Braking the cell's cycle and invigorating T-cell immunity against pancreatic cancer

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Pancreatic cancer has been an elusive target for immunotherapy. Redundant mechanisms of immune suppression have plagued efforts to elicit vigorous T-cell responses to this disease. Similar frustrations are evident in pancreatic cancer when considering efforts at targeting prominent oncogenic pathways. For example, cyclin-dependent kinase inhibitor 2A is very frequently mutated, suggesting that inhibition of cyclin-dependent kinase 4/6 (CDK4/6) may be a viable strategy against these aggressive tumours.[1] Unfortunately, resistance to targeting single oncogenic pathways typically prevails, necessitating a need for combination therapy. The choice of optimal combination approaches, however, is not a simple one. Of course, decisions must be carefully metered by preclinical efficacy data, on-target and off-target toxicities, patient selection and insight into mechanisms of action. These considerations may be even more relevant when combining tumour-directed, small molecule inhibitors with immunotherapy.

The article by Knudsen *et al*[2] addresses these issues by employing a data-driven approach to identify novel combinatorial therapies for pancreatic cancer. Their strategy was to systematically define other agents that cooperate with CDK4/6 inhibitors using a live cell imaging-based in vitro drug screen. Using this unbiased strategy, they identified the mitogen-activated protein kinase kinase 1 (MEK) inhibitor, trametinib, worked in concert with the CDK4/6 inhibitor; palbociclib to limit cell cycle progression and growth. These data were confirmed in vivo using a number of patient-derived xenograft models. Further analysis of molecular changes at the gene expression level revealed trametinib alone, or trametinib combined with palbociclib, upregulated genes related to antigen presentation and interferon production. Interestingly, loss of function experiments solidified that this regulation of immune-relevant genes occurred via a retinoblastoma (Rb)-dependent mechanism. Given these enticing data, the authors next pursued a series of in vivo studies to address whether combined CDK4/6 and MEK inhibition modulates response to clinically relevant immunotherapy approaches. Here they used immune competent mice bearing orthotopic pancreatic tumours to demonstrate that trametinib and palbociclib enhanced the efficacy of programmed death-ligand 1 (PD-L1) blockade, and did so in a cluster of differentiation 8 ($CD8^+$) T cell-dependent manner. Finally, the tumour-infiltrating lymphocytes from this study underwent single-cell RNAseq and revealed several alterations in cells present within the tumours. Among these were treatment-induced changes in the dominant myeloid cell populations, with gene expression profiles indicative of an M2–M1 shift in macrophages and increased chemokines that facilitate T-cell infiltration.

These data are enticing and define a mechanism whereby oncogenic pathway inhibitors 'tune' tumour cells to promote productive, T cell-mediated immune responses. Evidence for an Rb-dependent immunomodulatory mechanism further suggests that translation of this treatment combination may be viable, as Rb loss is infrequent in pancreatic tumours.[3 4] This work also validates prior studies implicating MEK inhibitors as a means to sensitise pancreatic tumours to CDK4/6 inhibition and does so in an unsupervised manner.[5 6] The application of PD-L1 blockade in concert with dual MEK and CDK4/6 inhibition represents a further advance, and suggests that targeted pathway inhibitors could possibly be individualised based on genotypic features of tumours to modulate immunogenicity.

Observations from this initial study might also prompt other questions of relevance to this treatment combination. First, the impact of MEK and CDK4/6 inhibition on stromal elements of pancreatic tumours remain undefined. Cancer-associated fibroblasts or pancreatic stellate cells may also be impacted by systemic administration of these inhibitors. These heterogeneous cell populations are notorious for cross-talk with malignant cells and for facilitating suppressed immune responses in the tumour microenvironment through a variety of mechanisms.[7] Second, it will be important to examine if this approach works in pancreatic tumours at metastatic sites. A strength of this study was the prudent use of orthotopic tumour models and KPC-derived cell lines that are resistant to programmed cell death protein 1/PD-L1 pathway blockade. However, the microenvironment of metastasis to liver or other anatomical sites may introduce further challenges for immunotherapy.[8] If this approach is considered for early-phase clinical trials, the highest likelihood would be in patients with disease at metastatic sites. Third, schedules of administration for CDK4/6 and MEK inhibitors may also influence efficacy when given in combination with immune checkpoint blockade. The Rb-dependent changes in immune features of tumours may be subject to temporal regulation that is schedule-dependent.

Taken together, this article highlights how combined CDK4/6 and MEK inhibitors exert their intended inhibitory effect on cell cycle progression while simultaneously modulating immune features of pancreatic cancer cells. This rational approach illustrates how targeted inhibitors can cooperate with PD-L1 blockade to invigorate T-cell responses in an otherwise immune-refractory tumour.

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