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582  Aberrant Activation of Notch Signaling Inhibits PROX1 Activity to Enhance the Malignant Behavior of Thyroid Cancer Cells
Dongwon Choi, Swapnika Ramu, Eunkyung Park, Eunson Jung, Sara Yang, Wonhyeok Jung, Inho Choi, Sunjoo Lee, Kyu Eui Kim, Young Jin Seoong, Mingu Hong, George Daghlian, Daniel Kim, Eugene Shin, Jung In Seo, Vicken Khatchadourian, Mengchen Zou, Wei Li, Roger De Filippo, Paul Kokorowski, Andy Chang, Steve Kim, Ana Bertoni, Tania Weber Furlanetto, Sung Shin, Meng Li, Yibu Chen, Alex Wong, Chester Koh, Jan Geliebter, and Young Kwon Hong

Précis: This study provides new insights into a potentially actionable molecular alteration underlying progression of aggressive thyroid cancers.

594  DNA Hypomethylation and Histone Variant macroH2A1 Synergistically Attenuate Chemotherapy-Induced Senescence to Promote Hepatocellular Carcinoma Progression

Précis: Epigenetic synergy between DNA methylation and histone variants contributes to the refractoriness of liver cancer cells to chemotherapy, with implications for identification of a biomarker of drug-induced senescent cells that may predict disease progression.

607  SIGMAR1 Regulates Membrane Electrical Activity in Response to Extracellular Matrix Stimulation to Drive Cancer Cell Invasiveness
David Crottès, Raphael Rapetti-Mauss, Francisco Alcaraz-Perez, Mélanie Tichet, Giuseppina Cariano, Sonia Martial, Hélène Guizouarn, Bernard Pellissier, Agnès Loubat, Alexandra Popa, Agnès Paquet, Marco Presta, Sophie Tartare-Deckert, Maria Luisa Cayuela, Patrick Martin, Franck Borgese, and Olivier Soria

Précis: An important regulator of ion channel activity in cancer cells is found to promote aggressive and invasive behaviors, with potential implications for new therapeutic approaches to treat cancer.

619  PBX3 and MEIS1 Cooperate in Hematopoietic Cells to Drive Acute Myeloid Leukemias Characterized by a Core Transcriptome of the MLL-Rearranged Disease
Zejuan Li, Ping Chen, Rui Su, Chao Hu, Yuanruan Li, Abdel G. Elkhalloun, Zhixiang Zuo, Sandeep Gurbuxani, Stephen Arnovitz, Hengyou Weng, Yungui Wang, Shenglai Li, Hao Huang, Mary Beth Neilly, Gang Greg Wang, Xi Jiang, Paul P. Liu, Jie Jin, and Jianjun Chen

Précis: A gene expression signature stimulated by two homeobox transcription factors in hematopoietic precursor offers intriguing new insights into how acute myeloid leukemias may arise.

PREVENTION AND EPIDEMIOLOGY

630  Systemic Chromosome Instability Resulted in Colonic Transcriptomic Changes in Metabolic, Proliferation, and Stem Cell Regulators in Sgo1−/− Mice

Précis: A mouse model of chromosome instability reveals aberrant regulation of unexpected pathways and offers new targets for therapeutic and preventive strategies.

643  Bereavement Is Associated with an Increased Risk of HPV Infection and Cervical Cancer: An Epidemiological Study in Sweden
Donghao Lu, Karin Sundström, Pär Sparén, Katja Fall, Arvid Sjölander, Joakim Dillner, Nathalie Ylitalo Helm, Hans-Olov Adami, Unnur Valdimarsdóttir, and Fang Fang

Précis: Women who experience the loss of an immediate family member are at a higher risk of developing cervical cancer, possibly related to an increased incidence of oncogenic HPV infections, with implications for identifying at-risk individuals who could benefit from increased screening.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

652  Hydroxamic Acid and Benzoic Acid–Based STAT3 Inhibitors Suppress Human Glioma and Breast Cancer Phenotypes In Vitro and In Vivo
Peibin Yue, Francisco Lopez-Tapia, David Paladino, Yifei Li, Chih-Hong Chen, Andrew T. Namanja, Tyvette Hillard, Yuan Chen, Marcus A. Tius, and James Turkson

Précis: STAT3 offers an attractive target for cancer therapy, but small molecule inhibitors with appealing pharmacologic and biologic properties in animals have been elusive.
Elucidation and Pharmacological Targeting of Novel Molecular Drivers of Follicular Lymphoma Progression
Brygida Bisikirska, Mukesh Bansal, Yao Shen, Julie Tenya-Feldstein, Raju Chaganti, and Andrea Califano

Précis: Computational interrogation of human B-cell regulatory networks enables the identification of key drivers of follicular lymphoma and provides a generalized approach for the systematic analysis of drug combinations that may offer the strongest antitumor responses.

