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**VIEWS In The Spotlight**

**The Aged Microenvironment of Melanoma Feeds Escape from Targeted Therapy** ..... 1255

E.D. Montal and R.M. White

*See article, p. 1282*

**Epigenetic Awakening of Viral Mimicry in Cancer** ..... 1258

M. Janin and M. Esteller

*See article, p. 1312*

**Loss of RNA-Binding Protein RBMS1 Promotes a Metastatic Transcriptional Program in Colorectal Cancer** ..... 1261

H. Carter

*See article, p. 1410*

**Science in Society**

**Cancer Research: The Lessons to Learn from COVID-19** ..... 1263

C. Bailey, J.R.M. Black, and C. Swanton

**REVIEW** **Toward a New Molecular Taxonomy of Diffuse Large B-cell Lymphoma** ..... 1267

D. Ennishi, E.D. Hsi, C. Steidl, and D.W. Scott

**RESEARCH BRIEF** **Changes in Aged Fibroblast Lipid Metabolism Induce Age-Dependent Melanoma Cell Resistance to Targeted**

**Therapy via the Fatty Acid Transporter FATP2** ..... 1282

G.M. Alicea, V.W. Rebecca, A.R. Goldman, M.E. Fane, S.M. Douglass, R. Behera, M.R. Webster, C.H. Kugel III, B.L. Ecker, M.C. Caino, A.V. Kossenkov, H.-Y. Tang, D.T. Frederick, K.T. Flaherty, X. Xu, Q. Liu, D.I. Gabrilovich, M. Herlyn, I.A. Blair, Z.T. Schug, D.W. Speicher, and A.T. Weeraratna

**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

C. Gstalder, D. Liu, D. Miao, B. Lutterbach, A.L. DeVine, C. Lin, M. Shettigar, P. Panchoi, E.I. Buchbinder, S.L. Carter, M.P. Manos, V. Rojas-Rudilla, R. Brennick, E. Gjini, P.-H. Chen, A. Lako, S. Rodig, C.H. Yoon, G.J. Freeman, D.A. Barbie, F.S. Hodi, W. Miles, E.M. Van Allen, and R. Haq

**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

G. Deblois, S.A. Madani Tonekaboni, G. Grillo, C. Martinez, Y.I. Kao, F. Tai, I. Ettayebi, A.-M. Fortier, P. Savage, A.N. Fedor, X. Liu, P. Guilhamon, E. Lima-Fernandes, A. Murison, H. Kwasne, W. Ba-alawi, D.W. Cescon, C.H. Arrowsmith, D.D. De Carvalho, B. Haibe-Kains, J.W. Locasale, M. Park, and M. Lupien

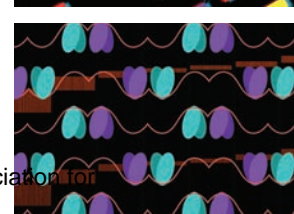
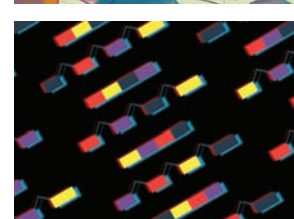
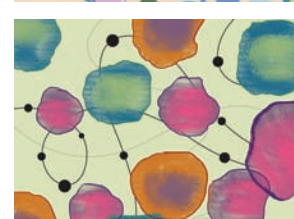
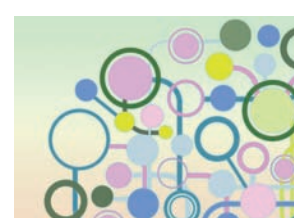
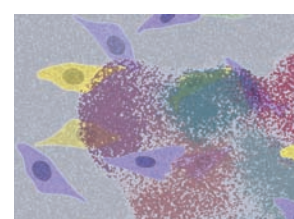
**Précis:** Taxane-resistant triple-negative breast cancer cells had altered methionine metabolism, leading to epigenetic changes at transposable elements and creating a therapeutic vulnerability to EZH2 inhibitors.

*See commentary, p. 1258*

**Single-Cell Analysis Reveals Fibroblast Clusters Linked to Immunotherapy Resistance in Cancer** ..... 1330



Y. Kieffer, H.R. Hocine, G. Gentric, F. Pelon, C. Bernard, B. Bourachot, S. Lameiras,



L. Albergante, C. Bonneau, A. Guyard, K. Tarte, A. Zinovyev, S. Baulande, G. Zalcman, A. Vincent-Salomon, and F. Mechta-Grigoriou

**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

B. Ngo, E. Kim, V. Osorio-Vasquez, S. Doll, S. Bustraan, R.J. Liang, A. Luengo, S.M. Davidson, A. Ali, G.B. Ferraro, G.M. Fischer, R. Eskandari, D.S. Kang, J. Ni, A. Plasger, V.K. Rajasekhar, E.R. Kastenhuber, S. Bacha, R.K. Sriram, B.D. Stein, S.F. Bakhoun, M. Snuderl, P. Cotzia, J.H. Healey, N. Mainolfi, V. Suri, A. Friedman, M. Manfredi, D.M. Sabatini, D.R. Jones, M. Yu, J.J. Zhao, R.K. Jain, K.R. Keshari, M.A. Davies, M.G. Vander Heiden, E. Hernando, M. Mann, L.C. Cantley, and M.E. Pacold

**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

D. Zhao, L. Cai, X. Lu, X. Liang, J. Li, P. Chen, M. Ittmann, X. Shang, S. Jiang, H. Li, C. Meng, I. Flores, J.H. Song, J.W. Horner, Z. Lan, C.-J. Wu, J. Li, Q. Chang, K.-C. Chen, G. Wang, P. Deng, D.J. Spring, Y.A. Wang, and R.A. DePinho

**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

Y. Zhou, C. Han, E. Wang, A.H. Lorch, V. Serafin, B.-K. Cho, B.T. Guttierrez Diaz, J. Calvo, C. Fang, A. Khodadadi-Jamayran, T. Tabaglio, C. Marier, A. Kuchmiy, L. Sun, G. Yacu, S.K. Filip, Q. Jin, Y.-H. Takahashi, D.R. Amici, E.J. Rendleman, R. Rawat, S. Bresolin, M. Paganin, C. Zhang, H. Li, I. Kandela, Y. Politanska, H. Abdala-Valencia, M.L. Mendillo, P. Zhu, B. Palhais, P. Van Vlierberghe, T. Taghon, I. Aifantis, Y.A. Goo, E. Guccione, A. Heguy, A. Tsigirigos, K.B. Wee, R.K. Mishra, F. Pflumio, B. Accordi, G. Basso, and P. Ntziachristos

**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

J. Yu, A. Navickas, H. Asgharian, B. Culbertson, L. Fish, K. Garcia, J.P. Olegario, M. Dermitt, M. Dodel, B. Hänisch, Y. Luo, E.M. Weinberg, R. Dienstmann, R.S. Warren, F.K. Mardakheh, and H. Goodarzi

**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

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#### 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, Gstalder 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<sup>+</sup> 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 Gstalder and colleagues on page 1296.



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