggests that the human TACC3 protein plays a crucial role in microtubule nucleation. The nucleation of centrosome microtubules is selectively inhibited in ovarian cancer cells when TACC3 expression is perturbed, indicating that TACC3 is required for centrosome-mediated microtubule nucleation (Yao et al., 2014). The depletion of TACC3 influences the assembly of γ-TuRC from the γ-tubulin small complex (γ-TuSC) and reduces γ-TuRC proteins to the centrosomes (Singh, Stoddard, Gireesh, & Manna, 2014), which is consistent with a recent report that the loss of TACC3 affects centrosome integrity by disrupting the localization of components of γ-TuRC at the centrosomes (Suhail et al., 2015). Until now, it has been well established that the TACC3 protein regulates microtubule nucleation by affecting γ-tubulin ring complexes. Although maskin is highly homologous to TACC3, differences between these two proteins exist, which may explain the fact that TACC3 regulates microtubule nucleation at the centrosome whereas maskin does not.

However, it is still not clear whether and/or how the other two functions of centrosomes are affected by TACC3, even though TACC3 is required for anchoring microtubules to the centrosome (Albee & Wiese, 2008). Although much data strongly supports that TACC3 is required for the centrosome-mediated microtubule nucleation, it is still unclear whether it is sufficient to explain the function of TACC3 protein in mitosis. An unsolved question about TACC3 is how a protein that is primarily localized to the centrosome has such a strong effect on spindle organization, especially chromosome alignment. This implies that TACC3 not only regulates microtubule nucleation at the centrosomes, but also has a wider range of functions in mitosis that is mediated by other effector proteins. Thus, the identification of TACC3 interacting proteins is beneficial to uncover the novel functions of TACC3, and subsequently the signaling pathways that TACC3 is involved. Furthermore, mapping the proteins’ interaction network will be conducive to reveal the molecular mechanism of TACC3 working.

3 | TACC3 ACTS AS A PLUS END-TRACKING PROTEIN VIA THE TACC3/CH-TOG COMPLEX

Ch-TOG family members are potent microtubule polymerases that play an essential role in stabilizing spindle microtubules. Ch-TOG directly binds to microtubules and acts as a plus end-tracking protein, influencing the dynamics of the microtubule plus ends (Brouhard et al., 2008; Zanic, Widlund, Hyman, & Howard, 2013). Ch-TOG regulates the stability of the microtubule plus end mainly by stimulating growth rates at the microtubule plus ends and counteracting the activity of XKCM1 (a member of the mitotic centromere-associated kinesin family), the microtubule catastrophe factor (Kinoshita, Arna1, Desai, Drechsel, & Hyman, 2001; Noetzel, Drechsel, Hyman, & Kinoshita, 2005; Tournebize et al., 1999). In addition, ch-TOG depleted cells display...
mitotic defects, with spindles that are highly disorganized (Barr & Bakal, 2015; Gergely et al., 2003).

A member of the ch-TOG family in Drosophila melanogaster is associated with D-TACC (a homologue of TACC3), indicating that there may be a link between these two proteins in spindle assembly (Cullen & Ohkura, 2001; Gergely, 2002; Lee et al., 2001). Native maskin and XMAP215 (a ch-TOG homologue in Xenopus) can form a one-to-one complex at the centrosomes to stabilize microtubules by increasing the affinity of XMAP215 to the microtubule (Kinoshita et al., 2005). Studies in different systems show that reducing the level of TACC3 impairs the correct localization of ch-TOG to the centrosome (Bellanger & Gönzcy, 2003; Cullen & Ohkura, 2001; Kinoshita et al., 2005; Le, Tsai, Andrews, & Ahringer, 2003; Lee et al., 2001; Sato, Vardy, Garcia, Koonrugsu, & Toda, 2004; Srayko, Quintin, Schwager, & Hyman, 2003), while increasing TACC3 results in more recruitment of ch-TOG/XMAP215 to the spindle poles (Peset et al., 2005; Lee et al., 2001). Maskin is also reported to regulate the ability of XMAP215 to anchor the microtubule minus end (Albee & Wiese, 2008).

