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Weibin Zou, Huilin Zheng, Tong-Chuan He, Jinjia Chang, Yang-Xin Fu, and Weimin Fan

**Precis**:

The ability to visualize and quantify drug-induced apoptosis of human tumor cells in vivo may address questions about how apoptosis is controlled by the tumor microenvironment.

**Precis**:

A receptor for extracellular ATP is found to promote tumorigenesis in vivo, providing mechanistic insight into how the biochemical composition of the tumor milieu may support growth and metastasis.

**Precis**:

This study challenges the notion that immune effectors simply destroy targets and instead postulates that they are involved in induction of tumor cell autophagy and resistance to anticancer therapy and potentially involved in repair.

**Precis**:

Targeted delivery of an immune-stimulating factor in tumors using a stem cell-based vector can stanch immune suppression in the tumor microenvironment and derepress antitumor immunity.
**Molecular and Cellular Pathobiology**

**Inhibitory Roles of Signal Transducer and Activator of Transcription 3 in Antitumor Immunity during Carcinogen-Induced Lung Tumorigenesis**
Shoichi Ihara, Hiroshi Kida, Hisashi Arase, Lokesh P. Tripathi, Yi-An Chen, Tetsuya Kimura, Mitsuhiro Yoshida, Yozo Kashiwa, Haruhiko Hirata, Reiko Fukamizu, Ruriko Inoue, Takashi Kijima, Kenji Mizuguchi, Isao Tachibana, and Atsushi Kumanogoh

**Precis:** Tissue-specific genetic deletion of STAT3 in lung epithelium decreases susceptibility to lung carcinogenesis and promotes NK cell-mediated antitumor immunity, offering the first strong genetic proof for STAT3 signaling as a cancer therapeutic target for lung cancer treatment.

**Vav3-Rac1 Signaling Regulates Prostate Cancer Metastasis with Elevated Vav3 Expression Correlating with Prostate Cancer Progression and Posttreatment Recurrence**
Kai-Ti Lin, Jianli Gong, Chien-Feng Li, Te-Hsuan Jang, Wen-Ling Chen, Huei-Jane Chen, and Lu-Hai Wang

**Precis:** Findings highlight a cell adhesion signaling pathway that may contribute centrally to invasive metastasis of prostate cancer.

**Stromal Estrogen Receptor-α Promotes Tumor Growth by Normalizing an Increased Angiogenesis**
Christel Pécqueux, Isabelle Raymond-Letron, Silvia Blacher, Frédéric Boudou, Marine Adlammerini, Marie-José Fouque, Philippe Rochaix, Agnès Noël, Jean-Michel Foldart, Andrée Krust, Pierre Chamoun, Laurent Brouchet, Jean-François Arnal, and Françoise Lenfant

**Precis:** Findings reveal that estrogens drive breast tumor growth in part by supporting the ability of endothelial cells in the tumor microenvironment, deepening our understanding of the molecular mechanisms involved in ER-positive tumorigenesis and how ER-positive tumors might be managed.

**Prevention and Epidemiology**

**Postmenopausal Hormone Therapy Is Associated with a Reduced Risk of Colorectal Cancer Lacking CDKN1A Expression**
Jennifer H. Lin, Teppei Morikawa, Andrew T. Chan, Aya Kuchiba, Kaori Shima, Katsuhiko Nosho, Gregory Kirkner, Shumin M. Zhang, JoAnn E. Manson, Edward Giovannucci, Charles S. Fuchs, and Shuji Ogino

**Precis:** A reduction in colorectal cancer risk among U.S. women using postmenopausal hormone therapy may be due to the effect of these medications on a central cell-cycle regulator.

**Adipokines Linking Obesity with Colorectal Cancer Risk in Postmenopausal Women**
Gloria Y.F. Ho, Tao Wang, Marc J. Gunter, Howard D. Strickler, Mary Cushman, Robert C. Kaplan, Sylvia Wassertbeil-Smoller, Xiaoxuan Xue, Swapnil N. Raiputhak, Rowan T. Chlebowski, Mara Z. Vitolins, Philipp E. Scherer, and Thomas E. Rohan

**Precis:** A high level of leptin is an independent risk factor for colorectal cancer, and hyperleptinemia together with hyperinsulinemia may partially explain the association of obesity with colorectal cancer in postmenopausal women.

**Therapeutics, Targets, and Chemical Biology**

**An NQO1 Substrate with Potent Antitumor Activity That Selectively Kills by PARP1-Induced Programmed Necrosis**
Xiumei Huang, Ying Dong, Erik A. Bey, Jessica A. Kilgore, Joseph S. Bair, Long-Shan Li, Malina Patel, Elizabeth J. Parkinson, Yiguang Wang, Noelle S. Williams, Jinming Gao, Paul J. Hergenrether, and David A. Boothman

**Precis:** Therapeutic programmed necrosis can be achieved in tumors using bioactive substrates of the cytosolic NAD(P)H:quinone oxidoreductase 1 (NQO1) enzyme that is overexpressed in most solid cancers and can create extensive tumor-selective ROS bursts, damaging tumor cell DNA and rapidly killing cells.

