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Review

Targeting mitosis exit: A brake for cancer cell proliferation

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ABSTRACT

The transition from mitosis to interphase, referred to as mitotic exit, is a critical mitotic process which involves activation and inactivation of multiple mitotic kinases and counteracting protein phosphatases. Loss of mitotic exit checkpoints is a common feature of cancer cells, leading to mitotic dysregulation and confers cancer cells with oncogenic characteristics, such as aberrant proliferation and microtubule-targeting agent (MTA) resistance. Since MTA resistance results from cancer cells prematurely exiting mitosis (mitotic slippage), blocking mitotic exit is believed to be a promising anticancer strategy. Moreover, based on this theory, simultaneous inhibition of mitotic exit and additional cell cycle phases would likely achieve synergistic antitumor effects. In this review, we divide the molecular regulators of mitotic exit into four categories based on their different regulatory functions: 1) the anaphase-promoting complex/cyclosome (APC/C, a ubiquitin ligase), 2) cyclin B, 3) mitotic kinases and phosphatases, 4) kinesins and microtubule-binding proteins. We also review the regulators of mitotic exit and propose prospective anticancer strategies targeting mitotic exit, including their strengths and possible challenges to their use.

1. Introduction

Cancer is the second leading cause of death and is estimated to account for 9.6 million death globally in 2018 (http://www.who.int/cancer/en/). Many physiological factors are involved in cancer therapy, such as inflammation, metabolism, angiogenesis and cell cycle [1–6]. Loss of mitosis regulation is a common feature of cancer cells, resulting in cell cycle dysregulation and aberrant proliferation [7]. Microtubule-targeting agents (MTAs), such as taxanes (taxol, docetaxel) and vinca alkaloids (vinblastine, vincristine, vinorelbine, vindesine, vinflunine), which induce mitotic arrest by disturbing microtubule assembly, have been successfully used for decades to treat a number of solid tumors [8]. Through different mechanisms, both taxanes and vinca alkaloids alter microtubule dynamics and inhibit spindle function to suppress mitosis *via* activation of the spindle assembly checkpoint (SAC) (Fig. 1), which induces cell cycle arrest during abnormal mitosis [9]. However, the effects of MTA-induced SAC are not permanent, cancer cells may survive SAC-dependent mitotic arrest by prematurely exiting mitosis and slipping into a tetraploid G1 state to start a new cell cycle (Fig. 1) [10]. Such premature mitotic exit, termed as “mitotic slippage”, is the major mechanism by which cancer cells bypass the mitotic inhibition of MTAs, limits the efficacy of MTA in cancer therapy [11]. As a counter to this strategy, blocking mitotic exit may provide an efficient anticancer strategy. More importantly, due to SAC-independent surveillance, the strategy targeting mitotic exit has some significant advantages over SAC inhibition, such as broad antitumor activity and reduced cytotoxic side effects [12]. Consequently, an increasing number of mitotic exit inhibitors are being tested in preclinical and/or clinical anticancer studies (Table 1). In this review, we summarize important regulators of mitotic exit, and discuss potential benefits and challenges of targeting mitotic exit for cancer therapy, highlighting the newest findings from both basic and clinical antitumor studies.

2. Regulation of mitotic exit

Mitotic exit depends on multiple precise regulatory steps, including the activation of the mitotic ubiquitin ligase APC/C and the inactivation of a series of mitotic kinases [13,14]. In addition to the canonical mitotic kinase/phosphatase pathways, newly identified regulators of mitotic exit, such as kinesins, are constantly being added to our list of cell division components [15]. Notably, many of regulators are closely related to the development and progression of tumors, indicating potential for translation to therapeutics. Based on their different regulatory roles in mitotic exit, we divide the regulators into four categories: 1) the anaphase-promoting complex/cyclosome (APC/C, a ubiquitin ligase); 2) cyclin B (the most important cyclin controlling mitotic exit); 3)

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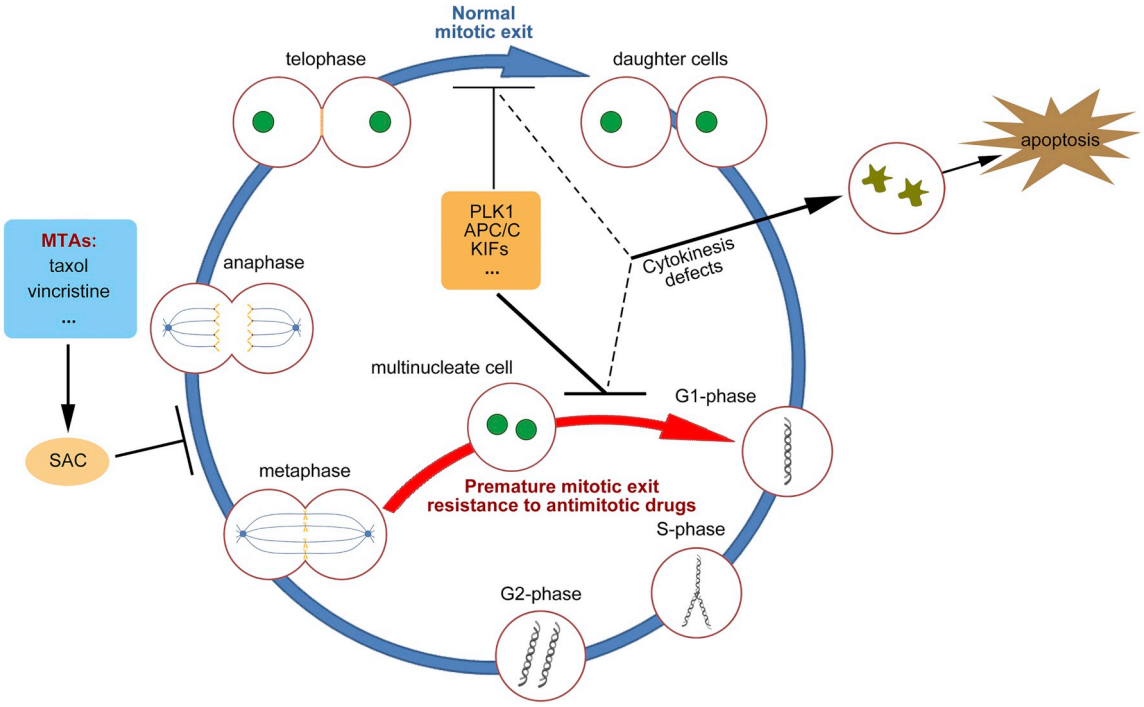

Fig. 1. A potential strategy that targets mitotic exit for cancer therapy. Taxol and other MTAs induce SAC to prevent/reduce cancer cells from entering anaphase. However, some cancer cells slip out of this arrested process by premature exit. Thus, blocking mitotic exit at the last mitotic step of cytokinesis by targeting molecular regulators, such as PLK1, PP2A or mitotic kinesins, together with MTAs can act synergistically to inhibit cancer cell proliferation by suppressing mitosis at both telophase and metaphase. Eventually these cancer cells undergo apoptosis triggered by suppression of mitotic exit.