Modulation of EZH2 Expression by MEK-ERK or PI3K-AKT Signaling in Lung Cancer Is Dictated by Different KRAS Oncogene Mutations

Précis: For those lung cancer patients whose tumors harbor KRAS mutations, the specific type of mutation determines which kinase effector signaling pathways to target along with the histone methyltransferase EZH2, defined here as a novel KRAS effector.

Deguelin Analogue SH-1242 Inhibits Hsp90 Activity and Exerts Potent Anticancer Efficacy with Limited Neurotoxicity
Su-Chan Lee, Hye-Young Min, Hoon Choi, Song Yi Bae, Kwan Hee Park, Seung Yeob Hyun, Ho Jin Lee, Jayoung Moon, Shin-Hyung Park, Jun Yong Kim, Hongghan An, So-Jung Park, Ji Hae Seo, Seungbeom Lee, Young-Myeong Kim, Hyun-Ju Park, Sang Kook Lee, Jeewoo Lee, Jeeyeon Lee, Ryu-Won Kim, Young-Ger Suh, and Ho-Young Lee

Précis: This study reports an important advance in the development of Hsp90 inhibitors as cancer therapeutics, a drug class that is appealing in principle but limited to date by significant toxic side-effects that have impeded clinical development.

Agonists of the TRAIL Death Receptor DR5 Sensitize Intestinal Stem Cells to Chemotherapy-Induced Cell Death and Trigger Gastrointestinal Toxicity
Niklas K. Finnberg, Prashanth Gokare, Arunasalam Navaraj, Krystle A. Lang Kuhs, George Cerniglia, Hideo Yagita, Kazuyoshi Takeda, Noboru Motoyama, and Wafik S. El-Deiry

Précis: These findings suggest a strategy to reduce gastrointestinal toxicities that arise from combining chemotherapy with TRAIL death receptor agonists, with clinical implications for developing these agents for cancer therapy.

Therapeutic Targeting of Tumor-Derived R-Spondin Attenuates β-Catenin Signaling and Tumorigenesis in Multiple Cancer Types
Cécile Charrier, Janak Raval, Fumiko Axelrod, Chris Bond, Jennifer Cain, Cristina Dee-Hoskins, Shirley Ma, Marcus M. Fischer, Jalpa Shah, Jie Wei, May Ji, Andrew Lam, Michelle Stroud, Wan-Ching Yen, Pete Yeung, Belinda Cancilla, Gilbert O’Young, Min Wang, Ann M. Kapoun, John Lewicki, Timothy Hoey, and Austin Gurney

Précis: R-spondin proteins are defined as enhancers of tumorigenic Wnt/β-catenin signaling, suggesting a novel mechanistic strategy to target β-catenin-driven cancers.

Recurrent MLK4 Loss-of-Function Mutations Suppress JNK Signaling to Promote Colon Tumorigenesis

Précis: This study establishes a tumor suppressor role for a kinase that is frequently inactivated by mutation in colon cancer, leading to inactivation of JNK pathway signaling, aberrant cell proliferation, and enhanced tumor growth.

Myc Induces miRNA-Mediated Apoptosis in Response to HDAC Inhibition in Hematologic Malignancies
Clare M. Adams, Scott W. Hiebert, and Christine M. Eischen

Précis: This study highlights a surprising role for Myc in activating a miRNA-mediated apoptotic program, the implications of which increase understanding of how HDAC inhibitors selectively target malignant cells.
Integrated Genomic Analysis of Pancreatic Ductal Adenocarcinomas Reveals Genomic Rearrangement Events as Significant Drivers of Disease

Stephen J. Murphy, Steven N. Hart, Geoffrey C. Halling, Sarah H. Johnson, James B. Smadbeck, Travis Drucker, Joema Felipe Lima, Fariborz Rakhshan Rohakhtar, Faye R. Harris, Farhad Kosari, Subhaya Subramanian, Gloria M. Petersen, Timothy D. Wiltshire, Benjamin R. Kipp, Mark J. Truty, Robert R. McWilliams, Fergus J. Couch, and George Vasmatzis

Précis: Large genomic rearrangements may perturb signaling pathways that drive pancreatic cancer initiation, affecting progression to the same extent as point mutations, underscoring the need for comprehensive genomic analysis to elucidate disease mechanisms.

Correction: Development of a New Tracking Tool for the Human Monomeric Laminin-γ2 Chain In Vitro and In Vivo

ABOUT THE COVER

The monomeric Casitas B-lineage lymphoma (c-Cbl, CBL) RING finger ubiquitin ligase (blue) can bind to phosphorylated RTK (orange peptide) via the TKID domain. Upon phosphorylation, CBL undergoes a large conformational change that positions the ubiquitin-conjugating enzyme E2 (green) active site close to RTK. Cancer mutation sites are mapped on the structure of the complex and are shown in yellow; Zn ions are shown as blue balls. Other stages of the CBL activation cycle are depicted in Figure 1 of the article. For details, see article by Li and colleagues on page 561.