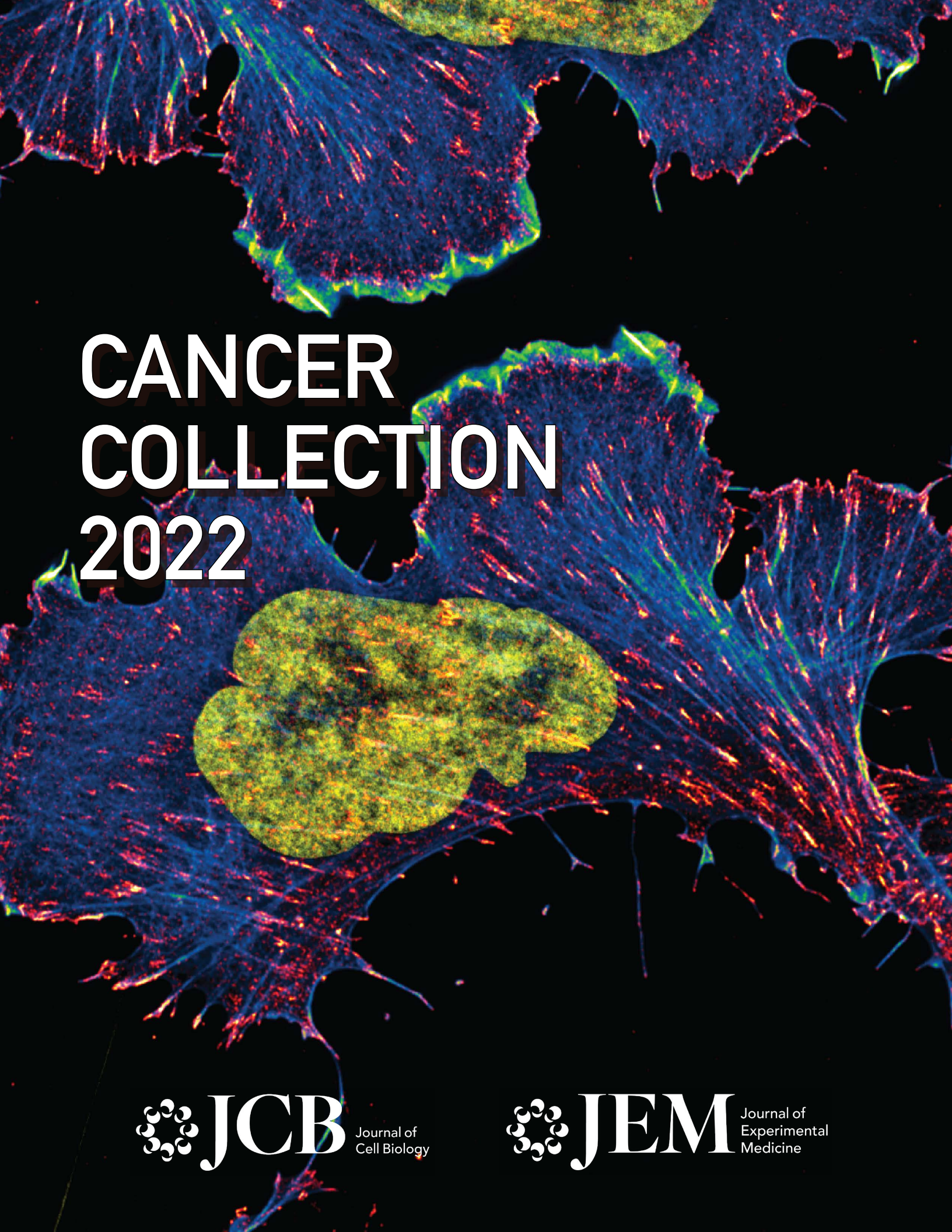
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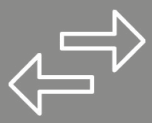

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On the cover: The image shows a CYRI-A and -B double knockout Ewing's sarcoma cell spreading on a fibronectin matrix. These cells display a characteristic C shape with broad lamellipodia and copious numbers of integrin adhesions. DNA labelled by DAPI is shown in yellow, F-actin labelled by phalloidin in cyan, and integrin α5 in red.

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https://doi.org/10.1083/jcb.202012114

See the associated article on page 8.

CANCER COLLECTION 2022

The editors of the *Journal of Cell Biology* (*JCB*) and the *Journal of Experimental Medicine* (*JEM*) 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 at left to view the full online collections and sign up for email alerts to receive the latest research. Don't miss the online collection on Cancer Biology 2022 from our sister journal *Life Science Alliance* (*LSA*) by scanning the QR code on page 6.

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JCB Journal of Cell Biology

TARGETING MIR-146 COULD UNMASK HIDDEN VULNERABILITY IN BREAST CANCER STEM CELLS

A pair of miRNAs that help maintain cancer stem cells could be new therapeutic targets to make the cells more susceptible to certain chemotherapies

Many tumors contain a small population of cancer stem cells that initiate tumor growth and give rise to the various cell types found in tumors. Moreover, because cancer stem cells are often resistant to radio- and chemotherapies, they can survive and promote tumor relapse and metastasis after initial rounds of treatment. In breast cancer, for example, tumors containing a relatively high number of cancer stem cells have a much poorer prognosis than tumors with fewer stem cells.

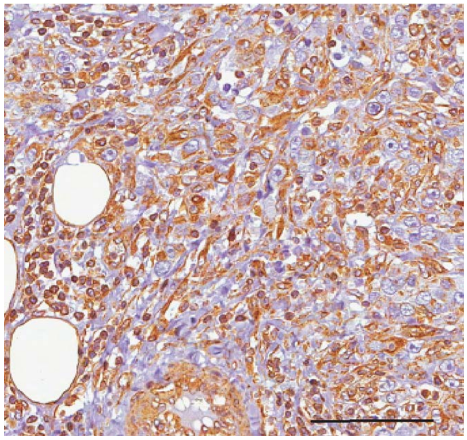
Eliminating these stem cells may therefore be crucial for the successful treatment of breast cancer and other tumor types. One class of molecule that might help cancer stem cells to persist within tumors is miRNAs. These short RNA molecules control the fate and identity of cells by regulating the levels of protein-encoding mRNAs.

"We wanted to identify miRNAs required for the maintenance of normal mammary stem cells that are inherited by cancer stem cells and could represent potential therapeutic targets in breast cancer," says Francesco Nicassio, a principal investigator and Center Coordinator of the Center for Genomic Science at the Italian Institute of Technology in Milan.

Nicassio and colleagues, including co-senior author Pier Paolo Di Fiore, a group leader at the European Institute of Oncology and professor at the University of Milan, identified two closely related miRNAs, miR-146a and miR-146b, that are present in breast cancer stem cells as well as normal mammary stem cells. The levels of these two miRNAs tended to be highly elevated in aggressive breast cancers that have a high number of cancer stem cells and a poor prognosis.