Table 1
Small molecule compounds that target mitotic exit.

Agents	Cancer types	Clinical phase	Current stage*
APC/C			
proTAME	Cervical cancer cell line [45]	No data	Preclinical study
Apcin	Osteosarcoma, colorectal and lung cancer cell lines [46]	No data	Preclinical study
Aurora Kinases			
Alisertib	Prostate cancer [167], leiomyosarcoma [168]	I/II/III	A:20; C:15; T:1; O:21
AMG 900	Acute myeloid leukemia [169]	I/III	A:1; C:1; T:1; O:0
AT9283	Myeloma [170], leukemia [171]	I/II	A:0; C:4; T:1; O:0
AZD1152	Acute myeloid leukemia [172], lymphoma [74]	I/II/III	A:0; C:6; T:2; O:0
AZD1152-HQPA	Neurological malignancy [173]	I	A:0; C:2; T:0; O:0
Danusertib	Leukemia [77]	II	A:0; C:1; T:1; O:1
ENMD-2076	Leukemia [174], ovarian cancer, colorectal cancer [76]	I/II	A:0; C:5; T:0; O:3
GSK-1070916	Acute lymphoblastic leukemia [175]	I	A:0; C:1; T:0; O:0
MK-5108	NSCLC [176]	I	A:0; C:1; T:0; O:0
PF-03814735	Melanoma and colon cancer [177]	I	A:0; C:1; T:0; O:0
SNS-314	Colon cancer [178]	I	A:0; C:1; T:0; O:0
TAK-901	Colorectal cancer, NSCLC [179]	I	A:0; C:2; T:0; O:0
Tozasertib	NSCLC [180], breast cancer [181]	I	A:0; C:1; T:6; O:0
PLK1			
BI 2536	NSCLC [182], acute myeloid leukemia [183]	I/II	A:0; C:10; T:1; O:0
GSK461364	Colorectal adenocarcinoma, esophageal cancer [184]	I	A:0; C:1; T:0; O:0
NMS-1286937	Colon cancer, pancreatic cancer [185]	I	A:0; C:1; T:0; O:0
Rigosertib (sodium)	Pancreatic cancer [186], leukemia [187]	I/II/III	A:5; C:21; T:0; O:9
TAK-960	Ovarian cancer, colorectal cancer [188]	I	A:0; C:1; T:0; O:0
Volasertib	NSCLC [189], acute myeloid leukemia [190]	I/II/III	A:7; C:10; T:0; O:6
PP2A			
LB-100	Ovarian, testicular, breast, and prostate cancers [116]	I	A:1; C:0; T:0; O:1
KIF (Eg5)			
Ispinesib	Head and neck squamous cell carcinoma [191], breast cancer [192]	I/II	A:0; C:16; T:0; O:0
SB-743921	Lymphoma [193]	I/II	A:0; C:2; T:0; O:0
ARRY-520	Myeloid leukemia [141]	I/II	A:1; C:5; T:0; O:2
AZD4877	Urothelial cancer [194], acute myeloid leukemia [195]	I/II	A:0; C:3; T:3; O:2
MK0731	Ovarian cancer, NSCLC [196]	I	A:0; C:1; T:0; O:0
Litronesib	NSCLC, colorectal cancer [197]	I/II	A:0; C:7; T:1; O:0

The inhibitor drug information obtained from www.MedChemExpress.cn. (Inhibitors, Agonists, Screening Libraries). Adapted from information obtained from clinicaltrials.gov.

* A: active clinical trial, not recruiting; C: completed clinical trial; T: terminated clinical trial; O: recruiting clinical trial and other.

Table 2
Cancer-associated characteristics of molecules regulating mitotic exit.

Targets	Characteristics in cancer
Ubiquitin ligase	
APC/C	High activity of APC/C predicts poor prognosis of colorectal cancer and NSCLC patients [25,26]. The coactivator CDC20 and substrates of APC/C, such as HEC1 and Ect2, demonstrate oncogenic characteristics [42].
Kinases and phosphotase	
CDK1/cyclin B complex	High level of cyclin B represents high incidence of relapse of breast cancer and leads to the resistance of prostate cancer to mTOR inhibitor [50–52].
Aurora kinases	Inhibition of Aurora A or B kinases, suppresses the viability of prostate, cervical and colorectal cancer cells [69,70].
PLK1	PLK1 overexpression predicts poor prognosis in pancreas, gastric, prostate and breast cancers. Inhibition of PLK1 reduces the drug resistance, such as cisplatin and gemcitabine [87–90].
PP2A	PP2A suppresses the proliferation of cancer cells and promotes apoptosis [107,108]; whereas PP2A inhibition increases chemo- and radio-sensitizing properties of medulloblastoma and osteosarcoma cells [198,199].
KIFs and related proteins	
Eg5	Eg5 is broadly overexpressed in cancer cells, its inhibition leads to mitotic arrest and subsequently apoptosis [119].
MPHOSPH1	MPHOSPH1 is overexpressed in HCC and bladder cancers [130,131]. Inhibition of MPHOSPH1 leads to post-mitotic apoptosis and increases the sensitivity of HCC cells to taxol [131].
PRC1	PRC1 is upregulated in HCC, bladder and breast cancers [130,135–137]. PRC1 expression was associated with early HCC recurrence and poor patient outcome. Its suppression attenuates the proliferation of HCC and bladder cancer cells [138].

mitotic kinases and phosphatases; 4) kinesins and microtubule-binding proteins (Table 2).

2.1. The anaphase-promoting complex/cyclosome

APC/C, a large ubiquitin ligase comprised of at least 13 subunits, plays critical roles in cellular processes such as development, genomic stability, metabolism, apoptosis and cell cycle regulation [16,17]. Before anaphase, APC/C binds to its co-activator, cell division cycle protein 20 homologue (Cdc20), to form an E3 ubiquitin ligase. Activated APC/C^{Cdc20} targets specific substrates, such as cyclin B and securin, for degradation by the 26S proteasome and subsequently initiates the anaphase [16,17]. To ensure proper progression from mitotic exit, APC/C is kept inactive by the SAC until all chromosomes attach to microtubules originating from the opposite spindle poles (Fig. 2). In human cells, the well-characterized components of SAC include Mad1, Mad2, Mad3 (BubR1), Bub1, Bub3, and Mps1 (Fig. 2). SAC is activated by unattached kinetochores, inhibiting APC/C^{Cdc20} from binding its substrates (*e.g.*, cyclin B or securin), thereby blocking the metaphase/anaphase transition (Fig. 2). However, in MTA-resistant cancer cells, even with sustained activated SAC, cyclin B is still slowly degraded under MTA treatment [18]. Once cyclin B levels drop beneath a critical threshold, the cell can often exit mitosis into a polyploidy interphase, thereby survive the fatal mitotic arrest (Fig. 2). Consistent with what observed in human cells, similar mitotic regulatory roles of APC/C and its co-activators have been reported in mouse models [19]. For examples, Cdc20 genetically deleted mouse shows failed embryogenesis, the embryos are arrested in metaphase at the two-cell stage with high levels of cyclin B, suggesting a critical role of Cdc20 in mitotic exit [20]. Cdh1, another APC/C cofactor, is not required for mitotic exit in both human cell lines and mouse embryonic fibroblasts; however, in cells lacking Cdh1, the G1 phase is shortened and the S phase is prolonged [21]. In summary, APC/C plays an essential role in cell cycle regulation, such as mitotic exit (with Cdc20) and G1 phase (with Cdh1).

