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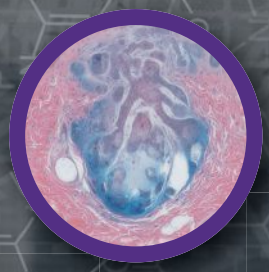
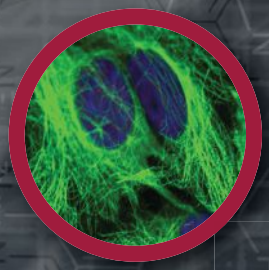
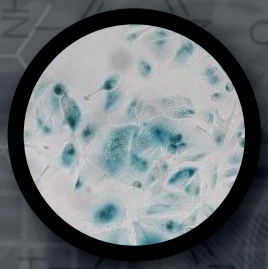

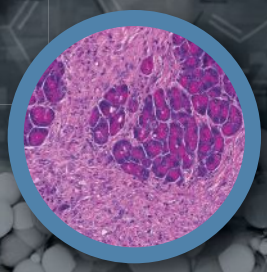
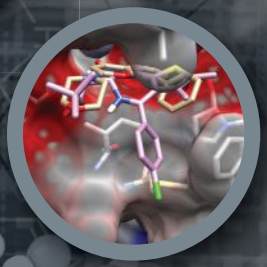

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The AACR is proud to present "The Best of the AACR Journals," a collection of the most-cited articles published in 2015 across the AACR journal portfolio. We congratulate the authors of these outstanding articles for their tireless efforts and contributions to the cancer research field. **To find out more about the authors, access the authors' profiles online at: aacrjournals.org/content/bestof-author-profiles**

Each journal's section in the collection includes the most-cited review article and the four most-cited research articles based on the total number of citations from date of publication through January 2017.

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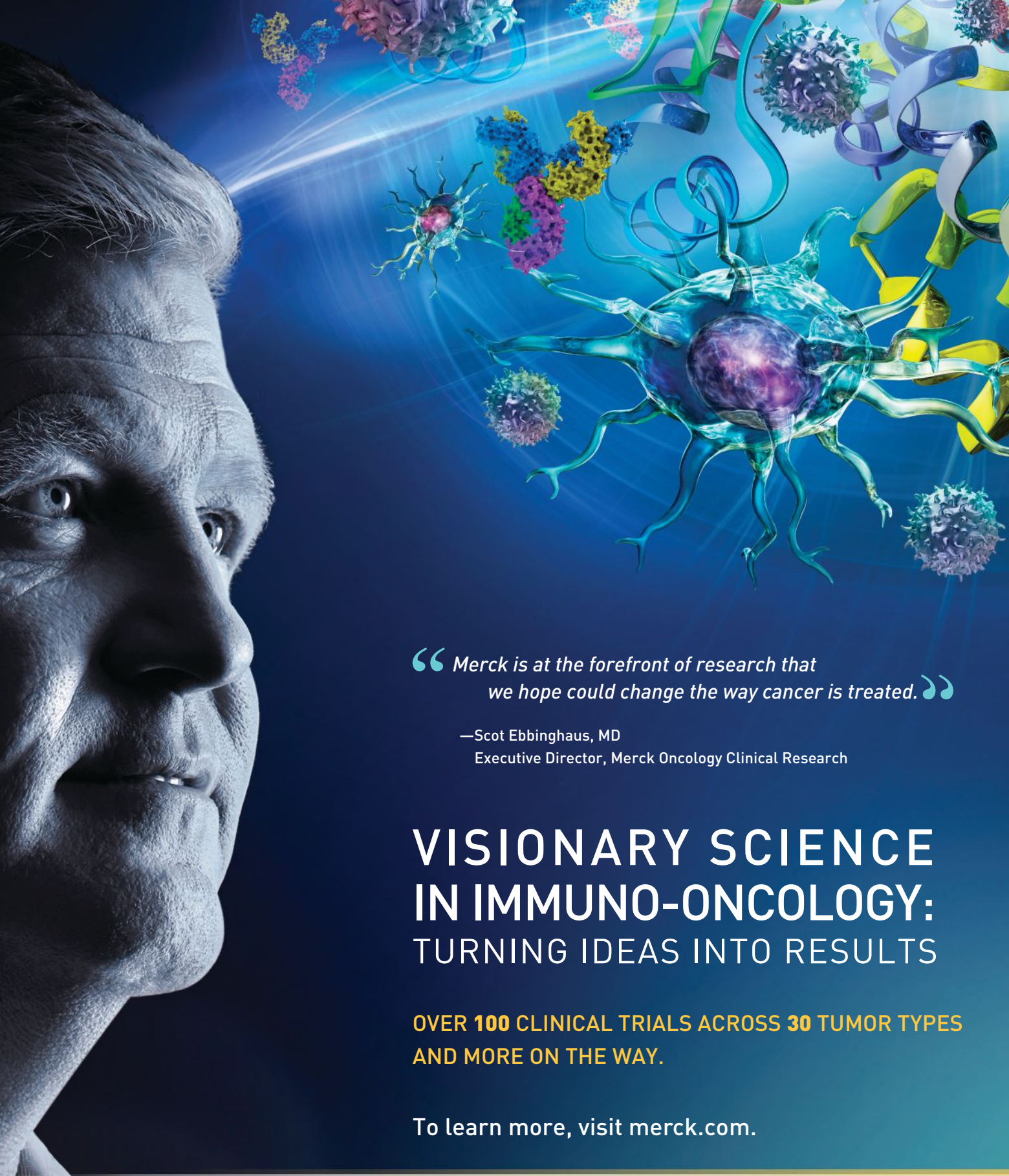

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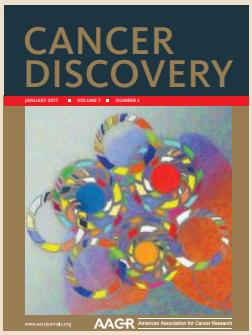

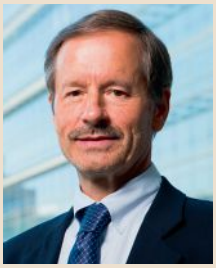

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Scope

Cancer Discovery publishes high-impact, peer-reviewed articles describing major advances in research and clinical trials. As the premier cancer information resource, the Journal also presents Review Articles, Perspectives and Commentaries, News stories, and Research Watch summaries of important journal articles to its readers to keep them informed about the latest findings in the field. Topics span the spectrum of cancer research and medicine from the laboratory to the clinic and epidemiologic studies.

Review Article

Endoplasmic Reticulum Stress–Activated Cell Reprogramming in Oncogenesis

Eric Chevet, Claudio Hetz, and Afshin Samali

Eric Chevet

Claudio Hetz

Afshin Samali

Abstract

Stress induced by the accumulation of unfolded proteins in the endoplasmic reticulum (ER) is observed in many human diseases, including cancers. Cellular adaptation to ER stress is mediated by the unfolded protein response (UPR), which aims at restoring ER homeostasis. The UPR has emerged as a major pathway in remodeling cancer gene expression, thereby either preventing cell transformation or providing an advantage to transformed cells. UPR sensors are highly regulated by the formation of dynamic protein scaffolds, leading to integrated reprogramming of the cells. Herein, we describe the regulatory mechanisms underlying UPR signaling upon cell intrinsic or extrinsic challenges, and how they engage cell transformation programs and/or provide advantages to cancer cells, leading to enhanced aggressiveness or chemoresistance. We discuss the emerging cross-talk between the UPR and related metabolic processes to ensure maintenance of protein homeostasis and its impact on cell transformation and tumor growth.

Significance: ER stress signaling is dysregulated in many forms of cancer and contributes to tumor growth as a survival factor, in addition to modulating other disease-associated processes, including cell migration, cell transformation, and angiogenesis. Evidence for targeting the ER stress signaling pathway as an anticancer strategy is compelling, and novel agents that selectively inhibit the UPR have demonstrated preliminary evidence of preclinical efficacy with an acceptable safety profile. *Cancer Discov; 5(6); 586–97. ©2015 AACR.*

Cancer Discov; 5(6); 586–97; published OnlineFirst June 2015; doi: 10.1158/2159-8290.CD-14-1490

Research Brief

The Vigorous Immune Microenvironment of Microsatellite Instable Colon Cancer Is Balanced by Multiple Counter-Inhibitory Checkpoints

Drew M. Pardoll

Franck Housseau

Nicolas J. Llosa, Michael Cruise, Ada Tam, Elizabeth C. Wicks, Elizabeth M. Hechenbleikner, Janis M. Taube, Richard L. Blosser, Hongni Fan, Hao Wang, Brandon S. Luber, Ming Zhang, Nickolas Papadopoulos, Kenneth W. Kinzler, Bert Vogelstein, Cynthia L. Sears, Robert A. Anders, Drew M. Pardoll, and Franck Housseau

Abstract

We examined the immune microenvironment of primary colorectal cancer using immunohistochemistry, laser capture microdissection/qRT-PCR, flow cytometry, and functional analysis of tumor-infiltrating lymphocytes. A subset of colorectal cancer displayed high infiltration with activated $CD8^+$ cytotoxic T lymphocyte (CTL) as well as activated Th1 cells characterized by IFNγ production and the Th1 transcription factor Tbet. Parallel analysis of tumor genotypes revealed that virtually all of the tumors with this active Th1/CTL microenvironment had defects in mismatch repair, as evidenced by microsatellite instability (MSI). Counterbalancing this active Th1/CTL microenvironment, MSI tumors selectively demonstrated highly upregulated expression of multiple immune checkpoints, including five—PD-1, PD-L1, CTLA-4, LAG-3, and IDO—currently being targeted clinically with inhibitors. These findings link tumor genotype with the immune microenvironment, and explain why MSI tumors are not naturally eliminated despite a hostile Th1/CTL microenvironment. They further suggest that blockade of specific checkpoints may be selectively efficacious in the MSI subset of colorectal cancer.

Significance: The findings reported in this article are the first to demonstrate a link between a genetically defined subtype of cancer and its corresponding expression of immune checkpoints in the tumor microenvironment. The mismatch repair–defective subset of colorectal cancer selectively upregulates at least five checkpoint molecules that are targets of inhibitors currently being clinically tested. *Cancer Discov; 5(1); 43–51. ©2014 AACR.*

Cancer Discov; 5(1); 43–51. ©2014; Published OnlineFirst January 2015; doi: 10.1158/2159-8290.CD-14-0863

Research Brief

Response to MET Inhibitors in Patients with Stage IV Lung Adenocarcinomas Harboring *MET* Mutations Causing Exon 14 Skipping

Paul K. Paik

Paul K. Paik, Alexander Drilon, Pang-Dian Fan, Helena Yu, Natasha Rekhtman, Michelle S. Ginsberg, Laetitia Borsu, Nikolaus Schultz, Michael F. Berger, Charles M. Rudin, and Marc Ladanyi

Abstract

Mutations in the *MET* exon 14 RNA splice acceptor and donor sites, which lead to exon skipping, deletion of the juxtamembrane domain containing the CBL E3-ubiquitin ligase-binding site, and decreased turnover of the resultant aberrant MET protein, were previously reported to be oncogenic in preclinical models. We now report responses to the MET inhibitors crizotinib and cabozantinib in four patients with stage IV lung adenocarcinomas harboring mutations leading to *MET* exon 14 skipping, highlighting a new therapeutic strategy for the 4% of lung adenocarcinoma patients whose tumors harbor this previously underappreciated genetic alteration.

