

Bypass kinase pathways lead to acquired CDK4/6 inhibitor resistance

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Abstract

Background: Cyclin Dependent Kinase-4/6 (CDK4/6) kinase inhibitors have shown clinical benefit in treatment of solid tumor types, including breast cancer. However, resistance is common, and the underpinning mechanisms of action are not well understood. Given the dependence of CDK4/6 inhibitors on retinoblastoma tumor suppressor (RB) function for activity, this class of agents may be particularly effective in tumor types for which RB loss is infrequent or occurs late in tumor progression.

Methods: Here, models of acquired palbociclib resistance were generated in early stage, RB positive cancers, and assessed via unbiased global gene expression and phosphoproteomic profiling.

Results: Acquired palbociclib resistance resulted in cross-resistance to other CDK4/6 inhibitors under clinical testing. Furthermore, cells showing acquired resistance exhibited aggressive *in vitro* and *in vivo* phenotypes without genetic loss of RB or RB pathway members, including enhanced proliferative capacity, migratory potential, and characteristics of epithelial to mesenchymal transition. Further analyses through integration of RNA sequencing and phospho-proteomics identified activation of the MAPK signaling pathway as a mediator of CDK4/6 inhibitor resistance, capable of bypassing CDK4/6 activity. However, this altered kinase dependence resulted in sensitization to MEK inhibitors, suggestive of new clinical opportunities in CDK4/6 resistant tumors.

Conclusions: The studies herein not only identify activation of the MAPK pathway as capable of bypassing the CDK4/6 requirement and promoting aggressive tumor characteristics, but nominate MEK inhibitors as potential mechanisms to treat or prevent CDK4/6 inhibitor resistance.

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