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RESEARCH BRIEF
Changes in Aged Fibroblast Lipid Metabolism Induce Age-Dependent Melanoma Cell Resistance to Targeted Therapy via the Fatty Acid Transporter FATP2 1282
Précis: Aged dermal fibroblasts secreted altered levels of several lipids, which entered melanoma cells via the fatty acid transporter FATP2, the inhibition of which synergized with targeted therapy in aged mice.
See commentary, p. 1255

RESEARCH ARTICLES
Inactivation of Fbxw7 Impairs dsRNA Sensing and Confers Resistance to PD-1 Blockade 1296
Précis: Loss of function of the tumor-suppressor gene Fbxw7 conferred resistance to PD-1 blockade by decreasing expression of dsRNA sensors, leading to an altered tumor immune microenvironment.

Epigenetic Switch–Induced Viral Mimicry Evasion in Chemotherapy-Resistant Breast Cancer 1312
Précis: Taxane-resistant triple-negative breast cancer cells had altered methionine metabolism, leading to epigenetic changes at transposable elements and creating a therapeutic vulnerability to EZH2 inhibitors.
See commentary, p. 1258

Single-Cell Analysis Reveals Fibroblast Clusters Linked to Immunotherapy Resistance in Cancer 1330
Y. Kieffer, H.R. Hocine, G. Gentic, F. Pelon, C. Bernard, B. Bourachot, S. Lameiras,

Précis: An immunosuppressive subtype of cancer-associated fibroblast was heterogeneous, with only certain subsets modulating immune-cell infiltration in the tumor microenvironment and immunotherapy response.

Limited Environmental Serine and Glycine Confer Brain Metastasis Sensitivity to PHGDH Inhibition .......... 1352


Précis: The serine-synthesis enzyme PHGDH was necessary and sufficient for metastasis to the brain, where amino acid availability is limited, and PHGDH inhibition suppressed brain metastasis.

Chromatin Regulator CHD1 Remodels the Immunosuppressive Tumor Microenvironment in PTEN-Deficient Prostate Cancer ................. 1374


Précis: The tumor suppressor CHD1 increased IL6 expression to recruit myeloid-derived suppressor cells to Pten-null prostate tumors, and CHD1 depletion or IL6 inhibition enhanced the efficacy of immune checkpoint blockade.

Posttranslational Regulation of the Exon Skipping Machinery Controls Aberrant Splicing in Leukemia .......... 1388


Précis: Increased exon skipping, particularly affecting proteasome-related transcripts, was mediated by elevated serine/arginine-rich splicing factor 6 (SRSF6) levels in T-cell acute lymphoblastic leukemia.

RBMS1 Suppresses Colon Cancer Metastasis through Targeted Stabilization of Its mRNA Regulon .... 1410


Précis: A new analytic method identified RBMS1, which acted as a posttranscriptional regulator that bound and stabilized the 3′ untranslated region of target mRNAs, as a suppressor of metastasis in colorectal cancer.

See commentary, p. 1261

ON THE COVER

Although PD-1 blockade has become a mainstay treatment for melanoma, it is not always effective. In a patient with metastatic melanoma in which all tumors but one responded to PD-1 blockade, Gstaider and colleagues found that the tumor-suppressor gene FBXW7 had a loss-of-function mutation. In immunocompetent mice, Fbxw7 deficiency in melanomas disrupted double-stranded RNA (dsRNA)-sensing pathways, leading to alterations in the tumor immune microenvironment that included a decrease in the CD8+ T-cell infiltration that PD-1 blockade normally induces. Restoration of dsRNA sensing in these melanomas conferred sensitivity to anti-PD-1. This work suggests that reactivation of dsRNA-sensing pathways in patients with FBXW7-mutant melanoma may be therapeutically relevant. For more information, see the article by Gstaider and colleagues on page 1296.