Significance: Oncogenic mutations in the *MET* exon 14 splice sites that cause exon 14 skipping occur in 4% of lung adenocarcinomas. We report responses to the MET inhibitors crizotinib and cabozantinib in patients with lung adenocarcinomas harboring *MET* exon 14 splice site mutations, identifying a new potential therapeutic target in this disease. *Cancer Discov; 5(8); 842–9. ©2015 AACR.*

Cancer Discov; 5(8); 842–9; Published OnlineFirst August 2015; doi: 10.1158/2159-8290.CD-14-1467

Research Brief

Heterogeneity Underlies the Emergence of *EGFR*^{T790} Wild-Type Clones Following Treatment of T790M-Positive Cancers with a Third-Generation EGFR Inhibitor

Lecia V. Sequist

Zofia Piotrowska, Matthew J. Niederst, Chris A. Karlovich, Heather A. Wakelee, Joel W. Neal, Mari Mino-Kenudson, Linnea Fulton, Aaron N. Hata, Elizabeth L. Lockerman, Anuj Kalsy, Subba Digumarthy, Alona Muzikansky, Mitch Raponi, Angel R. Garcia, Hillary E. Mulvey, Melissa K. Parks, Richard H. DiCecca, Dora Dias-Santagata, A. John Iafrate, Alice T. Shaw, Andrew R. Allen, Jeffrey A. Engelman, and Lecia V. Sequist

Abstract

Rociletinib is a third-generation EGFR inhibitor active in lung cancers with T790M, the gatekeeper mutation underlying most first-generation EGFR drug resistance. We biopsied patients at rociletinib progression to explore resistance mechanisms. Among 12 patients with T790M-positive cancers at rociletinib initiation, six had T790–wild-type rociletinib-resistant biopsies. Two T790–wild-type cancers underwent small cell lung cancer transformation; three T790M-positive cancers acquired *EGFR* amplification. We documented T790–wild-type and T790M-positive clones coexisting within a single pre-rociletinib biopsy. The pretreatment fraction of T790M-positive cells affected response to rociletinib. Longitudinal circulating tumor DNA (ctDNA) analysis revealed an increase in plasma EGFR-activating mutation, and T790M heralded rociletinib resistance in some patients, whereas in others the activating mutation increased but T790M remained suppressed. Together, these findings demonstrate the role of tumor heterogeneity when therapies targeting a singular resistance mechanism are used. To further improve outcomes, combination regimens that also target T790–wild-type clones are required.

Significance: This report documents that half of T790M-positive *EGFR*-mutant lung cancers treated with rociletinib are T790–wild-type upon progression, suggesting that T790–wild-type clones can emerge as the dominant source of resistance. We show that tumor heterogeneity has important clinical implications and that plasma ctDNA analyses can sometimes predict emerging resistance mechanisms. *Cancer Discov; 5(7); 713–22. ©2015 AACR.*

Cancer Discov; 5(7); 713–22; Published OnlineFirst July 2015; *doi: 10.1158/2159-8290.CD-15-0399*

Research Brief

Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets

Priscilla K. Brastianos

Scott L. Carter

William C. Hahn

Priscilla K. Brastianos, Scott L. Carter, Sandro Santagata, Daniel P. Cahill, Amaro Taylor-Weiner, Robert T. Jones, Eliezer M. Van Allen, Michael S. Lawrence, Peleg M. Horowitz, Kristian Cibulskis, Keith L. Ligon, Josep Tabernero, Joan Seoane, Elena Martinez-Saez, William T. Curry, Ian F. Dunn, Sun Ha Paek, Sung-Hye Park, Aaron McKenna, Aaron Chevalier, Mara Rosenberg, Frederick G. Barker II, Corey M. Gill, Paul Van Hummelen, Aaron R. Thorner, Bruce E. Johnson, Mai P. Hoang, Toni K. Choueiri, Sabina Signoretti, Carrie Sougnez, Michael S. Rabin, Nancy U. Lin, Eric P. Winer, Anat Stemmer-Rachamimov, Matthew Meyerson, Levi Garraway, Stacey Gabriel, Eric S. Lander, Rameen Beroukhim, Tracy T. Batchelor, José Baselga, David N. Louis, Gad Getz, and William C. Hahn

Abstract

Brain metastases are associated with a dismal prognosis. Whether brain metastases harbor distinct genetic alterations beyond those observed in primary tumors is unknown. We performed whole-exome sequencing of 86 matched brain metastases, primary tumors, and normal tissue. In all clonally related cancer samples, we observed branched evolution, where all metastatic and primary sites shared a common ancestor yet continued to evolve independently. In 53% of cases, we found potentially clinically informative alterations in the brain metastases not detected in the matched primary-tumor sample. In contrast, spatially and temporally separated brain metastasis sites were genetically homogenous. Distal extracranial and regional lymph node metastases were highly divergent from brain metastases. We detected alterations associated with sensitivity to PI3K/AKT/mTOR, CDK, and HER2/EGFR inhibitors in the brain metastases. Genomic analysis of brain metastases provides an opportunity to identify potentially clinically informative alterations not detected in clinically sampled primary tumors, regional lymph nodes, or extracranial metastases.

Significance: Decisions for individualized therapies in patients with brain metastasis are often made from primary-tumor biopsies. We demonstrate that clinically actionable alterations present in brain metastases are frequently not detected in primary biopsies, suggesting that sequencing of primary biopsies alone may miss a substantial number of opportunities for targeted therapy. *Cancer Discov; 5(11); 1164–77. ©2015 AACR.*

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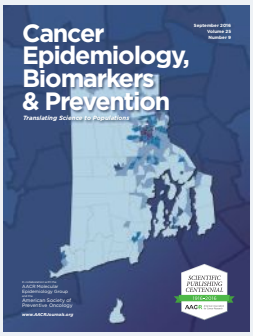

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Editor-in-Chief

Scope

Cancer Epidemiology, Biomarkers & Prevention publishes original, peer-reviewed, population-based research on cancer etiology, prevention, surveillance, and survivorship. The following topics are of special interest: descriptive, analytical, and molecular epidemiology; biomarkers including assay development, validation, and application; chemoprevention and other types of prevention research in the context of descriptive and observational studies; the role of behavioral factors in cancer etiology and prevention; survivorship studies; risk factors; and the science of cancer health disparities. Besides welcoming manuscripts that address individual subjects in any of the relevant disciplines, *CEBP* editors encourage the submission of manuscripts with a transdisciplinary approach.

Review Article

Prevalence of Major Risk Factors and Use of Screening Tests for Cancer in the United States

Stacey A. Fedewa, Ann Goding Sauer, Rebecca L. Siegel, and Ahmedin Jemal

Stacey A. Fedewa

Abstract

Much of the suffering and death from cancer could be prevented by more systematic efforts to reduce tobacco use, improve diet, increase physical activity, reduce obesity, and expand the use of established screening tests. Monitoring the prevalence of cancer risk factors and screening is important to measure progress and strengthen cancer prevention and early detection efforts. In this review article, we provide recent prevalence estimates for several cancer risk factors, including tobacco, obesity, physical activity, nutrition, ultraviolet radiation exposure as well as human papillomavirus and hepatitis B vaccination coverage and cancer screening prevalence in the United States. In 2013, cigarette smoking prevalence was 17.8% among adults nationally, but ranged from 10.3% in Utah to 27.3% in West Virginia. In addition, 15.7% of U.S. high school students were current smokers. In 2011–2012, obesity prevalence was high among both adults (34.9%) and adolescents (20.5%), but has leveled off since 2002. About 20.2% of high school girls were users of indoor tanning devices, compared with 5.3% of boys. In 2013, cancer screening prevalence ranged from 58.6% for colorectal cancer to 80.8% for cervical cancer and remains low among the uninsured, particularly for colorectal cancer screening where only 21.9% of eligible adults received recommended colorectal cancer screening. *Cancer Epidemiol Biomarkers Prev; 24(4); 637–52. ©2015 AACR.*

Cancer Epidemiol Biomarkers Prev; 24(4); 637–52; Published OnlineFirst April 2015; doi: 10.1158/1055-9965.EPI-15-0134

Research Article

Quality of Physician Communication about Human Papillomavirus Vaccine: Findings from a National Survey

Melissa B. Gilkey, Teri L. Malo, Parth D. Shah, Megan E. Hall, and Noel T. Brewer

Melissa B. Gilkey

Abstract

Background: Improving the quality of physicians' recommendations for human papillomavirus (HPV) vaccination is critical to addressing low coverage. Thus, we sought to describe HPV vaccine communication practices among primary care physicians.

Methods: Pediatricians and family physicians (n = 776) completed our national online survey in 2014. We assessed the quality of their HPV vaccine recommendations on strength of endorsement (i.e., saying the vaccine is important), timeliness (recommending it by ages 11–12), consistency (recommending it routinely vs. using a risk-based approach), and urgency (recommending same-day vaccination).

Results: A sizeable minority of physicians reported that they do not strongly endorse HPV vaccine (27%) or deliver timely recommendations for girls (26%) or boys (39%). Many physicians (59%) used a risk-based approach to recommending HPV vaccine, and only half (51%) usually recommended same-day vaccination. Overall recommendation quality was lower among physicians who were uncomfortable talking about HPV vaccine or who believed parents did not value it. Quality was higher among physicians who began discussions by saying the child was due for HPV vaccine versus giving information or eliciting questions.

Conclusion: Many physicians in our national sample reported recommending HPV vaccine inconsistently, behind schedule, or without urgency. These practices likely contribute to under-immunization among adolescents, and may convey ambivalence to parents.

Impact: As one of the first studies to assess multiple aspects of recommendation quality, these findings can inform the many state and national initiatives that aim to improve communication about HPV vaccine so as to address the persistent underuse of a powerful tool for cancer prevention. *Cancer Epidemiol Biomarkers Prev; 24(11); 1673–9. ©2015 AACR.*

Cancer Epidemiol Biomarkers Prev; 24(11); 1673–9; Published OnlineFirst November 2015; doi: 10.1158/1055-9965.EPI-15-0326

Research Article

Circulating Tumor DNA Is Effective for the Detection of EGFR Mutation in Non–Small Cell Lung Cancer: A Meta-analysis

Mantang Qiu, Jie Wang, Youtao Xu, Xiangxiang Ding, Ming Li, Feng Jiang, Lin Xu, and Rong Yin

Mantang Qiu

Abstract

Background: Circulating tumor DNA (ctDNA) has offered a minimally invasive and feasible approach for detection of EGFR mutation for non–small cell lung cancer (NSCLC). This meta-analysis was designed to investigate the diagnostic value of ctDNA, compared with current "gold standard," tumor tissues.

Methods: We searched PubMed, EMBASE, Cochrane Library, and Web of Science to identify eligible studies that reported the sensitivity and specificity of ctDNA for detection of EGFR mutation status in NSCLC. Eligible studies were pooled to calculate the pooled sensitivity, specificity, and diagnostic odds ratio (DOR). The summary ROC curve (SROC) and area under SROC (AUSROC) were used to evaluate the overall diagnostic performance.

Results: Twenty-seven eligible studies involving 3,110 participants were included and analyzed in our meta-analysis, and most studies were conducted among Asian population. The pooled sensitivity, specificity, and DOR were 0.620 [95% confidence intervals (CI), 0.513–0.716), 0.959 (95% CI, 0.929–0.977), and 38.270 (95% CI, 21.090–69.444), respectively. The AUSROC was 0.91 (95% CI, 0.89–0.94), indicating the high diagnostic performance of ctDNA.

Conclusion: ctDNA is a highly specific and effective biomarker for the detection of EGFR mutation status.

