

## Chapter 2

# Current and Next Generation Antimitotic Therapies in Cancer

Jeffrey A. Ecsedy, Mark Manfredi, Arijit Chakravarty,  
and Natalie D'Amore

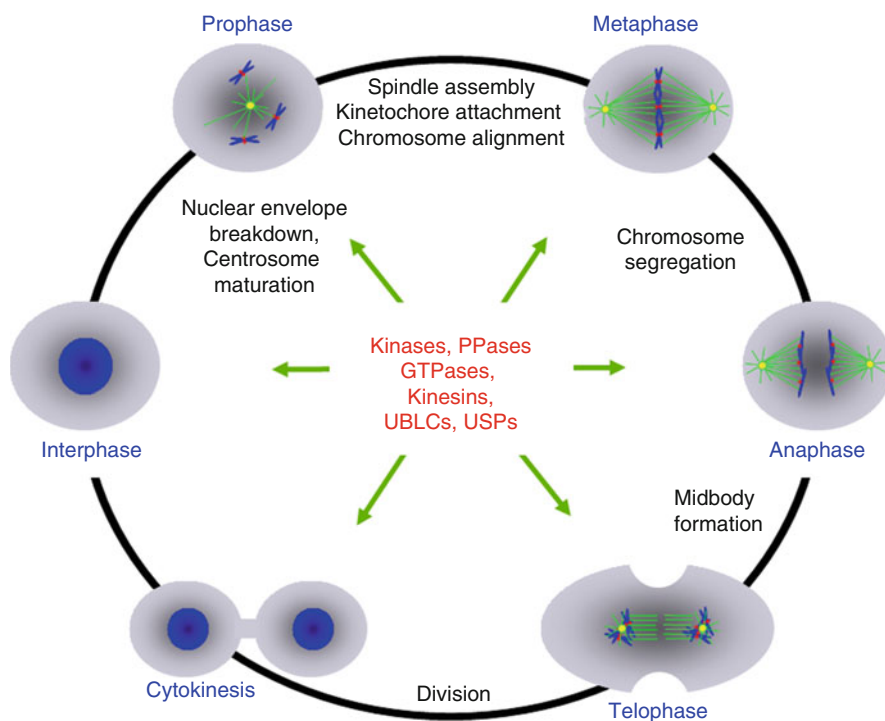
### 2.1 Current Therapeutic Application of Antimicrotubule Agents

The neatly ordered, symmetrical appearance of the microtubule spindle during mitotic cell division belies the highly dynamic nature of this critical event during mitosis. In organizing the mitotic spindle and executing a successful division, a wide array of proteins cooperate to line up and then move chromosomes along their microtubule scaffolds (Fig. 2.1). The disruption of the mitotic machinery as a chemotherapeutic approach therefore has the potential to cause cancer cell death or arrest without affecting normal, nondividing tissue. Traditional antimitotic agents comprise those that directly interfere with microtubule dynamics, essential for mitotic spindle assembly and the subsequent alignment and segregation of DNA to daughter cells. Antimicrotubule agents currently being used in clinical setting are the taxanes, vinca alkaloids, and epothilones. These agents are used in a host of cancer types as single agents and in combination with other oncology therapeutics.

Paclitaxel (brand name Taxol), the first taxane identified, was discovered in extracts of bark from the Pacific yew tree in the early 1960s and was approved for the treatment of ovarian cancer three decades later in 1992. Docetaxel (brand name Taxotere) is a semisynthetic derivative of paclitaxel that is more soluble and has demonstrated distinct clinical activity in some cancers, including metastatic breast cancer (Jones et al. 2005). In general, paclitaxel and docetaxel have a similar spectrum of clinical activity including ovarian, lung, breast, bladder, and prostate cancers. Even though both paclitaxel and docetaxel have been used clinically for many years, their utility continues to expand into new indications and in new combinations with other agents.

