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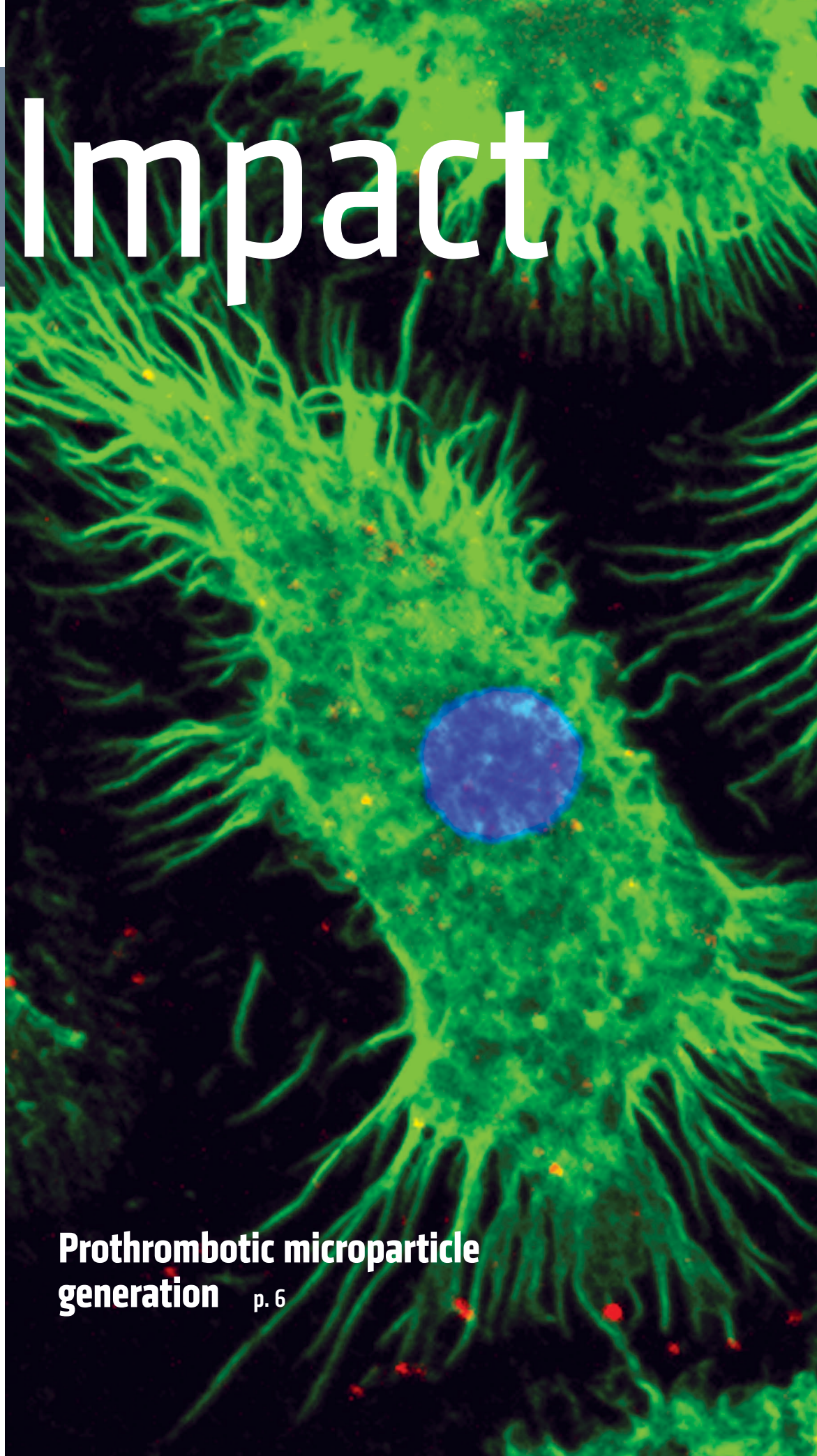
A summary of this month's **Journal of Clinical Investigation**



Prothrombotic microparticle generation p. 6

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APRIL 2015

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JCI Impact

April 2015

Featured Editor

The JCI's Editorial Board is composed of peer scientists at Duke University Medical Center, the University of North Carolina, Duke-NUS, and the Sanford-Burnham Medical Research Institute. Editorial Board members review and oversee peer review of each manuscript that is submitted to the JCI, and the board meets weekly to discuss the manuscripts undergoing review.

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Vann Bennett, M.D., Ph.D., Associate Editor, is a Howard Hughes Investigator and George Barth Geller Professor of Biochemistry at Duke University Medical Center. Dr. Bennett discovered adducins as well as the ankyrin family of adaptor proteins, which connect diverse integral membrne proteins to the spectrin-based membrane skeleton. His research deals with the molecular basis for functional organization of plasma membrane domains, with a focus on axon initial segments and epithelial lateral membranes, as well as the roles of ankyrin-B in metabolism. Dr. Bennett is a member of the American Society for Clinical Investigation, the American Academy of Arts and Sciences, the National Academy of Sciences, and the Association of American Physicians.

Publication highlights

Bennett V, Stenbuck PJ. Identification and partial purification of ankyrin, the high affinity membrane attachment site for human erythrocyte spectrin. *J Biol Chem*. 1979;254(7):2533–2541.

Lorenzo DN, Badea A, Davis J, Hostettler J, He J, Zhong G, Zhuang X, Bennett V. A PIK3C3-ankyrin-B-dynactin pathway promotes axonal growth and multiorganelle transport. *J Cell Biol*. 2014;207(6):735–752.

Jenkins PM, Kim N, Jones SL, Tseng WC, Svitkina TM, Yin HH, Bennett V. Giant ankyrin-G: a critical innovation in vertebrate evolution of fast and integrated neuronal signaling. *Proc Natl Acad Sci U S A*. 2015;112(4):957–964.

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E-mail: staff@the-jci.org

Research articles in the current issue of the JCI

Bone biology

MicroRNA-188 regulates age-related switch between osteoblast and adipocyte differentiation

Chang-Jun Li, Peng Cheng, Meng-Ke Liang, Yu-Si Chen, Qiong Lu, Jin-Yu Wang, Zhu-Ying Xia, Hou-De Zhou, Xu Cao, Hui Xie, Er-Yuan Liao, and Xiang-Hang Luo **http://jci.me/77716**

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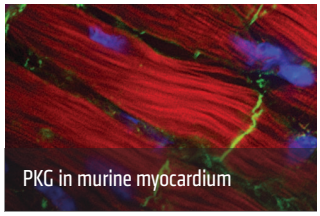

PKG in murine myocardium

Cardiology

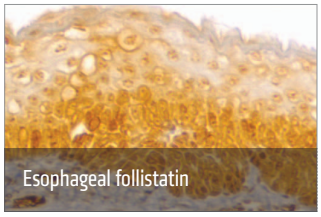
Normalization of Naxos plakoglobin levels restores cardiac function in mice

Zhiwei Zhang, Matthew J. Stroud, Jianlin Zhang, Xi Fang, Kunfu Ouyang, Kensuke Kimura, Yongxin Mu, Nancy D. Dalton, Yusu Gu, William H. Bradford, Kirk L. Peterson, Hongqiang Cheng, Xinmin Zhou, and Ju Chen **http://jci.me/80335**

Endocrinology

STAT3 upregulation in pituitary somatotroph adenomas induces growth hormone hypersecretion

Cuiqi Zhou, Yonghui Jiao, Renzhi Wang, Song-Guang Ren, Kolja Wawrowsky, and Shlomo Melmed **http://jci.me/78173**


Esophageal follistatin

Gastroenterology

BMP-driven NRF2 activation in esophageal basal cell differentiation and eosinophilic esophagitis