Impact: ctDNA analysis will be a key part of personalized cancer therapy of NSCLC. *Cancer Epidemiol Biomarkers Prev; 24(1); 206–12. ©2014 AACR.*

Cancer Epidemiol Biomarkers Prev; 24(1); 206–12; Published OnlineFirst January 2015; doi: 10.1158/1055-9965.EPI-14-0895

CEBP Report

Survivors of Childhood Cancer in the United States: Prevalence and Burden of Morbidity

Siobhan M. Phillips

Siobhan M. Phillips, Lynne S. Padgett, Wendy M. Leisenring, Kayla K. Stratton, Ken Bishop, Kevin R. Krull, Catherine M. Alfano, Todd M. Gibson, Janet S. de Moor, Danielle Blanch Hartigan, Gregory T. Armstrong, Leslie L. Robison, Julia H. Rowland, Kevin C. Oeffinger, and Angela B. Mariotto

Abstract

Background: No studies have estimated the population-level burden of morbidity in individuals diagnosed with cancer as children (ages 0–19 years). We updated prevalence estimates of childhood cancer survivors as of 2011 and burden of morbidity in this population reflected by chronic conditions, neurocognitive dysfunction, compromised health-related quality of life, and health status (general health, mental health, functional impairment, functional limitations, pain, and fear/anxiety).

Methods: Surveillance, Epidemiology, and End Results (SEER) Program data from 1975 to 2011 were used to update the prevalence of survivors of childhood cancers in the United States. Childhood Cancer Survivor Study data were used to obtain estimates of morbidity burden indicators, which were then extrapolated to SEER data to obtain population-level estimates.

Results: There were an estimated 388,501 survivors of childhood cancer in the United States as of January 1, 2011, of whom 83.5% are ≥5 years after diagnosis. The prevalence of any chronic condition among ≥5-year survivors ranged from 66% (ages 5–19) to 88% (ages 40–49). Estimates for specific morbidities ranged from 12% (pain) to 35% (neurocognitive dysfunction). Generally, morbidities increased by age. However, mental health and anxiety remained fairly stable, and neurocognitive dysfunction exhibited initial decline and then remained stable by time since diagnosis.

Conclusions: The estimated prevalence of survivors of childhood cancer is increasing, as is the estimated prevalence of morbidity in those ≥5 years after diagnosis.

Impact: Efforts to understand how to effectively decrease morbidity burden and incorporate effective care coordination and rehabilitation models to optimize longevity and well-being in this population should be a priority. *Cancer Epidemiol Biomarkers Prev; 24(4); 653–63. ©2015 AACR.*

Cancer Epidemiol Biomarkers Prev; 24(4); 653–63; Published OnlineFirst April 2015; doi: 10.1158/1055-9965.EPI-14-1418

Research Article

International Variation in Female Breast Cancer Incidence and Mortality Rates

Carol E. DeSantis

Carol E. DeSantis, Freddie Bray, Jacques Ferlay, Joannie Lortet-Tieulent, Benjamin O. Anderson, and Ahmedin Jemal

Abstract

Background: Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related death among women worldwide. Herein, we examine global trends in female breast cancer rates using the most up-to-date data available.

Methods: Breast cancer incidence and mortality estimates were obtained from GLOBOCAN 2012 (globocan.iarc.fr). We analyzed trends from 1993 onward using incidence data from 39 countries from the International Agency for Research on Cancer and mortality data from 57 countries from the World Health Organization.

Results: Of 32 countries with incidence and mortality data, rates in the recent period diverged—with incidence increasing and mortality decreasing—in nine countries mainly in Northern/Western Europe. Both incidence and mortality decreased in France, Israel, Italy, Norway, and Spain. In contrast, incidence and death rates both increased in Colombia, Ecuador, and Japan. Death rates also increased in Brazil, Egypt, Guatemala, Kuwait, Mauritius, Mexico, and Moldova.

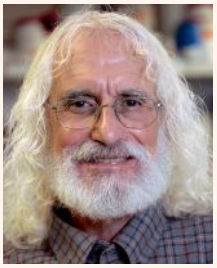
Conclusions: Breast cancer mortality rates are decreasing in most high-income countries, despite increasing or stable incidence rates. In contrast and of concern are the increasing incidence and mortality rates in a number of countries, particularly those undergoing rapid changes in human development. Wide variations in breast cancer rates and trends reflect differences in patterns of risk factors and access to and availability of early detection and timely treatment.

Impact: Increased awareness about breast cancer and the benefits of early detection and improved access to treatment must be prioritized to successfully implement breast cancer control programs, particularly in transitioning countries. *Cancer Epidemiol Biomarkers Prev; 24(10); 1495–506. ©2015 AACR.*

Cancer Epidemiol Biomarkers Prev; 24(10); 1495–506; Published OnlineFirst October 2015; doi: 10.1158/1055-9965.EPI-15-0535

Cancer Immunology Research

Robert D. Schreiber, PhD
Editor-in-Chief



Philip D. Greenberg, MD
Editor-in-Chief

Scope

Cancer Immunology Research publishes outstanding original articles reporting major advances in cancer immunology that span the discipline from basic investigations in host-tumor interactions to developmental therapeutics in model systems, early translational studies in patients, and late-stage clinical trials. The Journal disseminates knowledge of immunology to the cancer research community, catalyzing cross-disciplinary work that yields a deeper understanding of the host-tumor relationship, more potent cancer treatments, and improved clinical outcomes.

Masters of Immunology

NKG2D Receptor and Its Ligands in Host Defense

Lewis L. Lanier

Lewis L. Lanier

Abstract

NKG2D is an activating receptor expressed on the surface of natural killer (NK) cells, $CD8^+$ T cells, and subsets of $CD4^+$ T cells, invariant NKT cells (iNKT), and γδ T cells. In humans, NKG2D transmits signals by its association with the DAP10 adapter subunit, and in mice alternatively spliced isoforms transmit signals either using DAP10 or DAP12 adapter subunits. Although NKG2D is encoded by a highly conserved gene (*KLRK1*) with limited polymorphism, the receptor recognizes an extensive repertoire of ligands, encoded by at least eight genes in humans (*MICA*, *MICB*, *RAET1E*, *RAET1G*, *RAET1H*, *RAET1I*, *RAET1L*, and *RAET1N*), some with extensive allelic polymorphism. Expression of the NKG2D ligands is tightly regulated at the level of transcription, translation, and posttranslation. In general, healthy adult tissues do not express NKG2D glycoproteins on the cell surface, but these ligands can be induced by hyperproliferation and transformation, as well as when cells are infected by pathogens. Thus, the NKG2D pathway serves as a mechanism for the immune system to detect and eliminate cells that have undergone "stress." Viruses and tumor cells have devised numerous strategies to evade detection by the NKG2D surveillance system, and diversification of the NKG2D ligand genes likely has been driven by selective pressures imposed by pathogens. NKG2D provides an attractive target for therapeutics in the treatment of infectious diseases, cancer, and autoimmune diseases. *Cancer Immunol Res; 3(6); 575–82. ©2015 AACR.*

Cancer Immunol Res; 3(6); 575–82; Published OnlineFirst June 2015; doi: 10.1158/2326-6066.CIR-15-0098

Research Article

Antibody-Dependent Cellular Cytotoxicity Activity of a Novel Anti–PD-L1 Antibody Avelumab (MSB0010718C) on Human Tumor Cells

Jeffrey Schlom

Benjamin Boyerinas, Caroline Jochems, Massimo Fantini, Christopher R. Heery, James L. Gulley, Kwong Yok Tsang, and Jeffrey Schlom

Abstract

Several anti–PD-1/PD-L1 monoclonal antibodies (mAb) are currently providing evidence of clinical benefit in subsets of cancer patients. The mode of action of these mAbs is to inhibit PD-1 on immune cells interacting with PD-L1 on tumor cells. These mAbs are either designed or engineered to eliminate antibody-dependent cell-mediated cytotoxicity (ADCC), which, however, has been implicated as an important mechanism in several highly effective mAb-mediated cancer therapies. A fully human anti–PD-L1 mAb would potentially be able to block PD-1/PD-L1 interactions and also mediate the ADCC lysis of tumor cells. MSB0010718C (designated avelumab) is a fully human IgG1 anti–PD-L1 mAb. The studies reported here demonstrate (i) the ability of avelumab to lyse a range of human tumor cells in the presence of PBMC or NK effectors; (ii) IFNγ can enhance tumor cell PD-L1 expression and, in some cases, enhance ADCC tumor cell lysis; (iii) purified NK cells are potent effectors for avelumab; (iv) similar levels of avelumab-mediated ADCC lysis of tumor cells are seen using purified NK as effectors from either healthy donors or cancer patients; (v) very low levels of avelumab-mediated lysis are seen using whole PBMCs as targets; this finding complements results seen in analyses of PBMC subsets of patients receiving avelumab; and (vi) the addition of IL12 to NK cells greatly enhances avelumab-mediated ADCC. These studies thus provide an additional mode of action for an anti–PD-L1 mAb and support the rationale for further studies to enhance avelumab-mediated ADCC activity. *Cancer Immunol Res; 3(10); 1148–57. ©2015 AACR.*

Cancer Immunol Res; 3(10); 1148–57; Published OnlineFirst October 2015; doi: 10.1158/2326-6066.CIR-15-0059

Research Article

The Nonsignaling Extracellular Spacer Domain of Chimeric Antigen Receptors Is Decisive for *In Vivo* Antitumor Activity

Stanley R. Riddell

Michael Hudecek, Daniel Sommermeyer, Paula L. Kosasih, Anne Silva-Benedict, Lingfeng Liu, Christoph Rader, Michael C. Jensen, and Stanley R. Riddell

Abstract

The use of synthetic chimeric antigen receptors (CAR) to redirect T cells to recognize tumor provides a powerful new approach to cancer immunotherapy; however, the attributes of CARs that ensure optimal *in vivo* tumor recognition remain to be defined. Here, we analyze the influence of length and composition of IgG-derived extracellular spacer domains on the function of CARs. Our studies demonstrate that CD19-CARs with a long spacer from IgG4 hinge-CH2-CH3 are functional *in vitro* but lack antitumor activity *in vivo* due to interaction between the Fc domain within the spacer and the Fc receptor–bearing myeloid cells, leading to activation-induced T-cell death. We demonstrate that *in vivo* persistence and antitumor effects of CAR-T cells with a long spacer can be restored by modifying distinct regions in the CH2 domain that are essential for Fc receptor binding. Our studies demonstrate that modifications that abrogate binding to Fc receptors are crucial for CARs in which a long spacer is obligatory for tumor recognition as shown here for a ROR1-specific CAR. These results demonstrate that the length and composition of the extracellular spacer domain that lacks intrinsic signaling function can be decisive in the design of CARs for optimal *in vivo* activity. *Cancer Immunol Res; 3(2); 125–35. ©2014 AACR.*

Cancer Immunol Res; 3(2); 125–35.; Published OnlineFirst February 2015; doi: 10.1158/2326-6066.CIR-14-0127

Research Article

Differential Expression of PD-L1 between Primary and Metastatic Sites in Clear-Cell Renal Cell Carcinoma

Sabina Signoretti

Marcella Callea, Laurence Albiges, Mamta Gupta, Su-Chun Cheng, Elizabeth M. Genega, André P. Fay, Jiaxi Song, Ingrid Carvo, Rupal S. Bhatt, Michael B. Atkins, F. Stephen Hodi, Toni K. Choueiri, David F. McDermott, Gordon J. Freeman, and Sabina Signoretti

