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Commentary

Antimitotic drugs in cancer chemotherapy: Promises and pitfalls

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ABSTRACT

Cancer cells usually display higher proliferation rates than normal cells. Some currently used antitumor drugs, such as vinca alkaloids and taxanes, act by targeting microtubules and inhibiting mitosis. In the last years, different mitotic regulators have been proposed as drug target candidates for antitumor therapies. In particular, inhibitors of Cdks, Chks, Aurora kinase and Polo-like kinase have been synthesized and evaluated *in vitro* and in animal models and some of them have reached clinical trials. However, to date, none of these inhibitors has been still approved for use in chemotherapy regimes. We will discuss here the most recent preclinical information on those new antimitotic drugs, as well as the possible molecular bases underlying their lack of clinical efficiency. Also, advances in the identification of other mitosis-related targets will be also summarized.

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1. Currently used antimitotic drugs in cancer chemotherapy

Although cell behavior is quite heterogeneous among different types of tumors, and even among patients, a frequent feature of tumor cells is the increased rate of proliferation when compared to normal cells. This capacity is usually a consequence of unresponsiveness to growth inhibitory signals, self-sufficiency in growth factors or both [1]. Moreover, some of the compounds used in cancer chemotherapy that were initially identified in unbiased screening have lately been shown to act by blocking mitosis and subsequently inducing cell death. Vinca alkaloids and taxanes are the two groups of anticancer drugs targeting mitosis which are currently in use for the treatment of a variety of tumors including, breast cancer, lung cancer, neuroblastoma, rhabdomyosarcoma, acute leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma. Although these two families of compounds have different chemical structure and origin, all of them bind to β-tubulin and disturb the dynamics of microtubules. Reorganization of microtubules is a critical event during mitosis, orchestrating the relocalization of centrosomes and the correct segregation of sister chromatids in daughter cells. Vinca alkaloids (vincristine, vinblastine, vindesine and vinorelbine) prevent the polymerization of microtubules, while taxanes (paclitaxel and docetaxel) stabilize pre-existing microtubules, what also impedes the formation of the mitotic spindle. Recently, a new family of microtubule-targeting compounds, the epothilones, have been developed and approved for taxane-resistant breast tumors. A significant concern about anti-microtubule agents (MTA) is that these compounds cause significant side effects such as neutropenia and neurotoxicity. Loss of neutrophils is a consequence of the toxicity of MTA on dividing precursor cells and neurotoxicity is probably related to the critical role of microtubule turnover in neurons. However, the major inconvenience in using MTAs in chemotherapy is their limited efficacy as single agents. These limitations prompted the search for more specific mitosis-targeting drugs, with enhanced therapeutic potency and fewer side effects. Mitosis-specific kinases and microtubule-motor proteins were identified as potential drug targets and accordingly several inhibitors have been developed in the last years.

2. The promises: preclinical data on mitosis-targeting drugs

2.1. Cdks and Chks inhibitors

Cyclin-dependent kinases and checkpoint kinases control transitions during cell cycle phases (Fig. 1). Cyclin-dependent kinase 1 (Cdk1) regulates cell entry into mitosis by phosphorylating several proteins that orchestrate different aspects of cell division, such as chromosome condensins, nuclear lamins, centrosome and microtubule-associated proteins and Golgi matrix proteins. Other Cdks are activated at different stages of cell cycle and their activity is required for G1/S or G2/M transitions. On the other hand, checkpoint kinases are activated in response to DNA damage to arrest cell cycle progression until the damage is repaired. Two of the first Cdk or Chk inhibitors proposed for cancer treatment were UCN-01 and flavopiridol (alvocidib). UCN-01 is a staurosporine analog (7-hydroxystaurosporine) that indeed

