## BREAKING ADVANCES

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## REVIEWS

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## INTEGRATED SYSTEMS AND TECHNOLOGIES

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## MICROENVIRONMENT AND IMMUNOLOGY

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Identification of Two Distinct Carcinoma-Associated Fibroblast Subtypes with Differential Tumor-Promoting Abilities in Oral Squamous Cell Carcinoma

Daniela Elena Costea, Allison Hills, Amani H. Osman, Johanna Thurlow, Gabriela Kalma, Xiaohong Huang, Claudia Pena Murillo, Himalaya Parajuli, Salwa Suliman, Keerthi K. Kulasekara, Anne Chr. Johannessen, and Max Partridge

Precis: Cancer-associated fibroblasts sustain the tumor microenvironment, and unraveling their heterogeneity may point to targetable weaknesses.

Myeloid Cell Receptor LRP1/CD91 Regulates Monocyte Recruitment and Angiogenesis in Tumors

Nicole D. Staudt, Minji Jo, Jingjing Hu, Jeanne M. Bristow, Donald P. Pizzo, Alban Gaultier, Scott R. VandenBerg, and Steven L. Gonias

Precis: A signaling system that controls recruitment of tumor-associated macrophages may have a very important role in determining the amount of VEGF that is secreted into the tumor microenvironment.

miR-124 Inhibits STAT3 Signaling to Enhance T Cell–Mediated Immune Clearance of Glioma

Jun Wei, Fei Wang, Ling-Yuan Kong, Shao Xu, Tiffany Doucette, Scott R. VandenBerg, and Steven L. Gonias

Precis: This study highlights approaches to plumb the untapped potential of microRNA in generalized immunotherapeutic strategies to treat cancer.

Dynamic Mast Cell–Stromal Cell Interactions Promote Growth of Pancreatic Cancer

Ying Ma, Rosa F. Hwang, Craig D. Logsdon, and Stephen E. Ullrich

Precis: Mast cells are being ascribed unexpected but important roles in the cancer microenvironment, increasing interest in targeting them for therapeutic purposes.

Membrane versus Soluble Isoforms of TNF-α Exert Opposing Effects on Tumor Growth and Survival of Tumor-Associated Myeloid Cells

Shidrokh Ardestani, Bin Li, Desiree L. Deskins, Huiyun Wu, Pierre P. Massion, and Pampee P. Young

Precis: Controversies about the role of TNF-α in cancer progression may be explained by the findings from this study, which offer a basis to understand its contradictory effects on tumor progression.

SENP1 deSUMOylates and Regulates Pin1 Protein Activity and Cellular Function

Chun-Hau Chen, Che-Chang Chang, Tae Ho Lee, ManLi Luo, Pengyu Huang, Pei-Hsin Liao, Shao Wei, Fu-An Li, Ruey-Hwa Chen, Xiao Zhen Zhou, Hsiu-Ming Shih, and Kun Ping Lu

Precis: Unraveling Pin1 regulation may improve strategies to attack cancer, given that Pin1 controls the function of numerous oncogenes and tumor suppressor genes.

Endothelial Cell Protein C Receptor Opposes Mesothelioma Growth Driven by Tissue Factor

Shiva Keshava, Sanghamitra Sahoo, Torry A. Tucker, Steven Idell, L. Vijaya Mohan Rao, and Usha R. Pendurthi

Precis: This study enhances our understanding of how the procoagulant protein tissue factor drives the growth of many human cancers.

Mitogenic Insulin Receptor-A Is Overexpressed in Human Hepatocellular Carcinoma due to EGFR-Mediated Dysregulation of RNA Splicing Factors

Hamza Chettouh, Laetitia Cartoux, Lynda Aoudjehane, Dominique Wendum, Audrey Clapéron, Yves Chrétien, Colette Rey, Olivier Scatton, Olivier Soubran, Filomena Conti, Françoise Praz, Chantal Housset, Olivier Rosmorduc, and Christèle Desbois-Mouthon

Precis: Increased expression of a specific insulin receptor isoform may mediate adverse effects of hyperinsulinemia on liver cancer development.

