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**REVIEW Response and Resistance to RAS Inhibition in Cancer.....1325**

R.Y. Ebricht, J. Dilly, A.T. Shaw, and A.J. Aguirre

**RESEARCH BRIEF Somatic Uniparental Disomy of PTEN in Endothelial Cells Causes Vascular Malformations in Patients with PTEN Hamartoma Tumor Syndrome.....1350**

S.D. Castillo, X. Perosanz, A.K. Ressler, M. Ivars, J. Rodríguez, C. Rovira, E.M. Nola, J. Llana, J. Grego-Bessa, M. Roldán, R. Arnau, A. Martínez-Romero, I. Barber, M. Bejarano, A. Vicente, V. Celis, H. Salvador, J. Mora, D.A. Marchuk, E. Baselga, and M. Graupera

**Précis:** Vascular anomalies are frequent in patients with PHTS. Loss of the *PTEN* gene in endothelial cells causes PHTS-related vascular malformations, which are reduced by PI3K signaling inhibitors in a novel mouse model as well as in patients.

*See commentary, p. 1306*

**RESEARCH ARTICLES Trends in Cancer Incidence and Mortality Rates in Early-Onset and Older-Onset Age Groups in the United States, 2010–2019.....1363**

M.S. Shiels, A.T. Haque, A. Berrington de González, M.C. Camargo, M.A. Clarke, B.C. Davis Lynn, E.A. Engels, N.D. Freedman, G.L. Gierach, J.N. Hofmann, R.R. Jones, E. Loftfield, R. Sinha, L.M. Morton, and S.J. Chanock

**Précis:** In the U.S., incidence rates of some cancers have increased in 15- to 49-year-olds with concomitant increases in older age groups, suggesting that changes in risk factor prevalence and/or improvements in detection could impact risk across age ranges.

*See commentary, p. 1309*

**Precancerous Cells Initiate Glioblastoma Evolution and Contribute to Intratumoral Heterogeneity.....1377**

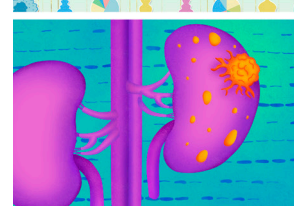
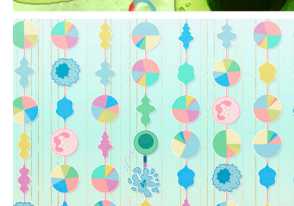
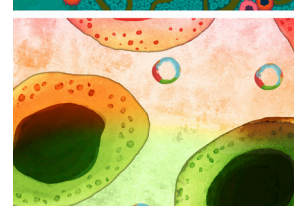
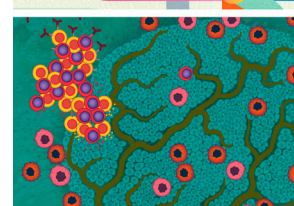
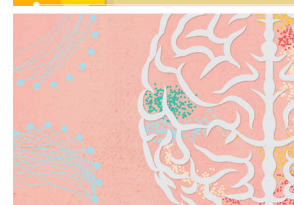
H.J. Kim, K.W. Kim, D.H. Cha, J. Yoo, E.H. Kim, J.H. Chang, S.-G. Kang, J.W. Park, J.H. Kim, Y. Lee, E. Lim, Y. Kim, M.H. Kim, X. Li, J.H. Lee, and J.H. Lee

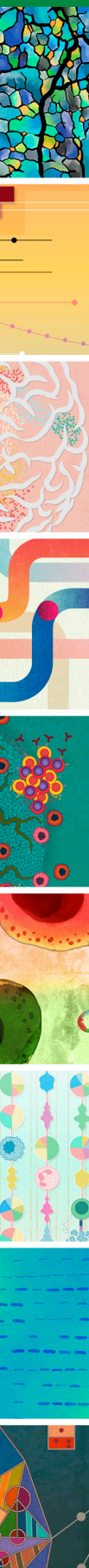
**Précis:** Single-cell analyses of a spontaneous glioblastoma mouse model and tumor-free subventricular zone tissues from patients identify precancerous cells, arising via an oligodendrocyte progenitor lineage, that initiate gliomagenesis and drive intratumoral heterogeneity.

*See commentary, p. 1312*

**Direct Inhibition of RAS Reveals the Features of Oncogenic Signaling Driven by RAS G12 and Q61 Mutations.....1392**

M. Marasco, D. Kumar, S. Garcia Borrego, T. Seale, G. Maddalena, R. Mezzadra, K. Belanger, S. Cole, B. Perez, W. Luan, R. Mukherjee, I. Aricescu, V. Markov, Y. Zhu, S. Arena, A. Bardelli, E. de Stanchina, S.W. Lowe, R.A. Burkhardt, J.W. Zimmerman, R. Yaeger, S.E. Kopetz, N. Rosen, and S. Misale





**Précis:** RAS inhibition reveals how *RAS* mutations dictate oncogenic signaling and response to therapy, suggests codon-specific treatments against multiple cancers, and explains the high frequency of *RAS*<sup>Q61</sup> mutations in EGFR inhibitor-resistant colorectal cancer.

