
Rockefeller University Press
2025 CANCER COLLECTION
JCB Journal of Cell Biology
JEM Journal of Experimental Medicine
Life Science Alliance

TOOLS FOR DISCOVERY

INSTRUCTIONS FOR AUTHORS

JCB
www.jcb.org

Journal of Cell Biology (JCB) publishes advances in any area of basic cell biology as well as applied cellular advances in fields such as cancer biology, immunology, neurobiology, stem cell biology, and metabolism. All editorial decisions on research manuscripts are made through collaborative consultation between professional editors with scientific training and academic editors who are active in the field. JCB was established in 1955.

JEM
www.jem.org

Journal of Experimental Medicine (JEM) publishes papers providing novel conceptual insight into immunology, cancer biology, neuroscience, vascular biology, microbial pathogenesis, and stem cell biology. All editorial decisions are made by active scientists in conjunction with professional editors. JEM was established in 1896.

JGP
www.jgp.org

Journal of General Physiology (JGP) publishes mechanistic and quantitative cellular and molecular physiology of the highest quality; provides a best in class author experience; and nurtures future generations of researchers. All editorial decisions on research manuscripts are made through a collaborative consultation between the Editor-in-Chief and Associate Editors, all of whom are active scientists. JGP was established in 1918.

JHI
www.jhumimmunity.org

Journal of Human Immunity (JHI) is the community's first dedicated journal for research on human inborn errors of immunity (IEI) and is the official journal of the International Alliance for Primary Immunodeficiency Societies (IAPIDS). JHI publishes novel insights into the physiology and pathology of human immunity through the study of genetic defects and their phenocopies, including the study of leukocytes and other cells. JHI was established in 2025.

www.lsajournal.org

Life Science Alliance (LSA) is a global, open-access, editorially independent, and peer-reviewed journal launched in 2018 by an alliance of EMBO Press, Rockefeller University Press, and Cold Spring Harbor Laboratory Press. Life Science Alliance is committed to rapid, fair, and transparent publication of valuable research from across all areas in the life sciences.

WHY SUBMIT TO ROCKEFELLER UNIVERSITY PRESS JOURNALS

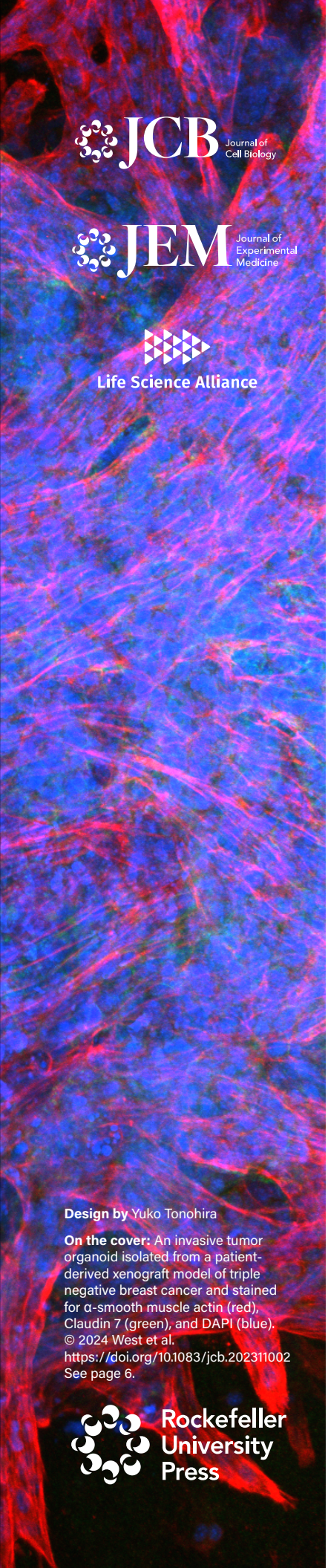
Format Neutral
You may submit your papers in ANY format.

Transfer Policy
We welcome submissions that include reviewer comments from another journal.

Fair and Fast
Articles appear online one to two days after author proofs are returned.

Rockefeller University Press

RUPRESS.ORG



JCB Journal of Cell Biology

JEM Journal of Experimental Medicine

Life Science Alliance

Design by Yuko Tonohira

On the cover: An invasive tumor organoid isolated from a patient-derived xenograft model of triple negative breast cancer and stained for α-smooth muscle actin (red), Claudin 7 (green), and DAPI (blue).

https://doi.org/10.1083/jcb.202311002
See page 6.

Rockefeller University Press

CANCER COLLECTION 2025

The editors of the *Journal of Cell Biology* (*JCB*), *Journal of Experimental Medicine* (*JEM*), and *Life Science Alliance* (*LSA*) are pleased to present a special combined collection of recently published articles that elucidate new advances within the field of cancer research. If you enjoy this collection, we encourage you to scan the QR codes below to view the full online collections and sign up for email alerts to receive the latest research.

