

CANCER RESEARCH

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BREAKING INSIGHTS

1923 Highlights from Recent Cancer Literature

REVIEW

1925 **Insights into the Links between MYC and 3D Chromatin Structure and Epigenetics Regulation: Implications for Cancer Therapy**
Fatemeh Amjadi-Moheb, Alireza Paniri, and Haleh Akhavan-Niaki

CANCER RESEARCH HIGHLIGHTS

1937 **Towards Taming the Bugs to Improve the Drugs for Breast Cancer**
Dipali Sharma
See related article, p. 2195

1940 **Moving Toward the Ideal Autologous Adoptive T-cell Therapy for Cancer**
Brian H. Ladle
See related article, p. 2184

GENOME AND EPIGENOME

1942 **miR-31 Displays Subtype Specificity in Lung Cancer**
Mackenzie L. Davenport, John B. Echols, Austin D. Silva, Joshua C. Anderson, Philip Owens, Clayton Yates, Qing Wei, Shuko Harada, Douglas R. Hurst, and Mick D. Edmonds
These findings demonstrate the oncogenic properties of miR-31 in specific subtypes of lung cancer and highlight it as a potential therapeutic target in these subtypes.

1954

Loss-of-Function Variants in the Tumor-Suppressor Gene *PTPN14* Confer Increased Cancer Risk

Thorhildur Olafsdottir, Simon N. Stacey, Gardar Sveinbjornsson, Gudmar Thorleifsson, Kristjan Norland, Bardur Sigurgeirsson, Kristin Thorisdottir, Arni Kjalar Kristjansson, Laufey Tryggvadottir, Kavita Y. Sarin, Rafn Benediktsson, Jon G. Jonasson, Asgeir Sigurdsson, Aslaug Jonasdottir, Snaedis Kristmundsdottir, Hakon Jonsson, Arnaldur Gylfason, Asmundur Oddsson, Run Fridriksdottir, Sigurjon A. Gudjonsson, Florian Zink, Sigrun H. Lund, Solvi Rognvaldsson, Pall Melsted, Valgerdur Steinhorsdottir, Julius Gudmundsson, Evgenia Mikaelsdottir, Pall I. Olason, Lilja Stefansdottir, Hannes P. Eggertsson, Bjarni V. Halldorsson, Unnur Thorsteinsdottir, Tomas T. Agustsson, Karl Olafsson, Jon H. Olafsson, Patrick Sulem, Thorunn Rafnar, Daniel F. Gudbjartsson, and Kari Stefansson

This study identifies the tumor-suppressor gene *PTPN14* as a high-impact BCC predisposition gene and indicates that inactivation of *PTPN14* by germline sequence variants may lead to increased risk of cervical cancer.

1965

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Tet2 Inactivation Enhances the Antitumor Activity of Tumor-Infiltrating Lymphocytes

Minjung Lee, Jianfang Li, Jia Li, Shaohai Fang, Joanna Zhang, Anh Tran Tram Vo, Wei Han, Hongxiang Zeng, Sevinj Isgandarova, Margarita Martinez-Moczygemba, Yubin Zhou, Deqiang Sun, and Yun Huang

This study suggests that ablation of TET2⁺ from TILs could promote their antitumor function by reshaping chromatin accessibility for key transcription factors and enhancing the transcription of genes essential for antitumor activity.

1977

Chr20q Amplification Defines a Distinct Molecular Subtype of Microsatellite Stable Colorectal Cancer

Baoyi Zhang, Kevin Yao, Emily Zhou, Lanjing Zhang, and Chao Cheng

This study shows that chromosome 20q amplification occurs predominately in microsatellite-stable colorectal cancer and defines a distinct subtype with good prognosis, high chromosomal instability, distinct mutation profiles, and low immune infiltrations.

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METABOLISM AND CHEMICAL BIOLOGY

- 1988** **Fat Induces Glucose Metabolism in Nontransformed Liver Cells and Promotes Liver Tumorigenesis**
Lindsay A. Broadfield, João André Gonçalves Duarte, Roberta Schmieder, Dorien Broekaert, Koen Veys, Mélanie Planque, Kim Vriens, Yasuaki Karasawa, Francesco Napolitano, Suguru Fujita, Masashi Fujii, Miki Eto, Bryan Holvoet, Roman Vangoitsenhoven, Juan Fernandez-Garcia, Joke Van Elsen, Jonas Dehairs, Jia Zeng, James Dooley, Rebeca Alba Rubio, Jos van Pelt, Thomas G.P. Grünewald, Adrian Liston, Chantal Mathieu, Christophe M. Deroose, Johannes V. Swinnen, Diether Lambrechts, Diego di Bernardo, Shinya Kuroda, Katrien De Bock, and Sarah-Maria Fendt
With obesity-induced hepatocellular carcinoma on a rising trend, this study shows in normal, nontransformed livers that fat induces glucose metabolism similar to an oncogenic transformation.

