# Cancer Research
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**TUMOR AND STEM CELL BIOLOGY**

**6144** The Blebbishield Emergency Program Overrides Chromosomal Instability and Phagocytosis Checkpoints in Cancer Stem Cells
Goodwin G. Jinesh and Ashish M. Kamat

Précis: These findings demonstrate how cancer stem cells utilize apoptosis to evade genomic instability and immune phagocytosis checkpoints to ultimately drive cellular transformation.

**6157** Retention of Interstitial Genes between TMPRSS2 and ERG Is Associated with Low-Risk Prostate Cancer
Stephen J. Murphy, Farhad Kosari, R. Jeffrey Karnes, Aqsa Nasir, Sarah H. Johnson, Athanasios G. Gaitatzes, James B. Smadbeck, Laureano J. Rangel, George Vasmatzis, and John C. Cheville

Précis: Newly characterized TMPRSS2-ERG fusions serve as molecular markers of risk in prostate cancer whose utilization could greatly improve patient management.

**6168** miR-130a Deregulates PTEN and Stimulates Tumor Growth
Huijun Wei, Ri Cui, Julian Bahr, Nicola Zanesi, Zhenghua Luo, Wei Meng, Guang Liang, and Carlo M. Croce

Précis: Cell death signaling studies in a H-Ras–dependent model system reveal an oncogenic microRNA with potential utility as a theranostic marker in multiple cancers.

**6179** Mechano-Signal Transduction in Mesenchymal Stem Cells Induces Prosaposin Secretion to Drive the Proliferation of Breast Cancer Cells
Seiichiro Ishihara, David R. Inman, Wan-Ju Li, Suzanne M. Ponik, and Patricia J. Keely

Précis: Noncancerous and multipotent cells found in the tumor microenvironment regulate tumor growth and inhibit metastasis via secretion of prosaposin in response to matrix stiffness.

**6190** Histone Acetyltransferase KAT6A Upregulates PI3K/AKT Signaling through TRIM24 Binding
Deguan Lv, Feng Jia, Yanli Hou, Youzhou Song, Angel A. Alvarez, Weiwei Zhang, Wei-Qiang Gao, Bo Hu, Shi-Yuan Cheng, Jianwei Ge, Yanxin Li, and Haizhong Feng

Précis: These findings identify a specific chromatin acetylation event in the PI3K genetic locus as a critical event in the development of deadly gliomas.

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

**6202** Mitochondrial Genomic Backgrounds Affect Nuclear DNA Methylation and Gene Expression
Carolyn J. Vivian, Amanda E. Brinker, Stefan Graw, Devin C. Koestler, Christophe Legendre, Gerald C. Gooden, Bodour Salhia, and Danny R. Welch

Précis: These striking results suggest that mitochondrial DNA polymorphisms can selectively alter DNA methylation and gene expression patterns in the nuclear genome.

**6215** FGF19 Protects Hepatocellular Carcinoma Cells against Endoplasmic Reticulum Stress via Activation of FGFR4–GSK3β–Nrf2 Signaling
Yong Teng, Huakan Zhao, Lixia Gao, Wenfa Zhang, Austin Y. Shull, and Chloe Shay

Précis: These findings show how a member of the fibroblast growth factor provides a cytoprotective role against endoplasmic reticulum stress in liver cancer, with potential implications for therapeutic management of this disease.

**6226** Skp2-Mediated Stabilization of MTH1 Promotes Survival of Melanoma Cells upon Oxidative Stress
Jia Yu Wang, Guang Zhi Liu, James S. Wilmott, Ting La, Yu Chen Feng, Hamed Yari, Xu Guan Yan, Rick F. Thorne, Richard A. Scolyer, Xu Dong Zhang, and Lei Jin

Précis: These findings identify a critical regulatory pathway for upregulation of a pathway that helps protect dNTP pools in cancer cells from oxidative damage, with potential implications for improving cancer therapeutic targeting.
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**6365**  PD-1 Expression in Head and Neck Squamous Cell Carcinomas Derives Primarily from Functionally Anergic CD4\(^+\) TILs in the Presence of PD-L1\(^+\) TAMs  
**Précis:** These results point to the importance of CD4\(^+\) T helper cells as pivotal regulators of PD-L1 levels in determining the response of a common type of head and neck cancers to PD1 immune checkpoint therapy.