The researchers found that miR-146a/b are required to maintain the pool of cancer stem cells. Depleting these two miRNAs from patient-derived cancer cells reduced the ability of these cells to form new tumors when implanted into mice.

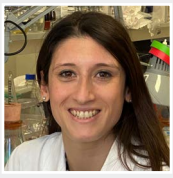
Nicassio and colleagues determined that miR-146a/b regulate hundreds of mRNAs, thereby controlling numerous cellular processes such as metabolism and DNA replication. Depleting miR-146a/b from cancer stem cells might alter these processes in ways that leave the cells more vulnerable to chemotherapy. Nicassio and colleagues found that reducing miR-146a/b levels made breast cancer stem cells over 20 times more sensitive to methotrexate, significantly improving this metabolic inhibitor's ability to restrict tumor growth in mice.



Tumor sample from a breast cancer patient expressing high levels of the microRNAs miR-146a and miR-146b. © 2021 Tordonato et al.

"While the molecular details remain to be determined, our results clearly show that reducing miR-146a/b levels represents an attractive approach to overcome some forms of drug resistance in the clinical setting, unmasking a 'hidden vulnerability' exploitable for the development of anti-cancer stem cell therapies," Nicassio says.

RESEARCHER DETAILS



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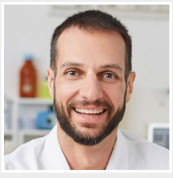

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ORIGINAL PAPER

Tordonato, C., M.J. Marzi, G. Giangreco, S. Freddi, P. Bonetti, D. Tosoni, P.P. Di Fiore, and F. Nicassio. 2021. miR-146 connects stem cell identity with metabolism and pharmacological resistance in breast cancer. *J. Cell Biol.* 220 (5): e202009053.

https://doi.org/10.1083/jcb.202009053

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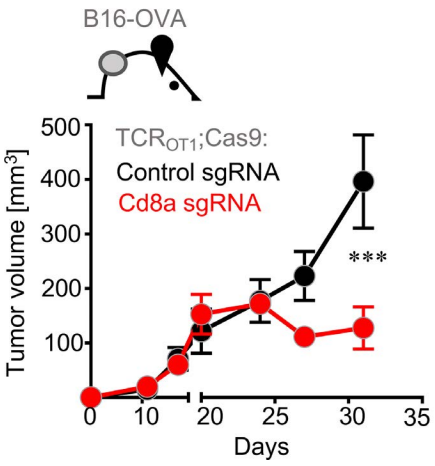
INTERMEDIATE TCR SIGNAL STRENGTH OPTIMIZES ANTI-TUMOR IMMUNE RESPONSE

High and low levels of TCR signaling limit the efficacy of tumor-reactive T cells in different ways that result in tumor immune evasion



In mice injected with B15-OVA melanoma cells, T cells lacking the CD8α coreceptor (red), which show an intermediate level of TCR signaling, slow tumor growth more than control T cells (black) that have a high TCR signal strength. © 2021 Shakiba et al.

The affinity of a T cell receptor (TCR) for its ligand, and the subsequent strength of TCR signaling, is a key determinant of the T cell's response. Tumor-reactive CD8 T cells recognize a broad range of antigens, with some cells expressing TCRs that bind to self-proteins with low affinity, and other cells sporting TCRs with a high affinity for tumor-specific neoantigens.

"We wanted to assess how TCR signal strength impacts tumor-specific T cell differentiation and dysfunction and how it contributes to the phenotypic and functional heterogeneity of the T cell pool within tumors," explains Andrea Schietinger, a cancer immunologist at Memorial Sloan Kettering Cancer Center in New York.

To address these questions, Schietinger and colleagues, including first author Mojdeh Shakiba, developed a cancer mouse model in which the tumor expresses one of several closely related antigens with distinct affinities for a specific TCR. The researchers then analyzed the activity and differentiation state of adoptively transferred T cells expressing this TCR.

Within weeks, tumor-infiltrating T cells exposed to a high affinity antigen became dysfunctional, upregulating inhibitory receptors such as PD1 and ceasing production of the effector molecules IFN-γ and TNF-α. In contrast, T cells exposed to a lower affinity antigen also upregulated PD1, but they managed to sustain IFN-γ and TNF-α production ex vivo.

Schietinger and colleagues found that exposure to high affinity ligands drives epigenetic remodeling and transcriptional upregulation of genes associated with T cell dysfunction and exhaustion. "Thus, TCR signal strength drives distinct transcriptional and epigenetic programs that underlie T cell functional heterogeneity in tumors," Schietinger says.

However, though T cells exposed to low affinity ligands manage to sustain effector molecule production ex vivo, they aren't any better at restricting tumor growth. "Whereas high TCR signal strength leads to T cell dysfunction, low TCR signal strength results in functional inertness, a state defined by lack of in vivo anti-tumor function, despite retention of an effector-like functional molecular program," Schietinger explains.

The researchers wondered whether lowering signal strength in high affinity T cells could overcome dysfunction. They explored a therapeutically applicable strategy to alter TCR signal strength by deleting the CD8a coreceptor, and found that T cells lacking this protein showed intermediate levels of TCR signaling. *CD8a*-deficient T cells were more effective than control cells at slowing tumor growth in mice.

"Thus, there is a critical 'Goldilocks' range of TCR signal strength for tumor-reactive T cells, which preserves cell-intrinsic functional molecular programs and enables anti-tumor activity in vivo," Schietinger says. "Lowering TCR signal strength in high-affinity cells and/or targeting neoantigens within an intermediate range, instead of those with highest affinity, could therefore improve T cell–based immunotherapies."

RESEARCHER DETAILS

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ORIGINAL PAPER

Shakiba, M., P. Zumbo, G. Espinosa-Carrasco, L. Menocal, F. Dündar, S.E. Carson, E.M. Bruno, F.J. Sanchez-Rivera, S.W. Lowe, S. Camara, R.P. Koche, V.P. Reuter, N.D. Socci, B. Whitlock, F. Tamzalit, M. Huse, M.D. Hellmann, D.K. Wells, N.A. Defranoux, D. Betel, M. Philip, and A. Schietinger. 2021. TCR signal strength defines distinct mechanisms of T cell dysfunction and cancer evasion. *J. Exp. Med.* 219 (2): e20201966.

https://doi.org/10.1084/jem.20201966

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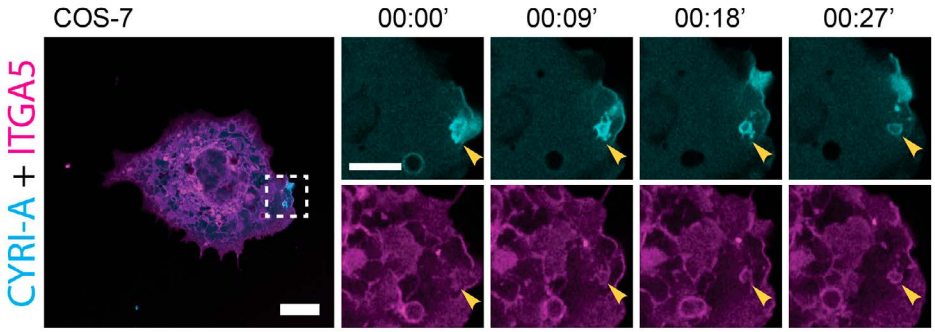
CYRI-A CONTROLS INTEGRIN MACROPINOCYTOSIS

Study reveals that a negative regulator of RAC1-triggered actin assembly promotes integrin uptake by macropinocytosis, thereby suppressing cancer cell invasion



A time-lapse series shows the internalization of integrin α5 (magenta) into a macropinosome (yellow arrowhead) that transiently recruits CYRI-A (cyan). © 2021 Le et al.

