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Immune Cell–Poor Melanomas Benefit from PD-1 Blockade after Targeted Type I IFN Activation ........... 674

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Friboulet and colleagues report that ceritinib, a next-generation ALK inhibitor that is more selective and potent than crizotinib, is active in preclinical models of both crizotinib-naïve and crizotinib-resistant non-small cell lung cancer (NSCLC). Ceritinib retained activity against the most common crizotinib-resistant ALK mutants, although some secondary ALK mutations did confer resistance to both crizotinib and ceritinib. Structural analyses provided a mechanistic basis for these findings, as the most common secondary ALK mutations that inhibit binding of crizotinib are not predicted to impair ceritinib binding, but other mutations, which the authors have identified in patients with acquired resistance to ceritinib, are predicted to reduce ceritinib binding through steric hindrance or conformational changes of the ALK catalytic domain. For details, please see the article by Friboulet and colleagues on page 662.

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Epithelial-to-Mesenchymal Transition Activates PERK-eIF2α and Sensitizes Cells to Endoplasmic Reticulum Stress 702


Précis: Elevated ECM synthesis and secretion activates the PERK arm of the UPR and renders cells that have undergone EMT vulnerable to ER stress-inducing agents.

p38MAPK Plays a Crucial Role in Stromal-Mediated Tumorigenesis 716


Précis: The secretory phenotype of cancer-associated fibroblasts that promotes tumor growth is post-transcriptionally controlled by p38MAPK.

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Human and Mouse VEGFA-Amplified Hepatocellular Carcinomas Are Highly Sensitive to Sorafenib Treatment 730


Précis: VEGFA amplifications frequently occur in mouse and human hepatocellular carcinomas and drive dependence on VEGFA signaling via manipulation of the tumor microenvironment.

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