BREAKING ADVANCES

2763 Highlights from Recent Cancer Literature

REVIEWS

2765 Antiangiogenic VEGF-Ax: A New Participant in Tumor Angiogenesis
Sandeepa M. Eswarappa and Paul L. Fox

2770 Tackling Crizotinib Resistance: The Pathway from Drug Discovery to the Pediatric Clinic
Elizabeth R. Tucker, Laura S. Danielson, Paolo Innocenti, and Louis Chesler

MICROENVIRONMENT AND IMMUNOLOGY

2775 Breast Cancer Cell–Derived GM-CSF Licenses Regulatory Th2 Induction by Plasmacytoid Predendritic Cells in Aggressive Disease Subtypes
Cristina Ghirelli, Fabien Reyal, Marine Jeanmougin, Raphael Zollinger, Philémon Sirven, Paula Michea, Christophe Caux, Nathalie Bendliss-Vermare, Marie-Hélène Donnadieu, Martial Caly, Virginie Fourchotte, Anne Vincent-Salomon, Brigitte Sigal-Zafrani, Xavier Sastre-Garau, and Vassili Soumelis

Precis: This study describes a mechanism through which an aggressive breast cancer activates pDC to promote a regulatory Th2 response, with implications for therapeutic targeting of a tumor-immune axis of growing recognition in its significance to malignancy.

2780 NOS Inhibition Modulates Immune Polarization and Improves Radiation-Induced Tumor Growth Delay

Precis: NOS inhibition has long been studied in cancer to limited impact, but these new preclinical results show how inhibiting NOS in patients after they undergo radiotherapy can relieve immune escape in the tumor microenvironment and greatly improve treatment responses.

2786 Tumor-Promoting Desmoplasia Is Disrupted by Depleting FAP-Expressing Stromal Cells

Precis: This report identifies a stromal cell population expressing the fibroblast activation protein (FAP), which is required for the desmoplastic response seen in many human carcinomas, also showing how FAP-expressing cells promote tumor growth via immune suppression and immune-independent remodeling of the stromal microenvironment.

2791 Pharmacological Inhibition of β3 Integrin Reduces the Inflammatory Toxicities Caused by Oncolytic Adenovirus without Compromising Anticancer Activity
Ashley Browne, Laura A. Tookman, Carin K. Ingemarsdotter, Russell D. Bouwman, Katrina Pirlo, Yaohe Wang, Iain A. McNeish, and Michelle Lockley

Precis: This work describes a novel and clinically feasible strategy to facilitate the safe delivery of systemic viral anticancer therapies by using clinically available β3 integrin inhibitors to control the problematic inflammatory side effects induced by these effective anticancer agents.

2798 Definition of Prostaglandin E2–EP2 Signals in the Colon Tumor Microenvironment That Amplify Inflammation and Tumor Growth
Xiaojun Ma, Tomohiro Aoki, Tatsuki Tsutsumiyama, and Shuh Narumiya

Precis: These findings show how prostaglandin signaling in neutrophils and cancer-associated fibroblasts in the colorectal tumor microenvironment shape its inflammatory character, providing a mechanistic rationale to use EP2 antagonists as an alternative to aspirin for chemoprevention.

2803 Definition of Prostaglandin E2–EP2 Signals in the Colon Tumor Microenvironment That Amplify Inflammation and Tumor Growth
Xiaojun Ma, Tomohiro Aoki, Tatsuki Tsutsumiyama, and Shuh Narumiya

Precis: These findings show how prostaglandin signaling in neutrophils and cancer-associated fibroblasts in the colorectal tumor microenvironment shape its inflammatory character, providing a mechanistic rationale to use EP2 antagonists as an alternative to aspirin for chemoprevention.
Molecular and Cellular Pathobiology

2833  TET2 Mutations Affect Non-CpG Island DNA Methylation at Enhancers and Transcription Factor–Binding Sites in Chronic Myelomonocytic Leukemia
Jumpei Yamazaki, Jaroslav Jelinek, Yue Lu, Matteo Cesaroni, Jozef Madzo, Frank Neumann, Rong He, Rodolphe Taby, Aparna Vasanthakumar, Trisha Macrae, Kelly R. Ostler, Hagop M. Kantarjian, Shoudan Liang, Marcos R. Estecio, Lucy A. Godley, and Jean-Pierre J. Issa

Précis: Results show how mutations in a leukemia-associated gene act epigenetically by influencing the DNA methylation of hematopoietic-specific enhancers that affect leukemia development.

Prevention and Epidemiology

2844  Mitochondrial DNA Copy Number in Peripheral Blood Cells and Risk of Developing Breast Cancer
Alina Lemnrau, Mark N. Brook, Olivia Fletcher, Penny Coulson, Katarzyna Tomczyk, Michael Jones, Alan Ashworth, Anthony Swerdlow, Nick Orr, and Montserrat Garcia-Closas

Précis: The use of mtDNA copy number measured in blood samples prior to diagnosis is associated with elevated risk of developing breast cancer.

Therapeutics, Targets, and Chemical Biology

2851  Enhanced MET Translation and Signaling Sustains K-Ras–Driven Proliferation under Anchorage-Independent Growth Conditions
Saori Fujita-Sato, Jacqueline Galeas, Morgan Pruitt, Cameron Pitt, Anatoly Irisman, Sourav Bandopadhyay, Davide Ruggero, and Frank McCormick

Précis: These results suggest that to drive malignant cell growth K-Ras requires the activity of the Met receptor kinase, a therapeutic target already being explored in the clinic, with implications in addressing the long-standing challenge of how to attack K-Ras–driven human tumors.

