

JCI

This Month

July 2016

A summary of the most recent articles in
**The Journal of
Clinical Investigation**
and **JCI Insight**

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transplant rejection **2**

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signaling promotes
tumor formation **3**

sFLT1 levels predict
preeclampsia **4**

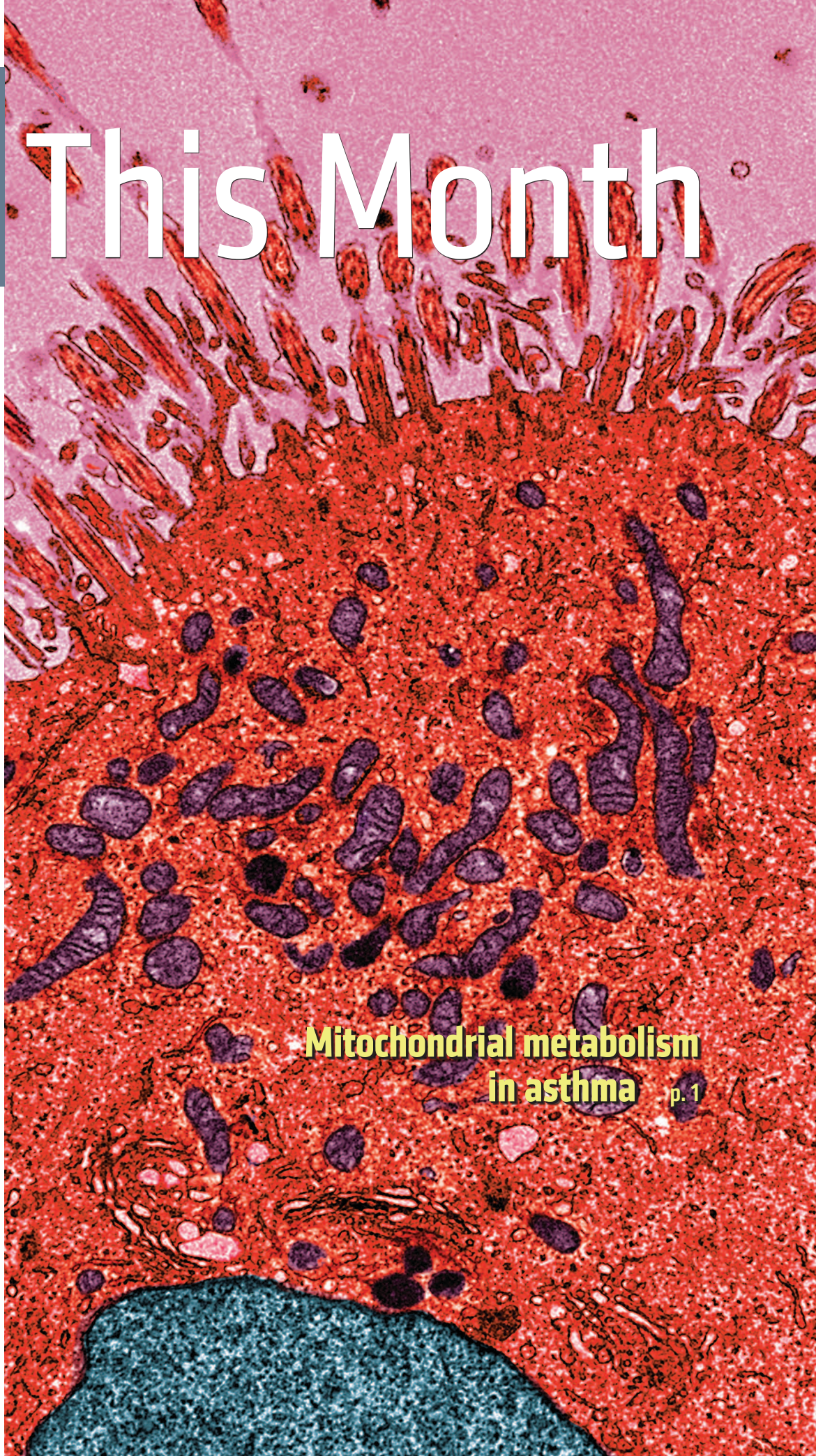
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**Mitochondrial metabolism
in asthma** p. 1



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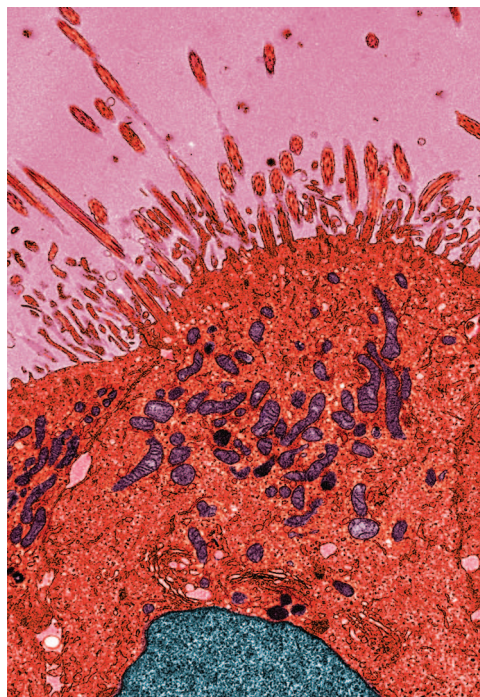
ISSN 2324-7703 (print)

ISSN 2325-4556 (online)

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ON THE JCI COVER

Mitochondrial arginine flux regulates inflammation in asthma



Asthma is a chronic inflammatory disorder characterized by airway constriction and excess mucus production. Asthmatics have increased levels of exhaled nitric oxide (NO) due to the conversion of arginine to NO and citrulline in airway epithelial cells during inflammation. In this month's issue of the *JCI*, a research team led by Serpil Erzurum examined whether changes in arginine metabolism, rather than the generation of NO per se, contribute to the pathophysiology of asthma. They report that arginase 2 (ARG2), a mitochondrial enzyme that catabolizes arginine, is higher in human asthmatic airway epithelium. Overexpression of ARG2 in bronchial epithelial

cells in vitro increased oxygen consumption rates and mitochondrial oxidative metabolism. Additionally, ARG2 overexpression resulted in decreased expression of STAT6, a signal transducer of pulmonary inflammatory responses. Mice lacking *Arg2* exhibited lower mitochondrial membrane potential and decreased reactive oxygen species production. Moreover, in an ovalbumin allergen model of asthma, *Arg2*^{-/-} mice had higher expression of the Th2 cytokine IL-13, greater levels of Th2 inflammation, and increased mucus production. Taken together, these findings reveal a protective role for arginine metabolism in maintaining airway epithelial cell bioenergetics and inhibiting inflammation. The accompanying image is a false-colored electron micrograph showing the ultrastructure of mitochondria in bronchial epithelium from an asthmatic.

