

BREAKING ADVANCES

- 1671** Highlights from Recent Cancer Literature

CANCER RESEARCH 75th ANNIVERSARY COMMENTARIES

- 1673** Commentary on Folkman: "Tumor Angiogenesis Factor"
Rebecca G. Bagley
- 1675** Tumor Cell Invasion—Not All Barriers Are Created Equal
Danny R. Welch

REVIEWS

- 1677** Kruppel-like Pluripotency Factors as Modulators of Cancer Cell Therapeutic Responses
Mark K. Farrugia, Daniel B. Vanderbilt, Mohamad A. Salkeni, and J. Michael Ruppert
- 1683** Combining Epigenetic and Immunotherapy to Combat Cancer
Katherine B. Chiappinelli, Cynthia A. Zahnow, Nita Ahuja, and Stephen B. Baylin

PRIORITY REPORTS

- 1690** Notch4 Signaling Induces a Mesenchymal–Epithelial–like Transition in Melanoma Cells to Suppress Malignant Behaviors
Ehsan Bonyadi Rad, Heinz Hammerlindl, Christian Wels, Ulrich Popper, Dinoop Ravindran Menon, Heimo Breiteneder, Melitta Kitzwoegerer, Christine Hafner, Meenhard Herlyn, Helmut Bergler, and Helmut Schaidler
Précis: The finding that Notch4 exerts tumor suppressive effects in melanoma cells sheds light on the observed clinical ineffectiveness of pan-Notch inhibition in melanoma patients and calls for more targeted approaches.
- 1698** A Preclinical Model of Chronic Alcohol Consumption Reveals Increased Metastatic Seeding of Colon Cancer Cells in the Liver
Hwi-Jin Im, Hyeong-Geug Kim, Jin-Seok Lee, Hyo-Seon Kim, Jung-Hyo Cho, Il-Joo Jo, Sung-Joo Park, and Chang-Gue Son
Précis: The link between chronic alcohol consumption and increased liver metastasis of colon cancer cells is attributed in this study to alcohol-induced hepatic inflammatory mechanisms, which engender immune escape.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 1705** The Cancer Stem Cell Fraction in Hierarchically Organized Tumors Can Be Estimated Using Mathematical Modeling and Patient-Specific Treatment Trajectories
Benjamin Werner, Jacob G. Scott, Andrea Sottoriva, Alexander R.A. Anderson, Arne Traulsen, and Philipp M. Altrock
Précis: Patient-specific data were used to develop a mathematical model that estimates the fraction of tumor-initiating cells during multiple stages of tumor growth and therapy-induced tumor regression, offering new opportunities to monitor and adjust treatment regimens accordingly.
- 1714** Genomic Landscape of Somatic Alterations in Esophageal Squamous Cell Carcinoma and Gastric Cancer
Nan Hu, Mitsutaka Kadota, Huaitian Liu, Christian C. Abnet, Hua Su, Hailong Wu, Neal D. Freedman, Howard H. Yang, Chaoyu Wang, Chunhua Yan, Leming Wang, Sheryl Gere, Amy Hutchinson, Guohong Song, Yuan Wang, Ti Ding, You-Lin Qiao, Jill Koshiol, Sanford M. Dawsey, Carol Giffen, Alisa M. Goldstein, Philip R. Taylor, and Maxwell P. Lee
Précis: These findings illuminate the genomic landscape of genome instability and mutation profiles that underlie the development of gastric cancer and esophageal squamous cell carcinoma.
- 1724** Distinct Subtypes of Gastric Cancer Defined by Molecular Characterization Include Novel Mutational Signatures with Prognostic Capability
Xiangchun Li, William K.K. Wu, Rui Xing, Sunny H. Wong, Yuxin Liu, Xiaodong Fang, Yanlin Zhang, Mengyao Wang, Jiaqian Wang, Lin Li, Yong Zhou, Senwei Tang, Shaoliang Peng, Kunlong Qiu, Longyun Chen, Kexin Chen, Huanming Yang, Wei Zhang, Matthew T.V. Chan, Youyong Lu, Joseph J.Y. Sung, and Jun Yu
Précis: This study represents an important milestone in the molecular stratification of gastric cancer, which is not a single disease and where subtype classification is still evolving to improve clinical prognosis and treatment.
- 1733** An Atlas of the Human Kinome Reveals the Mutational Landscape Underlying Dysregulated Phosphorylation Cascades in Cancer
Aleksandra Olow, Zhongzhong Chen, R. Hannes Niedner, Denise M. Wolf, Christina Yau, Aleksandr Pankov, Evelyn Pei Rong Lee, Lamorna Brown-Swigart, Laura J. van 't Veer, and Jean-Philippe Coppé
Précis: By curating a large number of public databases, this study created a large map of human kinase circuits that can be globally interrogated to identify mutated signaling nodes in cancers and to select actionable targets for therapy.