JOURNAL OF CELL BIOLOGY

JOURNAL OF EXPERIMENTAL MEDICINE

LIFE SCIENCE ALLIANCE

READ FULL COLLECTIONS ONLINE

TFEB lactylation enhances autophagy in cancer cells

The transcription factor TFEB is a major regulator of lysosomal biogenesis and autophagy. There is growing evidence that posttranslational modifications play a crucial role in regulating TFEB activity.

We show that lactate molecules can covalently modify TFEB, leading to its lactylation and stabilization. Mechanistically, lactylation at K91 prevents TFEB from interacting with the E3 ubiquitin ligase WWP2, thereby inhibiting TFEB ubiquitination and proteasome degradation, resulting in increased TFEB activity and autophagy flux.

Using a specific antibody against lactylated K91, enhanced TFEB lactylation was observed in clinical human pancreatic cancer samples. Our results suggest that lactylation is a novel mode of TFEB regulation and that lactylation of TFEB may be associated with high levels of autophagy in rapidly proliferating cells, such as cancer cells.

ORIGINAL PAPER

Huang, Y., G. Luo, K. Peng, Y. Song, Y. Wang, H. Zhang, J. Li, X. Qiu, M. Pu, X. Liu, C. Peng, D. Neculai, Q. Sun, T. Zhou, P. Huang, and W. Liu. 2024. Lactylation stabilizes TFEB to elevate autophagy and lysosomal activity. *J. Cell Biol.* 223 (11): e202308099. https://doi.org/10.1083/jcb.202308099

RESEARCHER DETAILS


Yewei Huang
PhD student
Zhejiang University


Gan Luo
PhD student
Zhejiang University


Kesong Peng
PhD student
Zhejiang University


Tianhua Zhou
Professor
Zhejiang University
tzhou@zju.edu.cn


Pintong Huang
Professor
Zhejiang University
huangpintong@zju.edu.cn


Wei Liu
Professor
Zhejiang University
liuwei666@zju.edu.cn

Ribosome MARylation modulates stress granules and translation in ovarian cancer cells

Mono(ADP-ribosyl)ation (MARylation) is emerging as a critical regulator of ribosome function and translation. We demonstrate that RACK1, an integral component of the ribosome, is MARylated by the mono(ADP-ribosyl) transferase (MART) PARP14 in ovarian cancer cells.

MARylation of RACK1 is required for stress granule formation and promotes the colocalization of RACK1 in stress granules with G3BP1, eIF3η, and 40S ribosomal proteins. In parallel, we observed reduced translation of a subset of mRNAs, including those encoding key cancer regulators (e.g., AKT).

Treatment with a PARP14 inhibitor or mutation of the sites of MARylation on RACK1 blocks these outcomes, as well as the growth of ovarian cancer cells in culture and in vivo. To reset the system after prolonged stress and recovery, the ADP-ribosyl hydrolase TARG1 deMARylates RACK1, leading to the dissociation of the stress granules and the restoration of translation.

Collectively, our results demonstrate a therapeutically targetable pathway that controls polysome assembly, translation, and stress granule dynamics in ovarian cancer cells.

ORIGINAL PAPER

Challa, S., T. Nandu, H.B. Kim, X. Gong, C.W. Renshaw, W.-C. Li, X. Tan, M.W. Aljardali, C.V. Camacho, J. Chen, and W.L. Kraus. 2025. RACK1 MARylation regulates translation and stress granules in ovarian cancer cells. *J. Cell Biol.* 224 (2): e202401101. https://doi.org/10.1083/jcb.202401101

RESEARCHER DETAILS


Sridevi Challa, PhD
Assistant Professor of Obstetrics and Gynecology
University of Chicago
sridevi.challa@bsd.uchicago.edu


W. Lee Kraus PhD
Professor and Director
Cecil H. and Ida Green Center for Reproductive Biology Sciences,
University of Texas Southwestern Medical Center
lee.kraus@utsouthwestern.edu

JCB Journal of Cell Biology

Human culture cells assemble asymmetric spindles

Centrosomes are the main microtubule-organizing centers in animal cells. Due to the semiconservative nature of centrosome duplication, the two centrosomes differ in age. In asymmetric stem cell divisions, centrosome age can induce an asymmetry in half-spindle lengths. However, whether centrosome age affects the symmetry of the two half-spindles in tissue culture cells thought to divide symmetrically is unknown.