Increased mitochondrial arginine metabolism supports bioenergetics in asthma

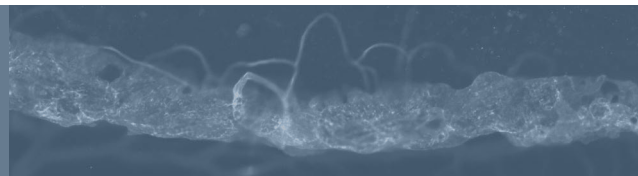
Weiling Xu, Sudakshina Ghosh, Suzy A.A. Comhair, Kewal Asosingh, Allison J. Janocha, Deloris A. Mavrikis, Carole D. Bennett, Lourdes L. Gruca, Brian B. Graham, Kimberly A. Queisser, Christina C. Kao, Samuel H. Wedes, John M. Petrich, Rubin M. Tuder, Satish C. Kalhan, and Serpil C. Erzurum <http://jci.me/82925>

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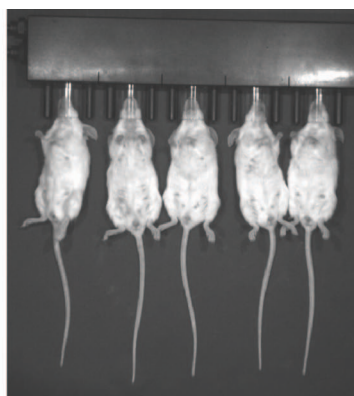
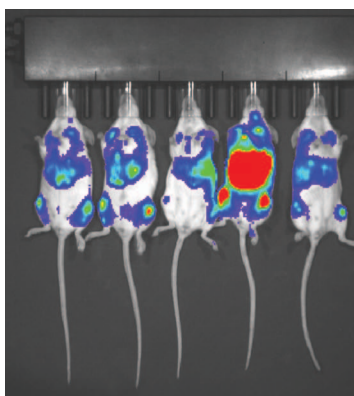
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TRANSPLANTATION

Programmed death ligand-1 mediates pathologic immune responses in graft-versus-host disease

Immunosuppressive therapies that inhibit T cells are used to prevent graft-versus-host disease (GVHD) in bone marrow transplantation recipients. Although expressing programmed death ligand-1 (PD-L1) on recipient tissues reduces the antihost immune response, PD-L1 may also act on donor T cells to alter immune responses in GVHD. Asim Saha and colleagues observed that PD-L1 expression is upregulated on donor T cells in patients with GVHD. In mice, PD-L1-deficient donor T cells had lower expression of gut homing receptors and inflammatory cytokines and less activity in bioenergetics pathways than wild-type donor T cells. PD-L1 deficiency was also associated with reduced recipient mortality in a mouse model of GVHD, without affecting graft-versus-leukemia responses (see the accompanying image). These findings suggest that PD-L1 modulates the donor T cell-associated immune response during GVHD, providing insights into the biological function of PD-L1 on activated T cells and potential preventive strategies for this life-threatening condition.



Programmed death ligand-1 expression on donor T cells drives graft-versus-host disease lethality

Asim Saha, Roddy S. O'Connor, Govindarajan Thangavelu, Scott B. Lovitch, Durga Bhavani Dandamudi, Caleph B. Wilson, Benjamin G. Vincent, Victor Tkachev, Jan M. Pawlicki, Scott N. Furlan, Leslie S. Kean, Kazutoshi Aoyama, Patricia A. Taylor, Angela Panoskaltsis-Mortari, Rocio Foncea, Parvathi Ranganathan, Steven M. Devine, Joel S. Burrill, Lili Guo, Catarina Sacristan, Nathaniel W. Snyder, Ian A. Blair, Michael C. Milone, Michael L. Dustin, James L. Riley, David A. Bernlohr, William J. Murphy, Brian T. Fife, David H. Munn, Jeffrey S. Miller, Jonathan S. Serody, Gordon J. Freeman, Arlene H. Sharpe, Laurence A. Turka, and Bruce R. Blazar
<http://jci.me/85796>

Prophylactic antibiotic treatment improves skin graft survival in mice

Although genetic mismatch between transplant donors and recipients is a major determinant of allograft rejection, transplant outcomes are also influenced by environmental factors. Organs that are considered sterile have better transplant outcomes than bacteria-colonized organs, suggesting that microbiota contribute to the immune response to allografts. Yuk Man Lei and colleagues determined that treating donor and recipient mice with broad-spectrum antibiotics prior to transplantation prolonged the survival of minor antigen-mismatched skin grafts relative to that in untreated mice. The prolonged graft survival correlated with reductions in alloreactive T cell priming. Allograft rejection was also delayed between germ-free donor and recipient mice, and colonization of germ-free recipients with fecal bacteria from normal mice, but not mice pretreated with antibiotics, accelerated graft rejection. The findings suggest that antibiotic treatment is a potential strategy for enhancing allograft acceptance. In the accompanying Commentary, Mandy Ford discusses evidence that the microbiome compositions of allograft donors and recipients contribute to transplant outcomes.

The composition of the microbiota modulates allograft rejection

Yuk Man Lei, Luqiu Chen, Ying Wang, Andrew T. Stefka, Luciana L. Molinero, Betty Theriault, Keston Aquino-Michaels, Ayelet S. Sivan, Cathryn R. Nagler, Thomas F. Gajewski, Anita S. Chong, Caroline Bartman, and Maria-Luisa Alegre
<http://jci.me/85295>

► Related Commentary

Micromanaging alloimmunity

Mandy L. Ford <http://jci.me/88621>

ONCOLOGY

The NOTCH transcriptional mediator RBPJ activates brain tumor growth

In the adult brain, formation of glioblastomas occurs as a result of aberrant activation of quiescent neural stem cells. A number of therapies for glioblastoma target NOTCH signaling because of its essential role in neural stem cell differentiation; however, NOTCH antagonists have demonstrated limited efficacy in clinical trials. Qi Xie and colleagues determined that direct targeting of RBPJ, a central transcription mediator of NOTCH activity, more effectively suppresses human brain tumor cell proliferation than NOTCH signaling inhibitors. In brain tumor cells, RBPJ was required for cell proliferation and regulated transcriptional programs that were distinct from NOTCH signaling. Activated RBPJ bound CDK9 to promote transcriptional elongation in these cells. In the accompanying Commentary, Xing Fan discusses how this study informs potential therapies that target RBPJ-mediated transcriptional regulators.