The RAC1 GTPase initiates the assembly of branched actin networks by activating the Scar/WAVE complex, which, in turn, stimulates the Arp2/3 complex to promote branched actin polymerization. Numerous cellular processes rely on the dynamic regulation of this RAC1-actin assembly pathway. In 2018, Laura Machesky and colleagues at the Cancer Research UK Beatson Institute discovered that a protein called CYRI-B suppresses the signaling pathway by competing with the Scar/WAVE complex for RAC1 binding, thereby limiting the size of Arp2/3-driven lamellipodial cell protrusions.

"However, the cellular functions of the related protein CYRI-A have never been described, and nothing was known about the dynamics of CYRI proteins in live cells," Machesky says.

Machesky and colleagues, including first author Anh Hoang Le, found that, like CYRI-B, CYRI-A binds to active RAC1 and limits the size of lamellipodia. The two CYRI proteins were therefore able to functionally compensate for each other in regulating cancer cell spreading and migration.

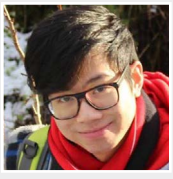
Despite these overlapping functions, however, CYRI-A and CYRI-B showed different localizations in live cells: CYRI-A, in particular, showed a striking localization to macropinosomes, large vesicles internalized from the plasma membrane by macropinocytosis. This endocytic process, which internalizes extracellular nutrients and plasma membrane receptor proteins, depends on the formation of membrane ruffles driven by RAC1 and branched actin assembly.

Machesky and colleagues determined that CYRI-A is transiently recruited to nascent macropinosomes by active RAC1 shortly after actin begins to assemble around these vesicles. All three proteins are then lost from macropinosomes as they mature within the cytosol. Cells lacking CYRI proteins showed reduced levels of macropinocytosis, suggesting that the CYRI-mediated suppression of RAC1 signaling and subsequent actin disassembly is necessary for the completion of this endocytic process.

Integrin adhesion receptors are a major cargo internalized by macropinocytosis, and Machesky and colleagues found that Ewing sarcoma cells lacking CYRI proteins had increased levels of integrin α5β1 at the cell surface. Accordingly, these cells displayed enhanced invasiveness and anchorage-independent growth in 3D environments.

"Overall, our data provide a mechanism linking the function of CYRIs in macropinocytosis to the invasive capacity of cancer cells through modulating integrin trafficking and signaling," Machesky says. "This could have important implications for cancers where RAC1 pathways are disrupted or enhanced, such as in melanomas where RAC1 activating mutations are considered to be drivers."

RESEARCHER DETAILS



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ORIGINAL PAPER

Le, A.H., T. Yelland, N.R. Paul, L. Fort, S. Nikolaou, S. Ismail, and L.M. Machesky. 2021. CYRI-A limits invasive migration through macropinosome formation and integrin uptake regulation. *J. Cell Biol.* 220 (9): e202012114.

https://doi.org/10.1083/jcb.202012114

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OBESITY SUPPRESSES CD8 T CELL RESPONSES IN CANCER

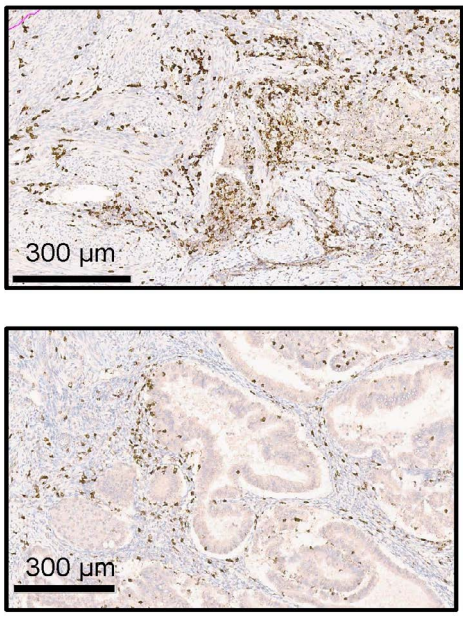
Reduced T cell infiltration and effector function can be partially reversed by weight loss and/or immunotherapy in mice and humans

Obesity increases the risk of numerous cancers, including endometrial, esophageal, and colorectal cancer. Excessive weight gain is associated with increased production of various hormones, such as leptin and insulin, that can promote tumor growth and metastasis. Moreover, recent studies have suggested that obesity can also suppress anti-tumor immune responses.

"We recently demonstrated that obesity impairs the anti-tumor response of NK cells by inducing lipid uptake and metabolic paralysis," says Lydia Lynch of Harvard Medical School and Trinity College Dublin. "We therefore hypothesized that CD8 T cell responses might be similarly affected."

Lynch and colleagues, including first author Lydia Dyck, found that, after subcutaneously injecting two different cancer cell lines, tumor growth was enhanced in obese mice fed a high fat diet. Obese tumors contained fewer CD8 T cells, probably, in part, due to a reduction in the expression of chemokines and other proteins involved in T cell extravasation and tumor infiltration.

The CD8 T cells that did manage to infiltrate into the tumors of obese mice appeared to be functionally suppressed, expressing lower levels of effector molecules such as IFN-γ and granzyme B compared with tumor-infiltrating T cells in lean mice. However, the expression of PD-1 and other proteins involved in the immune checkpoint that suppresses T cell function was similar in both lean and obese tumors. "This suggests that obesity promotes an 'immune-cold' tumor phenotype through mechanisms other than accelerating immune checkpoint–driven T cell exhaustion," Lynch says.



Immunohistochemical staining shows that the number of CD8 T cells is reduced in a tumor sample from an endometrial cancer patient with a BMI of 46 (bottom), compared with a patient with a BMI of 26.5 (top). © 2022 Dyck et al.

Nor does obesity appear to promote T cell dysfunction by inducing lipid uptake, as previously seen in NK cells. Instead, the researchers found, obesity appears to impair tumor-resident T cell function by disrupting amino acid metabolism. For example, CD8 T cells in obese tumors expressed lower levels of SLC7A5, a transporter protein required to take up the amino acids T cells need to sustain their activity.