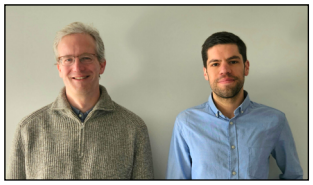
We show that in human epithelial and fibroblastic cell lines, centrosome age imposes a mild spindle asymmetry that leads to asymmetric cell daughter sizes. At the mechanistic level, we show that this asymmetry depends on a cenexin-bound pool of the mitotic kinase Plk1, which favors the preferential accumulation on old centrosomes of the microtubule nucleation–organizing proteins pericentrin, γ-tubulin, and Cdk5Rap2, and microtubule regulators TPX2 and ch-TOG. Consistently, we find that old centrosomes have a higher microtubule nucleation capacity.

We postulate that centrosome age breaks spindle size symmetry via microtubule nucleation even in cells thought to divide symmetrically.

ORIGINAL PAPER

Thomas, A., and P. Meraldi. 2024. Centrosome age breaks spindle size symmetry even in cells thought to divide symmetrically. *J. Cell Biol.* 223 (8): e202311153. https://doi.org/10.1083/jcb.202311153

RESEARCHER DETAILS



Patrick Meraldi (L)
Professor
University of Geneva
patrick.meraldi@unige.ch

Alexandre Thomas (R)
Postdoctoral Fellow
University of Geneva

Macrophage protrusions promote melanoma invasion

Macrophages are primary cells of the innate immune system that mediate tumor progression. However, the motile behavior of macrophages and interactions with tumor cells are not well understood.

We exploited the optical transparency of larval zebrafish and performed real-time imaging of macrophage–melanoma interactions. We found that macrophages are highly motile in the tumor microenvironment. Macrophages extend dynamic projections between tumor cells that precede invasive melanoma migration. Modulating macrophage motility with a dominant inhibitory mutation in Rac2 inhibits recruitment to the tumor and impairs tumor invasion. However, a hyperactivating mutation in Rac2 does not affect macrophage recruitment but limits macrophage projections into the melanoma mass and reduces invasive melanoma cell migration.

Taken together, these findings reveal a role for Rac2-mediated macrophage protrusive motility in melanoma invasion.

ORIGINAL PAPER

Ramakrishnan, G., V. Miskolci, M. Hunter, M.A. Giese, D. Münch, Y. Hou, K.W. Eliceiri, M.R. Lasarev, R.M. White, and A. Huttenlocher. 2025. Real-time imaging reveals a role for macrophage protrusive motility in melanoma invasion. *J. Cell Biol.* 224 (2): e202403096. https://doi.org/10.1083/jcb.202403096

RESEARCHER DETAILS

Gayathri Ramakrishnan
Graduate student
University of Wisconsin-Madison School of Medicine and Public Health
(Now a postdoctoral researcher at the University of California, San Diego)

Anna Huttenlocher
Professor
University of Wisconsin-Madison School of Medicine and Public Health
huttenlocher@wisc.edu

Claudin7 suppresses breast cancer invasion and metastasis

Metastasis initiates when cancer cells escape from the primary tumor, which requires changes to intercellular junctions. Claudins are transmembrane proteins that form the tight junction, and their expression is reduced in aggressive breast tumors. However, claudins' roles during breast cancer metastasis remain unclear.

We used gain- and loss-of-function genetics in organoids isolated from murine breast cancer models to establish that Cldn7 suppresses invasion and metastasis. Transcriptomic analysis revealed that Cldn7 knockdown induced smooth muscle actin (SMA)–related genes and a broader mesenchymal phenotype. We validated our results in human cell lines, fresh human tumor tissue, bulk RNA-seq, and public single-cell RNA-seq data. We consistently observed an inverse relationship between Cldn7 expression and expression of SMA-related genes. Furthermore, knockdown and overexpression of SMA-related genes demonstrated that they promote breast cancer invasion.

Our data reveal that Cldn7 suppresses breast cancer invasion and metastasis through negative regulation of SMA-related and mesenchymal gene expression.

ORIGINAL PAPER

West, J.J., R. Golloshi, C.Y. Cho, Y. Wang, P. Stevenson, G. Stein-O'Brien, E.J. Fertig, and A.J. Ewald. 2024. Claudin 7 suppresses invasion and metastasis through repression of a smooth muscle actin program. *J. Cell Biol.* 223 (12): e202311002. https://doi.org/10.1083/jcb.202311002

RESEARCHER DETAILS

Junior J. West
Assistant Professor
Department of Molecular, Cellular, and Developmental Biology
University of Michigan Ann Arbor

Andrew J. Ewald
Virginia DeAcetis Professor and Director of Cell Biology
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University School of Medicine
andrew.ewald@jhmi.edu

JEM Journal of Experimental Medicine

Pan-cancer immunological markers of immune checkpoint inhibitor response

Identifying pan-tumor biomarkers that predict responses to immune checkpoint inhibitors (ICI) is critically needed. In the AMADEUS clinical trial (NCT03651271), patients with various advanced solid tumors were assessed for changes in intratumoral CD8 percentages and their response to ICI.