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MICROENVIRONMENT AND IMMUNOLOGY

1746 Calreticulin Expression in Human Non–Small Cell Lung Cancers Correlates with Increased Accumulation of Antitumor Immune Cells and Favorable Prognosis



Jitka Fucikova, Etienne Becht, Kristina Iribarren, Jeremy Goc, Romain Remark, Diane Damotte, Marco Alifano, Priyanka Devi, Jerome Biton, Claire Germain, Audrey Lupo, Wolf Herve Fridman, Marie-Caroline Dieu-Nosjean, Guido Kroemer, Catherine Sautès-Fridman, and Isabelle Cremer

Précis: These findings highlight the potential for calreticulin, a potent "eat-me" signal on cancer cells that triggers antitumor immune responses, to serve as a clinical prognostic biomarker in patients with non-small cell lung cancer.

1757 TGF β Signaling Intersects with CD103 Integrin Signaling to Promote T-Lymphocyte Accumulation and Antitumor Activity in the Lung Tumor Microenvironment

Marie Boutet, Ludiane Gauthier, Marine Leclerc, Gwendoline Gros, Vincent de Montpreville, Nathalie Théret, Emmanuel Donnadieu, and Fathia Mami-Chouaib

Précis: New mechanistic insights into the antitumorigenic role of TGF β reveal its participation in inside-out integrin signaling to promote the recruitment and activity of T lymphocytes in the tumor microenvironment.

1770 Exosomes Derived from Hypoxic Oral Squamous Cell Carcinoma Cells Deliver miR-21 to Normoxic Cells to Elicit a Prometastatic Phenotype

Ling Li, Chao Li, Shaoxin Wang, Zhaohui Wang, Jian Jiang, Wei Wang, Xiaoxia Li, Jin Chen, Kun Liu, Chunhua Li, and Guiquan Zhu

Précis: Tumor cells in hypoxic regions may remotely educate cells in oxygen-rich regions to invasively invade local tissue by secreting exosomes, which deliver proinvasive miRNAs to the recipient cells.

1781 Chromogranin A Is Preferentially Cleaved into Proangiogenic Peptides in the Bone Marrow of Multiple Myeloma Patients

Mimma Bianco, Anna Maria Gasparri, Barbara Colombo, Flavio Curmis, Stefania Girlanda, Maurilio Ponzoni, Maria Teresa Sabrina Bertilaccio, Arianna Calcinotto, Angelina Sacchi, Elisabetta Ferrero, Marina Ferrarini, Marta Chesi, P. Leif Bergsagel, Matteo Bellone, Giovanni Tonon, Fabio Ciceri, Magda Marcatti, Federico Caligaris-Cappio, and Angelo Corti

Précis: Angiogenesis during multiple myeloma appears to be regulated by bone marrow–derived signals that alter the balance of circulating anti- and proangiogenic chromogranin A polypeptides, with potential prognostic and therapeutic implications for patients with this hematological malignancy.

1792 Basophil Recruitment into Tumor-Draining Lymph Nodes Correlates with Th2 Inflammation and Reduced Survival in Pancreatic Cancer Patients

Lucia De Monte, Sonja Wörmann, Emanuela Brunetto, Silvia Heltai, Gilda Magliacane, Michele Reni, Anna Maria Paganoni, Helios Recalde, Anna Mondino, Massimo Falconi, Francesca Aleotti, Gianpaolo Balzano, Hana Algül, Claudio Doglioni, and Maria Pia Protti

Précis: These findings suggest a new strategy to attack pancreatic cancers by undermining basophil-mediated signals in the tumor microenvironment that drive pathogenic inflammation and poor patient outcomes.