APC/C can be blocked by endogenous inhibitors, such as Emi1 (early mitotic inhibitor 1) and Emi2 (endogenous meiotic inhibitor 2), which constitute the Emi/Erp protein family of APC/C inhibitors that controls cell division [19]. The expression of Emi2 is restricted to early embryos, spermatocytes and maturing oocytes [22]. Through inhibition of APC/C^{Cdc20}, Emi2 functions as a cytostatic factor that causes long-term M phase arrest of mature oocytes [22]. In contrast, Emi1, which is expressed in many somatic tissues, antagonizes the activity of APC/C^{Cdh1} and delays G1/S transition [23,24]. Structurally, Emi1 consists of a conserved D-box, a ZBR (zinc-binding region) motif and a C-terminus RL tail; the D-box and the RL tail bind to APC/C^{Cdh1} and block the accessibility of substrate to APC/C^{Cdh1}, and the ZBR motif inhibits APC/CE3 ligase activity [19].

Due to its critical role in mitosis, it is not surprising that APC/C was reported to be directly or indirectly connected to cancer. One example is the APC/C co-activators Cdc20 and Cdh1, which were identified respectively as an oncoprotein and a tumor suppressor. Cdc20 mainly functions in chromosome segregation and mitotic exit; its knockdown inhibits the ubiquitin ligase ability of APC/C to degrade cyclin B1, thus blocking mitotic exit and subsequent apoptosis of cancer cells through a SAC-independent manner [12]. In patients with colorectal cancer or non-small cell lung cancer (NSCLC), a high expression level of Cdc20 predicts a poor prognosis [25,26]. In addition to Cdc20, Cdh1 is another well-studied APC/C cofactor that regulates the APC/C E3 ligase to play a key role in late M and G1 phases [27]. Moreover, Cdh1 has a tumor suppressor role, its expression is significantly decreased in many solid tumors, including ovary, prostate, breast, colon, brain and liver cancers [28–31], whereas its suppression leads to centrosome amplification, incorrect chromosome segregation, and aberrant mitotic exit, thus inducing genetic instability and tumorigenesis [32]. Cdh1 deficient mice consistently show increased susceptibility to spontaneous tumors, such as fibroadenomas and mammary gland adenocarcinomas [33].

APC/C subunits are also associated with cancer. A large number of mutations in APC/C holoenzyme subunits have been identified that disturb cell cycle progression and promote proliferation of cancer cells [34]. In addition, post-translational modifications (PTMs), such as small ubiquitin-related modifier (SUMO) proteins [35], play a critical role in APC/C subunit functions during mitotic exit. Potential SUMOylation sites of the APC/C subunits have been previously suggested [36] and two recent reports identify subunit APC4 as the major SUMOlyation target in the APC/C complex (Fig. 3) [37,38]. APC4 is SUMOylated at Lys^{772} and Lys^{798} during M-phase, which peaks at anaphase initiation when cyclin B1 starts to be degraded. Through increasing APC/C ubiquitylation activity, SUMOylation of APC4 is required for accurate mitotic exit progression. Disruption of the SUMO conjugation machinery results in a delay in mitosis and defects in mitotic chromosome separation suggesting a novel mitotic exit regulatory mechanism *via* SUMOylation of APC/C [37,38]. Since APC/C is closely linked to cancer development and progression, inhibition of SUMOylation on functional subunits of APC/C, such as APC4, provides a rational anticancer strategy (Table 2), although thorough mechanistic studies are needed.

The substrates of APC/C also play key roles in cancer progression (Table 2). Epithelial cell transforming sequence 2 (Ect2) is a substrate of APC/C-Cdh1 that is degraded through the ubiquitination pathway after mitosis [39]. Ect2 is a guanine nucleotide exchange factor that positively regulates the Rho GTPase pathway, controlling later events in mitotic exit progression such as cytokinesis [40,41]. Ect2 plays an oncogenic role in multiple solid tumors, including lung, breast and liver cancers in which the signaling axes of KRAS/TP53, E3-ligase E6AP and Rho/ERK are involved [42–44]. Whether Ect2 contributes to its