Surprisingly, treating obese mice with anti–PD-1 antibodies to inactivate the immune checkpoint led to a partial restoration of CD8 T cell metabolism and effector function, resulting in complete tumor rejection.

Lynch and colleagues then examined the effect of obesity on anti-tumor immunity in human endometrial cancer. Tumor samples from patients with a higher BMI contained reduced numbers of CD8 T cells and an "immune-cold" phenotype. Moreover, six of nine patients who underwent metabolic surgery to induce weight loss experienced significant tumor regression.

"Together, our findings highlight that immune dysfunction in obesity is reversible," Lynch says. "While obesity suppressed CD8 T cells in tumors and promoted tumor growth, immunotherapy or weight loss was able to reverse these defects in mice and humans, resulting in tumor rejection."

RESEARCHER DETAILS

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ORIGINAL PAPER

Dyck, L., H. Prendeville, M. Raverdeau, M.M. Wilk, R.M. Loftus, A. Douglas, J. McCormack, B. Moran, M. Wilkinson, E.L. Mills, M. Doughty, A. Fabre, H. Heneghan, C. LeRoux, A. Hogan, E.T. Chouchani, D. O'Shea, D. Brennan, and L. Lynch. 2022. Suppressive effects of the obese tumor microenvironment on CD8 T cell infiltration and effector function. *J. Exp. Med.* 219 (3): e20210042.

https://doi.org/10.1084/jem.20210042

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JCB Journal of Cell Biology

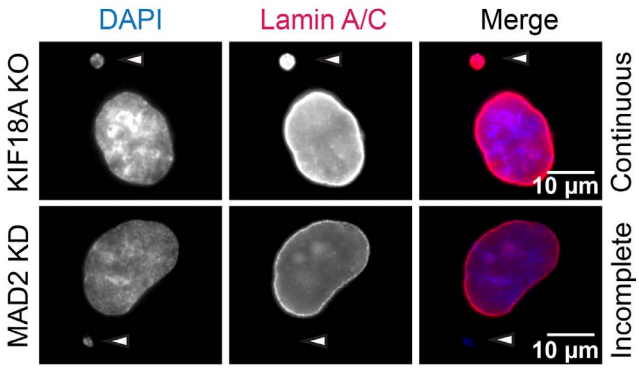
NOT ALL MICRONUCLEI DRIVE GENOMIC INSTABILITY

Micronuclei generated by KIF18A loss and chromosome misalignment are able to form a stable nuclear envelope and therefore do not promote tumorigenesis

Micronuclei, consisting of intact or fragmented chromosomes separated from the main nucleus, can be generated by a variety of errors, including defects in DNA replication or repair and incorrect attachments between spindle microtubules and mitotic chromosomes. Micronuclei are therefore used as biomarkers of genomic instability in tumors, but recent studies have shown that micronuclei can actively cause genomic instability and drive tumorigenesis themselves, likely because the chromosomes within micronuclei are unable to replicate properly and/or are exposed to damage in the cytoplasm as micronuclear envelopes lose their integrity.

In 2019, Jason Stumpff and colleagues at the University of Vermont, together with Laura Reinholdt's team at The Jackson Laboratory, found that mice lacking a functional version of the kinesin motor protein KIF18A form micronuclei due to chromosome misalignment and asynchronous segregation in mitosis. "Paradoxically, however, *Kif18a* mutant mice do not develop spontaneous tumors," Stumpff says. "These results raise questions about the conditions under which micronuclei might induce genomic instability and tumorigenesis in vivo."

Stumpff and colleagues, including first author Leslie Sepaniac, tested two potential explanations for this paradox. One possibility is that the tumor suppressor p53 induces cell cycle arrest and stops *Kif18a* mutant cells from proliferating once they develop micronuclei. Sepaniac et al. crossed *Kif18a* mutant mice with p53-deficient strains that are prone to form thymic lymphomas. Though micronuclei were generated in both normal and tumor tissues, loss of KIF18A function had little effect on the animals' survival, suggesting that p53 is not involved in preventing these micronuclei from accelerating tumorigenesis.



A micronucleus (white arrowhead) generated by the loss of KIF18A and chromosome misalignment (top row) recruits large amounts of the nuclear envelope component Lamin A/C (red). But Lamin recruitment is reduced around a micronucleus resulting from the loss of the spindle assembly checkpoint protein MAD2 (bottom row). © 2021 Sepaniac et al.

Instead, the researchers found, micronuclei generated by the loss of *Kif18a* fail to promote genomic instability because they are capable of forming a stable nuclear envelope. Unlike micronuclei produced by other mechanisms, such as incorrect microtubule–kinetochore attachment, micronuclei resulting from the loss if *Kif18a* can recruit a wider variety of nuclear envelope components along with additional membrane to accommodate micronucleated chromosomes as they decondense after mitosis.

The reason for this may be that the lagging chromosomes that end up being packaged into micronuclei in *Kif18a*-deficient cells are located nearer to the spindle poles, where nuclear envelope assembly pathways may be more active. In contrast, lagging chromosomes in cells with incorrect kinetochore–microtubule attachments are located nearer to the spindle midzone, where nuclear envelope assembly may be impaired, leaving the micronuclei prone to genomic instability.

"Overall, our data indicate that the type of insult that leads to micronucleus formation can determine micronuclear stability, and we propose that intact micronuclei mitigate the overall risk to genome integrity in cells with chromosome alignment defects," Stumpff says.

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ORIGINAL PAPER

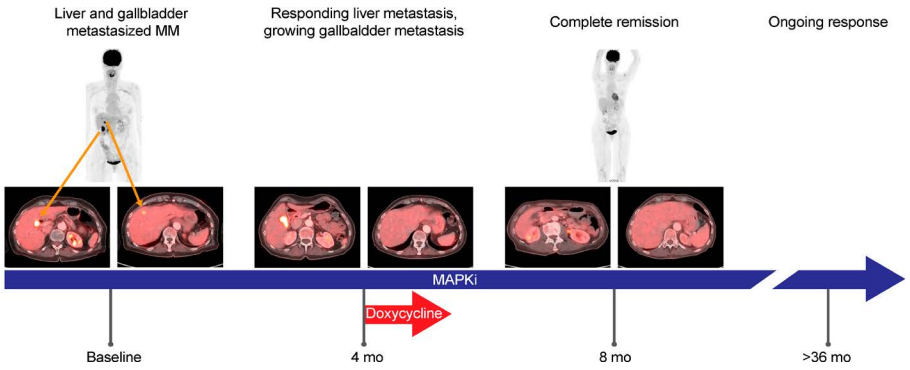
Sepaniac, L.A., W. Martin, L.A. Dionne, T.M. Stearns, L.G. Reinholdt, and J. Stumpff. 2021. Micronuclei in *Kif18a* mutant mice form stable micronuclear envelopes and do not promote tumorigenesis. *J. Cell Biol.* 220 (11): e202101165.

https://doi.org/10.1083/jcb.202101165

Scan for original paper →

MELANOMA CELLS MAY BE VULNERABLE TO COMMON ANTIBIOTICS

Activation of the integrated stress response in therapy-resistant melanomas leaves them sensitive to tetracyclines that inhibit mitochondrial translation



Case presentation of a metastatic melanoma patient who showed resistance to MAPK inhibitor therapy before being treated with doxycycline for a skin infection. © 2021 Vendramin et al.

