

CANCER DISCOVERY CONTENTS

FEBRUARY 2017 ■ VOLUME 7 ■ NUMBER 2

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VIEWS In The Spotlight

JAK Mutations as Escape Mechanisms to Anti-PD-1 Therapy 128

A. Marabelle, S. Aspeslagh, S. Postel-Vinay, and J.-C. Soria

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Epigenomic Inactivation of RasGAPs Activates RAS Signaling in a Subset of Luminal B Breast Cancers 131

R. Sears and J.W. Gray

See article, p. 202

Tuning Chromosomal Instability to Optimize Tumor Fitness 134

M.E. Burkard and B.A. Weaver

See article, p. 218

REVIEW Targeting ALK: Precision Medicine Takes on Drug Resistance 137

J.J. Lin, G.J. Riely, and A.T. Shaw

RESEARCH BRIEFS

Blastic Plasmacytoid Dendritic Cell Neoplasm Is Dependent on BCL2 and Sensitive to Venetoclax 156

J. Montero, J. Stephansky, T. Cai, G.K. Griffin, L. Cabal-Hierro, K. Togami, L.J. Hogdal, I. Galinsky, E.A. Morgan, J.C. Aster, M.S. Davids, N.R. LeBoeuf, R.M. Stone, M. Konopleva, N. Pemmaraju, A. Letai, and A.A. Lane

Précis: The hematologic malignancy blastic plasmacytoid dendritic cell neoplasm is characterized by sensitivity to BCL2 inhibition with venetoclax *in vitro*, in patient-derived xenografts, and in patients with relapsed/refractory disease.

Cellular Senescence Promotes Adverse Effects of Chemotherapy and Cancer Relapse 165



M. Demaria, M.N. O'Leary, J. Chang, L. Shao, S. Liu, F. Alimirah, K. Koenig, C. Le, N. Mitin, A.M. Deal, S. Alston, E.C. Academia, S. Kilmarx, A. Valdovinos, B. Wang, A. de Bruin, B.K. Kennedy, S. Melov, D. Zhou, N.E. Sharpless, H. Muss, and J. Campisi

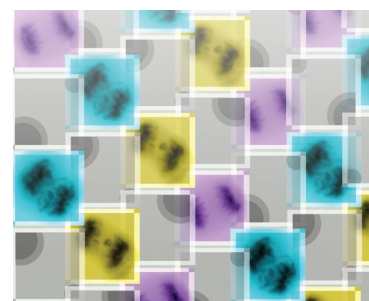
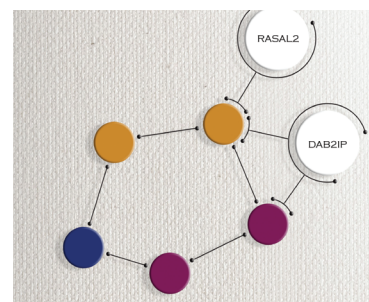
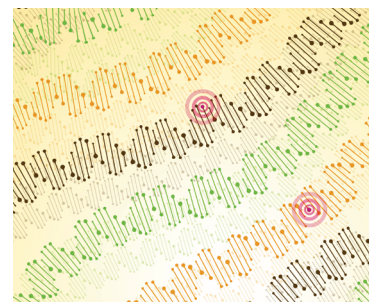
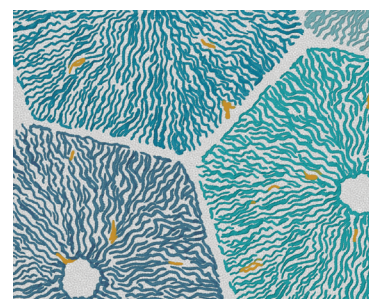
Précis: Chemotherapy-induced senescent noncancerous cells promote therapy-associated side effects, tumor metastasis, and relapse.