Patients were grouped based on tumoral CD8 levels: those with CD8 <15% (CD8-low) received nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA4) and those with CD8 ≥15% (CD8-high) received nivolumab monotherapy. 79 patients (72 CD8-low and 7 CD8-high) were treated. The disease control rate was 25.0% (18/72; 95% CI: 15.8–35.2) in CD8-low and 14.3% (1/7; 95% CI: 1.1–43.8) in CD8-high. Tumors from 35.9% (14/39; 95% CI: 21.8–51.4) of patients converted from CD8 <15% pretreatment to ≥15% after treatment.

Multiomic analyses showed that CD8-low responders had an inflammatory tumor microenvironment pretreatment, enhanced by an influx of CD8 T cells, CD4 T cells, B cells, and macrophages upon treatment. These findings reveal crucial pan-cancer immunological features for ICI response in patients with metastatic disease.

ORIGINAL PAPER

Tsimberidou, A.M., F.A. Alayli, K. Okrah, A. Drakaki, D.N. Khalil, S. Kummar, S.A. Khan, F.S. Hodi, D.Y. Oh, C.R. Cabanski, S. Gautam, S.L. Meier, M. Amouzgar, S.M. Pfeiffer, R. Kageyama, E. Yang, M. Spasic, M.T. Tetzlaff, W.C. Foo, T.J. Hollmann, Y. Li, M. Adamow, P. Wong, J.S. Moore, S. Velichko, R.O. Chen, D. Kumar, S. Bucktrout, R. Ibrahim, U. Dugan, L. Salvador, V.M. Hubbard-Lucey, J. O'Donnell-Tormey, S. Santulli-Marotto, L.H. Butterfield, D.M. Da Silva, J. Fairchild, T.M. LaVallee, L.J. Padrón, and P. Sharma. 2024. Immunologic signatures of response and resistance to nivolumab with ipilimumab in advanced metastatic cancer. *J. Exp. Med.* 221 (10): e20240152. https://doi.org/10.1084/jem.20240152

RESEARCHER DETAILS

Apostolia M. Tsimberidou MD, PhD, FASCO, FAAAS
Professor, Department of Investigational Cancer Therapeutics
Katherine Russell Dixie Distinguished Endowed Professor
The University of Texas MD Anderson Cancer Center

Farah A. Alayli
Translational Medicine Lead
Parker Institute for Cancer Immunotherapy

Kwame Okrah
Staff Data Scientist
Parker Institute for Cancer Immunotherapy

Padmanee Sharma, MD, PhD
Associate VP of Immunobiology
T.C. and Jeanette D. Hsu Endowed Chair in Cell Biology
Professor of Genitourinary Medical Oncology
Professor of Immunology
Scientific Director of the Immunotherapy Platform
Director of Scientific Programs for the James P. Allison Institute
The University of Texas MD Anderson Cancer Center
padsharma@mdanderson.org

Hypoxia promotes acquired resistance to immune checkpoint inhibitors in lung cancer

Despite the established use of immune checkpoint inhibitors (ICIs) to treat non-small cell lung cancer (NSCLC), only a subset of patients benefit from treatment and ~50% of patients whose tumors respond eventually develop acquired resistance (AR). To identify novel drivers of AR, we generated murine *Msh2* knock-out (KO) lung tumors that initially responded but eventually developed AR to anti-PD-1, alone or in combination with anti-CTLA-4.

Resistant tumors harbored decreased infiltrating T cells and reduced cancer cell–intrinsic MHC-I and MHC-II levels, yet remained responsive to IFNγ.

Resistant tumors contained extensive regions of hypoxia, and a hypoxia signature derived from single-cell transcriptional profiling of resistant cancer cells was associated with decreased progression-free survival in a cohort of NSCLC patients treated with anti-PD-1/PD-L1 therapy. Targeting hypoxic tumor regions using a hypoxia-activated pro-drug delayed AR to ICIs in murine *Msh2* KO tumors.

Thus, this work provides a rationale for targeting tumor metabolic features, such as hypoxia, in combination with immune checkpoint inhibition.