Cancer cells can survive drug treatments by upregulating the integrated stress response (ISR) pathway, which activates the transcription factor ATF4 and results in a global reduction of protein synthesis that allows the cells to become quiescent. These quiescent cells persist and may eventually give rise to drug-resistant cells that drive tumor recurrence.

A team of researchers led by Eleonora Leucci and Jean-Christophe Marine at KU Leuven discovered that, although ISR activation suppresses cytosolic translation in melanoma cells, it dramatically increases the activity of ribosomes inside mitochondria. This could fit with the fact that, in many tumors, persistent, drug-tolerant cancer cells show an increased dependence on mitochondrial metabolism.

"We reasoned that the increased synthesis of mitochondrial proteins in cells harboring an activated ISR might sensitize them to tetracycline antibiotics that inhibit mitochondrial translation," Leucci says.

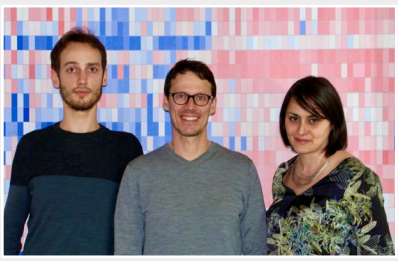
Leucci and colleagues, including first author Roberto Vendramin, found that tetracyclines inhibited the growth of multiple human melanoma cell lines with an activated ISR pathway, suggesting that these antibiotics might target residual, drug-tolerant tumor cells. In $BRAF^{V600E}$ melanoma patient-derived xenograft models, mice treated with standard-of-care MAPK inhibitors initially respond but then go on to acquire resistance. Additional treatment with tetracyclines delayed or prevented the development of resistance, and significantly increased the animals' survival.

Tetracyclines also restricted the growth of several patient-derived melanomas intrinsically resistant to either targeted therapy or immune checkpoint blockade. These lines, too, showed high levels of ISR activity. Accordingly, pharmacologically inhibiting the ISR pathway, or depleting ATF4, prevented tetracyclines from blocking the growth of melanoma cells.

Because tetracyclines, such as doxycycline, are already in widespread clinical use and are generally well-tolerated over extended periods, these antibiotics could be used to overcome therapy resistance in human melanoma patients. In support of this, Leucci and colleagues identified a metastatic melanoma patient who happened to be treated with doxycycline for a concurrent skin infection. The patient initially showed resistance to MAPK inhibitors but, following doxycycline treatment, subsequent rounds of therapy induced a complete regression of the tumor, a response that persisted for more than three years.

"Overall, our findings indicate that targeting mitochondrial translation with antibiotics of the tetracycline family is a promising therapeutic avenue that can be easily implemented in the clinic for the treatment of a large spectrum of melanoma patients, including those with limited therapeutic options," Leucci says. "We also provide evidence that patient stratification should be guided by ATF4 levels, which could be used as an accompanying biomarker to predict efficacy."

RESEARCHER DETAILS



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ORIGINAL PAPER

Vendramin, R., V. Katopodi, S. Cinque, A. Konnova, Z. Knezevic, S. Adnane, Y. Verheyden, P. Karras, E. Demesmaeker, F.M. Bosisio, L. Kucera, J. Rozman, I. Gladwyn-Ng, L. Rizzotto, E. Dassi, S. Millevoi, O. Bechter, J.-C. Marine, and E. Leucci. 2021. Activation of the integrated stress response confers vulnerability to mitoribosome-targeting antibiotics in melanoma. *J. Exp. Med.* 218 (9): e20210571.

https://doi.org/10.1084/jem.20210571

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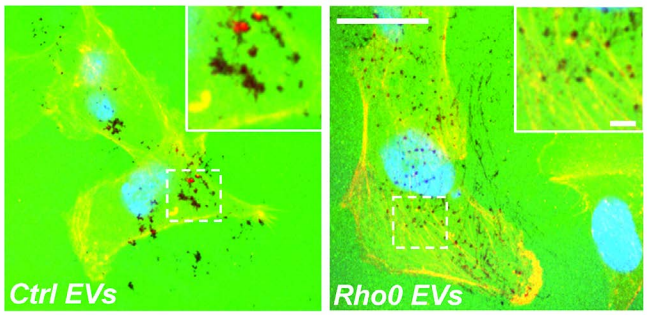
JCB Journal of Cell Biology

mtDNA-CONTAINING EXTRACELLULAR VESICLES TRANSFER INVASIVENESS

Study identifies a PINK1-dependent pathway that enables metabolically stressed cancer cells to promote invasive characteristics in other cells



mtDNA-containing EVs produced by metabolically stressed donor cells cause recipient cells (left) to transport MT1-MMP (red) to the cell surface and degrade the underlying collagen matrix (green). EVs released from mtDNA-deficient cells have no such effect on recipient cells (right). © 2021 Rabas et al.

Cancer cells cope with the metabolically stressful environment of tumors by increasing synthesis of the antioxidant glutathione, and upregulating glutaminolysis to maintain the TCA cycle and promote cell growth. These two pathways result in elevated levels of extracellular glutamate, which can be detected in both patients and mouse models of breast cancer.

In 2017, Jim Norman and colleagues at the Beatson Institute for Cancer Research found that extracellular glutamate activates metabotropic glutamate receptor 3 (mGluR3) and stimulates the Rab27-dependent delivery of endosomes containing the matrix metalloproteinase MT1-MMP to the plasma membrane. This allows the metabolically stressed cancer cells to degrade the surrounding extracellular matrix and invade other tissues.

"Rab27 GTPases also control the release of extracellular vesicles (EVs), which are important mediators of intercellular communication during cancer progression," Norman explains. Accordingly, Norman and colleagues, including co-first authors Nicolas Rabas and Sarah Palmer, determined that the activation of mGluR3 by extracellular glutamate also stimulates the Rab27-dependent release of EVs from breast cancer cells.

The researchers found that these EVs contain large amounts of mitochondrial DNA (mtDNA), and that the packaging of mtDNA into EVs depends on PINK1, a kinase best known for its role in promoting the turnover of damaged mitochondria via the mitophagy pathway. Unlike mitophagy, however, the production of mtDNA-containing EVs doesn't require either PINK1's kinase activity or autophagy proteins such as Atg5. Instead, Norman and colleagues suggest, PINK1 may promote the packaging of mtDNA into EVs by facilitating the formation of contacts between mitochondria and late endosomes.