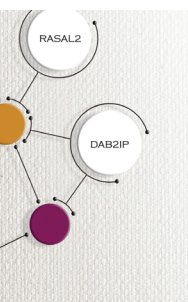
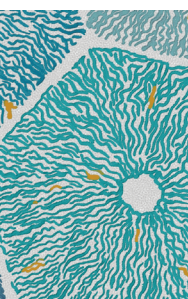
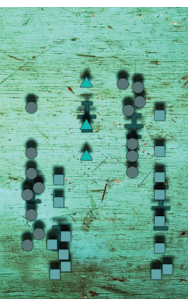
The Rodent Liver Undergoes Weaning-Induced Involution and Supports Breast Cancer Metastasis 177



E.T. Goddard, R.C. Hill, T. Nemkov, A. D'Alessandro, K.C. Hansen, O. Maller, S. Mongoue-Tchokote, M. Mori, A.H. Partridge, V.F. Borges, and P. Schedin

Précis: Weaning-induced liver involution establishes a prometastatic liver micro-environment in rodents, which may explain the increased risk for liver metastasis in patients with postpartum breast cancer.





RESEARCH ARTICLES

Primary Resistance to PD-1 Blockade Mediated by *JAK1/2* Mutations 188



D.S. Shin, J.M. Zaretsky, H. Escuin-Ordinas, A. Garcia-Diaz, S. Hu-Lieskovan, A. Kalbasi, C.S. Grasso, W. Hugo, S. Sandoval, D.Y. Torrejon, N. Palaskas, G. Abril-Rodriguez, G. Parisi, A. Azhdam, B. Chmielowski, G. Cherry, E. Seja, B. Berent-Maoz, I.P. Shintaku, D.T. Le, D.M. Pardoll, L.A. Diaz, Jr, P.C. Tumeh, T.G. Graeber, R.S. Lo, B. Comin-Anduix, and A. Ribas

Précis: Loss-of-function *JAK1/2* mutations induce loss of PD-L1 expression to drive primary resistance to anti-PD-1 therapy.

See commentary, p. 128

Loss of RasGAP Tumor Suppressors Underlies the Aggressive Nature of Luminal B Breast Cancers 202



S.N. Olsen, A. Wronski, Z. Castaño, B. Dake, C. Malone, T. De Raedt, M. Enos, Y.S. DeRose, W. Zhou, S. Guerra, M. Loda, A. Welm, A.H. Partridge, S.S. McAllister, C. Kuperwasser, and K. Cichowski

Précis: Expression of the RasGAPs DAB2IP and RASAL2 is concomitantly lost in a subset of aggressive luminal B breast tumors, promoting invasion and metastasis via activation of RAS and NF- κ B signaling.

See commentary, p. 131



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APC/C Dysfunction Limits Excessive Cancer Chromosomal Instability 218

L. Sansregret, J.O. Patterson, S. Dewhurst, C. López-García, A. Koch, N. McGranahan, W.C.H. Chao, D.J. Barry, A. Rowan, R. Instrell, S. Horswell, M. Way, M. Howell, M.R. Singleton, R.H. Medema, P. Nurse, M. Petronczki, and C. Swanton

Précis: Reduced activity of the APC/C complex induces a mild mitotic delay that reduces segregation errors to allow tumor cells to circumvent the deleterious effects of excessive CIN.

See commentary, p. 134

ON THE COVER

Shin and colleagues performed whole-exome sequencing of pretreatment biopsies from 23 patients with metastatic melanoma and 16 patients with metastatic colon cancer treated with anti-PD-1 therapy and identified a concomitant loss-of-function *JAK1* mutation and amplification of the *JAK* locus in one of the patients with melanoma and a concomitant homozygous truncating *JAK1* mutation and LOH at the *JAK1* locus in one of the patients with colon cancer. Loss-of-function *JAK1/2* mutations abrogated IFN γ -mediated signaling and subsequent upregulation of PD-L1 in patient-derived melanoma cell lines. Analysis of the Cancer Cell Line Encyclopedia and The Cancer Genome Atlas databases revealed that truncating *JAK1/2* mutations occurred in multiple types of cancer and were associated with significantly decreased overall survival in patients with melanoma or breast, prostate, and lung cancers. These findings describe the mechanism by which loss-of-function kinase mutations induce primary resistance to anti-PD-1 therapy. For details, please see the article by Shin and colleagues on page 188.

