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**3272** These findings provide evidence for a novel molecular mechanism that explains the high levels of hypoxia and desmoplasia that contribute to therapy resistance in pancreatic cancer.

**3285** These findings suggest a paradigm that helps to explain how a single mutant KRAS allele can cooperate with mutant PIK3CA to impart a transformed phenotype.
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Anja Rudolph, Csaba Toth, Michael Hoffmeister, Wilfried Roth, Esther Herpel, Peter Schirmacher, Hermann Brenner, and Jenny Chang-Claude

Précis: Expression of estrogen receptor β, the predominant estrogen receptor in colon tissue, appears to be involved in the reduction of colorectal cancer risk that may arise with use of oral contraceptives or menopausal hormone therapy.

3325 Lineage Relationship of Gleason Patterns in Gleason Score 7 Prostate Cancer
Irina V. Kovtun, John C. Cherille, Stephen J. Murphy, Sarah H. Johnson, Shabnam Zarei, Farhad Kosari, William R. Sukov, R. Jeffrey Karnes, and Stefan Knapp

Précis: This work has important clinical implications because it demonstrates that changes associated with aggressive tumor behavior can be identified prior to the morphologic changes characteristic of aggressive prostate cancer.

3326 Collagen Prolyl Hydroxylases Are Essential for Breast Cancer Metastasis
Daniele M. Gilkes, Pallavi Chaturvedi, Saumendra Bajpai, Carmen C. Wong, Hong Wei, Denis Wirtz, and Gregg L. Semenza

Précis: Although collagen prolyl hydroxylases have been implicated broadly in cancer pathophysiology, their precise contributions have not been well understood, an important gap in knowledge addressed by this study.

3327 Interleukin-1β Promotes Skeletal Colonization and Progression of Metastatic Prostate Cancer Cells with Neuroendocrine Features
Qingxin Liu, Mike R. Russell, Kristina Shahriri, Danielle L. Jernigan, Mercedes I. Lioni, Fernando U. Garcia, and Alessandro Fatatis

Précis: The identification of IL-1β as an important mediator of metastasis in prostate cancer should prompt immediate testing of anti-IL-1β strategies to treat advanced disease.

3336 DNA Methylation-Mediated Repression of miR-886-3p Predicts Poor Outcome of Human Small Cell Lung Cancer
Jianzhong Cao, Yongmei Song, Nan Bi, Jie Shen, Wenyang Liu, Jing Fan, Guogui Sun, Tong Tong, Jie He, Yaun Kai Shi, Xun Zhang, Ning Lu, Yinghua He, Hongyu Zhang, Kelong Ma, Xiaoying Luo, Lei X. Hui Deng, Jinh Cheng, Jingde Zhu, Luhua Wang, and Qimin Zhan

Précis: These findings identify a little-studied microRNA the epigenetic downregulation of which strongly affects clinical outcomes and malignant cell behaviors in small-cell lung cancer.

3347 Bevacizumab-Induced Normalization of Blood Vessels in Tumors Hampers Antibody Uptake

Précis: Bevacizumab treatment decreases tumor uptake of antibodies by vessel normalization, and this should be taken into account in the design of clinical trials that combine bevacizumab with other antibodies.

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3316 Inhibition of Tumor Cell Migration by LD22-4, an N-Terminal Fragment of 24-kDa FGFR2, Is Mediated by Neurophilin 1
Ling Zhang, Graham C. Parry, and Eugene G. Levin

Précis: Definition of a cell surface receptor for an inhibitor of cancer cell migration suggests a novel approach to tumor suppression.

3332 PFI-1, a Highly Selective Protein Interaction Inhibitor, Targeting BET Bromodomains
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Précis: This study suggests that it may be possible to target an important transcriptional regulatory domain that has been implicated in a broad number of aggressive blood cancers, as a generalizable therapeutic approach.

3347 Bevacizumab-Induced Normalization of Blood Vessels in Tumors Hampers Antibody Uptake

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<td><strong>Précis:</strong> By providing deeper insights into the pharmacodynamic requirements for the cytotoxic effects of the paradigm kinase inhibitor imatinib, this study may more broadly assist the development of maximally effective kinase inhibitors for cancer treatment.</td>
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<td><strong>Précis:</strong> This study offers proof of principle for using antiangiogenic drugs to enhance the efficacy of adoptive T-cell therapies for cancer treatment.</td>
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<td><strong>Précis:</strong> Preclinical results show that resistance to the widely used EGFR targeting drug cetuximab, which occurs widely in the clinic, could be prevented by administration of inhibitors of the hedgehog pathway, which appears to be emerging as a major factor in cancer drug resistance more broadly.</td>
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<td>3393</td>
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<td><strong>Précis:</strong> This study provides the basis for the sensitization of cancer cells to DNA damaging agents by targeting the mTOR pathway and gives insight into potential strategies that may enhance therapeutic activity or reduce sequelae from high-dose therapies, particularly in children.</td>
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<td><strong>Précis:</strong> This study offers important new mechanistic insights into how leukemia cells migrate, with potentially important implications for understanding how to block invasive growth by these cells.</td>
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<td><strong>Précis:</strong> This mechanistically extensive study reveals a core pathway of support for cancer stem-like cells in head and neck squamous carcinomas, with implications for new treatment strategies in this setting.</td>
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<td><strong>Précis:</strong> A virus that infects a large proportion of brain tumors in a mouse model.</td>
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<td><strong>Précis:</strong> These findings offer a novel mechanism to enhance our understanding of the tumor-suppressive function of Notch signaling in cancer, with implications in many solid tumor settings.</td>
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www.aacrjournals.org
Dual Role of the Antioxidant Enzyme Peroxiredoxin 6 in Skin Carcinogenesis

Frank Rolfs, Marcel Huber, Florian Gruber, Friederike Bühm, Herbert J. Pfister, Valery N. Bochkov, Erwin Tschachler, Reinhard Dummer, Daniel Hohl, Matthias Schäfer, and Sabine Werner

Précis: Antioxidant functions do not contribute exclusively to tumor suppression, as widely believed, but can also promote tumor development depending on the stage of the disease.

Growth of Triple-Negative Breast Cancer Cells Relies upon Coordinate Autocrine Expression of the Proinflammatory Cytokines IL-6 and IL-8


Précis: Findings offer a preclinical proof of principle to improve therapy of triple-negative breast cancer, a particularly aggressive disease subtype lacking effective mechanism-based interventions.

ABOUT THE COVER

In gliomas, constitutive metabolism of the essential amino acid tryptophan leads to the accumulation of the tryptophan metabolite quinolinic acid. Quinolinic acid is used by tumor cells to generate NAD⁺, thus contributing to the resistance towards radiotherapy and chemotherapy by replenishing depleted intracellular NAD pools. Using Western blot analyses and immunohistochemistry, it was found that the key enzyme leading to accumulation of quinolinic acid, 3-hydroxyanthranilate oxygenate (3-HAO), is expressed by tumor-infiltrating monocytes. Thus, infiltrating monocytes contribute to resistance to cytotoxic therapies in malignant gliomas. For details, see article by Sahm and colleagues on page 3225.