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Précis: Tumor initiation, via either chemical mutagens or genetic models of Ras activation, produces long-lived, but latent, mutated cells that require chronic tumor promoter exposure to form cancers.

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Antitumor Activity of Vebreltinib and Characterization of Clinicogenomic Features in Solid Tumors with MET Rearrangements.....1129

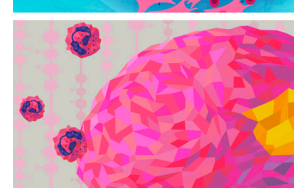
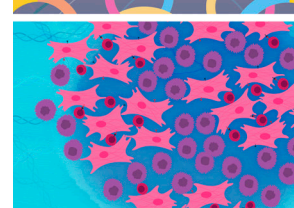
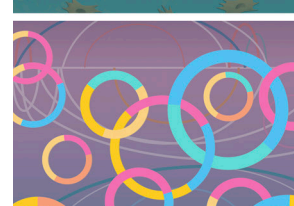
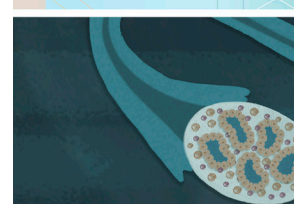
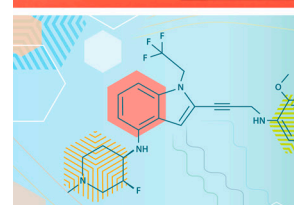
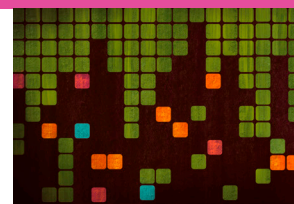
S. Nakazawa, F. Pecci, I. Odintsov, D. Gazgalis, F.H. Gottlieb, B. Ricciuti, L. Zullo, J.V. Alessi, A. Di Federico, M. Aldea, E. Garbo, M.M. Gandhi, A. Saini, W.W. Feng, J. Jiang, S. Baldacci, F. Facchinetti, M. Makarem, M.-A. Locquet, K. Haratani, D. Haradon, B. Besse, A. Italiano, J. Remon, P. Lavaud, D. Vasseur, D. Planchard, Y. Sato, Y. Watanabe, S. Owen, A.B. Cortot, H. Mahran, M.D. Forster, J. Niu, P. Tomasini, S.S. Leong, K. Tay, E. Esteban, A. Minchom, S.H. Kizilbash, M. Cruz-Correa, K.-H.P. Yu, X. Zhang, P. Chen, M. Sangem, J. Che, L.M. Sholl, P.A. Jänne, and M.M. Awad

Précis: MET rearrangements were detected in 0.04% of solid tumors, with a phase II trial showing a 50% response rate and a 79% disease control rate to vebreltinib, confirming MET rearrangements as actionable targets across cancers.

RESEARCH ARTICLES **Pan-Cancer Analysis of Oncogenic MET Fusions Reveals Distinct Pathogenomic Subsets with Differential Sensitivity to MET-Targeted Therapy.....1141**

C.A. Febres-Aldana, M. Vojnic, I. Odintsov, T. Zhang, R. Cheng, C.Z. Beach, D. Lu, M.S. Mattar, A.M. Gazzo, L. Gili, M. Harshan, A. Ameri, S. Machnicki, X. Xiao, W.W. Lockwood, X.-y. Zhou, Q. Yao, A. Drilon, N. Rekhtman, N. Shah, A. Li, Z. Liu, S.-R. Yang, M.A. Davare, M. Ladanyi, and R. Somwar

Précis: MET fusions with homodimerizing partners are highly sensitive to MET inhibition and exhibit unique fusion etiopathogenesis and pathobiological properties, underscoring the importance of fusion curation for targeted therapy eligibility.



Restoration of the Tumor Suppressor Function of Y220C-Mutant p53 by Rezatapo, a Small-Molecule Reactivator.....1159

A.M. Puzio-Kuter, L. Xu, M.K. McBrayer, R. Dominique, H.H. Li, B.J. Fahr, A.M. Brown, A.E. Wiebesiek, B.M. Russo, C.L. Mulligan, H. Yang, J. Battaglia, K.A. Robell, D.H. Thomas, K.-S. Huang, A. Solovoyov, B.D. Greenbaum, J.D. Oliner, T.W. Davis, M.L. Dumble, M.L. Johnson, S. Xiong, P. Yang, G. Lozano, M.M. Fellous, B.T. Vu, A.M. Schram, A.J. Levine, and M.V. Poyurovsky

Précis: Rezatapo restores tumor suppressor function to p53^{Y220C} by correcting its conformation, reactivating transcriptional programs, and inducing antitumor effects in preclinical models and ongoing clinical trials.

Multimodal Spatial Profiling Reveals Immune Suppression and Microenvironment Remodeling in Fallopian Tube Precursors to High-Grade Serous Ovarian Carcinoma.....1180

T. Kader, J.-R. Lin, C.B. Hug, S. Coy, Y.-A. Chen, I. de Bruijn, N. Shih, E. Jung, R.J. Pelletier, M. Lopez Leon, G. Mingo, D.K. Omran, J.S. Lee, C. Yapp, B.A. Satravada, R. Kundra, Y. Xu, S. Chan, J.B. Tefft, J.L. Muhlich, S.H. Kim, S.M. Gysler, J. Agudo, J.R. Heath, N. Schultz, C.W. Drescher, P.K. Sorger, R. Drapkin, and S. Santagata

Précis: The microenvironment of ovarian cancer precursors within the fallopian tube epithelium progressively shifts from immune surveillance to immunosuppression during the progression from precancer to high-grade serous ovarian cancer.