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J.A. Ecsedy (✉) • M. Manfredi • A. Chakravarty • N. D'Amore  
Department of Oncology, Millennium Pharmaceuticals, Inc.,  
40 Landsdowne Street, Cambridge, MA 02139, USA  
e-mail: Jeffrey.Ecsedy@mpi.com



**Fig. 2.1** Overview of normal progression through mitosis. A diverse array of kinases, phosphatases (PPases), GTPases, kinesins, ubiquitin-like conjugators (UBLs), and ubiquitin specific proteases (USPs) orchestrate the various stages of mitosis; including prophase, metaphase, anaphase, telophase, and cytokinesis. Some of the critical events that occur during each of these stages are highlighted

Abraxane™ is paclitaxel formulated in albumin-bound nanoparticles, eliminating the need for Cremophor-EL in the formulation, a vehicle that on its own has demonstrated toxicities and necessitates premedication (Ibrahim et al. 2002). Abraxane was approved on clinical data that demonstrated greater activity and safety than paclitaxel in patients with metastatic breast cancer.

The toxicities associated with each of the taxanes are similar, and include neutropenia as the major dose limiting toxicity, along with significant peripheral neuropathy. In fact, dose reductions are frequent in heavily pretreated patients to mitigate the severity of these toxicities. Interestingly, in clinical studies dose reductions did not reduce the clinical response of the agents, suggesting that the optimal biological dose may be lower than the maximum tolerated dose (Salminen et al. 1999). Weekly administration of the taxanes has become more frequently used as clinical data demonstrated less myelosuppression with no decrease in clinical response (Gonzalez-Angulo and Hortobagyi 2008). Interestingly, in breast cancer studies, weekly paclitaxel showed better response rates than once every 3 week dosing (Seidman et al. 2008). However, weekly paclitaxel has demonstrated greater neuropathy than the every 3 week schedule.

The vinca alkaloids were discovered in the 1950s from extracts of the leaves of the periwinkle plant (*Catharanthus roseus*). The vinca alkaloids were originally considered for use as antidiabetic agents, however, it was quickly learned that they possessed antiproliferative activity. Vincristine and Vinblastine, both microtubule destabilizers are the oldest and most studied members within this class of microtubule binding agents, and are now standard of care agents in various cancer types. Vincristine is used for treating several tumor types, including Non-Hodgkin and Hodgkin lymphoma and certain pediatric cancers, while vinblastine is used for treating testicular, Hodgkin lymphoma, lung, head, and neck, and breast cancer. More recently vinorelbine, a semisynthetic vinca alkaloid, was discovered to have a better preclinical profile than other family members (Krikorian and Breillout 1991). Vinorelbine was approved for treating NSCLC and has shown promising activity in breast, head and neck, ovarian, and squamous cell carcinoma (Burstein et al. 2003; Jahanzeb et al. 2002). Toxicities associated with the various vinca alkaloid members are similar, with neutropenia and peripheral neuropathy being dose limiting.

The epothilones are a newer class of tubulin binding agents that were first isolated in the 1990s from the myxobacterium *Sorangium cellulosum* (Bollag et al. 1995). There are several naturally occurring (epothilone A, B, C, and D) and semisynthetic variants currently under clinical investigation, with Ixabepilone, a derivative of epothilone B, now approved for the treatment of advanced breast cancer (Fumoleau et al. 2007). Similar to the taxanes, the epothilones promote microtubule stability, and in fact share the same binding site with paclitaxel. The perceived advantages over the taxanes include greater potency and decreased likelihood for resistance resulting from drug pumps and tubulin mutations (Kowalski et al. 1997; Wartmann and Altmann 2002). Moreover, the epothilones are formulated in vehicles that are better tolerated than the cremophor used for paclitaxel (Sessa et al. 2007; Watkins et al. 2005).

There are several differences in the toxicities and clinical activity between the various epothilones. Patupilone is the natural product epothilone B and is in phase III studies versus doxorubicin in ovarian, fallopian tube, and peritoneal cancers. Patupilone demonstrated Phase II single agent activity in several tumor types including colorectal, gastric, hepatocellular, non-small cell lung cancer, ovarian, and renal cancer (Harrison et al. 2009). Unlike the taxanes and other epothilones, diarrhea rather than neutropenia was the major dose limiting toxicity in all the schedules tested (Rubin et al. 2005). Interestingly, there was little neutropenia or significant peripheral neuropathy seen in the trials.