In fact, TACC3 directly forms a one-to-one complex with ch-TOG, and therefore enhances the microtubule-stabilizing activity of ch-TOG to the centrosomes in vitro (Kinoshita et al., 2005), implying that TACC3/ch-TOG complexes play a role at the centrosome. It was originally proposed that TACC3/ch-TOG is important for promoting spindle assembly by stabilizing the microtubule minus ends at the centrosome or by opposing the inhibitory activity of mitotic centromere-associated kinesin (Barr and Gergely, 2008; Kinoshita et al., 2005; Peset et al., 2005). Furthermore, the TACC3/ch-TOG complex is identified in the growing tips of microtubules (Gutiérrezcaballer et al., 2015), which indicates that TACC3/ch-TOG complexes are given a new function. Since ch-TOG proteins exert their effects mainly on the plus ends of microtubules (Brouhard et al., 2008; Tournebize et al., 1999), it will be interesting to explore TACC3/ch-TOG in spindle organization.

Recently, an investigation of the TACC3/ch-TOG complex revealed an asymmetric interaction promoting microtubule elongation (Mortuza et al., 2014). The TACC3/ch-TOG complex is proposed to help stabilize the plus ends of newly formed microtubules as they emerge from the centrosome in Drosophila (Lee et al., 2001). It seems that a functional relationship exists between TACC3 and ch-TOG on the plus ends of the microtubules, which means that TACC3 may also act as a plus end-tracking protein. In addition, mounting evidence demonstrates that TACC3 functions to promote microtubule assembly by regulating the plus ends of the microtubules which is highly dependent on its interaction with ch-TOG (Gutiérrezcaballer et al., 2015). TACC3 and ch-TOG affect each other’s protein stability and localization to microtubule plus ends, and TACC3 localization at the MT plus end overlaps with ch-TOG in nondividing Xenopus cells (Nwagbara et al., 2014). In human cells, TACC3 is confirmed to work as a plus end-tracking protein in mitosis and the TACC3/ch-TOG complex tracks the growing tips of microtubules to regulate microtubule plus end dynamics (Gutiérrezcaballer et al., 2015).

TACC3 participates in a variety of biological processes with different proteins during mitosis, and thus, it is difficult to assess the function of TACC3 working alone as a plus end-tracking protein without affecting other functions. We see a role for TACC3 in modulating microtubules dynamics mainly through the TACC3/ch-TOG complex, while the direct function of TACC3 as a plus end-tracking protein is still obscure. Future studies should focus on whether there are other novel roles of TACC3 as a plus end-tracking protein in addition to adjusting microtubule dynamics, especially the roles that are different from other plus end-tracking proteins.

4 | TACC3 CROSSLINKS MICROTUBULES TO STABILIZE KINETOCHORE FIBERS BY FORMING THE TACC3/CH-TOG/CLATHRIN COMPLEX

Clathrin is best known for its roles in membrane trafficking (Royle, 2012). Other reports also show that clathrin co-localizes with the microtubules of the spindle apparatus during mitosis (Royle, Bright, & Lagnado, 2005). Specifically, it localizes to the kinetochore fibers of the spindle. Furthermore, the knockdown of clathrin by RNA interference (RNAi) destabilizes the kinetochore fibers of the mitotic spindle, suggesting a functional role of clathrin in the spindle (Royle et al., 2005).

However, it is reported that clathrin has no microtubule-binding domains, which suggests that other factors are required to recruit clathrin to the mitotic spindle (Royle, 2012). Similar defects of the mitotic spindle are caused by the depletion of clathrin or TACC3, suggesting a direct link between these two proteins (Gergely et al., 2003; Royle et al., 2005). Clathrin is identified as a TACC3-interacting protein by quantitative proteomics combined with bacterial artificial chromosome TransgeneOmicis (Hubner et al., 2010). The direct interaction between TACC3 and clathrin suggests that TACC3 is a partner of clathrin at the mitotic spindle (Fu et al., 2010). Clathrin is essential for TACC3-associated spindle regulation (Lin, Hu, & Shih, 2010), and growing evidence proposes a mode that the N-terminal domain of clathrin and the TACC domain of TACC3 in tandem make a microtubule interaction surface (Hood et al., 2013). Furthermore, clathrin is also uncovered in a TACC3/ch-TOG/clathrin complex at the mitotic spindle (Booth, Hood, Prior, & Royle, 2011). Additionally, it is interesting that clathrin promotes centrosome maturation by stabilizing the microtubule-binding protein ch-TOG (Foraker et al., 2012).

