REVIEWS

The Two Faces of Capsaicin
Ann M. Bode and Zigang Dong

Transcriptional Control of Cellular Metabolism by mTOR Signaling
Jessica L. Yecies and Brendan D. Manning

PRIORITY REPORT

CREB Is a Novel Nuclear Target of PTEN Phosphatase
Tingting Gu, Zhong Zhang, Jianli Wang, Junyi Guo, Wen Hong Shen, and Yuxin Yin

Précis: This study offers important insights into the function of the PTEN phosphatase in the nucleus, where this important tumor suppressor appears to act to suppress cancer in addition to its well-described roles in the cytoplasm.

MICROENVIRONMENT AND IMMUNOLOGY

A Critical Role for GRP78/BiP in the Tumor Microenvironment for Neovascularization during Tumor Growth and Metastasis
Dezheng Dong, Christopher Stapleton, Biquan Luo, Shigang Xiong, Wei Ye, Yi Zhang, Niyati Jhaveri, Genyuan Zhu, Risheng Ye, Zhi Liu, Kevin W. Bruhn, Noah Craft, Susan Groshen, Florence M. Hofman, and Amy S. Lee

Précis: Endothelial cell specific knockout illustrates a critical role for a stress chaperone in the tumor microenvironment, extending its known role in tumor cells and deepening its significance to therapeutic and imaging applications.

INTEGRATED SYSTEMS AND TECHNOLOGIES

Mathematical Modeling Predicts Synergistic Antitumor Effects of Combining a Macrophage-Based, Hypoxia-Targeted Gene Therapy with Chemotherapy
Markus R. Owen, I. Johanna Stamper, Munitta Muthana, Giles W. Richardson, Jon Dobson, Claire E. Lewis, and Helen M. Byrne

Précis: This study uses multiscale mathematical modeling to study how hypoxic tumor cells can be attacked most effectively, using a proposed cell-based therapy that takes advantage of several targeting principles.

A Multicellular Basis for the Origination of Blast Crisis in Chronic Myeloid Leukemia
Rainer K. Sachs, Kerstin Johnsson, Philip Hahnfeldt, Janet Luo, Allen Chen, and Lynn Lattky

Précis: A comprehensive mechanistic mathematical model gives evidence that the main driving mechanism for CML blast crisis origination is interaction between leukemic and normal cells.

Enhanced Efficacy of Therapeutic Cancer Vaccines Produced by Co-Treatment with Mycobacterium tuberculosis Heparin-Binding Hemagglutinin, a Novel TLR4 Agonist
In Duk Jung, Soo Kyung Jeong, Chang-Min Lee, Kyung Tae Noh, Deok Rim Heo, Yong Kyoo Shin, Cheol-Heui Yun, Won-Jung Koh, Shizuo Akira, Jake Whang, Hwa-Jung Kim, Won Sun Park, Sung Jae Shin, and Yeong-Min Park

Précis: This study offers a clear rationale for the development of a powerful new vaccine adjuvant for dendritic cell-based immunotherapies, an emerging area of cancer therapy with the first FDA-approved product appearing in 2010.
In Vivo Inhibition of Human CD19-Targeted Effector T Cells by Natural T Regulatory Cells in a Xenotransplant Murine Model of B Cell Malignancy

James C. Lee, Erik Hayman, Hollie J. Pegram, Elmer Santos, Glen Heller, Michel Sadelan, and Renier Brentjens

**Précis:** Successful application of adoptive therapy of cancer using autologous T cells genetically targeted to tumor associated antigens is dependent upon prior depletion of tumor infiltrating regulatory T cells.

IRF8 Regulates Acid Ceramidase Expression to Mediate Apoptosis and Suppresses Myelogeneous Leukemia

Xiaolin Hu, Dafeng Yang, Mary Zimmerman, Feiyan Liu, Jine Yang, Swati Kannan, Andreas Burchert, Zdzislaw Szulc, Alicja Bielawska, Keiko Ozato, and Kebin Liu

**Précis:** Findings define how a critical tumor suppressor gene becomes attenuated in chronic myeloid leukemia, and how this attenuation leads to apoptotic resistance and disease progression.