Ixabepilone is a derivative of epothilone B which has greater metabolic stability than the parent natural product. Ixabepilone was approved from a phase II study as a single agent for patients with advanced breast cancer who are resistant to prior treatment with an anthracycline, taxane, and capecitabine (Perez et al. 2007). Ixabepilone has demonstrated activity in bladder, breast, non-Hodgkin lymphoma, non-small cell lung cancer, pancreatic, prostate, renal, and sarcoma (summarized in (Harrison et al. 2009)). Unlike patupilone, in a phase II study ixabepilone failed to demonstrate activity in colorectal cancer suggesting that these agents may have a different spectrum of clinical activity. Ixabepilone completed a pivotal phase III trial in advanced breast cancer in combination with capecitabine where it demonstrated

greater activity than capecitabine alone (Thomas et al. 2007). Particularly interesting was the improved progression free survival in the combination group in patients with triple negative breast cancer, a patient population that has a high unmet medical need. The dose limiting toxicities in the majority of the trials were neutropenia and fatigue. The epothilones represent a promising new class of tubulin-binding antimicrotubule agents that have already differentiated themselves from the taxanes.

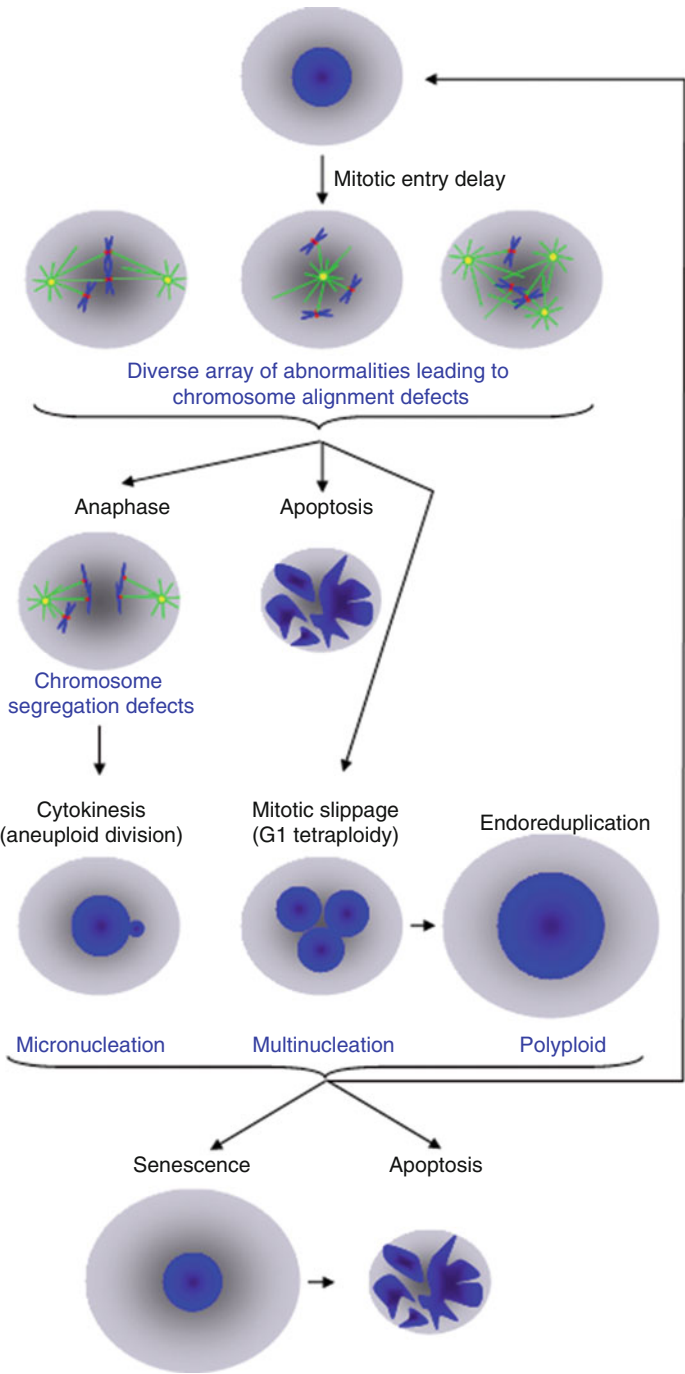
## 2.2 Antimitotic Agents: Mechanism of Action

