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AUTHOR'S VIEW

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BORA-dependent PLK1 regulation: A new weapon for cancer therapy?

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ABSTRACT

The mitotic kinase polo like kinase 1 (PLK1) is overexpressed in many cancers and its inhibition slows down proliferation and increases apoptosis in cancer cell lines. Understanding how PLK1 is activated is therefore crucial for the development of novel PLK1 inhibitors with anticancer properties. We recently identified a conserved regulatory loop leading to PLK1 activation that involves cyclin-dependent kinase 1 (CDK1).

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Despite tremendous progress in understanding how mitotic entry is regulated, some aspects remain elusive and novel factors regulating this process are still being discovered. Among these factors is aurora borealis (BORA), which emerged as a critical regulator of polo like kinase (PLK1).[1] At the end of the G2 phase of the cell cycle, BORA facilitates phosphorylation of the activation loop of PLK1 by the kinase Aurora A.[1] Although PLK1 and BORA are not strictly required for triggering mitotic entry, both of them become essential for G2/M checkpoint recovery after DNA damage.[1,2]

Our teams previously demonstrated that cyclin-dependent kinase 1 (CDK-1) phosphorylates the *C. elegans* ortholog of BORA, suppressor of PAR two (SPAT-1), and that this phosphorylation is crucial for timely mitotic entry in the early embryo.[3] We showed that phosphorylated SPAT-1 enhances the activation of PLK-1 by aurora A in vitro.[3] In our recent report published in *Cell reports*, we used a combination of mass spectrometry, in vitro biochemical assays, and cell biological approaches to extend our findings to human BORA.[4] We have identified 3 conserved Sp/Tp phosphosites in the N-terminal regions of BORA and SPAT-1 that are crucial for BORA and SPAT-1 function both *in vitro* and *in vivo*. Mutation of these serine and threonine residues to non-phosphorylable alanine abolished the ability of BORA and SPAT-1 to activate PLK1 in vitro and in vivo. When the 3 conserved phosphosites were mutated, BORA was unable to support recovery from G2/M DNA damage checkpoint arrest in HeLa cells and SPAT-1 was defective in timely mitotic progression in *C. elegans* embryos. Our data support the existence of a regulatory loop connecting PLK1 and CDK1 activation in which PLK1 activates CDK1 through cell division cycle 25 (CDC25), and conversely CDK1 activates PLK1 via BORA phosphorylation (Fig. 1).[2,3,4] This feedback loop may contribute to CDK1 activation and may become crucial in triggering mitosis under stress, for instance in G2/M-checkpoint arrest. Although CDK1 was known to control PLK1 localization in space and time during mitosis by priming PLK1 substrates, our results reveal a critical role of CDK1 in PLK1 activation.[1,2,4]

Given the central role of PLK1 in G2-checkpoint recovery and mitosis, it is not surprising to observe PLK1 overexpression in many cancers, in correlation with increased aggressiveness and poor prognosis.[5,6] Indeed, upregulation of PLK1 in cancer cells might not only promote cell cycle progression, but also allow cells to escape DNA damage-mediated cell cycle arrest. This "constitutive" G2-checkpoint recovery may result in enhanced genomic instability and capacity to escape the intrinsic apoptotic pathway: 2 well-known hallmarks of cancer.[7]

PLK1 is an attractive target for anticancer drugs and several PLK1 inhibitors have been generated over the past years. Many of these inhibitors demonstrated promising pre-clinical results but little clinical activity. So far, the most effective molecule is volasertib (BI6727), which is currently being investigated in clinical trials and has shown some clinical benefits in ovarian cancers and acute myeloid leukemia.[8,9] The most frequent and dose-limiting side effect of PLK1 inhibitors was hematological toxicity, mainly neutropenia and leukopenia.[8,9]

Volasertib targets PLK1 kinase activity but can also inhibit PLK2 and PLK3, 2 other members of the polo-like kinase family.[7] The discovery of physiologic non-catalytic inhibitors of PLKs, such as microtubule-associated protein 205 (MAP205) and matrimony (MTRM), may guide the design of new drugs that inhibit PLK1 binding to its substrates rather than its activity. Some inhibitors of PLK1 polo box domain (PBD), such as poloxin, purpurogallin, and thymoquinone, are currently undergoing preclinical trials.[5] Interestingly, a compound that appears to affect the BORA/PLK1 interaction can reduce the proliferation of lung cancer cells in culture more efficiently than thymoquinone.[10] Since BORA has been suggested to be the only activator of PLK1 in mitosis, identifying inhibitors of the BORA/PLK1 interaction might overcome the potential

