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Cyclin-Dependent Kinase 4/6 Inhibition in Cancer Therapy

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Cell Cycle News & Views

Cyclin-dependent kinase 4/6 inhibition in cancer therapy

Comment on: Dean JL, et al. *Cell Cycle* 2012; 11:2756–61; PMID:22767154
and McClendon AK, et al. *Cell Cycle* 2012; 11:2747–55; PMID:22751436

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Cyclin-dependent kinases (CDKs) drive cell cycle progression and control transcriptional processes. The dysregulation of multiple CDK family members occurs commonly in human cancer; in particular, the cyclin D-CDK4/6-retinoblastoma protein (RB)-INK4 axis is universally disrupted, facilitating cancer cell proliferation and prompting long-standing interest in targeting CDK4/6 as an anticancer strategy. Most agents that have been tested inhibit multiple cell cycle and transcriptional CDKs and have carried toxicity. However, several selective and potent inhibitors of CDK4/6 have recently entered clinical trial. PD0332991, the first to be developed, resulted from the introduction of a 2-aminopyridyl substituent at the C2-position of a pyrido(2,3-*d*)pyrimidin-7-one backbone, affording exquisite selectivity toward CDK4/6.¹ PD0332991 arrests cells in G₁ phase by blocking RB phosphorylation at CDK4/6-specific sites and does not inhibit the growth of RB-deficient cells.² Phase I studies conducted in patients with advanced RB-expressing cancers demonstrated mild side effects and dose-limiting toxicities of neutropenia and thrombocytopenia, with prolonged stable disease in 25% of patients.^{3,4} In *cyclin D1*-translocated mantle cell lymphoma, PD0332991 extinguished CDK4/6 activity in patients' tumors, resulting in markedly reduced proliferation, and translating to more than 1 year of stability or response in 5 of 17 cases.⁵

Two recent papers from the Knudsen laboratory make several important observations that will help guide the continued clinical development of CDK4/6 inhibitors. In the study by Dean et al., surgically resected patient breast tumors were grown on a tissue culture matrix in the presence or absence of PD0332991. Crucially, these cultures retained associated stromal components known to play important roles in cancer pathogenesis and therapeutic sensitivities, as well as key histological and molecular features of the primary tumor, including expression of ER, HER2 and Ki-67. Similar to results in breast cancer cell lines,⁶ the authors demonstrate that only

RB-positive tumors have growth inhibition in response to PD0332991, irrespective of ER or HER2 status, while tumors lacking RB were completely resistant. This result underscores RB as the predominant target of CDK4/6 in breast cancer cells and the primary marker of drug response in primary patient-derived tumors. As expected, RB-negative tumors routinely demonstrated robust expression of p16^{INK4A}; however, p16^{INK4A} expression was not always a surrogate marker for RB loss, supporting the importance of direct screening of tumors for RB expression to select patients appropriate for CDK4/6 inhibitor clinical trials.

In the second study, McClendon et al. investigated the efficacy of PD0332991 in combination with doxorubicin in triple-negative breast cancer cell lines. Again, RB functionality was paramount in determining response to either PD0332991 monotherapy or combination treatment. In RB-deficient cancer cells, CDK4/6 inhibition had no effect in either instance. However, in RB-expressing cancer cells, CDK4/6 inhibition and doxorubicin provided a cooperative cytostatic effect, although doxorubicin-induced cytotoxicity was substantially reduced, assessed by markers for mitotic catastrophe and apoptosis. Additionally, despite cytostatic cooperativity, CDK4/6 inhibition maintained the viability of RB-proficient cells in the presence of doxorubicin, which repopulated the culture after removal of drug. These results reflect previous data demonstrating that ectopic expression of p16^{INK4A} can protect cells from the lethal effects of DNA damaging and anti-mitotic chemotherapies.⁷ Similar results have been reported in MMTV-c-neu mice bearing RB-proficient HER2-driven tumors, where PD0332991 compromised carboplatin-induced regressions,⁸ suggesting that DNA-damaging treatments should not be combined concomitantly with CDK4/6 inhibition in RB-proficient tumors.

To combine CDK4/6 inhibition with cytotoxics, sequential treatment may be considered, in which CDK4/6 inhibition is followed by

DNA damaging chemotherapy; cells relieved of G₁ arrest may synchronously enter S phase, where they may be most susceptible to agents disrupting DNA synthesis. Release of myeloma cells from a prolonged PD0332991-mediated G₁ block leads to S phase synchronization; interestingly, all scheduled gene expression is not completely restored (including factors critical to myeloma survival such as IRF4), further favoring apoptotic responses to cytotoxic agents.⁹ Furthermore, in RB-deficient tumors, CDK4/6 inhibitors may be used to maximize the therapeutic window between transformed and non-transformed cells treated with chemotherapy. In contrast to RB-deficient cancer cells, RB-proficient non-transformed cells arrested in G₁ in response to PD0332991 are afforded protection from DNA damaging agents, thereby reducing associated toxicities, including bone marrow suppression.⁸

In summary, the current work provides evidence for RB expression as a determinant of response to CDK4/6 inhibition in primary tumors and highlights the complexity of combining agents targeting the cell cycle machinery with DNA damaging treatments.

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