Following their release from metabolically stressed cancer cells, mtDNA-containing EVs enhance the invasiveness of other cells that internalize them from the extracellular milieu, the researchers found. mtDNA appears to activate the pattern recognition receptor TLR9 in recipient cells, stimulating MT1-MMP trafficking and extracellular matrix degradation.

"Taken together, our data indicate that mtDNA is packaged via a PINK1-dependent mechanism into EVs released by breast cancer cells and that mtDNA is a key EV cargo both necessary and sufficient to transfer glutaminolysis-driven invasive phenotypes between cells," Norman says.

The researchers suggest that serum levels of glutamate and mtDNA-containing EVs may be useful biomarkers to assess tumor aggressiveness in breast cancer patients. In addition, they note, it may also be important to investigate whether chemotherapeutic agents stimulate the release of mtDNA-containing EVs and thereby unintentionally increase tumor invasiveness.

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ORIGINAL PAPER

Rabas, N., S. Palmer, L. Mitchell, S. Ismail, A. Gohlke, J.S. Riley, S.W.G. Tait, P. Gammage, L.L. Soares, I.R. Macpherson, and J.C. Norman. 2021. PINK1 drives production of mtDNA-containing extracellular vesicles to promote invasiveness. *J. Cell Biol.* 220 (12): e202006049.

https://doi.org/10.1083/jcb.202006049

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SUPPRESSING METASTASIS BY INDUCING CANCER CELL DORMANCY

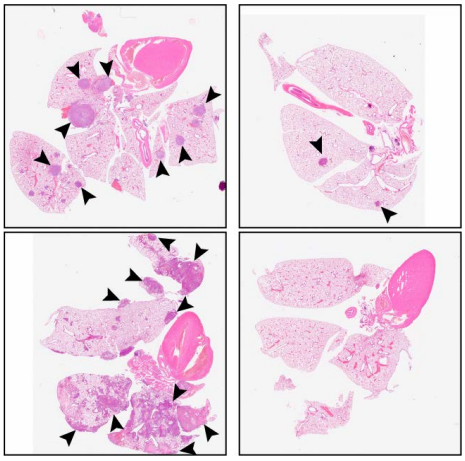
An agonist of the nuclear receptor NR2F1 prevents the growth of metastatic tumors in mice by forcing cancer cells into a dormant state in which they are unable to proliferate

Many cancer patients relapse, often years or decades after their initial treatment, and develop new tumors that regrow in the same location or metastasize to other parts of the body. These secondary tumors are often resistant to treatment and are produced by individual tumor cells that may remain dormant for long periods before being reactivated to start proliferating again. Patient relapse might therefore be prevented if researchers can find a way to keep remaining cancer cells in a dormant state.

Maria Soledad Sosa and Julio A. Aguirre-Ghiso previously found that the ability of cancer cells to remain dormant is controlled by the nuclear receptor NR2F1, which activates a genetic program that prevents the cancer cells from proliferating. NR2F1 levels are usually low in primary tumors but elevated in dormant disseminated cancer cells. Levels of the NR2F1 protein then decline once more when cancer cells start proliferating again and form new tumors.

"We therefore thought that activating NR2F1 using a small molecule could be an attractive clinical strategy to induce cancer cell dormancy and prevent recurrence and metastasis," Aguirre-Ghiso explains.

Sosa and Aguirre-Ghiso's teams used a computer-based screening approach to identify a drug, named C26, that activates NR2F1. The researchers found that treating patient-derived head and neck squamous cell carcinoma (HNSCC) cells with C26 boosted the levels of NR2F1 and arrested cell proliferation.



Compared with a control (left panels), C26 treatment (right panels) reduces the number of metastatic tumors in the lungs of mice injected with HSNCC cells. © 2021 Khalil et al.

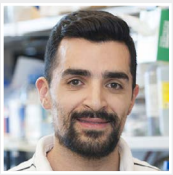
Animals injected with patient-derived HNSCC cells typically form large primary tumors that spread to the lungs after the original tumor is surgically removed. Treatment with C26 reduced the size of primary tumors, and, after surgery, further doses of C26 completely blocked the growth of metastatic tumors. Instead, the rodent's lungs contained just a few dormant disseminated cancer cells unable to proliferate even after cessation of the treatment.

The researchers determined that, by activating NR2F1, C26 forces cancer cells into a long-lived state of dormancy characterized by a unique pattern of gene activity. Cancer patients whose tumors display a similar pattern of gene activity tend to go longer without relapsing, suggesting that inducing this dormancy program with C26-type drugs could be effective in humans.

"Drugs that activate NR2F1 might be particularly useful in breast cancer," says Sosa. "NR2F1 is enriched in ER-positive tumors when compared to ER-negative tumors, and activating NR2F1 might be able to suppress reawakening of dormant cancer cells kept in that state by anti-estrogen therapies." However, because C26 treatment elevates the levels of NR2F1, the approach may also be useful for other cancers with inherently low levels of the receptor protein.

"Overall, our study reveals a mechanism-based and rationally designed strategy to exploit NR2F1-activated dormancy as a therapeutic option to prevent metastatic relapse," Aguirre-Ghiso says.

RESEARCHER DETAILS



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ORIGINAL PAPER

Khalil, B.D., R. Sanchez, T. Rahman, C. Rodriguez-Tirado, S. Moritsch, A. Rodriguez Martinez, B. Miles, E. Farias, M. Mezei, A.R. Nobre, D. Singh, N. Kale, K.C. Sproll, M.S. Sosa, and J.A. Aguirre-Ghiso. 2021. An NR2F1-specific agonist suppresses metastasis by inducing cancer cell dormancy. *J. Exp. Med.* 219 (1): e20210836.

https://doi.org/10.1084/jem.20210836

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JCB Journal of Cell Biology

A CELLULAR TRANSPORT PATHWAY LIMITS BRAIN TUMOR GROWTH

Study reveals that expression of the Rab35 GTPase is reduced in many glioblastoma patients and that enhancing its activity could be a new therapeutic strategy for this aggressive brain cancer

Glioblastoma is the most aggressive type of brain cancer, and because it is largely untreatable, the average patient dies within 14 months of diagnosis. Like in other cancers, the proliferation and spread of glioblastoma cells depends on growth signaling driven by receptor proteins on the outside of the cell. The levels of these receptor proteins and thus their signaling capacity are controlled by cellular transport pathways that internalize the receptors and then either degrade them or return them to the cell surface.