RBPJ maintains brain tumor-initiating cells through CDK9-mediated transcriptional elongation

Qi Xie, Qiulian Wu, Leo Kim, Tyler E. Miller, Brian B. Liao, Stephen C. Mack, Kailin Yang, Daniel C. Factor, Xiaoguang Fang, Zhi Huang, Wenchao Zhou, Kareem Alazem, Xiuxing Wang, Bradley E. Bernstein, Shideng Bao, and Jeremy N. Rich

<http://jci.me/86114>

► Related Commentary

γ -Secretase inhibitor-resistant glioblastoma stem cells require RBPJ to propagate

Xing Fan

<http://jci.me/88619>

Dickkopf1 promotes tumor growth through cytoskeleton-associated protein 4

Dickkopf1 (DKK-1) inhibits oncogenic Wnt/ β -catenin signaling, but in some cancers, it has been shown to increase tumorigenesis through a separate, unknown mechanism. Hirokazu Kimura and colleagues identified a pathway through which DKK-1 promotes rather than inhibits cellular proliferation. They found that DKK-1 stimulated cellular proliferation in canine epithelial cells by interacting with cytoskeleton-associated protein 4 (CKAP4) at a different DKK-1 domain than the Wnt/ β -catenin pathway. Cellular proliferation associated with DKK-1 secretion required CKAP4-mediated activation of the PI3K and AKT pathways. In human pancreatic and lung cancers, expression of both DKK-1 and CKAP4 was associated with poorer clinical outcomes than expression of either protein alone. Moreover, anti-CKAP4 antibodies suppressed xenograft tumor formation by human cancer cell lines (see the image). In the accompanying Commentary, Peter Klein and colleagues discuss the potential for targeting DKK-1/CKAP4 signaling as a therapy for certain cancers.

CKAP4 is a Dickkopf1 receptor and is involved in tumor progression

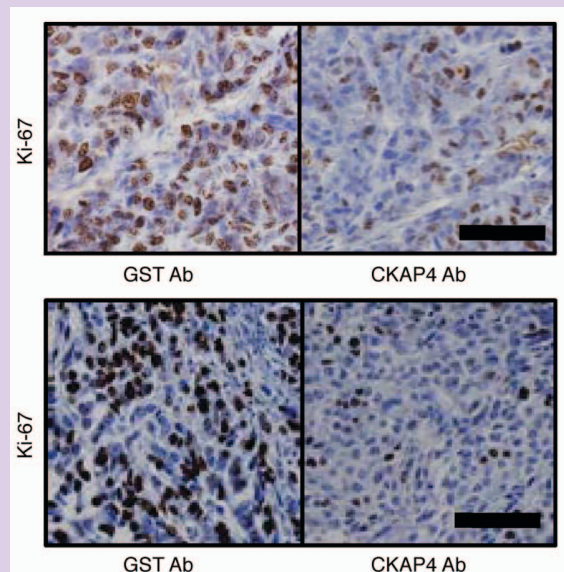
Hirokazu Kimura, Katsumi Fumoto, Kensaku Shojima, Satoshi Nojima, Yoshihito Osugi, Hideo Tomihara, Hidetoshi Eguchi, Yasushi Shintani, Hiroko Endo, Masahiro Inoue, Yuichiro Doki, Meinoshin Okumura, Eiichi Morii, and Akira Kikuchi

<http://jci.me/84658>

► Related Commentary

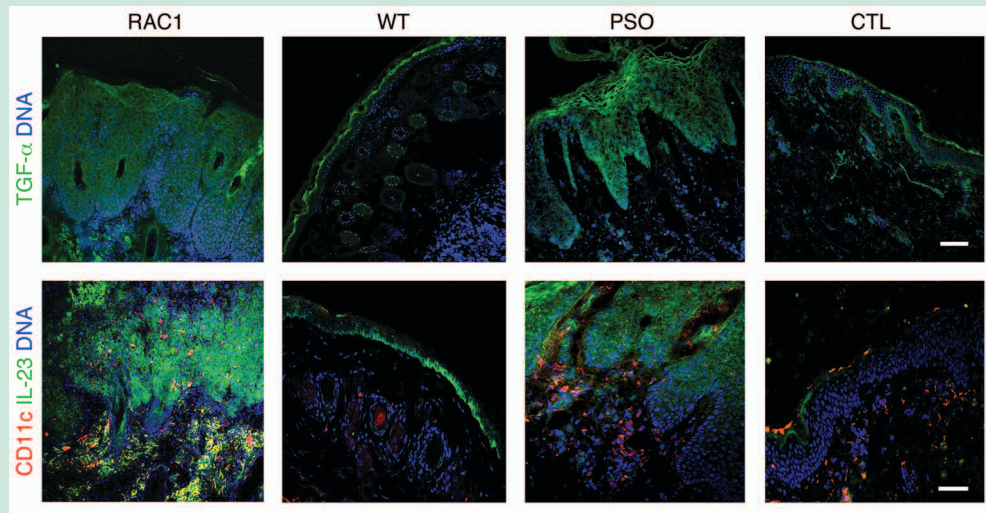
CKAP4 is identified as a receptor for Dickkopf in cancer cells

Dheeraj Bhavanasi, Kelsey F. Speer, and Peter S. Klein <http://jci.me/88620>



DERMATOLOGY

Hyperactivation of the GTPase RAC1 promotes psoriasis phenotype in mice



In psoriasis, aberrant interactions between the epithelia and immune system lead to chronic inflammation and skin lesions. Immunosuppressive treatments for psoriasis put patients at risk for serious infections, so determining the specific pathways that drive pathogenesis could lead to safer, more effective therapies. Mårten Winge and colleagues determined that the small GTPase RAC1 was

hyperactivated in epidermis samples from psoriasis patients. In mice, RAC1 hyperactivity led to the development of psoriasis-like skin lesions and joint abnormalities. Moreover, activation of RAC1 in healthy human keratinocytes recapitulated the elevations in proliferative and inflammatory pathway signaling observed in psoriasis patients and in the mouse model (see the accompanying image). Inhibiting

RAC1 in xenografts from psoriasis patients reduced inflammation and the formation of skin lesions in recipient mice. This mechanistic link between RAC1 hyperactivation and psoriasis suggests that RAC1 is a potential target for treating this disease.

