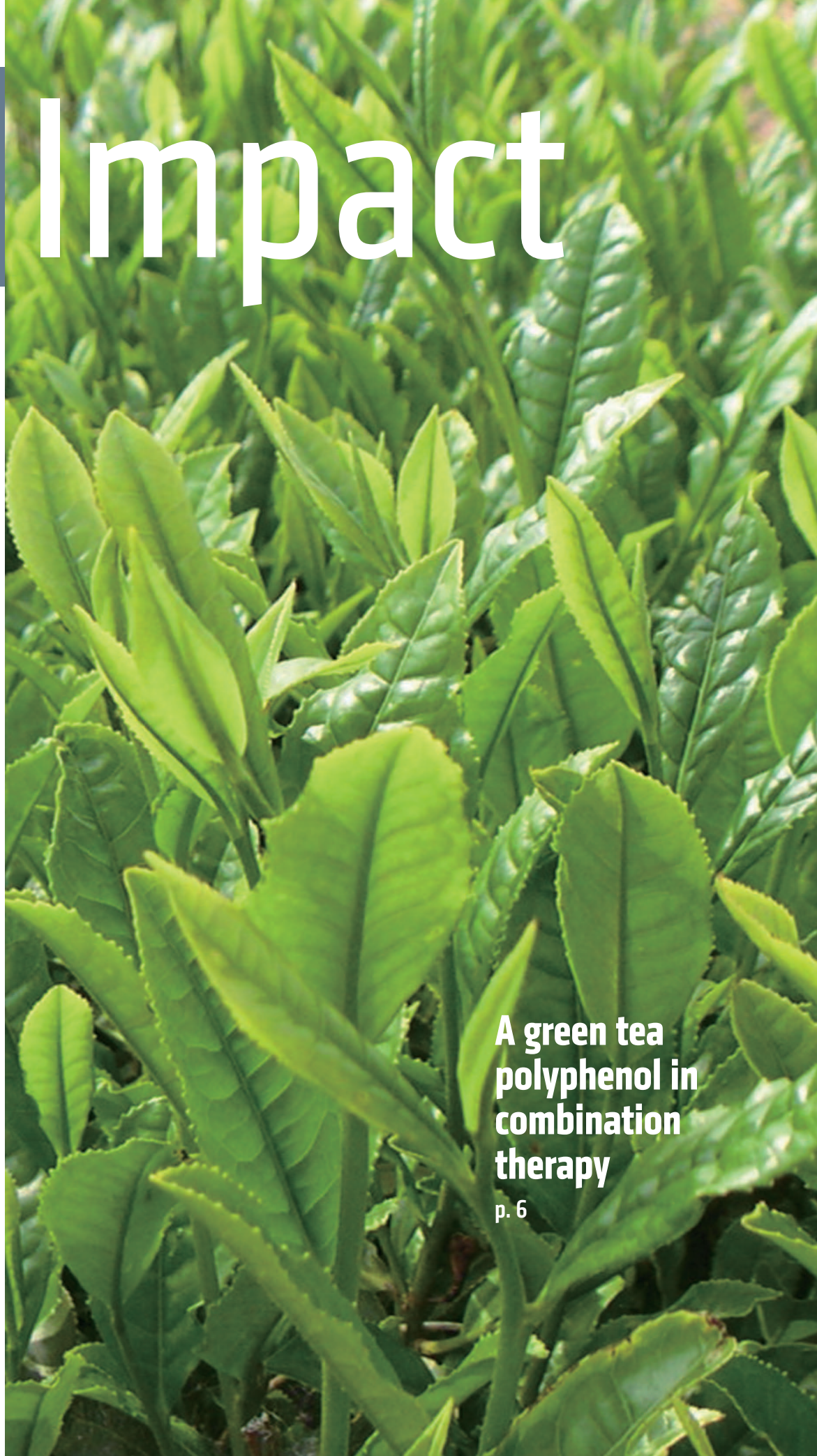
JCI Impact

A summary of this month's **Journal of Clinical Investigation**



A green tea polyphenol in combination therapy

p. 6

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JCI Impact
February 2013

Of Note

Top cited, 2012

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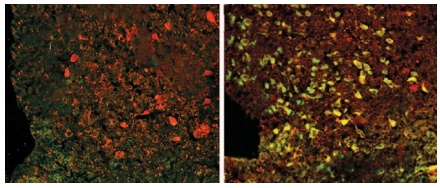
With a new year under way, we've looked back to find the top-cited research articles and reviews published in 2012:

Research articles



Obesity is associated with hypothalamic injury in rodents and humans
Joshua P. Thaler, Chun-Xia Yi, Ellen A. Schur, Stephan J. Guyenet, Bang H. Hwang, Marcelo O. Dietrich, Xiaolin Zhao, David A. Sarruf, Vitaly Izgur, Kenneth R. Maravilla, Hong T. Nguyen, Jonathan D. Fischer, Miles E. Matsen, Brent E. Wisse, Gregory J. Morton, Tamas L. Horvath, Denis G. Baskin, Matthias H. Tschöp, and Michael W. Schwartz
Published January 2012 **jci.me/59660** **Times cited: 31**

Cardiac natriuretic peptides act via p38 MAPK to induce the brown fat thermogenic program in mouse and human adipocytes
Marica Bordicchia, Dianxin Liu, Ez-Zoubir Amri, Gerard Ailhaud, Paolo Dessi-Fulgheri, Chaoying Zhang, Nobuyuki Takahashi, Riccardo Sarzani, and Sheila Collins
Published March 2012 **jci.me/59701** **Times cited: 24**

Brown adipose tissue oxidative metabolism contributes to energy expenditure during acute cold exposure in humans
Véronique Ouellet, Sébastien M. Labbé, Denis P. Blondin, Serge Phoenix, Brigitte Guérin, François Haman, Eric E. Turcotte, Denis Richard, and André C. Carpentier
Published February 2012 **jci.me/60433** **Times cited: 19**

Reviews

Macrophage plasticity and polarization: in vivo veritas
Antonio Sica and Alberto Mantovani
Published March 2012 **jci.me/59643** **Times cited: 33**

Glucagonocentric restructuring of diabetes: a pathophysiologic and therapeutic makeover
Roger H. Unger and Alan D. Cherrington
Published January 2012 **jci.me/60016** **Times cited: 12**

From keratinocyte to cancer: the pathogenesis and modeling of cutaneous squamous cell carcinoma
Vladimir Ratushny, Michael D. Gober, Ryan Hick, Todd W. Ridky, and John T. Seykora
Published February 2012 **jci.me/57415** **Times cited: 11**

Citation information is from Web of Science and Scopus.