1804 Fibroblast-Mediated Collagen Remodeling Within the Tumor Microenvironment Facilitates Progression of Thyroid Cancers Driven by Brai^{V600E} and Pten Loss

Lee Ann Jolly, Sergey Novitskiy, Phillip Owens, Nicole Massoll, Nikki Cheng, Wei Fang, Harold L. Moses, and Aime T. Franco

Précis: Thyroid cancers tend to be manageable clinically, but more aggressive forms that can be problematic appear to be driven by extracellular matrix remodeling events that facilitate progression, with implications for identifying therapeutic targets in this setting.

MOLECULAR AND CELLULAR PATHOBIOLOGY

1814 Mutational Landscape and Antiproliferative Functions of ELF Transcription Factors in Human Cancer

Mizuo Ando, Masahito Kawazu, Toshihide Ueno, Daizo Koinuma, Koji Ando, Junji Koya, Keisuke Kataoka, Takahiko Yasuda, Hiroyuki Yamaguchi, Kazutaka Fukumura, Azusa Yamato, Manabu Soda, Eirin Sai, Yoshihiro Yamashita, Takahiro Asakage, Yasushi Miyazaki, Mineo Kurokawa, Kohei Miyazono, Stephen D. Nimer, Tatsuya Yamasoba, and Hiroyuki Mano

Précis: This study reveals that ELF transcription factors are inactivated frequently in a wide range of human cancers, where they can function as tumor suppressors.

1825 The Ephrin-A1/EPHA2 Signaling Axis Regulates Glutamine Metabolism in HER2-Positive Breast Cancer

Victoria M. Youngblood, Laura C. Kim, Deanna N. Edwards, Yoonha Hwang, Pranav R. Santapuram, Steven M. Stirdivant, Pengcheng Lu, Fei Ye, Dana M. Brantley-Sieders, and Jin Chen

Précis: This study highlights a potential opportunity to therapeutically target glutamine-dependent cells that support tumor growth.

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1837 Phytoestrogen Suppresses Efflux of the Diagnostic Marker Protoporphyrin IX in Lung Carcinoma

Hirofumi Fujita, Keisuke Nagakawa, Hirotsugu Kobuchi, Tetsuya Ogino, Yoichi Kondo, Keiji Inoue, Taro Shuin, Toshihiko Utsumi, Kozo Utsumi, Junzo Sasaki, and Hideyo Ohuchi

Précis: The efficacy of photodynamic diagnostic approaches in lung carcinoma may finally improve upon the finding here that accumulation of the fluorescent diagnostic marker protoporphyrin IX in malignant tissues can be enhanced through phytoestrogen pretreatment.

1847 RASSF1A Directly Antagonizes RhoA Activity through the Assembly of a Smurf1-Mediated Destruction Complex to Suppress Tumorigenesis



Min-Goo Lee, Seong-In Jeong, Kyung-Phil Ko, Soon-Ki Park, Byung-Kyu Ryu, Ick-Young Kim, Jeong-Kook Kim, and Sung-Gil Chi

Précis: These findings provide mechanistic insights into the tumor suppressor role of RASSF1A in a variety of cancers, where it appears to antagonize the oncogenic activity of the small GTPase RhoA.

1860 Mutational Landscape of Aggressive Prostate Tumors in African American Men

Karla J. Lindquist, Pamela L. Paris, Thomas J. Hoffmann, Niall J. Cardin, Rémi Kazma, Joel A. Mefford, Jeffrey P. Simko, Vy Ngo, Yalei Chen, Albert M. Levin, Dhananjay Chitale, Brian T. Helfand, William J. Catalona, Benjamin A. Rybicki, and John S. Witte

Précis: The first whole genome sequencing study of prostate tumors in African American patients reveals novel somatic mutation patterns not previously reported in patients of European descent that may help identify the genetic determinants underlying higher prostate cancer incidence and mortality rate in this susceptible patient cohort.

1869 Deletion of Interstitial Genes between *TMPRSS2* and *ERG* Promotes Prostate Cancer Progression

Douglas E. Linn, Kathryn L. Penney, Roderick T. Bronson, Lorelei A. Mucci, and Zhe Li

Précis: Genomic deletions that occur during production of an oncogenic fusion gene in some prostate cancers are found to help drive malignant progression, with potential implications for new prognostic markers in this setting.