ORIGINAL PAPER

Robles-Oteíza, C., K. Hastings, J. Choi, I. Sirois, A. Ravi, F. Expósito, F. de Miguel, J.R. Knight, F. López-Giráldez, H. Choi, N.D. Socci, T. Merghoub, M. Awad, G. Getz, J. Gainor, M.D. Hellmann, É. Caron, S.M. Kaech, and K. Politi. 2025. Hypoxia is linked to acquired resistance to immune checkpoint inhibitors in lung cancer. *J. Exp. Med.* 222 (1): e20231106. https://doi.org/10.1084/jem.20231106

RESEARCHER DETAILS

Camila Robles-Oteíza
PhD student
Yale School of Medicine

Susan M. Kaech
Professor and Director
NOMIS Center for Immunobiology and Microbial Pathogenesis, Salk Institute
skaech@salk.edu

Katerina Politi
Professor
Yale School of Medicine
katerina.politi@yale.edu

Targeting IRE1α alleviates chemotherapy-induced anorexia

Platinum-based chemotherapy drugs can lead to the development of anorexia, a detrimental effect on the overall health of cancer patients. However, managing chemotherapy-induced anorexia and subsequent weight loss remains challenging due to limited effective therapeutic strategies. Growth differentiation factor 15 (GDF15) has recently gained significant attention in the context of chemotherapy-induced anorexia.

We report that hepatic GDF15 plays a crucial role in regulating body weight in response to chemo drugs cisplatin and doxorubicin. Cisplatin and doxorubicin treatments induce hepatic *Gdf15* expression and elevate circulating GDF15 levels, leading to hunger suppression and subsequent weight loss. Mechanistically, selective activation by chemotherapy of hepatic IRE1α-XBP1 pathway of the unfolded protein response (UPR) upregulates *Gdf15* expression. Genetic and pharmacological inactivation of IRE1α is sufficient to ameliorate chemotherapy-induced anorexia and body weight loss.

These results identify hepatic IRE1α as a molecular driver of GDF15-mediated anorexia and suggest that blocking IRE1α RNase activity offers a therapeutic strategy to alleviate the adverse anorexia effects in chemotherapy.

RESEARCHER DETAILS

Yuexiao Tang
Assistant Research Fellow
Tongde Hospital of Zhejiang Province

Tao Yao
PhD student
Zhejiang University

Wei Chen
Professor
Tongde Hospital of Zhejiang Province
viogro@163.com

Bo Shan
Professor
Zhejiang University
boshan@zju.edu.cn

Ying Wu
Associate Professor
Tongde Hospital of Zhejiang Province
wuying@sibs.ac.cn

ORIGINAL PAPER
Tang, Y., T. Yao, X. Tian, X. Xia, X. Huang, Z. Qin, Z. Shen, L. Zhao, Y. Zhao, B. Diao, Y. Ping, X. Zheng, Y. Xu, H. Chen, T. Qian, T. Ma, B. Zhou, S. Xu, Q. Zhou, Y. Liu, M. Shao, W. Chen, B. Shan, and Y. Wu. 2024. Hepatic IRE1α-XBP1 signaling promotes GDF15-mediated anorexia and body weight loss in chemotherapy. *J. Exp. Med.* 221 (7): e20231395. https://doi.org/10.1084/jem.20231395

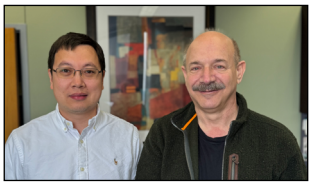
MHC-II disruption suppresses melanoma and enhances immunotherapy in mice

Immune checkpoint inhibitors interfere with T cell exhaustion but often fail to cure or control cancer long-term in patients. Using a genetic screen in C57BL/6J mice, we discovered a mutation in host *H2-Aa* that caused strong immune-mediated resistance to mouse melanomas.

H2-Aa encodes an MHC class II α chain, and its absence in C57BL/6J mice eliminates all MHC-II expression. *H2-Aa* deficiency, specifically in dendritic cells (DC), led to a quantitative increase in type 2 conventional DC (cDC2) and a decrease in cDC1. *H2-Aa*–deficient cDC2, but not cDC1, were essential for melanoma suppression and effectively cross-primed and recruited CD8 T cells into tumors. Lack of T regulatory cells, also observed in *H2-Aa* deficiency, contributed to melanoma suppression. Acute disruption of H2-Aa was therapeutic in melanoma-bearing mice, particularly when combined with checkpoint inhibition, which had no therapeutic effect by itself.

Our findings suggest that inhibiting MHC-II may be an effective immunotherapeutic approach to enhance immune responses to cancer.