Abstract

PD-L1 expression in primary clear-cell renal cell carcinoma (ccRCC) increases the likelihood of response to anti–PD-1 inhibition, but fails to identify all responders. We hypothesized that PD-L1 levels assessed in randomly selected areas of the primary tumors may not accurately reflect expression levels in metastatic lesions, which are the target of systemic therapy. Therefore, we compared PD-L1 expression in a series of primary ccRCC and their metastases. Tissue blocks from 53 primary ccRCCs and 76 corresponding metastases were retrieved. Areas with predominant and highest nuclear grade were selected. Slides were immunostained with a validated anti–PD-L1 antibody (405.9A11). Membranous expression in tumor cells was quantified using H-score. Expression in tumor-infiltrating mononuclear cells (TIMC) was quantified using a combined score. Discordant tumor cell PD-L1 staining between primary tumors and metastases was observed in 11 of 53 cases (20.8%). Overall, tumor cell PD-L1 levels were not different in primary tumors and metastases ($P = 0.51$). Tumor cell PD-L1 positivity was associated with higher T stage ($P = 0.03$) and higher Fuhrman nuclear grade ($P < 0.01$). Within individual lesions, PD-L1 positivity was heterogeneous and almost exclusively detected in high nuclear grade areas ($P < 0.001$). No difference was found in PD-L1 levels in TIMCs between primary tumors and metastases ($P = 0.82$). The heterogeneity of PD-L1 expression in ccRCC suggests that its assessment as a predictive biomarker for PD-1 blockade may require analysis of metastatic lesions. Notably, because PD-L1 expression was mostly detected in high nuclear grade areas, to avoid false-negative results, these areas should be specifically selected for assessment. *Cancer Immunol Res; 3(10); 1158–64. ©2015 AACR.*

Cancer Immunol Res; 3(10); 1158–64; Published OnlineFirst October 2015; doi: 10.1158/2326-6066.CIR-15-0043

Research Article

PD-L1 Expression Correlates with Tumor-Infiltrating Lymphocytes and Response to Neoadjuvant Chemotherapy in Breast Cancer

David L. Rimm

Hallie Wimberly, Jason R. Brown, Kurt Schalper, Herbert Haack, Matthew R. Silver, Christian Nixon, Veerle Bossuyt, Lajos Pusztai, Donald R. Lannin, and David L. Rimm

Abstract

Programmed death 1 ligand 1 (PD-L1) is an immune regulatory molecule that limits antitumor immune activity. Targeting of PD-L1 and other immune checkpoint proteins has shown therapeutic activity in various tumor types. The expression of PD-L1 and its correlation with response to neoadjuvant chemotherapy in breast cancer has not been studied extensively. Our goal was to assess PD-L1 expression in a cohort of breast cancer patients treated with neoadjuvant chemotherapy. Pretreatment biopsies from 105 patients with breast cancer from Yale New Haven Hospital that subsequently received neoadjuvant chemotherapy were assessed for PD-L1 protein expression by automated quantitative analysis with a rabbit monoclonal antibody (E1L3N) to the cytoplasmic domain of PD-L1. In addition, tumor-infiltrating lymphocytes (TIL) were assessed on hematoxylin and eosin slides. PD-L1 expression was observed in 30% of patients, and it was positively associated with hormone-receptor–negative and triple-negative status and high levels of TILs. Both TILs and PD-L1 measured in the epithelium or stroma predicted pathologic complete response (pCR) to neoadjuvant chemotherapy in univariate and multivariate analyses. However, because they are strongly associated, TILs and PD-L1 cannot both be included in a significant multivariate model. PD-L1 expression is prevalent in breast cancer, particularly hormone-receptor–negative and triple-negative patients, indicating a subset of patients that may benefit from immune therapy. Furthermore, PD-L1 and TILs correlate with pCR, and high PD-L1 predicts pCR in multivariate analysis. *Cancer Immunol Res; 3(4); 326–32. ©2014 AACR.*

Cancer Immunol Res; 3(4); 326–32; Published OnlineFirst April 2015; doi: 10.1158/2326-6066.CIR-14-0133

Cancer Prevention Research

Scott M. Lippman, MD
Editor-in-Chief

Scope

Cancer Prevention Research is devoted exclusively to cancer prevention. The Journal publishes important original studies, reviews, and commentaries within the major topic areas of biology of premalignancy, risk factors and risk assessment, early detection research, immunoprevention, and chemopreventive and other interventions, including the basic science behind them. The Journal includes preclinical, clinical and translational research, with special attention given to molecular discoveries and an emphasis on building a translational bridge between the basic and clinical sciences.

Review Article

Salpingectomy as a Means to Reduce Ovarian Cancer Risk

Mary B. Daly, Charles W. Dresher, Melinda S. Yates, Joanne M. Jeter, Beth Y. Karlan, David S. Alberts, and Karen H. Lu

Mary B. Daly

Abstract

Bilateral salpingo-oophorectomy (BSO) has become the standard-of-care for risk reduction in women at hereditary risk of ovarian cancer. Although this procedure significantly decreases both the incidence of and mortality from ovarian cancer, it affects quality of life, and the premature cessation of ovarian function may have long-term health hazards. Recent advances in our understanding of the molecular pathways of ovarian cancer point to the fallopian tube epithelium as the origin of most high-grade serous cancers (HGSC). This evolving appreciation of the role of the fallopian tube in HGSC has led to the consideration of salpingectomy alone as an option for risk management, especially in premenopausal women. In addition, it is postulated that bilateral salpingectomy with ovarian retention (BSOR), may have a public health benefit for women undergoing benign gynecologic surgery. In this review, we provide the rationale for salpingectomy as an ovarian cancer risk reduction strategy. *Cancer Prev Res; 8(5); 342–8. ©2015 AACR.*

Cancer Prev Res; 8(5); 342–8; Published OnlineFirst May 2015; doi: 10.1158/1940-6207.CAPR-14-0293

Research Article

Salivary microRNAs Show Potential as a Noninvasive Biomarker for Detecting Resectable Pancreatic Cancer

Zijun Xie, Xiaoyu Yin, Bo Gong, Wenjing Nie, Bin Wu, Xuchao Zhang, Jian Huang, Pingyou Zhang, Zhiwei Zhou, and Zijun Li

Zijun Xie

Abstract

Early surgery is vital in the treatment of pancreatic cancer, which is often fatal. However, there is currently no useful noninvasive biomarker to screen for pancreatic cancer. Studies have documented that many salivary molecules can be used to detect systemic diseases. We investigated whether salivary miRNAs are useful biomarkers for detecting resectable pancreatic cancer. Using an Agilent microarray, salivary miRNAs were profiled from saliva samples of 8 patients with resectable pancreatic cancer and 8 healthy controls. Candidate biomarkers identified in the profiles were subjected to validation using quantitative PCR and an independent sample set of 40 patients with pancreatic cancer, 20 with benign pancreatic tumors (BPT), and 40 healthy controls. The validated salivary miRNA biomarkers were evaluated within three discriminatory categories: pancreatic cancer versus healthy control, pancreatic cancer versus BPT, and pancreatic cancer versus noncancer (healthy control + BPT). miR-3679-5p showed significant downregulation in the pancreatic cancer group within the three categories (P = 0.008, 0.007, and 0.002, respectively), whereas miR-940 showed significant upregulation in pancreatic cancer (P = 0.006, 0.004, and 0.0001, respectively). Logistic regression models combining the two salivary miRNAs were able to distinguish resectable pancreatic cancer within the three categories, showing sensitivities of 72.5%, 62.5%, and 70.0% and specificities of 70.0%, 80.0%, and 70.0%, respectively. Salivary miR-3679-5p and miR-940 possess good discriminatory power to detect resectable pancreatic cancer, with reasonable specificity and sensitivity. This report provides a new method for the early detection of pancreatic cancer and other systemic diseases by assessing salivary miRNAs. *Cancer Prev Res; 8(2); 165–73. ©2014 AACR.*

Cancer Prev Res; 8(2); 165–73.; Published OnlineFirst February 2015; doi: 10.1158/1940-6207.CAPR-14-0192

Research Article

Notch1 Mutations Are Drivers of Oral Tumorigenesis

Evgeny Izumchenko, Kai Sun, Sian Jones, Mariana Brait, Nishant Agrawal, Wayne Koch, Christine L. McCord, David R. Riley, Samuel V. Angiuoli, Victor E. Velculescu, Wei-Wen Jiang, and David Sidransky

David Sidransky

Abstract

Disruption of NOTCH1 signaling was recently discovered in head and neck cancer. This study aims to evaluate NOTCH1 alterations in the progression of oral squamous cell carcinoma (OSCC) and compare the occurrence of these mutations in Chinese and Caucasian populations. We used a high-throughput PCR-based enrichment technology and next-generation sequencing (NGS) to sequence *NOTCH1* in 144 samples collected in China. Forty-nine samples were normal oral mucosa from patients undergoing oral surgery, 45 were oral leukoplakia biopsies, and 50 were chemoradiation-naïve OSCC samples with 22 paired-normal tissues from the adjacent unaffected areas. *NOTCH1* mutations were found in 54% of primary OSCC and 60% of premalignant lesions. Importantly, almost 60% of patients with leukoplakia with mutated *NOTCH1* carried mutations that were also identified in OSCC, indicating an important role of these clonal events in the progression of early neoplasms. We then compared all known *NOTCH1* mutations identified in Chinese patients with OSCC with those reported in Caucasians to date. Although we found obvious overlaps in critical regulatory *NOTCH1* domains alterations and identified specific mutations shared by both groups, possible gain-of-function mutations were predominantly seen in Chinese population. Our findings demonstrate that premalignant lesions display *NOTCH1* mutations at an early stage and are thus *bona fide* drivers of OSCC progression. Moreover, our results reveal that NOTCH1 promotes distinct tumorigenic mechanisms in patients from different ethnical populations. *Cancer Prev Res; 8(4); 277–86. ©2014 AACR.*

Cancer Prev Res; 8(4); 277–86; Published OnlineFirst April 2015; doi: 10.1158/1940-6207.CAPR-14-0257

Research Article

Metabolomic Markers of Altered Nucleotide Metabolism in Early Stage Adenocarcinoma

William R. Wikoff, Dmitry Grapov, Johannes F. Fahrmann, Brian DeFelice, William N. Rom, Harvey I. Pass, Kyoungmi Kim, UyenThao Nguyen, Sandra L. Taylor, David R. Gandara, Karen Kelly, Oliver Fiehn, and Suzanne Miyamoto

Suzanne Miyamoto

Abstract

Adenocarcinoma, a type of non–small cell lung cancer, is the most frequently diagnosed lung cancer and the leading cause of lung cancer mortality in the United States. It is well documented that biochemical changes occur early in the transition from normal to cancer cells, but the extent to which these alterations affect tumorigenesis in adenocarcinoma remains largely unknown. Herein, we describe the application of mass spectrometry and multivariate statistical analysis in one of the largest biomarker research studies to date aimed at distinguishing metabolic differences between malignant and nonmalignant lung tissue. Gas chromatography time-of-flight mass spectrometry was used to measure 462 metabolites in 39 malignant and nonmalignant lung tissue pairs from current or former smokers with early stage (stage IA–IB) adenocarcinoma. Statistical mixed effects models, orthogonal partial least squares discriminant analysis and network integration, were used to identify key cancer-associated metabolic perturbations in adenocarcinoma compared with nonmalignant tissue. Cancer-associated biochemical alterations were characterized by (i) decreased glucose levels, consistent with the Warburg effect, (ii) changes in cellular redox status highlighted by elevations in cysteine and antioxidants, alpha- and gamma-tocopherol, (iii) elevations in nucleotide metabolites 5,6-dihydrouracil and xanthine suggestive of increased dihydropyrimidine dehydrogenase and xanthine oxidoreductase activity, (iv) increased 5′-deoxy-5′-methylthioadenosine levels indicative of reduced purine salvage and increased *de novo* purine synthesis, and (v) coordinated elevations in glutamate and UDP-N-acetylglucosamine suggesting increased protein glycosylation. The present study revealed distinct metabolic perturbations associated with early stage lung adenocarcinoma, which may provide candidate molecular targets for personalizing therapeutic interventions and treatment efficacy monitoring. *Cancer Prev Res; 8(5); 410–8. ©2015 AACR.*

Cancer Prev Res; 8(5); 410–8; Published OnlineFirst May 2015; doi: 10.1158/1940-6207.CAPR-14-0329

Research Article

Effects of Switching to Electronic Cigarettes with and without Concurrent Smoking on Exposure to Nicotine, Carbon Monoxide, and Acrolein