1882 Ovarian Cancers Harboring Inactivating Mutations in *CDK12* Display a Distinct Genomic Instability Pattern Characterized by Large Tandem Duplications

Tatiana Popova, Elodie Manié, Valentina Boeva, Aude Battistella, Oumou Goundiam, Nicholas K. Smith, Christopher R. Mueller, Virginie Raynal, Odette Mariani, Xavier Sastre-Garau, and Marc-Henri Stern

Précis: Certain ovarian cancers display a distinct genomic instability phenotype associated with massive genomic tandem duplications and impairment of a kinase that regulates C-terminal phosphorylation of RNA polymerase II.

1892 Cystine Deprivation Triggers Programmed Necrosis in VHL-Deficient Renal Cell Carcinomas

Xiaohu Tang, Jianli Wu, Chien-Kuang Ding, Min Lu, Melissa M. Keenan, Chao-Chieh Lin, Chih-An Lin, Charles C. Wang, Daniel George, David S. Hsu, and Jen-Tsan Chi

Précis: Renal cell carcinomas exhibiting classical loss of the VHL tumor suppressor are addicted to cystine, a point of vulnerability that can be exploited selectively to trigger necrotic cell death, strengthening the rationale to develop antimetabolites as cancer therapy.

1904 Small RNAs Recruit Chromatin-Modifying Enzymes MMSET and Tip60 to Reconfigure Damaged DNA upon Double-Strand Break and Facilitate Repair

Qinhong Wang and Michael Goldstein

Précis: This study presents a mechanism by which DNA double-strand break-induced small RNAs participate in the repair of damaged DNA through the modulation of chromatin remodeling events and provides supporting evidence for the role of specialized RNAs in regulating DNA damage responses.

PREVENTION AND EPIDEMIOLOGY

1916 Discordant Haplotype Sequencing Identifies Functional Variants at the 2q33 Breast Cancer Risk Locus



Nicola J. Camp, Wei-Yu Lin, Alex Bigelow, George J. Burghel, Timothy L. Mosbrugger, Marina A. Parry, Rosalie G. Waller, Sushilaben H. Rigas, Pei-Yi Tai, Kristofer Berrett, Venkatesh Rajamanickam, Rachel Cosby, Ian W. Brock, Brandt Jones, Dan Connley, Robert Sargent, Guoying Wang, Rachel E. Factor, Philip S. Bernard, Lisa Cannon-Albright, Stacey Knight, Ryan Abo, Theresa L. Werner, Malcolm W.R. Reed, Jason Gertz, and Angela Cox

Précis: A novel approach for identifying the specific functional variants linked to breast cancer risk may bridge the gap between genetic associations and relevant mechanisms of disease.

1926 The Proliferative Activity of Mammary Epithelial Cells in Normal Tissue Predicts Breast Cancer Risk in Premenopausal Women

Sung Jin Huh, Hannah Oh, Michael A. Peterson, Vanessa Almendro, Rong Hu, Michaela Bowden, Rosina L. Lis, Maura B. Cotter, Massimo Loda, William T. Barry, Kornelia Polyak, and Rulla M. Tamimi

Précis: The fraction of proliferative mammary epithelial cells in normal breast tissue of premenopausal women predicts prospective breast cancer risk, with potential implications for care and screening frequency in high-risk women.

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1935 Low Levels of Circulating Adiponectin Are Associated with Multiple Myeloma Risk in Overweight and Obese Individuals

Jonathan N. Hofmann, Brenda M. Birman, Lauren R. Teras, Ruth M. Pfeiffer, Ye Wang, Demetrius Albanes, Dalsu Baris, Graham A. Colditz, Anneclaire J. De Roos, Graham G. Giles, H. Dean Hosgood, Qing Lan, Ola Landgren, Linda M. Liao, Nathaniel Rothman, Stephanie J. Weinstein, Michael N. Pollak, Marian L. Neuhouser, and Mark P. Purdue

Précis: The findings of this large prospective study reveal an obesity-associated factor that confers an increased risk of multiple myeloma in heavy individuals, with implications for identifying at-risk patients who could benefit from early screening and therapeutic intervention.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

1942 Phosphatase PTP4A3 Promotes Triple-Negative Breast Cancer Growth and Predicts Poor Patient Survival

Petra den Hollander, Kathryn Rawls, Anna Tsimelzon, Jonathan Shepherd, Abhijit Mazumdar, Jamal Hill, Suzanne A.W. Fuqua, Jenny C. Chang, C. Kent Osborne, Susan G. Hilsenbeck, Gordon B. Mills, and Powel H. Brown

Précis: This study emphasizes the importance of phosphatases in triple-negative breast cancer by demonstrating PTP4A3 as a protumorigenic factor and an independent predictor of poor overall survival in this aggressive breast cancer subtype, with implications for the development of new targeted therapies.