Full articles online,
jci.me/123/2

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Research articles in the current issue of the JCI

Cardiology

Renal tubular NEDD4-2 deficiency causes NCC-mediated salt-dependent hypertension

Caroline Ronzaud, Dominique Loffing-Cueni, Pierrette Hausel, Anne Debonneville, Sumedha Ram Malsure, Nicole Fowler-Jaeger, Natasha A. Boase, Romain Perrier, Marc Maillard, Baoli Yang, John B. Stokes, Robert Koesters, Sharad Kumar, Edith Hummler, Johannes Loffing, and Olivier Staub **jci.me/61110**

With related Commentary by David H. Ellison

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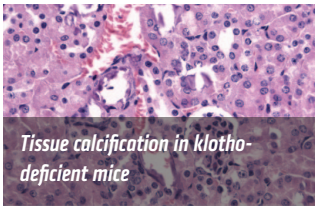

Tissue calcification in klotho-deficient mice

Spironolactone ameliorates PIT1-dependent vascular osteoinduction in klotho-hypomorphic mice

Jakob Voelkl, Ioana Alesutan, Christina B. Leibrock, Leticia Quintanilla-Martinez, Volker Kuhn, Martina Feger, Sobuj Mia, Mohamed S.E. Ahmed, Kevin P. Rosenblatt, Makoto Kuro-o, and Florian Lang **jci.me/64093**

With related Attending Physician by L. Darryl Quarles

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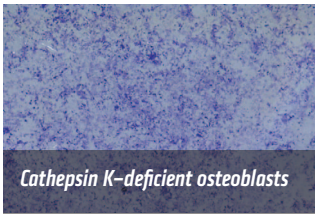

Cathepsin K–deficient osteoblasts

Endocrinology

Osteoclast-specific cathepsin K deletion stimulates S1P-dependent bone formation

Sutada Lotinun, Riku Kiviranta, Takuma Matsubara, Jorge A. Alzate, Lynn Neff, Anja Lüth, Ilpo Koskivirta, Burkhard Kleuser, Jean Vacher, Eero Vuorio, William C. Horne, and Roland Baron **jci.me/64840**

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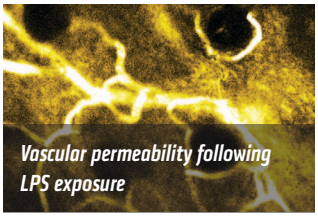
Dynamic visualization of RANKL and Th17-mediated osteoclast function

Junichi Kikuta, Yoh Wada, Toshiyuki Kowada, Ze Wang, Ge-Hong Sun-Wada, Issei Nishiyama, Shin Mizukami, Nobuhiko Maiya, Hisataka Yasuda, Atsushi Kumanogoh, Kazuya Kikuchi, Ronald N. Germain, and Masaru Ishii **jci.me/65054**



Vascular permeability following LPS exposure

Inflammation

Blockade of NOX2 and STIM1 signaling limits lipopolysaccharide-induced vascular inflammation

Rajesh Kumar Gandhirajan, Shu Meng, Harish C. Chandramoorthy, Karthik Mallilankaraman, Salvatore Mancarella, Hui Gao, Roshanak Razmpour, Xiao-Feng Yang, Steven R. Houser, Ju Chen, Walter J. Koch, Hong Wang, Jonathan Soboloff, Donald L. Gill, and Muniswamy Madesh **jci.me/65647**

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Platelet ITAM signaling is critical for vascular integrity in inflammation

Yacine Boulaftali, Paul R. Hess, Todd M. Getz, Agnieszka Cholka, Moritz Stolla, Nigel Mackman, A. Phillip Owens III, Jerry Ware, Mark L. Kahn, and Wolfgang Bergmeier **jci.me/65154**

iRHOM2 is a critical pathogenic mediator of inflammatory arthritis

Priya Darshinee A. Issuree, Thorsten Maretzky, David R. McIlwain, Sébastien Monette, Xiaoping Qing, Philipp A. Lang, Steven L. Swendeman, Kyung Hyun Park-Min, Nikolaus Binder, George D. Kalliolias, Anna Yarilina, Keisuke Horiuchi, Lionel B. Ivashkiv, Tak W. Mak, Jane E. Salmon, and Carl P. Blobel **jci.me/66168**

With related Commentary by Stefan F. Lichtenthaler

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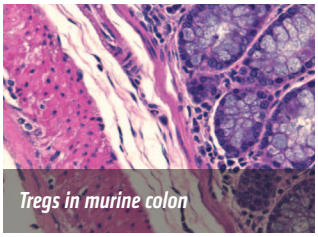
Immunology

Regulation of dendritic cell activation by microRNA let-7c and BLIMP1

Sun Jung Kim, Peter K. Gregersen, and Betty Diamond **jci.me/64712**



Tregs in murine colon

Specialized role of migratory dendritic cells in peripheral tolerance induction

Juliana Idoyaga, Christopher Fiorese, Lori Zbytnuik, Ashira Lubkin, Jennifer Miller, Bernard Malissen, Daniel Mucida, Miriam Merad, and Ralph M. Steinman **jci.me/65260**

An obligate cell-intrinsic function for CD28 in Tregs

Ruan Zhang, Alexandria Huynh, Gregory Whitcher, JiHoon Chang, Jonathan S. Maltzman, and Laurence A. Turka **jci.me/65013**

Superior T memory stem cell persistence supports long-lived T cell memory

Enrico Lugli, Maria H. Dominguez, Luca Gattinoni, Pratip K. Chattopadhyay, Diane L. Bolton, Kaimei Song, Nichole R. Klatt, Jason M. Brenchley, Monica Vaccari, Emma Gostick, David A. Price, Thomas A. Waldmann, Nicholas P. Restifo, Genoveffa Franchini, and Mario Roederer **jci.me/66327**

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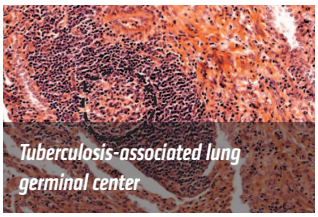

Tuberculosis-associated lung germinal center

CXCR5$^+$ T helper cells mediate protective immunity against tuberculosis

Samantha R. Slight, Javier Rangel-Moreno, Radha Gopal, Yinyao Lin, Beth A. Fallert Junecko, Smriti Mehra, Moises Selman, Enrique Becerril-Villanueva, Javier Baquera-Heredia, Lenin Pavon, Deepak Kaushal, Todd A. Reinhart, Troy D. Randall, and Shabaana A. Khader **jci.me/65728**

Probiotic/prebiotic supplementation of antiretrovirals improves gastrointestinal immunity in SIV-infected macaques

Nichole R. Klatt, Lauren A. Canary, Xiaoyong Sun, Carol L. Vinton, Nicholas T. Funderburg, David R. Morcock, Mariam Quiñones, Clayton B. Deming, Molly Perkins, Daria J. Hazuda, Michael D. Miller, Michael M. Lederman, Julie A. Segre, Jeffrey D. Lifson, Elias K. Haddad, Jacob D. Estes, and Jason M. Brenchley **jci.me/66227**

With related Attending Physician by Martin J. Wolff et al.

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Coal tar induces AHR-dependent skin barrier repair in atopic dermatitis

Ellen H. van den Bogaard, Judith G.M. Bergboer, Mieke Vonk-Bergers, Ivonne M.J.J. van Vlijmen-Willems, Stanleyson V. Hato, Pieter G.M. van der Valk, Jens Michael Schröder, Irma Joosten, Patrick L.J.M. Zeeuwen, and Joost Schalkwijk **jci.me/65642**

With related Commentary by W.H. Irwin McLean and Alan D. Irvine

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Peptide-mediated desmoglein 3 crosslinking prevents pemphigus vulgaris autoantibody-induced skin blistering

Volker Spindler, Vera Rötzer, Carina Dehner, Bettina Kempf, Martin Gliem, Mariya Radeva, Eva Hartlieb, Gregory S. Harms, Enno Schmidt, and Jens Waschke **jci.me/60139**

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Muscle biology

Acylated and unacylated ghrelin impair skeletal muscle atrophy in mice

Paolo E. Porporato, Nicoletta Filigheddu, Simone Reano, Michele Ferrara, Elia Angelino, Viola F. Gnocchi, Flavia Prodam, Giulia Ronchi, Sharmila Fagoonee, Michele Fornaro, Federica Chianale, Gianluca Baldanzi, Nicola Surico, Fabiola Sinigaglia, Isabelle Perroteau, Roy G. Smith, Yuxiang Sun, Stefano Geuna, and Andrea Graziani
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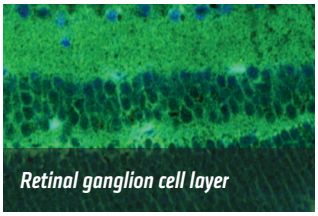
Retinal ganglion cell layer