Ming Jiang, Wei-Yao Ku, Zhongren Zhou, Evan S. Dellon, Gary W. Falk, Hiroshi Nakagawa, Mei-Lun Wang, Kuancan Liu, Jun Wang, David A. Katzka, Jeffrey H. Peters, Xiaopeng Lan, and Jianwen Que **http://jci.me/78850**

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Genetics

Frequent somatic reversion of *KRT1* mutations in ichthyosis with confetti

Keith A. Choate, Yin Lu, Jing Zhou, Peter M. Elias, Samir Zaidi, Amy S. Paller, Anita Farhi, Carol Nelson-Williams, Debra Crumrine, Leonard M. Milstone, and Richard P. Lifton **http://jci.me/64415**

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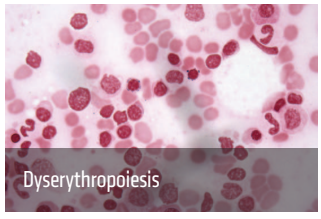
Dyserythropoiesis

Hematology

X-linked macrocytic dyserythropoietic anemia in females with an *ALAS2* mutation

Vijay G. Sankaran, Jacob C. Ulirsch, Vassili Tchaikovskii, Leif S. Ludwig, Aoi Wakabayashi, Senkottuvelan Kadirvel, R. Coleman Lindsley, Rafael Bejar, Jiahai Shi, Scott B. Lovitch, David F. Bishop, and David P. Steensma **http://jci.me/78619**

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Caspase-1–mediated pathway promotes generation of thromboinflammatory microparticles

Andrea S. Rothmeier, Patrizia Marchese, Brian G. Petrich, Christian Furlan-Freguia, Mark H. Ginsberg, Zaverio M. Ruggeri, and Wolfram Ruf **http://jci.me/79329**

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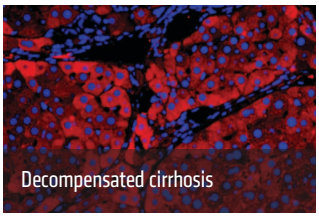
RASA3 is a critical inhibitor of RAP1-dependent platelet activation

Lucia Stefanini, David S. Paul, Raymond F. Robledo, E. Ricky Chan, Todd M. Getz, Robert A. Campbell, Daniel O. Kechele, Caterina Casari, Raymond Piatt, Kathleen M. Caron, Nigel Mackman, Andrew S. Weyrich, Matthew C. Parrott, Yacine Boulaftali, Mark D. Adams, Luanne L. Peters, and Wolfgang Bergmeier **http://jci.me/77993**



Decompensated cirrhosis

Hepatology

Resetting the transcription factor network reverses terminal chronic hepatic failure

Taichiro Nishikawa, Aaron Bell, Jenna M. Brooks, Kentaro Setoyama, Marta Melis, Bing Han, Ken Fukumitsu, Kan Handa, Jianmin Tian, Klaus H. Kaestner, Yoram Vodovotz, Joseph Locker, Alejandro Soto-Gutierrez, and Ira J. Fox **http://jci.me/73137**

Immunology

Cherubism allele heterozygosity amplifies microbe-induced inflammatory responses in murine macrophages

Virginie Prod'Homme, Laurent Boyer, Nicholas Dubois, Aude Mallavialle, Patrick Munro, Xavier Mouska, Isabelle Coste, Robert Rottapel, Sophie Tartare-Deckert, and Marcel Deckert **http://jci.me/71081**

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Mucosal-associated invariant T cell alterations in obese and type 2 diabetic patients

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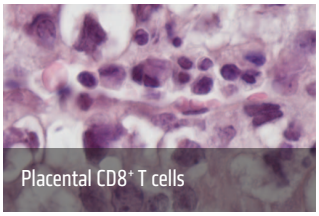

Placental CD8$^+$ T cells

CXCR3 blockade protects against *Listeria monocytogenes* infection–induced fetal wastage

Vandana Chaturvedi, James M. Ertelt, Tony T. Jiang, Jeremy M. Kinder, Lijun Xin, Kathryn J. Owens, Helen N. Jones, and Sing Sing Way **http://jci.me/78578**

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NOTCH reprograms mitochondrial metabolism for proinflammatory macrophage activation

Jun Xu, Feng Chi, Tongsheng Guo, Vasu Punj, W.N. Paul Lee, Samuel W. French, and Hidekazu Tsukamoto **http://jci.me/76468**

Infectious disease

Palivizumab epitope–displaying virus-like particles protect rodents from RSV challenge

Jeanne H. Schickli, David C. Whitacre, Roderick S. Tang, Jasmine Kaur, Heather Lawlor, Cory J. Peters, Joyce E. Jones, Darrell L. Peterson, Michael P. McCarthy, Gary Van Nest, and David R. Milich **http://jci.me/78450**

Human prion protein sequence elements impede cross-species chronic wasting disease transmission

Timothy D. Kurt, Lin Jiang, Natalia Fernández-Borges, Cyrus Bett, Jun Liu, Tom Yang, Terry R. Spraker, Joaquín Castilla, David Eisenberg, Qingzhong Kong, and Christina J. Sigurdson **http://jci.me/79408**

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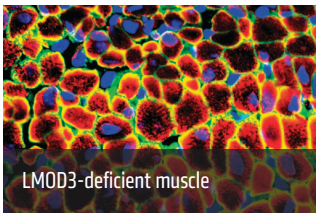
Identification and validation of N-acetyltransferase 2 as an insulin sensitivity gene

Joshua W. Knowles, Weijia Xie, Zhongyang Zhang, Indumathi Chennemsetty, Themistocles L. Assimes, Jussi Paananen, Ola Hansson, James Pankow, Mark O. Goodarzi, Ivan Carcamo-Orive, Andrew P. Morris, Yii-Der I. Chen, Ville-Petteri Mäkinen, Andrea Ganna, Anubha Mahajan, Xiuqing Guo, Fahim Abbasi, Danielle M. Greenawalt, Pek Lum, Cliona Molony, Lars Lind, Cecilia Lindgren, Leslie J. Raffel, Philip S. Tsao, The RISC Consortium, The EUGENE2 Study, The GUARDIAN Consortium, The SAPPHIRe Study, Eric E. Schadt, Jerome I. Rotter, Alan Sinaiko, Gerald Reaven, Xia Yang, Chao A. Hsiung, Leif Groop, Heather J. Cordell, Markku Laakso, Ke Hao, Erik Ingelsson, Timothy M. Frayling, Michael N. Weedon, Mark Walker, and Thomas Quertermous **http://jci.me/74692**


LMOD3-deficient muscle

Muscle biology

Severe myopathy in mice lacking the MEF2/SRF-dependent gene leiomodin-3

Bercin K. Cenik, Ankit Garg, John R. McAnally, John M. Shelton, James A. Richardson, Rhonda Bassel-Duby, Eric N. Olson, and Ning Liu **http://jci.me/80115**

Nephrology

KIM-1–mediated phagocytosis reduces acute injury to the kidney

Li Yang, Craig R. Brooks, Sheng Xiao, Venkata Sabbisetti, Melissa Y. Yeung, Li-Li Hsiao, Takaharu Ichimura, Vijay Kuchroo, and Joseph V. Bonventre
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BAI1 regulates spatial learning and synaptic plasticity in the hippocampus

Dan Zhu, Chenchen Li, Andrew M. Swanson, Rosa M. Villalba, Jidong Guo, Zhaobin Zhang, Shannon Matheny, Tatsuro Murakami, Jason R. Stephenson, Sarah Daniel, Masaki Fukata, Randy A. Hall, Jeffrey J. Olson, Gretchen N. Neigh, Yoland Smith, Donald G. Rainnie, and Erwin G. Van Meir **http://jci.me/74603**

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Identification of a human synaptotagmin-1 mutation that perturbs synaptic vesicle cycling