RESEARCHER DETAILS



Hexin Shi (L)
Assistant Professor
Center for the Genetics of Host Defense,
University of Texas Southwestern Medical Center
hexin.shi@utsouthwestern.edu

Bruce Beutler (R)
Professor and Director
Center for the Genetics of Host Defense,
University of Texas Southwestern Medical Center
bruce.beutler@utsouthwestern.edu

ORIGINAL PAPER
Shi, H., D. Medler, J. Wang, R. Browning, A. Liu, S. Schneider, C.Duran Bojorquez, A. Kumar, X. Li, J. Quan, S. Ludwig, J.J. Moresco, C. Xing, E.M.Y. Moresco, and B. Beutler. 2024. Suppression of melanoma by mice lacking MHC-II: Mechanisms and implications for cancer immunotherapy. *J. Exp. Med.* 221 (12): e20240797. https://doi.org/10.1084/jem.20240797

JEM Journal of Experimental Medicine

An inositol-sensing pathway promotes castration-resistant prostate cancer

Acquisition of prostate cancer stem cells (PCSCs) manifested during androgen ablation therapy (ABT) contributes to castration-resistant prostate cancer (CRPC). However, little is known about the specific metabolites critically orchestrating this process.

We show that IMPA1-derived inositol enriched in PCSCs is a key metabolite crucially maintaining PCSCs for CRPC progression and ABT resistance. Notably, conditional *Impa1* knockout in the prostate abrogates the pool and properties of PCSCs to orchestrate CRPC progression and prolong the survival of *TRAMP* mice. IMPA1-derived inositol serves as a cofactor that directly binds to and activates IMPDH2, which synthesizes guanylate nucleotides for maintaining PCSCs with $AR^{low/-}$ features leading to CRPC progression and ABT resistance.

The IMPA1/inositol/IMPDH2 axis is upregulated in human prostate cancer, and its overexpression predicts poor survival outcomes. Genetically and pharmacologically targeting the IMPA1/inositol/IMPDH2 axis abrogates CRPC and overcomes ABT resistance in various CRPC xenografts, patient-derived xenograft (PDX) tumor models, and *TRAMP* mouse models. Our study identifies IMPDH2 as an inositol sensor whose activation by inositol represents a key mechanism for maintaining PCSCs for CRPC and ABT resistance.

RESEARCHER DETAILS

Che-Chia Hsu
Assistant Professor
Duke University School of Medicine

Hui-Kuan Lin
Professor
Duke University School of Medicine
hui-kuan.lin@duke.edu

ORIGINAL PAPER
Hsu, C.-C., G. Wang, C.-F. Li, X. Zhang, Z. Cai, T. Chen, B.-S. Pan, R.K. Manne, G. Deep, H. Gu, Y. Wang, D. Peng, V. Penugurti, X. Zhou, Z. Xu, Z. Chen, M. Chen, A.J. Armstrong, J. Huang, H.-Y. Li, and H.-K. Lin. 2024. IMPA1-derived inositol maintains stemness in castration-resistant prostate cancer via IMPDH2 activation. *J. Exp. Med.* 221 (11): e20231832. https://doi.org/10.1084/jem.20231832

Visualizing nascent metastases ex vivo

Ischemic conditions such as hypoxia and nutrient starvation, together with interactions with stromal cells, are critical drivers of metastasis. These conditions arise deep within tumor tissues, and thus, observing nascent metastases is exceedingly challenging. We thus developed the 3MIC—an ex vivo model of the tumor microenvironment—to study the emergence of metastatic features in tumor cells in a 3-dimensional (3D) context. Here, tumor cells spontaneously create ischemic-like conditions, allowing us to study how tumor spheroids migrate, invade, and interact with stromal cells under different metabolic conditions.

Consistent with previous data, we show that ischemia increases cell migration and invasion, but the 3MIC allowed us to directly observe and perturb cells while they acquire these pro-metastatic features. Interestingly, our results indicate that medium acidification is one of the strongest pro-metastatic cues and also illustrate using the 3MIC to test anti-metastatic drugs on cells experiencing different metabolic conditions.

Overall, the 3MIC can help dissect the complexity of the tumor microenvironment for the direct observation and perturbation of tumor cells during the early metastatic process.

ORIGINAL PAPER

Anandi, L., J. Garcia, M. Ros, L. Janská, J. Liu, and C. Carmona-Fontaine. 2024. Direct visualization of emergent metastatic features within an ex vivo model of the tumor microenvironment. *Life Science Alliance*. 8 (1) e202403053. https://doi.org/10.26508/lsa.202403053

RESEARCHER DETAILS

Libi Anandi
Postdoctoral researcher
New York University

Jeremy Garcia
PhD student
New York University

Carlos Carmona-Fontaine
Associate Professor
New York University
cf97@nyu.edu

Reprogramming TAMs by modulating arginine metabolism

HER2+ breast tumors have abundant immune-suppressive cells, including M2-type tumor-associated macrophages (TAMs). Although TAMs consist of the immune-stimulatory M1 type and immune-suppressive M2 type, the M1/M2-TAM ratio is reduced in immune-suppressive tumors, contributing to their immunotherapy refractoriness. M1- versus M2-TAM formation depends on differential arginine metabolism, where M1-TAMs convert arginine to nitric oxide (NO) and M2-TAMs convert arginine to polyamines (PAs).

