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Molecular Profiling Reveals Unique Immune and Metabolic Features of Melanoma Brain Metastases 628

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 646

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.

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BCL6 Evolved to Enable Stress Tolerance in Vertebrates and Is Broadly Required by Cancer Cells to Adapt to Stress 662

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.
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