

CANCER DISCOVERY

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ONLINE For more News and Research Watch, visit *Cancer Discovery* online at <http://CDnews.aacrjournals.org>.

VIEWS In The Spotlight

Untangling the Fiber Yarn: Butyrate Feeds Warburg to Suppress Colorectal Cancer 1368

C. Sebastián and R. Mostoslavsky

See article, p. 1387

Mitochondrial One-Carbon Metabolism Maintains Redox Balance during Hypoxia 1371

I. Martínez-Reyes and N.S. Chandel

See article, p. 1406

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M. López-Guerra, S. Xargay-Torrent, and D. Colomer

See article, p. 1448

REVIEW **Universes Collide: Combining Immunotherapy with Targeted Therapy for Cancer** 1377

J.A. Wargo, Z.A. Cooper, and K.T. Flaherty

RESEARCH BRIEFS

A Gnotobiotic Mouse Model Demonstrates That Dietary Fiber Protects against Colorectal Tumorigenesis in a Microbiota- and Butyrate-Dependent Manner 1387

D.R. Donohoe, D. Holley, L.B. Collins, S.A. Montgomery, A.C. Whitmore, A. Hillhouse, K.P. Curry, S.W. Renner, A. Greenwalt, E.P. Ryan, V. Godfrey, M.T. Heise, D.S. Threadgill, A. Han, J.A. Swenberg, D.W. Threadgill, and S.J. Bultman

Précis: Butyrate produced from fiber by bacteria in the colonic lumen preferentially accumulates in colorectal cancer cells, where it acts as an HDAC inhibitor and suppresses tumor growth.

See commentary, p. 1368

Comprehensive Genomic Profiling of Pancreatic Acinar Cell Carcinomas Identifies Recurrent RAF Fusions and Frequent Inactivation of DNA Repair Genes 1398



J. Chmielecki, K.E. Hutchinson, G.M. Frampton, Z.R. Chalmers, A. Johnson, C. Shi, J. Elvin, S.M. Ali, J.S. Ross, O. Basturk, S. Balasubramanian, D. Lipson, R. Yelensky, W. Pao, V.A. Miller, D.S. Klimstra, and P.J. Stephens

Précis: Pancreatic acinar cell carcinoma is characterized by recurrent and potentially actionable genomic alterations, including *BRAF* and *RAF1* fusions and mutually exclusive DNA repair deficiencies.

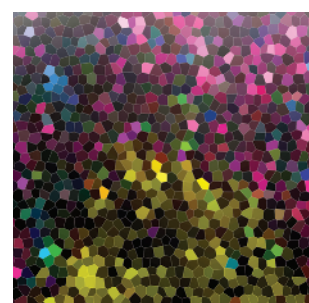
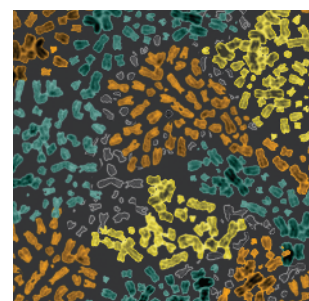
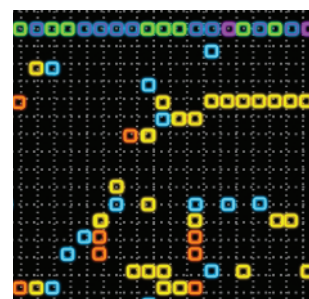
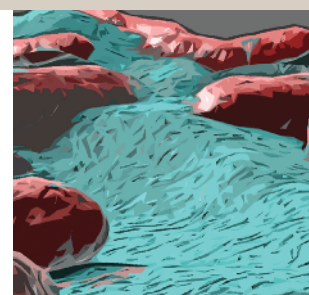
RESEARCH ARTICLES

Serine Catabolism Regulates Mitochondrial Redox Control during Hypoxia 1406

J. Ye, J. Fan, S. Venneti, Y.-W. Wan, B.R. Pawel, J. Zhang, L.W.S. Finley, C. Lu, T. Lindsten, J.R. Cross, G. Qing, Z. Liu, M. Celeste Simon, J.D. Rabinowitz, and C.B. Thompson

Précis: Induction of the serine catabolic enzyme SHMT2 promotes MYC-dependent tumor growth by maintaining redox homeostasis and protecting against hypoxia-induced cell death.

See commentary, p. 1371



Mutation-Specific RAS Oncogenicity Explains NRAS Codon 61 Selection in Melanoma 1418

C.E. Burd, W. Liu, M.V. Huynh, M.A. Waqas, J.E. Gillahan, K.S. Clark, K. Fu, B.L. Martin, W.R. Jeck, G.P. Souroullas, D.B. Darr, D.C. Zedek, M.J. Miley, B.C. Baguley, S.L. Campbell, and N.E. Sharpless

Précis: The codon-specific oncogenicity of mutant NRAS in melanoma may be explained by the increased abundance of active GTP-bound NRAS^{Q61R} compared with NRAS^{G12D}.

PARP1-Driven Poly-ADP-Ribosylation Regulates BRCA1 Function in Homologous Recombination-Mediated DNA Repair 1430

Y. Hu, S.A. Petit, S.B. Ficarro, K.J. Toomire, A. Xie, E. Lim, S.A. Cao, E. Park, M.J. Eck, R. Scully, M. Brown, J.A. Marto, and D.M. Livingston

Précis: PARP1-mediated modification of BRCA1 is required for RAP80-BRCA1-PARP1 complex integrity and fine-tunes double-strand break repair to maintain chromosome stability.

 AC icon indicates Author Choice

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Access to Follicular Dendritic Cells Is a Pivotal Step in Murine Chronic Lymphocytic Leukemia B-cell Activation and Proliferation 1448

K. Heinig, M. Gätjen, M. Grau, V. Stache, I. Anagnostopoulos, K. Gerlach, R.A. Niesner, Z. Cseresnyes, A.E. Hauser, P. Lenz, T. Hehlhans, R. Brink, J. Westermann, B. Dörken, M. Lipp, G. Lenz, A. Rehm, and U.E. Höpken

Précis: CXCR5-CXCL13 signaling promotes trafficking of murine CLL cells to follicular dendritic cell networks in the spleen that enhance tumor cell proliferation and leukemic progression.

See commentary, p. 1374

Acknowledgment to Reviewers 1466

ON THE COVER

Donohoe and colleagues used a gnotobiotic mouse model colonized with bacteria that converts fiber into butyrate to show that a high-fiber diet does protect against colorectal tumorigenesis but that the effect is dependent on butyrate and the composition of the gut microbiota. Butyrate serves as the main mitochondrial energy source for normal colonocytes but accumulates in cancer cells, which are instead dependent on glucose due to increased glycolysis associated with the Warburg effect. Accumulation of butyrate, an endogenous histone deacetylase inhibitor, is associated with increased histone acetylation in colorectal tumors and increased expression of genes with known roles in apoptosis and cell-cycle arrest. These findings indicate that dietary fiber can protect against colorectal cancer and suggest that gut microbiome studies should be integrated with future epidemiologic studies on fiber and colorectal cancer risk. For details, please see the article by Donohoe and colleagues on page 1387.