We hypothesize that such distinct arginine metabolism in M1- versus M2-TAMs is attributed to different availability of BH_4 (NO synthase cofactor) and that its replenishment would reprogram M2-TAMs to M1-TAMs. Recently, we reported that sepiapterin (SEP), the endogenous BH_4 precursor, elevates the expression of M1-TAM markers within HER2+ tumors. Here, we show that SEP restores BH_4 levels in M2-like macrophages, which then redirects arginine metabolism to NO synthesis and converts M2 type to M1 type. The reprogrammed macrophages exhibit full-fledged capabilities of antigen presentation and induction of effector T cells to trigger immunogenic cell death of HER2+ cancer cells.

This study substantiates the utility of SEP in the metabolic shift of the HER2+ breast tumor microenvironment as a novel immunotherapeutic strategy.

ORIGINAL PAPER

Fernando, V., X. Zheng, V. Sharma, O. Sweef, E.-S. Choi, and S. Furuta. 2024. Reprogramming of breast tumor–associated macrophages with modulation of arginine metabolism. *Life Science Alliance*. 7 (11): e202302339. https://doi.org/10.26508/lsa.202302339

RESEARCHER DETAILS

Veani Fernando
PhD student
University of Toledo
(Now a postdoctoral researcher at University of Colorado Anschutz Medical Campus)

Saori Furuta
Associate Professor
Case Western Reserve University School of Medicine
sxf494@case.edu

A computational tool to identify malignant cells in pediatric acute myeloid leukemia

Pediatric acute myeloid leukemia (AML) is an aggressive blood cancer with a poor prognosis and high relapse rate. Current challenges in the identification of immunotherapy targets arise from patient-specific blast immunophenotypes and their change during disease progression. To overcome this, we present a new computational research tool to rapidly identify malignant cells.

We generated single-cell flow cytometry profiles of 21 pediatric AML patients with matched samples at diagnosis, remission, and relapse. We coupled a classifier to an autoencoder for anomaly detection and classified malignant blasts with 90% accuracy. Moreover, our method assigns a developmental stage to blasts at the single-cell level, improving current classification approaches based on differentiation of the dominant phenotype. We observed major immunophenotype and developmental stage alterations between diagnosis and relapse. Patients with KMT2A rearrangement had more profound changes in their blast immunophenotypes at relapse compared to patients with other molecular features.

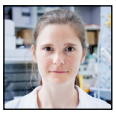
Our method provides new insights into the immunophenotypic composition of AML blasts in an unbiased fashion and can help to define immunotherapy targets that might improve personalized AML treatment.

ORIGINAL PAPER

Driessen, A., S. Unger, A.-p. Nguyen, R.E. Ries, S. Meshinchi, S. Kreutmair, C. Alberti, P. Sumazin, R. Aplenc, M.S. Redell, B. Becher, and M. Rodríguez Martínez. 2024. Identification of single-cell blasts in pediatric acute myeloid leukemia using an autoencoder. *Life Science Alliance*. 7(11): e202402674. https://doi.org/10.26508/lsa.202402674

RESEARCHER DETAILS

Alice Driessen
PhD student
IBM Research Europe



Susanne Unger
Research Associate
Institute of Experimental Immunology, University of Zurich

Burkhard Becher
Professor
Institute of Experimental Immunology, University of Zurich
becher@immunology.uzh.ch

María Rodríguez Martínez
Technical Leader of Systems Biology
IBM Research Europe
(Now an Associate Professor at Yale School of Medicine)
maria.rodriguezmartinez@yale.edu

An optimized CMS classifier for colorectal cancer

Consensus Molecular Subtype (CMS) classification of colorectal cancer (CRC) tissues is complicated by RNA degradation upon formalin-fixed paraffin-embedded (FFPE) preservation. We present an FFPE-curated CMS classifier.

The CMSFFPE classifier was developed using genes with a high transcript integrity in FFPE-derived RNA. We evaluated the classification accuracy in two FFPE-RNA datasets with matched fresh-frozen (FF) RNA data, and an FF-derived RNA set. An FFPE-RNA application cohort of metastatic CRC patients was established, partly treated with anti-EGFR therapy. Key characteristics per CMS were assessed. Cross-referenced with matched benchmark FF CMS calls, the CMSFFPE classifier strongly improved classification accuracy in two FFPE datasets compared with the original CMSClassifier (63.6% versus 40.9% and 83.3% versus 66.7%, respectively). We recovered CMS-specific recurrence-free survival patterns (CMS4 versus CMS2: hazard ratio 1.75, 95% CI 1.24–2.46).

