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Précis: CDK4/6 inhibitors derepress NFAT to promote IL2 secretion, enhance T-cell activation and tumor infiltration, and cooperate with anti–PD-1 antibodies to boost antitumor immunity in vivo.
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Précis: Gastrointestinal stromal tumors exhibit a transcriptional dependence on FOXF1, which binds enhancers to promote expression of genes, including ETV1 and KIT, required for tumor growth.
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ON THE COVER
Deng, Wang, Jenkins, and colleagues found that cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors augment PD-1 blockade by increasing the activity of PD-1 overexpressing T cells. CDK4/6 inhibition relieved NFAT suppression by preventing CDK6-mediated NFAT phosphorylation, thereby promoting NFAT signaling, IL2 secretion, and T-cell activity. In vivo, CDK4/6 inhibition enhanced T-cell tumor infiltration despite reducing T-cell proliferation, and CDK4/6 inhibitors cooperated with anti–PD-1 therapy to induce T-cell-mediated antitumor immunity, synergizing with PD-1 blocking antibodies in multiple syngeneic tumor models. These results describe a mechanism by which CDK4/6 inhibitors may promote T-cell activity and improve the efficacy of anti–PD-1 therapy, suggesting that combined treatment with CDK4/6 inhibitors and immune checkpoint blockade may be beneficial in patients with cancer. For details, please see the article by Deng, Wang, Jenkins, and colleagues on page 216.
**CANCER DISCOVERY**

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