RAC1 activation drives pathologic interactions between the epidermis and immune cells

Mårten C.G. Winge,

Bungo Ohyama, Clara N. Dey,

Lisa M. Boxer, Wei Li, Nazanin Ehsani-Chimeh, Allison K. Truong, Diane Wu, April W. Armstrong, Teruhiko Makino, Matthew Davidson, Daniela Starcevic, Andreas Kislat, Ngon T. Nguyen, Takashi Hashimoto, Bernard Homey, Paul A. Khavari, Maria Bradley, Elizabeth A. Waterman, and M. Peter Marinkovich
<http://jci.me/85738>

REPRODUCTIVE BIOLOGY

Increased soluble VEGF receptor expression drives pregnancy-associated hypertension in mice

During pregnancy, some women develop a hypersensitivity to vasoconstrictors that leads to preeclampsia, a dangerous hypertensive disorder. High circulating levels of a soluble variant of the VEGF receptor 1 (sFLT1) predict the onset of preeclampsia, suggesting that excess sFLT1 in pregnancy may contribute to vasoconstrictor sensitivity. Suzanne Burke and colleagues determined that overexpression of sFLT1 in pregnant mice was sufficient to induce vasoconstrictor sensitivity and hypertension that resembled clinical preeclampsia. sFLT1-overexpressing mice also developed impairments in endothelial NOS that led to vasoconstrictor sensitivity and deleterious effects on fetal health. Sildenafil, an enhancer of NO signaling, reversed vasoconstrictor sensitivity, ameliorated hypertension, enhanced uterine blood flow, and improved fetal outcomes in mice

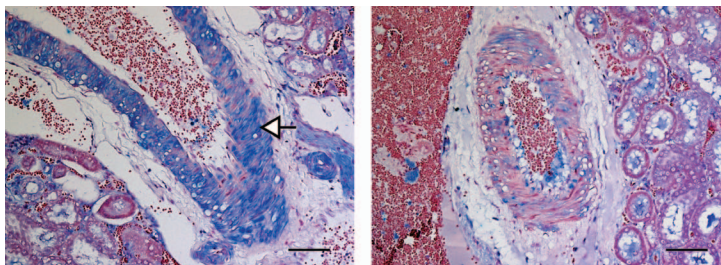
with preeclampsia. These findings suggest that high circulating levels of sFLT1 underly vasoconstrictor sensitization in preeclampsia and identify a potential therapeutic target for improving adverse outcomes related to the disorder.

Soluble fms-like tyrosine kinase 1 promotes angiotensin II sensitivity in preeclampsia

Suzanne D. Burke, Zsuzsanna K. Zsengellér, Eliyahu V. Khankin, Agnes S. Lo, Augustine Rajakumar, Jennifer J. DuPont, Amy McCurley, Mary E. Moss, Dongsheng Zhang, Christopher D. Clark, Alice Wang, Ellen W. Seely, Peter M. Kang, Isaac E. Stillman, Iris Z. Jaffe, and S. Ananth Karumanchi
<http://jci.me/83918>

NEPHROLOGY

Salt-sensitive hypertension-associated renal vascular dysfunction is mediated by p66Shc



Salt-sensitive hypertension induces dysfunctional responses in the renal vasculature that promote nephropathy and end-stage renal disease. Excess signaling through the Src homology 2 domain-containing adaptor protein p66Shc may mediate oxidative stress in vascular damage, but the role of p66Shc signaling in maintaining renal vascular tone is unknown. Bradley Miller and colleagues determined that p66Shc expression was

elevated in the renal arteries of a rat model of salt-sensitive hypertension (see the accompanying image). Inducing p66Shc deficiency in salt-sensitive rats normalized the mobilization of intracellular calcium stores in smooth muscle cells of the renal vasculature, which prevented the rats from developing dysfunctional microvascular responses and glomerular damage. These findings suggest that p66Shc regulates renal vascular tone and promotes hypertension-induced responses that contribute to renal damage.

p66Shc regulates renal vascular tone in hypertension-induced nephropathy

Bradley Miller, Oleg Palygin, Victoriya A. Rufanova, Andrew Chong, Jozef Lazar, Howard J. Jacob, David Mattson, Richard J. Roman, Jan M. Williams, Allen W. Cowley Jr., Aron M. Geurts, Alexander Staruschenko, John D. Imig, and Andrey Sorokin

<http://jci.me/75079>

NEUROSCIENCE

Scopolamine acts on inhibitory neurons to initiate rapid antidepressant responses

Recent reports have demonstrated that very low doses of the nonselective muscarinic acetylcholine receptor (M-AChR) antagonist scopolamine can produce rapid relief from clinical symptoms of depression. In preclinical models, the antidepressant response to scopolamine is attributed to inhibition of M1-AChRs, but the cellular mechanisms supporting its effects on behavior are not known. Eric Wohleb and colleagues determined that scopolamine produces antidepressant responses in mice through blockade of M1-AChRs on inhibitory interneurons in the medial prefrontal cortex. Although multiple subtypes of inhibitory neurons express M1-AChRs, only blockade of M1-AChRs on somatostatin-producing interneurons was required for the antidepressant response in mice. The identification of a specific cellular target for scopolamine's antidepressant effects provides insight into potential rapid-acting pharmacotherapies for depression.

GABA interneurons mediate the rapid antidepressant-like effects of scopolamine

Eric S. Wohleb, Min Wu, Danielle M. Gerhard, Seth R. Taylor, Marina R. Picciotto, Meenakshi Alreja, and Ronald S. Duman

<http://jci.me/85033>

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HEPATOLOGY

Methanobactin treatment attenuates copper toxicity-induced liver damage in rats

In **Wilson disease (WD)**, **functional impairment** of the copper transporter ATP7B reduces copper secretion into bile, which leads to toxic copper accumulation in the liver. Existing pharmacological therapies usually fail to restore copper homeostasis in patients with acute WD, which leaves transplantation as the only treatment option for the resulting liver damage. Josef Lichtmannegger, Christin Leitzinger, and colleagues assessed the therapeutic potential of the bacterial peptide methanobactin as an enzyme replacement therapy in a rat model of acute WD. In ATP7B-deficient rats, short-term treatment with methanobactin attenuated liver damage and mitochondrial impairment (see the image). Furthermore, the treatment prevented hepatocyte death and postponed liver failure in the WD model. In the accompanying Commentary, Stephen Kaler discusses the therapeutic potential for methanobactin as an intervention for liver damage in acute WD.

