Mesothelin-Targeted CARs: Driving T Cells to Solid Tumors
A. Morello, M. Sadelain, and P.S. Adusumilli

Tumor Heterogeneity and Lesion-Specific Response to Targeted Therapy in Colorectal Cancer

Précis: Acquisition of distinct resistance mechanisms in individual metastases within the same patient can result in differential responses to subsequent targeted therapies between lesions. See commentary, p. 122

Diverse and Targetable Kinase Alterations Drive Histiocytic Neoplasms

Précis: Recurrent kinase fusion proteins involving BRAF, ALK, and NTRK1 and activating MAP2K1 and ARAF mutations were identified in BRAFV600E–wild-type histiocytic neoplasms, sensitizing cells to kinase inhibitors.
Whole Genome Sequencing Defines the Genetic Heterogeneity of Familial Pancreatic Cancer ................. 166

Précis: Germline whole-genome sequencing of a large cohort of patients with familial pancreatic cancer identified candidate susceptibility genes and revealed high genetic heterogeneity.

RESEARCH ARTICLES

Recurrent Fusions in \( MYB \) and \( MYBL1 \) Define a Common, Transcription Factor–Driven Oncogenic Pathway in Salivary Gland Adenoid Cystic Carcinoma ....... 176
K.J. Brayer, C.A. Frerich, H. Kang, and S.A. Ness

Précis: RNA-seqning analysis of adenoid cystic carcinomas detected a recurrent translocation fusing \( MYB \) to \( NFIB \) as well as translocations fusing \( MYBL1 \) to \( NFIB \) or \( RAD51B \), and demonstrated that these \( MYB \) and \( MYBL1 \) fusions are interchangeable oncogenic drivers.

Loss of PTEN Promotes Resistance to T Cell–Mediated Immunotherapy .......... 202

Précis: PTEN loss reduces T-cell infiltration and drives immunotherapy resistance in melanoma by increasing immunosuppressive cytokine production and inhibiting autophagy.

See commentary, p. 128

ON THE COVER

The molecular mechanisms that promote resistance to T cell–mediated immunotherapy in patients with melanoma remain unclear. Peng and colleagues found that loss of PTEN in melanoma cells suppressed T cell–driven antitumor responses both in vitro and in vivo. Consistent with this finding, PTEN-negative melanomas exhibited impaired infiltration and function of CD8+ T cells and decreased sensitivity to immunotherapy. This immune-suppressive effect was mediated by upregulation of the expression of immunosuppressive cytokines and inhibition of autophagy in the absence of PTEN. Selective inhibition of the PI3Kβ isoform restored the sensitivity of PTEN-null melanoma cells to T cell–mediated immunotherapy. These results support the notion that loss of PTEN drives resistance to immunotherapy in melanoma and suggest that combined treatment with PI3K–AKT inhibitors may enhance the clinical efficacy of immunotherapies. For details, please see the article by Peng and colleagues on page 202.