Dysregulated Expression of FOXM1 Isoforms Drives Progression of Pancreatic Cancer

Xiangyu Kong, Lei Li, Zhaoshen Li, Xiangdong Le, Chen Huang, Zhiliang Jia, Jiujie Cui, Suyun Huang, Liwei Wang, and Keping Xie

Precis: This study identifies a class of FOXO family transcription factors as key effectors in a program of pancreatic cancer development driven by the transcription factors Sp1 and KLH4, with potential implications for understanding the pathophysiology of other cancers in which these FOXO isoforms have been implicated.
**The Steroid Receptor Coactivator-3 Is Required for the Development of Castration-Resistant Prostate Cancer**

Jean C-Y. Tien, Zhaoliang Liu, Lan Liao, Fen Wang, Yixiang Xu, Ye-Lin Wu, Niya Zhou, Michael Ittmann, and Jianming Xu

*Précis:* These findings offer a preclinical proof of concept to therapeutically target a transcriptional coactivator in castration-resistant prostate cancer, the development of which is responsible for nearly all prostate cancer deaths.

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**Tid1-L Inhibits EGFR Signaling in Lung Adenocarcinoma by Enhancing EGFR Ubiquitinylation and Degradation**

Chi-Yuan Chen, Chia-Ing Jan, Jeng-Fan Lo, Shuen-Chen Yang, Yih-Leong Chang, Szu-Hua Pan, Wen-Lung Wang, Tse-Ming Hong, and Pan-Chyr Yang

*Précis:* The clinical validation of EGFR targeting approaches in lung non–small cell lung carcinoma, also known as lung adenocarcinoma, has increased the significance of studies to understand EGFR downregulation in this setting.

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**Impact of Body Mass Index on the Risk of Colorectal Adenoma in a Metabolically Healthy Population**

Kyung Eun Yun, Yoosoo Chang, Hyun-Suk Jung, Chan-Won Kim, Min-Jung Kwon, Sung Keun Park, Eunju Sung, Hocheol Shin, Hye Soon Park, and Seungho Ryu

*Précis:* Excess weight confers an increased risk of developing colorectal adenomas, independent of whether an individual is metabolically healthy or not, suggesting a potential causal link between excess adipose tissue and colorectal cancer risk.

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**Genome-Wide Association Study of Genetic Predictors of Overall Survival for Non–Small Cell Lung Cancer in Never Smokers**

Xifeng Wu, Liang Wang, Yuanqing Ye, Jeremiah A. Aakre, Xia Pu, Gee-Chen Chang, Pan-Chyr Yang, Jack A. Roth, Randolph S. Marks, Scott M. Lippman, Joe Y. Chang, Charles Lu, Claude Deschamps, Wu-Chou Su, Wen-Chang Wang, Ming-Shyan Huang, David W. Chang, Yan Li, V. Shane Pankratz, John D. Minna, Wun Ki Hong, Michelle A.T. Hildebrandt, Chao Agnes Hsuung, and Ping Yang

*Précis:* Although most patients with lung cancer were smokers, the much smaller numbers of never-smokers with lung cancer are less understood with regard to the biologic underpinnings of their clinical outcomes.
TUMOR AND STEM CELL BIOLOGY

Th-MYCN Mice with Caspase-8 Deficiency Develop Advanced Neuroblastoma with Bone Marrow Metastasis

Tal Teitz, Madoka Inoue, Marcus B. Valentine, Kejin Zhu, Jerold E. Rehg, Wei Zhao, David Finkelstein, Yong-Dong Wang, Melissa D. Johnson, Christopher Calabrese, Marcelo Rabinstein, Razqallah Hakem, William A. Weiss, and Jill M. Lahti

Précis: An in vivo model of neuroblastoma that undergoes bone marrow metastasis will be useful to enable better studies of dissemination processes and therapeutic candidates.

miR-214 Coordinates Melanoma Progression by Upregulating ALCAM through TFAP2 and miR-148b Downmodulation

Elisa Penna, Francesca Orso, Daniela Cimino, Irene Vercellino, Elena Grassi, Elena Quaglino, Emilia Turco, and Daniela Taverna

Précis: By establishing a critical pathway to coordinate metastatic dissemination in melanoma, this study offers an initial preclinical proof of concept for targeting its elements as a rational approach to block or reverse this deadly process.