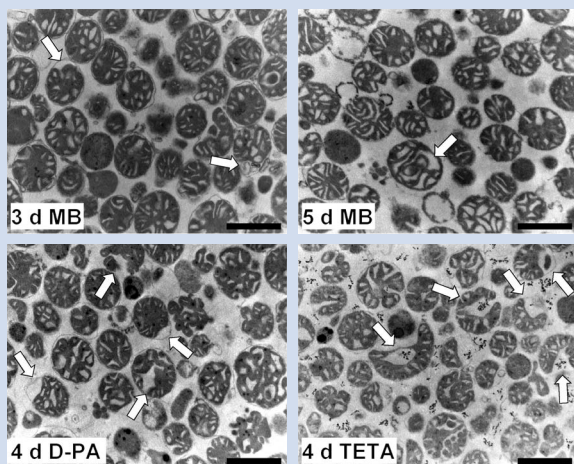
Methanobactin reverses acute liver failure in a rat model of Wilson disease

Josef Lichtmannegger, Christin Leitzinger, Ralf Wimmer, Sabine Schmitt, Sabine Schulz, Yaschar Kabiri, Carola Eberhagen, Tamara Rieder, Dirk Janik, Frauke Neff, Beate K. Straub, Peter Schirmacher, Alan A. DiSpirito, Nathan Bandow, Bipin S. Baral, Andrew Flatley, Elisabeth Kremmer, Gerald Denk, Florian P. Reiter, Simon Hohenester, Friederike Eckardt-Schupp, Norbert A. Dencher, Jerzy Adamski, Vanessa Sauer, Christoph Niemietz, Hartmut H.J. Schmidt, Uta Merle, Daniel Nils Gotthardt, Guido Kroemer, Karl Heinz Weiss, and Hans Zischka <http://jci.me/85226>

► Related Commentary

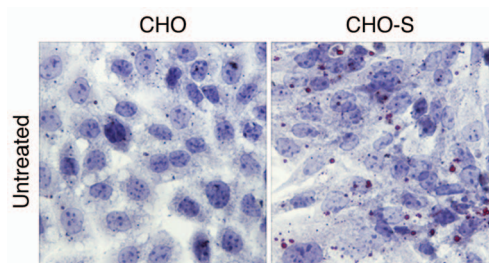
Microbial peptide de-coppers mitochondria: implications for Wilson disease

Stephen G. Kaler <http://jci.me/88617>



METABOLISM

The amyloid precursor protein regulator SORLA modulates lipid metabolism



The gene encoding **SORLA**, a sorting receptor for amyloid precursor protein, is associated with Alzheimer's disease and obesity, suggesting a genetic link between neurodegeneration and metabolic dysregulation. After correlating SORLA levels with human body mass, Vanessa Schmidt and colleagues examined how SORLA expression affected adiposity in mice. SORLA deficiency attenuated accumulation of fat deposits in animals on a high-fat diet. In contrast, overexpressing SORLA in adipose tissue exacerbated obesity and caused glucose intolerance. SORLA promoted lipid accumulation in adipocytes and CHO cells by targeting insulin receptors to the cell surface and facilitating insulin-induced suppression of lipolysis (see the accompanying image). These results suggest that SORLA-mediated protein sorting is a common mechanism underlying risk for obesity and neurodegenerative disease.

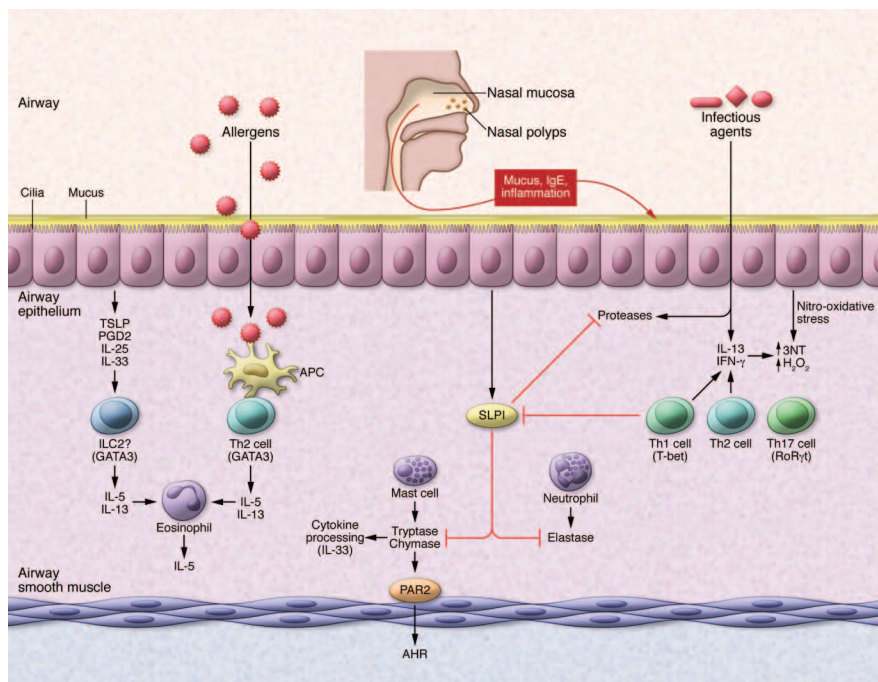
SORLA facilitates insulin receptor signaling in adipocytes and exacerbates obesity

Vanessa Schmidt, Nadja Schulz, Xin Yan, Annette Schürmann, Stefan Kempa, Matthias Kern, Matthias Blüher, Matthew N. Poy, Gunilla Olivecrona, and Thomas E. Willnow

<http://jci.me/84708>

REVIEWS

Defining and differentiating severe asthma endotypes



The term asthma encompasses a variety of disease phenotypes that range from a very mild form of disease that is easily controlled by current therapies to a very severe form of disease that is poorly controlled by the current standard of care. These various disease endotypes are characterized by different underlying pathobiological mechanisms, necessitating specific treatment strategies. Importantly, recent clinical trials for patients with severe asthma have been more successful when therapies were guided by specific patient characteristics rather than a simple diagnosis of severe asthma. In this Review, Anuradha Ray, Sally Wenzel, and colleagues discuss our current understanding of severe asthma, detailing phenotypic differences between severe asthma and milder forms of the disease. Additionally, they detail the molecular and immunological pathways involved in severe asthma (see the accompanying image), which may serve as future therapeutic targets.