MOLECULAR CELL BIOLOGY

- 2002** **Targeting eIF4A-Dependent Translation of KRAS Signaling Molecules**
A C Kamini Singh, Jianan Lin, Nicolas Lecomte, Prathibha Mohan, Askan Gokce, Viraj R. Sanghvi, Man Jiang, Olivera Grbovic-Huezo, Antonija Burćul, Stefan G. Stark, Paul B. Romesser, Qing Chang, Jerry P. Melchor, Rachel K. Beyer, Mark Duggan, Yoshiyuki Fukase, Guangli Yang, Ouathék Ouerfelli, Agnes Viale, Elisa de Stanchina, Andrew W. Stamford, Peter T. Meinke, Gunnar Rättsch, Steven D. Leach, Zhengqing Ouyang, and Hans-Guido Wendel
These findings document the coordinate, eIF4A-dependent translation of RAS-related oncogenic signaling molecules and demonstrate therapeutic efficacy of eIF4A blockade in pancreatic adenocarcinoma.
- 2015** **HDAC11 Regulates Glycolysis through the LKB1/AMPK Signaling Pathway to Maintain Hepatocellular Carcinoma Stemness**
Lei Bi, Yidan Ren, Maoxiao Feng, Peng Meng, Qin Wang, Weiping Chen, Qinlian Jiao, Yuli Wang, Lutao Du, Fuqiong Zhou, Yucui Jiang, Feiyan Chen, Chuanxin Wang, Bo Tang, and Yunshan Wang
This study finds that HDAC11 suppresses LKB1 expression in HCC to promote cancer stemness, progression, and sorafenib resistance, suggesting the potential of targeting HDAC11 to treat HCC and overcome kinase inhibitor resistance.
- 2029** **PLEKHA4 Promotes Wnt/ β -Catenin Signaling-Mediated G₁-S Transition and Proliferation in Melanoma**
Adnan Shami Shah, Xiaofu Cao, Andrew C. White, and Jeremy M. Baskin
This study establishes that melanoma cell proliferation requires the protein PLEKHA4 to promote pathological Wnt signaling for proliferation, highlighting PLEKHA4 inhibition as a new avenue for the development of targeted therapies.

- 2044** **The miR-181a-SFRP4 Axis Regulates Wnt Activation to Drive Stemness and Platinum Resistance in Ovarian Cancer**
Anil Belur Nagaraj, Matthew Knarr, Sreeja Sekhar, R. Shae Connor, Peronne Joseph, Olga Kovalenko, Alexis Fleming, Arshia Surti, Elmar Nurmammedov, Luca Beltrame, Sergio Marchini, Michael Kahn, and Analisa DiFeo
These results demonstrate that miR-181a is an activator of Wnt signaling that drives stemness and chemoresistance in HGSOc and may be targeted therapeutically in recurrent disease.
- 2056** **Data-Driven Computational Modeling Identifies Determinants of Glioblastoma Response to SHP2 Inhibition**
Evan K. Day, Qing Zhong, Benjamin Purow, and Matthew J. Lazzara
These findings demonstrate that allosteric SHP2 inhibitors have multivariate and context-dependent effects in glioblastoma that may make them useful components of some combination therapies, but not others.
- 2071** **Targeting Pan-ETS Factors Inhibits Melanoma Progression**
Lee Huang, Yougang Zhai, Jennifer La, Jason W. Lui, Stephen P.G. Moore, Elizabeth C. Little, Sixia Xiao, Adil J. Haresi, Candice Brem, Jag Bhawan, and Deborah Lang
These findings identify YK-4-279 as a promising therapeutic agent against melanoma by targeting multiple ETS family members and blocking their ability to act as transcription factors.
- 2086** **Therapeutic Targeting of DGKA-Mediated Macropinocytosis Leads to Phospholipid Reprogramming in Tuberous Sclerosis Complex**
Andrii Kovalenko, Andres Sanin, Kosmas Kosmas, Long Zhang, Ji Wang, Elie W. Akl, Krinio Giannikou, Clemens K. Probst, Thomas R. Hougaard, Ryan W. Rue, Vera P. Krymskaya, John M. Asara, Hilaire C. Lam, David J. Kwiatkowski, Elizabeth P. Henske, and Harilaos Filippakis
This study identifies macropinocytosis and phospholipid metabolism as novel mechanisms of metabolic homeostasis in mTORC1-hyperactive cells and suggest ritanserin as a novel therapeutic strategy for use in mTORC1-hyperactive tumors, including pancreatic cancer.