Neurobiology

Deimination restores inner retinal visual function in murine demyelinating disease

Mabel Enriquez-Algeciras, Di Ding, Fabrizio G. Mastronardi, Robert E. Marc, Vittorio Porciatti, and Sanjoy K. Bhattacharya
jci.me/64811

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Patients with type 1 diabetes exhibit altered cerebral metabolism during hypoglycemia

Kim C.C. van de Ven, Cees J. Tack, Arend Heerschap, Marinette van der Graaf, and Bastiaan E. de Galan **jci.me/62742**

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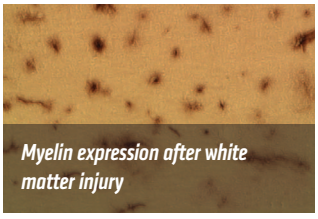
Myelin expression after white matter injury

Oligodendrocyte precursors induce early blood-brain barrier opening after white matter injury

Ji Hae Seo, Nobukazu Miyamoto, Kazuhide Hayakawa, Loc-Duyen D. Pham, Takakuni Maki, Cenk Ayata, Kyu-Won Kim, Eng H. Lo, and Ken Arai **jci.me/65863**

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Oncology

NOD2-mediated dysbiosis predisposes mice to transmissible colitis and colorectal cancer

Aurélie Couturier-Maillard, Thomas Secher, Ateequr Rehman, Sylvain Normand, Adèle De Arcangelis, Robert Haesler, Ludovic Huot, Teddy Grandjean, Aude Bressenot, Anne Delanoye-Crespin, Olivier Gaillot, Stefan Schreiber, Yves Lemoine, Bernhard Ryffel, David Hot, Gabriel Nùñez, Grace Chen, Philip Rosenstiel, and Mathias Chamaillard **jci.me/62236**

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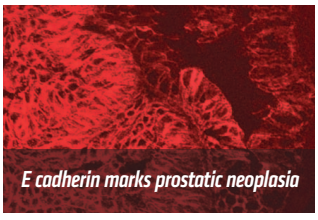
E cadherin marks prostatic neoplasia

β4 Integrin signaling induces expansion of prostate tumor progenitors

Toshiaki Yoshioka, Javier Otero, Yu Chen, Young-Mi Kim, Jason A. Koutcher, Jaya Satagopan, Victor Reuter, Brett Carver, Elisa de Stanchina, Katsuhiko Enomoto, Norman M. Greenberg, Peter T. Scardino, Howard I. Scher, Charles L. Sawyers, and Filippo G. Giancotti **jci.me/60720**

With related Commentary by Max S. Wicha

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Behavioral stress accelerates prostate cancer development in mice

Sazzad Hassan, Yelena Karpova, Daniele Baiz, Dana Yancey, Ashok Pullikuth, Anabel Flores, Thomas Register, J. Mark Cline, Ralph D'Agostino Jr., Nika Danial, Sandeep Robert Datta, and George Kulik **jci.me/63324**

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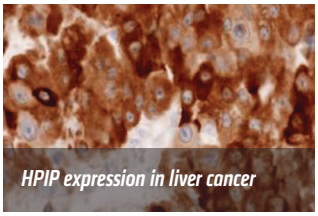
HPIP expression in liver cancer

Hepatitis B virus X protein represses miRNA-148a to enhance tumorigenesis
Xiaojie Xu, Zhongyi Fan, Lei Kang, Juqiang Han, Chengying Jiang, Xiaofei Zheng, Ziman Zhu, Huabo Jiao, Jing Lin, Kai Jiang, Lihua Ding, Hao Zhang, Long Cheng, Hanjiang Fu, Yi Song, Ying Jiang, Jiahong Liu, Rongfu Wang, Nan Du, and Qinong Ye **jci.me/64265**

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EWS/ATF1 expression induces sarcomas from neural crest–derived cells in mice
Kazunari Yamada, Takatoshi Ohno, Hitomi Aoki, Katsunori Semi, Akira Watanabe, Hiroshi Moritake, Shunichi Shiozawa, Takahiro Kunisada, Yukiko Kobayashi, Junya Toguchida, Katsuji Shimizu, Akira Hara, and Yasuhiro Yamada **jci.me/63572**

KDM2B promotes pancreatic cancer via Polycomb-dependent and -independent transcriptional programs
Alexandros Tzatsos, Polina Paskaleva, Francesco Ferrari, Vikram Deshpande, Svetlana Stoykova, Gianmarco Contino, Kwok-Kin Wong, Fei Lan, Patrick Trojer, Peter J. Park, and Nabeel Bardeesy **jci.me/64535**

67-kDa laminin receptor increases cGMP to induce cancer-selective apoptosis
Motofumi Kumazoe, Kaori Sugihara, Shuntaro Tsukamoto, Yuhui Huang, Yukari Tsurudome, Takashi Suzuki, Yumi Suemasu, Naoki Ueda, Shuya Yamashita, Yoonhee Kim, Koji Yamada, and Hirofumi Tachibana **jci.me/64768**

With related Commentary by Chung S. Yang and Hong Wang

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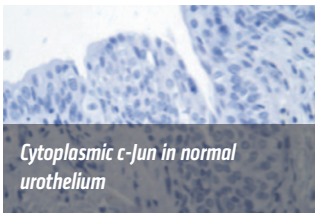
Cytoplasmic c-Jun in normal urothelium

Loss of SPARC in bladder cancer enhances carcinogenesis and progression
Neveen Said, Henry F. Frierson, Marta Sanchez-Carbayo, Rolf A. Brekken, and Dan Theodorescu **jci.me/64782**

mTORC1 inhibition restricts inflammation-associated gastrointestinal tumorigenesis in mice
Stefan Thiem, Thomas P. Pierce, Michelle Palmieri, Tracy L. Putoczki, Michael Buchert, Adele Preaudet, Ryan O. Farid, Chris Love, Bruno Catimel, Zhengdeng Lei, Steve Rozen, Veena Gopalakrishnan, Fred Schaper, Michael Hallek, Alex Boussioutas, Patrick Tan, Andrew Jarnicki, and Matthias Ernst **jci.me/65086**

Liver acid sphingomyelinase inhibits growth of metastatic colon cancer
Yosuke Osawa, Atsushi Suetsugu, Rie Matsushima-Nishiwaki, Ichiro Yasuda, Toshiji Saibara, Hisataka Moriwaki, Mitsuru Seishima, and Osamu Kozawa **jci.me/65188**

MicroRNA-374a activates Wnt/β-catenin signaling to promote breast cancer metastasis
Junchao Cai, Hongyu Guan, Lishan Fang, Yi Yang, Xun Zhu, Jie Yuan, Jueheng Wu, and Mengfeng Li **jci.me/65871**

The tumorigenic *FGFR3-TACC3* gene fusion escapes miR-99a regulation in glioblastoma
Brittany C. Parker, Matti J. Annala, David E. Cogdell, Kirsi J. Granberg, Yan Sun, Ping Ji, Xia Li, Joy Gumin, Hong Zheng, Limei Hu, Olli Yli-Harja, Hannu Haapasalo, Tapio Visakorpi, Xiuping Liu, Chang-gong Liu, Raymond Sawaya, Gregory N. Fuller, Kexin Chen, Frederick F. Lang, Matti Nykter, and Wei Zhang **jci.me/67144**

