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Dysregulated Glutamate Transporter SLC1A1 Propels Cystine Uptake via Xc⁻ for Glutathione Synthesis in Lung Cancer

553  
Wenzheng Guo, Kaimi Li, Beibei Sun, Dongliang Xu, Lingfeng Tong, Huijing Yin, Yueling Liao, Hongyong Song, Tong Wang, Bo Jing, Min Hu, Shuli Liu, Yanbin Kuang, Jing Ling, Qi Li, Yadi Wu, Qi Wang, Feng Yao, Binhua P. Zhou, Shu-Hai Lin, and Jiong Deng

This study characterizes altered mitochondria functionality of the metastatic cell state in lung cancer and opens new avenues for metastasis-specific therapeutic targeting.

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Estrogen Receptor Alpha Mutations in Breast Cancer Cells Cause Gene Expression Changes through Constant Activity and Secondary Effects  
Spencer Arnesen, Zannel Blanchard, Michelle M. Williams, Kristofer C. Berrett, Zheqi Li, Steffi Oesterreich, Jennifer K. Richer, and Jason Gertz

This study demonstrates the multiple roles of mutant ER in breast cancer progression, including constant ER activity and secondary regulatory effects on gene expression and chromatin accessibility.

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### MOLECULAR CELL BIOLOGY

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SCIRT IncRNA Restrains Tumorigenesis by Opposing Transcriptional Programs of Tumor-Initiating Cells  
Sladjana Zagorac, Alex de Giorgio, Aleksandra Dabrowska, Mark Kalisz, Nuria Casas-Vila, Paul Cathcart, Angela Yiu, Silvia Ottaviani, Neta Degani, Ylenia Lombardo, Alistair Tweedie, Tracy Nissan, Keith W. Vance, Igor Ulitsky, Justin Stebbing, and Leandro Castellano

These findings show that a novel IncRNA SCIRT counteracts breast tumorigenesis by opposing transcriptional networks associated with cell cycle and self-renewal.

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### TUMOR BIOLOGY AND IMMUNOLOGY

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<td>These findings show that loss of miRNA let-7d and active HIF1 signaling promotes breast cancer brain metastasis via PDGF and that pharmacologic inhibition of PDGFR suppresses brain metastasis, suggesting novel therapeutic opportunities.</td>
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<td>This study identifies previously unknown role for PDGFB-to-PDGFRβ paracrine signaling in the promotion of breast cancer brain metastases and support the prognostic and therapeutic clinical utility of this pathway for patients.</td>
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<td>A high-content screen identified niclosamide as an effective drug that restricts tumor cell extravasation by enhancing endothelial barrier stability through modulation of molecular signaling, chemokines, and tumor-endothelial cell interactions.</td>
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<td>These findings show that loss of miRNA let-7d and active HIF1 signaling promotes breast cancer brain metastasis via PDGF and that pharmacologic inhibition of PDGFR suppresses brain metastasis, suggesting novel therapeutic opportunities.</td>
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<td>This study identifies Hyal2-expressing tumor-associated myeloid cells of monocyte-macrophage lineage as contributors to hyaluronan degradation in bladder cancer tissue, leading to accumulation of inflammatory and proangiogenic low molecular weight hyaluronan fragments.</td>
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<td>These findings demonstrate that myeloid cells provide a major source of WntSA to facilitate metastatic potential in melanoma cells and rely on WntSA for their immunosuppressive function.</td>
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<td>FRβ serves as both a means to identify and target MDSCs and TAMs within the tumor, allowing for delivery of immunomodulatory compounds to tumor myeloid cells in a variety of cancers.</td>
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Cyclophosphamide and Vinorelbine Activate Stem-Like CD8\(^+\) T Cells and Improve Anti-PD-1 Efficacy in Triple-Negative Breast Cancer

A C
Paolo Falvo, Stefania Orecchioni, Roman Hillje, Alessandro Raveane, Patrizia Mancuso, Chiara Camisaschi, Lucilla Luzi, PierGiuseppe Pelicci, and Francesco Bertolini

A combinatorial therapy in mouse models of breast cancer increases checkpoint inhibition by activating antigen-presenting cells, enhancing intratumoral Tcf1\(^+\) stem-like CD8\(^+\) T cells, and increasing progenitor exhausted CD8\(^+\) T cells.

