An Actionable AKT1 Fusion Is Identified in a Pediatric Cancer

- A LAMTOR1–AKT1 fusion was identified in a pediatric patient with an epithelioid neoplasm.
- A brief dramatic response to an AKT inhibitor confirmed LAMTOR1–AKT1 as an oncogenic driver.
- Residual mTORC1 activity was responsible for resistance to AKT inhibition in the setting of LAMTOR1–AKT1.

Although AKT1 has a role in the pathogenesis of many cancers, thus far no oncogenic fusions have been found involving this gene. Slotkin, Diolaiti, and colleagues report the identification and characterization of an AKT1 fusion in which the exon 1 of late endosomal/lysosomal Adaptor, MAPK and mTOR activator 1 (LAMTOR1) was fused in-frame with exons 5–14 of AKT1 in a 12-year-old patient with a histopathologically indeterminate epithelioid neoplasm. The patient was treated with the ATP-competitive pan-AKT inhibitor ipatasertib via compassionate use, representing the first use of this drug for pediatric cancer. The treatment was tolerable and resulted in a dramatic response, confirming AKT1 as an oncogenic driver in this patient. However, the patient developed resistance to the drug, and the tumor progressed two months after initiation of treatment. Evaluation of cell lines and patient-derived xenografts (PDX) established from one of the patient’s affected lymph nodes excised after initiation of ipatasertib revealed that unlike AKT1, which is predominantly localized to the cytoplasm, the LAMTOR1–AKT1 fusion protein localized to the cell membrane. The patient-derived cells demonstrated AKT activity that was mostly sensitive to AKT inhibition, but with residual mTORC1 activity responsible for resistance. Combination treatment using AKT1 and mTOR inhibitors thus resulted in increased in vivo inhibition of growth in a PDX model. Together, these results identifying a previously uncharacterized actionable AKT1 fusion and mechanism of resistance highlight the potential for incorporation of molecular profiling into treatment and patient-driven discovery of actionable oncogenic alterations.

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Stroma–Tumor Metabolic Cross-Talk Promotes PDAC Tumor Progression

- Lysophosphatidylcholines secreted by PSC-derived CAFs support membrane synthesis and PDAC growth.
- Hydrolysis of PSC-derived autotaxin lipids by PDAC cell-secreted autotaxin generates the signaling lipid LPA.
- Pharmacologic inhibition of autotaxin represents a potential therapeutic strategy for PDAC.

Pancreatic ductal adenocarcinoma (PDAC) stimulates the transdifferentiation of pancreatic stellate cells (PSC) into activated cancer-associated fibroblasts (CAF), but the role of CAFs in PDAC progression remains unclear. Auciello, Bulusu, and colleagues show that PSC-derived CAFs undergo extensive lipid remodeling to support PDAC cell metabolism and growth. Differentiation of PSCs into CAFs results in depletion of lipid droplets and increased production of lysophosphatidylcholines (LPC). These stroma-derived lipids were taken up by PDAC cells and promoted membrane synthesis and PDAC cell growth. In addition, PSC-derived LPCs were hydrolyzed by PDAC cell-secreted autotaxin to generate lysophosphatidic acid (LPA), a potent extracellular mediator of proliferation and migration. Conditioned media from PSCs activated AKT signaling in PDAC cells in a paracrine and autotaxin-dependent manner. Stromal LPA was sufficient to induce PDAC cell proliferation and migration, both of which were blocked by pharmacologic inhibition of autotaxin or LPA receptor. Expression of autotaxin was low in healthy pancreas but abundant in both mouse and human pancreatic tumors. Subcutaneous cotransplantation of PDAC cells and PSCs resulted in increased intratumoral LPA levels and enhanced tumor growth, whereas pharmacologic inhibition or genetic ablation of autotaxin in orthotopic tumor models suppressed PDAC growth, implicating the stromal LPC–autotaxin–LPA axis in PDAC progression in vivo. Taken together, these results identify a critical role for stroma-derived lysophospholipid secretion in paracrine regulation of PDAC proliferation and migration and suggest this signaling axis as a potential therapeutic target in patients with PDAC.