Inhibition of the mitotic machinery results in a diverse array of outcomes, primarily leading to cell death or arrest (Fig. 2.2). As the effect of antimitotic agents is not limited to cancer cells alone, the dose-limiting toxicities of these drugs in a clinical setting frequently manifest in rapidly dividing tissue and are often accompanied by severe peripheral neuropathy in the case of antimicrotubule agents. Therefore, the narrow therapeutic index of antimitotic agents necessitates a precise understanding of the mechanism of action of these drugs to maximize the chances of rational development of these therapies.

Our understanding of the basic science underlying antimitotic therapies has been primarily developed using taxanes, including paclitaxel and docetaxel. Taxanes stabilize microtubules by altering the kinetics of microtubule depolymerization. In mammalian cells grown in culture, high concentrations of paclitaxel cause the aggregation of microtubules (Schiff and Horwitz 1980). At lower concentrations that resemble exposures achieved in clinical settings, the primary effect of paclitaxel is to stabilize microtubules, and thereby dampen the dynamic instability of microtubules that is a requisite for efficient spindle assembly. As a result of this dampening, microtubules are unable to grow and shrink rapidly, and their ability to bind to condensed chromosomes during mitosis is compromised. Efficient chromosome alignment is thus affected, and this failure of chromosome alignment leads to mitotic delays mediated via the spindle assembly

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**Fig. 2.2** (continued) and their inhibition can lead to delayed mitotic entry. Once in mitosis, perturbation of a variety of targets leads to dramatic abnormalities in centrosome maturation/separation, mitotic spindle formation, chromosome condensation, attachment of microtubules to kinetochores, and spindle assembly checkpoint signaling among other events, leading to chromosome alignment defects. The fate of these cells is varied, and can include apoptosis directly from mitosis, anaphase initiation accompanied by chromosome segregation defects leading to an aneuploid division, or exit from mitosis without cytokinesis via mitotic slippage leading to G1 tetraploid cells (double the normal DNA content at this stage). The interphase cells derived from these abnormal mitotic divisions often present as micronucleated or multinucleated. G1 tetraploid cells may undergo additional rounds of DNA replication via a process referred to as endoreduplication resulting in polyploid cells. Ultimately, these cells will eventually die via apoptosis or become senescent, which themselves can eventually undergo apoptosis. Lastly, if cells survive the events associated with an abnormal division, they can undergo additional rounds of mitotic division



**Fig. 2.2** Inhibition of the mitotic machinery can lead to a diverse array of outcomes. Several targets for antimitotic therapy participate in the transition from the G2 portion of the cell cycle to mitosis,

checkpoint. The spindle assembly checkpoint ensures that chromosomes are properly aligned to the metaphase plate prior to the anaphase initiation where sister chromatids segregate to opposite poles. Interestingly, at low concentrations of paclitaxel, inefficient chromosome alignment has been shown to occur without prolonged mitotic arrest, and the effect of paclitaxel is thus not dependent on its ability to induce mitotic arrest or delays (Chen and Horwitz 2002; Kelling et al. 2003).

For paclitaxel as well as its analog docetaxel, *in vitro* studies have demonstrated the presence of abnormal DNA contents and cell death even at concentrations where prolonged mitotic arrest does not occur (Chen and Horwitz 2002; Hernandez-Vargas et al. 2007a, b). Consistent with this finding, preclinical studies in xenograft models have failed to demonstrate a clear relationship between the degree of mitotic arrest and tumor growth inhibition (Gan et al. 1998; Milross et al. 1996; Schimming et al. 1999), and similar findings have been reported in a clinical setting (Symmans et al. 2000). This frustrating lack of a relationship between mitotic arrest and anticancer effect has represented somewhat of an obstacle for the rational development of anti-mitotic drugs, and clearly a more precise understanding of the means by which these drugs kill cells would facilitate their rational development.