CD73-Deficient Mice Have Increased Antitumor Immunity and Are Resistant to Experimental Metastasis

John Stagg, Upulie Divisekera, Helene Duret, Tim Sparwasser, Michele W.L. Teng, Phillip K. Darcy, and Mark J. Smyth

**Précis:** Findings offer preclinical proof-of-concept for therapeutic targeting of a important cell surface-based driver of immune escape in cancer, perhaps involved in many types of human cancer.

FLT3-Mediated p38–MAPK Activation Participates in the Control of Megakaryopoiesis in Primary Myelofibrosis


**Précis:** Findings advance understanding of the pathophysiology of primary myelofibrosis, a bone marrow–derived disease, and suggest applications for drugs that target a key megakaryocytic signaling pathway as a new strategy to evaluate for treating this disease.

DLC1 Interaction with S100A10 Mediates Inhibition of In Vitro Cell Invasion and Tumorigenicity of Lung Cancer Cells through a RhoGAP-Independent Mechanism

Xuyu Yang, Nicholas C. Popescu, and Drazen B. Zimonjic

**Précis:** Findings reveal a mechanism through which plasminogen activator-dependent conversion of plasminogen to plasmin is attenuated, reducing tumor cell capacity for invasion and metastasis in the tumor microenvironment.

MicroRNA-301 Mediates Proliferation and Invasion in Human Breast Cancer

Wei Shi, Kate Gerster, Nehad M. Alajez, Jasmine Tsang, Levi Waldron, Melanie Pintilie, Angela B. Hui, Jenna Sykes, Christine P’ng, Naomi Miller, David McCready, Anthony Fyles, and Fei-Fei Liu

**Précis:** This study establishes a novel nodal oncomiR in breast cancer that acts through several pathways to promote metastatic tumor progression.
The Neuronal Differentiation Factor NeuroD1 Downregulates the Neuronal Repellent Factor Slit2 Expression and Promotes Cell Motility and Tumor Formation of Neuroblastoma
Peng Huang, Satoshi Kishida, Dongliang Cao, Yuko Murakami-Tonami, Ping Mu, Masato Nakaguro, Naoshi Koide, Ichiro Takeuchi, Akira Onishi, and Kenji Kadomatsu
Précis: Findings establish the critical role of a neuronal differentiation factor in neuroblastoma and its functional relationship with a neuronal repellent factor.

Overexpression of a Novel Activator of PAK4, the CDK5 Kinase–Associated Protein CDK5RAP3, Promotes Hepatocellular Carcinoma Metastasis
Grace Wing-Yan Mak, Mandy Man-Lok Chan, Veronica Yee-Law Leong, Joyce Man-Fong Lee, Tai-On Yau, Irene Oi-Lin Ng, and Yick-Pang Ching
Précis: A gene implicated in cancer progression proves to directly support metastasis by activating a PAK kinase implicated in invasive cell motility.

Functional Cooperation of RKTG with p53 in Tumorigenesis and Epithelial–Mesenchymal Transition
Yuhui Jiang, Xiaoduo Xie, Zhigang Li, Zheng Wang, Yuxuan Zhang, Zhiqiang Ling, Yi Pan, Zhenzhuan Wang, and Yan Chen

Cytoplasmic CUL9/PARC Ubiquitin Ligase Is a Tumor Suppressor and Promotes p53-Dependent Apoptosis
Xin-Hai Pei, Feng Bai, Zhijun Li, Matthew D. Smith, Gabrielle Whitewolf, Ran Jin, and Yue Xiong
Précis: This study identifies a potential p53 activating E3 ligase located in the cytoplasm that functions as a tumor suppressor.

Frequent Truncating Mutation of TFAM Induces Mitochondrial DNA Depletion and Apoptotic Resistance in Microsatellite-Unstable Colorectal Cancer
Précis: A class of mutations that lead to mitochondrial DNA depletion and apoptotic resistance may be important drivers of tumorigenesis in most microsatellite-unstable colorectal cancers.
High Plasma Levels and Effective Lymphatic Uptake of Docetaxel in an Orally Available Nanotransporter Formulation

Taher Nassar, Suha Attili-Qadri, Oshrat Harush-Frenkel, Shimon Farber, Shimon Lecht, Philip Lazarovici, and Simon Benita

Précis: An oral nanocarrier of docetaxel favors lymphatic uptake in preclinical studies, potentially stimulating clinical studies that could allow docetaxel chemotherapy to be switched from intravenous to oral delivery in patients.