See article, p. 617.
Increasing evidence suggests that melanoma brain metastases (MBM) possess unique molecular features, but a comprehensive comparison to extracranial metastases has not yet been undertaken. Fischer and colleagues performed RNA sequencing (RNA-seq) on 88 surgically resected MBMs and 42 patient-matched extracranial metastases [and whole-exome sequencing, T-cell receptor (TCR) sequencing, and immunohistochemistry when tissue was sufficient]. MBMs from individual patients clustered together based on immune cell signaling: Those with expression profiles indicative of higher immune cell infiltrate expressed higher levels of PD-L1 and had higher overall survival. MBMs that had undergone prior radiation therapy displayed high innate immune cell infiltrate and were enriched for IFNα/β and IFNγ signaling networks. Although there was heterogeneity among MBMs, MBMs showed significantly lower T-cell infiltration than patient-matched extracranial metastases. PD-L1 expression did not differ significantly between matched samples, and TCR sequencing indicated no difference in T-cell reactivity, yet there were distinct T-cell repertoires in T-cell clones from MBMs versus extracranial metastases. RNA-seq of intracranial melanoma xenografts showed increased oxidative phosphorylation (OXPHOS) compared with extracranial metastases, which was confirmed in patient MBMs. Metabolic profiling of intracranial xenografts also revealed increased concentrations of TCA cycle metabolites, which was indicative of enriched OXPHOS. In xenografts, pharmacologic inhibition of mitochondrial complex I with IACS-010759, a drug currently in phase I clinical trials, impaired MBM formation and extended overall survival. Collectively, this integrative analysis of MBMs provides key insights into the unique features and pathogenesis of brain metastasis and identifies clinically relevant strategies for preventing or treating these deadly tumors.

See article, p. 628.

Inhibition of the DNA Damage Response Promotes Antitumor Immunity

Although immune checkpoint blockade (ICB) has emerged as a promising therapeutic approach in several cancers, its success varies widely across cancer types. ICB has had limited efficacy to date in small cell lung cancer (SCLC), which is associated with relatively low PD-L1 expression, high immunosuppression, and low T-cell infiltration despite having one of the highest tumor mutation burdens among solid tumors. Inhibitors of the DNA damage response (DDR) have shown preclinical activity in SCLC, and some evidence suggests that DDR inhibition may affect immune responses. Sen and colleagues demonstrate that knockdown or targeted inhibition of the DDR proteins CHK1 and PARP in SCLC cell lines and mouse models increased expression of PD-L1 and increased T-cell infiltration in vivo. Combining DDR inhibition (via prexasertib or olaparib) with PD-L1 blockade significantly reduced or completely eliminated tumor formation in mouse models of SCLC; of note, depletion of CD8+ T cells significantly rescued tumor growth, suggesting that cytotoxic T cells are required for the antitumor activity of combined treatment. Treatment with DDR inhibitors activated the STING pathway of the innate immune response by causing DNA damage and generating cytoplasmic DNA, which is sensed by cGAS. Depletion of either cGAS or STING from SCLC xenograft tumors abrogated the antitumor effects of combined inhibition of CHK1/PARP and PD-L1. Taken together, these results highlight the role of the innate immune response in DDR inhibitor-mediated upregulation of PD-L1 in SCLC and show that combined targeting of DDR and PD-L1 may serve as an effective therapy in patients with SCLC.

See article, p. 646.
BCL6 is a transcriptional repressor that promotes the survival of germinal center (GC) B cells in the face of genotoxic and replicative stress and functions as an oncogene in diffuse large B-cell lymphoma. BCL6 is also expressed in many solid tumors, suggesting that it may be more broadly linked to cellular stress responses.

Fernando, Marullo, and colleagues found that heat shock factor 1 (HSF1), master regulator of the stress response, directly induced transcription of BCL6 in GC B cells and aggressive solid tumors and was required for normal GC formation. HSF1 induction of BCL6 expression was evolutionarily conserved across vertebrate species and necessary for cellular adaptation to repetitive stress. This function of BCL6 was mediated by the highly conserved BCL6 BTB corepressor-binding domain and repression of stress-associated genes such as TOX, which encodes a transcription factor that inhibits nonhomologous end joining DNA repair. The HSF1–BCL6–TOX axis was also active in cancer cells due to intrinsic oncogenic stress and secondary to DNA damage by cytotoxic chemotherapy. HSF1 knockdown or inhibition of the BCL6 BTB domain promoted sensitization to cytotoxic chemotherapy in part by inducing TOX expression and reducing DNA repair. Treatment with a BCL6 BTB small-molecule inhibitor diminished chemotolerance in vivo, resulting in greater inhibition of tumor growth.

These findings identify an evolutionarily conserved mechanism of stress adaptation that is hijacked by cancer cells to enable stress tolerance and suggest that therapeutic targeting of BCL6 may overcome this protective response.

See article, p. 662.