**Activated T Cells Break Tumor Immunosuppression by Macrophage Reeducation.....1410**

R. Trotta, S. Ravis, S. Zhao, M.-P. Orban, S. Trusso Cafarello, I. Charatsidou, J. Pozniak, J. Dehairs, L. Vanheer, C.A. Pulido Vicuna, V. Boecxstaens, O. Bechter, F.M. Bosio, J.V. Swinnen, J.-C. Marine, and M. Mazzone

**Précis:** In human and murine melanomas, HPGDS identifies a subset of immunosuppressive tumor-associated macrophages, whereas HPGDS downregulation through TNF $\alpha$  release by activated CD8<sup>+</sup> T cells signals efficient anti-PD-1 treatment.

**Cytosolic Phospholipase A2 Determines Intercellular Heterogeneity of Stress Granules and Chemotherapy Response.....1437**

A. Redding, G. Fonteneau, S. Heinrich, M.M. Gaida, and E. Grabocka

**Précis:** Phospholipase signaling drives stress granule formation in a cell cycle-dependent manner, generating tumor cell sensitivity to phospholipase inhibition in combination with G2-stalling chemotherapeutics in orthotopic models of pancreatic ductal adenocarcinoma.

**HPV16-Expressing Tumors Release Multiple IL1 Ligands to Orchestrate Systemic Immunosuppression Whose Disruption Enables Efficacy of a Therapeutic Vaccine.....1458**

M. Lecointre, J. Guillot, R. Marcone, D. Ozdoganlar, M. Cayatte, E. Jaensson Gyllenbäck, D. Liberg, N. Fournier, K. Homicsko, and D. Hanahan

**Précis:** IL1RAP blockade reverses IL1-induced systemic immunosuppression in HPV16<sup>+</sup> cancers, enabling efficacy of a therapeutic vaccine, and survival benefit is further enhanced in combination with anti-CTLA4 in a preclinical model.

**Requirement for Cyclin D1 Underlies Cell-Autonomous HIF2 Dependence in Kidney Cancer.....1484**

N.H. Shirole, D. Kesar, Y. Lee, A. Goodale, S. Syamala, S. Kukreja, R. Li, X. Qiu, W. Yu, S. Goldman, P. Cejas, H.W. Long, K. Adelman, J.G. Doench, W.R. Sellers, and W.G. Kaelin Jr

**Précis:** The cell-intrinsic antiproliferative effects of HIF2 inhibitors in kidney cancer are caused by loss of cyclin D1 activity, and upregulation of cyclin D2 or D3 are potential resistance mechanisms.

**ROR $\gamma$  Bridges Cancer-Driven Lipid Dysmetabolism and Myeloid Immunosuppression.....1505**

A. Bleve, M. Incerti, F.M. Consonni, V. Garlatti, G. Ballerini, C. Pandolfo, M.N. Monari, S. Serio, D. Pistillo, M. Sironi, C. Ali, M. Manfredi, E. Barberis, G. Finocchiaro, M.A. Cassatella, C. Panico, G. Condorelli, and A. Sica

**Précis:** Tumor-related IL6/IL1 $\beta$ -dependent induction of hepatic PCSK9 downregulates hepatic LDL receptor (LDLR) expression, activating ROR $\gamma$ -dependent expansion of suppressive protumor myeloid populations and favoring tumor progression.

**ON THE COVER** Stress granules (SG) are non-membranous organelles that comprise assemblies of RNA and protein which form under cellular stress and promote cell survival. In exploring the mechanisms that govern the dynamics of SG formation in cancer cells, Redding and colleagues found that pancreatic cancer cells exhibited an unexpectedly high degree of cell-to-cell heterogeneity in SG levels in response to various stress stimuli. Fluctuation in cellular SG levels corresponded to changes in cell cycle, with SG formation peaking during G2 phase. Comparison of G2-phase synchronized versus asynchronous pancreatic cancer cells highlighted the upregulation during G2 phase of the lipid molecule 15-deoxy-delta-12,14-prostaglandin J2 (15d-PGJ2), which is a known positive regulator of SG formation. Mechanistically, the cell-cycle dependent upregulation of 15d-PGJ2 was due to the enhanced activity of the calcium-dependent phospholipase A2 (cPLA2) during G2, which was highest during G2 but otherwise cleaved by caspase-3 activity during G1 and S phases. The relationship between G2 and SG formation was confirmed in orthotopic mouse models of pancreatic cancer, and, notably, pharmacologic inhibition of cPLA2 sensitized orthotopic pancreatic tumors to oxaliplatin, a G2-arrest-inducing chemotherapy. Thus, this study highlights the interplay between cell-cycle and SG formation that gives rise to pancreatic tumor cell heterogeneity and proposes a potential strategy for pancreatic cancer treatment. For more information, see the article by Redding and colleagues on page 1437. Artwork by Bianca Dunn.

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