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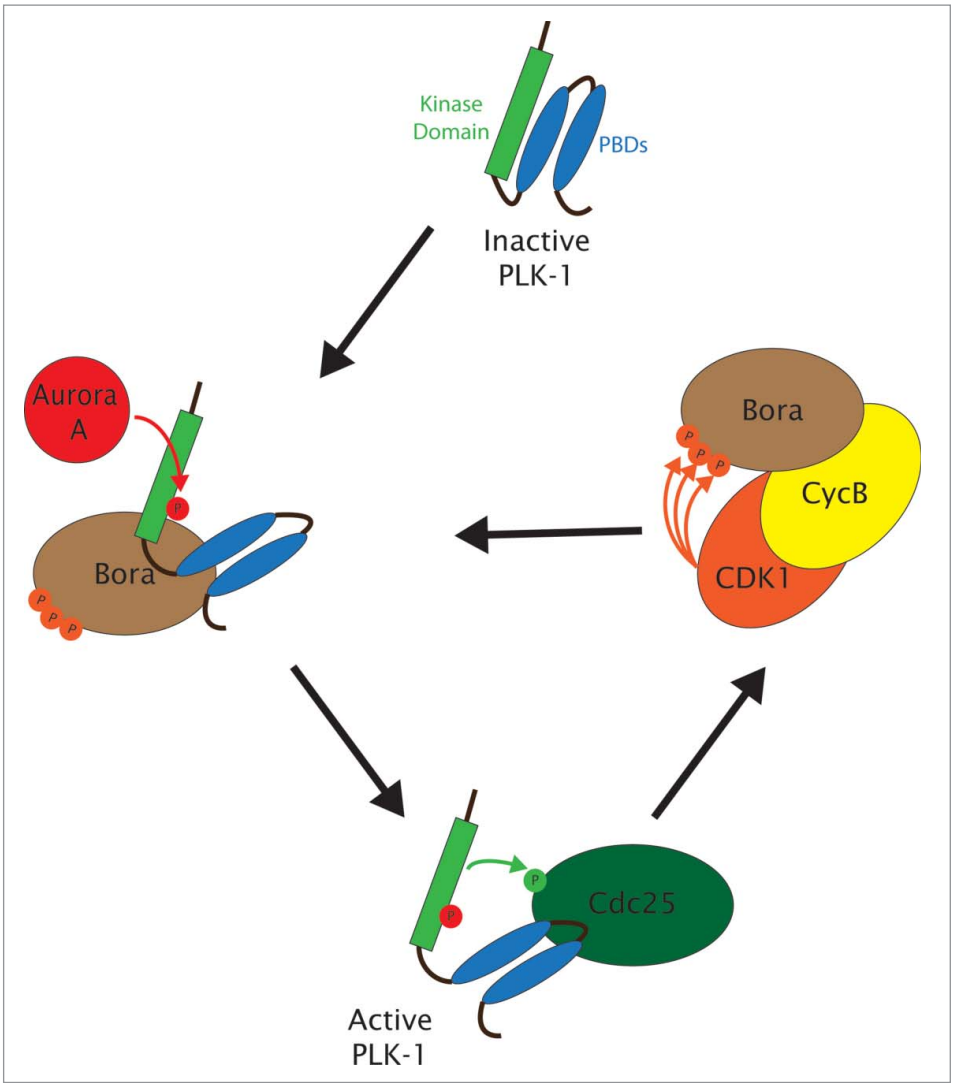

Figure 1. CDK1 phosphorylates BORA on 3 sites to activate PLK1. Schematic of the regulatory loop between polo like kinase 1 (PLK1) and cyclin-dependent kinase 1 (CDK1) in mitotic entry. Before mitosis, BORA is phosphorylated by cyclin B/CDK1, triggering PLK1 activation. Phospho-BORA can interact with PLK1, promoting phosphorylation of the kinase domain by aurora A kinase. This event activates PLK1 which, in turn, can phosphorylate cell division cycle 25 (CDC25) promoting further CDK1 activation.

cross reactivity of anti-PLK1 drugs with other members of the polo family.[1,2] This holds true if we assume that BORA is not required for PLK2 and PLK3 activity, something that remains to be tested.

A more challenging approach could be to develop inhibitors of BORA. To date BORA has been reported to have only a minor role in normal cell cycle progression; however, inactivation of BORA has only been performed using RNAi, which might not result in full depletion. Combining BORA inhibitors with low concentrations of PLK1 inhibitors may lead to more efficient therapies with reduced side effects and increased clinical activity. Given the role of BORA in G2/M DNA damage checkpoint recovery, another attractive possibility would be to combine potential BORA inhibitors with DNA damaging agents, such as platinum derivatives or with more targeted radiation.

Elucidating the mechanisms underlying PLK1 activation by BORA is therefore of major interest for the understanding of cancer progression and for the development of new therapeutic approaches.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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