Current concepts of severe asthma

Anuradha Ray, Mahesh Roundhal, Timothy B. Oriss, Prabir Ray, and Sally E. Wenzel <http://jci.me/84144>

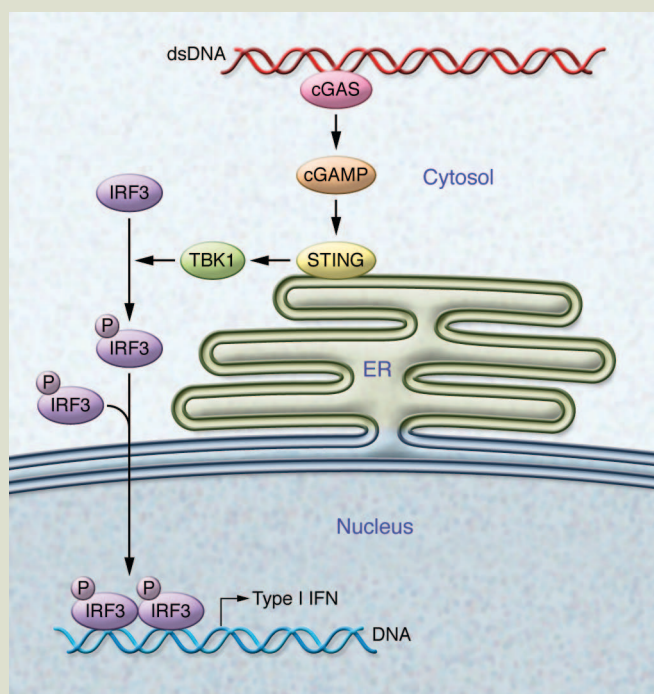
Putting the STING on cancer

A number of human cancers induce spontaneous adaptive immune responses that are characterized by the infiltration of the tumor with tumor antigen-specific T cells, indicating that innate immune cells recognize tumors. Recent studies have indicated that the stimulator of interferon genes pathway (STING pathway), which drives the expression of IFN-related genes in response to cytosolic DNA (see the accompanying image), is a major innate immune pathway involved in the generation of spontaneous antitumor T cell responses. Thomas Gajewski and colleagues review the role of STING in the tumor setting, including the molecular basis of endogenous STING activation. Additionally, Gajewski and colleagues discuss the rationale for and progress in the development of therapeutic STING agonists for cancer immunotherapy.

The host STING pathway at the interface of cancer and immunity

Leticia Corrales, Sarah M. McWhirter, Thomas W. Dubensky Jr., and Thomas F. Gajewski

<http://jci.me/86892>



AIDS/HIV

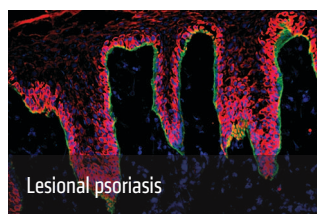
IL-15 promotes activation and expansion of CD8⁺ T cells in HIV-1 infection

Souheil-Antoine Younes, Michael L. Freeman, Joseph C. Mudd, Carey L. Shive, Arnold Reynaldi, Soumya Panigrahi, Jacob D. Estes, Claire Deleage, Carissa Lucero, Jodi Anderson, Timothy W. Schacker, Miles P. Davenport, Joseph M. McCune, Peter W. Hunt, Sulggi A. Lee, Sergio Serrano-Villar, Robert L. Debernardo, Jeffrey M. Jacobson, David H. Canaday, Rafick-Pierre Sekaly, Benigno Rodriguez, Scott F. Sieg, and Michael M. Lederman <http://jci.me/85996>

ANGIOGENESIS

Foxc1 and Foxc2 deletion causes abnormal lymphangiogenesis and correlates with ERK hyperactivation

Anees Fatima, Ying Wang, Yutaka Uchida, Pieter Norden, Ting Liu, Austin Culver, William H. Dietz, Ford Culver, Meredith Millay, Yoh-suke Mukoyama, and Tsutomu Kume <http://jci.me/80465>



Lesional psoriasis

DERMATOLOGY

RAC1 activation drives pathologic interactions between the epidermis and immune cells ► p. 4

Mårten C.G. Winge, Bungo Ohyama, Clara N. Dey, Lisa M. Boxer, Wei Li, Nazanin Ehsani-Chimeh, Allison K. Truong, Diane Wu, April W. Armstrong, Teruhiko Makino, Matthew Davidson, Daniela Starcevic, Andreas Kislat, Ngon T. Nguyen, Takashi Hashimoto, Bernard Homey, Paul A. Khavari, Maria Bradley, Elizabeth A. Waterman, and M. Peter Marinkovich <http://jci.me/85738>

DEVELOPMENT

Transcription factor TLX1 controls retinoic acid signaling to ensure spleen development

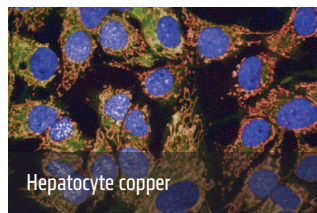
Elisa Lenti, Diego Farinello, Kazunari K. Yokoyama, Dmitry Penkov, Laura Castagnaro, Giovanni Lavorgna, Kenly Wuputra, Lisa L. Sandell, Naomi E. Butler Tjaden, Francesca Bernassola, Nicoletta Caridi, Anna De Antoni, Michael Wagner, Katja Kozinc, Karen Niederreither, Francesco Blasi, Diego Pasini, Gregor Majdic, Giovanni Tonon, Paul A. Trainor, and Andrea Brendolan <http://jci.me/82956>

HEMATOLOGY

S6K1 regulates hematopoietic stem cell self-renewal and leukemia maintenance

Joydeep Ghosh, Michihiro Kobayashi, Baskar Ramdas, Anindya Chatterjee, Peilin Ma, Raghuveer Singh Mali, Nadia Carlesso, Yan Liu, David R. Plas, Rebecca J. Chan, and Reuben Kapur <http://jci.me/84565>

HEPATOLOGY



Hepatocyte copper

Methanobactin reverses acute liver failure in a rat model of Wilson disease ► p. 6

Josef Lichtmanegger, Christin Leitzinger, Ralf Wimmer, Sabine Schmitt, Sabine Schulz, Yaschar Kabiri, Carola Eberhagen, Tamara Rieder, Dirk Janik, Frauke Neff, Beate K. Straub, Peter Schirmacher, Alan A. DiSpirito, Nathan Bandow, Bipin S. Baral, Andrew Flatley, Elisabeth Kremmer, Gerald Denk, Florian P. Reiter, Simon Hohenester, Friederike Eckardt-Schupp, Norbert A. Dencher, Jerzy Adamski, Vanessa Sauer, Christoph Niemietz, Hartmut H.J. Schmidt, Uta Merle, Daniel Nils Gotthardt, Guido Kroemer, Karl Heinz Weiss, and Hans Zischka <http://jci.me/85226>

IMMUNOLOGY

Uropathogenic *Escherichia coli* strain CFT073 disrupts NLRP3 inflammasome activation

Anna Waldhuber, Manoj Puthia, Andreas Wieser, Christine Cirl, Susanne Dürr, Silke Neumann-Pfeifer, Simone Albrecht, Franziska Römmeler, Tina Müller, Yunji Zheng, Sören Schubert, Olaf Groß, Catharina Svanborg, and Thomas Miethke <http://jci.me/81916>

