RESEARCH ARTICLES

Oral Mucosal Organoids as a Potential Platform for Personalized Cancer Therapy .................. 852
Précis: Organoids derived from head and neck squamous cell carcinoma (HNSCC) and matching normal tissue allow for the in vitro characterization of the genetics, histology, and drug sensitivity of HNSCC.
See commentary, p. 828

Rational Targeting of Cooperating Layers of the Epigenome Yields Enhanced Therapeutic Efficacy against AML .................... 872
Précis: Analysis of a long-term primary acute myeloid leukemia (AML) ex vivo culture platform shows that combined targeting of enhancers with an LSD1 inhibitor and promoters with 5-azacytidine shows greater efficacy than monotherapy, particularly in TET2-mutant AML.

Targeting Mitochondrial Structure Sensitizes Acute Myeloid Leukemia to Venetoclax Treatment ........... 890
Précis: Depletion of mitochondrial proteins involved in maintenance of mitochondrial function and structure including the chaperonin CLPB is synthetically lethal with venetoclax in acute myeloid leukemia cells.
See commentary, p. 831

IN THIS ISSUE
Highlighted research articles ......................... 813

NEWS IN BRIEF
Important news stories affecting the community .......... 818

NEWS IN DEPTH
Understanding Hyperprogression in Cancer .................. 821
Microbiota Manipulated to Enhance Immunity ............... 822

RESEARCH WATCH
Selected highlights of recent articles of exceptional significance from the cancer literature .............. 823

ONLINE
For more News and Research Watch, visit Cancer Discovery online at http://cancerdiscovery.aacrjournals.org/CDNews.

VIEWS
In The Spotlight
Predictive Potential of Head and Neck Squamous Cell Carcinoma Organoids .................. 828
S.J. Hill and A.D. D’Andrea
See article, p. 852

Mitochondrial Homeostasis in AML and Gasping for Response in Resistance to BCL2 Blockade ...831
M.R. Savona and J.C. Rathmell
See article, p. 890
See article, p. 910

Lymphoma Chemotherapy: Hungry Macrophages Strike the Final Blow ..................... 834
F. Duval and M. De Palma
See article, p. 944

REVIEW
Cellular Plasticity in Cancer ...837
S. Yuan, R.J. Norgard, and B.Z. Stanger

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The TP53 Apoptotic Network Is a Primary Mediator of Resistance to BCL2 Inhibition in AML Cells


Précis: Inactivation of p53 and proapoptotic proteins promotes resistance to venetoclax in acute myeloid leukemia by inducing changes in mitochondrial homeostasis and cellular metabolism.

See commentary, p. 834

A Gain-of-Function p53-Mutant Oncogene Promotes Cell Fate Plasticity and Myeloid Leukemia through the Pluripotency Factor FOXH1


Mechanisms of Lymphoma Clearance Induced by High-Dose Alkylating Agents


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ON THE COVER

Chen, Glytsou, and colleagues performed a genome-wide CRISPR/Cas9 screen for genes whose inactivation would sensitize acute myeloid leukemia (AML) cells to venetoclax and identified regulators of mitochondrial organization and function, including the mitochondrial chaperonin CLPB. CLPB is elevated in AML and maintains mitochondrial cristae structure, whereas its loss promotes apoptosis by inducing cristae remodeling and mitochondrial stress responses. CLPB ablation synergized with venetoclax alone and in combination with azacitidine to inhibit AML growth. In a complementary study, Nechiporuk and colleagues performed a genome-wide CRISPR/Cas9 screen for genes whose inactivation confers venetoclax resistance in AML cells and identified members of the TP53–BAX apoptotic network. p53 and BAX expression were inversely correlated with venetoclax sensitivity in primary AML samples, and loss of p53 and BAX were associated with perturbed mitochondrial homeostasis and inhibition of a general mitochondrial stress response. Venetoclax-resistant TP53-mutant AML cells acquired a dependency on NTRK signaling for survival and were sensitive to TRK inhibitors. Together, these studies provide insights into biological mechanisms underlying responses to venetoclax in AML and suggest potential strategies to overcome venetoclax resistance. For details, please see the article by Chen, Glytsou, and colleagues on page 890 and the article by Nechiporuk and colleagues on page 910. Cover art by Yi Hu.

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