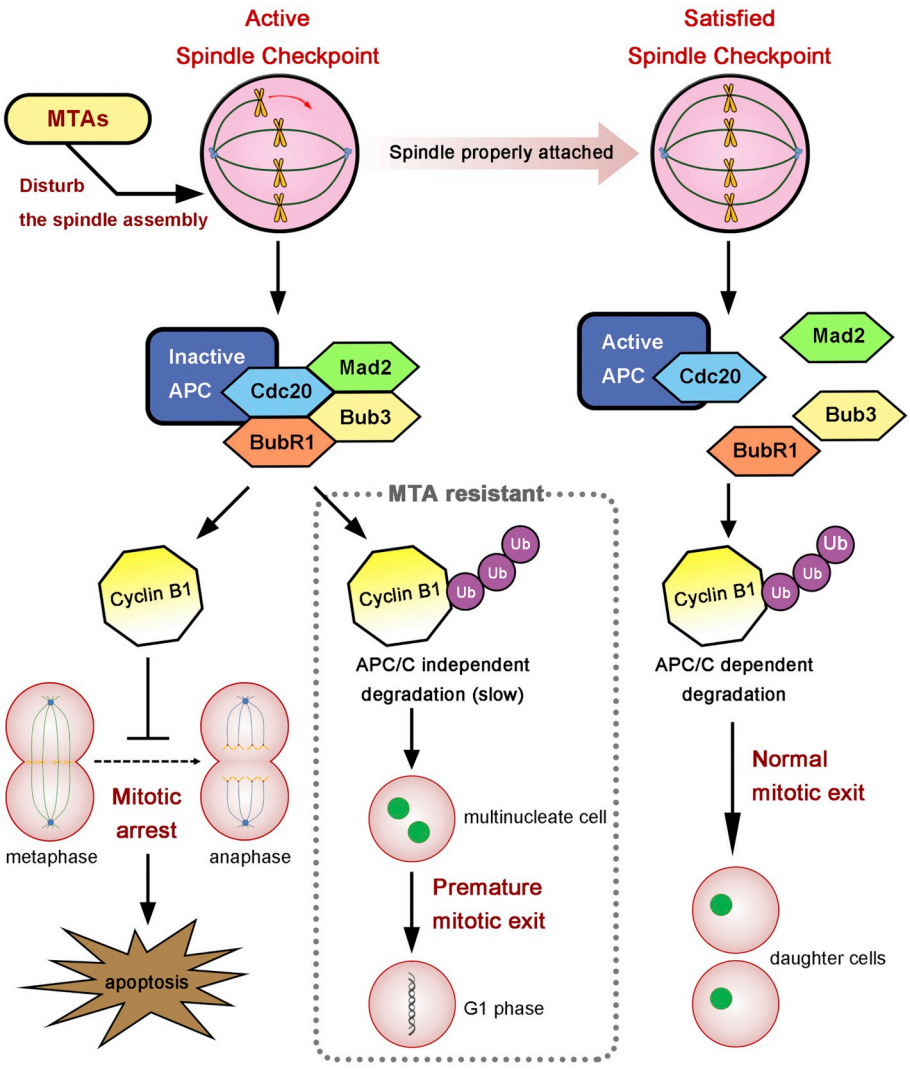

Fig. 2. Different cell fates following SAC activation. MTAs, such as taxol, impair the assembly/disassembly dynamic balance of microtubule, thereby activate SAC through unattached kinetochores. SAC components, such as Mad2, Mad3 (BubR1), Bub1 and Bub3, form the mitotic checkpoint complex (MCC), and inhibit Cdc20 from aiding substrate recognition by the APC/C, thereby blocking the E3 ligase activity of the APC/C complex, leading to inhibition of prometaphase to anaphase transition and mitotic arrest. MTAs-treated cancer cells go through a prolonged mitotic arrest that can culminate in mitotic cell death. However, MTA resistant cancer cells can take an alternative route known as "mitotic slippage" to escape mitotic cell death. Specifically, cancer cells exit mitosis prematurely through slow degradation of cyclin B1, even with SAC sustainedly activated. Without proper chromosome segregation and cytokinesis, the escaped cancer cells enter the next interphase as multinucleated tetraploid cells.

tumorigenic function by regulating mitotic exit remains to be determined.

Considering the pivotal role of APC/Cdc20 in controlling mitotic exit progression, developing specific inhibitors of the complex is an attractive target for cancer treatment. Several APC/C inhibitors have been developed (Table 1), such as TAME (tosyl-L-arginine methyl ester) [45] and apcin [46]. proTAME disrupts the interaction between APC and Cdc20 and releases Cdc20 from the APC/C, thus increasing Cdc20 auto-ubiquitination and stabilization of cyclin B1 [45]. In HeLa cells, this disruption leads to anaphase delay and eventually blockage of mitotic exit [47]. The other inhibitor, apcin, competitively inhibits the ubiquitination of Cdc20 substrates and prevents substrate recognition by Cdc20 [46]. Notably, since TAME and apcin inhibit APC/C through different mechanisms, using them in a combination treatment increases the stability of APC substrates, including cyclin B1, securin and cyclin A2, thus synergistically blocking mitotic exit in cancer cells [46]. In addition, combining APC/C inhibition with chemotherapeutic drugs, such as paclitaxel or Aurora A inhibitor [48], also generates potent antitumor efficacy through inducing significant inhibition of mitotic exit and massive apoptosis in cancer cells. Moreover, inhibition of APC/C, by proTAME or loss of Cdh1, increases the sensitivity of cancer cells to chemotherapeutic agents, such as the DNA topoisomerase 2-alpha (Top2α) inhibitor, etoposide [49]. Although no APC/C inhibitor has entered clinical trials at present, the positive preclinical results suggest that blocking mitotic exit by APC/C inhibition represents a promising cancer therapy, either as a mono-therapy or as a combinatory therapy with additional chemotherapeutic agents [46].

2.2. Cyclin B

The cyclin family controls the progression of cells through cell cycle by activating CDK enzymes. Based on their behavior in the cell cycle, cyclins can be divided into four classes, G1 cyclins, G1/S cyclins, S cyclins, and M cyclins. As the most important and well-studied M cyclin, cyclin B constitutes the regulatory subunit of CDK1/cyclin B complex, also referred to as mitosis promoting factor (MPF), that controls entry into and exit from mitosis [16]. In late metaphase, cyclin B is rapidly degraded by APC/C through the 26S proteasome pathway (Fig. 4), eventually initiating mitotic exit [16].

Cyclin B has been shown to correlate with various cancers (Table 2); its overexpression predicts poor prognoses in patients with endometrial endometrioid adenocarcinoma, squamous cell carcinoma and breast cancer [50–52]. As a diagnostic marker for breast cancer, more than 70% of patients with high expression of cyclin B relapsed within eight years, whereas the relapse rate of those with low cyclin B levels was less than 10% [53]. Mechanistically, upregulation of cyclin B, which promotes G2/M transition, is the main reason that prostate cancer cells become resistant to the mTOR inhibitor everolimus; knockdown of cyclin B re-sensitizes prostate cancer cells to everolimus by decreasing the number of cells that accumulate at the G2/M-phase [54]. Notably, mitotic exit blockage by cyclin B stabilization, for example by expressing degradation-resistant or non-degradable cyclin B1 [12], generates

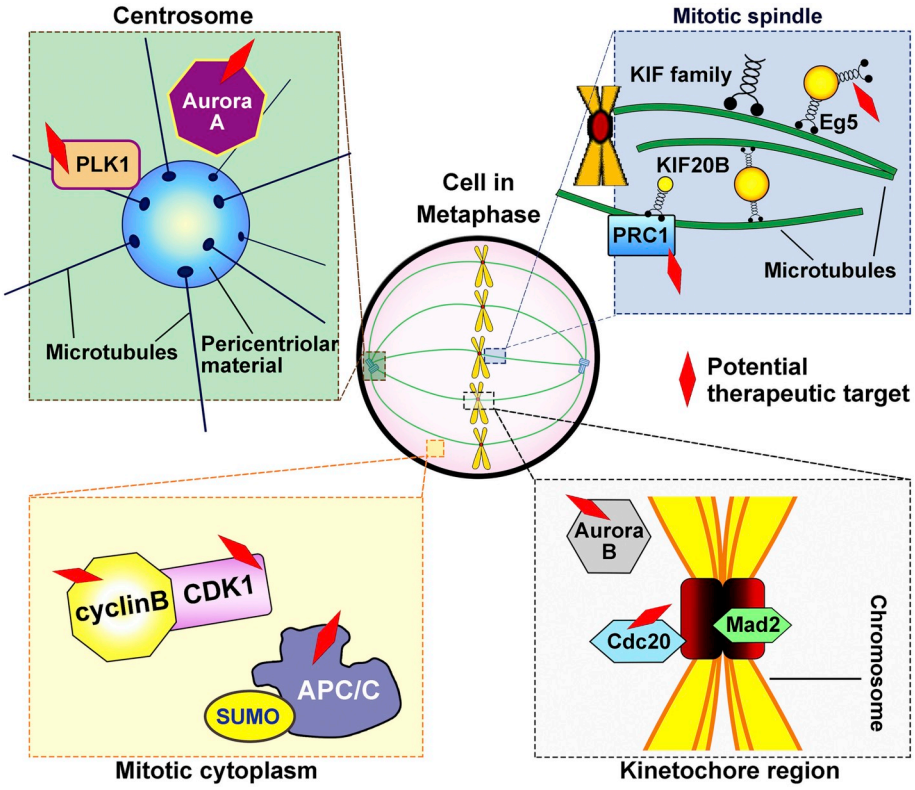

Fig. 3. The location of mitotic proteins during metaphase. The four cellular structures are: centrosomal region (upper left), mitotic spindle region (upper right), mitotic cytoplasm region (lower left) and kinetochore region (lower right). Some of the mitotic proteins locate at different cellular substructures during mitosis, such as cyclin B, whereas the others settle at fixed locations to function, including Aurora B and Eg5. Red diamonds represent potential therapeutic targets. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

