RESEARCH BRIEF

Constitutive Signaling from an Engineered IL7 Receptor Promotes Durable Tumor Elimination by Tumor-Redirected T Cells ........... 1238

Précis: Expression of a constitutive IL7R in chimeric antigen receptor (CAR)-expressing T cells allows selective activation of immunostimulatory cytokine signaling and enhances CAR-T cell expansion and antitumor activity.

RESEARCH ARTICLES

Recurrent Tumor Cell–Intrinsic and –Extrinsic Alterations during MAPKi-Induced Melanoma Regression and Early Adaptation ............. 1248

Précis: Integrated analysis of melanoma tumors and patient-derived cell lines defines recurrent tumor cell–intrinsic and immune microenvironment alterations linked to early MAPK inhibitor resistance.

A Unified Approach to Targeting the Lysosome’s Degradative and Growth Signaling Roles ............. 1266

Précis: A screen of chloroquine compounds identifies an inhibitor of both lysosomal anabolic and catabolic functions with enhanced antitumor activity compared with existing inhibitors of catabolic function.

See commentary, p. 1216

In The Spotlight

Trapping Cancers as They Adapt to Survive ................. 1216
R. Haq

See article, p. 1248

Targeting the Lysosome for Cancer Therapy .......... 1218
C.G. Towers and A. Thorburn

See article, p. 1266

Insights into Epigenetic Remodeling in VHL-Deficient Clear Cell Renal Cell Carcinoma ................. 1221
C.J. Ricketts and W.M. Linehan

See article, p. 1284

REVIEW

Tissue Force Programs Cell Fate and Tumor Aggression ............. 1224
J.J. Northey, L. Przybyla, and V.M. Weaver

Précis: A unified approach to targeting the lysosome’s degradative and growth signaling roles.
VHL Deficiency Drives Enhancer Activation of Oncogenes in Clear Cell Renal Cell Carcinoma


Précis: Loss of VHL enhances HIF2α–HIF1β binding at clear cell renal cell carcinoma gene enhancers, facilitating p300 recruitment and expression of lineage-specific cancer genes.

Notch Shapes the Innate Immunophenotype in Breast Cancer


Précis: NOTCH-recruited tumor-associated macrophages induce Notch-mediated IL1β, CCL2, and TGFβ paracrine signaling to promote a protumorigenic tumor microenvironment in breast cancer.

TOX Regulates Growth, DNA Repair, and Genomic Instability in T-cell Acute Lymphoblastic Leukemia


Précis: A transgenic zebrafish screen identified TOX as an oncogenic driver in T-ALL, and TOX was shown to inhibit recruitment of KU70/KU80 to DNA repair sites to suppress NHEJ and promote genomic instability.

A screen of dimeric compounds based on antimalarial heterocycles identified the anticancer compound DQ661, which concurrently inhibited lysosomal catabolism and mTORC1 signaling. DQ661 bound to the lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1), which promotes proteolysis of palmitoylated proteins, and PPT1 inhibition phenocopied DQ661 treatment, resulting in palmitoylated protein accumulation and reduced mTORC1 signaling and lysosomal catabolism. In vivo, DQ661 could be combined with chemotherapy, and it suppressed the growth of melanoma xenografts and mouse colon and pancreatic tumors. The identification of DQ661 demonstrates that inhibitors concurrently targeting both mTORC1 signaling and lysosomal catabolism can suppress tumor growth. For details, please see the article by Rebecca, Nicastri, McLaughlin, and colleagues on page 1266.

ON THE COVER

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