Hayden McRobbie, Anna Phillips, Maciej L. Goniewicz, Katie Myers Smith, Oliver Knight-West, Dunja Przulj, and Peter Hajek

Abstract

Concern has been raised about the presence of toxicants in electronic cigarette (EC) aerosol, particularly carbonyl compounds (e.g., acrolein) that can be produced by heating glycerol and glycols used in e-liquids. We investigated exposure to carbon monoxide (CO), nicotine (by measuring cotinine in urine), and to acrolein (by measuring its primary metabolite, S-(3-hydroxypropyl) mercapturic acid (3-HPMA) in urine) before and after 4 weeks of EC (green smoke, a "cig-a-like" EC, labeled 2.4% nicotine by volume) use, in 40 smokers. Thirty-three participants were using EC at 4 weeks after quitting, 16 (48%) were abstinent (CO-validated) from smoking during the previous week (EC only users), and 17 (52%) were "dual users." A significant reduction in CO was observed in EC-only users [−12 ppm, 95% confidence interval (CI), −16 to −7, 80% decrease) and dual users (−12 ppm, 95%CI, −19 to −6, 52% decrease). Cotinine levels also declined, but to a lesser extent (EC-only users: −184 ng/mg creatinine; 95% CI, −733 to −365, 17% decrease; and dual users: −976 ng/mg creatinine; 95%CI, −1,682 to −270, 44% decrease). Mean 3-HPMA levels had decreased at 4 weeks by 1,280 ng/mg creatinine (95%CI, −1,699 to −861, 79% decrease) in EC-only users and by 1,474 ng/mg creatinine (95%CI, −2,101 to −847, 60% decrease) in dual users. In dual users, EC use significantly reduced exposure to CO and acrolein because of a reduction in smoke intake. EC may reduce harm even in smokers who continue to smoke, but long-term follow-up studies are needed to confirm this. *Cancer Prev Res; 8(9); 873–8. ©2015 AACR.*

Cancer Prev Res; 8(9); 873–8; Published OnlineFirst September 2015; doi: 10.1158/1940-6207.CAPR-15-0058

Cancer Research

George C. Prendergast, PhD
Editor-in-Chief

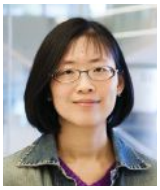
Scope

Cancer Research publishes original studies, reviews, and opinion pieces offering significance and broad impact to a diverse audience spanning basic, preclinical, clinical, prevention, and epidemiologic research. *Cancer Research* seeks manuscripts that offer pathobiological and translational impact to inform the personal, clinical, and societal problems posed by cancer. The main scope of the Journal is captured in its primary subsections, which focus on molecular and cellular pathobiology, tumor and stem cell biology, therapeutics and targets, microenvironment and immunology, prevention and epidemiology, and integrated systems and technology.

Review Article

Classifying Cancers Based on T-cell Infiltration and PD-L1

Michele W.L. Teng, Shin Foong Ngiow, Antoni Ribas, and Mark J. Smyth



Michele W.L. Teng

Mark J. Smyth

Abstract

Cancer immunotherapy may become a major treatment backbone in many cancers over the next decade. There are numerous immune cell types found in cancers and many components of an immune reaction to cancer. Thus, the tumor has many strategies to evade an immune response. It has been proposed that four different types of tumor microenvironment exist based on the presence or absence of tumor-infiltrating lymphocytes and programmed death-ligand 1 (PD-L1) expression. We review this stratification and the latest in a series of results that shed light on new approaches for rationally designing ideal combination cancer therapies based on tumor immunology. *Cancer Res; 75(11); 2139–45. ©2015 AACR.*

Cancer Res; 75(11); 2139–45; Published OnlineFirst June 2015; doi: 10.1158/0008-5472.CAN-15-0255

Research Article

Long Noncoding RNA MALAT1 Promotes Aggressive Renal Cell Carcinoma through Ezh2 and Interacts with miR-205

Hiroshi Hirata, Yuji Hinoda, Varahram Shahryari, Guoren Deng, Koichi Nakajima, Z. Laura Tabatabai, Nobuhisa Ishii, and Rajvir Dahiya

Rajvir Dahiya

Abstract

Recently, long noncoding RNAs (lncRNA) have emerged as new gene regulators and prognostic markers in several cancers, including renal cell carcinoma (RCC). In this study, we investigated the contributions of the lncRNA MALAT1 in RCC with a specific focus on its transcriptional regulation and its interactions with Ezh2 and miR-205. We found that MALAT1 expression was higher in human RCC tissues, where it was associated with reduced patient survival. MALAT1 silencing decreased RCC cell proliferation and invasion and increased apoptosis. Mechanistic investigations showed that MALAT1 was transcriptionally activated by c-Fos and that it interacted with Ezh2. After MALAT1 silencing, E-cadherin expression was increased, whereas β-catenin expression was decreased through Ezh2. Reciprocal interaction between MALAT1 and miR-205 was also observed. Lastly, MALAT1 bound Ezh2 and oncogenesis facilitated by MALAT1 was inhibited by Ezh2 depletion, thereby blocking epithelial–mesenchymal transition via E-cadherin recovery and β-catenin downregulation. Overall, our findings illuminate how overexpression of MALAT1 confers an oncogenic function in RCC that may offer a novel theranostic marker in this disease. *Cancer Res; 75(7); 1322–31. ©2015 AACR.*

Cancer Res; 75(7); 1322–31; Published OnlineFirst April 2015; doi: 10.1158/0008-5472.CAN-14-2931

Research Article

Human Pancreatic Cancer Tumors Are Nutrient Poor and Tumor Cells Actively Scavenge Extracellular Protein

Jurre J. Kamphorst, Michel Nofal, Cosimo Commisso, Sean R. Hackett, Wenyun Lu, Elda Grabocka, Matthew G. Vander Heiden, George Miller, Jeffrey A. Drebin, Dafna Bar-Sagi, Craig B. Thompson, and Joshua D. Rabinowitz

Joshua D. Rabinowitz

Abstract

Glucose and amino acids are key nutrients supporting cell growth. Amino acids are imported as monomers, but an alternative route induced by oncogenic KRAS involves uptake of extracellular proteins via macropinocytosis and subsequent lysosomal degradation of these proteins as a source of amino acids. In this study, we examined the metabolism of pancreatic ductal adenocarcinoma (PDAC), a poorly vascularized lethal KRAS-driven malignancy. Metabolomic comparisons of human PDAC and benign adjacent tissue revealed that tumor tissue was low in glucose, upper glycolytic intermediates, creatine phosphate, and the amino acids glutamine and serine, two major metabolic substrates. Surprisingly, PDAC accumulated essential amino acids. Such accumulation could arise from extracellular proteins being degraded through macropinocytosis in quantities necessary to meet glutamine requirements, which in turn produces excess of most other amino acids. Consistent with this hypothesis, active macropinocytosis is observed in primary human PDAC specimens. Moreover, in the presence of physiologic albumin, we found that cultured murine PDAC cells grow indefinitely in media lacking single essential amino acids and replicate once in the absence of free amino acids. Growth under these conditions was characterized by simultaneous glutamine depletion and essential amino acid accumulation. Overall, our findings argue that the scavenging of extracellular proteins is an important mode of nutrient uptake in PDAC. *Cancer Res; 75(3); 544–53. ©2014 AACR.*

Cancer Res; 75(3); 544–53; Published OnlineFirst February 2015; doi: 10.1158/0008-5472.CAN-14-2211

Research Article

Establishment and Characterization of a Cell Line from Human Circulating Colon Cancer Cells

Laure Cayrefourcq, Thibault Mazard, Simon Joosse, Jérôme Solassol, Jeanne Ramos, Eric Assenat, Udo Schumacher, Valérie Costes, Thierry Maudelonde, Klaus Pantel, and Catherine Alix-Panabières

Catherine Alix-Panabières

Abstract

Circulating tumor cells (CTC) in blood are promising new biomarkers potentially useful for prognostic prediction and monitoring of therapies in patients with solid tumors including colon cancer. Moreover, CTC research opens a new avenue for understanding the biology of metastasis in patients with cancer. However, an in-depth investigation of CTCs is hampered by the very low number of these cells, especially in the blood of patients with colorectal cancer. Thus, the establishment of cell cultures and permanent cell lines from CTCs has become the most challenging task over the past year. Here, we describe, for the first time, the establishment of cell cultures and a permanent cell line from CTCs of one patient with colon cancer. The cell line designated CTC-MCC-41 has been cultured for more than one year, and the cells have been characterized at the genome, transcriptome, proteome, and secretome levels. This thorough analysis showed that CTC-MCC-41 cells resemble characteristics of the original tumor cells in the patient with colon cancer and display a stable phenotype characterized by an intermediate epithelial/mesenchymal phenotype, stem cell–like properties, and an osteomimetic signature, indicating a bone marrow origin. Functional studies showed that CTC-MCC-41 cells induced rapidly *in vitro* endothelial cell tube formation and *in vivo* tumors after xenografting in immunodeficient mice. The establishment of this first colon cancer CTC line allows now a wealth of functional studies on the biology of CTCs as well as *in vitro* and *in vivo* drug testing. *Cancer Res; 75(5); 892–901. ©2015 AACR.*

Cancer Res; 75(5); 892–901; Published OnlineFirst March 2015; doi: 10.1158/0008-5472.CAN-14-2613

Research Article

Multiplex Genome-Edited T-cell Manufacturing Platform for "Off-the-Shelf" Adoptive T-cell Immunotherapies

Laurent Poirot, Brian Philip, Cécile Schiffer-Mannioui, Diane Le Clerre, Isabelle Chion-Sotinel, Sophie Derniame, Pierrick Potrel, Cécile Bas, Laetitia Lemaire, Roman Galetto, Céline Lebuhotel, Justin Eyquem, Gordon Weng-Kit Cheung, Aymeric Duclert, Agnès Gouble, Sylvain Arnould, Karl Peggs, Martin Pule, Andrew M. Scharenberg, and Julianne Smith

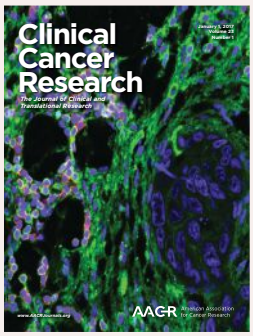
Julianne Smith

Abstract

Adoptive immunotherapy using autologous T cells endowed with chimeric antigen receptors (CAR) has emerged as a powerful means of treating cancer. However, a limitation of this approach is that autologous CAR T cells must be generated on a custom-made basis. Here we show that electroporation of transcription activator–like effector nuclease (TALEN) mRNA allows highly efficient multiplex gene editing in primary human T cells. We use this TALEN-mediated editing approach to develop a process for the large-scale manufacturing of T cells deficient in expression of both their αβ T-cell receptor (TCR) and CD52, a protein targeted by alemtuzumab, a chemotherapeutic agent. Functionally, T cells manufactured with this process do not mediate graft-versus-host reactions and are rendered resistant to destruction by alemtuzumab. These characteristics enable the administration of alemtuzumab concurrently or prior to engineered T cells, supporting their engraftment. Furthermore, endowing the TALEN-engineered cells with a CD19 CAR led to efficient destruction of $CD19^+$ tumor targets even in the presence of the chemotherapeutic agent. These results demonstrate the applicability of TALEN-mediated genome editing to a scalable process, which enables the manufacturing of third-party CAR T-cell immunotherapies against arbitrary targets. As such, CAR T-cell immunotherapies can therefore be used in an "off-the-shelf" manner akin to other biologic immunopharmaceuticals. *Cancer Res; 75(18); 3853–64. ©2015 AACR.*

Cancer Res; 75(18); 3853–64; Published OnlineFirst September 2015; doi: 10.1158/0008-5472.CAN-14-3321

Clinical Cancer Research



Keith T. Flaherty, MD
Editor-in-Chief

Scope

Clinical Cancer Research publishes innovative clinical and translational cancer research studies that bridge the laboratory and the clinic. The Journal is especially interested in clinical trials evaluating new treatments, accompanied by research on pharmacology, and molecular alterations or biomarkers that predict response or resistance to treatment. The Journal also prioritizes laboratory and animal studies of new drugs and molecule-targeted agents with the potential to lead to clinical trials, and studies of targetable mechanisms of oncogenesis, progression of the malignant phenotype, and metastatic disease.