suppressive effects on cancer cells through inducing efficient mitotic blockade and significant apoptosis, and further sensitizes cancer cells to apoptosis inducers, such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [55]. Targeting cyclin B for degradation provides an interesting anticancer strategy. However, before this strategy can be applied, the broad and vital functions of cyclin B on cell cycle and other physiologic processes in normal cells need to be accounted for. For example, to reduce the possibility of generating toxic side effects, the application of targeting cyclin B is likely limited to the cancer cells that are much more dependent on cyclin B stabilization compared to normal cells.

2.3. Mitotic kinases and phosphatases

Kinases and phosphatases involved in the regulation of mitotic exit include Aurora kinases, Polo-like kinase 1 (PLK1) and Protein phosphatase 2A (PP2A).

2.3.1. Aurora kinases

Aurora kinases, including Aurora A, Aurora B and Aurora C, are a serine/threonine kinase family that plays an important role in cell division and proliferation [56]. Throughout mitosis, Aurora A is localized at centrosomes and spindle poles, controlling microtubule dynamics, centrosome separation and spindle assembly (Fig. 3) [57]. Aurora B is mainly localized at chromosomes and centromeres in early mitosis, while during mitotic exit it re-localizes to the spindle midzone and midbody (Fig. 3) [58]. Aurora C, which seems to have evolved from Aurora B, plays an important role during meiosis and early embryonic development [59].

Previous studies on Aurora A mainly focused on its roles during early mitotic events, including centrosome maturation, G2/M transition, and mitotic spindle assembly [57]. Later developments of specific inhibitors have led to the demonstration that Aurora A also functions at mitotic exit, such as cytokinesis initiation [60]. Recently, a novel Aurora A involved mechanism that ensures faithful mitotic exit was identified [61]. CREB-binding protein (CBP), a well characterized histone and non-histone acetyltransferase, acetylates and stabilizes

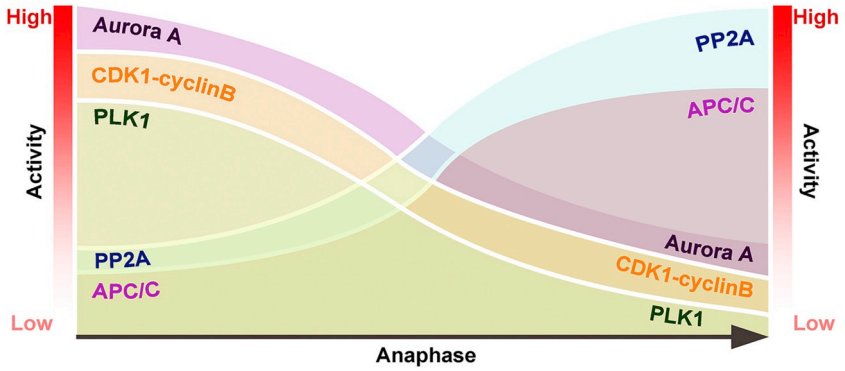

Fig. 4. The temporal activity of the mitotic kinases during mitotic exit. Alteration of critical mitotic regulators, such as cyclin B degradation, Aurora kinases and PLK1 downregulation, APC/C and PP2A phosphatase activation, are involved in mitotic exit, playing essential roles during anaphase and telophase.

targeting protein for Xenopus kinesin-like protein 2 (TPX2), a critical regulator of many aspects of the spindle assembly, to promote Aurora A activation; whereas at later stage of mitosis, the binding of CoA synthase (COASY) to CBP interferes with CBP-mediated acetylation of TPX2, thereby promoting Aurora A inactivation and proper mitotic exit (Fig. 4) [61]. Given that overexpressed Aurora A is commonly observed in various cancers, usually accompanied by MTA resistance [62], it is not surprising that a low level of COASY predicts poor clinical outcomes in primary tumors and COASY inhibition increases resistance of cancer cells to taxol [61]. Reactivation of COASY, which efficiently suppresses Aurora A and blocks mitotic exit of cancer cells, seems like a rational target for treatment of carcinomas with reduced COASY. To test this strategy, further study to clarify the molecular mechanisms underlying COASY regulation of mitotic exit and taxol resistance is needed.

Aurora B plays a well-established role in the correction of erroneous kinetochore-microtubule attachments and mitotic exit initiation, thereby ensuring chromosome bi-orientation and faithful segregation during anaphase [63]. The oncogenic role of Aurora B has also been reported. Aurora B is overexpressed in various cancers including acute myeloid leukemia and colorectal cancer [64,65], whereas knockdown of Aurora B by small hairpin RNAs (shRNAs) inhibits proliferation of xenografts [66]. Elevated expression of Aurora B predicts poor prognosis and represents a tendency toward higher grades of malignancy in different neoplastic lesions. Its level directly correlates with Gleason grade in prostate cancer [67], Duke's grade in colorectal cancer [68], and dedifferentiation in ovary and thyroid carcinoma [69,70]. Notably, in prostate cancer cells, ablation of cyclin K, a regulatory subunit of CDK12 and CDK13, induced downregulation of Aurora B, as well as apoptosis and mitotic catastrophe at late M-phase in an Aurora B-dependent manner [71]. Recently, cyclin K was identified as a downstream target of the MLL/SET methyltransferase protein SETD1A, regulating the DNA damage response of acute myeloid leukemia (AML) cells at S phase [72]. Therefore, targeting cyclin K in cancer cells not only interferes with Aurora B expression, which blocks mitotic exit, but also disrupts S phase, putting dual brakes on the cell cycle at both S phase and mitotic exit generating potent antitumor effects.

To date, many inhibitors targeting Aurora kinases have been reported and some of them have entered clinical trials to evaluate their anticancer effects (Table 1). Among these inhibitors, Alisertib (MLN8237, selective Aurora A inhibitor) and AZD1152 (selective Aurora B inhibitor) have successfully entered phase III clinical trials [73,74]. Treatment with Alisertib, for example, produced mild to modest single-agent anti-tumor activity in phase II studies on various advanced solid tumors, including breast cancer, lung cancer, squamous cell cancer of head and neck (SCCHN), gastro-esophageal adenocarcinoma, epithelial ovarian, fallopian tube carcinomas, and primary peritoneal carcinoma [73,75]. However, outside of these two agents, limited efficacy against solid tumors using other Aurora kinase inhibitors was observed in clinical trials [76]. One plausible explanation for these results may be the slower proliferation rate of cells in solid tumors compared with xenograft models. Therefore, Aurora kinase inhibitors may be more suitable for treating hematologic malignancies due to their greater homogeneity and higher proliferation rates compared to solid tumors [77].