1954 Identification of DNA Methylation–Independent Epigenetic Events Underlying Clear Cell Renal Cell Carcinoma

Elinne Becket, Sameer Chopra, Christopher E. Duymich, Justin J. Lin, Jueng Soo You, Kurinji Pandiyan, Peter W. Nichols, Kimberly D. Siegmund, Jessica Charlet, Daniel J. Weisenberger, Peter A. Jones, and Gangning Liang

Précis: An approach to identify new epigenetically regulated therapeutic targets, beyond standard DNA methylation profiling, may complement current genetic-based treatment strategies.

1965 Small-Molecule Inhibition of GCNT3 Disrupts Mucin Biosynthesis and Malignant Cellular Behaviors in Pancreatic Cancer

Chinthalapally V. Rao, Naveena B. Janakiram, Venkateshwar Madka, Gaurav Kumar, Edgar J. Scott, Gopal Pathuri, Taylor Bryant, Hannah Kutche, Yuting Zhang, Laura Biddick, Hariprasad Gali, Yan D. Zhao, Stan Lightfoot, and Altaf Mohammed

Précis: The identification of an enzyme in the mucin biosynthesis pathway offers new opportunities to overcome poor anticancer drug delivery, which is associated with excessive mucin production in pancreatic cancer and other cancers.

1975 Pharmacological Inhibition of the Histone Lysine Demethylase KDM1A Suppresses the Growth of Multiple Acute Myeloid Leukemia Subtypes

John P. McGrath, Kaylyn E. Williamson, Srividya Balasubramanian, Shobu Odate, Shilpi Arora, Charlie Hatton, Thomas M. Edwards, Thomas O'Brien, Steven Magnuson, David Stokoe, Danette L. Daniels, Barbara M. Bryant, and Patrick Trojer

Précis: Multiple AML subtypes appear to rely critically on a particular lysine-specific demethylase, especially subtypes harboring RUNX1-RUNX1T1 translocations, rendering these aggressive blood tumors highly sensitive to therapeutic eradication by pharmacological inhibitors of this enzyme.

TUMOR AND STEM CELL BIOLOGY

1989 Small-Molecule Prodigiosin Restores p53 Tumor Suppressor Activity in Chemoresistant Colorectal Cancer Stem Cells via c-Jun-Mediated Δ Np73 Inhibition and p73 Activation

Varun V. Prabhu, Bo Hong, Joshua E. Allen, Shengliang Zhang, Amriti R. Lulla, David T. Dicker, and Wafik S. El-Deiry

Précis: These findings illuminate the mechanism underlying the antitumor effects of the small molecule prodigiosin in colorectal cancer stem cells, offering a preclinical rationale for the clinical study of p73-activating approaches to treat refractory and recurrent colorectal cancers.

2000 Aspirin Suppresses the Acquisition of Chemoresistance in Breast Cancer by Disrupting an NF κ B–IL6 Signaling Axis Responsible for the Generation of Cancer Stem Cells

Shilpi Saha, Shravanti Mukherjee, Poulami Khan, Kirti Kajal, Minakshi Mazumdar, Argha Manna, Sanhita Mukherjee, Sunanda De, Debarshi Jana, Diptendra K. Sarkar, and Tanya Das

Précis: These results suggest that aggressive recurrence of breast cancer after chemotherapy might be suppressed in part with aspirin, which appears to disrupt the de novo generation of chemoresistant cancer stem-like cells.