Kate Baker, Sarah L. Gordon, Detelina Grozeva, Margriet van Kogelenberg, Nicola Y. Roberts, Michael Pike, Edward Blair, Matthew E. Hurles, W. Kling Chong, Torsten Baldeweg, Manju A. Kurian, Stewart G. Boyd, UK10K Consortium, Michael A. Cousin, and F. Lucy Raymond **http://jci.me/79765**

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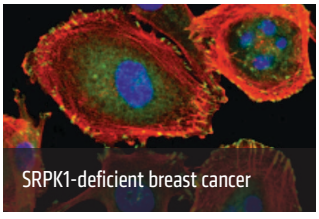
SRPK1-deficient breast cancer

Oncology

Tumor cell migration screen identifies SRPK1 as breast cancer metastasis determinant

Wies van Roosmalen, Sylvia E. Le Dévédec, Ofra Golani, Marcel Smid, Irina Pulyakhina, Annemieke M. Timmermans, Maxime P. Look, Di Zi, Chantal Pont, Marjo de Graauw, Suha Naffar-Abu-Amara, Catherine Kirsanova, Gabriella Rustici, Peter A.C. 't Hoen, John W.M. Martens, John A. Foekens, Benjamin Geiger, and Bob van de Water **http://jci.me/74440**

RNF4-mediated polyubiquitination regulates the Fanconi anemia/BRCA pathway

Jenny Xie, Hyungjin Kim, Lisa A. Moreau, Shannon Puhalla, Judy Garber, Muthana Al Abo, Shunichi Takeda, and Alan D. D'Andrea **http://jci.me/79325**

Casein kinase 1α–dependent feedback loop controls autophagy in RAS-driven cancers

Jit Kong Cheong, Fuquan Zhang, Pei Jou Chua, Boon Huat Bay, Andrew Thorburn, and David M. Virshup **http://jci.me/78018**

With related Commentary by Ravi K. Amaravadi

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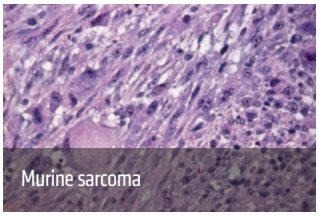
Murine sarcoma

A versatile modular vector system for rapid combinatorial mammalian genetics

Joachim Albers, Claudia Danzer, Markus Rechsteiner, Holger Lehmann, Laura P. Brandt, Tomas Hejhal, Antonella Catalano, Philipp Busenhart, Ana Filipa Gonçalves, Simone Brandt, Peter K. Bode, Beata Bode-Lesniewska, Peter J. Wild, and Ian J. Frew **http://jci.me/79743**

Co-clinical assessment identifies patterns of BRAF inhibitor resistance in melanoma

Lawrence N. Kwong, Genevieve M. Boland, Dennie T. Frederick, Timothy L. Helms, Ahmad T. Akid, John P. Miller, Shan Jiang, Zachary A. Cooper, Xingzhi Song, Sahil Seth, Jennifer Kamara, Alexei Protopopov, Gordon B. Mills, Keith T. Flaherty, Jennifer A. Wargo, and Lynda Chin **http://jci.me/78954**

Compensatory glutamine metabolism promotes glioblastoma resistance to mTOR inhibitor treatment

Kazuhiro Tanaka, Takashi Sasayama, Yasuhiro Irino, Kumi Takata, Hiroaki Nagashima, Naoko Satoh, Katsusuke Kyotani, Takashi Mizowaki, Taichiro Imahori, Yasuo Ejima, Kenta Masui, Beatrice Gini, Huijun Yang, Kohkichi Hosoda, Ryohei Sasaki, Paul S. Mischel, and Eiji Kohmura **http://jci.me/78239**

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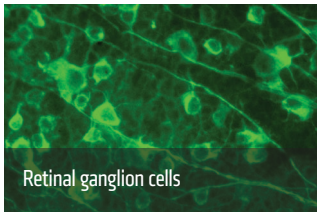
Retinal ganglion cells

Ophthalmology

NRF2 promotes neuronal survival in neurodegeneration and acute nerve damage

Wenjun Xiong, Alexandra E. MacColl Garfinkel, Yiqing Li, Larry I. Benowitz, and Constance L. Cepko **http://jci.me/79735**

Activated mTORC1 promotes long-term cone survival in retinitis pigmentosa mice

Aditya Venkatesh, Shan Ma, Yun Z. Le, Michael N. Hall, Markus A. Rüegg, and Claudio Punzo **http://jci.me/79766**

With related Commentary for Ophthalmology articles by Pavitra S. Ramachandran, Ji Yun Song, and Jean Bennett

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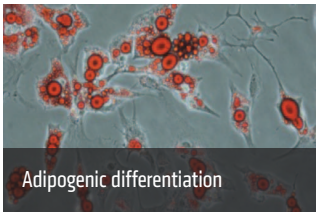
Reproductive biology

Progesterone and HMOX-1 promote fetal growth by $CD8^+$ T cell modulation

María Emilia Solano, Mirka Katharina Kowal, Greta Eugenia O'Rourke, Andrea Kristina Horst, Kathrin Modest, Torsten Plösch, Roja Barikbin, Chressen Catharina Remus, Robert G. Berger, Caitlin Jago, Hoang Ho, Gabriele Sass, Victoria J. Parker, John P. Lydon, Francesco J. DeMayo, Kurt Hecher, Khalil Karimi, and Petra Clara Arck **http://jci.me/68140**


Adipogenic differentiation

Stem cells

S-nitrosoglutathione reductase–dependent PPARγ denitrosylation participates in MSC-derived adipogenesis and osteogenesis

Yenong Cao, Samirah A. Gomes, Erika B. Rangel, Ellena C. Paulino, Tatiana L. Fonseca, Jinliang Li, Marilia B. Teixeira, Cecilia H. Gouveia, Antonio C. Bianco, Michael S. Kapiloff, Wayne Balkan, and Joshua M. Hare **http://jci.me/73780**

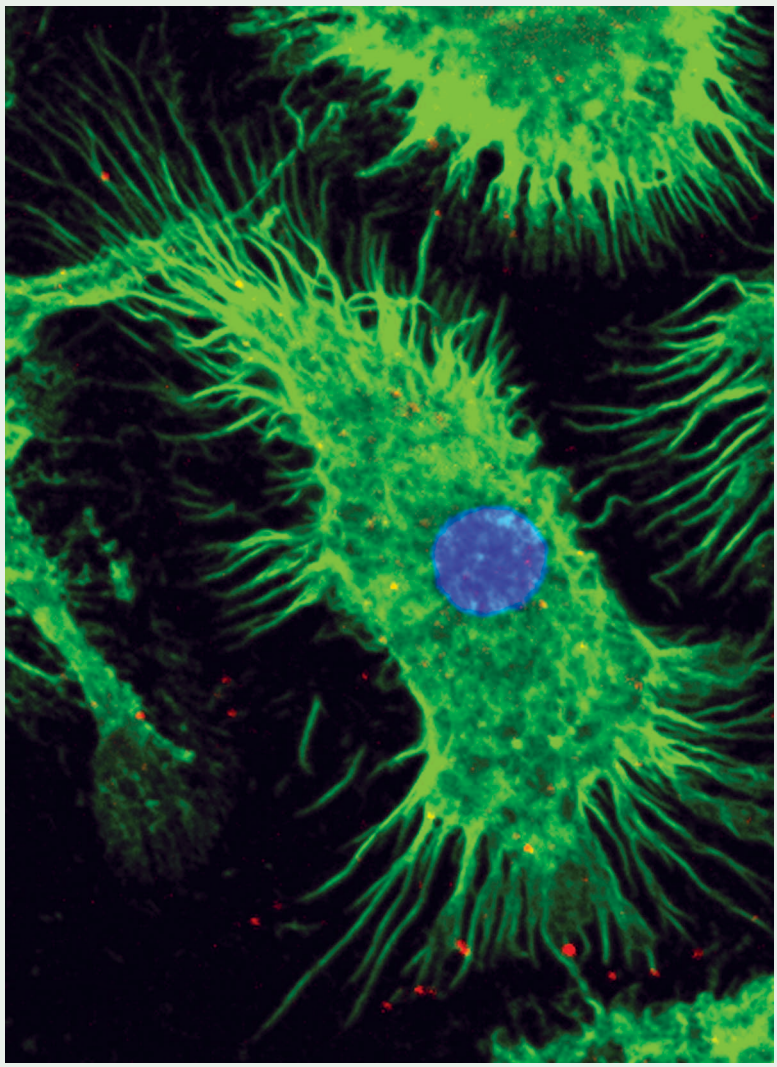
Vascular biology

Maternal anti-platelet β3 integrins impair angiogenesis and cause intracranial hemorrhage

