

# Contents

# Cancer Research

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## BREAKING ADVANCES

- 377 | **Highlights from Recent Cancer Literature**

## REVIEWS

- 379 | **JNK-Induced Apoptosis, Compensatory Growth, and Cancer Stem Cells**  
Fei Chen
- 387 | **Metastasis-Associated Protein 1/Nucleosome Remodeling and Histone Deacetylase Complex in Cancer**  
Da-Qiang Li, Suresh B. Pakala, Sujit S. Nair, Jeyanthi Eswaran, and Rakesh Kumar

## PRIORITY REPORTS

- 395 | **Stress-Regulated Transcription Factor ATF4 Promotes Neoplastic Transformation by Suppressing Expression of the INK4a/ARF Cell Senescence Factors**  
Michiko Horiguchi, Satoru Koyanagi, Akinori Okamoto, Satoshi O. Suzuki, Naoya Matsunaga, and Shigehiro Ohdo
- Précis:** A gene overexpressed in many cancers that promotes cell survival in stressed tumor microenvironments is found to also exert a major role in suppressing a central pathway of cellular senescence.*
- 402 | **Increased Survival of Glioblastoma Patients Who Respond to Antiangiogenic Therapy with Elevated Blood Perfusion**  
A. Gregory Sorensen, Kyrre E. Emblem, Pavlina Polaskova, Dominique Jennings, Heisoog Kim, Marek Ancukiewicz, Meiyun Wang, Patrick Y. Wen, Percy Ivy, Tracy T. Batchelor, and Rakesh K. Jain
- Précis:** This seminal study provides direct clinical evidence that the survival of a cancer patient is prolonged by antiangiogenic therapy if the therapy achieves increased tumor blood perfusion, in support of the vascular normalization hypothesis for cancer treatment.*

## CLINICAL STUDIES

- 408 | **Genetic Variants in Oxidative Stress-Related Genes Predict Chemoresistance in Primary Breast Cancer: A Prospective Observational Study and Validation**  
Ke-Da Yu, A-Ji Huang, Lei Fan, Wen-Feng Li, and Zhi-Ming Shao
- Précis:** This study offers compelling evidence that genetic polymorphisms in oxidative stress-related genes in the host affect chemosensitivity, such that host gene status must be considered to optimize personalized chemotherapy beyond variations in simply the tumor cells themselves.*

## MICROENVIRONMENT AND IMMUNOLOGY

- 420 | **Interleukin-10 Ablation Promotes Tumor Development, Growth, and Metastasis**  
Takashi Tanikawa, Cailin Moira Wilke, Ilona Kryczek, Grace Y. Chen, John Kao, Gabriel Núñez, and Weiping Zou
- Précis:** This study of cancer susceptibility and progression in mice lacking IL-10 challenges the generally held view that this immune inhibitory cytokine supports cancer, instead offering powerful evidence that endogenous IL-10 actually suppresses cancer by impeding the development of 2 key cellular mechanisms of immune escape.*
- 430 | **Potent Induction of Tumor Immunity by Combining Tumor Cryoablation with Anti-CTLA-4 Therapy**  
Rebecca Waitz, Stephen B. Solomon, Elena N. Petre, Anne E. Trumble, Marcella Fassò, Larry Norton, and James P. Allison
- Précis:** One use of the recently approved immune activating drug ipilimumab may be to enhance the benefits of tumor cryoablation, a simple older treatment strategy being explored anew in breast and prostate cancers, where it might be very effectively combined with immunotherapy to enhance cure rates in patients with localized tumors.*

- 440 **Platelet-Derived MHC Class I Confers a Pseudonormal Phenotype to Cancer Cells That Subverts the Antitumor Reactivity of Natural Killer Immune Cells**  
Theresa Placke, Melanie Örgel, Martin Schaller, Gundram Jung, Hans-Georg Rammensee, Hans-Georg Kopp, and Helmut Rainer Salih  
*Précis:* This important paper elucidates a fascinating mechanism of immune escape from NK cells in which platelets function to shield cancer cells and promote their metastatic spread.
- 449 **Chromogranin A Regulates Tumor Self-Seeding and Dissemination**  
Eleonora Dondossola, Luca Crippa, Barbara Colombo, Elisabetta Ferrero, and Angelo Corti  
*Précis:* Findings define a role for a circulating regulator of multidirectional trafficking of tumor cells between tumors, blood, and normal tissues, with general implications for metastasis formation and tumor progression.
- 460 **Tumor Suppressive MicroRNAs miR-34a/c Control Cancer Cell Expression of ULBP2, a Stress-Induced Ligand of the Natural Killer Cell Receptor NKG2D**  
Anja Heinemann, Fang Zhao, Sonali Pechlivanis, Jürgen Eberle, Alexander Steinle, Sven Diederichs, Dirk Schadendorf, and Annette Paschen  
*Précis:* The perspective that tumor suppressor functions often manifest as immune responses against tumor cells is quickly widening with broader investigations in more valid immunocompetent models of cancer.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 472 **Role of JNK in Mammary Gland Development and Breast Cancer**  
Cristina Cellurale, Nomeda Girnius, Feng Jiang, Julie Cavanagh-Kyros, Shaolei Lu, David S. Garlick, Arthur M. Mercurio, and Roger J. Davis  
*Précis:* This study offers in vivo evidence that the JNK stress kinases have a tumor suppressor function in the setting of mammary carcinogenesis, a role that likely extends to many other settings of epithelial carcinogenesis.