The TACC3/ch-TOG/clathrin complex stabilizes the kinetochore fibers by acting as an intermicrotubule bridge (Figure 1A). Furthermore, the TACC3/ch-TOG/clathrin intermicrotubule bridge stabilizes the k-fibers by physical crosslinking, and possibly by reducing the rate of microtubules catastrophe. The depletion of clathrin results in k-fibers that lack the shortest type of intermicrotubule bridges, which is similar to TACC3 depletion (Cheeseman, Booth, Hood, Prior, & Royle, 2011). Destroying the structure of the TACC3/ch-TOG/clathrin complex mainly disrupts short intermicrotubule bridges, suggesting that the complex plays a role mainly in the short intermicrotubule bridges to stabilize the spindle (Booth et al., 2011). Knocksidesways (KS), a method used for rapidly and specifically removing TACC3/ch-TOG/clathrin nonmotor complexes from k-fibers, is performed to examine the role of TACC3/ch-TOG/clathrin complex at specific stages of mitosis.
The depletion of TACC3/ch-TOG/clathrin complexes at NEBD (nuclear envelope break-down) results in a severely prolonged pro-metaphase, and its depletion after metaphase causes a delay in anaphase onset (Cheeseman et al., 2013). Furthermore, the knockdown of the TACC3/ch-TOG/clathrin complexes during metaphase reduces k-fibers tension, and changes the spindle shape and dynamic (Cheeseman et al., 2013). The TACC3/ch-TOG/clathrin complex also contributes to the stability of centrosomal tubulin according to the results that centrosomal loss of the complex components induces γ-tubulin dispersion and centrosome fragmentation (Foraker et al., 2012).

Although numerous studies have explored the mechanisms of how members of the TACC3/ch-TOG/clathrin interact with one another and how the complex interacts with microtubules, further studies are required. Furthermore, the links between TACC3/ch-TOG and TACC3/ch-TOG/clathrin is still unintelligible, even though some experiments suggest that TACC3/ch-TOG/clathrin is changed from TACC3/ch-TOG (Burgess et al., 2015). Future studies should focus on clearing up the links and differences among the various processes that TACC3 participates in during mitosis. A full understanding of TACC3 must be given high priority, which will allow us to develop novel therapeutic strategies that destroying the spindle of cancer cells while not influencing normal cells. Until now, it is established that TACC3 plays a pivotal role in the stabilization of the kinetochore fibers by crosslinking microtubules through the formation of the TACC3/ch-TOG/clathrin complex.

5 | THE MITOTIC ROLES OF TACC3 ARE REGULATED BY AURORA-A AND OTHER PROTEINS

5.1 | Aurora-A

Aurora-A, belonging to a highly conserved family of serine-threonine protein kinases, is essential for cell-cycle regulation. Aurora-A localizes
to the centrosomes and spindle, and disruption of Aurora-A function causes centrosome disorganization and spindle defects. The activity of Aurora-A is required for regulating multiple stages of mitotic progression in somatic cells. Importantly, Aurora-A is up-regulated in a variety of cancers, implying that Aurora-A may be a potential target for cancer treatment. Silencing Aurora-A by RNAi or its inhibition by MLN8054 (a selective small molecule inhibitor of Aurora-A) in human tumor cells causes mitotic arrest and eventually apoptosis (Hata et al., 2005; Hirota et al., 2003; Manfredi et al., 2007; Marumoto et al., 2003).

Experiments performed in Xenopus show that maskin is phosphorylated by Aurora-A on S558 (Kinosita et al., 2005). MLN8054 treatment mis-localizes TACC3 away from the centrosomes in a concentration-dependent manner, suggesting that the phosphorylation of TACC3 by Aurora-A is essential for its proper localization to centrosomes (Leroy et al., 2007). Moreover, the knockdown of Aurora A clearly abolishes the acentrosomal microtubule aster formation mediated by TACC3 phosphorylation (Fu et al., 2013). Silencing and rescue experiments performed using different phosphorylation variants of TACC3 show that the nonphosphorylatable version of TACC3 does not rescue the defects observed in the TACC3 silenced cells (Lioutas & Vernos, 2014). A conserved serine at Ser558 in TACC3 is phosphorylated by Aurora-A, which is essential for its proper localization to centrosomes and the mitotic spindle and, subsequently, the central spindle assembly (Leroy et al., 2007; Lioutas & Vernos, 2014).

