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These findings suggest that p53-deficient cancer cells activate the mevalonate pathway via SREBP2 and promote the synthesis of ubiquinone that plays an essential role in reducing oxidative stress and supports the synthesis of pyrimidine nucleotide.

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204 **Twist1-Induced Epithelial Dissemination Requires Prkd1 Signaling**

Dan Georgess, Veena Padmanaban, Orit Katarina Sirka, Kester Coutinho, Alex Choi, Gabriela Frid, Neil M. Neumann, Takanari Inoue, and Andrew J. Ewald

Twist1 is a known regulator of metastatic cell behaviors but not directly targetable. This study provides a molecular explanation for how Twist1-induced dissemination works and demonstrates that it can be targeted.

219 **RNA-Binding Protein *ZFP36L1* Suppresses Hypoxia and Cell-Cycle Signaling**

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Aereas Aung, Vardhman Kumar, Jomkuan Theprungsirikul, Shruti K. Davey, and Shyni Varghese

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276 **Epigenetic *SMAD3* Repression in Tumor-Associated Fibroblasts Impairs Fibrosis and Response to the Antifibrotic Drug Nintedanib in Lung Squamous Cell Carcinoma**

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This study implicates the selective epigenetic repression of *SMAD3* in SCC-TAFs in the clinical failure of nintedanib in SCC and supports that patients with ADC may benefit from antifibrotic drugs targeting stromal TGFβ1/SMAD3.

291 **The Interaction of Platelets with Colorectal Cancer Cells Inhibits Tumor Growth but Promotes Metastasis**

Léa Plantureux, Diane Mège, Lydie Crescence, Estelle Carminita, Stéphane Robert, Sylvie Cointe, Nicolas Brouilly, Walid Ezzedine, Françoise Dignat-George, Christophe Dubois, and Laurence Panicot-Dubois

Tumor cell interaction with platelets produces chimeric extracellular vesicles that suppress primary tumor growth by activating tumor-eliminating macrophages, while promoting metastasis through EMT and endothelial activation.

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Tony Navas, Robert J. Kinders, Scott M. Lawrence, Katherine V. Ferry-Galow, Suzanne Borgel, Melinda G. Hollingshead, Apurva K. Srivastava, Sergio Y. Alcoser, Hala R. Makhlouf, Rodrigo Chuaqui, Deborah F. Wilsker, Mariam M. Konaté, Sarah B. Miller, Andrea Regier Voth, Li Chen, Tomas Vilimas, Jyothi Subramanian, Lawrence Rubinstein, Shivaani Kummar, Alice P. Chen, Donald P. Bottaro, James H. Doroshow, and Ralph E. Parchment

Despite the role of EMT in metastasis and drug resistance, no standardized assessment of EMT phenotypic heterogeneity in human carcinomas exists; the EMT-IFA allows for clinical monitoring of tumor adaptation to therapy.

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AC Yuan-Yuan Qu, Rui Zhao, Hai-Liang Zhang, Qian Zhou, Fu-Jiang Xu, Xuan Zhang, Wen-Hao Xu, Ning Shao, Shu-Xian Zhou, Bo Dai, Yao Zhu, Guo-Hai Shi, Yi-Jun Shen, Yi-Ping Zhu, Cheng-Tao Han, Kun Chang, Yan Lin, Wei-Dong Zang, Wei Xu, Ding-Wei Ye, Shi-Min Zhao, and Jian-Yuan Zhao

These findings uncover molecular mechanisms underlying lipid accumulation in ccRCC, suggesting the AMPK–GATA3–ECHS1 pathway as a potential therapeutic target and prognostic biomarker.

334 **CoA Synthase (*COASY*) Mediates Radiation Resistance via PI3K Signaling in Rectal Cancer**

Sylvain Ferrandon, Jennifer DeVecchio, Leonardo Duraes, Hanumant Chouhan, Georgios Karagkounis, Jacqueline Davenport, Matthew Orloff, David Liska, and Matthew F. Kalady

COASY is a novel radiotherapy response modulator in rectal cancer that regulates PI3K activation and DNA repair. Furthermore, COASY levels directly correlate with radiation response and serve as a predictive biomarker.

POPULATION AND PREVENTION SCIENCE

347 **Penetrance Estimates Over Time to First and Second Primary Cancer Diagnosis in Families with Li-Fraumeni Syndrome: A Single Institution Perspective**

Seung Jun Shin, Elissa B. Dodd-Eaton, Fan Gao, Jasmina Bojadzieva, Jingxiao Chen, Xianhua Kong, Christopher I. Amos, Jing Ning, Louise C. Strong, and Wenyi Wang

These findings present an open-source R package LFSPRO that could be used for genetic counseling and health management of individuals with LFS as it estimates the risk of both first and second primary cancer diagnosis.

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354 **Penetrance of Different Cancer Types in Families with Li-Fraumeni Syndrome: A Validation Study Using Multicenter Cohorts**

Seung Jun Shin, Elissa B. Dodd-Eaton, Gang Peng, Jasmina Bojadzieva, Jingxiao Chen, Christopher I. Amos, Megan N. Frone, Payal P. Khincha, Phuong L. Mai, Sharon A. Savage, Mandy L. Ballinger, David M. Thomas, Ying Yuan, Louise C. Strong, and Wenyi Wang

These findings provide specific penetrance estimates for LFS-associated cancers, which will likely impact the management of families at high risk of LFS.

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CORRECTIONS

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362 **Correction: Targeting of PYK2 Synergizes with EGFR Antagonists in Basal-like TNBC and Circumvents HER3-Associated Resistance via the NEDD4–NDRG1 Axis**

Nandini Verma, Anna-Katharina Müller, Charu Kothari, Effrosini Panayotopoulou, Amir Kedan, Michael Selitrennik, Gordon B. Mills, Lan K. Nguyen, Sungyoung Shin, Thomas Karn, Uwe Holtrich, and Sima Lev

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Marie Bénéteau, Sophie Daburon, Jean-François Moreau, Jean-Luc Taupin, and Patrick Legembre

364 **Editor's Note: p38 Mitogen-activated Protein Kinase Pathway Suppresses Cell Survival by Inducing Dephosphorylation of Mitogen-activated Protein/Extracellular Signal-regulated Kinase Kinase1,2**

Song-Ping Li, Melissa R. Junttila, Jiahuai Han, Veli-Matti Kähäri, and Jukka Westermarck

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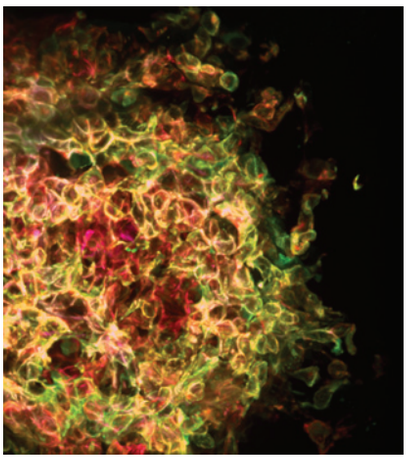

The transcription factor Twist1 is known to promote breast cancer invasion and metastasis, but the molecular changes controlled by Twist1 during these processes remain elusive. Georgess and colleagues used organotypic culture combined with RNA-sequencing and functional assays to identify of Prkd1 as a direct and druggable transcriptional target of Twist1. Prkd1 kinase activity is required for dissemination as it downregulates cell-cell adhesion and drives matrix-directed invasion and persistent migration. Prkd1 expression correlates with increased metastatic burden in breast cancer patients and is required for efficient metastasis in a mouse model for basal breast cancer. For details, see the article by Georgess and colleagues on page 204.

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