Cancer Stem-like Cell Marker CD44 Promotes Bone Metastases by Enhancing Tumorigenicity, Cell Motility, and Hyaluronan Production

Toru Hiraga, Susumu Ito, and Hiroaki Nakamura

Précis: This important study provides an initial glimpse of the functional meaning of a cell surface protein widely associated with stem-like cell properties in human cancer.

Stress-Response Protein RBM3 Attenuates the Stem-like Properties of Prostate Cancer Cells by Interfering with CD44 Variant Splicing

Yu Zeng, Dana Wodzenski, Dong Gao, Takumi Shiraiishi, Naoki Terada, Youqiang Li, Donald J. Vander Griemd, Jun Luo, Chuize Kong, Robert H. Getzenberg, and Prakash Kulkarni

Précis: This study focuses on a member of a little-studied family of stress regulators in cancer, the cold shock proteins, offering new perspectives on how stress alters RNA splicing for a modulator of stem cell-like character in malignant disease.

G-CSF Receptor Positive Neuroblastoma Subpopulations Are Enriched in Chemotherapy-Resistant or Relapsed Tumors and Are Highly Tumorigenic

Danielle M. Hsu, Saurabh Agarwal, Ashley Benham, Cristian Coarfa, Denae N. Truhan, Zhao Chen, Paris N. Stowers, Amy N. Courtney, Anna Lakoma, Eveline Barbieri, Leonid S. Metelitsa, Preeti Gunaratna, Eugene S. Kim, and Jason M. Shohet

Précis: Stem-like cells in an aggressive pediatric tumor uniformly express the receptor for G-CSF, which, as a means to elevate white blood cell counts, is commonly given to patients where it might unsuspectingly contribute to progression.

Connective Tissue Growth Factor Activates Pluripotency Genes and Mesenchymal–Epithelial Transition in Head and Neck Cancer Cells

Cheng-Chi Chang, Wen-Hao Hsu, Chen-Chien Wang, Chun-Hung Chou, Mark Yen-Ping Kuo, Been-Ren Lin, Shyh-Kuan Tai, Min-Liang Kuo, and Muh-Hwa Yang

Précis: These findings provide insights into epithelial plasticity during progression of head and neck cancers that are rapidly rising in incidence, perhaps also providing a basis for improvement in their classification.

Nrf2 Prevents Initiation but Accelerates Progression through the Kras Signaling Pathway during Lung Carcinogenesis

Hironori Satoh, Takashi Moriguchi, Jun Takai, Masahito Ebina, and Masayuki Yamamoto

Précis: The Nrf2 cellular antioxidant system has different roles during cancer initiation and progression, much like TNF, such that Nrf2 inhibitors offer more rational tools than Nrf2 activators to attack established malignancy.

Corrections: Cell Surface Expression of Epidermal Growth Factor Receptor and Her-2 with Nuclear Expression of Her-4 in Primary Osteosarcoma

Correction: Helicobacter pylori Cytotoxin-Associated Gene A Activates the Signal Transducer and Activator of Transcription 3 Pathway In Vitro and In Vivo
ABOUT THE COVER

CD44, a cancer stem-like cell marker, has been implicated in cancer cell migration, invasion, and metastasis. This study shows that CD44 expression in cancer cells promotes bone metastases by enhancing tumorigenicity, cell migration and invasion, and production of hyaluronan, the primary ligand for CD44. Using a mouse model of bone metastasis, it was found that 4-methylumbelliferone, an inhibitor of hyaluronan synthesis, inhibited bone metastases of MDA-MB-231 human breast cancer cells with reduced number of osteoclasts. For details, see article by Hiraga and colleagues on page 4112.