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AUTHOR'S VIEW

Sustaining the spindle assembly checkpoint to improve cancer therapy

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ABSTRACT

To prevent chromosome segregation errors, the spindle assembly checkpoint (SAC) delays mitosis exit until proper spindle assembly. We found that the FCP1 phosphatase and its downstream target WEE1 kinase oppose the SAC, promoting mitosis exit despite malformed spindles. We further showed that targeting this pathway might be useful for cancer therapy.

Abbreviations: AMCD, antimicrotubule cancer drug; CDK1, cyclin-dependent kinase 1; MCL-1, myeloid cell leukemia 1; SAC, spindle assembly checkpoint

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Mitosis is the fastest phase of the cell division cycle. Nevertheless, the safeguard mechanism of the spindle assembly checkpoint (SAC) can delay mitosis exit until proper spindle formation.[1] However, through still unclear mechanisms, an exceedingly long prolongation of mitosis can translate into activation of the apoptotic program.[2] During the normal timing of mitosis, the cyclin B-dependent kinase (CDK) 1 performs anti-apoptotic functions such as inhibitory phosphorylation of caspases.[3] However, as the time of mitosis is extended (for instance if spindle assembly is somehow hampered), a progressive degradation of the antiapoptotic myeloid cell leukemia (MCL) 1 protein appears to dramatically change the sensitivity of cells to apoptotic cell death.[3,4] Indeed, it has been shown that impairing mitosis exit by depleting cells of CDC20, the crucial ubiquitin-ligase coactivator required for mitotic cyclin degradation and CDK1 inactivation, promotes a prolonged mitotic arrest that ends up in a deadly fate even in the absence of spindle defects.[5]

Exposure of cells, especially aneuploid cancer cells, to drugs that impair microtubule physiology and spindle assembly, such as the widely used antimicrotubule cancer drugs (AMCDs) taxanes and vinca alkaloids, induces a SAC-dependent mitotic delay. At therapeutic concentrations, AMCDs appear to induce a very transient mitotic delay in cancer cells. Some cells die in mitosis but others appear to exit from mitosis despite malformed spindles.[4,6] This involves an adaptation-like mechanism by which cancer cells slip through the SAC and exit mitosis abnormally and prematurely in the absence of a correctly assembled spindle. Such slipped, and even more aneuploid, cells either stop dividing or die at later stages; however, it is possible they that may give rise to resistant clones.[4,6] A recently developed model suggests that, during AMCD-induced prolonged mitosis, proapoptotic signals accumulate but the cells may survive if they slip through mitosis before a certain proapoptotic signal threshold has been reached. Conversely, cells die if the threshold is reached before slippage.[4,6] Thus, a better understanding of how cells slip through AMCD-activated SAC may provide clues to improve AMCD efficacy in cancer cell killing.

By studying the mechanisms of mitosis exit, we previously reported a novel, transcription-independent, and crucial role for the essential RNA polymerase II-C-terminal domain phosphatase FCP1 in bringing about CDK1 inactivation at the end of mitosis.[7] We identified cyclin degradation pathway components, such as CDC20, a deubiquitinating enzyme USP44, and the CDK1 inhibitory kinase WEE1, as crucial FCP1 targets.[7] At mitosis exit, FCP1 dephosphorylates WEE1, reactivating it to dampen CDK1 activation, and also CDC20 and USP44, promoting ubiquitin-dependent cyclin B degradation.

Recently, we analyzed the relevance of FCP1 in SAC slippage and sensitivity to therapeutic AMCD concentrations.[8] We found that FCP1 affected SAC slippage, mitosis exit, and cell death in the presence of AMCDs. Depleting FCP1 protracted the time that cells spent in mitosis in the presence of AMCDs.[8] In addition, in FCP1-depleted AMCD-treated cells, the levels of MCL-1 protein substantially decreased during prolonged mitosis and significantly higher rates of apoptotic cell death were induced.[8] In addition, we found that WEE1 was reactivated in an FCP1-dependent manner during prolonged mitosis in AMCD-treated cells and had a crucial role in promoting SAC slippage by reducing CDK1 activity, which is otherwise required to sustain the SAC.[9] Indeed, genetic or chemical downregulation of WEE1 significantly extended mitosis and promoted cell death in several AMCD-treated cancer cell lines and primary human adult lymphoblastic leukemia cells. Thus, the FWC (FCP1-WEE1-CDK1) pathway opposes the SAC and promotes slippage

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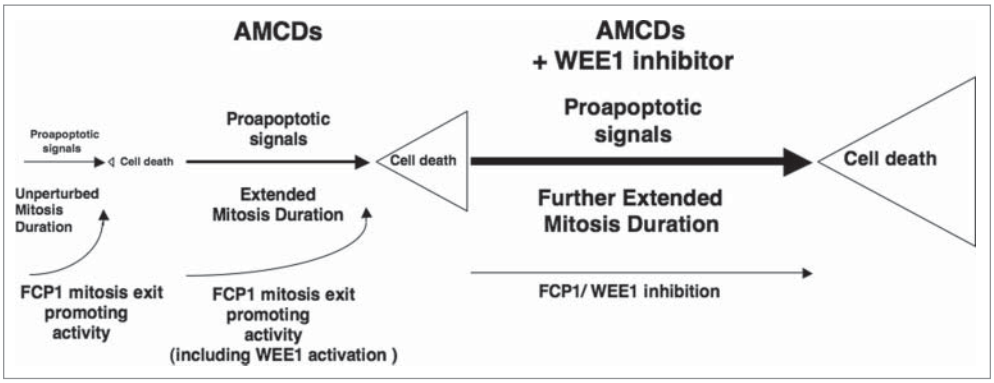

Figure 1. Impact of FCP1/WEE1 inhibition on antimicrotubule cancer drug (AMCD) treatment. The FCP1 phosphatase promotes mitosis exit during unperturbed mitosis as well as slippage through an AMCD-activated spindle assembly checkpoint (SAC). Inhibiting FCP1 or its downstream WEE1 kinase can delay slippage, further extend mitosis, and, by giving proapoptotic signals more time to accumulate (or allowing more time for degradation of antiapoptotic signals), increase the chances of a deadly fate for AMCD-treated cancer cells.

under AMCD regimens. On the contrary, its inhibition prolongs mitotic duration, leading to accumulation of proapoptotic signals and eventually to cell death in AMCD-treated cancer cells.[8]

WEE1 kinase is known to control the onset of mitosis through inhibitory phosphorylation of CDK1. WEE1 is also a crucial kinase that prevents mitosis onset in cells with incompletely replicated or damaged DNA. Since it has been observed that forcing cells with damaged DNA into mitosis strongly promotes cell death, WEE1 inhibitors have been produced with the aim of anticancer combination therapy with DNA damaging drugs, and an orally available agent is currently in clinical trials.[10] Based on our findings, we hypothesize that inhibiting WEE1 under AMCD treatment would promote more efficient cancer cell killing by delaying slippage, thus increasing the chances for proapoptotic signal accumulation (see Fig. 1). Given the availability of a clinically usable WEE1 inhibitor, we suggest that it would be worthwhile to perform clinical trials in which the WEE1 inhibitor is combined with AMCD-based cancer therapy. Such a therapeutic combination would be particularly important in clinical settings in which AMCDs are used as monotherapeutic agents as second line treatments, as in the case of prostate cancer and several solid and hematological malignancies.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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