2863  Vacuolar-ATPase Inhibition Blocks Iron Metabolism to Mediate Therapeutic Effects in Breast Cancer
Lina S. Schneider, Karin von Schwarzenberg, Thorsten Leht, Melanie Ulrich, Rebekka Kubsch-Dohnen, Johanna Liebl, Dirk Trauner, Dirk Menche, and Angelika M. Vollmar

Précis: Inhibition of a vacuolar ATPase that functions as an ion pump in maintaining cellular metabolic pathways in cancer appears to selectively disturb iron metabolic pathways, thereby blocking tumor growth.

2875  An In Vivo Method to Identify microRNA Targets Not Predicted by Computation Algorithms: p21 Targeting by miR-92a in Cancer
Xiaoping Su, Huaming Wang, Wei Ge, Mingjin Yang, Jin Hou, Taoyong Chen, Nan Li, and Xuetao Cao

Précis: This study describes a new method for in vivo miRNA precipitation (miRIP), which can identify target-specific miRNAs for an mRNA not otherwise identified by current in silico methods.

2886  Secalonic Acid-D Represses HIF1α/VEGF-Mediated Angiogenesis by Regulating the Akt/mTOR/p70S6K Signaling Cascade

Précis: These findings offer a preclinical validation of the antiangiogenic uses for a novel mycotoxin in the generalized treatment of solid tumors.

2897  KRAS Genomic Status Predicts the Sensitivity of Ovarian Cancer Cells to Decitabine
Michelle L. Stewart, Pablo Tamayo, Andrew J. Wilson, Stephanie Wang, Yun Min Chang, Jong W. Kim, Dineo Khabele, Alykhan F. Shamji, and Stuart L. Schreiber

Précis: These findings define a mechanistic basis and a biomarker to predict the sensitivity of ovarian cancer cells to a cytotoxic DNA methyltransferase inhibitor, with potentially generalizable applications.

2907  Targeting Pancreatic Cancer Metastasis by Inhibition of Vav1, a Driver of Tumor Cell Invasion

Précis: These findings offer a preclinical rationale for repositioning the well-established drug azathioprine to inhibit metastasis of deadly pancreatic cancers.
Evidence Suggesting That Discontinuous Dosing of ALK Kinase Inhibitors May Prolong Control of ALK⁺ Tumors


Précis: This important study shows how kinase upregulation in cancer cells can foster resistance to a kinase inhibitory drug, but that this upregulation also sensitizes cells to kinase-mediated toxicities that can be exploited by altering the drug dosing schedule, as a strategy to defeat the drug resistance.

Noninvasive Imaging of Tumor PD-L1 Expression Using Radiolabeled Anti–PD-L1 Antibodies

Sandra Heskamp, Willemijn Hobo, Janneke D.M. Molkenboer-Kuenen, Daniel Olive, Wim J.G. Oyen, Harry Dolstra, and Otto C. Boerman

Précis: PD-L1 expression in tumors is important for PD-1/PD-L1-based therapeutics and can be monitored noninvasively using SPECT/CT imaging, which may more readily enable patient selection for trials of this type of antibody-based immune checkpoint therapy.

Genetic Identification of SEMA3F as an Antilymphangiogenic Metastasis Suppressor Gene in Head and Neck Squamous Carcinoma

Colleen L. Doçi, Constantinos M. Mikelis, Michael S. Lionakis, Alfredo A. Molinolo, and J. Silvio Guikkind

Précis: By focusing on recurrent 3p21 deletions in head and neck cancers, this study identifies a novel metastasis suppressor gene that offers an appealing prognostic biomarker and therapeutic target in this setting.

Androgen-Induced TMPRSS2 Activates Matriptase and Promotes Extracellular Matrix Degradation, Prostate Cancer Cell Invasion, Tumor Growth, and Metastasis

Chun-Jung Ko, Cheng-Chung Huang, Hsin-Ying Lin, Chun-Pai Juan, Shao-Wei Lan, Hsin-Yi Shyu, Shang-Ru Wu, Pei-Wen Hsiao, Hsiang-Po Huang, Chia-Tung Shun, and Ming-Shyue Lee

Précis: This important study shows how the serine protease TMPRSS2 promotes the growth, invasion, and metastasis of prostate cancer cells via activation of the matrix protease matriptase, with implications that targeting these two proteases may offer new options to treat advanced prostate cancer.

ABOUT THE COVER

In normal epithelial cells, there is a balance of pro- and antiangiogenic and lymphangiogenic factors maintaining proper tissue homeostasis. During malignant transformation, early loss of one such factor, the lymphatic endothelial cell inhibitor SEMA3F, is necessary to enable pathologic lymphangiogenesis. As the squamous cell carcinoma cells develop a more aggressive phenotype, acquired expression of surface receptors like neuropilin 2 (NRP2), a receptor typically expressed at high levels on lymphatic endothelial cells, further facilitate tumor vascularity, expansion, and metastatic spread. Thus, expression of SEMA3F may function in both an autocrine and paracrine fashion through NRP2 to inhibit tumor growth, lymphatic invasion, and metastasis. For details, see article by Doçi and colleagues on page 2937.