Issaka Yougbaré, Sean Lang, Hong Yang, Pingguo Chen, Xu Zhao, Wei-She Tai, Darko Zdravic, Brian Vadasz, Conglei Li, Siavash Piran, Alexandra Marshall, Guangheng Zhu, Heidi Tiller, Mette Kjaer Killie, Shelley Boyd, Howard Leong-Poi, Xiao-Yan Wen, Bjorn Skogen, S. Lee Adamson, John Freedman, and Heyu Ni **http://jci.me/77820**

Editor's picks

Shedding light on procoagulant microparticle formation and release



Acute thrombosis occurs when an atherosclerotic plaque ruptures and recruits platelets to the injury site, which further narrows blood flow through vessels. This complex process is mediated by crosstalk between inflammatory pathways and thrombus formation. Macrophages are activated by a damage signal, extracellular ATP, which binds to the P2X7 receptor (P2RX7) and promotes the generation of procoagulant microparticles containing tissue factor (TF). In this month's issue of the *JCI*, Andrea Rothmeier et al. provide new insights into the processes underlying microparticle generation and identify a critical role for activated caspase-1 downstream of P2RX7. They show that activation of macrophage P2RX7 triggered extracellular release of thioredoxin (TRX), a component of the TRX/TRX reductase (TRXR) system that controls the redox state of many proteins. The intracellular depletion of TRX caused actin remodeling and induced the formation of filopodia, one of the initial steps in generating microparticles. Inhibiting TRXR prevented the incorporation of TF into filopodia and blocked the release of procoagulant microparticles. The research team subsequently found that uncoupling TRX and TRXR triggered inflammasome formation and activation of caspase-1. In turn, active caspase-1 promoted the activity of calpain protease, which released TF from the cytoskeleton and allowed its trafficking to filopodia, and facilitated microparticle release. Taken together, the findings in this work uncover a caspase-1–dependent pathway that drives the formation of procoagulant microparticles in macrophages. The accompanying image shows inflammasome-dependent translocation of TF (red) onto filopodia (actin, green) following stimulation of PR2X7 in macrophages (nuclei, blue).

Caspase-1–mediated pathway promotes generation of thromboinflammatory microparticles

Andrea S. Rothmeier, Patrizia Marchese, Brian G. Petrich, Christian Furlan-Freguia, Mark H. Ginsberg, Zaverio M. Ruggeri, and Wolfram Ruf **http://jci.me/79329**

NEUROSCIENCE

Synaptotagmin-1 mutation identified in a child with a severe neurodevelopmental disorder

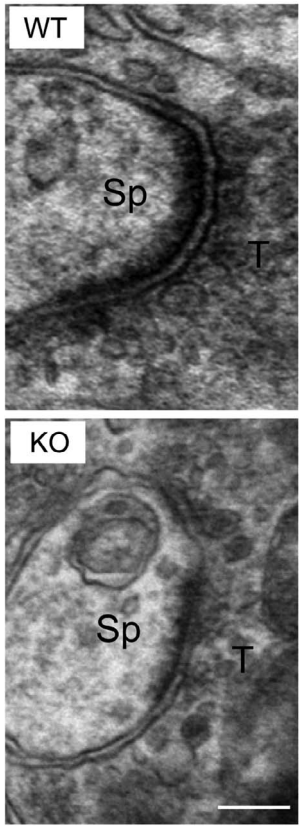
Synaptotagmin-1 (SYT1) is a calcium-sensitive protein that couples neuronal activity to fast synchronous vesicle release and reuptake in the central nervous system. Kate Baker and colleagues describe a neurological disorder associated with a mutation in *SYT1*. The patient exhibited dyskinetic movement disorder, with onset in early childhood, severe motor delay, and profound cognitive impairment. MRI revealed normal brain structure, but EEGs showed extensive neurophysiological disturbances. Whole-exome sequencing identified a rare de novo missense variant in *SYT1* (I368T), altering a residue known to be essential for evoked vesicle fusion and locomotion in *Drosophila*. To investigate the functional consequences of the variant in mammalian cells, rat SYT1^{I368T} was expressed in murine primary hippocampal neurons. The mutant SYT1 altered the kinetics of synaptic vesicle fusion and recycling. This case highlights critical presynaptic mechanisms controlling neurotransmission that could underlie other severe neurodevelopmental disorders.

Identification of human synaptotagmin-1 mutation that perturbs synaptic vesicle cycling

Kate Baker, Sarah L. Gordon, Detelina Grozeva, Margriet van Kogelenberg, Nicola Y. Roberts, Michael Pike, Edward Blair, Matthew E. Hurles, W. Kling Chong, Torsten Baldeweg, Manju A. Kurian, Stewart G. Boyd, UK10K Consortium, Michael A. Cousin, and F. Lucy Raymond **http://jci.me/79765**

Loss of brain-specific angiogenesis inhibitor 1 impairs hippocampal synaptic plasticity

Synaptic plasticity, or the ability of synapses to strengthen or weaken connections, is thought to underlie learning and memory. In this issue, Dan Zhu and colleagues demonstrate that loss of brain-specific angiogenesis inhibitor 1 (BAI1) in mice causes severe deficits in hippocampus-dependent spatial learning and memory that are accompanied by electrophysiological changes and thinning of the hippocampal postsynaptic densities (see the accompanying image). Mechanistically, BAI1 prevents polyubiquitination and degradation of the canonical postsynaptic density component PSD-95 by binding to the E3 ubiquitin ligase murine double minute 2 (MDM2). Restoration of PSD-95 expression in the hippocampal neurons of *Bai1*-KO mice ameliorated synaptic plasticity deficits.



BAI1 regulates spatial learning and synaptic plasticity in the hippocampus

Dan Zhu, Chenchen Li, Andrew M. Swanson, Rosa M. Villalba, Jidong Guo, Zhaobin Zhang, Shannon Matheny, Tatsuro Murakami, Jason R. Stephenson, Sarah Daniel, Masaki Fukata, Randy A. Hall, Jeffrey J. Olson, Gretchen N. Neigh, Yoland Smith, Donald G. Rainnie, and Erwin G. Van Meir **http://jci.me/74603**

HEMATOLOGY

ALAS2 mutation causes X-linked macrocytic dyserythropoietic anemia

Macrocytic anemia with abnormal erythropoiesis is characteristic of a variety of hematopoietic disorders. Vijay Sankaran and colleagues describe a family with multiple female members with macrocytic anemia. Whole-exome sequencing of the three affected family members and one unaffected member identified a mutation in one allele of the X-chromosomal gene aminolevulinic acid synthase (*ALAS2*), an erythroid-specific mitochondrial enzyme that is required for heme biosynthesis. Enzyme kinetic analysis of WT and mutant ALAS2 showed that the mutation impairs binding of an essential cofactor, resulting in a loss of function. Surprisingly, the severity of the anemia phenotype was not associated with severe skewing of X inactivation toward the mutant allele. Instead, cells expressing the mutant allele exhibited an early block in erythropoiesis, leading to perturbed erythropoiesis in cells expressing the normal allele.