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TUMOR BIOLOGY AND IMMUNOLOGY

2101 **The Irradiated Brain Microenvironment Supports Glioma Stemness and Survival via Astrocyte-Derived Transglutaminase 2**

Tracy J. Berg, Carolina Marques, Vasiliki Pantazopoulou, Elinn Johansson, Kristoffer von Stedingk, David Lindgren, Pauline Jeannot, Elin J. Pietras, Tobias Bergström, Fredrik J. Swartling, Valeria Governa, Johan Bengzon, Mattias Belting, Hakan Axelsson, Massimo Squatrito, and Alexander Pietras

These findings presented here indicate that radiotherapy can result in a tumor-supportive microenvironment, the targeting of which may be necessary to overcome tumor cell therapeutic resistance and recurrence.

2116 **YAP and β -Catenin Cooperate to Drive Oncogenesis in Basal Breast Cancer**

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Hazel M. Quinn, Regina Vogel, Oliver Popp, Philipp Mertins, Linxiang Lan, Clemens Messerschmidt, Alexandro Landshammer, Kamil Lisek, Sophie Château-Joubert, Elisabetta Marangoni, Elle Koren, Yaron Fuchs, and Walter Birchmeier

These findings show that YAP cooperates with β -catenin in basal-like breast cancer to regulate CSCs and that targeting this interaction may be a novel CSC therapy for patients with basal-like breast cancer.

2128 **Targeting IGF Perturbs Global Replication through Ribonucleotide Reductase Dysfunction**

Guillaume Rieunier, Xiaoning Wu, Letitia E. Harris, Jack V. Mills, Ashwin Nandakumar, Laura Colling, Elena Seraia, Stephanie B. Hatch, Daniel V. Ebner, Lisa K. Folkes, Ulrike Weyer-Czernilofsky, Thomas Bogenrieder, Anderson J. Ryan, and Valentine M. Macaulay

This study identifies regulation of ribonucleotide reductase function and dNTP supply by IGFs and demonstrates that IGF axis blockade induces replication stress and reciprocal co-dependence on ATM.

2142 **Tumor-Derived Pericytes Driven by EGFR Mutations Govern the Vascular and Immune Microenvironment of Gliomas**

Berta Segura-Collar, María Garranzo-Asensio, Beatriz Herranz, Esther Hernández-SanMiguel, Teresa Cejalvo, Bárbara S. Casas, Ander Matheu, Ángel Pérez-Núñez, Juan Manuel Sepúlveda-Sánchez, Aurelio Hernández-Lain, Verónica Palma, Ricardo Gargini, and Pilar Sánchez-Gómez

This study identifies the EGFR-related mechanisms that govern the capacity of glioma cells to transdifferentiate into pericytes, regulating the vascular and the immune phenotype of the tumors.

2157 **Activated ALK Cooperates with N-Myc via Wnt/ β -Catenin Signaling to Induce Neuroendocrine Prostate Cancer**

Kenji Unno, Zachary R. Chalmers, Sahithi Pamarthy, Rajita Vataapalli, Yara Rodriguez, Barbara Lysy, Hanlin Mok, Vinay Sagar, Huiying Han, Young A. Yoo, Sheng-Yu Ku, Himisha Beltran, Yue Zhao, and Sarki A. Abdulkadir

These findings demonstrate that coactivation of ALK and N-Myc induces NEPC by stimulating the Wnt/ β -catenin pathway, which can be targeted therapeutically.

2171 **Ubiquitin-Specific Protease 6 Functions as a Tumor Suppressor in Ewing Sarcoma through Immune Activation**

Ian C. Henrich, Kanika Jain, Robert Young, Laura Quick, Jarrett M. Lindsay, Daniel H. Park, Andre M. Oliveira, Gerd A. Blobel, and Margaret M. Chou

This study reveals a novel tumor-suppressive function for USP6 by inducing an immunostimulatory microenvironment, suggesting that USP6 activity may be exploited to enhance immunotherapy regimens.

TRANSLATIONAL SCIENCE

2184 **T Cells Expanded from PD-1⁺ Peripheral Blood Lymphocytes Share More Clones with Paired Tumor-Infiltrating Lymphocytes**

Tiepeng Li, Lingdi Zhao, Yonghao Yang, Yao Wang, Yong Zhang, Jindong Guo, Guangyu Chen, Peng Qin, Benling Xu, Baozhen Ma, Fang Zhang, Yiman Shang, Qingjun Li, Kai Zhang, Dongfeng Yuan, Chaojie Feng, Yan Ma, Zhiyong Liu, Zhichao Tian, Hongle Li, Shengdian Wang, and Quanli Gao

This study harnesses the tumor reactivity of PD-1⁺ PBLs, developing a method to expand T cells from these clones as a potential therapeutic strategy and TIL substitute in patients with cancer.