2.3.2. Polo-like kinase 1

Polo-like kinase 1 (PLK1) belongs to the Polo-like kinases family, which contains five serine/threonine protein kinase members, PLK1-PLK5. Of the five human PLKs, PLK1 has been extensively studied due to its key roles in the DNA damage checkpoint and cell-cycle regulation [78–80]. The mitotic functions of PLK1 are becoming clear. During mitotic entry, PLK1 is activated by Aurora A kinase and its co-factor Bora (Fig. 3) [81], the latter alters the conformation of PLK1, allowing Aurora A to phosphorylate PLK1 on Thr^{210} and initiating mitotic entry [82]. While upon initiation of anaphase, the level of PLK1, which accumulated during S phase peaking at the G2/M phase transition, declined rapidly (Fig. 4), indicating a role in mitotic exit [83]. In addition, APC/C and insulin receptor substrate (IRS) pathways are also involved in PLK1-associated mitotic exit. On one hand, PLK1 can promote APC/C mediated degradation of cyclin B to trigger anaphase and subsequent mitotic exit [84]; on the other hand, PLK1 can phosphorylate IRS proteins to prevent premature mitotic exit *via* Akt inactivation [85].

Due to the close relationship of PLK1 with cell-cycle regulation and DNA damage repair, it is not surprising that PLK1 is overexpressed and implicated in a variety of cancers, including melanoma, colorectal cancer and NSCLC (Table 2) [86]. Moreover, PLK1 overexpression predicts poor prognosis in pancreas, gastric, prostate and breast cancers [87–90]. Additionally, PLK1 selective inhibitors, such as BI 2536 and BI 6727, significantly delay mitotic exit and trigger apoptosis of cancer cells [91]. However, through degradation of cyclin B1 and downregulation of Aurora B activity during mitotic arrest, these inhibitors promote mitotic slippage at high concentrations, which protects cancer cells from apoptosis rather than killing them [91], suggesting that beneficial therapeutic effects will require identification of an optimized dosage of PLK1 inhibitors.

Suppressing PLK1 also enhances the antitumor activity of chemotherapeutic drugs [59]. For example, knockdown of PLK1 enhances cisplatin chemo-sensitivity of p53-mutant epidermoid squamous carcinoma cells by upregulating p73 expression [60]; whereas in pancreatic cancer cells, inhibition of PLK1 by GSK461364 increases the cytotoxicity of gemcitabine [53]. In addition, upregulating PLK1 promotes taxol resistance in breast cancer cells by suppressing the taxol-induced postmitotic apoptosis [61]. Recently, an association between PLK1 expression and cisplatin resistance of epithelial ovarian cancer (EOC) was reported [92]. Compared with cisplatin sensitive cells, resistant EOC cells exhibited increased spindle checkpoint activity and upregulated PLK1, which made cisplatin-resistant EOC cells more vulnerable to mitotic blockage following PLK1 inhibition. Moreover, low levels of PLK1 predicted volasertib (a PLK1 inhibitor) resistance of EOC cells, whereas APC/Cdc20 inhibition increased volasertib sensitivity of EOC cells [92]. Therefore, when PLK1 inhibitors are combined with chemotherapeutic drugs, potent antitumor effects may be achieved by effectively blocking mitotic exit. This conclusion was further supported by a recent clinical trial that compared the efficacy of gemcitabine monotherapy with a combined therapy of gemcitabine with the PLK1 inhibitor rigosertib on metastatic pancreatic adenocarcinoma. The combined therapy produced a better partial response rate in patients (19%) than with gemcitabine alone (13%) [93].

Multiple PLK1 specific inhibitors have been developed that exhibit potent anti-tumor effects *in vitro* and *in vivo* [94,95], some have entered clinical trials (Table 1); however, only a few compounds, such as rigosertib and volasertib, proceeded to phase III trials to test anticancer efficacy, with other inhibitors showing less-than-ideal response rates [86]. Consequently, to combat the limitations of monotherapy, combination treatments have become more frequently employed in recent years [93].

Intriguingly, despite PLK1's reported oncogenic functions in many solid tumors, PLK1 may play different roles in certain cancer subtypes because blocking mitotic exit could also be a double-edged sword. For example, in adenomatous polyposis coli (APC) truncated colon cancer cells, which is a major form of colon cancer linked to cancer-related APC mutations, PLK1 inhibition generates tumor promotion effects [96]. Under these circumstances, the mitotic suppressive effects of blocking PLK1 is attenuated, instead, increased proliferation and apoptosis inhibitory effects are produced through accumulated chromosomal instability (CIN) in colon cancer cells [96], which is a hallmark of human neoplasms [97]. Consistently, a low PLK1 level represents a poor prognosis for colon cancer patients with APC non-sense mutations [96]. In breast cancer cells, PLK1 also demonstrates a tumor suppressive role in modulating estrogen-dependent transcription of tumor suppressor genes [98]. Therefore, optimal application of PLK1

suppression is essential for clinical cancer treatment. For instance, cancers with p53 deficiency and/or RAS mutations and high PLK1 expression may be particularly sensitive to PLK1 inhibitors [99,100]. However, for genetically unstable cancers, which are adapted to mitotic arrest by triggering premature mitotic exit, such as colon cancer with APC mutation, PLK1-targeting drugs may not be an appropriate choice.

2.3.3. Protein phosphatase 2A

Protein phosphatase 2A (PP2A) is one of the most prevalent serine/threonine phosphatases, which accounts for approximately 50% of the cellular serine/threonine protein phosphatase activity [101]. PP2A is a heterotrimeric enzyme. The core enzyme includes the scaffolding subunit "A", the regulatory subunit "B", and catalytic subunit "C". There are two unique scaffolding isoforms (Aα and Aβ), two unique catalytic subunit isoforms (Cα and Cβ), and four structurally diverse regulatory subunits (PR55 (B55), PR56/61 (B56/PR61), PR72/130, and PR93/110). These isoforms and subunits, respectively, determine the substrate specificity and subcellular localization of PP2A [101,102]. PP2A regulates a broad range of essential cellular processes, including mitosis, proliferation, metabolism and apoptosis. Specifically, its role in mitotic exit has been well studied. During the metaphase/anaphase transition, PP2A/B56 dephosphorylates and inactivates Cdc25C phosphatase, which in turn leads to CDK1 phosphorylation at Tyr^{15} and cyclin B degradation initiating mitotic exit [103]. Moreover, a recent study demonstrated that PP2A/B56 boosts mitotic exit through dephosphorylation at Ser^{92} in Cdc20, which promotes APC/Cdc20 assembly and triggers metaphase/anaphase transition [104].