X-linked macrocytic dyserythropoietic anemia in females with an *ALAS2* mutation

Vijay G. Sankaran, Jacob C. Ulirsch, Vassili Tchaikovskii, Leif S. Ludwig, Aoi Wakabayashi, Senkottuvelan Kadirvel, R. Coleman Lindsley, Rafael Bejar, Jiahai Shi, Scott B. Lovitch, David F. Bishop, and David P. Steensma
http://jci.me/78619

OPHTHALMOLOGY

Cone cell survival pathways in retinitis pigmentosa

Retinitis pigmentosa (RP) is an inherited degenerative eye disease characterized by the progressive loss of photoreceptor cells. In this issue, two groups of investigators, led by Constance Cepko and Claudio Punzo, exploited two different pathways to improve cone cell survival in murine models of RP. Dying cones exhibit increased oxidative stress. To counter this increase, Cepko and colleagues augmented cellular antioxidant defense mechanisms by administering adeno-associated virus (AAV) vectors encoding NRF2, a master transcription factor for antioxidant genes. Increased NRF2 expression prolonged cone survival in photoreceptor degeneration models and protected retinal ganglion cells in an optic nerve crush model. Dying cones in RP also exhibit signs of starvation. Punzo and colleagues show that activation of the metabolic regulator mTORC1 prolongs cone survival (see the accompanying image) and maintains cone function by improving glucose uptake and utilization, thereby elevating NADPH levels and preventing caspase 2–mediated cell death. In the accompanying Commentary, Jean Bennett and colleagues discuss how these pathways could be therapeutically targeted to treat multiple blinding disorders.

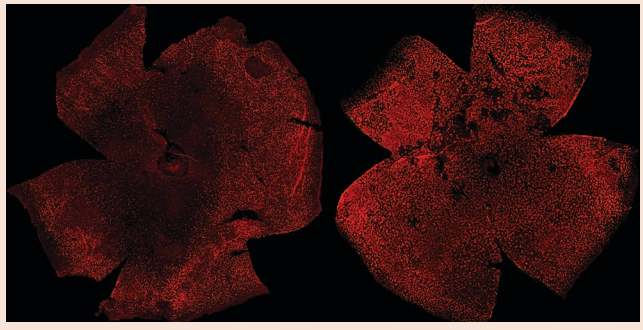
Related Research

NRF2 promotes neuronal survival in neurodegeneration and acute nerve damage
Wenjun Xiong, Alexandra E. MacColl Garfinkel, Yiqing Li, Larry I. Benowitz, and Constance L. Cepko **http://jci.me/79735**

Activated mTORC1 promotes long-term cone survival in retinitis pigmentosa mice
Aditya Venkatesh, Shan Ma, Yun Z. Le, Michael N. Hall, Markus A. Rüegg, and Claudio Punzo **http://jci.me/79766**

Related Commentary

Exploiting metabolic and antioxidant pathways to maintain vision in blinding disease
Pavitra S. Ramachandran, Ji Yun Song, and Jean Bennett
http://jci.me/80821



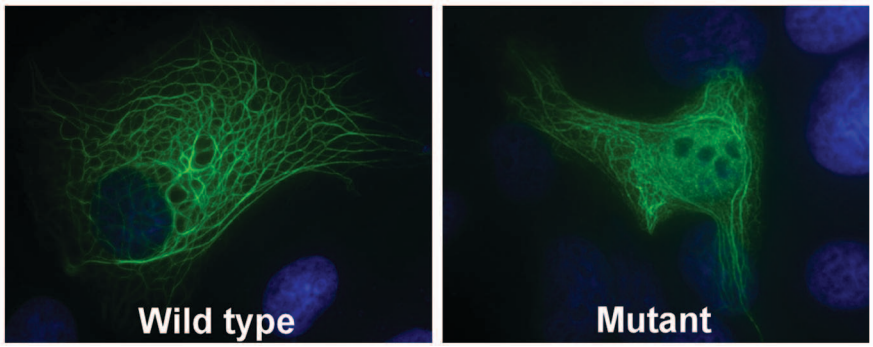
GENETICS

Keratin 1 frameshift mutation causes ichthyosis with confetti

Ichthyosis with confetti (IWC) is a rare autosomal dominant skin disorder caused by frameshift mutations in keratin 10 (*KRT10*) that result in dry, thickened, and scaly skin. Over time, small clonal patches of normal skin appear via revertant mosaicism. In this issue, Keith Choate and colleagues describe a new subtype of IWC in a cohort of patients that presented with red, scaly skin at birth and abnormal thickening of the palms and soles that worsened during childhood; these patients developed spots of normal skin starting in their twenties. The authors identified a frameshift mutation in *KRT1* that causes a partial collapse of the cytoplasmic intermediate filament network and mislocalizes KRT1 to the nucleus (see accompanying image). As with *KRT10* mutations, reversion occurred via mitotic recombination, and the authors propose that cytokeratin filament network dysfunction in mutant cells may contribute to cellular events resulting in genetic reversion.

Frequent somatic reversion of *KRT1* mutations in ichthyosis with confetti

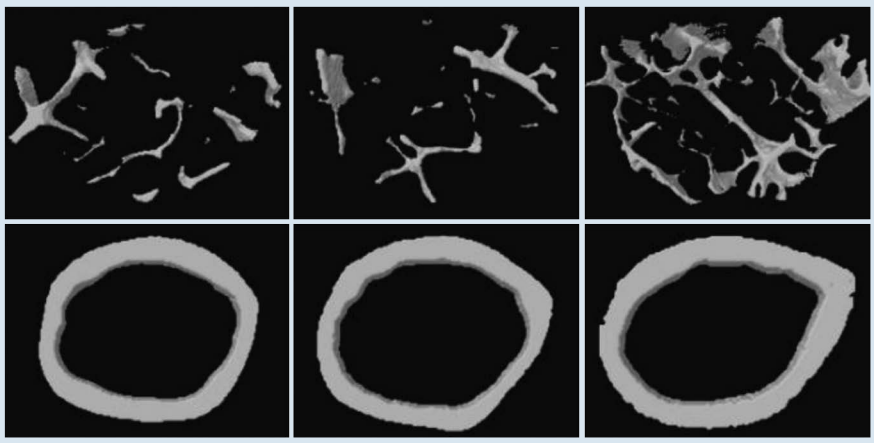
Keith A. Choate, Yin Lu, Jing Zhou, Peter M. Elias, Samir Zaidi, Amy S. Paller, Anita Farhi, Carol Nelson-Williams, Debra Crumrine, Leonard M. Milstone, and Richard P. Lifton **http://jci.me/64415**



BONE BIOLOGY

miR-188 controls the age-related switch between osteogenesis and adipogenesis

Bone marrow mesenchymal stem cells (BMSCs) can differentiate into either osteoblasts or adipocytes, and the proportion of BMSCs differentiating into adipocytes increases with age. Chang-Jun Li and colleagues demonstrate that miR-188 regulates the age-related switch that increases adipocyte differentiation. They found that levels of miR-188 in BMSCs increased with age in mice and humans. Mice lacking miR-188 exhibited marked decreases in age-associated bone loss and fat accumulation in bone marrow compared with control mice, while overexpression of miR-188 in osteoblast progenitors increased age-associated bone loss and bone marrow fat accumulation. Importantly, intra–bone marrow injection of a miR-188–targeted antagomiR reduced age-associated bone loss (see the accompanying image) and fat accumulation in the bone marrow, suggesting that miR-188 is a potential therapeutic target for the treatment of age-associated bone loss.