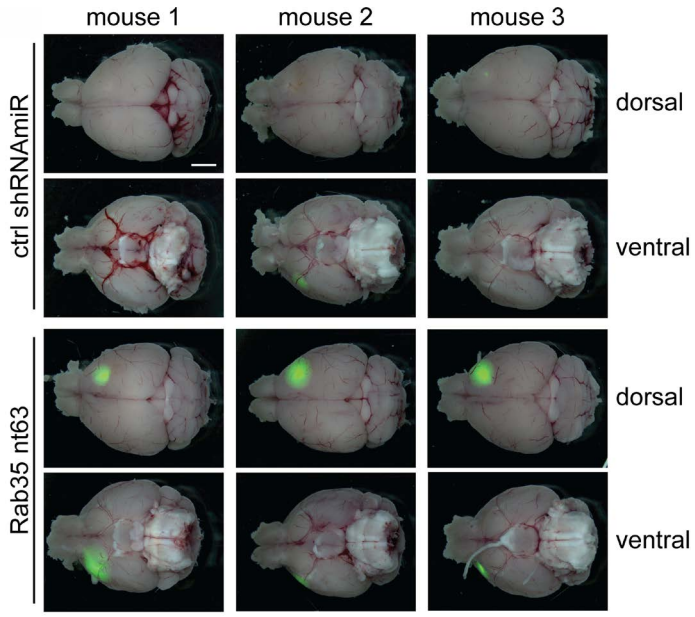
In normal, healthy cells, these transport pathways are regulated by small GTPases. "We previously demonstrated that the levels of a small GTPase called Rab35 are decreased in human glioblastoma," says Peter S. McPherson of The Montreal Neurological Institute-Hospital, McGill University. "We thus sought to investigate the role of Rab35 in the progression of glioblastoma."

McPherson and colleagues, including first author Gopinath Kulasekaran, found that reducing the levels of Rab35 increased the growth and spread of brain tumors in mice, thereby shortening the animals' life span. In contrast, elevating Rab35 levels reduced tumor growth and prolonged the animals' survival.

The researchers discovered that Rab35 is activated by a pathway involving another small GTPase called Arf5. Together, Arf5 and Rab35 control the transport of the epidermal growth factor receptor (EGFR), a key driver of glioblastoma, thereby restricting the ability of cells to migrate and invade through tissues, and limiting the ability of brain tumor–initiating cells to replicate. In glioblastoma cells lacking Rab35, EGFR is increasingly recycled to the cell surface instead of being degraded, enhancing the receptor's signaling activity. Inhibiting EGFR activation with the cancer drug erlotinib reduced the production of a protein called SPOCD1, which is known to promote the proliferation and/or metastasis of multiple cancers.

McPherson and colleagues suggest that restoring the activity of Rab35 might limit the development of glioblastomas by altering the degradation and recycling of multiple cell surface receptors, including EGFR.

"Rab GTPases are emerging as an important new set of drug targets in cancer," McPherson says. "Our study reveals an unprecedented link between Rab and Arf proteins and identifies new loci for therapeutic intervention in glioblastoma."



Compared with control mice (top two rows), brain tumors (green) grow faster in the absence of Rab35 (bottom two rows). © 2021 Kulasekaran et al.

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ORIGINAL PAPER

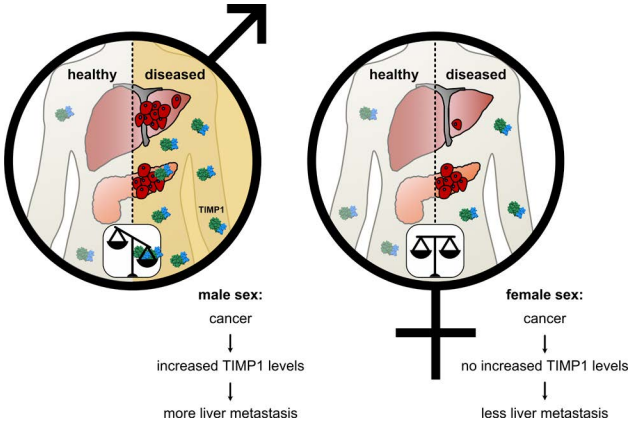
Kulasekaran, G., M. Chaineau, V.E.C. Piscopo, F. Vergineli, M. Fotouhi, M. Girard, Y. Tang, R. Dali, R. Lo, S. Stifani, and P.S. McPherson. 2021. An Arf/Rab cascade controls the growth and invasiveness of glioblastoma. *J. Cell Biol.* 220 (2): e202004229.

https://doi.org/10.1083/jcb.202004229

Scan for original paper →

TIMP1 DRIVES SEX DISPARITY IN PANCREATIC CANCER

Study reveals that the male-specific upregulation of TIMP1 in pancreatic cancers causes increased liver metastasis and decreased survival in male patients



Increased expression of the secretory factor TIMP1 in a subpopulation of male pancreatic cancer patients underlies sex disparities in liver metastasis and survival. © 2021 Hermann et al.

For most types of cancer, the prognosis for male patients is significantly worse than it is for females. This cannot be attributed to sex-specific differences in lifestyle, such as smoking, alcohol consumption, and diet only. Instead, it is becoming increasingly clear that sex-biased intrinsic factors contribute to the differences in cancer progression between male and female patients, although the identity of these factors is largely still unknown.

"Given the clinical observations of sex disparity in cancer survival and the fact that metastasis accounts for the vast majority of cancer-associated deaths, we wanted to address sex differences in survival and metastasis of one of the most lethal and efficiently metastasizing cancer entities, namely pancreatic cancer," says Achim Krüger of the Technical University of Munich.

By analyzing a database of over 200,000 pancreatic cancer patients, Krüger and colleagues, including first author Chris Hermann, determined that survival times are shorter in males. This is not dependent on lifestyle differences, because, in the well-established KPC mouse model of pancreatic cancer, male mice also had shorter survival times than female animals.

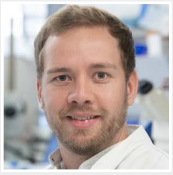
Liver metastasis is particularly common and a leading cause of death in pancreatic cancer. Krüger and colleagues found that the frequency of liver metastasis was higher in male than female patients, whereas the incidence of metastases in other tissues was similar in both sexes. Transcriptional profiling revealed that a metastasis-promoting gene expression signature is specifically upregulated in the livers of both male patients and male KPC mice.

This gene expression signature in the liver, which is linked to the formation of a receptive niche for metastatic cancer cells, can be induced by tumor-derived secretory factors that reach distant organs via the bloodstream. Krüger's team found that TIMP1, a secretory factor that promotes liver metastasis, was specifically upregulated in both the primary tumors and blood plasma of male pancreatic cancer patients. TIMP1 expression was also increased in male KPC mice; deleting the *TIMP1* gene prevented induction of the metastasis-promoting gene expression program and abolished sex differences in liver metastasis and survival.