How and why do antimitotic therapies elicit an antitumor response? The question has been surprisingly difficult to answer. Over the years, our understanding of the effects of antimitotic drugs has matured, with some surprises along the way. At this point, it has been well established that antimitotic compounds compromise the ability of cells to execute a successful division – cells will either fail to divide with a prolonged mitotic arrest that leads directly to cell death, or they divide abnormally, with an unequal distribution of DNA (Gascoigne and Taylor 2008; Rieder and Maiato 2004; Weaver and Cleveland 2005). Following such an unsuccessful division, cells may continue to cycle or undergo cell-cycle arrest or death. This diversity of outcomes following treatment with antimitotic agents has been shown to be dependent on cell type as well as on concentration of the antimitotic agent used (Gascoigne and Taylor 2008; Orth et al. 2008; Shi et al. 2008). Apoptosis has been shown to occur both during mitosis and in interphase following mitosis (Gascoigne and Taylor 2008; Shi et al. 2008). This may occur in part due to DNA double strand breaks that occur subsequent to treating cells with antimitotic agents (Dalton et al. 2007; Lei and Erikson 2008; Quignon et al. 2007). As apoptosis is not the only means of cell death in a solid tumor setting (Abend 2003), and forms of cell cycle arrest such as senescence contribute substantially to antitumor efficacy in preclinical models (Roninson et al. 2001), caution should be used in over interpreting switches toward and away from apoptosis as being indicators of drug sensitivity or resistance.

What implications do these mechanistic findings have for the rational development of antimitotic therapies? Clearly, the overreliance on the mitotic index as a means for optimizing drug development is one potential pitfall. The mitotic index is useful as a marker of drug effect, but more careful optimization of drugs in development can also be conducted by interrogating other effects of antimitotic agents that appear to be independent of mitotic arrest such as chromosome alignment or spindle bipolarity defects (Chakravarty et al. 2010). Another aspect of the complex biology of antimitotic agents is that there appears to be more flexibility in dosing these

agents than was originally assumed. The prolonged mitotic arrest model suggests that sustained high concentrations of drug are required for antitumor effect. Findings with weekly taxane therapies, which have equivalent efficacy to once-every-three weeks taxane therapies, suggest that the same effect can be obtained by splitting the total dose of drug administered.

## 2.3 Next Generation Antimitotics

The Aurora kinases and Polo-like Kinases (PLKs) have obligate functions for normal cell cycle progression through mitosis. These kinases are the focus of intensive efforts by pharmaceutical companies as well as clinical and basic researchers for developing anticancer drugs. Therefore, these two kinase families are deserving of an in-depth description as examples of next-generation antimitotic targets.

### 2.3.1 Aurora Kinases

The Aurora kinases, first identified in yeast (Ip11), *Xenopus* (Eg2), and *Drosophila* (Aurora), are critical regulators of mitosis (Andresson and Ruderman 1998; Chan and Botstein 1993; Glover et al. 1995; Roghi et al. 1998). In humans, three isoforms of Aurora kinase exist, including Aurora A, Aurora B, and Aurora C. Aurora A and Aurora B play critical roles in the normal progression of cells through mitosis, whereas Aurora C activity is largely restricted to meiotic cells.

Aurora C is predominantly expressed in testis (Tseng et al. 1998), though it has been detected in other cell types as well, including certain cancer cell lines (Kimura et al. 1999; Sasai et al. 2004; Takahashi et al. 2000). Forced overexpression of Aurora C in experimental models results in supernumerary centrosomes and polyploidy, and thus has been linked to oncogenic transformation (Dutertre et al. 2005). Despite these observations, however, it remains unclear if Aurora C functions in the mitotic division of somatic cells or in the natural history of cancer. Thus, this section will focus on the function of Aurora A and Aurora B in mitosis, their role in oncogenesis and on their utility as targets for cancer therapeutic intervention.