It has been reported that PP2A functions as a tumor suppressor that is inactivated in colorectal and breast cancers (Table 2) [105,106]. PP2A attenuates the growth of cancer cells by suppressing the PI3K/Akt/mTOR, Wnt/β-catenin or c-Myc signaling pathways [107,108], and induces apoptosis through modulation of p53 and BCL-2 pathway [109]. Recently, a new regulatory mechanism by which PP2A blocks mitotic exit was reported. Knockdown of MASTL, a key cell cycle kinase that negatively regulates PP2A/B55 phosphatase complexes, impairs proliferation of a subset of breast cancer cells through reactivation of PP2A/B55 *in vitro* and *in vivo* [110]. Moreover, reduction of MASTL blocked mitotic exit of cancer cells, which significantly suppressed cell cycle and induced apoptosis [110]. This interesting result suggest that there is therapeutic potential in activating PP2A by suppressing its endogenous inhibitors in cancer cells. Similarly, a recent study reported an anticancer strategy by reactivating PP2A through suppressing SET (SET nuclear proto-oncogene) [111], which is a natural inhibitor of PP2A [112]. This study demonstrated that FTY720 (Fingolimod), an immunosuppressant approved by the FDA for multiple sclerosis [113], could disrupt SET-induced inhibitory effect on PP2A, leading to PP2A dephosphorylation and reactivation, suppressing malignant mesothelioma cell viability *in vitro* and *in vivo* [111]. Therefore, to better understand and treat malignancies that have low PP2A activity, endogenous suppressors of PP2A are worthy of further mechanistic and therapeutic studies.

Intriguingly, although traditionally regarded as a tumor suppressor, inhibition of PP2A has been recently demonstrated as a novel anticancer strategy (Table 2). In particular, senescence is a major protective mechanism for cancer cells to generate resistance to radiotherapy and conventional chemotherapy, which preferentially affect dividing cells [114]. However, during G2 phase, PP2A activation restrains Ras signaling to maintain cell quiescence, which is essential to induce cell senescence [115]. Therefore, by driving senescent cells into mitosis, inhibition of PP2A brings chemo- and radio-sensitizing properties to resistant cancers, *e.g.* medulloblastoma and osteosarcoma [76,77]. Some small molecule inhibitors of PP2A, such as LB100 (Table1), have already entered clinical trials for ovarian, testicular, breast, and prostate cancer treatment [116].

2.4. Kinesins and microtubule-binding proteins

Kinesin superfamily proteins (KIFs) are present in eukaryotes; more than 40 KIFs have been identified in humans [117]. KIFs largely function as molecular motors that bind to the microtubule network. KIFs contain a highly conserved motor domain, which hydrolyzes ATP and enables KIFs to bind and move across microtubules toward the plus-end of the microtubule (Fig. 3) [118]. KIFs participate in various cellular activities, including mitosis and intracellular transport of vesicles and organelles [118]. During mitosis, the activity of KIFs on the spindle microtubules are precisely regulated, ensuring the exact sequence of mitotic events throughout the progression of mitosis. In cancer cells, however, aberrant expression of some critical mitotic KIFs, such as Eg5, is commonly observed, and often leads to premature sister chromatid segregation [119]. This abnormal process usually results in mitotic arrest, premature mitotic exit or aneuploidy, which are believed to induce further malignant progression [120].

Accumulating evidence indicates that many KIFs play oncogenic roles through their mitotic functions (Table 2). For instances, KIF4A is overexpressed in 66% of small-cell lung cancers (SCLC) and 36% of NSCLC, and its upregulation is associated with decreased survival time for NSCLC patients [121,122]; depletion of KIF4A or its cofactor PHF14 inhibited mitotic exit and suppressed growth of NSCLC cells [123]. KIF23 is a highly studied member of the KIF family and is considered to be an oncogene. Inhibition of KIF23 causes arrest at mitotic exit in glioma, malignant pleural mesothelioma, primary lung cancer and HCC cells, without effecting non-proliferating cells [124–127]. Additionally, KIF20B, which is an important motor kinesin protein required for completion of cytokinesis [128,129], was reported to be an oncogene in bladder cancer [130]. Recently, we also reported on its oncogenic role in HCC development and taxol sensitivity through its essential function at cytokinesis [131–133].

In addition to KIFs, some microtubule-binding proteins also play important roles in mitosis, such as the protein regulator of cytokinesis 1 (PRC1). As a conservative non-motor crosslinking protein and a substrate of CDKs, PRC1 binds to the mitotic spindle in a highly dynamic manner (Fig. 3) [130]. Previous work has shown that PRC1 is required for the completion of cytokinesis in eukaryotic cells, and down-regulation of PRC1 leads to multinucleate cells [134]. In cancer cells, such as bladder cancer and gastric carcinoma, knockdown of PRC1 suppresses the cell cycle at late anaphase and G2/M phase, significantly inhibiting cell viability [130,135]; whereas overexpressed PRC1 is observed in breast, bladder, prostate and stomach cancers, and its elevated expression is highly correlated with short survival for patients, suggesting the prognostic potential of PRC1 as a tumor progression biomarker [130,135–137]. Recently, we demonstrated the oncogenic regulation of PRC1 in HCC progression [138]. In addition to its overexpression in HCC, we found that knockdown of PRC1 blocks mitotic exit at telophase through triggering cytokinesis failure, and, therefore, acts synergistically with taxol (triggering mitotic arrest at metaphase) to suppress HCC cells simultaneously at metaphase and telophase [138]. As a proof of concept, we applied this dual-suppression strategy (blocking mitosis at metaphase and telophase simultaneously) by combining taxol with PRC1 and KIF20B reduction and found that both therapies exhibited potent antitumor effects against an HCC xenograft [131,132,138,139].

Currently, multiple KIF specific inhibitors (the vast majority of which are Eg5 inhibitors) are in clinical trial (Table 1, only Eg5 inhibitors are shown). Although potent efficacy has been observed in preclinical studies, certain kinesin (Eg5) specific inhibitors showed disappointing results as monotherapy [117], presumably due to the much longer doubling time of human cancer tissues than that of the animal models used in preclinical studies [140]. Therefore, similar to Aurora kinase inhibitors, KIF inhibitors will likely have greater efficacy against hematologic malignancies due to their higher homogeneity and higher proliferation rates relative to solid tumors [141]. In addition,

combining KIF inhibitors with other chemotherapeutic drugs, such as taxol, which blocks cell cycle of cancer cell simultaneously at anaphase and metaphase, will be an attractive option for clinical studies [132,138].

3. Potential advantages and challenges of therapeutic strategy targeting mitotic exit

As discussed above, premature mitotic exit is a major mechanism for cancer cells to bypass the cytotoxic effects of MTAs (Fig. 1). Therefore, therapeutic strategies targeting mitotic exit have obvious advantages against such drug-resistant cancers (Table 2). First, due to their small effect on microtubules, mitotic exit inhibitors have lower neurotoxic effects such as peripheral neuropathy, which often accompany MTAs treatment [142]; second, targeting mitotic exit is independent of SAC or p53 surveillance, and thus may exhibit broader antitumor effects [143]; third, targeting mitotic exit sensitizes cancer cells to MTAs cytotoxicity, therefore combined treatment of MTAs with inhibition of mitotic exit may bring a synergistic antitumor effect [144,145]. However, despite these advantages, there are still challenges remaining, such as the possibility to produce CIN and a relatively lower cancer cell-killing ability.

