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AUTHOR'S VIEW

Re-investigating PLK1 inhibitors as antimitotic agents

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ABSTRACT
Polo-like kinase 1 (PLK1) plays key roles during mitosis, prompting the development of PLK1 inhibitors for anticancer therapy. We recently determined that PLK1 is crucially required for entry into mitosis. Hence, we discuss the potential and limitations of PLK1 inhibition strategies to promote mitotic arrest and death of cancer cells.

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Polo-like kinase 1 (PLK1) is a core regulator of cell division and an emerging target for anti-cancer therapy.[1] Previous work revealed that PLK1 is required for centrosome maturation, bipolar spindle assembly, chromosome arm resolution, chromosome alignment and segregation, spindle-assembly checkpoint signaling and cytokinesis. Interestingly, titrating PLK1 activity supports that distinct thresholds are required to fulfill these functions during mitosis.[2] PLK1 is overexpressed in a wide range of human cancers and might contribute to chromosome instability and tumor aggressiveness.[3] Whereas PLK1 targets several key regulators of CyclinB1-CDK1 (Cyclin-Dependent Kinase 1), the master mitotic driver, its requirement for entry into mitosis during normal cell cycles remains puzzling. Indeed, perturbation experiments have generated contradictory results, with either a G2 phase arrest or a mitotic (prometaphase) block, which might originate from the relative efficiency of PLK1 inhibition. Conversely, similar perturbation assays showed that PLK1 is critical to promote G2 checkpoint recovery and mitotic entry after DNA damage, possibly linked to a higher PLK1 activity threshold required to counteract DNA damage response (DDR).[4]

In our recent work published in *Cell Reports*, we investigated whether PLK1 is required for commitment to mitosis during normal cell cycles by combining careful evaluation of PLK1 inhibitors in a dose-dependent manner, a chemical genetics model to target PLK1 activity (PLK1^{as}: ATP-analog sensitive[5]) and time-lapse recordings of asynchronous somatic cell populations.[6] Whereas partial loss of PLK1 activity promoted a mitotic arrest phenotype with a progressive dose-dependent slowing down of mitotic entry, its inhibition up to completion fully prevented entry into mitosis. Importantly, all cells that could still achieve mitotic entry in the presence of high doses of PLK1 inhibitors exhibited a residual PLK1 activity. Hence, our results show that PLK1 is crucially required for commitment to mitosis and support that a modest PLK1 activity threshold is sufficient to promote mitotic entry.[6] Interestingly, the comparison of some untransformed versus transformed cells revealed that the latter ones required higher PLK1 inhibitor doses to inhibit mitotic entry, related to their higher PLK1 expression level. Using a FRET (Förster Resonance Energy Transfer)-based phosphorylation biosensor, we determined that PLK1 is rapidly activated in late G2 shortly before CyclinB1-CDK1. PLK1 activation is dependent on upstream kinase Aurora-A and we provide evidence that it further relies on CyclinA2-CDK activity levels, possibly through CDK-dependent phosphorylation of protein aurora borealis (BORA) that promotes Aurora-A-dependent PLK1 activation (Fig. 1).[7] Indeed, stimulation of CyclinA2-CDK activity from late S phase, using Wee1 inhibitor AZD1175 (MK-1775), rapidly induced a premature activation of PLK1 that preceded CyclinB1-CDK1 activation and unscheduled mitotic entry. Also, endogenous CyclinA2 and PLK1 progressively interact during normal G2 phase and this interaction was significantly promoted following CyclinA2-CDK stimulation.[6]

Because PLK1 activity is essential during mitosis, small inhibitory compounds have been developed and are currently under clinical investigation.[1] These compounds may potentially reproduce the antimitotic and anticancer effects of paclitaxel, a microtubule poison used for the treatment of breast, ovarian and lung cancers, without its neurotoxic side effects. Consistently, in cultured normal or cancer cells, a persistent mitotic arrest following PLK1 inhibition promotes the induction of cell death by apoptosis. Nonetheless, cell populations exhibit an intrinsic heterogeneity of drug response and the fraction of cells that arrest in G2, due to PLK1 inhibition up to completion, is protected from the apoptotic response.[6,8] Hence, in therapeutic applications, a careful drug dosage might be required to enrich for mitotic arrest and cell death phenotypes. On the other hand, a modest inhibition of PLK1 activity in nonmalignant