Sildenafil Reverses ABCB1- and ABCG2-Mediated Chemotherapeutic Drug Resistance

Zhi Shi, Amit K. Tiwari, Suneet Shukla, Robert W. Robey, Satyakam Singh, In-Wha Kim, Susan E. Bates, Xingxiang Peng, Ioana Abraham, Suresh V. Ambudkar, Tanaji T. Talele, Li-Wu Fu, and Zhe-Sheng Chen

Précis: A drug used widely to treat erectile dysfunction in men is found to abrogate two common mechanisms of chemotherapeutic drug resistance, with immediate potential applications to improve the treatment of many advanced cancers.

Inhibition of NEDD8-Activating Enzyme Induces Rereplication and Apoptosis in Human Tumor Cells Consistent with Deregulating CDT1 Turnover

Michael A. Milhollen, Usha Narayanan, Teresa A. Soucy, Petter O. Velby, Peter G. Smith, and Benjamin Amidon

Précis: DNA re-replication elicited in cancer cells by a small molecule inhibitor currently in Phase I trials creates an unrecoverable cellular insult, with implications for gaining deeper understanding of a unique therapeutic mechanism of cytotoxicity in cancer treatment.

PDK1 Attenuation Fails to Prevent Tumor Formation in PTEN-Deficient Transgenic Mouse Models


Précis: This study employed a novel RNAi approach useful for context-dependent target validation in vivo, applying it to demonstrate that the protein kinase PDK1 is not a rate limiting factor for PI3K-pathway activation or tumor formation in PTEN-deficient mouse models.

Frizzled 4 Regulates Stemness and Invasiveness of Migrating Glioma Cells Established by Serial Intracranial Transplantation

Xun Jin, Hee-Young Jeon, Kyeung Min Joo, Jun-Kyum Kim, Juyoun Jin, Sung Hak Kim, Bong Gu Kang, Samuel Beck, Se Jeong Lee, Joong Kyu Kim, Ae-Kyung Park, Yuong-Yang Park, Yun-Jaie Choi, Do-Hyun Nam, and Hyunggee Kim

Précis: Findings define an important role in glioma recurrence and poor prognosis for a G-protein coupled receptor that is part of the Wnt signaling family governing stemness and invasiveness of glioma stem cells.

FOXQ1 Regulates Epithelial-Mesenchymal Transition in Human Cancers

Yuanyuan Qiao, Xia Jiang, Shuet Theng Lee, R.K. Murthy Karuturi, Shing Chuan Hooi, and Qiang Yu

Précis: Findings identify a member of the FOXO family of transcription factors as a critical regulator of EMT, stem cell properties, and chemotherapeutic resistance in cancer cells.
EMT and Stem Cell–Like Properties Associated with miR-205 and miR-200: Epigenetic Silencing Are Early Manifestations during Carcinogen-Induced Transformation of Human Lung Epithelial Cells
Carmen S. Tellez, Daniel E. Juri, Kieu Do, Amanda M. Bernauer, Cindy L. Thomas, Leah A. Damiani, Mathewes Tessema, Shuguang Leng, and Steven A. Belinsky

Precis: This study extends present concepts of how EMT contributes to cancer progression by showing that it can also contribute to cancer initiation, by promoting clonal expansion and stem-like properties in premalignant lung epithelial cells.

Human CD271-Positive Melanoma Stem Cells Associated with Metastasis Establish Tumor Heterogeneity and Long-term Growth
Gianluca Civenni, Anne Walter, Nikita Kobert, Daniela Mihic-Probst, Marie Zipser, Benedetta Belloni, Burkhardt Seifert, Holger Moch, Reinhard Dummer, Maries van den Broek, and Lukas Sommer

Precis: Using immunocompetent mouse models and methodologies to better preserve cell surface epitopes allowed the identification of a melanoma stem cell marker associated with metastatic disease.