Review Article

Interleukin-6 as a Therapeutic Target

Jean-François Rossi, Zhao-Yang Lu, Michel Jourdan, and Bernard Klein

Jean-François Rossi

Abstract

Human IL6 is a cytokine produced by many cell types that has pleiotropic effects. In agreement, anti-IL6 therapy reduces inflammation, hepatic acute phase proteins, and anemia and has antiangiogenic effects. Blocking IL6 has demonstrated therapeutic efficacy with drug registration in Castleman disease and inflammatory diseases (rheumatoid arthritis) without major toxicity. Interestingly, the inhibition of C-reactive protein (CRP) production is a trustworthy surrogate marker of anti-IL6 therapy efficacy. Clinically registered IL6 inhibitors include siltuximab, an anti-IL6 mAb, and tocilizumab, an anti-IL6R mAb. In various cancers, in particular plasma cell cancers, large randomized trials showed no efficacy of IL6 inhibitors, despite a full inhibition of CRP production in treated patients *in vivo*, the numerous data showing an involvement of IL6 in these diseases, and initial short-term treatments demonstrating a dramatic inhibition of cancer cell proliferation *in vivo*. A likely explanation is the plasticity of cancer cells, with the presence of various subclones, making the outgrowth of cancer subclones possible using growth factors other than IL6. In addition, current therapeutic strategies used in these cancers already target IL6 activity. Thus, anti-IL6 therapeutics are able to neutralize IL6 production *in vivo* and are safe and useful in inflammatory diseases and Castleman disease. *Clin Cancer Res; 21(6); 1248–57. ©2015 AACR.*

Clin Cancer Res; 21(6); 1248–57; Published OnlineFirst March 2015; doi: 10.1158/1078-0432.CCR-14-2291

Research Article

Integrative and Comparative Genomic Analysis of HPV-Positive and HPV-Negative Head and Neck Squamous Cell Carcinomas

Tanguy Y. Seiwert

Tanguy Y. Seiwert, Zhixiang Zuo, Michaela K. Keck, Arun Khattri, Chandra S. Pedamallu, Thomas Stricker, Christopher Brown, Trevor J. Pugh, Petar Stojanov, Juok Cho, Michael S. Lawrence, Gad Getz, Johannes Brägelmann, Rebecca DeBoer, Ralph R. Weichselbaum, Alexander Langerman, Louis Portugal, Elizabeth Blair, Kerstin Stenson, Mark W. Lingen, Ezra E.W. Cohen, Everett E. Vokes, Kevin P. White, and Peter S. Hammerman

Abstract

Purpose: The genetic differences between human papilloma virus (HPV)–positive and –negative head and neck squamous cell carcinomas (HNSCC) remain largely unknown. To identify differential biology and novel therapeutic targets for both entities, we determined mutations and copy-number aberrations in a large cohort of locoregionally advanced HNSCC.

Experimental Design: We performed massively parallel sequencing of 617 cancer-associated genes in 120 matched tumor/normal samples (42.5% HPV-positive). Mutations and copy-number aberrations were determined and results validated with a secondary method.

Results: The overall mutational burden in HPV-negative and HPV-positive HNSCC was similar with an average of 15.2 versus 14.4 somatic exonic mutations in the targeted cancer-associated genes. HPV-negative tumors showed a mutational spectrum concordant with published lung squamous cell carcinoma analyses with enrichment for mutations in *TP53*, *CDKN2A*, *MLL2*, *CUL3*, *NSD1*, *PIK3CA*, and *NOTCH* genes. HPV-positive tumors showed unique mutations in *DDX3X*, *FGFR2/3* and aberrations in *PIK3CA*, *KRAS*, *MLL2/3*, and *NOTCH1* were enriched in HPV-positive tumors. Currently targetable genomic alterations were identified in *FGFR1*, *DDR2*, *EGFR*, *FGFR2/3*, *EPHA2*, and *PIK3CA*. *EGFR*, *CCND1*, and *FGFR1* amplifications occurred in HPV-negative tumors, whereas 17.6% of HPV-positive tumors harbored mutations in fibroblast growth factor receptor genes (*FGFR2/3*), including six recurrent *FGFR3* S249C mutations. HPV-positive tumors showed a 5.8% incidence of KRAS mutations, and DNA-repair gene aberrations, including 7.8% BRCA1/2 mutations, were identified.

Conclusions: The mutational makeup of HPV-positive and HPV-negative HNSCC differs significantly, including targetable genes. HNSCC harbors multiple therapeutically important genetic aberrations, including frequent aberrations in the FGFR and PI3K pathway genes. *Clin Cancer Res; 21(3); 632–41. ©2014 AACR.*

Clin Cancer Res; 21(3); 632–41; Published OnlineFirst July 2014; doi: 10.1158/1078-0432.CCR-13-3310

Research Article

A Pilot Trial Using Lymphocytes Genetically Engineered with an NY-ESO-1–Reactive T-cell Receptor: Long-term Follow-up and Correlates with Response

Paul F. Robbins

Paul F. Robbins, Sadik H. Kassim, Thai L.N. Tran, Jessica S. Crystal, Richard A. Morgan, Steven A. Feldman, James C. Yang, Mark E. Dudley, John R. Wunderlich, Richard M. Sherry, Udai S. Kammula, Marybeth S. Hughes, Nicholas P. Restifo, Mark Raffeld, Chyi-Chia R. Lee, Yong F. Li, Mona El-Gamil, and Steven A. Rosenberg

Abstract

Purpose: Although adoptive cell therapy can be highly effective for the treatment of patients with melanoma, the application of this approach to the treatment of other solid tumors has been limited. The observation that the cancer germline (CG) antigen NY-ESO-1 is expressed in 70% to 80% and in approximately 25% of patients with synovial cell sarcoma and melanoma, respectively, prompted us to perform this first-in-man clinical trial using the adoptive transfer of autologous peripheral blood mononuclear cells that were retrovirally transduced with an NY-ESO-1–reactive T-cell receptor (TCR) to heavily pretreated patients bearing these metastatic cancers.

Experimental Design: HLA-*0201 patients with metastatic synovial cell sarcoma or melanoma refractory to standard treatments and whose cancers expressed NY-ESO-1 received autologous TCR-transduced T cells following a lymphodepleting preparative chemotherapy. Response rates using Response Evaluation Criteria in Solid Tumors (RECIST), as well as immunologic correlates of response, are presented in this report.

Results: Eleven of 18 patients with NY-ESO-1$^+$ synovial cell sarcomas (61%) and 11 of 20 patients with NY-ESO-1$^+$ melanomas (55%) who received autologous T cells transduced with an NY-ESO-1–reactive TCR demonstrated objective clinical responses. The estimated overall 3- and 5-year survival rates for patients with synovial cell sarcoma were 38% and 14%, respectively, whereas the corresponding estimated survival rates for patients with melanoma were both 33%.

Conclusions: The adoptive transfer of autologous T cells transduced with a retrovirus encoding a TCR against an HLA-A*0201 restricted NY-ESO-1 epitope can be an effective therapy for some patients bearing synovial cell sarcomas and melanomas that are refractory to other treatments. *Clin Cancer Res; 21(5); 1019–27. ©2014 AACR.*

Clin Cancer Res; 21(5); 1019–27; Published OnlineFirst March 2015; doi: 10.1158/1078-0432.CCR-14-2708

Research Article

Androgen Receptor Gene Aberrations in Circulating Cell-Free DNA: Biomarkers of Therapeutic Resistance in Castration-Resistant Prostate Cancer

Colin C. Collins

Kim N. Chi

Arun A. Azad, Stanislav V. Volik, Alexander W. Wyatt, Anne Haegert, Stephane Le Bihan, Robert H. Bell, Shawn A. Anderson, Brian McConeghy, Robert Shukin, Jenny Bazov, Jack Youngren, Pamela Paris, George Thomas, Eric J. Small, Yuzhuo Wang, Martin E. Gleave, Colin C. Collins, and Kim N. Chi

Abstract

Purpose: Although novel agents targeting the androgen–androgen receptor (AR) axis have altered the treatment paradigm of metastatic castration-resistant prostate cancer (mCRPC), development of therapeutic resistance is inevitable. In this study, we examined whether AR gene aberrations detectable in circulating cell-free DNA (cfDNA) are associated with resistance to abiraterone acetate and enzalutamide in mCRPC patients.

Experimental Design: Plasma was collected from 62 mCRPC patients ceasing abiraterone acetate (n = 29), enzalutamide (n = 19), or other agents (n = 14) due to disease progression. DNA was extracted and subjected to array comparative genomic hybridization (aCGH) for chromosome copy number analysis, and Roche 454 targeted next-generation sequencing of exon 8 in the AR.

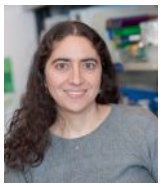
Results: On aCGH, AR amplification was significantly more common in patients progressing on enzalutamide than on abiraterone or other agents (53% vs. 17% vs. 21%, $P = 0.02$, χ^2). Missense AR exon 8 mutations were detected in 11 of 62 patients (18%), including the first reported case of an F876L mutation in an enzalutamide-resistant patient and H874Y and T877A mutations in 7 abiraterone-resistant patients. In patients switched onto enzalutamide after cfDNA collection (n = 39), an AR gene aberration (copy number increase and/or an exon 8 mutation) in pretreatment cfDNA was associated with adverse outcomes, including lower rates of PSA decline ≥ 30% ($P = 0.013$, χ^2) and shorter time to radiographic/clinical progression ($P = 0.010$, Cox proportional hazards regression).

Conclusions: AR gene aberrations in cfDNA are associated with resistance to enzalutamide and abiraterone in mCRPC. Our data illustrate that genomic analysis of cfDNA is a minimally invasive method for interrogating mechanisms of therapeutic resistance in mCRPC. *Clin Cancer Res; 21(10); 2315–24. ©2015 AACR.*

Clin Cancer Res; 21(10); 2315–24; Published OnlineFirst February 2015; doi: 10.1158/1078-0432.CCR-14-2666

Research Article

Pilot Trial of Combined BRAF and EGFR Inhibition in *BRAF*-Mutant Metastatic Colorectal Cancer Patients


Rona Yaeger

Rona Yaeger, Andrea Cercek, Eileen M. O'Reilly, Diane L. Reidy, Nancy Kemeny, Tamar Wolinsky, Marinela Capanu, Marc J. Gollub, Neal Rosen, Michael F. Berger, Mario E. Lacouture, Efsevia Vakiani, and Leonard B. Saltz

Abstract

Purpose: *BRAF*-mutant metastatic colorectal cancer (mCRC) forms an aggressive subset of colorectal cancer with minimal response to selective RAF inhibitors. Preclinical data show that reactivation of EGFR signaling occurs in colorectal tumor cells treated with RAF inhibitors and that the addition of an EGFR inhibitor enhances antitumor activity. These data suggest that combined therapy with RAF and EGFR inhibitors could be an effective strategy for treating *BRAF* V600E mCRC.

Experimental Design: We undertook a pilot trial to assess the response rate and safety of the BRAF inhibitor vemurafenib combined with anti-EGFR antibody panitumumab in patients with *BRAF*-mutant mCRC. Patients received standard approved doses of panitumumab and vemurafenib.