The phosphorylation of TACC3 by Aurora-A on S558 is also required for the efficient centrosomal localization of the TACC3/ch-TOG complex, which implies that the likely function of Aurora-A in regulating the spindle is through the TACC3/ch-TOG complex to the mitotic centrosomes rather than directly regulating its activity toward the microtubules (Barr & Gergely, 2007; Brittl & Ohkura, 2005; Kinosita et al., 2005). Additionally, integrin-linked kinase (ILK) is also required for Aurora-TACC3/ch-TOG interaction at the centrosomes (Fielding, Dobreva, Mcdonald, Foster, & Dedhar, 2008). Depleting ILK expression or inhibiting its kinase activity disrupts the interaction of Aurora A with the TACC3/ch-TOG complexes during mitosis (Fielding et al., 2008).

At the beginning, a model was proposed that clathrin recruits TACC3 to the spindle (Lin et al., 2010). In the ‘clathrin recruits TACC3’ model, clathrin is the primary recruitment factor for the TACC3/ch-TOG/clathrin complex to bind the microtubules. However, clathrin, known for its role in membrane trafficking, is mainly in the cytoplasm not the spindle, and clathrin cannot bind the microtubules (Charrasse et al., 1998; Peset et al., 2005; O’Brien et al., 2005). As described above, if the model that clathrin recruits TACC3 is correct, it is difficult to explain some results. Since ch-TOG maintains microtubule attachments, a novel sixth TOG domain in ch-TOG is thought to be required for it to complex to microtubules. However, experiments show that the TOG domain is required for the microtubule localization of ch-TOG but not TACC3/clathrin (Hood et al., 2013). The overexpression of ch-TOG or clathrin do not affect the distribution of the other complex members, but overexpressing TACC3 increases the amount of ch-TOG and clathrin recruited to the spindle, suggesting that TACC3 may be the primary factor that recruits the other two complex components to the spindle (Booth et al., 2011). Meanwhile, a model is proposed that TACC3 binds directly to microtubules, ch-TOG binds to TACC3 and clathrin binds to TACC3/ch-TOG sub-complexes crosslinking them on adjacent microtubules (Booth et al., 2011). Since Aurora-A plays a crucial role in the regulating the mitotic function of TACC3, exploring the role of Aurora-A in the ‘TACC3 recruits clathrin’ model is helpful for understanding the molecular mechanism of TACC3/ch-TOG/clathrin.

TACC3/ch-TOG not only localizes to the centrosomes but also to the plus end of the microtubules. A recent study proposes that TACC3/ch-TOG tracks the growing tips of microtubules independent of Aurora-A phosphorylation (Gutiérrez-zabalber et al., 2015), which is consistent with a previous study that TACC3 and ch-TOG interact in an Aurora-A-independent manner (Thakur et al., 2014). This may explain why some TACC3/ch-TOG complexes localize to the centrosome while others are at the microtubule plus end. Furthermore, the phosphorylation of TACC3 specifically by Aurora-A is required for the formation of the TACC3/ch-TOG/clathrin complex (Fu et al., 2010). The discovery that the clathrin-TACC3 interaction is S558 phosphorylation dependent confirms the notion that pho-S558-dependent TACC3 is crucial for its regulation of spindle function (Lin et al., 2010). Thus, the model can be further elaborated as follows: first, ch-TOG binds to TACC3; then the complex is recruited to microtubules after TACC3 phosphorylation by Aurora-A; third, clathrin is added to the pTACC3 and finally, the TACC3/ch-TOG/clathrin complex is formed (Figure 1B). The model is consistent with a recent study that the interaction between Aurora-A and TACC3 promotes TACC3 to transform TACC3-ch-TOG as the microtubule-polymerase to TACC3-ch-TOG-clathrin complexes to crosslink the k-fibers (Burgess et al., 2015).