Aurora A and Aurora B are structurally closely related. Their catalytic domains lie in the C-terminus, where they differ in only a few amino acids. Greater diversity exists in their noncatalytic N-terminal domains. It is the sequence diversity in this region of Aurora A and Aurora B that dictates their interactions with distinct protein partners, allowing these kinases to have unique subcellular localizations and functions within mitotic cells. Consequently, attempts are in progress to develop small molecule inhibitor drugs targeting Aurora A, Aurora B, or both of these kinases simultaneously, as each of these approaches may provide unique modalities for the treatment of cancer.

The Aurora A gene (*AURKA*) localizes to chromosome 20q13.2, which is commonly amplified or overexpressed at a high incidence in a diverse array of tumor

types (Bischoff et al. 1998; Camacho et al. 2006; Chng et al. 2006; Ikezoe et al. 2007; Sen et al. 2002). Increased Aurora A expression has been correlated to the etiology of cancer and to a worsened prognosis (Fraizer et al. 2004; Guan et al. 2007; Jeng et al. 2004; Landen et al. 2007; Miyoshi et al. 2001; Sakakura et al. 2001; Sen et al. 2002). This concept has been supported in experimental models, demonstrating that Aurora A overexpression leads to oncogenic transformation (Goepfert et al. 2002; Li et al. 2009; Wang et al. 2006a, b; Zhang et al. 2008; Zhou et al. 1998). Overexpression of Aurora A kinase is suspected to result in a stoichiometric imbalance between Aurora A and its regulatory partners, leading to chromosomal instability and subsequent transforming events. The potential oncogenic role of Aurora A has led to considerable interest in targeting this kinase for the treatment of cancer. However as Aurora A activity is requisite for normal mitotic progression, there is still no reason to suspect that cancers overexpressing Aurora A would be more or less sensitive to Aurora A targeted inhibition. Overexpression of Aurora B has also been reported in some cancers (Ikezoe et al. 2007). Similar to the case with Aurora A, overexpression of Aurora B has been correlated to a worsened prognosis in some cancers. In cases where either Aurora A or Aurora B have been demonstrated to be overexpressed, it is not always clear if the apparent overexpression is due to increased levels of protein per mitotic cell or more simply due to a higher mitotic index in some tumors.

During a normal cell cycle, Aurora A is first expressed in the G2 stage where it localizes to centrosomes and functions in centrosome maturation and separation as well as in the entry of cells into mitosis. Although Aurora A kinase inhibition results in a delayed mitotic entry (Marumoto et al. 2002), cells commonly enter mitosis despite having inactive Aurora A. In mitotic cells, Aurora A predominantly localizes to centrosomes and the proximal portion of incipient mitotic spindles. There it interacts with and phosphorylates a diverse set of proteins that collectively function in the formation of mitotic spindle poles and spindles, the attachment of spindles to sister chromatid at the kinetochores, the subsequent alignment and separation of chromosome, the spindle assembly checkpoint, and cytokinesis (Barr and Gergely 2007; Bischoff and Plowman 1999; Carmena and Earnshaw 2003; Giet et al. 2005).

The outcomes associated with inhibition of Aurora A have been studied using several experimental techniques; including gene mutation, RNA interference, antibody microinjection, and ATP-competitive small molecule kinase inhibitors (Glover et al. 1995; Hoar et al. 2007; Kaestner et al. 2009; Katayama et al. 2001; Marumoto et al. 2003; Sasai et al. 2008). Aurora A inhibition initially leads to the formation of abnormal mitotic spindles, either monopolar, bipolar, or tripolar with misaligned chromosomes, often accompanied by centrosome separation defects. These defects lead to a mitotic arrest, which presumably is mediated by activation of the spindle assembly checkpoint. The fate of these arrested cells can vary. In cases, prolonged mitotic arrest may lead directly to apoptosis. Some cells may also exit mitosis without undergoing cytokinesis resulting in G1 tetraploidy. Still further, cells may divide at a high frequency, albeit with severe chromosome segregation defects. In the latter two outcomes, the abnormal mitotic divisions can lead to deleterious aneuploidy resulting in cell death or arrest. This diversity in outcomes resulting from Aurora A kinase

inhibition is shared by other antimitotic therapies (Gascoigne and Taylor 2008). Interestingly, the outcomes associated with Aurora A inhibition in many ways phenocopy those associated with Aurora A overexpression, supporting the idea that there exist stoichiometric requirements on Aurora A for normal mitosis to occur.