With related Commentary by Ivan Babic and Paul S. Mischel

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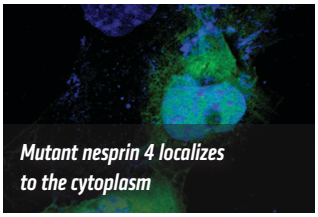
Mutant nesprin 4 localizes to the cytoplasm

Otology

The LINC complex is essential for hearing
Henning F. Horn, Zippora Brownstein, Danielle R. Lenz, Shaked Shivatzki, Amiel A. Dror, Orit Dagan-Rosenfeld, Lilach M. Friedman, Kyle J. Roux, Serguei Kozlov, Kuan-Teh Jeang, Moshe Frydman, Brian Burke, Colin L. Stewart, and Karen B. Avraham **jci.me/66911**

With related Commentary by Howard Worman and Neil Segil

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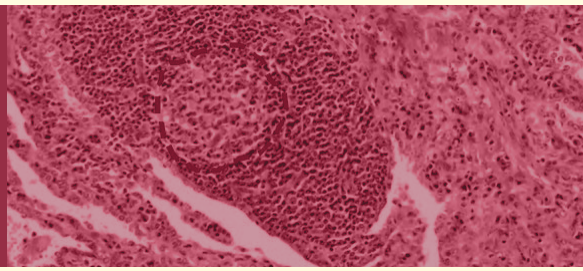
Editor's picks



A green tea cocktail to fight cancer?

Green tea plants

Green tea has long been touted for its health benefits and has even been shown to inhibit tumorigenesis in animal models. However, the mechanism of this effect is incompletely understood. In this issue, Motofumi Kumazoe and colleagues show that treating multiple myeloma cells with the active component in green tea, the polyphenol EGCG, activates a membrane receptor called 67LR, resulting in increased levels of the signaling molecule cGMP and, ultimately, induction of apoptosis. However, the concentration of EGCG required to initiate this effect was high, in part because the tumor cells expressed an inhibitor of cGMP called phosphodiesterase 5 (PDE5). By adding a negative regulator of PDE5, Kumazoe et al. found that the dose of EGCG required to induce apoptosis was dramatically reduced.

In the accompanying commentary, Chung Yang and Hong Wang point out that many prostate cancer patients already take PDE5-selective inhibitors (e.g., Viagra) after prostatectomy to treat erectile dysfunction. If their cancer samples overexpress 67LR and PDE5, it is possible that adding an EGCG supplement or a green tea beverage might prevent prostate cancer recurrence. However, they warn that cancer cells that express low levels of 67LR may be activated by EGCG, and thus this compound may paradoxically promote the growth of some tumors.

67-kDa laminin receptor increases cGMP to induce cancer-selective apoptosis
Motofumi Kumazoe, Kaori Sugihara, Shuntaro Tsukamoto, Yuhui Huang, Yukari Tsurudome, Takashi Suzuki, Yumi Suemasu, Naoki Ueda, Shuya Yamashita, Yoonhee Kim, Koji Yamada, and Hirofumi Tachibana jci.me/64768

Related Commentary

Cancer therapy combination: green tea and a phosphodiesterase 5 inhibitor?
Chung S. Yang and Hong Wang
jci.me/67589

ONCOLOGY

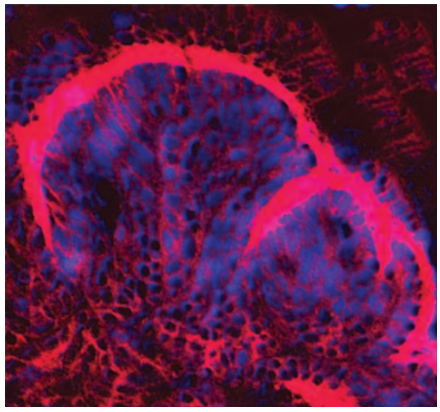
Integrins identify tumor progenitors

In conventional prostate cancer therapy, androgen ablation targets the bulk of the tumor population. However, hormone resistance often develops, and when prostate cancer metastasizes in men following androgen ablation, it is incurable. In this issue, Toshiaki Yoshioka and colleagues describe a subpopulation of prostate cancer cells with stem cell–like properties that may mediate hormone-resistant tumor growth and metastasis. They find that these cells are enriched with an integrin protein called β4, which helps anchor the cells to the basement membrane. Furthermore, the β4 integrin was found to combine with two cell surface receptor signaling molecules, ErbB2 and c-Met, and to promote their ability to activate ERK and AKT signaling and, hence, promote cell proliferation. Thus, Yoshioka et al. have described a cancer stem cell marker that is directly connected to the signaling pathways that control the growth of those cells.

In the accompanying commentary, Max Wicha emphasizes that, by identifying this key signaling pathway, Yoshioka et al. have provided insight into new therapeutic strategies that might target this population and have a unique capacity to reduce metastasis.

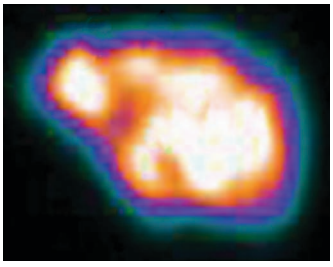
The figure shows β4 integrin staining in a tumor lesion.

β4 Integrin signaling induces expansion of prostate tumor progenitors
Toshiaki Yoshioka, Javier Otero, Yu Chen, Young-Mi Kim, Jason A. Koutcher, Jaya Satagopan, Victor Reuter, Brett Carver, Elisa de Stanchina, Katsuhiko Enomoto, Norman M. Greenberg, Peter T. Scardino, Howard I. Scher, Charles L. Sawyers, and Filippo G. Giancotti **jci.me/60720**



Related Commentary
B4 androgen ablation: attacking the prostate cancer stem cell
Max S. Wicha **jci.me/67460**

Hepatitis B virus promotes tumorigenesis by blocking expression of miR-148a



Viruses prompt oncogenic transformation by genetically altering infected cells, and several recent studies have demonstrated that viruses alter the expression of microRNAs. Xiaojie Xu and colleagues report that miR-148a is repressed by hepatitis B virus (HBV) X protein (HBx) to promote growth and metastasis of hepatocellular carcinoma. miR-148a repressed the expression of the oncogene hematopoietic pre–B cell leukemia transcription factor–interacting protein (HPIP). Expression of HBx suppressed p53-mediated activation of miR-148a, increasing proliferation, invasion, and metastasis in an mTOR-dependent manner. The image shows a PET scan of miR-148a–deficient mouse liver.

Hepatitis B virus X protein represses miRNA-148a to enhance tumorigenesis
Xiaojie Xu, Zhongyi Fan, Lei Kang, Juqiang Han, Chengying Jiang, Xiaofei Zheng, Ziman Zhu, Huabo Jiao, Jing Lin, Kai Jiang, Lihua Ding, Hao Zhang, Long Cheng, Hanjiang Fu, Yi Song, Ying Jiang, Jiahong Liu, Rongfu Wang, Nan Du, and Qinong Ye **jci.me/64265**

New fusion gene in glioblastoma

Understanding the genetic aberrations that drive tumor growth is critical to the development of targeted molecular therapeutics. Here, Brittany Parker and colleagues used RNA sequencing to search for chromosomal translocation events in human glioblastoma patient samples and found a subset of cases that harbored a duplication event resulting in the fusion of the tyrosine kinase FGFR3 with the mitotic protein TACC3. Another group recently described the same fusion event and suggested that the protein promotes tumor progression by localizing to the mitotic spindle, where it causes chromosomal instability. Parker et al. show that the tumorigenicity stems in part from the fact that the fusion gene lacks a microRNA binding site, and thus the fusion protein has enhanced stability.