Key molecular and clinical associations of the CMSs were confirmed. In particular, we demonstrated the predictive value of CMS2 and CMS3 for anti-EGFR therapy response (CMS2&3: odds ratio 5.48, 95% CI 1.10–27.27). The CMSFFPE classifier is an optimized FFPE-curated research tool for CMS classification of clinical CRC samples.

ORIGINAL PAPER

de Back, T.R., T. Wu, P.J.M. Schafrat, S. ten Hoorn, M. Tan, L. He, S.R. van Hooff, J. Koster, L.E. Nijman, G.R Vink, I.J Beumer, C.C. Elbers, K.J. Lenos, D.W. Sommeijer, X. Wang, and L. Vermeulen. 2024. A consensus molecular subtypes classification strategy for clinical colorectal cancer tissues. *Life Science Alliance*. 7(8): e202402730. https://doi.org/10.26508/lsa.202402730

RESEARCHER DETAILS

Tim R. de Back
PhD student
Amsterdam University Medical Center

Tan Wu
PhD student
The Chinese University of Hong Kong

Dirkje W. Sommeijer
Medical Oncologist
Amsterdam University Medical Center

Xin Wang
Associate Professor
The Chinese University of Hong Kong

Louis Vermeulen
Professor
Amsterdam University Medical Center
l.vermeulen@amsterdamumc.nl

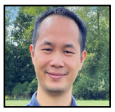
A preclinical model for NUT carcinoma

NUT carcinoma (NC) is an aggressive cancer with no effective treatment. About 70% of NUT carcinoma is associated with chromosome translocation events that lead to the formation of a *BRD4::NUTM1* fusion gene. Because the *BRD4::NUTM1* gene is unequivocally cytotoxic when ectopically expressed in cell lines, questions remain on whether the fusion gene can initiate NC.

We report the first genetically engineered mouse model for NUT carcinoma that recapitulates the human t(15;19) chromosome translocation in mice. We demonstrated that the mouse t(2;17) syntenic chromosome translocation, forming the *Brd4::Nutm1* fusion gene, could induce aggressive carcinomas in mice. The tumors present histopathological and molecular features similar to human NC, with enrichment of undifferentiated cells. Similar to the reports of human NC incidence, *Brd4::Nutm1* can induce NC from a broad range of tissues with a strong phenotypical variability.

The consistent induction of poorly differentiated carcinoma demonstrated a strong reprogramming activity of BRD4::NUTM1. The new mouse model provides a critical preclinical model for NC that will lead to better understanding and therapy development for NC.

RESEARCHER DETAILS



Dejin Zheng
Postdoctoral researcher
Michigan State University

Ahmed A. Elnegiry
Postdoctoral researcher
Michigan State University

Chenxiang Luo
Postdoctoral researcher
Michigan State University

Mayra F. Tsoi
Assistant Professor
Michigan State University
tsoimayr@msu.edu

Bin Gu
Assistant Professor
Michigan State University
gubin1@msu.edu

ORIGINAL PAPER
Zheng, D., A.A. Elnegiry, C. Luo, M.A. Bendahou, L. Xie, D. Bell, Y. Takahashi, E. Hanna, G.I. Mias, M.F. Tsoi, and B. Gu. 2024. *Brd4::Nutm1* fusion gene initiates NUT carcinoma in vivo *Life Science Alliance*. 7(7): e202402602. https://doi.org/10.26508/lsa.202402602

JCB Journal of Cell Biology

Print ISSN: 0021-9525.
Online ISSN: 1540-8140

Rockefeller University Press

JEM Journal of Experimental Medicine

Print ISSN 0022-1007
Online ISSN 1540-9538

Rockefeller University Press

Life Science Alliance

www.life-science-alliance.org

ISSN: 2575-1077

EMBOpress

Rockefeller University Press

CSH PRESS Cold Spring Harbor Laboratory Press

JHI Journal of Human Immunity

The International Alliance for Primary Immunodeficiency Societies and **Rockefeller University Press** are proud to launch ***JHI***, the official journal of IAPIDS and its member societies.

iapids INTERNATIONAL ALLIANCE FOR PRIMARY IMMUNODEFICIENCY SOCIETIES

Rockefeller University Press

> **A new scientific journal is needed when a new field of study matures to such a point that it can no longer be considered adequately or sufficiently covered by existing journals.**

Jean-Laurent Casanova, MD, PhD
EDITOR-IN-CHIEF, *JOURNAL OF HUMAN IMMUNITY*

***Explore** the inaugural editorial and submit your research to JHI, the community's first dedicated journal for research on human inborn errors of immunity.*

jhumimmunity.org @jhumimmunity.org @jhumimmunity