MicroRNA-188 regulates age-related switch between osteoblast and adipocyte differentiation

Chang-Jun Li, Peng Cheng, Meng-Ke Liang, Yu-Si Chen, Qiong Lu, Jin-Yu Wang, Zhu-Ying Xia, Hou-De Zhou, Xu Cao, Hui Xie, Er-Yuan Liao, and Xiang-Hang Luo **http://jci.me/77716**

IMMUNOLOGY

Mucosal invariant T cells play a role in obesity-associated inflammation

Obesity and type 2 diabetes (T2D) are associated with chronic low-grade inflammation and immune cell infiltration of adipose tissue. Mucosal-associated invariant T (MAIT) cells are innate-like T cells that recognize bacterial ligands and are enriched in mucosal and inflamed tissues. Isabelle Magalhaes, Karine Pingris, and colleagues found that the frequency of circulating MAIT cells was dramatically decreased in patients with T2D and/or severe obesity; however, MAIT cells were markedly enriched in adipose tissue. Both the circulating and adipose tissue–resident MAIT cells in these patients had an activated phenotype characterized by elevated cytokine production. Bariatric surgery–induced weight loss restored circulating MAIT cell frequency and reduced the production of inflammatory cytokines by these cells.

Mucosal-associated invariant T cell alterations in obese and type 2 diabetic patients

Isabelle Magalhaes, Karine Pingris, Christine Poitou, Stéphanie Bessoles, Nicolas Venteclef, Badr Kiaf, Lucie Beaudoin, Jennifer Da Silva, Omran Allatif, Jamie Rossjohn, Lars Kjer-Nielsen, James McCluskey, Séverine Ledoux, Laurent Genser, Adriana Torcivia, Claire Soudais, Olivier Lantz, Christian Boitard, Judith Aron-Wisnewsky, Etienne Larger, Karine Clément, and Agnès Lehuen

http://jci.me/78941

Enhanced inflammatory response to infection may underlie cherubism

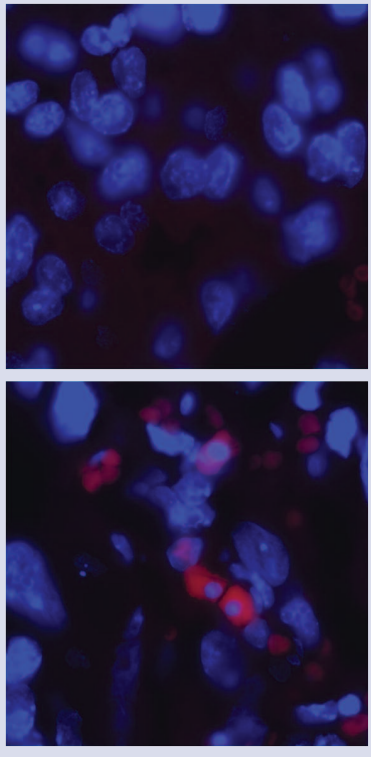
Cherubism is a rare autoinflammatory bone disorder characterized by bone loss and the accumulation of fibrous tissue in the mandible. In humans, the disease is caused by autosomal dominant point mutations in the gene encoding the adaptor protein 3BP2 (*SH3BP2*), which are thought to promote osteoclast activity and impair osteoblast differentiation. In mice, however, the trait is recessive, suggesting that additional factors contribute to pathogenesis. Virginie Prod'Homme and colleagues found that macrophages from *Sh3bp2*-deficient mice had markedly reduced antiinflammatory responses to microbial challenge and exhibited decreased phagocytosis and that 3BP2 was required for the activation of signaling components that mediate macrophage response to infection. Notably, the introduction of a single cherubism-associated *Sh3bp2* allele enhanced LPS-induced inflammation. These data indicate that infection may drive pathological events leading to cherubism.

Cherubism allele heterozygosity amplifies microbe-induced inflammatory responses in murine macrophages

Virginie Prod'Homme, Laurent Boyer, Nicholas Dubois, Aude Mallavialle, Patrick Munro, Xavier Mouska, Isabelle Coste, Robert Rottapel, Sophie Tartare-Deckert, and Marcel Deckert **http://jci.me/71081**

Chemokine dysregulation drives fetal wastage in prenatal infection

Maternal infection during pregnancy by prenatal pathogens such as *Listeria monocytogenes* causes fetal wastage and stillbirth. Recent studies have indicated that fetal wastage resulting from prenatal *L. monocytogenes* infection does not necessarily require in utero microbial invasion; rather, overriding immune tolerance to paternal-fetal antigens results in rejection of the fetus. In this issue, Vandana Chaturvedi and colleagues demonstrate that infection-induced dysregulation of decidual chemokine expression allows harmful IFN-γ–producing maternal T cells to infiltrate the maternal-fetal interface. *L. monocytogenes* infection in pregnant mice triggered placental recruitment of CXCL9-producing acute inflammatory cells that recruit maternal $CD8^+$ T cells with fetal specificity (see the accompanying image). Activated maternal T cells with fetal specificity upregulated expression of the chemokine receptor CXCR3. Notably, CXCR3 blockade protected against fetal wastage triggered by *L. monocytogenes* infection and noninfectious disruptions in fetal tolerance associated with pregnancy. These results indicate that chemokine neutralization strategies could protect against immune-mediated pregnancy complications.



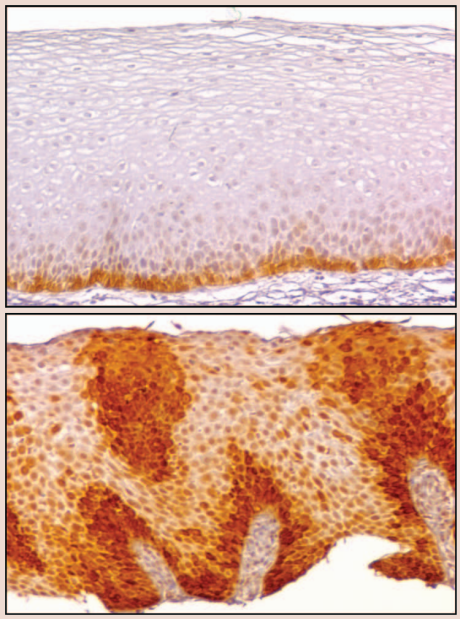
CXCR3 blockade protects against *Listeria monocytogenes* infection–induced fetal wastage

Vandana Chaturvedi, James M. Ertelt, Tony T. Jiang, Jeremy M. Kinder, Lijun Xin, Kathryn J. Owens, Helen N. Jones, and Sing Sing Way

http://jci.me/78578

GASTROENTEROLOGY

Impaired BMP signaling promotes basal progenitor hyperplasia in eosinophilic esophagitis



Eosinophilic esophagitis (EoE) is an allergic inflammatory condition in which basal progenitor cells in the lining of the esophagus become hyperplastic. Bone morphogenetic proteins (BMPs) were previously shown to be required for the differentiation of the stratified squamous epithelium that lines the esophagus. Using murine genetic models, Ming Jiang and colleagues demonstrate that BMP signaling is specifically activated in differentiated cells, but is absent in basal progenitor cells due to expression of the endogenous BMP antagonist follistatin. BMP signaling decreased proliferation and increased differentiation of basal progenitor cells in the esophagus through activation of the NRF2-mediated oxidative stress pathway. Importantly, reduced squamous differentiation in a mouse model of EoE and in biopsies from human EoE patients was associated with high levels of follistatin and decreased BMP signaling. The accompanying image shows follistatin expression in normal and EoE biopsies.