See related commentary, p. 1940

2195 **Gut Microbiota Condition the Therapeutic Efficacy of Trastuzumab in HER2-Positive Breast Cancer**

Martina Di Modica, Giorgio Gargari, Viola Regondi, Arianna Bonizzi, Stefania Arioli, Beatrice Belmonte, Loris De Cecco, Elena Fasano, Francesca Bianchi, Alessia Bertolotti, Claudio Tripodo, Laura Villani, Fabio Corsi, Simone Guglielmetti, Andrea Balsari, Tiziana Triulzi, and Elda Tagliabue

Evidence of gut microbiota involvement in trastuzumab efficacy represents the foundation for new therapeutic strategies aimed at manipulating commensal bacteria to improve response in trastuzumab-resistant patients.

See related commentary, p. 1937

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2207 **Pronociceptive Roles of Schwann Cell-Derived Galectin-3 in Taxane-Induced Peripheral Neuropathy**

Madoka Koyanagi, Satoshi Imai, Mayuna Matsumoto, Yoko Iguma, Nobuko Kawaguchi-Sakita, Takeshi Kotake, Yuki Iwamitsu, Mpumelelo Ntoga, Ren Hiraiwa, Kazuki Nagayasu, Mamiko Saigo, Takashi Ogihara, Atsushi Yonezawa, Tomohiro Omura, Shunsaku Nakagawa, Takayuki Nakagawa, and Kazuo Matsubara

These findings demonstrate that the elevation of plasma galectin-3 is a CIPN-related pathological change common to humans and mice, and that targeting galectin-3 is a therapeutic option to delay CIPN progression.

2220 **Targeting the HuR Oncogenic Role with a New Class of Cytoplasmic Dimerization Inhibitors**

Natalia Filippova, Xiuhua Yang, Subramaniam Ananthan, Jennifer Calano, Vibha Pathak, Larry Bratton, Rakesh H. Vekariya, Sixue Zhang, Edward Ofori, Emily N Hayward, David Namkoong, David K. Crossman, Michael R. Crowley, Peter H King, James Mobley, and Louis B. Nabors

These findings utilize a cell-based mechanism of action assay with a structure-activity relationship compound development pathway to discover inhibitors that target HuR dimerization, a mechanism required for cancer promotion.

CONVERGENCE AND TECHNOLOGIES

2234 **Cytoplasmic Localization of Prostate-Specific Membrane Antigen Inhibitors May Confer Advantages for Targeted Cancer Therapies**

Jessica Matthias, Johann Engelhardt, Martin Schäfer, Ulrike Bauder-Wüst, Philipp T. Meyer, Uwe Haberkorn, Matthias Eder, Klaus Kopka, Stefan W. Hell, and Ann-Christin Eder

This study uses STED fluorescence microscopy to reveal the subcellular fate of PSMA/PSMA inhibitor complexes near the molecular level, providing insights of great clinical interest and suggestive of advantageous targeted therapies.

POPULATION AND PREVENTION SCIENCE

2246 **Association of the Age at Menarche with Site-Specific Cancer Risks in Pooled Data from Nine Cohorts**

Barbara J. Fuhrman, Steven C. Moore, Celia Byrne, Issam Makhoul, Cari M. Kitahara, Amy Berrington de González, Martha S. Linet, Elisabete Weiderpass, Hans-Olov Adami, Neal D. Freedman, Linda M. Liao, Charles E. Matthews, Rachael Z. Stolzenberg-Solomon, Mia M. Gaudet, Alpa V. Patel, I-Min Lee, Julie E. Buring, Alicja Wolk, Susanna C. Larsson, Anna E. Prizment, Kim Robien, Michael Spriggs, David P. Check, Neil Murphy, Marc J. Gunter, Harold L. Van Dusen Jr, Regina G. Ziegler, and Robert N. Hoover

Age at menarche is associated with risk for seven cancers in middle-aged women, and understanding the shared underlying causal pathways across these cancers may suggest new avenues for cancer prevention.

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ABOUT THE COVER

Immunofluorescence staining of the postpartum mouse mammary gland shows membrane-bound β -catenin (white) and nuclei (blue). YAP increases β -catenin activity to facilitate the luminal to basal transdifferentiation of mammary cells and promotes basal-like cancer formation. Targeting the YAP/TEAD4/ β -catenin complex offers a potential therapeutic strategy for treating basal-like breast cancers. For details, see article by Quinn and colleagues on page 2116.