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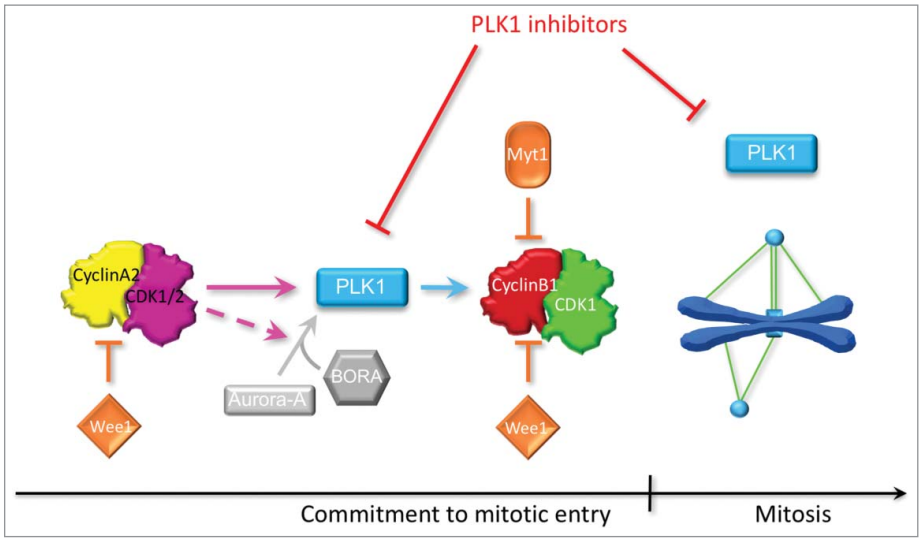

Figure 1. Polo-like kinase 1 (PLK1) is required for entry and progression into mitosis. Schematic of some molecular mechanisms that control commitment to mitosis. PLK1 activity is critical to set up CyclinB1-CDK1 (Cyclin-Dependent Kinase 1) activation and entry into mitosis. Its activation in late G2 phase (not depicted) relies on upstream kinase Aurora-A, through the recruitment of protein aurora borealis (BORA), and CyclinA2-CDK activity level by poorly identified mechanisms. PLK1 inhibitors induce either a G2 or a mitotic (prometaphase) arrest, related to PLK1 inhibition efficiency.

human cells may allow mitotic exit and result in the appearance of tetraploid progeny.[2] When proliferating, tetraploid cells are genetically instable and can promote tumorigenesis. As mentioned above, G2 or mitotic arrest following PLK1 inhibition is not only concentration dependent but also related to PLK1 expression level. Because mitotic arrest promotes apoptosis, this raises the possibility that tumors that specifically overexpress PLK1 could exhibit an exacerbate sensitivity to PLK1 inhibitors than normal tissue counterpart and represent a favorable situation for PLK1 inhibition strategies. This attractive hypothesis will require further investigations.

The therapeutic effectiveness of PLK1 inhibitors to kill cancer cells is likely to be limited by the fraction of cells that reach mitosis during each period of drug treatment. A possible strategy to improve their overall efficiency might be to combine their use with small-molecule kinase inhibitors that promote a premature mitosis. Wee1 inhibitory kinase targets S-phase promoting CyclinA2-CDK2 activities whereas Wee1 and Myt1 cooperatively down-regulate M-phase promoting CyclinB-CDK1 complexes. In cell culture, either Wee1 (MK1775, >100-fold selectivity for Wee1 over Myt1) or Wee1&Myt1 (PD0166285) inhibitors promote unscheduled mitosis from late S phase, possibly related to CyclinB1 expression profile, and most cells complete cell division. However, a major difference is that following Wee1, but not Wee1&Myt1, inhibition, premature entry into mitosis remains dependent on PLK1 activity.[6] Consistently, we observed that Wee1 inhibition induces a premature PLK1 activation that precedes CyclinB1-CDK1 activation and unscheduled mitosis. Thus, it is possible that dual Wee1 and Myt1 inhibition, instead of Wee1 inhibition alone, may provide a way to improve the therapeutic efficiency of antimitotic agents such as PLK1 inhibitors (or inhibitors of its upstream activator Aurora-A). The first Wee1&Myt1 inhibitor (PD0166285) was shown to target some other tyrosine kinase activities.[9] Hence, a major challenge remains to develop small-molecule kinase inhibitors that achieve kinase selectivity against Wee1 and Myt1.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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