Glycolysis determines dichotomous regulation of T cell subsets in hypoxia

Yang Xu, Arindam Chaudhury, Ming Zhang, Barbara Savoldo, Leonid S. Metelitsa, John Rodgers, Jason T. Yustein, Joel R. Neilson, and Gianpiero Dotti <http://jci.me/85834>

METABOLISM

Increased mitochondrial arginine metabolism supports bioenergetics in asthma ► p. 1

Weiling Xu, Sudakshina Ghosh, Suzy A.A. Comhair, Kewal Asosingh, Allison J. Janocha, Deloris A. Mavrakakis, Carole D. Bennett, Lourdes L. Gruca, Brian B. Graham, Kimberly A. Queisser, Christina C. Kao, Samuel H. Wedes, John M. Petrich, Rubin M. Tudor, Satish C. Kalhan, and Serpil C. Erzurum <http://jci.me/82925>

SORLA facilitates insulin receptor signaling in adipocytes and exacerbates obesity ► p. 6

Vanessa Schmidt, Nadja Schulz, Xin Yan, Annette Schürmann, Stefan Kempa, Matthias Kern, Matthias Blüher, Matthew N. Poy, Gunilla Olivecrona, and Thomas E. Willnow <http://jci.me/84708>

NEPHROLOGY

p66Shc regulates renal vascular tone in hypertension-induced nephropathy ► p. 5

Bradley Miller, Oleg Palygin, Victoriya A. Rufanova, Andrew Chong, Jozef Lazar, Howard J. Jacob, David Mattson, Richard J. Roman, Jan M. Williams, Allen W. Cowley Jr., Aron M. Geurts, Alexander Staruschenko, John D. Imig, and Andrey Sorokin <http://jci.me/75079>

Paracellular epithelial sodium transport maximizes energy efficiency in the kidney

Lei Pei, Glenn Solis, Mien T.X. Nguyen, Nikhil Kamat, Lynn Magenheimer, Min Zhou, Jiahua Li, Joshua Curry, Alicia A. McDonough, Timothy A. Fields, William J. Welch, and Alan S.L. Yu <http://jci.me/83942>

Autoantibodies against thrombospondin type 1 domain-containing 7A induce membranous nephropathy

Nicola M. Tomas, Elion Hoxha, Anna T. Reinicke, Lars Fester, Udo Helmchen, Jens Gerth, Friederike Bachmann, Klemens Budde, Friedrich Koch-Nolte, Gunther Zahner, Gabriele Rune, Gerard Lambeau, Catherine Meyer-Schwesinger, and Rolf A.K. Stahl <http://jci.me/85265>

NEUROSCIENCE

Phosphorylation state-dependent modulation of spinal glycine receptors alleviates inflammatory pain

Mario A. Acuña, Gonzalo E. Yévenes, William T. Ralvenius, Dietmar Benke, Alessandra Di Lio, Cesar O. Lara, Braulio Muñoz, Carlos F. Burgos, Gustavo Moraga-Cid, Pierre-Jean Corringer, and Hanns Ulrich Zeilhofer <http://jci.me/83817>

GABA interneurons mediate the rapid antidepressant-like effects of scopolamine ► p. 5

Eric S. Wohleb, Min Wu, Danielle M. Gerhard, Seth R. Taylor, Marina R. Picciotto, Meenakshi Alreja, and Ronald S. Duman <http://jci.me/85033>

Persistent 7-tesla phase rim predicts poor outcome in new multiple sclerosis patient lesions

Martina Absinta, Pascal Sati, Matthew Schindler, Emily C. Leibovitch, Joan Ohayon, Tianxia Wu, Alessandro Meani, Massimo Filippi, Steven Jacobson, Irene C.M. Cortese, and Daniel S. Reich <http://jci.me/86198>

ONCOLOGY

Notch promotes tumor metastasis in a prostate-specific *Pten*-null mouse model

Oh-Joon Kwon, Li Zhang, Jianghua Wang, Qingtai Su, Qin Feng, Xiang H.F. Zhang, Sendurai A. Mani, Robia Paulter, Chad J. Creighton, Michael M. Ittmann, and Li Xin <http://jci.me/84637>

ONCOLOGY

RBPJ maintains brain tumor-initiating cells through CDK9-mediated transcriptional elongation ► p. 3

Qi Xie, Qiulian Wu, Leo Kim, Tyler E. Miller, Brian B. Liao, Stephen C. Mack, Kailin Yang, Daniel C. Factor, Xiaoguang Fang, Zhi Huang, Wenchao Zhou, Kareem Alazem, Xiuxing Wang, Bradley E. Bernstein, Shideng Bao, and Jeremy N. Rich <http://jci.me/86114>

CKAP4 is a Dickkopf1 receptor and is involved in tumor progression ► p. 3

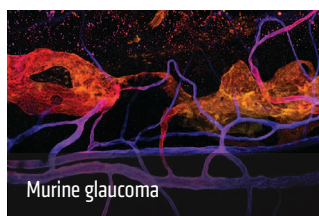
Hirokazu Kimura, Katsumi Fumoto, Kensaku Shojima, Satoshi Nojima, Yoshihito Osugi, Hideo Tomihara, Hidetoshi Eguchi, Yasushi Shintani, Hiroko Endo, Masahiro Inoue, Yuichiro Doki, Meinoshin Okumura, Eiichi Morii, and Akira Kikuchi <http://jci.me/84658>

Clinical responses with T lymphocytes targeting malignancy-associated κ light chains

Carlos A. Ramos, Barbara Savoldo, Vicky Torrano, Brandon Ballard, Huimin Zhang, Olga Dakhova, Enli Liu, George Carrum, Rammurti T. Kamble, Adrian P. Gee, Zhuoyoung Mei, Meng-Fen Wu, Hao Liu, Bambi Grilley, Cliona M. Rooney, Malcolm K. Brenner, Helen E. Heslop, and Gianpietro Dotti <http://jci.me/86000>

CD47-blocking immunotherapies stimulate macrophage-mediated destruction of small-cell lung cancer

Kipp Weiskopf, Nadine S. Jahchan, Peter J. Schnorr, Sandra Cristea, Aaron M. Ring, Roy L. Maute, Anne K. Volkmer, Jens-Peter Volkmer, Jie Liu, Jing S. Lim, Dian Yang, Garrett Seitz, Thuyen Nguyen, Di Wu, Kevin Jude, Heather Guerston, Amira Barkal, Francesca Trapani, Julie George, John T. Poirier, Eric E. Gardner, Linde A. Miles, Elisa de Stanchina, Shane M. Lofgren, Hannes Vogel, Monte M. Winslow, Caroline Dive, Roman K. Thomas, Charles M. Rudin, Matt van de Rijn, Ravindra Majeti, K. Christopher Garcia, Irving L. Weissman, and Julien Sage <http://jci.me/81603>