Ivan Babic and Paul Mischel explain in the accompanying commentary that it remains unclear how this fusion protein preferentially activates downstream signaling, and this mechanism will need to be unraveled to develop targeted therapeutics.

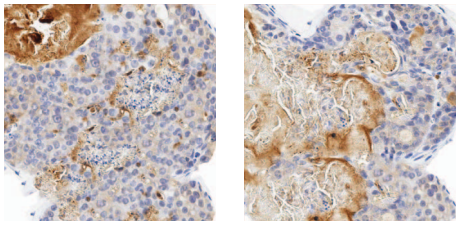
The tumorigenic *FGFR3-TACC3* gene fusion escapes miR-99a regulation in glioblastoma
Brittany C. Parker, Matti J. Annala, David E. Cogdell, Kirsi J. Granberg, Yan Sun, Ping Ji, Xia Li, Joy Gumin, Hong Zheng, Limei Hu, Olli Yli-Harja, Hannu Haapasalo, Tapio Visakorpi, Xiuping Liu, Chang-gong Liu, Raymond Sawaya, Gregory N. Fuller, Kexin Chen, Frederick F. Lang, Matti Nykter, and Wei Zhang **jci.me/67144**

Related Commentary
Multiple functions of a glioblastoma fusion oncogene
Ivan Babic and Paul S. Mischel **jci.me/67658**

ONCOLOGY

Explaining the molecular links between stress and cancer

The connection between behavioral stress and cancer has been intensely studied, but the mechanisms that underlie this link remain largely unknown. Now, Sazzad Hassan and colleagues show in two mouse models of prostate cancer that behavioral stress promotes tumor progression in part by blocking the apoptosis of cancer cells. Hassan et al. found that signaling through the adrenergic receptor led to inactivation of the antiapoptotic protein BCL2-associated death promoter (BAD). Furthermore, they showed that a chronic increase of adrenaline may contribute to the development of resistance to antihormone therapy in prostate cancer.



Archana Nagaraja and colleagues in the accompanying commentary suggest that stress pathways may be targeted to prevent cancer progression, but this will require identification of the patient subsets most likely to benefit as well as further dissection of the complex molecular interactions involved. The figure shows reduced apoptosis in prostate glands of stressed mice.

Behavioral stress accelerates prostate cancer development in mice

Sazzad Hassan, Yelena Karpova, Daniele Baiz, Dana Yancey, Ashok Pullikuth, Anabel Flores, Thomas Register, J. Mark Cline, Ralph D'Agostino Jr., Nika Danial, Sandeep Robert Datta, and George Kulik **jci.me/63324**

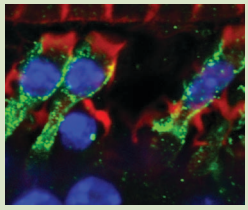
Related Commentary

Why stress is BAD for cancer patients

Archana S. Nagaraja, Guillermo N. Armaiz-Pena, Susan K. Lutgendorf, and Anil K. Sood **jci.me/67887**

OTOLOGY

Connecting the nucleus and cytoplasm—a LINC to hearing loss



The perception of sound requires specialized hair cells in the cochlea that respond to sound wave vibrations. In this article, Henning Horn, Zippora Brownstein, and colleagues report on the study of two families with inherited hearing loss. They mapped the defect to a mutation in the gene that encodes nesprin-4 (*Nesp4*), a protein in the nuclear envelope that is part of the linker of nucleoskeleton and cytoskeleton (LINC) complex. Horn et al. found that in mice missing *Nesp4* or another LINC gene, *Sun1,* cochlear hair cells formed normally, but the mice suffered progressive hearing loss associated with a change in the position of the nucleus in these hair cells. This work underscores the importance of nuclear positioning in sensory cells and reveals a new mechanism in the pathophysiology of deafness.

In the accompanying commentary, Howard Worman and Neil Segil point out that, although both inner and outer hair cells express these LINC proteins, the inner cells are unaffected in the mutant mice. Thus, an unknown property of the outer cells makes them particularly sensitive to nuclear positioning, and additional research into the functional role of these proteins is necessary to understand the differential importance of the LINC complex.

Image shows nuclear mislocalization in outer hair cells in nesprin-4 mutant mice.

The LINC complex is essential for hearing

Henning F. Horn, Zippora Brownstein, Danielle R. Lenz, Shaked Shivatzki, Amiel A. Dror, Orit Dagan-Rosenfeld, Lilach M. Friedman, Kyle J. Roux, Serguei Kozlov, Kuan-Teh Jeang, Moshe Frydman, Brian Burke, Colin L. Stewart, and Karen B. Avraham **jci.me/66911**

Related Commentary

Nucleocytoplasmic connections and deafness

Howard J. Worman and Neil Segil **jci.me/67454**

Gut dysbiosis increases inflammation and cancer risk

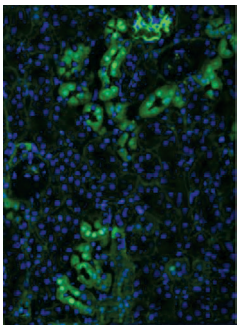
Instability in the composition of gut bacterial communities (dysbiosis) has been linked to common human intestinal disorders, including inflammatory bowel disease and colorectal cancer; however, it is not clear whether dysbiosis causes these disorders or is merely a symptom. Using a murine genetic model of dysbiosis, Aurélie Couturier-Maillard and colleagues found that dysbiosis increased intestinal inflammation and the risk for inflammation-associated colon cancer. Antibiotic treatment or transplantation of fecal material from wild-type mice reduced disease risk and instigated long-term, beneficial alterations in intestinal bacteria. These results demonstrate that gut bacterial communities play an integral role in protecting against intestinal inflammation and associated tumorigenesis.

NOD2-mediated dysbiosis predisposes mice to transmissible colitis and colorectal cancer

Aurélie Couturier-Maillard, Thomas Secher, Ateequr Rehman, Sylvain Normand, Adèle De Arcangelis, Robert Haesler, Ludovic Huot, Teddy Grandjean, Aude Bressenot, Anne Delanoye-Crespin, Olivier Gaillot, Stefan Schreiber, Yves Lemoine, Bernhard Ryffel, David Hot, Gabriel Nùñez, Grace Chen, Philip Rosenstiel, and Mathias Chamaillard **jci.me/62236**

CARDIOLOGY

Understanding salt balance



Regulating sodium transport across membranes of renal epithelial cells is critical for maintaining normal blood pressure. Liddle syndrome is a genetic form of hypertension that has been linked to mutations in the sodium channel ENaC; these mutations block ubiquitination and degradation of the channel, mediated by the ubiquitin ligase NEDD4-2, and lead to excessive ENaC activity in the membrane of renal epithelial cells. To better understand the role of NEDD4-2 in sodium balance, Caroline Ronzaud and colleagues generated a mouse model in which the gene could be selectively deleted in nephrons of adult mice. In this model, ENaC accumulated in the cytoplasm, but not in the cell membrane of nephrons as hypothesized. However, the sodium chloride cotransporter NCC, which is the target of thiazide diuretics commonly used to treat hypertension, did accumulate in the membrane, and the mice displayed characteristics of increased NCC activity.

In the accompanying commentary, David Ellison points out that the mice with inducible NEDD4-2 deficiency are hypertensive but have a normal sodium balance, and thus do not suffer from classic Liddle syndrome. This suggests that NEDD4-2 may have a separate developmental role and that the molecular mechanism that underlies Liddle syndrome may be more complicated than previously believed.

The figure shows renal tubules critical for salt exchange.

