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Collaboration of Kras and Androgen Receptor Signaling Stimulates EZH2 Expression and Tumor-Propagating Cells in Prostate Cancer
Houjian Cai, Sanaz Memarzadeh, Tanya Stoyanova, Zanna Beharry, Andrew S. Kraft, and Owen N. Witte

NFAT1 Supports Tumor-induced Anergy of CD4+ T Cells
Brian T. Abe, Daniel S. Shin, Enric Mocholi, and Fernando Macian

Précis: Results directly implicate CD4+ T-cell anergy in immune escape, opening the possibility of targeting a transcription factor known to induce T-cell anergy as a general strategy to improve any immunotherapy or immunochemotherapy for cancer treatment.

Activation of Robo1 Signaling of Breast Cancer Cells by Slit2 from Stromal Fibroblast Restrains Tumorigenesis via Blocking PI3K/Akt/β-Catenin Pathway

Précis: Finding show how stromal fibroblasts can suppress the tumorigenicity of breast cancer cells, offering a potentially broad spectrum marker for clinical prognosis of breast cancers.

Précis: Prometastatic effects of platelets are organ specific, perhaps explaining the failure of antiplatelet therapy in patients and revealing an unexpected prometastatic role for endothelia-derived P-selectin in lung and liver metastasis.

Précis: This study offers mechanistic insights into how prostate cancer progresses to its deadly final stage when metastatic capabilities emerge, revealing how upregulation of a key transcriptional regulator is linked to the generation of cancer progenitor cells that may be crucial at this stage.
Ink4a/Arf Inactivation with Activation of the NF-κB/IL-6 Pathway Is Sufficient to Drive the Development and Growth of Angiosarcoma
Jinming Yang, Sara Kantrow, Jiqing Sai, Oriana E. Hawkins, Mark Boothby, Gregory D. Ayers, Eric D. Young, Elizabeth G. Demicco, Alexander J. Lazar, Dina Lev, and Ann Richmond

Precis: Results offer clinical implications for targeting the NF-κB/IL-6/STAT3 pathway to treat angiosarcoma, a rare but aggressive cancer of endothelial or lymph vessel cells that is poorly understood.

Ectopic ATP Synthase Blockade Suppresses Lung Adenocarcinoma Growth by Activating the Unfolded Protein Response
Hsin-Yi Chang, Hsuan-Cheng Huang, Tsui-Chin Huang, Pan-Chyr Yang, Yi-Ching Wang, and Hsueh-Fen Juan

Precis: Findings elucidate a feature of mitochondrial ATP synthase expressed at the plasma membrane in lung cancer cells that might be exploited therapeutically.

MicroRNA-21 Modulates the Levels of Reactive Oxygen Species by Targeting SOD3 and TNFα
Xiangming Zhang, Wooi-Loon Ng, Ping Wang, LinIn Tian, Erica Werner, Huichen Wang, Paul Doetsch, and Ya Wang

Precis: An oncogenic microRNA thought to promote cancer mainly by affecting expression of growth regulatory genes may actually do so by regulating genes that promote reactive oxygen species formation, a root driver of carcinogenesis.

Truncated DNMT3B Isoform DNMT3B7 Suppresses Growth, Induces Differentiation, and Alters DNA Methylation in Human Neuroblastoma
Kelly R. Ostler, Qiwei Yang, Timothy J. Looney, Li Zhang, Aparna Vasanthakumar, Yufeng Tian, Mashar Kocherginsky, Stacey L. Raimondi, Jessica G. DeMaio, Helen R. Salwen, Song Gu, Alexandre Chlenski, Arlene Naranjo, Amy Gill, Radhika Peddinti, Bruce T. Lahn, Susan L. Cohn, and Lucy A. Godley

Precis: This study provides insights into the mechanistic basis for epigenetic changes in neuroblastoma, acting at the level of DNA methylation, with the potential to leverage treatments that use all-trans retinoic acid in this disease.

Unphosphorylated STAT1 Promotes Sarcoma Development through Repressing Expression of Fas and Bad and Conferring Apoptotic Resistance

Precis: Findings provide a molecular mechanism to explain the opposing functions between phosphorylated and unphosphorylated STAT1 in the control of the development of aggressive soft-tissue tumors.