See commentary, p. 1093

Aged and BRCA-Mutated Stromal Cells Drive Epithelial Cell Transformation.....1203

G.L. Garcia, T. Orellana, G. Gorecki, L. Frisbie, R. Baruwai, S. Suresh, E. Goldfeld, I. Beddows, I.P. MacFawn, A.K. Britt, M.M. Hale, A.T. Elhaw, B.R. Isett, N. Hempel, R. Bao, H. Shen, R.J. Buckanovich, T. Finkel, R. Drapkin, T.R. Soong, T.C. Bruno, H.I. Atiya, and L.G. Coffman

Précis: Mesenchymal stem cells utilize the JNK/c-JUN/WT1 axis to generate lipid aldehydes, which induce epithelial DNA damage, mutation, and oncogenesis.

See commentary, p. 1093

Spatial-Temporal Diversity of Extrachromosomal DNA Shapes Urothelial Carcinoma Evolution and the Tumor Immune Microenvironment.....1225

W. Lv, Y. Zeng, C. Li, Y. Liang, H. Tao, Y. Zhu, X. Sui, Y. Li, S. Jiang, Q. Gao, E. Rodriguez-Fos, G. Prasad, Y. Wang, R. Zhou, Z. Xu, X. Pan, L. Chen, X. Xiang, H. Teng, C. Sun, T. Qin, W. Dong, Y. Li, X. Lan, X. Li, L. Lin, L. Bolund, H. Yang, R.G.W. Verhaak, B.M. Faltas, J.B. Hansen, S. Wu, P.S. Mischel, A.G. Henssen, V. Bafna, J. Luebeck, B. Regenberg, Y. Luo, C. Lin, and P. Han

Précis: This study reveals the crucial role of ecDNA in driving urothelial carcinoma evolution, heterogeneity, and early tumorigenesis, while also elucidating associated immune evasion mechanisms that offer insights for targeted therapies.

Cancer-Associated Fibroblasts Serve as Decoys to Suppress NK Cell Anticancer Cytotoxicity in Breast Cancer.....1247

A. Ben-Shmuel, Y. Gruper, C. Halperin, O. Levi-Galibov, H. Rosenberg-Fogler, D. Barki, G. Carradori, Y. Stein, G. Yagel, M. Naumova, S. Mayer, M. Dadiani, D. Morzaev-Sulzbach, O. Golani, R. Nevo, Z. Porat, E. Nili Gal-Yam, and R. Scherz-Shouval

Précis: Cancer-associated fibroblasts are targeted and killed by NK cells through upregulation of ligands for NK cell receptors, resulting in reduced expression of surface activating receptors on NK cells and suppression of NK cell killing of cancer cells.

See commentary, p. 1096

Functional Reprogramming of Neutrophils within the Brain Tumor Microenvironment by Hypoxia-Driven Histone Lactylation.....1270

A. Ugolini, A. De Leo, X. Yu, F. Scirocchi, X. Liu, B. Peixoto, D. Scocozza, A. Pace, M. Perego, A. Gardini, L. D'Angelo, J.K.C. Liu, A.B. Etame, A. Rughetti, M. Nuti, A. Santoro, M.A. Vogelbaum, J.R. Conejo-Garcia, P.C. Rodriguez, and F. Veglia

Précis: Hypoxia induces lactate production in neutrophils, leading to increased histone lactylation, and targeting this lactylation counteracts neutrophil-induced immunosuppression within glioblastoma tumors.

Correction

Editor's Note: Small-Molecule Inhibition of the Acyl-Lysine Reader ENL as a Strategy against Acute Myeloid Leukemia.....1297

ON THE COVER

Seminal studies in mouse skin tumor models, performed over seven decades ago, laid the foundation for the field's conceptualization of tumorigenesis as a two-step process, in which an initiating mutational event poises a tissue for transformation and a subsequent tumor-promoting event, involving proliferation and inflammation, is required for malignant tumorigenesis. While these classical models of tumorigenesis, in which mice receive an initiating dose of a chemical carcinogen, followed by promotional tissue damage, continue to be widely used in research, the molecular mechanisms that underpin the mutational dynamics following the initiating event and the subsequent contribution of tumor-promoting processes to eventual tumor development remain incompletely understood. To shed light on these points, Li and colleagues studied variations of mouse skin tumor models, exposing mice to initiating events, via standard chemical carcinogens or an oncogenic mutation, and providing subsequent tumor-promotional events, in the form of tumor-promoting chemical damage or a range of clinically relevant risk factors such as obesity. These experiments demonstrated that cells carrying thousands of initiating event-induced mutations persist for long periods and only give rise to tumors in the context of a tumor-promoting event. These findings highlight the importance of understanding promotional risk factors in the context of cancer prevention and interception. For more information, see the article by Li and colleagues on page 1115. Artwork by Bianca Dunn.

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