Renal tubular NEDD4-2 deficiency causes NCC-mediated salt-dependent hypertension

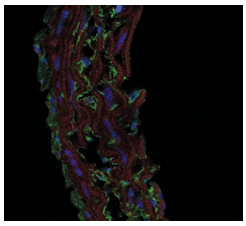
Caroline Ronzaud, Dominique Loffing-Cueni, Pierrette Hausel, Anne Debonneville, Sumedha Ram Malsure, Nicole Fowler-Jaeger, Natasha A. Boase, Romain Perrier, Marc Maillard, Baoli Yang, John B. Stokes, Robert Koesters, Sharad Kumar, Edith Hummler, Johannes Loffing, and Olivier Staub **jci.me/61110**

Related Commentary

Ubiquitylation and the pathogenesis of hypertension

David H. Ellison **jci.me/66882**

Spironolactone ameliorates vascular calcification in *klotho*-deficient mice



Patients with chronic kidney disease (CKD) frequently experience vascular calcification that can cause chronic heart failure. Similar to patients with CKD, mice hypomorphic for the FGF23 coreceptor klotho *(kl/kl)* exhibit hyperphosphatemia, hyperaldosteronism, and extensive vascular and soft tissue calcification. Vascular calcification involves dedifferentiation and reprogramming of vascular smooth muscle cells into an osteogenic and chondrogenic phenotype that promotes vascular calcification. Vascular smooth muscle cells express the aldosterone-sensitive mineralocorticoid receptor, which stimulates calcification. Jakob Voelkl and colleagues found that treatment with the mineralocorticoid receptor antagonist spironolactone reduced vascular calcification in *kl/kl* mice. Spironolactone also reduced the expression of osteoinductive factors in calcified tissues. Conversely, aldosterone promoted the expression of osteoinductive factors in cultured human aortic smooth muscle cells in a PIT1-dependent manner, suggesting that vascular calcification in CKD is likely fostered by elevated aldosterone levels. In a companion Attending Physician article, Darryl Quarles discusses the implications of these findings for the treatment of patients with CKD. The accompanying image shows expression of the osteogenic protein osterix (green) in the aortic tissue of *kl/kl* mice.

Spironolactone ameliorates PIT1-dependent vascular osteoinduction in klotho-hypomorphic mice

Jakob Voelkl, Ioana Alesutan, Christina B. Leibrock, Leticia Quintanilla-Martinez, Volker Kuhn, Martina Feger, Sobuj Mia, Mohamed S.E. Ahmed, Kevin P. Rosenblatt, Makoto Kuro-o, and Florian Lang **jci.me/64093**

Related Attending Physician

Reducing cardiovascular mortality in chronic kidney disease: something borrowed, something new

L. Darryl Quarles **jci.me/67203**

ENDOCRINOLOGY

Bone formation is enhanced by osteoclast-specific deletion of cathepsin K

Mutations in human cathepsin K *(CTSK)* cause pycnodysostosis, an autosomal recessive disease characterized by short stature and elevated bone density (osteopetrosis). In mice, global deletion of *Ctsk* results in decreased bone resorption and osteopetrosis, but also enhances the rate of bone formation. To determine the role of CTSK in bone formation, Sutada Lotinun and colleagues generated osteoclast- and osteoblast-specific *Ctsk* knockout mice. Bone volume and formation rate were enhanced by osteoclast-specific ablation of *Ctsk*, but were not affected by loss of *Ctsk* in osteoblasts. Further, deletion of *Ctsk* in osteoclasts increased production not only of bone formation factors by osteoclasts, but also of bone resorptive factors by osteoblasts. This study provides mechanistic insight into how inhibition of CTSK increases bone mass.

Osteoclast-specific cathepsin K deletion stimulates S1P-dependent bone formation

Sutada Lotinun, Riku Kiviranta, Takuma Matsubara, Jorge A. Alzate, Lynn Neff, Anja Lüth, Ilpo Koskivirta, Burkhard Kleuser, Jean Vacher, Eero Vuorio, William C. Horne, and Roland Baron **jci.me/64840**

IMMUNOLOGY

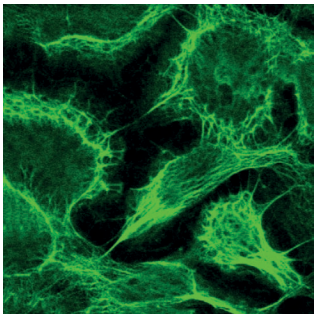
Primates maintain long-lived T memory stem cells

Memory T cells are a subset of antigen-specific T cells that sustain immunological memory and are expanded in response to the presence of their cognate antigen. T stem cell memory cells (T_{SCM} cells) serve as precursors of multiple memory cell subtypes and have enhanced self-renewal capacity. Enrico Lugli and colleagues characterized T_{SCM} cells in healthy and SIV-infected nonhuman primates. The cells identified in rhesus and pigtail macaques were the least-differentiated memory subset, were functionally distinct from conventional memory cells, and served as precursors of T_{CM} cells. Antigen-specific T_{SCM} cells were generated during infection and survived following the elimination of antigen. These results demonstrate that primates develop antigen-specific T_{SCM} cells and suggest that vaccination strategies should be designed to elicit the generation of these cells.

Superior T memory stem cell persistence supports long-lived T cell memory

Enrico Lugli, Maria H. Dominguez, Luca Gattinoni, Pratip K. Chattopadhyay, Diane L. Bolton, Kaimei Song, Nichole R. Klatt, Jason M. Brenchley, Monica Vaccari, Emma Gostick, David A. Price, Thomas A. Waldmann, Nicholas P. Restifo, Genoveffa Franchini, and Mario Roederer **jci.me/66327**

Small peptide ameliorates autoimmune skin blistering disease in mice

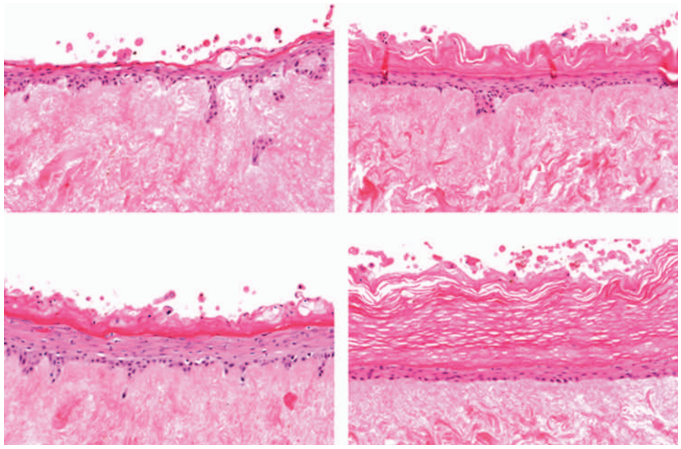


Pemphigus vulgaris is a life-threatening autoimmune disease that occurs when the immune system generates autoantibodies targeting the desmosomal adhesion molecules desmoglein 1 (DSG1) and DSG3. Antibody-mediated loss of desmoglein interactions induces cell dissociation that causes skin and mucous membrane blistering. The accompanying image shows keratin retraction in keratinocytes treated with pemphigus antibodies. Volker Spindler and colleagues applied a peptide that blocks autoantibody-mediated interference with DSG3 interactions. Importantly, the peptide, which can be applied topically, abrogated autoantibody-mediated skin blistering in mice, suggesting that it is a potential treatment for pemphigus vulgaris.