BMP-driven NRF2 activation in esophageal basal cell differentiation and eosinophilic esophagitis

Ming Jiang, Wei-Yao Ku, Zhongren Zhou, Evan S. Dellon, Gary W. Falk, Hiroshi Nakagawa, Mei-Lun Wang, Kuancan Liu, Jun Wang, David A. Katzka, Jeffrey H. Peters, Xiaopeng Lan, and Jianwen Que **http://jci.me/78850**

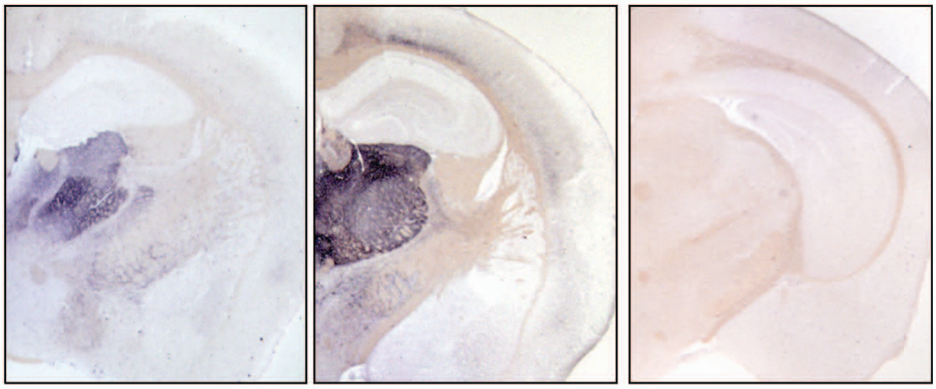
INFECTIOUS DISEASE

Sequence determinants of human susceptibility to chronic wasting disease prions

Chronic wasting disease (CWD) is a fatal prion disease that affects deer and elk. Mice expressing the human cellular prion protein appear to be resistant to CWD; however, some non-human primates are susceptible. To gain a better understanding of cross-species transmission of CWD, Timothy Kurt and colleagues sought to define the prion protein (PrP) sequence determinants that influence propagation. They engineered transgenic mice expressing human PrP or human-elk chimeric PrP with four amino acid substitutions. While mice expressing human PrP were resistant to CWD, those expressing the chimeric form were highly susceptible to CWD infection but less susceptible to human Creutzfeldt-Jakob disease prions. These studies identify the critical structural determinants of prion transmission. The accompanying image shows CWD PrP infection in mice expressing elk or deer chimeric PrP (left and middle) and human PrP (right).

Human prion protein sequence elements impede cross-species chronic wasting disease transmission

Timothy D. Kurt, Lin Jiang, Natalia Fernández-Borges, Cyrus Bett, Jun Liu, Tom Yang, Terry R. Spraker, Joaquín Castilla, David Eisenberg, Qingzhong Kong, and Christina J. Sigurdson **http://jci.me/79408**



ONCOLOGY

Glutamine metabolism compensates for mTOR inhibition in glioblastoma multiforme

The protein kinase mTOR integrates oncogenic and growth factor signaling to stimulate glycolytic metabolism and cell survival. Kazuhiro Tanaka and colleagues investigated metabolic reprogramming driven by mTOR inhibition in experimental models and clinical samples of glioblastoma multiforme (GBM). They found that glutaminase and glutamate levels are elevated in GBM patient tumors and are also increased following mTOR inhibition in GBM cell lines and xenografts. This compensatory elevation allows GBM cells to survive mTOR inhibitor treatment by using glutamine metabolism to produce α-ketoglutarate and stimulate the tricarboxylic acid cycle. Importantly, glutaminase inhibition sensitizes GBM cells to mTOR inhibitors. Combined inhibition of mTOR and glutaminase resulted in synergistic tumor growth restriction in a GBM xenograft model.

Compensatory glutamine metabolism promotes glioblastoma resistance to mTOR inhibitor treatment

Kazuhiro Tanaka, Takashi Sasayama, Yasuhiro Irino, Kumi Takata, Hiroaki Nagashima, Naoko Satoh, Katsusuke Kyotani, Takashi Mizowaki, Taichiro Imahori, Yasuo Ejima, Kenta Masui, Beatrice Gini, Huijun Yang, Kohkichi Hosoda, Ryohei Sasaki, Paul S. Mischel, and Eiji Kohmura

http://jci.me/78239

CK1α-mediated feedback loop attenuates oncogenic RAS–driven autophagy

Oncogenic RAS mutations can enhance basal autophagic flux, allowing cancer cells to cope with the stresses of rapid growth. Jit Kong Cheong, Fuquan Zhang, and colleagues identified the serine/threonine kinase casein kinase 1α (CK1α) as a key negative regulator of oncogenic RAS–induced autophagy. Cheong, Zhang, and colleagues demonstrate that the RAS/PI3K/AKT/mTOR signaling axis upregulates expression of CK1α, which phosphorylates the transcription factor FOXO3A to decrease its nuclear abundance and abrogate FOXO3A-mediated transactivation of autophagy-related genes. Depletion or pharmacologic inhibition of CK1α enhanced autophagic flux in RAS-driven cancer cells and sensitized them to a clinically approved autophagy inhibitor. The combination of CK1α and autophagy inhibition resulted in the accumulation of ineffective autophagic vesicles and subsequent cell death, thereby attenuating growth of RAS-driven tumor xenografts (see the accompanying image). In the accompanying Commentary, Ravi Amaravadi discusses how these results indicate that CK1α may be a suitable therapeutic target for the treatment of oncogenic RAS–driven cancers.

Casein kinase 1α–dependent feedback loop controls autophagy in RAS-driven cancers

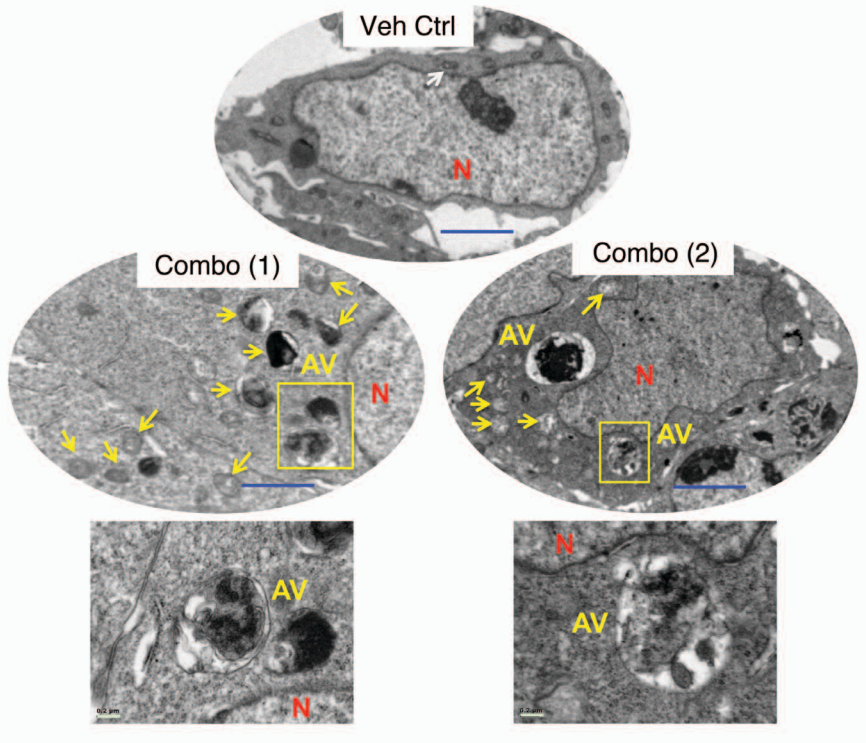
Jit Kong Cheong, Fuquan Zhang, Pei Jou Chua, Boon Huat Bay, Andrew Thorburn, and David M. Virshup