Krüger and colleagues determined that a high-risk subpopulation of males with elevated TIMP1 levels accounts for the differences in outcome between male and female pancreatic cancer patients. "Across three independent cohorts, TIMP1-high males had more than a threefold increased risk of developing liver metastases after primary tumor resection, compared with TIMP1-low males and female patients," Krüger explains. Notably, males with high TIMP1 expression also showed an elevated risk of forming liver metastases in colorectal cancer and melanoma.

"Taken together, our study reveals a lifestyle-independent sex disparity in liver metastasis and may open new avenues toward precision medicine," Krüger says.

RESEARCHER DETAILS



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Photos © T. Einberger/TUM

ORIGINAL PAPER

Hermann, C.D., B. Schoeps, C. Eckfeld, E. Munkhbaatar, L. Kniep, O. Prokopchuk, N. Wirges, K. Steiger, D. Häußler, P. Knolle, E. Poulton, R. Khokha, B.T. Grünwald, I.E. Demir, and A. Krüger. 2021. TIMP1 expression underlies sex disparity in liver metastasis and survival in pancreatic cancer. *J. Exp. Med.* 218 (11): e20210911.

https://doi.org/10.1084/jem.20210911

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JCB Journal of Cell Biology

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Highlighting some of the outstanding research published over the last year in the *Journal of Cell Biology* (*JCB*). From a study showing that focal adhesions can act as signaling hubs for mTORC1 to a structural analysis providing a spatiotemporal map of the centriole core, and another examining nucleus–mitochondrial contacts, these articles showcase the diverse interests of our community. We also highlight articles examining the regulation of macropinocytosis and integrin internalization as well as a role for TDP-43 in modulating oligodendrocyte metabolism, thus providing something for everyone in our diverse readership.

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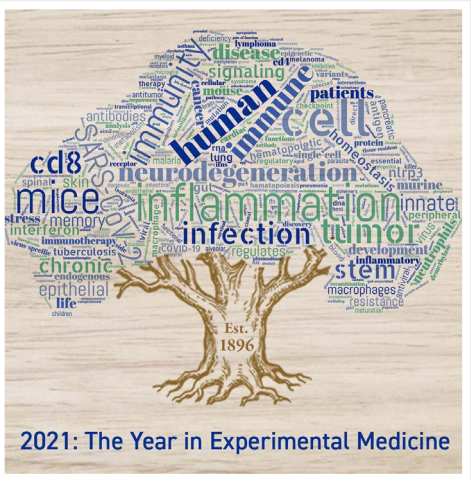

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Get started with these two articles and activities:

"T- and B-cell abnormalities, pneumocystis pneumonia and chronic lymphocytic leukemia associated with an AIOLOS defect in patients"

Hye Sun Kuehn, Sergio D. Rosenzweig, and colleagues

"Epitope convergence of broadly HIV-1 neutralizing IgA and IgG antibody lineages in a viremic controller"

Valérie Lorin, Félix A. Rey, Hugo Mouquet and colleagues

Accreditation

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Memorial Sloan Kettering Cancer Center, the *Journal of Experimental Medicine* (*JEM*) and Rockefeller University Press. Memorial Sloan Kettering Cancer Center is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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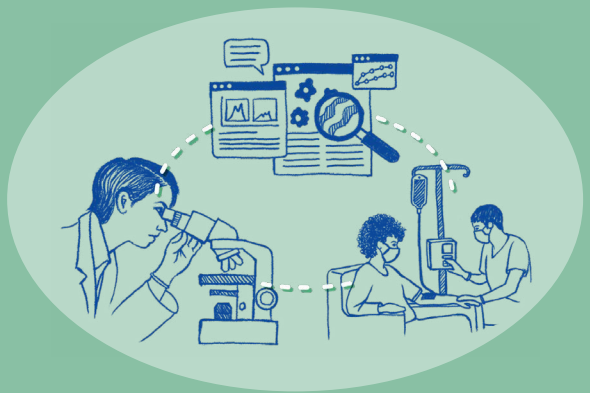

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JEM Journal of Experimental Medicine

Memorial Sloan Kettering Cancer Center

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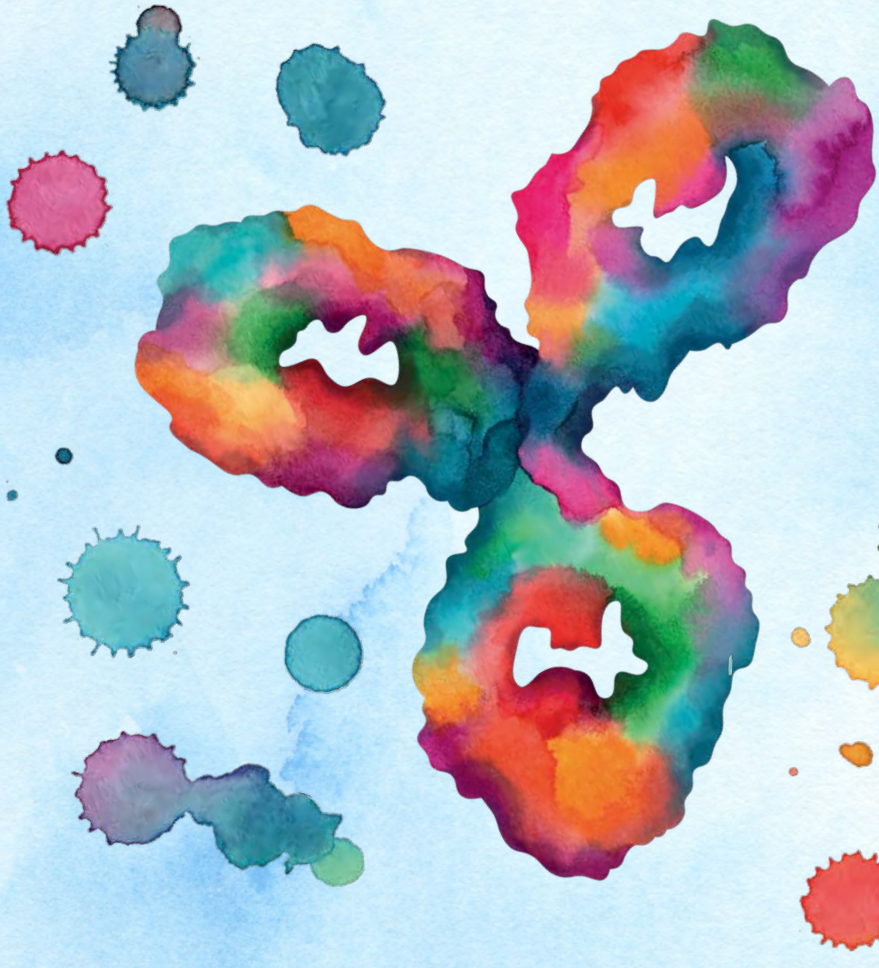

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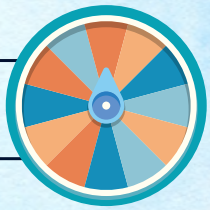

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