Hypoxia Predicts Aggressive Growth and Spontaneous Metastasis Formation from Orthotopically Grown Primary Xenografts of Human Pancreatic Cancer
Qing Chang, Igor Jurisica, Trevor Do, and David W. Hedley

Precis: Results offer experimental proof of the expected powerful effects of hypoxia on the progression of early stage pancreatic cancer, with potential to target these effects therapeutically.

Deletion of the Proline-Rich Region of the Murine Metastasis Susceptibility Gene Brd4 Promotes Epithelial-to-Mesenchymal Transition and Stem Cell-Like Conversion

Precis: Findings suggest how an important metastasis susceptibility gene may predispose tumor cells to convert to more de-differentiated or primitive states that are metastatically aggressive.

Ror1 Is a Pseudokinase That Is Crucial for Met-Driven Tumorigenesis
Alessandra Gentile, Luca Lazzari, Silvia Benvenuti, Livio Trusolino, and Paolo M. Comoglio

Precis: An uncharacterized member of the human kinome is revealed to be a pseudokinase that acts downstream of the MET oncoprotein, the activation of which mediates powerful effects on the progression of many types of human cancer.

CAMTA1, a 1p36 Tumor Suppressor Candidate, Inhibits Growth and Activates Differentiation Programs in Neuroblastoma Cells
Kai-Oliver Henrich, Tobias Bauer, Johannes Schulte, Volker Ehemann, Hedwig Deuhnzer, Sina Gogolin, Daniel Muth, Matthias Fischer, Axel Benner, Rainer König, Manfred Schwab, and Frank Westermann

Precis: Findings define properties of a gene involved in neuronal differentiation that support its assignment as a 1p36 tumor suppressor gene in neuroblastoma.

Cancer-Associated Loss-of-Function Mutations Implicate DAPK3 as a Tumor-Suppressing Kinase
John Brognard, You-Wei Zhang, Lorena A. Puto, and Tony Hunter

Precis: There has been a recent flood of cancer kinome sequence data, but the functional consequences of the reported protein kinase mutations have been inferred largely through statistical approaches, and our studies represent a critical first step in assessing the functional relevance of putative driver mutations experimentally.

Serglycin Is a Theranostic Target in Nasopharyngeal Carcinoma that Promotes Metastasis
Xin-Jian Li, Choon Kiat Ong, Yun Cao, Yan-Qun Xiang, Jian-Yong Shao, Aiseng Ooi, Li-Xia Peng, Wen-Hua Lu, Zhongfa Zhang, David Petillo, Li Qin, Ying-Na Bao, Fang-Jing Zheng, Claramae Shulyn Chia, N. Gopalakrishna Iyer, Tie-Bang Kang, Yi-Xin Zeng, Khee Chee Soo, Jeffrey M. Trent, Bin Tean Teh, and Chao-Nan Qian

Precis: Findings of this extensive study define a functionally important extracellular theranostic marker of metastasis in nasopharyngeal carcinoma, a common deadly cancer in Asia.
ABOUT THE COVER

Evasion from immune recognition contributes to tumor growth. Stagg and colleagues have recently identified CD73 expression on tumor cells as an important mechanism of tumor immune evasion. The cover image represents CD73 expression (green) detected by immunofluorescence on MDA-MB-231 breast cancer cells. Stagg and colleagues describe that CD73 expression on hematopoietic and nonhematopoietic host cells also contributes to tumor immune evasion. Using adoptive reconstitution of T regulatory cells (Treg), their study defines CD73 as an important immunosuppressive factor expressed by Treg that promotes tumor growth. Their study also reveals that nonhematopoietic expression of CD73, possibly on endothelial cells, enhances metastasis of circulating tumor cells. Finally, they report that anti-CD73 therapy inhibits the growth and metastatic potential of CD73-negative tumor cells. Taken together, their study suggests that CD73 may be targeted at multiple levels to induce anticancer effects. For details, see the article by Stagg and colleagues on page 2892 of this issue.
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