Aurora B localizes to the centromeres in preanaphase cells. There it plays a critical role in spindle bipolarity and the establishment and maintenance of the spindle assembly checkpoint (Adams et al. 2001; Ditchfield et al. 2003; Hauf et al. 2003; Murata-Hori and Wang 2002). During anaphase and telophase, Aurora B localizes to the spindle midzone and midbody, respectively. There, Aurora B functions in cytokinesis (Giet and Glover 2001; Yokoyama et al. 2005). Inhibition of Aurora B through the use of gene mutations, RNA interference or ATP competitive small molecule inhibitors leads to defects in the attachment of the spindle microtubules to kinetochores, chromosome segregation, and formation of the cleavage furrow (Adams et al. 2001; Ditchfield et al. 2003; Giet and Glover 2001; Honda et al. 2003; Murata-Hori and Wang 2002; Yokoyama et al. 2005). Aurora B inhibition also prevents the proper formation of the spindle assembly checkpoint, causing cells to exit mitosis prematurely without a mitotic arrest and often without completing cytokinesis (Ditchfield et al. 2003; Hauf et al. 2003). The fate of these G1 tetraploid cells is to die, arrest, or undergo additional rounds of DNA replication (endoreduplication) resulting in a DNA ploidy of  $>4N$ .

Many small molecule inhibitors of the Aurora kinases have been or are being tested in clinical trials in cancer patients. This comprises Aurora A selective inhibitors, Aurora B selective inhibitors, or dual Aurora A and Aurora B inhibitors. Some of these inhibitors lack functional selectivity as they concurrently inhibit multiple kinases in addition to the Aurora kinases. In these cases, multiple mechanisms of actions may attribute to the pharmacodynamic and clinical activity as well as to the toxicities observed. As the Aurora kinases have obligate function in all dividing cells, these inhibitors are being developed in a diverse array of solid and hematological cancers, in both single agent and combination settings. Some evidence for single agent antitumor activity has been reported, including partial responses and prolonged stabilized disease in several solid tumor and hematological malignancy indications.

### 2.3.2 *Polo-Like Kinases*

The first PLK was identified in *Drosophila melanogaster* (polo), with orthologs also found in yeast (*cdc5* and *plp1*) and *Xenopus* (Plx) (Kumagai and Dunphy 1996; Llamazares et al. 1991; Sunkel and Glover 1988). Each of these PLK orthologs are essential regulators of mitosis and are structurally and functionally related to the mammalian family member PLK1. The mammalian family is comprised of three additional members PLK2, PLK3, and PLK4. Like PLK1, PLK4 functions during mitosis, albeit in a different manner; PLK2 and PLK3 have nonmitotic roles in regulating the cell cycle (Winkles and Alberts 2005). Of the four mammalian PLK family members, PLK1 is the most extensively characterized and small molecule inhibitors

developed against this isoform are being evaluated in preclinical and clinical settings for the treatment of cancer. Thus, this section will focus on the function of PLK1, its potential role in tumorigenesis, and its promise as a target for cancer therapy.

Several studies exemplify PLK1 as a compelling target for therapeutic intervention. Overexpression of PLK1 transforms cells such that they form tumors when grown as xenografts in immunocompromised mice (Smith et al. 1997). Strengthening the notion that PLK1 may contribute to the promotion and progression of cancers, PLK1 is overexpressed in a broad spectrum of solid and hematological malignancies and this overexpression is correlated with poor prognosis and survival in patients (Kneisel et al. 2002; Takai et al. 2001) (Dietzmann et al. 2001; Gray et al. 2004; Kanaji et al. 2006; Knecht et al. 1999; Mito et al. 2005; Takahashi et al. 2003; Tokumitsu et al. 1999; Yamamoto et al. 2006). To date, mutations or amplification of the PLK1 gene has not been detected.