Markers of B-Cell Activation in Relation to Risk of Non-Hodgkin Lymphoma
Annalouise J. De Roos, Dana K. Mirick, Kerstin L. Edlefsen, Andrea Z. LaCroix, Kenneth J. Kopecy, Margaret M. Madeleine, Larry Magendantz, and Otoniel Martínez-Maza

Precis: Evidence from a study of postmenopausal women suggests that B-cell activation plays a prominent role in the pathogenesis of non-Hodgkin lymphomas, pointing toward avenues for development of early diagnostic tests for this disease.

Hematologic β-Tubulin VI Isoform Exhibits Genetic Variability That Influences Paclitaxel Toxicity
Luis J. Leandro-García, Susanna Leskela, Lucía Inglada-Pérez, Itigo Landa, Aguirre A. de Cubas, Agnieszka Maliszewska, Iñaki Comino-Méndez, Rocio Letón, Álvaro Gómez-Graña, Raúl Torres, Juan Carlos Ramírez, Sara Álvarez, José Rivera, Constantino Martínez, María Luisa Lozano, Alberto Casco, Mercedes Robledo, and Cristina Rodríguez-Antona

Precis: A genetic variation found in a tubulin isoform expressed only in hematopoietic cells may explain the patient variation in myelosuppression that occurs after treatment with microtubule binding drugs.

Systemic Combination Virotherapy for Melanoma with Tumor Antigen-Expressing Vesicular Stomatitis Virus and Adoptive T-Cell Transfer
Diana M. Rommelfanger, Phonphimon Wongthida, Rosa M. Diaz, Karen M. Kaluz, Jill M. Thompson, Timothy J. Kottek, and Richard G. Vile

Precis: Combining adoptive T-cell therapy with the immune stimulating benefits of oncolytic virotherapy might generate a truly systemic protocol for treatment of metastatic cancers without the need of direct access to the tumor.
B-Raf Activation Cooperates with PTEN Loss to Drive c-Myc Expression in Advanced Prostate Cancer
Jingqiang Wang, Takashi Kobayashi, Nicolas Floch, Carolyn Waugh Kinkade, Alvaro Aytes, David Dankort, Celine Lefebvre, Antonina Mitrofanova, Robert D. Cardill, Martin McMahon, Andrea Calafano, Michael M. Shen, and Cory Abate-Shen

Precise: This study describing a novel model of advanced castration-resistant prostate cancers suggests a generalized approach to target Myc activation, a long-standing goal in cancer research, by combining inhibitors of the PI3K/Akt/mTOR and MAPK signaling pathways.

Effective Photothermal Chemotherapy Using Doxorubicin-Loaded Gold Nanospheres that Target EphB4 Receptors in Tumors
Jian You, Rui Zhang, Chiyi Xiong, Meng Zhong, Maritess Melancon, Sanjay Gupta, Alpa M. Nick, Anil K. Sood, and Chun Li

Precise: A single nanodevice that targets tumor cells with both chemotherapy and phototherapy attacks is shown to exert a synergistic antitumor effect without increased toxicity in a preclinical mouse model.

Oxidation-Mediated DNA Cross-Linking Contributes to the Toxicity of 6-Thioguanine in Human Cells
Reto Brem and Peter Karran

Precise: Two key contributors to the cytotoxicity of anticancer and immunosuppressant thiopurine drugs are their incorporation into DNA and their ability to increase levels of reactive oxygen species.

HER2 Overexpression Renders Human Breast Cancers Sensitive to PARP Inhibition Independently of Any Defect in Homologous Recombination DNA Repair
Somaira Nowshereen, Tiffany Cooper, James A. Bonner, Albert F. LoBuglio, and Eddy S. Yang

Precise: Findings may broaden clinical applications for PARP inhibitors in treating HER2+ breast cancers, many of which ultimately become resistant to HER2 antibody therapies used widely in the clinic.