Peptide-mediated desmoglein 3 crosslinking prevents pemphigus vulgaris autoantibody-induced skin blistering

Volker Spindler, Vera Rötzer, Carina Dehner, Bettina Kempf, Martin Gliem, Mariya Radeva, Eva Hartlieb, Gregory S. Harms, Enno Schmidt, and Jens Waschke **jci.me/60139**

New mechanism explains an ancient cure: coal tar for atopic dermatitis



The multiple layers of the epidermis help to create a barrier that protects the body from environmental insults, and disruptions to the barrier are often associated with inflammatory conditions. Recently, human genetics studies identified an association between mutations in the gene encoding filaggrin, which helps to maintain the epithelial barrier, and atopic dermatitis (AD). In this issue, Ellen van den Bogaard et al. investigated the mechanism that explains the efficacy of coal tar, an ancient remedy for the disease. They found that elements in coal tar activate the aryl hydrocarbon receptor (AHR) signaling pathway, which was recently identified as critical in the development of the immune system, and which induces the differentiation of epithelial cells. Thus, by activating the pathway, coal tar helps to rebuild the deficient barrier that marks AD.

In the accompanying commentary, W. H. Irwin McLean and Alan Irvine point out that although it may be difficult to extract the active component(s) from coal tar, the identification of the AHR signaling pathway as its target opens the door for the development of new therapeutic strategies.

The image shows the stratum corneum in human skin samples cultured with or without coal tar.

Coal tar induces AHR-dependent skin barrier repair in atopic dermatitis

Ellen H. van den Bogaard, Judith G.M. Bergboer, Mieke Vonk-Bergers, Ivonne M.J.J. van Vlijmen-Willems, Stanleyson V. Hato, Pieter G.M. van der Valk, Jens Michael Schröder, Irma Joosten, Patrick L.J.M. Zeeuwen, and Joost Schalkwijk **jci.me/65642**

Related Commentary

Old King Coal—molecular mechanisms underlying an ancient treatment for atopic eczema

W.H. Irwin McLean and Alan Irvine **jci.me/67438**

Probiotics improve gut mucosal function in SIV-infected macaques

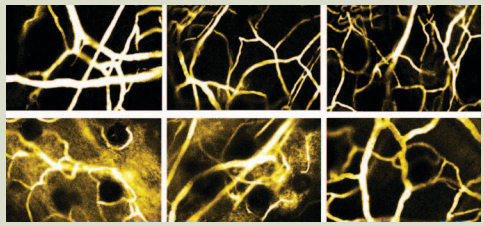
Antiretroviral (ARV) drugs are the first-line therapy for patients with HIV; however, ARV-treated HIV-infected individuals still have a higher mortality rate than uninfected individuals. During the course of infection, HIV patients develop damaged gut mucosa, allowing intestinal microbes to escape and enter the blood stream to cause systemic inflammation. The health of the gut mucosa is significantly influenced by the resident bacterial populations, and there is mounting evidence that probiotic supplements can ameliorate bacterial imbalances. Nichole Klatt and colleagues treated SIV-infected macaques with ARV, either alone or in combination with a mixture of probiotics. The macaques that received probiotics had enhanced gastrointestinal immune function and decreased inflammation compared with macaques treated with ARV alone. Probiotic treatment enhanced reconstitution and functionality of $CD4^+$ T cells and reduced fibrosis of colonic lymphoid follicles. Microarray analysis revealed that probiotic treatment upregulated expression of genes associated with APCs, indicating increased immune system function. In a companion Attending Physician article, Judith Aberg and colleagues discuss how these findings could benefit HIV patients.

Probiotic/prebiotic supplementation of antiretrovirals improves gastrointestinal immunity in SIV-infected macaques
Nichole R. Klatt, Lauren A. Canary, Xiaoyong Sun, Carol L. Vinton, Nicholas T. Funderburg, David R. Morcock, Mariam Quiñones, Clayton B. Deming, Molly Perkins, Daria J. Hazuda, Michael D. Miller, Michael M. Lederman, Julie A. Segre, Jeffrey D. Lifson, Elias K. Haddad, Jacob D. Estes, and Jason M. Brenchley **jci.me/66227**

▶ **Related Attending Physician**
Clash of the microbes: let's bring back the good guys
Martin J. Wolff, Michael A. Poles, and Judith A. Aberg **jci.me/66736**

INFLAMMATION

A STIM-ulating role for calcium in sepsis-induced injury



Despite advances in antimicrobial therapy, sepsis continues to be a major health problem, in part because the mechanisms by which it induces a systemic inflammatory response that leads to organ injury are incompletely understood. In this issue, Rajesh Gandhirajan and colleagues provide new insight into the molecular pathways that lead to this injury, revealing a role for store-operated Ca^{2+} entry (SOCe). Ca^{2+} entry and release from cells normally result in Ca^{2+} oscillations that are critical to gene expression and cellular responses to stress. Gandhirajan et al. found that the Ca^{2+} store–sensing protein STIM1 was required for SOCe, and mice lacking the protein in endothelial cells were protected from sepsis-induced tissue injury. They further demonstrated that blocking Ca^{2+} entry with a drug reduced inflammation and lung injury in their sepsis model. Thus, this pathway is a novel therapeutic target for the treatment of sepsis, although additional research will be required to translate the findings into clinical benefit. The image shows measurement of vascular permeability after exposure to LPS.

Blockade of NOX2 and STIM1 signaling limits lipopolysaccharide-induced vascular inflammation
Rajesh Kumar Gandhirajan, Shu Meng, Harish C. Chandramoorthy, Karthik Mallilankaraman, Salvatore Mancarella, Hui Gao, Roshanak Razmpour, Xiao-Feng Yang, Steven R. Houser, Ju Chen, Walter J. Koch, Hong Wang, Jonathan Soboloff, Donald L. Gill, and Muniswamy Madesh **jci.me/65647**

iRHOM2: a new target in arthritis

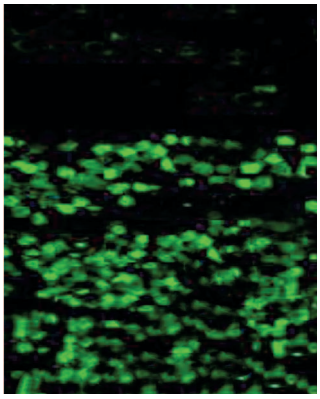
TNF-α is a cytokine that is implicated in the pathogenesis of inflammatory illnesses like sepsis and arthritis. The release of TNF-α from macrophages requires its cleavage by TNF-α converting enzyme (TACE), which itself must move from the membrane of the endoplasmic reticulum to the cell membrane to be active. The inactive intramembrane protease iRHOM2 has recently been implicated in the maturation of TACE, which is also known to be involved in the release of growth factors. In this issue, Priya Issuree and colleagues found that, in a mouse model of rheumatoid arthritis, the degree of inflammation and tissue damage was attenuated in the absence of iRHOM2 expression. Interestingly, whereas TACE deficiency is lethal in mice, iRHOM2-deficient mice are healthy, because in cells other than myeloid or lymphoid lineages, an alternative member of the iRHOM family was able to compensate. In the accompanying commentary, Stefan Lichtenthaler emphasizes that this myeloid-specific action of iRHOM2 makes it an attractive therapeutic target for rheumatoid arthritis.

iRHOM2 is a critical pathogenic mediator of inflammatory arthritis
Priya Darshinee A. Issuree, Thorsten Maretzky, David R. McIlwain, Sébastien Monette, Xiaoping Qing, Philipp A. Lang, Steven L. Swendeman, Kyung-Hyun Park-Min, Nikolaus Binder, George D. Kalliolias, Anna Yarilina, Keisuke Horiuchi, Lionel B. Ivashkiv, Tak W. Mak, Jane E. Salmon, and Carl P. Blobel **jci.me/66168**