The PLKs are highly conserved serine/threonine kinases distinguished by non-catalytic C-terminal domains of 60–70 amino acids termed the polo-box domain (PBD). The PBD serves as a binding module to phosphorylated motifs on other proteins mediating protein-protein interactions (Elia et al. 2003a, b; Lee et al. 1998). The kinase domain and PBD are thought to inhibit each other by intermolecular interaction during G1 and S phase, rendering the kinase inactive. Temporal control of PLK1 occurs during G2 by phosphorylation of the kinase domain, relieving interaction with the PBD. Cdk1 has emerged as a kinase that can phosphorylate proteins creating docking sites for the PBD of PLK1 (Fu et al. 2008; Neef et al. 2007; Wu et al. 2008). Spatial regulation of PLK1 occurs by the recruitment of the PBD to distinct mitotic locales enabling PLK1 to phosphorylate a variety of substrates that carry out divergent mitotic functions.

In G2, PLK1 localizes to centrosomes and redistributes elsewhere during mitosis. In metaphase, PLK1 is found at the centromeres and kinetochores, the spindle midzone in anaphase, and finally at the midbody during cytokinesis. PLK1 plays a role in regulating centrosome maturation, entry into mitosis, activity of the anaphase promoting complex, formation of and maintenance of a bipolar mitotic spindle, cytokinesis and mitotic exit (Eckerdt and Strebhardt 2006; Lane and Nigg 1996; Petronczki et al. 2007; Sumara et al. 2004; Toyoshima-Morimoto et al. 2001).

The consequences upon inhibition or downregulation of the protein have been studied by chemical and genetic tools, respectively (Lane and Nigg 1996; Lenart et al. 2007; Liu and Erikson 2002; Liu and Erikson 2003; Peters et al. 2006; Rudolph et al. 2009; Spankuch-Schmitt et al. 2002; Spankuch et al. 2004). Initial studies using small interfering RNA demonstrated that knockdown of PLK1 leads to prolonged mitotic delay and decreased cellular proliferation. Similar phenotypes are exhibited with small molecule inhibitors targeting the catalytic active site or those blocking the PBD in a broad range of tumor cell lines. Inhibition of PLK1 prevents localization at centrosomes and kinetochores, resulting in activation of the spindle assembly checkpoint. This manifests as a prometaphase mitotic delay characterized by monopolar or bipolar misaligned mitotic spindles that do not stably attach to kinetochores. Uniformly, studies have documented apoptosis as a consequence of this mitotic delay. Studies with a small molecule inhibitor also suggest that a cytostatic response results from the mitotic delay due to mitotic slippage (Gilmartin et al. 2009).

It has emerged that additional functions for PLK1 outside of mitosis exist. These include the possible involvement in the regulation of telomere stabilization, the regulation of DNA topoisomerase II, and DNA repair (Li et al. 2008; Svendsen et al. 2009). Activity of PLK1 is inhibited in the presence of DNA damage to ensure that these compromised cells do not progress into mitosis (Smits et al. 2000). However following satisfaction or relaxation of the DNA damage checkpoint, PLK1 is necessary to enable mitotic entry (van Vugt et al. 2004).

Small molecule inhibitors targeting the catalytic active site of PLK1 are under evaluation in clinical trials for both solid and hematological malignancies (Schoffski 2009). Clinical benefit has been observed for some tumor types in Phase I and has warranted Phase II studies for both single agent as well as combination trials.

## 2.4 Conclusion

Antimitotic approaches for therapeutic intervention of cancer have proven to be effective means for treating cancer. To date, these agents comprise the microtubule perturbing classes of molecules including the taxanes, the vinka alkaloids, and the epothilones. As the mechanism of action of these agents becomes clearer, more rational approaches for their clinical application as single agents or in combination with other therapeutics should emerge. Moreover, considerable efforts are ongoing to explore new modalities for perturbing the mitotic machinery by selectivity targeting key enzymatic mitotic regulators, for example the Aurora and PLKs. In early clinical testing, these agents have demonstrated promising activity, and molecules within these classes will likely emerge that provide improvements over current standard of care agents, including more manageable toxic side effects and improved responses in a distinct range of cancer indications alone or in combination with other therapeutic agents.

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