REVIEW Engineering Multidimensional Evolutionary Forces to Combat Cancer 587
C.E. McCoach and T.G. Bivona

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Patient-Driven Discovery, Therapeutic Targeting, and Post-Clinical Validation of a Novel AKT1 Fusion–Driven Cancer 605

Précis: The response to AKT inhibition in a pediatric patient with a LAMTOR1–AKT1 fusion confirms the AKT1 fusion as an oncogenic driver, and subsequent characterization of the fusion suggests potential ways to overcome resistance.

A Stromal Lysolipid–Autotaxin Signaling Axis Promotes Pancreatic Tumor Progression 617

Précis: Lysophosphatidylcholines secreted by activated stromal fibroblasts support pancreatic cancer cell proliferation and migration via autotaxin-mediated production of lysophosphatic acid.

See commentary, p. 578

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VIEWS In The Spotlight
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Metabolic Checkpoint of Immune Cells in Melanoma Brain Metastases 581
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Delivering a STINGing Blow to Small Cell Lung Cancer via Synergistic Inhibition of DNA-Damage Response and Immune-Checkpoint Pathways 584
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AMERICAN ASSOCIATION FOR CANCER RESEARCH
Molecular Profiling Reveals Unique Immune and Metabolic Features of Melanoma Brain Metastases


Précis: Comprehensive molecular profiling of patient-matched melanoma brain metastases and extracranial metastases unveil significant differences between these two metastatic populations.

See commentary, p. 581

Targeting DNA Damage Response Promotes Antitumor Immunity through STING-Mediated T-cell Activation in Small Cell Lung Cancer


Précis: Pharmacologic inhibition of PARP and CHK1 increases expression of PD-L1 and potentiates the antitumor effects of PD-L1 blockade via activation of the innate immune STING pathway.

See commentary, p. 584

BCL6 Evolved to Enable Stress Tolerance in Vertebrates and Is Broadly Required by Cancer Cells to Adapt to Stress


Précis: An evolutionarily conserved HSF1–BCL6 axis mediates stress adaptation across vertebrates and promotes tolerance to chemotherapy in cancer cells, in part via repression of the transcription factor TOX.

Sen and colleagues showed that treatment of human small cell lung cancer (SCLC) cell lines with inhibitors of the DNA damage response (DDR) components CHK1 and PARP resulted in increased expression of PD-L1. Further, inhibition of either CHK1 or PARP in immunocompetent genetically engineered mouse models (GEMM) of SCLC resulted in increased levels of cytosolic DNA, which activates the cGAS–STING innate immune signaling pathway to induce IRF3 activation and subsequently drive IFNβ-mediated increases in PD-L1 expression and T-cell recruitment in SCLC GEMMs. Consistent with these findings, treatment with a CHK1 or PARP inhibitor enhanced the efficacy of anti–PD-L1 therapy and resulted in SCLC tumor regression in vivo. Together, these findings suggest that combined targeting of DDR proteins and immune checkpoint blockade is a potential therapeutic strategy for patients with SCLC. For details, please see the article by Sen and colleagues on page 646.