Although TACC3 has a well-characterized role as a substrate of Aurora-A kinase, a new study reveals that TACC3 also plays a role in the activation of Aurora-A in vitro (Burgess et al., 2015), which is consistent with a previous experiment in Xenopus (Pascreau, Delcros, Cremet, Prigent, & Arlot-Bonnemains, 2005). TACC3 stimulates Aurora-A activity through TACC3act (residues 519–563), including S558 (Burgess et al., 2015). Thus, we do not understand whether this local activation of Aurora-A serves solely to enhance the phosphorylation of S558 on TACC3, and if not, the mechanism remains unknown. Aurora-A is considered as an intriguing target for anticancer therapeutic interventions because of its oncogenic potential and its essential role in mitosis (Carpinelli & Moll, 2009). In addition, inhibitors targeting Aurora-A have been designed for cancer treatment. However, there are no direct markers for measuring Aurora-A inhibition. As TACC3 is well established as a substrate of Aurora-A kinase, the phosphorylation level of TACC3 at S558 can be used as a novel measure of Aurora-A activity in cancers. Thus, it is meaningful to clearly understand mechanism between Aurora-A and TACC3.

5.2 | Other partners

NDEL1, a binding partner of LIS1, is also a specific substrate of Aurora-A kinase and binds to TACC3 (Mori et al., 2007). However, one interesting thing is that the phosphorylation of NDEL1 by Aurora-A kinase is essential for TACC3 recruitment to the centrosomes (Mori et al.,...
suggesting that NDEL1 may act as a key molecule that connects Aurora-A to TACC3. The roles of NDEL1 and Aurora-A have been well established (Takihara et al., 2012; Yamada, Hirotune, & Wynshaw-Boris, 2010), while the relationship between NDEL1 and TACC3 still needs further study.

In addition to the influence of Aurora-A on TACC3/ch-TOG/clathrin complex, several other proteins have an impact on it. Sorting nexin 9 (SNX9) is involved in the efficient recruitment of clathrin and TACC3 to the mitotic metaphase spindle (Ma, Robinson, & Chircop, 2013), which indicates that SNX9 may regulate the recruitment of TACC3/ch-TOG/clathrin complexes to the k-fibers. Besides, Hsp72, one isomorph of the Hsp70 family of Heat shock proteins, promotes the assembly of the TACC3/ch-TOG complex (O’Regan et al., 2015). Furthermore, blocking Hsp72 function influences the recruitment of TACC3/ch-TOG/clathrin complex to the k-fibers (O’Regan et al., 2015).

TACC3 is usually abnormally expressed in cancer cells, and thus, understanding the expression mechanism of TACC3 in the cell cycle is helpful for developing anticancer means. Experiments performed by Jeng et al. show that the TACC3 protein level is regulated during cell cycle progression via the ubiquitin-proteasome pathway (Jeng, Lin, Lin, & Shih, 2009). A special protein knockdown system targeting TACC3 reveals that Cdh1 mediated the degradation of TACC3 in the cells (Ohoka et al., 2014). Furthermore, Cdh1 is identified as an interacting protein of TACC3, and the depletion or overexpression of Cdh1 affects TACC3 expression and TACC3 stability in mitotic exit (Jeng et al., 2009). However, the current data is quite limited, and further studies are required to uncover the link between Cdh1 and TACC3.

6 | NOVEL ROLES OF TACC3 IN HUMAN CANCERS

TACC3 is up-regulated in various cancers, and it is actually down-regulated in several cancers. Thus, it remains unclear whether TACC3 acts as a tumor suppressor or an oncogene. However, it is clear that TACC3 deregulation is associated with tumorigenesis and cancer development. It is significant to explore whether TACC3 acts as a therapeutic for the treatment of human cancer. The aberrant expression of TACC3, especially its up-regulated expression in cancer cells, suggests that it might be a potential molecular marker for the diagnosis and prognosis of human cancers. TACC3 depletion may inhibit the proliferation and invasion of cancer cells by targeting the mitotic spindle. Furthermore, depletion of TACC3 renders cancer cells more sensitive to the antimitotube agent paclitaxel (Yim et al., 2009), which seems more effective for cancers with low levels of TACC3. EGFR/EGFR is a potent inducer of epithelial–mesenchymal transition (EMT) and it is accompanied by mutations and overexpression in some cancers. Recently, TACC3 was identified as a binding partner of EGFRs, stabilizing EGFR at the cell surface (Petschnigg et al., 2016), and the depletion of TACC3 destroys EGF-mediated EMT (Ha et al., 2013a). The knockdown of TACC3 reduces mitogenic signaling in nonsmall cell lung cancer cell lines (Petschnigg et al., 2016), which provides a new idea for the clinical treatment of cancer. Experimental data is exciting but, the clinical implications are still unclear, and thus, further studies are required before we fully understand the molecular mechanism.