http://jci.me/78018

▶ Related Commentary

Transcriptional regulation of autophagy in RAS-driven cancers

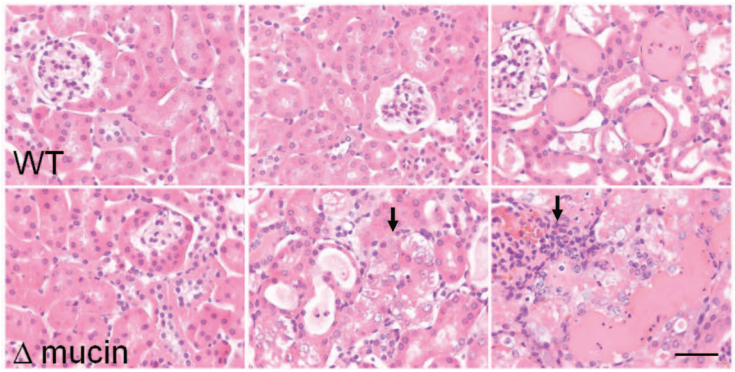
Ravi K. Amaravadi http://jci.me/81504



NEPHROLOGY

A protective role for KIM-1 in acute kidney injury

Kidney injury molecule 1 (KIM-1), a transmembrane protein with immunoglobulin and mucin domains, is markedly upregulated in the proximal tubule after kidney injury. While chronic overexpression of KIM-1 is deleterious, a study by Li Yang, Craig Brooks, and colleagues reveals that the mucin domain of KIM-1 protects the kidney after acute injury. Mice expressing a mucin domain–deficient form of KIM-1 (KIM-1Δmucin) were more susceptible to acute kidney injury (see the accompanying image). Loss of the mucin domain disrupted KIM-1–mediated phagocytosis in proximal tubular cells, which reduced clearance of apoptotic and necrotic cells and luminal debris after injury, thereby increasing immune infiltration and inflammation. Moreover, KIM-1–mediated phagocytosis in proximal tubular cells triggered PI3K-dependent downregulation of NF-κB activity, resulting in an antiinflammatory phenotype that was characterized by decreased expression of TLR4 and proinflammatory cytokines and reduced macrophage activation. Taken together, these data establish a protective role for KIM-1 after acute kidney injury.



KIM-1–mediated phagocytosis reduces acute injury to the kidney
Li Yang, Craig R. Brooks, Sheng Xiao, Venkata Sabbisetti, Melissa Y. Yeung, Li-Li Hsiao, Takaharu Ichimura, Vijay Kuchroo, and Joseph V. Bonventre
http://jci.me/75417

CONVERSATIONS WITH GIANTS IN MEDICINE

Bill Paul

William Paul, M.D., is the NIH Distinguished Investigator and Chief of the Laboratory of Immunology within the National Institute of Allergy and Infectious Diseases (NIAID). Paul discovered and characterized the cell signaling cytokine IL-4, demonstrating that IL-4 is required for B cell production of IgE, and determined the requirements for $CD4^+$ T cell differentiation. In an interview with *JCI* Editor-at-Large Ushma Neill, Paul discusses his early research experiences, as well as the influence of Michael Heidelberger on his decision to study immunology. Paul began his training in immunology in Nobel laureate Baruj Benacerraf's lab at New York University and then moved with Bennacerraf to the NIH in 1968, where he began to focus on T and B cell biology. His lab has served as a training ground for many noted immunologists, including Laurie Glimcher, Mark Davis, and Charlie Janeway.

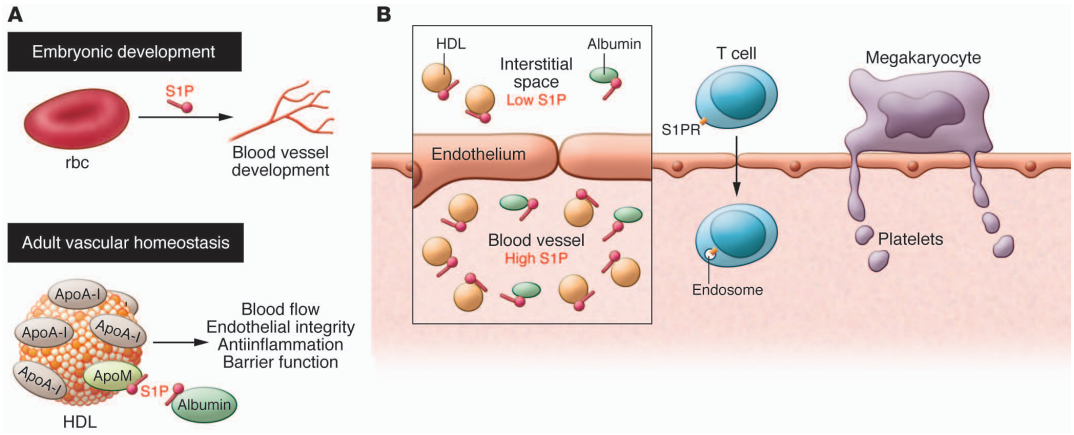
http://jci.me/81730

REVIEWS

Sphingosine-1-phosphate: an emerging target in human disease

Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid that interacts with five GPCRs in order to mediate diverse effects on cellular behavior, including migration, adhesion survival, and proliferation. In this issue, Richard Proia and Timothy Hla review the metabolism, transport, and signaling functions of S1P in vascular development (see the accompanying image), neurogenesis, and lymphocyte trafficking. Additionally, they discuss the pharmacological tools and murine models that are being used to identify roles for S1P in pathogenesis. S1P signaling has been implicated in multiple sclerosis, Sjögren-Larsson syndrome, influenza, acute lung injury, sickle cell disease, cancer, inflammatory bowel disease, and cardiovascular disease. Fingolimod (FTY720), a sphingosine analog that modulates $S1P_1$ receptor activity, has been approved for treatment of multiple sclerosis, and other regulators of S1P signaling are also potential therapeutic targets.

Emerging biology of sphingosine-1-phosphate: its role in pathogenesis and therapy
Richard L. Proia and Timothy Hla **http://jci.me/76369**



Guarding the brain in multiple sclerosis

Multiple sclerosis (MS) is characterized by inflammatory attacks on the CNS, followed by periods of recovery and repair. In this issue, Lawrence Steinman reviews the molecular mechanisms that mediate CNS recovery after inflammation. These guardian molecules include cytokines, antioxidants, neurotrophins, neurotransmitters, lipids, nuclear hormone receptors, serpins, and amyloid-forming molecules. Many of these molecules were identified by transcriptomic and proteomic analysis of MS lesions and are known to participate in a variety of physiological processes, suggesting that their roles in the pathophysiology of MS may be complex. For example, the presence of amyloid-forming molecules is generally considered to be detrimental; however, administration of αB crystallin in a murine model of MS actually attenuated inflammation. Further studies of the molecules present in MS lesions will reveal their role in the disease, potentially providing new therapeutic targets.

No quiet surrender: molecular guardians in multiple sclerosis brain
Lawrence Steinman **http://jci.me/74255**

HINDSIGHT

One receptor to bind them all

A prominent class of drug-drug interactions results from one drug accelerating the metabolism of another through activation of cytochrome P450 3A oxygenase (CYP3A). By the 1990s, multiple drugs had been shown to induce CYP3A; however, these drugs exhibited remarkable structural diversity and differentially upregulated CYP3A in murine and human cells, suggesting multiple receptors and complex regulation of CYP3A activation. In their 1998 *JCI* study, Steven Kliewer and colleagues reported on their cloning of the human ortholog of nuclear receptor PXR and demonstrated that PXR binds a response element in the *CYP3A4* promoter and is activated by a variety of CYP3A-inducing drugs. In this issue, Kliewer discusses how these findings introduced the concept that a nuclear receptor could act as a generalized xenobiotic sensor and provided a high-throughput method to identify CYP3A-inducing drugs.

Nuclear receptor PXR: discovery of a pharmaceutical anti-target
Steven A. Kliewer **http://jci.me/81244**