- 482 **Arsenic Trioxide Treatment Decreases the Oxygen Consumption Rate of Tumor Cells and Radiosensitizes Solid Tumors**  
Caroline Diepart, Oussama Karroum, Julie Magat, Olivier Feron, Julien Verrax, Pedro Buc Calderon, Vincent Grégoire, Philippe Leveque, Julie Stockis, Nicolas Danguet, Bénédicte F. Jordan, and Bernard Gallez  
*Précis:* This study offers a sound preclinical rationale for immediate clinical repositioning of arsenic trioxide, an approved treatment for acute promyelocytic leukemias, as a radiosensitizer for any solid tumor.
- 491 **Functional Interaction between Responses to Lactic Acidosis and Hypoxia Regulates Genomic Transcriptional Outputs**  
Xiaohu Tang, Joseph E. Lucas, Julia Ling-Yu Chen, Gregory LaMonte, Jianli Wu, Michael Changsheng Wang, Constantinos Koumenis, and Jen-Tsan Chi  
*Précis:* This provocative study suggests that lactic acidosis occurring in the microenvironment of many solid tumors can abolish canonical responses to hypoxia, suggesting that many models used for development of cancer-selective therapeutics against tumor hypoxia may be deeply flawed.

## PREVENTION AND EPIDEMIOLOGY

- 503 **Circulating Insulin-Like Growth Factors and IGF-Binding Proteins in PSA-Detected Prostate Cancer: The Large Case-Control Study ProtecT**  
Mari-Anne Rowlands, Jeff M.P. Holly, David Gunnell, Jenny Donovan, J. Athene Lane, Freddie Hamdy, David E. Neal, Steven Oliver, George Davey Smith, and Richard M. Martin  
*Précis:* This large UK-based case-control study suggests potentially important associations of circulating IGF-II, IGFBP-2, and IGFBP-3 in prostate cancers that are detected by the PSA test.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

516 **Regulation of Matrix Metalloproteinase Genes by E2F Transcription Factors: Rb–Raf-1 Interaction as a Novel Target for Metastatic Disease**

Jackie L. Johnson, Smitha Pillai, Danielle Pernazza, Saïd M. Sebti, Nicholas J. Lawrence, and Srikumar P. Chellappan

**Précis:** Matrix metalloproteases regulated by the Rb–E2F pathway may serve as its major connection to invasion and metastasis control, with implications for therapeutic intervention such as through targeting the Rb–Raf-1 interaction as illustrated in this study.

527 **Androgen Deprivation Causes Epithelial–Mesenchymal Transition in the Prostate: Implications for Androgen-Deprivation Therapy**

Yuting Sun, Bu-Er Wang, Kevin G. Leong, Peng Yue, Li Li, Suchit Jhunjhunwala, Darrell Chen, Kyounghee Seo, Zora Modrusan, Wei-Qiang Gao, Jeffrey Settleman, and Leisa Johnson

**Précis:** Findings argue that androgen-deprivation therapy, used widely in prostate cancer treatment, can trigger epithelial–mesenchymal transition, a foreboding event that may detract from the response to other treatments.

## TUMOR AND STEM CELL BIOLOGY

537 **Hyaluronan Synthase HAS2 Promotes Tumor Progression in Bone by Stimulating the Interaction of Breast Cancer Stem–Like Cells with Macrophages and Stromal Cells**

Hiroshi Okuda, Aya Kobayashi, Bo Xia, Misako Watabe, Sudha K. Pai, Shigeru Hirota, Fei Xing, Wen Liu, Puspa R. Pandey, Koji Fukuda, Vishnu Modur, Arnab Ghosh, Andrew Wilber, and Kounosuke Watabe

**Précis:** Findings define a mechanism used by cancer stem cells to produce an extracellular matrix glycosaminoglycan that may help seed a metastatic niche in foreign organ microenvironments, with major implications for antimetastatic therapy.

548 **Metastatic Progression with Resistance to Aromatase Inhibitors Is Driven by the Steroid Receptor Coactivator SRC-1**

Jean McBryan, Sarah M. Theissen, Christopher Byrne, Eamon Hughes, Sinead Cocchiglia, Stephen Sande, Jane O'Hara, Paul Tibbitts, Arnold D.K. Hill, and Leonie S. Young

**Précis:** This study reveals insights into the mechanism by which clinical resistance and metastatic progression occur with aromatase inhibitors, a first-line treatment for endocrine-sensitive breast cancers.

560 **p53 Negatively Regulates Transcription of the Pyruvate Dehydrogenase Kinase Pdk2**

Tanupriya Contractor and Chris R. Harris

**Précis:** This study reveals how p53 controls the Warburg effect, a universal property of cancer cells in which glycolysis is driven powerfully despite aerobic conditions that should otherwise favor oxidative phosphorylation.

## CORRECTION

568 **Correction: CD8<sup>+</sup> T Cells Regulate Bone Tumor Burden Independent of Osteoclast Resorption**

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## ABOUT THE COVER

Epithelial–mesenchymal transition (EMT) is a key developmental process and has also been implicated in cancer metastasis and therapeutic resistance. The factors contributing to EMT in human cancers remain unclear. Sun and colleagues show that androgen deprivation can promote EMT in normal mouse prostate as well as in human prostate cancer, revealing a potentially important consequence of a standard of care treatment for prostate malignancies. This image corresponds to an immunofluorescence staining of E-cadherin (epithelial marker) and vimentin (mesenchymal marker) in postcastration (androgen-deprived) mouse prostate tissue. Cells that express both markers are likely to be undergoing EMT. Red, Vimentin; green, E-cadherin; blue, DAPI. For details, see the article by Sun and colleagues on page 527 of this issue.