Fusion genes are chromosomal aberrations that are often found in cancers, which can be used as prognostic markers and drug targets in clinical practice. An FGFR3–TACC3 fusion protein is identified in many cancers (Costa et al., 2016). The TACC domain is highly conserved in fusion proteins, and its presence leads to increased and altered levels of FGFR3 activation, fusion protein phosphorylation and downstream signaling (Nelson et al., 2016). FGFR3-TACC3 triggers the activation of the ERK and Akt signaling pathways (Yuan et al., 2014), and the knock-down of TACC3 inactivates PI3K/Akt signaling in RCC and HCC cells (Guo & Liu, 2017; Zhou et al., 2011). Experiments suggest that FGFR3-TACC3 may be useful as a diagnostic marker and therapeutic target in cancers. Furthermore, the combined approach targeting FGFR3-TACC3 and its downstream proteins may further enhance the efficacy of FGFR or TACC3 aberrant targeted therapy. However, the molecular mechanism of the FGFR3-TACC3 protein in cancers is still not clear. One interesting phenomenon remains unclear, which is that the fusion protein frequently localizes to the mitotic spindle poles asymmetrically and relocates to the midbody in the late stages of mitosis, which is different that TACC3 during mitosis (Singh et al., 2012).

7 | CONCLUSIONS AND PERSPECTIVES

In this review, we summarized the recent research progress involving TACC3 and its complexes, especially TACC3/ch-TOG and TACC3/ch-TOG/clathrin, which are crucial for the initial assembly and the maintenance of the spindle structure and function. Studies published over the past years have accelerated our understanding of TACC3 in preventing faulty cell division and aneuploidy. However, some of the roles of TACC3 are still obscure.

7.1 | What role does TACC3 play in astral and interpolar microtubules?

Spindle MTs can be divided into three major classes, including the kinetochore fibers, astral microtubules and interpolar microtubules (Figure 1C). Clearly, TACC3 is found at the kinetochore microtubules, but whether it is also found at the interpolar microtubules and centrosome-associated astral microtubules is unclear. However, if it is found in these locations the question of what roles TACC3 plays needs to be clarified. The density of astral microtubules is substantially reduced when TACC3 is depleted as changes in k-fibers (Singh et al., 2014), which indicates that the TACC3/ch-TOG/clathrin complex may also exist in astral microtubules. Moreover, the plus end-tracking behavior of TACC3 is confirmed in astral and interpolar microtubules in mitotic cells (Gutiérrezcaballer et al., 2015). Recently, non-kMTs (not end at the kinetochore) are shown that play important roles in chromosome congression (Kajetz et al., 2016). These data provide a novel research perspective for TACC3 in mitosis, and it is crucial to gain a
better understanding of how TACC3 behaves in astral and interpolar microtubules during mitosis.

7.2 What role does TACC3 play in meiotic spindle organization?

In mitosis, the genome is duplicated once and segregated into two daughter cells. In contrast, meiosis consists of two rounds of consecutive cell divisions, meiosis I and meiosis II, with just a single round of DNA replication, which halves the chromosome complements in sperm or oocyte gametes. In mitosis and meiosis II, the sister chromatids are segregated to opposite poles during the metaphase-anaphase transition. However, in meiosis I, the sister kinetochores attach to microtubules with the same polarity, and the homologous chromosomes are separated in different directions, which in mitosis is regarded as a faulty attachment. Meiosis spindle formation differs from mitotic spindle formation, because it does not contain centrioles at the spindle poles. It mainly depends on a microtubule organize center to form the spindle during meiosis.

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