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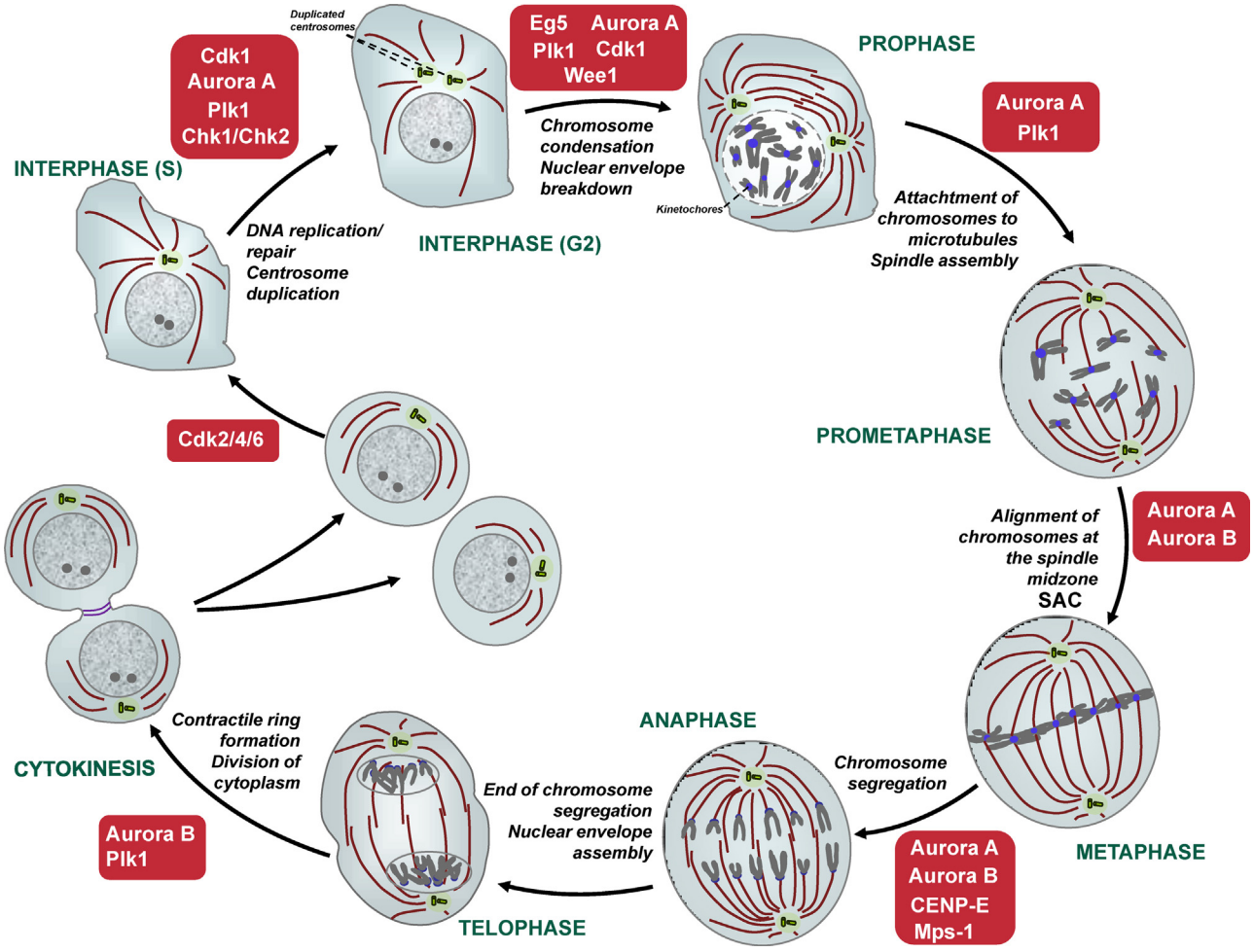

Fig. 1. Mitotic proteins as antitumor drug targets. Mitosis is a complex process requiring the step-wise participation of several regulatory proteins. Some of these proteins have been proposed to be relevant drug targets for antitumor therapies (red boxes) and accordingly protein inhibitors are in preclinical development and being tested in clinical trials. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

inhibits Cdk1/2, Chk1/2 as well as protein kinase C (PKC) (Table 1). UCN-01 has been shown to be an abrogator or the G2 checkpoint [2] and to induce apoptosis in cells of different origin [3,4]. Flavopiridol, a synthetic flavonoid based on plant extracts, was the first Cdk inhibitor to enter clinical trials (see point 3), two decades ago, but it has not yet been approved for use in the clinic due to its low antitumoral activity as a single agent *in vivo* [5].

P276-00 was identified as a selective and potent Cdk4 inhibitor that induces apoptosis in cell lines and synergizes with doxorubicin in xenograft models [6]. Other molecules have been described to inhibit Cdks and Chks and could in the future enter clinical trials. The Cdk and Erk5 inhbitor TG02 exhibits anti-myeloma activity on cell lines, patient plasma cells *ex vivo* and in mouse xenograft models. Moreover, TG02 enhanced the toxicity of bortezomib and lenalidomide in myeloma [7]. Sangivamycin-like molecule 6 (SLM6), an inhibitor of Cdk9, has only been tested in myeloma cells, showing higher activity than flavopiridol [8]. VMY-1-103 is a dansylated analog of purvalanol B that induces cell cycle arrest and apoptosis by inhibiting Cdk1 and also by disrupting the mitotic spindle apparatus [9].

2.2. Aurora A and B inhibitors

Aurora Ser/Thr kinases are critically involved in the control of mitosis (Aurora A and Aurora B) and meiosis (Aurora C). Aurora A localizes at the centrosome in early G2 phase and controls mitotic entry and bipolar spindle assembly (Fig. 1). Aurora B is the catalytic component of the 'chromosomal passenger complex' (CPC). In human cells, Aurora B could have up to 40 substrates related to kinetochores [10]. Phosphorylation of these substrates by Aurora A controls chromosome structure, cohesin removal, mitotic spindle formation, kinetochore assembly, correction of defective chromosome-spindle attachments and shortening of segregating chromosomes (Fig. 1). Thus, inhibition of Aurora A perturbs mitosis and can provoke mitotic arrest or chromosomal instability followed, in many cases by cell death [11]. This, together with the fact that Aurora kinases are frequently overexpressed in cancer cells [12], prompted the development of small aurora kinase inhibitors as potential anticancer agents. A large number of this kind of molecules have been developed in the last years (Table 1). Many of these compounds bind to the ATP cassette of aurora kinases and inhibit the three known proteins of the family as well as other non-mitotic kinases. Besides showing apoptotic activity, aurora kinase inhibitors have been reported to synergize with other antitumor drugs [11] and these promising preclinical results led some of these compounds to enter clinical trials (Table 2). Other compounds, such as ZM447439 and JNJ-7706621 are still under preclinical research (Table 2).

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