Results: Fifteen patients were treated. Performance status was Eastern Cooperative Oncology Group (ECOG) 0 in 4 patients (27%) and ECOG 1 in 11 patients (73%). All patients had progressed through at least one standard treatment regimen, and 8 (53%) had received previous fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy. Treatment was well tolerated, with less cutaneous toxicity than would be expected with either agent, and no cases of keratoacanthomas/squamous cell carcinomas. Tumor regressions were seen in 10 of 12 evaluable patients with partial responses in 2 patients (100% and 64% regression lasting 40 and 24 weeks, respectively), and stable disease lasting over 6 months in 2 patients.

Conclusions: Combined RAF and EGFR inhibition is well tolerated, with less cutaneous toxicity than would be expected with either agent, and results in modest clinical activity in this highly aggressive and chemoresistant subset of CRC. *Clin Cancer Res; 21(6); 1313–20. ©2015 AACR.*

Clin Cancer Res; 21(6); 1313–20; Published OnlineFirst March 2015; doi: 10.1158/1078-0432.CCR-14-2779

Molecular Cancer Research

Karen E. Knudsen, PhD
Editor-in-Chief

Scope

Molecular Cancer Research publishes articles describing novel basic cancer research discoveries of broad interest to the field. Studies must be of demonstrated significance, and the Journal prioritizes analyses performed at the molecular and cellular level that reveal novel mechanistic insight into pathways and processes linked to cancer risk, development, and/or progression. Areas of emphasis include all cancer-associated pathways (including cell-cycle regulation; cell death; chromatin regulation; DNA damage and repair; gene and RNA regulation; genomics; metabolism; oncogenes and tumor suppressors; and signal transduction), in addition to studies describing new molecular mechanisms and interactions that support cancer phenotypes.

Review Article

The Key Role of Calmodulin in *KRAS*-Driven Adenocarcinomas

Ruth Nussinov, Serena Muratcioglu, Chung-Jung Tsai, Hyunbum Jang, Attila Gursoy, and Ozlem Keskin

Ruth Nussinov

Abstract

KRAS4B is a highly oncogenic splice variant of the KRAS isoform. It is the only isoform associated with initiation of adenocarcinomas. Insight into why and how KRAS4B can mediate ductal adenocarcinomas, particularly of the pancreas, is vastly important for its therapeutics. Here we point out the overlooked critical role of calmodulin (CaM). Calmodulin selectively binds to GTP-bound K-Ras4B; but not to other Ras isoforms. Cell proliferation and growth require the MAPK (Raf/MEK/ERK) and PI3K/Akt pathways. We propose that Ca^{2+}/calmodulin promote PI3Kα/Akt signaling, and suggest how. The elevated calcium levels clinically observed in adenocarcinomas may explain calmodulin's involvement in recruiting and stimulating PI3Kα through interaction with its n/cSH2 domains as well as K-Ras4B; importantly, it also explains why K-Ras4B specifically is a key player in ductal carcinomas, such as pancreatic (PDAC), colorectal (CRC), and lung cancers. We hypothesize that calmodulin recruits and helps activate PI3Kα at the membrane, and that this is the likely reason for Ca^{2+}/calmodulin dependence in adenocarcinomas. Calmodulin can contribute to initiation/progression of ductal cancers via both PI3Kα/Akt and Raf/MEK/ERK pathways. Blocking the K-Ras4B/MAPK pathway and calmodulin/PI3Kα binding in a K-Ras4B/calmodulin/PI3Kα trimer could be a promising adenocarcinoma-specific therapeutic strategy. *Mol Cancer Res; 13(9); 1265–73. ©2015 AACR.*

Mol Cancer Res; 13(9); 1265–73; Published OnlineFirst September 2015; doi: 10.1158/1541-7786.MCR-15-0165

Research Article

lincRNA-RoR and miR-145 Regulate Invasion in Triple-Negative Breast Cancer via Targeting ARF6

Gabriel Eades, Benjamin Wolfson, Yongshu Zhang, Qinglin Li, Yuan Yao, and Qun Zhou

Qun Zhou

Abstract

Triple-negative (ER$^-$, HER2$^-$, PR$^-$) breast cancer (TNBC) is an aggressive disease with a poor prognosis with no available molecularly targeted therapy. Silencing of microRNA-145 (miR-145) may be a defining marker of TNBC based on molecular profiling and deep sequencing. Therefore, the molecular mechanism behind miR-145 downregulation in TNBC was examined. Overexpression of the long intergenic noncoding RNA regulator of reprogramming, lincRNA-RoR, functions as a competitive endogenous RNA sponge in TNBC. Interestingly, lincRNA-RoR is dramatically upregulated in TNBC and in metastatic disease and knockdown restores miR-145 expression. Previous reports suggest that miR-145 has growth-suppressive activity in some breast cancers; however, these data in TNBC indicate that miR-145 does not affect proliferation or apoptosis but instead, miR-145 regulates tumor cell invasion. Investigation of miR-145-regulated pathways involved in tumor invasion revealed a novel target, the small GTPase ADP-ribosylation factor 6 (*Arf6*). Subsequent analysis demonstrated that ARF6, a known regulator of breast tumor cell invasion, is dramatically upregulated in TNBC and in breast tumor metastasis. Mechanistically, ARF6 regulates E-cadherin localization and affects cell–cell adhesion. These results reveal a lincRNA-RoR/miR-145/ARF6 pathway that regulates invasion in TNBCs.

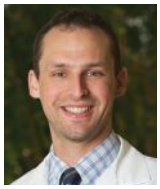
Implications: The lincRNA-RoR/miR-145/ARF6 pathway is critical to TNBC metastasis and could serve as biomarkers or therapeutic targets for improving survival. *Mol Cancer Res; 13(2); 330–8. ©2014 AACR.*

Mol Cancer Res; 13(2); 330–8; Published OnlineFirst February 2015; doi: 10.1158/1541-7786.MCR-14-0251

Research Article

Next-Gen Sequencing Exposes Frequent *MED12* Mutations and Actionable Therapeutic Targets in Phyllodes Tumors

Andi K. Cani, Daniel H. Hovelson, Andrew S. McDaniel, Seth Sadis, Michaela J. Haller, Venkata Yadati, Anmol M. Amin, Jarred Bratley, Santhoshi Bandla, Paul D. Williams, Kate Rhodes, Chia-Jen Liu, Michael J. Quist, Daniel R. Rhodes, Catherine S. Grasso, Celina G. Kleer, and Scott A. Tomlins



Scott A. Tomlins

Abstract

Phyllodes tumors are rare fibroepithelial tumors with variable clinical behavior accounting for a small subset of all breast neoplasms, yet little is known about the genetic alterations that drive tumor initiation and/or progression. Here, targeted next-generation sequencing (NGS) was used to identify somatic alterations in formalin-fixed paraffin-embedded (FFPE) patient specimens from malignant, borderline, and benign cases. NGS revealed mutations in *mediator complex subunit 12* (*MED12*) affecting the G44 hotspot residue in the majority (67%) of cases spanning all three histologic grades. In addition, loss-of-function mutations in *p53* (*TP53*) as well as deleterious mutations in the tumor suppressors *retinoblastoma* (*RB1*) and *neurofibromin 1* (*NF1*) were identified exclusively in malignant tumors. High-level copy-number alterations (CNA) were nearly exclusively confined to malignant tumors, including potentially clinically actionable gene amplifications in *IGF1R* and *EGFR*. Taken together, this study defines the genomic landscape underlying phyllodes tumor development, suggests potential molecular correlates to histologic grade, expands the spectrum of human tumors with frequent recurrent *MED12* mutations, and identifies *IGF1R* and *EGFR* as potential therapeutic targets in malignant cases.

Implications: Integrated genomic sequencing and mutational profiling provides insight into the molecular origin of phyllodes tumors and indicates potential druggable targets in malignant disease.

Visual Overview: http://mcr.aacrjournals.org/content/early/2015/04/02/1541-7786.MCR-14-0578/F1.large.jpg.

Mol Cancer Res; 13(4); 613–9. ©2015 AACR.

Mol Cancer Res; 13(4); 613–9; Published OnlineFirst April 2015; doi: 10.1158/1541-7786.MCR-14-0578

Research Article

Treatment Efficacy and Resistance Mechanisms Using the Second-Generation ALK Inhibitor AP26113 in Human NPM-ALK–Positive Anaplastic Large Cell Lymphoma

Monica Ceccon

M. Ceccon, L. Mologni, G. Giudici, R. Piazza, A. Pirola, D. Fontana, and C. Gambacorti-Passerini

Abstract

ALK is a tyrosine kinase receptor involved in a broad range of solid and hematologic tumors. Among 70% to 80% of ALK$^+$ anaplastic large cell lymphomas (ALCL) are caused by the aberrant oncogenic fusion protein NPM-ALK. Crizotinib was the first clinically relevant ALK inhibitor, now approved for the treatment of late-stage and metastatic cases of lung cancer. However, patients frequently develop drug resistance to Crizotinib, mainly due to the appearance of point mutations located in the ALK kinase domain. Fortunately, other inhibitors are available and in clinical trial, suggesting the potential for second-line therapies to overcome Crizotinib resistance. This study focuses on the ongoing phase I/II trial small-molecule tyrosine kinase inhibitor (TKI) AP26113, by Ariad Pharmaceuticals, which targets both ALK and EGFR. Two NPM-ALK$^+$ human cell lines, KARPAS-299 and SUP-M2, were grown in the presence of increasing concentrations of AP26113, and eight lines were selected that demonstrated resistance. All lines show IC_{50} values higher (130 to 1,000-fold) than the parental line. Mechanistically, KARPAS-299 populations resistant to AP26113 show NPM-ALK overexpression, whereas SUP-M2–resistant cells harbor several point mutations spanning the entire ALK kinase domain. In particular, amino acid substitutions: L1196M, S1206C, the double F1174V+L1198F and L1122V+L1196M mutations were identified. The knowledge of the possible appearance of new clinically relevant mechanisms of drug resistance is a useful tool for the management of new TKI-resistant cases.

Implications: This work defines reliable ALCL model systems of AP26113 resistance and provides a valuable tool in the management of all cases of relapse upon NPM-ALK–targeted therapy. *Mol Cancer Res; 13(4); 775–83. ©2014 AACR.*

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Research Article

Mechanistic Dissection of PARP1 Trapping and the Impact on *In Vivo* Tolerability and Efficacy of PARP Inhibitors

David Maag

Todd A. Hopkins, Yan Shi, Luis E. Rodriguez, Larry R. Solomon, Cherrie K. Donawho, Enrico L. DiGiammarino, Sanjay C. Panchal, Julie L. Wilsbacher, Wenqing Gao, Amanda M. Olson, DeAnne F. Stolarik, Donald J. Osterling, Eric F. Johnson, and David Maag

Abstract

Poly(ADP-ribose) polymerases (PARP1, -2, and -3) play important roles in DNA damage repair. As such, a number of PARP inhibitors are undergoing clinical development as anticancer therapies, particularly in tumors with DNA repair deficits and in combination with DNA-damaging agents. Preclinical evidence indicates that PARP inhibitors potentiate the cytotoxicity of DNA alkylating agents. It has been proposed that a major mechanism underlying this activity is the allosteric trapping of PARP1 at DNA single-strand breaks during base excision repair; however, direct evidence of allostery has not been reported. Here the data reveal that veliparib, olaparib, niraparib, and talazoparib (BMN-673) potentiate the cytotoxicity of alkylating agents. Consistent with this, all four drugs possess PARP1 trapping activity. Using biochemical and cellular approaches, we directly probe the trapping mechanism for an allosteric component. These studies indicate that trapping is due to catalytic inhibition and not allostery. The potency of PARP inhibitors with respect to trapping and catalytic inhibition is linearly correlated in biochemical systems but is nonlinear in cells. High-content imaging of γH2Ax levels suggests that this is attributable to differential potentiation of DNA damage in cells. Trapping potency is inversely correlated with tolerability when PARP inhibitors are combined with temozolomide in mouse xenograft studies. As a result, PARP inhibitors with dramatically different trapping potencies elicit comparable *in vivo* efficacy at maximum tolerated doses. Finally, the impact of trapping on tolerability and efficacy is likely to be context specific.