**6375**  CD155/TIGIT Signaling Regulates CD8\(^+\) T-cell Metabolism and Promotes Tumor Progression in Human Gastric Cancer  
Weiling He, Hui Zhang, Fei Han, Xinlin Chen, Run Lin, Wei Wang, Haibo Qiu, Zhenhong Zhuang, Qi Liao, Weijing Zhang, Qinbo Cai, Yongmei Cui, Wenting Jiang, Han Wang, and Zunfu Ke  
**Précis:** Gastric cancer cells negatively regulate CD8 T-cell metabolism and induce functional exhaustion of CD8 T cells via the CD155/TIGIT interaction in the tumor microenvironment.

**6389**  Localized Synchrotron Irradiation of Mouse Skin Induces Persistent Systemic Genotoxic and Immune Responses  
Jessica Venturra, Pavel N. Lobachevsky, Jason S. Palazzolo, Helen Forrester, Nicole M. Haynes, Alecia Yashkevich, Andrew W. Stevenson, Christopher J. Hall, Andreas Ntargaras, Vasilis Kotsarios, Gerasimos Ch. Pollakis, Gianna Potsi, Konstantinos Skordilis, Georgia Terzoudi, Ioannis S. Pateras, Vasilis G. Gorgoulis, Alexandros G. Georgakilas, Carl N. Sprung, and Olga A. Martin  
**Précis:** Brief low-dose exposures or ablative doses of radiation induce persistent biological effects in off-target tissues.

**6400**  Inflammatory Monocytes Promote Perineural Invasion via CCL2-Mediated Recruitment and Cathepsin B Expression  
**Précis:** These findings show how subversion of a nerve repair program mediates pathogenesis of peripheral nerve invasion by tumors, an ominous sign of poor prognosis, and suggest new targeted strategies to prevent or reverse this process.

**6415**  Survival Outcomes in Cancer Patients Predicted by a Partial EMT Gene Expression Scoring Metric  
Jason T. George, Mohit Kumar Jolly, Shengnan Xu, Jason A. Somarelli, and Herbert Levine  
**Précis:** This study highlights a valuable gene signature tool that may help illuminate malignant progression and clinical outcomes.

**6429**  Multiscale Modeling of Inflammation-Induced Tumorigenesis Reveals Competing Oncogenic and Oncoprotective Roles for Inflammation  
Yucheng Guo, Qing Nie, Adam L. MacLean, Yanda Li, Jinzhi Lei, and Shao Li  
**Précis:** These findings explore the evolutionary dynamics of tumorigenesis from pathway mutation to abnormal population dynamics.

**6442**  In Silico Modeling of Immunotherapy and Stroma-Targeting Therapies in Human Colorectal Cancer  
Jakob Nikolas Kather, Jan Poleszczuk, Meggy Suarez-Carmona, Johannes Krisam, Pornpimol Charoentong, Nektarios A. Valous, Cleo-Aron Wei, Luca Tavernar, Florian Leiss, Esther Herpel, Fee Klupp, Alexis Ulrich, Martin Schneider, Alexander Marx, Dirk Jager, and Niels Halama  
**Précis:** This study provides sound guidance for designing effective clinical immunotherapy for colorectal cancer, in showing the importance of targeting the stroma along with activating the adaptive immune system.

**6453**  Mitosis-Mediated Intravasation in a Tissue-Engineered Tumor–Microvessel Platform  
Andrew D. Wong and Peter C. Searson  
**Précis:** Direct observation of intravasation provides a framework for understanding the physical and biological factors involved in mediating this process.

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### INTEGRATED SYSTEMS AND TECHNOLOGIES

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Type II Diabetes and Incidence of Estrogen Receptor Negative Breast Cancer in African American Women

Julie R. Palmer, Nelys Castro-Webb, Kimberly Bertrand, Traci N. Bethea, and Gerald V. Denis

Précis: Analysis of a large cohort study reveals that African American women with type 2 diabetes have a 40% increased incidence of ER-negative breast cancer independent of obesity as a risk factor.

Correction: Breast Tumor Kinase Phosphorylates p190RhoGAP to Regulate Rho and Ras and Promote Breast Carcinoma Growth, Migration, and Invasion

ABOUT THE COVER

Apoptotic cells are known to get engulfed by immune cells. However, apoptotic cancer stem cells that resurrect by reconstructing themselves from apoptotic bodies (called blebbishields; red fluorescence) evade phagocytosis by immune cells (green fluorescence) through blebbishield-immune cell fusion to generate hybrid cells (termed PBSHMS cells; cover image was imaged at 1 week after fusion). PBSHMS cells exhibit chromosomal instability and are capable of tumorigenesis, and metastasis in nude mice demonstrates that these hybrids are not the product of phagocytosis. For details, see article by Jinesh and Kamat on page 6144.