Effective Combination Therapy for Malignant Glioma with TRAIL-Secreting Mesenchymal Stem Cells and Lipoxygenase Inhibitor MK886
Seong Mok Kim, Ji Sun Woo, Chung Heon Ryu, Jung Yeon Lim, and Sin-Soo Jeun

Precise: Lipoxygenase inhibitors might be repositioned to help TRAIL-based cancer treatment strategies break through persistent translational impediments.

CCN6 Modulates BMP Signaling via the Smad-Independent TAK1/p38 Pathway, Acting to Suppress Metastasis of Breast Cancer
Anupama Pal, Wei Huang, Xin Li, Kathy A. Toy, Zaneta Nikolovska-Coleska, and Celina G. Kleer

Precise: Findings identify a novel modifier pathway through which the extracellular matrix protein CCN6 limits the effects of the TGF-β signaling axis on breast cancer invasion and metastasis.

PCA-1/ALKBH3 Contributes to Pancreatic Cancer by Supporting Apoptotic Resistance and Angiogenesis
Ichiro Yamato, Masayuki Sho, Keiji Shimada, Kiyohiko Hotta, Yuko Ueda, Satoshi Yawada, Naoko Shigi, Noboru Konishi, Kazutake Tsujikawa, and Yoshiyuki Nakajima

Precise: Findings suggest functional insights for a little-studies DNA repair gene in the pathophysiology of pancreatic cancer, with possible impacts on progression and therapeutic management.

TGF-β and αvβ6 Integrin Act in a Common Pathway to Suppress Pancreatic Cancer Progression
Aram F. Hezel, Vikram Deshpande, Stephanie M. Zimmermann, Gianmarco Contino, Brinda Alagesan, Michael R. O’Dell, Lee B. Rivera, Jay Harper, Scott Lonning, Rolf A. Brekken, and Nabeel Bardeesy

Precise: Findings from this preclinical study provide support for the argument that blocking the TGF-β pathway may actually accelerate disease progression, challenging concepts about the potential benefit of such an approach in cancer patients.

The Antioxidant Tempol Reduces Carcinogenesis and Enhances Survival in Mice When Administered after Nonlethal Total Body Radiation
James B. Mitchell, Miriam R. Anver, Anastasia L. Sowers, Philip S. Rosenberg, Maria Figueroa, Angela Thetford, Murali C. Krishna, Paul S. Albert, and John A. Cook

Precise: Findings prompt human studies of an antioxidant compound that can limit radiation-induced secondary malignancies after radiation therapy, and that may reduce the risks of cancer in individuals exposed to nonlethal radiation as a result of nuclear accidents or attacks.

TUMOR AND STEM CELL BIOLOGY
Candidate Pathways for Promoting Differentiation or Quiescence of Oligodendrocyte Progenitor-like Cells in Glioma

Joseph D. Dougherty, Elena I. Fomchenko, Afua A. Akuffo, Eric Schmidt, Karim Y. Helmy, Elena Bazzoli, Cameron W. Brennan, Eric C. Holland, and Ana Milosevic

Précis: Translational profiling of mouse and human glioblastomas identified several candidate pathways that promote quiescence or differentiation rather than proliferation in these tumors, suggesting new therapeutic targets for combination treatment.

Correction: Deletion of the Endothelial Bmx Tyrosine Kinase Decreases Tumor Angiogenesis and Growth

Correction: Prognostic PET 18F-FDG Uptake Imaging Features Are Associated with Major Oncogenomic Alterations in Patients with Resected Non–Small Cell Lung Cancer

ABOUT THE COVER

Complete tumor eradication by thermal ablation therapy alone is often difficult because of sub-lethal thermal dose in some areas of the tumor. For photothermal ablation therapy, it is highly desirable to selectively deliver combined thermal ablation therapy and other treatment modalities such as chemotherapy through a single nanodevice. Using doxorubicin-loaded hollow gold nanospheres conjugated with a high-affinity cyclic peptide recognizing EphB4 receptors, it was found that targeted nanoparticles displayed significantly higher tumor uptakes than nanoparticles without peptidyl homing ligands. Moreover, treatment with near-infrared laser led to synergistic antitumor effect without increased toxicities in a preclinical mouse model. For details, see article by You and colleagues on page 4777.