Axl and Mertk Receptors Cooperate to Promote Breast Cancer Progression by Combined Oncogenic Signaling and Evasion of Host Antitumor Immunity

Viralkumar Davra, Sushil Kumar, Ke Geng, David Calianese, Dhriti Mehta, Varsha Gadiyar, Canan Kasikara, Kevin C. Lahey, Yun-juan Chang, Michael Wichroski, Chan Gao, Mariana S. De Lorenzo, Sergei V. Kotenko, Tessa Bergsbaken, Pankaj K. Mishra, William C. Gause, Michael Quigley, Thomas E. Spires, and Raymond B. Birge

This study demonstrates how TAM receptors act both as oncogenic tyrosine kinases and as receptors that mediate immune evasion in cancer progression.

Cisplatin-Mediated Upregulation of APE2 Binding to MYH9 Provokes Mitochondrial Fragmentation and Acute Kidney Injury

Yi Hu, Chan Yang, Tania Amorim, Mohsin Maqbool, Jenny Lin, Chen Li, Chuanfeng Fang, Li Xue, Ariel Kwart, Hua Fang, Mei Yin, Allison J. Janocha, Daixuke Tsuchimoto, Yusaku Nakabeppu, Xiaofeng Jiang, Alex Mejia-Garcia, Faiz Anwer, Jack Khouri, Xin Qi, Qing Y. Zheng, Jennifer S. Yu, Shan Yan, Thomas LaFramboise, Kenneth C. Anderson, Leal C. Herlitz, Nikhil C. Munshi, Jianhong Lin, and Jianjun Zhao

These results reveal and highlight an unexpected role of APE2 via its interaction with MYH9 and suggest that APE2 has the potential to prevent acute kidney injury in cisplatin-treated cancer patients.

Radomic Detection of EGFR Mutations in NSCLC

Giovanni Rossi, Emanuele Barabino, Alessandro Fedeli, Gianluca Ciccaro, Simona Coco, Alessandro Russo, Vincenzo Adamo, Francesco Buemi, Lodovica Zullo, Mariella Dono, Giuseppa De Luca, Luca Longo, Maria Giovanna Dal Bello, Marco Tagliamento, Angela Alama, Giuseppe Cittadini, Paolo Pronzato, and Carlo Genova

A novel method for the detection of EGFR mutations in NSCLC is described, which could improve the identification of EGFR mutant NSCLC patients.

Steroid Hormone Receptor and Infiltrating Immune Cell Status Reveals Therapeutic Vulnerabilities of ESRT-Mutant Breast Cancer


This study demonstrates how the status of steroid hormone receptors and infiltrating immune cells can predict therapeutic vulnerabilities in ESRT-mutant breast cancer.

Optimized Doxorubicin Chemotherapy for Diffuse Large B-cell Lymphoma Exploits Nanocarrier Delivery to Transferrin Receptors

Artavazd Arumov, Piumi Y. Liyanage, Avaad Trabolsi, Evan R. Roberts, Lingxiao Li, Braulio C.L.B. Ferreira, Zhen Gao, Yuguang Ban, Austin D. Newsam, Melissa W. Taggart, Francisco Vega, Daniel Bilbao, Roger M. Leblanc, and Jonathan H. Schatz

Targeted nanoparticle delivery of doxorubicin chemotherapy via the TRF1 receptor presents a new opportunity against high-risk DLBCL tumors using potency and precision.

For more information please visit www.aacrjournals.org
ABOUT THE COVER

Stromal specific activation of platelet-derived growth factor receptor-β (PDGFRβ) in the metastatic microenvironment promotes breast cancer metastasis to the brain. Specifically, the Fsp1-cre transgene was used to hyperactivate PDGFRβ in the mesenchymal population. A confocal image shows native tdTomato fluorescence (red) and GFAP (green) immunostaining in the brain stroma of a Fsp1-cre;Rosa26-LSL-tdTomato reporter mouse. The dual tdTomato(FSP1)/GFAP-positive cells represent a novel stromal population implicated in creating a prometastatic niche through PDGFRβ signaling. For details, see article by Thies and colleagues on page 606.