**MEK1/2 Inhibition Elicits Regression of Autochthonous Lung Tumors Induced by KRASG12D or BRAFV600E**
Christy L. Trejo, Joseph Juan, Silvestre Vicent, Alejandro Sweet-Cordero, and Martin McMahon

**Precis:** This study uses genetically engineered mouse models of human lung cancer to establish a preclinical proof of concept for MEK inhibitors as broadly effective therapy for lung tumors driven by activated Ras–Raf signaling.
Novel TOPK Inhibitor HI-TOPK-032 Effectively Suppresses Colon Cancer Growth

Dong Joon Kim, Yan Li, Kanamata Reddy, Mee-Hyun Lee, Myoung Ok Kim, Yong-Yeon Cho, Sung-Young Lee, Jong-Eun Kim, Ann M. Bode, and Zigang Dong

Précis: Findings identify a specific inhibitor of a MEK family member that shows effective preclinical efficacy against colorectal cancer, with great potential for improving therapy of this disease.

Mcl-1 Phosphorylation Defines ABT-737 Resistance That Can Be Overcome by Increased NOXA Expression in Leukemic B cells

Suparna Mazumder, Gaurav S. Choudhary, Sayer Al-harbi, and Alexandru Almasan

Précis: Findings provide insight into acquired resistance mechanisms to the BH3 domain mimetic ABT-737, which is currently being tested in the clinic as navitoclax.

Uncoupling of PI3K from ErbB3 Impairs Mammary Gland Development but Does Not Impact on ErbB2-Induced Mammary Tumorigenesis

Hicham Lahlou, Thomas Müller, Virginie Sanguin-Gendreau, Carmen Birchmeier, and William J. Muller

Précis: In the context of activated HER2-ErbB2 signaling, ErbB3-PI3K coupling is essential for normal mammary gland development but not mammary cancer progression.

Polycomb Protein EZH2 Regulates Tumor Invasion via the Transcriptional Repression of the Metastasis Suppressor RKIP in Breast and Prostate Cancer

Gang Ren, Stavroura Baritaki, Himangi Marathe, Jingwei Feng, Sungdae Park, Sandy Beach, Peter S. Bazeley, Anwar B. Beshir, Gabriel Fenteany, Rohit Mehra, Stephanie Daignault, Fahd Al-Mulla, Evan Keller, Ben Bonavida, Ivana de la Serna, and Kam C. Yeung

Précis: This study provides mechanistic insights into a novel metastasis suppressor in breast and prostate cancers, where it is a target of the histone methyltransferase EZH2, known to play an important role in malignant progression.

Genetic Ablation of SOX18 Function Suppresses Tumor Lymphangiogenesis and Metastasis of Melanoma in Mice

Tam Duong, Steven T. Proulx, Paola Luciani, Jean-Christophe Leroux, Michael Detmar, Peter Koopman, and Mathias Francois

Précis: A molecular switch used during embryonic development to control lymphangiogenesis is switched on during formation of the lymphatic vessels that drain tumors, suggesting new targeted strategies to block the escape of metastases that are often seeded through the lymphatic system.

Correction: Genome-Wide DNA Methylation Profiling of CpG Islands in Breast Cancer Identifies Novel Genes Associated with Tumorigenicity

Correction: ARID1A, a Factor That Promotes Formation of SWI/SNF-Mediated Chromatin Remodeling, Is a Tumor Suppressor in Gynecologic Cancers
ABOUT THE COVER

Adenosine 5'-triphosphate (ATP) is a common constituent of the tumor microenvironment where it modulates the anticancer immune response and stimulates tumor cell growth and apoptosis. One of the main cellular receptors mediating these effects is the P2X7 receptor. P2X7 is an ATP-gated plasma membrane ion channel coupled to inflammasome activation, release of inflammatory cytokines, generation of reactive oxygen species, and stimulation of apoptosis. However, paradoxically, Adinolfi and colleagues found that tumorigenesis was accelerated by overexpression of P2X7 in several tumor models, and accordingly, drastically reduced by P2X7 silencing. Adinolfi and colleagues results provide a logical explanation for the intriguing finding that most human malignant tumors overexpress this receptor (a specimen from human differentiated colon cancer stained with an anti-P2X7 polyclonal antibody is shown). For details, see article by Adinolfi et al. on page 2957 of this issue.