Implications: Understanding the context-specific relationships of trapping and catalytic inhibition with both tolerability and efficacy will aid in determining the suitability of a PARP inhibitor for inclusion in a particular clinical regimen. *Mol Cancer Res; 13(11); 1465–77. ©2015 AACR.*

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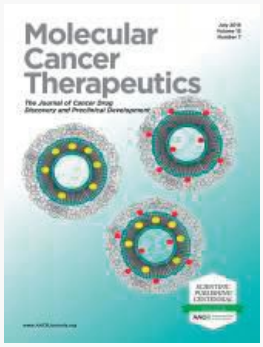
Molecular Cancer Therapeutics



Napoleone Ferrara, MD
Editor-in-Chief

Scope

Molecular Cancer Therapeutics strives to be the top choice for publishing the best science in the discovery and preclinical development of novel therapeutic agents for oncology, preclinical studies of approved therapeutics, mechanisms of drug action, mechanisms of drug resistance, biomarkers of drug response, novel models and technologies, and occasional drug toxicity mechanisms. While the Journal's main focus is on small molecule and protein drugs, other molecular entities may be considered.

Review Article

PD-L1 Expression as a Predictive Biomarker in Cancer Immunotherapy

Sandip Pravin Patel and Razelle Kurzrock

Sandip Pravin Patel

Abstract

The resurgence of cancer immunotherapy stems from an improved understanding of the tumor microenvironment. The PD-1/PD-L1 axis is of particular interest, in light of promising data demonstrating a restoration of host immunity against tumors, with the prospect of durable remissions. Indeed, remarkable clinical responses have been seen in several different malignancies including, but not limited to, melanoma, lung, kidney, and bladder cancers. Even so, determining which patients derive benefit from PD-1/PD-L1–directed immunotherapy remains an important clinical question, particularly in light of the autoimmune toxicity of these agents. The use of PD-L1 (B7-H1) immunohistochemistry (IHC) as a predictive biomarker is confounded by multiple unresolved issues: variable detection antibodies, differing IHC cutoffs, tissue preparation, processing variability, primary versus metastatic biopsies, oncogenic versus induced PD-L1 expression, and staining of tumor versus immune cells. Emerging data suggest that patients whose tumors overexpress PD-L1 by IHC have improved clinical outcomes with anti-PD-1–directed therapy, but the presence of robust responses in some patients with low levels of expression of these markers complicates the issue of PD-L1 as an exclusionary predictive biomarker. An improved understanding of the host immune system and tumor microenvironment will better elucidate which patients derive benefit from these promising agents. *Mol Cancer Ther; 14(4); 847–56. ©2015 AACR.*

Mol Cancer Ther; 14(4); 847–56; Published OnlineFirst April 2015; doi: 10.1158/1535-7163.MCT-14-0983

Research Article

Long Noncoding RNA ANRIL Promotes Non–Small Cell Lung Cancer Cell Proliferation and Inhibits Apoptosis by Silencing KLF2 and P21 Expression

Kai-hua Lu

Feng-qi Nie, Ming Sun, Jin-song Yang, Min Xie, Tong-peng Xu, Rui Xia, Yan-wen Liu, Xiang-hua Liu, Er-bao Zhang, Kai-hua Lu, and Yong-qian Shu

Abstract

Recent evidence highlights long noncoding RNAs (lncRNA) as crucial regulators of cancer biology that contribute to essential cancer cell functions such as cell proliferation, apoptosis, and metastasis. In non–small cell lung cancer (NSCLC), several lncRNAs' expressions are misregulated and have been nominated as critical actors in NSCLC tumorigenesis. LncRNA ANRIL was first found to be required for the PRC2 recruitment to and silencing of $p15^{INK4B}$, the expression of which is induced by the ATM–E2F1 signaling pathway. Our previous study showed that ANRIL was significantly upregulated in gastric cancer, and it could promote cell proliferation and inhibit cell apoptosis by silencing of miR99a and miR449a transcription. However, its clinical significance and potential role in NSCLC is still not documented. In this study, we reported that ANRIL expression was increased in NSCLC tissues, and its expression level was significantly correlated with tumor–node–metastasis stages and tumor size. Moreover, patients with high levels of ANRIL expression had a relatively poor prognosis. In addition, taking advantage of loss-of-function experiments in NSCLC cells, we found that knockdown of ANRIL expression could impair cell proliferation and induce cell apoptosis both in *vitro* and *vivo*. Furthermore, we uncover that ANRIL could not repress p15 expression in PC9 cells, but through silencing of KLF2 and P21 transcription. Thus, we conclusively demonstrate that lncRNA ANRIL plays a key role in NSCLC development by associating its expression with survival in patients with NSCLC, providing novel insights on the function of lncRNA-driven tumorigenesis. *Mol Cancer Ther; 14(1); 268–77. ©2014 AACR.*

Mol Cancer Ther; 14(1); 268–77; Published OnlineFirst January 2015; doi: 10.1158/1535-7163.MCT-14-0492

Research Article

Multiple Molecular Subtypes of Triple-Negative Breast Cancer Critically Rely on Androgen Receptor and Respond to Enzalutamide *In Vivo*

Jennifer K. Richer

Valerie N. Barton, Nicholas C. D'Amato, Michael A. Gordon, Hanne T. Lind, Nicole S. Spoelstra, Beatrice L. Babbs, Richard E. Heinz, Anthony Elias, Paul Jedlicka, Britta M. Jacobsen, and Jennifer K. Richer

Abstract

Triple-negative breast cancer (TNBC) has the lowest 5-year survival rate of invasive breast carcinomas, and currently there are no approved targeted therapies for this aggressive form of the disease. The androgen receptor (AR) is expressed in up to one third of TNBC and we find that all AR^+ TNBC primary tumors tested display nuclear localization of AR, indicative of transcriptionally active receptors. While AR is most abundant in the "luminal AR (LAR)" molecular subtype of TNBC, here, for the first time, we use both the new-generation anti-androgen enzalutamide and AR knockdown to demonstrate that the other non-LAR molecular subtypes of TNBC are critically dependent on AR protein. Indeed, AR inhibition significantly reduces baseline proliferation, anchorage-independent growth, migration, and invasion and increases apoptosis in four TNBC lines (SUM159PT, HCC1806, BT549, and MDA-MB-231), representing three non-LAR TNBC molecular subtypes (mesenchymal-like, mesenchymal stem–like, and basal-like 2). *In vivo*, enzalutamide significantly decreases viability of SUM159PT and HCC1806 xenografts. Furthermore, mechanistic analysis reveals that AR activation upregulates secretion of the EGFR ligand amphiregulin (AREG), an effect abrogated by enzalutamide *in vitro* and *in vivo*. Exogenous AREG partially rescues the effects of AR knockdown on proliferation, migration, and invasion, demonstrating that upregulation of AREG is one mechanism by which AR influences tumorigenicity. Together, our findings indicate that non-LAR subtypes of TNBC are AR dependent and, moreover, that enzalutamide is a promising targeted therapy for multiple molecular subtypes of AR^+ TNBC. *Mol Cancer Ther; 14(3); 769–78. ©2015 AACR.*

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Research Article

HOTAIR Long Noncoding RNA Promotes Gastric Cancer Metastasis through Suppression of Poly r(C)-Binding Protein (PCBP) 1

Zi-Zhen Zhang, Zhi-Yong Shen, Yan-Ying Shen, En-Hao Zhao, Ming Wang, Chao-Jie Wang, Hui Cao, and Jia Xu

Abstract

The objective of this study was to evaluate the role of HOTAIR long noncoding RNA in gastric cancer metastasis. We analyzed HOTAIR expression levels by real-time reverse transcription PCR and Northern blot analysis in 100 gastric tissues (50 gastric cancer tissues and 50 adjacent normal mucosa), and in four gastric cancer cell lines. Transient RNAi-mediated knockdown and pcDNA-mediated overexpression of HOTAIR were performed. Stable shRNA-mediated knockdown and lentiviral-mediated overexpression of HOTAIR were to study the role of HOTAIR on *in vivo* tumorigenicity and metastatic burden in the context of xenograft assays. Proteomic profiling was performed to decipher differential protein expression in cells with different HOTAIR expression levels. One of the differentially regulated proteins, Poly r(C)-binding protein (PCBP) 1, was subsequently validated and its function evaluated through xenograft assays. Expression of HOTAIR was significantly higher in cancerous tissues than in adjacent normal mucosa. HOTAIR expression levels dictated *in vitro* and *in vivo* tumorigenicity and metastatic potential in these cells. PCBP1 and HOTAIR have an inverse relationship, both at expression level and in function. A direct interaction between the two was confirmed through RNA immunoprecipitation coupled with quantitative real-time PCR. PCBP1 was confirmed to be an inhibitor of gastric cancer pathogenesis and as functionally opposite to HOTAIR long noncoding RNA. In conclusion, HOTAIR expression may serve as a potentially important disease biomarker for the identification of high-risk gastric cancer patients. Moreover, our findings provide mechanistic evidence for HOTAIR overexpression and PCBP1 downregulation and the ensuing malignant phenotype in both cultured and xenograft gastric cancer cells. *Mol Cancer Ther; 14(5); 1162–70. ©2015 AACR.*

Mol Cancer Ther; 14(5); 1162–70; Published OnlineFirst April 2015; doi: 10.1158/1535-7163.MCT-14-0695

Research Article

Anticancer Activity of a Novel Selective CYP17A1 Inhibitor in Preclinical Models of Castrate-Resistant Prostate Cancer

Martin E. Gleave

Paul J. Toren, Soojin Kim, Steven Pham, Azzra Mangalji, Hans Adomat, Emma S. Tomlinson Guns, Amina Zoubeidi, William Moore, and Martin E. Gleave

Abstract

VT-464 is a novel, nonsteroidal, small-molecule CYP17A1 inhibitor with 17,20-lyase selectivity. This study evaluates the anticancer activity of VT-464 compared with abiraterone (ABI) in castrate-resistant prostate cancer cell lines and xenograft models that are enzalutamide (ENZ)-responsive (C4-2) or ENZ-resistant (MR49C, MR49F). *In vitro*, androgen receptor (AR) transactivation was assessed by probasin luciferase reporter, whereas AR and AR-regulated genes and steroidogenic pathway enzymes were assessed by Western blot and/or qRT-PCR. The MR49F xenograft model was used to compare effects of oral VT-464 treatment to vehicle and abiraterone acetate (AA). Steroid concentrations were measured using LC-MS chromatography. VT-464 demonstrated a greater decrease in AR transactivation compared with ABI in C4-2 and both ENZ-resistant cell lines. At the gene and protein level, VT-464 suppressed the AR axis to a greater extent compared with ABI. Gene transcripts StAR, CYP17A1, HSD17B3, and SRD5A1 increased following treatment with ABI and to a greater extent with VT-464. *In vivo*, intratumoral androgen levels were significantly lower after VT-464 or AA treatment compared with vehicle, with the greatest decrease seen with VT-464. Similarly, tumor growth inhibition and PSA decrease trends were greater with VT-464 than with AA. Finally, an AR-antagonist effect of VT-464 independent of CYP17A1 inhibition was observed using luciferase reporter assays, and a direct interaction was confirmed using an AR ligand binding domain biolayer interferometry. These preclinical results suggest greater suppression of the AR axis with VT-464 than ABI that is likely due to both superior selective suppression of androgen synthesis and AR antagonism. *Mol Cancer Ther; 14(1); 59–69. ©2014 AACR.*

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