3.1. Advantages

3.1.1. Reduced side effects

MTAs have been broadly used for treating a number of solid tumors (*e.g.*, breast, oophoroma and lung cancers) [8,146,147], however, due to the essential role of microtubules in non-dividing cells, these anti-mitotic drugs may cause serious toxic effects in normal cells [148]. Specifically, microtubules play an important role in synaptic signaling in neuronal cells. Thus, it is not surprising that anti-microtubule drugs (*e.g.*, taxol) cause neuronal damage resulting in serious peripheral neuropathy in cancer patients [149]. The occurrence rate of peripheral neuropathy is estimated to be up to 80% of patients receiving taxol treatment [150]. In contrast, therapeutic compounds targeting mitotic exit, which specifically interfere with dividing cells with little effects on microtubules, exhibited much lower neurotoxicity [149,151]. For example, little toxic effect on non-dividing cells was observed in pre-clinical studies for the Aurora B inhibitor AZD1152 [152–154]; consistently, clinical results showed low neurotoxicity of AZD1152 when treating relapsed/refractory diffuse large B-cell lymphoma and acute myeloid leukemia [74,155,156].

3.1.2. Broad antitumor activity

Another limitation to the clinical application of MTAs is the intrinsic or acquired drug resistance [148]. For example, nearly half of breast cancer patients are resistant or become resistant to taxol over the course of treatment [48]. Since the taxol-resistant cells are usually SAC-hampered [48,157], whereas blocking mitotic exit inhibits cancer cells in a SAC-independent manner [149], blocking mitotic exit could efficiently kill cancer cells with dysfunctional-SAC [144,158]. Moreover, in addition to SAC-deficient cancer cells, mitotic blockage by inhibition of Cdc20 could also significantly suppress p53/pRb-mutated or null cancer cells that are often insensitive to MTAs [143,157,159], suggesting that blocking mitotic exit may be applied to treat MTA insensitive cancers, for example, tumors with dysfunctional-SAC or mutated p53/pRb [138].

3.1.3. Enhanced antitumor effects when combined with MTAs

Blocking mitotic exit increases the efficacy of MTAs against various cancers [48,146,159–161]. Based on our and others' studies, we proposed that the potent antitumor effect of combined therapy is probably due to the simultaneous inhibition of mitosis in cancer cells both at metaphase (MTA) and anaphase/telophase (mitotic exit inhibition). On one hand, the cells that escaped from metaphase inhibition (triggered by MTA) will be re-trapped in the anaphase/telophase arrest by blocking mitotic exit, on the other hand, MTA will further increase the cytotoxic effect of mitotic blockage through the microtubule poison characteristics, thus generating enhanced or even synergistic efficacy [138].

3.2. Challenges

Although targeting mitotic exit has shown promise in cancer therapy, there are still some problems that cannot be ignored.

3.2.1. Chromosomal instability and aneuploidy

The possibility of producing CIN and/or aneuploidy in cancer cells is a potential obstacle to therapies targeting mitotic exit. In general, many elements, such as defects in mitotic checkpoints, chromosome cohesion and mitotic spindle as well as merotelic attachment of kinetochores, can generate CIN, which is a main driver of cancer progression [97]. As discussed above, blocking mitotic exit could also induce CIN or aneuploidy in cancer cells, for example, through targeting KIFs such as KIF20B [131], or introducing foreign miRNAs such as miR-26a [162]. Therefore, a mechanistic study of CIN/aneuploidy in cancer cells, as well as reducing the possibility of generating CIN/aneuploidy, is vital for the successful application of anticancer strategy targeting mitotic exit. Importantly, since there is evidence that cancer cells with CIN or aneuploidy are more sensitive to certain chemotherapeutic drugs [163], to partly reduce or eliminate such side effects, combined treatment with additional drugs optimized to exploit the chemotherapeutic sensitivity is possible for cancer therapy. For instance, breast cancer cells with aneuploidy induced by loss of PI3K-C2α were more sensitive to taxane, and thus combined therapy of PI3K-C2α inhibition/taxol resulted in potent efficacy in pre-clinical models and in neoadjuvant settings [163]. Our recent studies also demonstrated that the HCC cells with aneuploidy due to reduction of endogenous KIF20B or PRC1 became more sensitive to three MTAs compared with diploid HCC cells [131,138]. These studies together suggest that combining MTAs with drugs targeting mitotic exit represent a worthwhile approach to clinical application.

3.2.2. Mild cytotoxic effects against cancer

Inhibition of mitotic exit alone may be insufficient to cause massive cell death. Many agents that are designed to specifically block mitosis, such as inhibitors of CDKS, PLK1 and KIFs, have shown disappointing clinical results when used in monotherapy [3,94]. Their failures are attributed to the relative insensitivity of cancer cells to mitotic arrest. Specifically, two different behaviors of cells appear when undergoing a long-term mitotic arrest, that is, mitotic cell death *vs* survival with mitotic slippage or premature mitotic exit [10]. The phenotype responding to mitotic arrest is determined by a series of complex factors, including the cell types, mitotic inhibitors, the duration of mitotic arrest, as well as intrinsic regulators such as the levels of MAD2 and the degradation rate of cyclin B [10]. The response to mitotic arrest (cell death *vs* survival) is essential for developing effective antimitotic strategies against cancer, for many cancer cells are intrinsically insensitive to mitotic arrest, for example, with high levels of inhibitor of apoptosis proteins (IAPs), or rapid decrease of cyclin B during mitotic exit [10]. However, compared with *in vitro* experiments, in clinical studies, the dosages of anti-mitotic drugs used are often not sufficient to trigger apoptosis of such intrinsicly drug resistant cancer cells, hence, only delayed mitotic exit is induced. To overcome this challenge, as discussed above, it is rational to combine additional potent cytotoxic drugs, such as MTAs, with mitotic exit inhibition to generate significant cancer-killing effects.

3.2.3. Side effects

Finally, although serious adverse effects, such as peripheral neuropathy, are rarely observed during administration of mitotic exit-

targeting compounds [142,149,151], general side effects, such as digestive tract anomalies (nausea and vomiting) and myelosuppression, are commonly produced during clinical trials [117,149]. Such adverse effects arise because mitotic exit inhibitors affect not only the cancer cells but also normal dividing cells in bone marrow and digestive tract. These adverse effects can often be reduced by decreasing the dosage [8,117], and furthermore, combined treatment with appropriate drugs may reduce these adverse effects [164,165]. For example, a clinical study showed that use of granulocyte stimulating factor, an adjunctive agent, reduces AZD1152-triggered neutropenia [166].

In summary, although major challenges remain, targeting mitotic exit is still a promising direction in cancer therapeutic research with new regulators and mechanisms being continually discovered. Further, in-depth molecular signaling pathway modulation will be fundamental to the development of effective therapeutic strategies targeting mitotic exit of cancer cells and bringing new insights into cancer treatment.

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Conflict of interest

The authors declare that they have no conflict of interest.

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