▶ **Related Commentary**
iRHOM2 takes control of rheumatoid arthritis
Stefan F. Lichtenthaler **jci.me/67548**

NEUROBIOLOGY

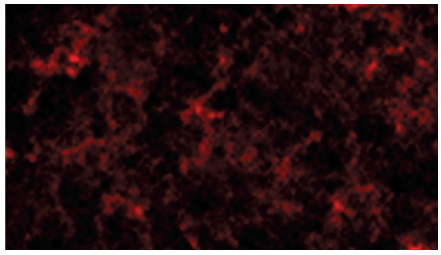
Reduced deimination contributes to loss of retinal function



Demyelinating diseases such as multiple sclerosis (MS) are frequently accompanied by loss of retinal function. Damage to retinal nerves has been attributed to immune system–mediated inflammation; however, other demyelinating disorders that cause retinal damage do not involve the immune system. Deimination is a posttranslational modification that is specifically impaired in the retinal ganglion cell layer of MS patients and in a transgenic mouse model of demyelinating disease (ND4 mice). The accompanying image shows the retinal ganglion cell layer in ND4 mice. Mabel Enriquez-Algeciras and colleagues found that reduced deimination accompanied decreased retinal function in patients with demyelinating disease and in ND4 mice that exhibited vision loss. Restoration of deimination enhanced neurite outgrowth and improved visual function in ND4 mice. These results suggest that the principal enzyme (PAD2) catalyzing deimination may be a suitable therapeutic target in demyelinating disease.

Deimination restores inner retinal visual function in murine demyelinating disease
Mabel Enriquez-Algeciras, Di Ding, Fabrizio G. Mastronardi, Robert E. Marc, Vittorio Porciatti, and Sanjoy K. Bhattacharya **jci.me/64811**

Oligodendrocyte precursors disrupt the BBB after white matter injury



Brain injury frequently leads to blood-brain barrier (BBB) dysfunction that permits the entry of immune cells, which can increase inflammation and induce further neural damage. Oligodendrocyte precursor cells (OPCs) are known to mediate repair after white matter injury, but they also release factors that could alter the BBB. Ji Hae Seo and colleagues examined the role of OPCs in the response to white matter injury in mice. They found that OPCs in hypoperfused brains expressed MMP9, an enzyme that induces BBB disruption. Treatment with the MMP inhibitor GM6001 reduced BBB leakage and neutrophil infiltration. These findings demonstrate that OPCs have deleterious effects on BBB function under pathological conditions. The image shows MMP9 secretion (red) by OPCs 3 days after injury.

Oligodendrocyte precursors induce early blood-brain barrier opening after white matter injury
Ji Hae Seo, Nobukazu Miyamoto, Kazuhide Hayakawa, Loc-Duyen D. Pham, Takakuni Maki, Cenk Ayata, Kyu-Won Kim, Eng H. Lo, and Ken Arai **jci.me/65863**

Diabetic brains develop coping mechanisms for hypoglycemic episodes

Patients with type 1 diabetes (T1DM) typically experience two to three hypoglycemic episodes per week. As T1DM is associated with increased risk of dementia and cognitive dysfunction, there is concern that hypoglycemic episodes could cause long-term damage to the brain. To determine the effects of hypoglycemia on brain glucose metabolism, Kim van de Ven and colleagues compared the effects of euglycemic and hypoglycemic conditions in patients with uncomplicated T1DM. Patients were infused with [1-^{13}C]glucose, and in vivo brain ^{13}C magnetic resonance spectroscopy was used to measure the time course of ^{13}C-label incorporation into different metabolites. Hypoglycemia did not significantly alter cerebral glucose metabolism in patients with T1DM compared with previous measurements of cerebral glucose metabolism in nondiabetic subjects. These findings indicate that the brains of patients with T1DM are resistant to moderate hypoglycemia.

Patients with type 1 diabetes exhibit altered cerebral metabolism during hypoglycemia
Kim C.C. van de Ven, Cees J. Tack, Arend Heerschap, Marinette van der Graaf, and Bastiaan E. de Galan **jci.me/62742**

CONVERSATIONS WITH GIANTS IN MEDICINE

Jeffrey Friedman

Jeffrey Friedman has made seminal contributions to our understanding of the molecular pathogenesis of obesity and the biological cues that compel us to eat and overeat. Among his most notable accomplishments is the cloning of the *ob* gene, which encodes the hormone leptin and helps the body to maintain appropriate fat mass. In this interview with *JCI* Editor at Large Ushma Neill, Friedman discusses his career path, the events leading to that discovery, and offers his perspective on how to best confront the growing prevalence of obesity.

jci.me/68394

HINDSIGHT

A key role for NO in endothelial function

The endothelium is the primary regulator of vascular homeostasis, mediating blood vessel tone, hemostasis, neutrophil recruitment, hormone trafficking, and fluid filtration. Many of these functions are regulated by NO, an endogenous, antiinflammatory vasodilator. In 1995, James Liao and colleagues demonstrated that NO inhibits NF-κB to prevent endothelial cell activation and immune cell recruitment. These findings helped identify the molecular mechanisms that underlie the vascular protective properties of NO. Since the publication of this study, a number of physiological conditions, such as laminar flow and pharmacological agents, including estrogen, statins, and ACE inhibitors, have been shown to enhance endothelium-derived NO and combat diseases associated with endothelial dysfunction.

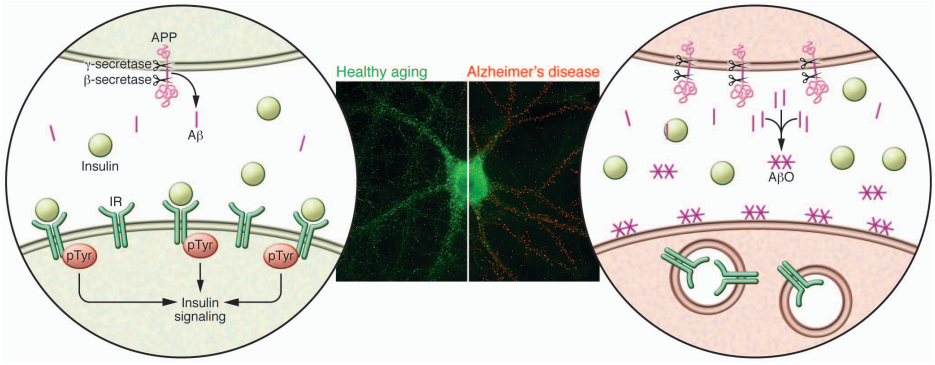
Linking endothelial dysfunction with endothelial cell activation

James K. Liao **jci.me/66843**

SCIENCE IN MEDICINE

Linking Alzheimer's disease and diabetes

Alzheimer's disease (AD) is a progressive brain disorder that is the most common cause of dementia. Studies in the last decade suggest an intriguing connection between AD and diabetes. Indeed, insulin resistance, a hallmark of type 2 diabetes, has also been observed in brain tissue from Alzheimer's patients. Fernanda De Felice reviews the mechanisms underlying defective brain insulin signaling in AD and highlights evidence that AD and diabetes share common inflammatory signaling pathways. Further, De Felice explores how cross-talk between peripheral tissues and the brain might influence AD development, and discusses preclinical findings supporting the use of antidiabetic agents as possible AD therapeutics. The accompanying image illustrates how A□ oligomers, which accumulate in AD, are associated with reduced insulin receptor levels on neuronal membranes.



Alzheimer's disease and insulin resistance: translating basic science into clinical applications

Fernanda G. De Felice **jci.me/64595**

Journal of Clinical Investigation Consulting Editors