2013 Combined Treatment with Epigenetic, Differentiating, and Chemotherapeutic Agents Cooperatively Targets Tumor-Initiating Cells in Triple-Negative Breast Cancer

Vanessa F. Merino, Nguyen Nguyen, Kideok Jin, Helen Sadik, Soonweng Cho, Preethi Korangath, Liangfeng Han, Yolanda M.N. Foster, Xian C. Zhou, Zhe Zhang, Roisin M. Connolly, Vered Stearns, Syed Z. Ali, Christina Adams, Qian Chen, Duoqia Pan, David L. Huso, Peter Ordentlich, Angela Brodie, and Saraswati Sukumar

Précis: The combined effects of HDAC inhibition, retinoid-induced cell differentiation, and chemotherapy appear to target tumor-initiating cells and trigger regressions in triple-negative breast cancer, with implications for overcoming disease recurrence due to residual cancer stem-like cell populations.

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- 2025** **Formation of Renal Cysts and Tumors in *Vhl/Trp53*-Deficient Mice Requires HIF1 α and HIF2 α**
Désirée Schönenberger, Sabine Harlander, Michal Rajski, Robert A. Jacobs, Anne-Kristine Lundby, Mojca Adlesic, Tomas Hejhal, Peter J. Wild, Carsten Lundby, and Ian J. Frew

Précis: This study highlights the complexity and multifaceted functions for oxygen-sensing pathways during the malignant progression of kidney cancers.

- 2037** **Candidate Antimetastasis Drugs Suppress the Metastatic Capacity of Breast Cancer Cells by Reducing Membrane Fluidity**
Weina Zhao, Sara Prijic, Bettina C. Urban, Michael J. Tisza, Yan Zuo, Lin Li, Zhi Tan, Xiaoling Chen, Sendurai A. Mani, and Jeffrey T. Chang

Précis: Increased membrane fluidity appears to be an inherent feature of metastatic breast cancer cells and represents a new target, for which therapeutic agents already exist, in the prevention of cancer metastasis.

LETTERS TO THE EDITOR

- 2050** **REG3 β Plays a Key Role in IL17RA Protumoral Effect—Letter**
Qing Li, Jun-Li Liu, and Zu-Hua Gao

- 2051** **REG3 β Plays a Key Role in IL17RA Protumoral Effect—Response**
Celine Loncle, Laia Bonjoch, Emma Folch-Puy, Maria Belen Lopez-Millan, Sophie Lac, Maria Inés Molejon, Eduardo Chuluyan, Pierre Cordelier, Pierre Dubus, Gwen Lomberk, Raul Urrutia, Daniel Closa, and Juan L. Iovanna

CORRECTION

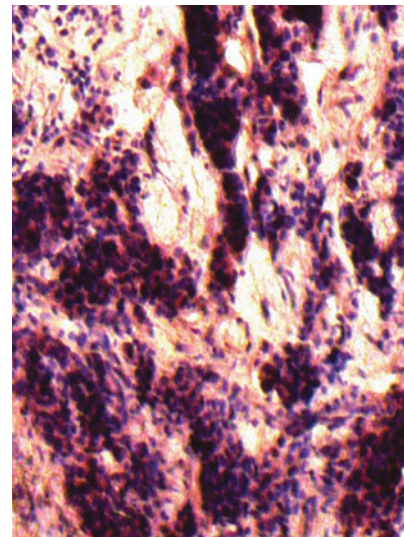
- 2052** **Correction: Lupeol Suppresses Cisplatin-Induced Nuclear Factor- κ B Activation in Head and Neck Squamous Cell Carcinoma and Inhibits Local Invasion and Nodal Metastasis in an Orthotopic Nude Mouse Model**

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ABOUT THE COVER

Accumulating evidence suggests a major role for cancer stem cells (CSC) in chemoresistance. An interplay between breast CSCs and non-CSCs involving NF κ B/IL6 paracrine loop was decoded as the mechanism responsible for expansion of invasive, chemoresistant CSC population in patients suffering from disease relapse after chemotherapy. The image shows immunostaining for NF κ B (brown), a pivotal inflammatory regulator, in primary tumors of patients with breast cancer that acquired aggressive phenotype following chemotherapy. Prior treatment with aspirin suppressed acquisition of chemoresistance by perturbing NF κ B nuclear translocation in pre-existing CSCs. Thus, combining aspirin and chemotherapy may offer a new treatment strategy to improve recurrence-free survival of breast cancer patients. For details, see article by Saha and colleagues on page 2000.



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