Murine glaucoma

OPHTHALMOLOGY

Angiopoietin receptor TEK mutations underlie primary congenital glaucoma with variable expressivity

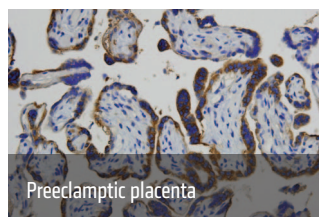
Tomokazu Souma, Stuart W. Thompson, Benjamin R. Thomson, Owen M. Siggs, Krishnakumar Kizhatil, Shinji Yamaguchi, Liang Feng, Vachirane Limvipuvadh, Kristina N. Whisenhunt, Sebastian Maurer-Stroh, Tammy L. Yanovitch, Luba Kalaydjieva, Dimitar N. Azmanov, Simone Finzi, Lucia Mauri, Shahrbanou Javadiyan, Emmanuelle Souzeau,

Tiger Zhou, Alex W. Hewitt, Bethany Kloss, Kathryn P. Burdon, David A. Mackey, Keri F. Allen, Jonathan B. Ruddle, Sing-Hui Lim, Steve Rozen, Khanh-Nhat Tran-Viet, Xiaorong Liu, Simon John, Janey L. Wiggs, Francesca Pasutto, Jamie E. Craig, Jing Jin, Susan E. Quaggin, and Terri L. Young <http://jci.me/85830>

PULMONOLOGY

MicroRNA-140-5p and SMURF1 regulate pulmonary arterial hypertension

Alexander M.K. Rothman, Nadine D. Arnold, Josephine A. Pickworth, James Iremonger, Loredana Ciucan, Robert M.H. Allen, Sabine Guth-Gundel, Mark Southwood, Nicholas W. Morrell, Matthew Thomas, Sheila E. Francis, David J. Rowlands, and Allan Lawrie <http://jci.me/83361>



Preclampsic placenta

REPRODUCTIVE BIOLOGY

Soluble fms-like tyrosine kinase 1 promotes angiotensin II sensitivity in preeclampsia ► p. 4

Suzanne D. Burke, Zsuzsanna K. Zsengellér, Eliyahu V. Khankin, Agnes S. Lo, Augustine Rajakumar, Jennifer J. DuPont, Amy McCurley, Mary E. Moss, Dongsheng Zhang, Christopher D. Clark, Alice Wang, Ellen W. Seely, Peter M. Kang, Isaac E. Stillman, Iris Z. Jaffe, and S. Ananth Karumanchi <http://jci.me/83918>

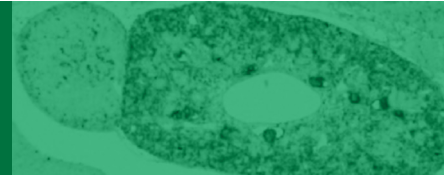
TRANSPLANTATION

The composition of the microbiota modulates allograft rejection ► p. 2

Yuk Man Lei, Luqiu Chen, Ying Wang, Andrew T. Stefka, Luciana L. Molinero, Betty Theriault, Keston Aquino-Michaels, Ayelet S. Sivan, Cathryn R. Nagler, Thomas F. Gajewski, Anita S. Chong, Caroline Bartman, and Maria-Luisa Alegre <http://jci.me/85295>

Programmed death ligand-1 expression on donor T cells drives graft-versus-host disease lethality ► p. 2

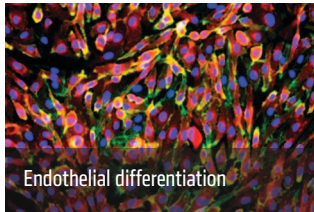
Asim Saha, Roddy S. O'Connor, Govindarajan Thangavelu, Scott B. Lovitch, Durga Bhavani Dandamudi, Caleph B. Wilson, Benjamin G. Vincent, Victor Tkachev, Jan M. Pawlicki, Scott N. Furlan, Leslie S. Kean, Kazutoshi Aoyama, Patricia A. Taylor, Angela Panoskaltis-Mortari, Rocio Foncea, Parvathi Ranganathan, Steven M. Devine, Joel S. Burrill, Lili Guo, Catarina Sacristan, Nathaniel W. Snyder, Ian A. Blair, Michael C. Milone, Michael L. Dustin, James L. Riley, David A. Bernlohr, William J. Murphy, Brian T. Fife, David H. Munn, Jeffrey S. Miller, Jonathan S. Serody, Gordon J. Freeman, Arlene H. Sharpe, Laurence A. Turka, and Bruce R. Blazar <http://jci.me/85796>



Hyperleptinemia is associated with impaired pulmonary host defense

Niki D.J. Ubags, Renee D. Stapleton, Juanita H.J. Vernooij, Elianne Burg, Jenna Bement, Catherine M. Hayes, Sebastian Ventrone, Lennart Zabeau, Jan Tavernier, Matthew E. Poynter, Polly E. Parsons, Anne E. Dixon, Matthew J. Wargo, Benjamin Littenberg, Emiel F.M. Wouters, and Benjamin T. Suratt

<http://jci.me/82101>



Effects of cellular origin on differentiation of human induced pluripotent stem cell-derived endothelial cells

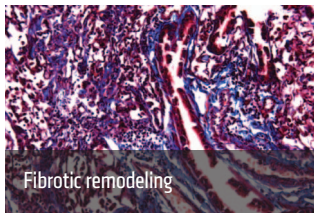
Shijun Hu, Ming-Tao Zhao, Fereshteh Jahanbani, Ning-Yi Shao, Won Hee Lee, Haodong Chen, Michael P. Snyder, and Joseph C. Wu

<http://jci.me/85558>

Single-cell analysis of glandular T cell receptors in Sjögren's syndrome

Michelle L. Joachims, Kerry M. Leehan, Christina Lawrence, Richard C. Pelikan, Jacen S. Moore, Zijian Pan, Astrid Rasmussen, Lida Radfar, David M. Lewis, Kiely M. Grundahl, Jennifer A. Kelly, Graham B. Wiley, Mikhail Shugay, Dmitriy M. Chudakov, Christopher J. Lessard, Donald U. Stone, R. Hal Scofield, Courtney G. Montgomery, Kathy L. Sivils, Linda F. Thompson, and A. Darise Farris

<http://jci.me/85609>



Attenuation of lung fibrosis in mice with a clinically relevant inhibitor of glutathione-S-transferase π

David H. McMillan, Jos L.J. van der Velden, Karolyn G. Lahue, Xi Qian, Robert W. Schneider, Martina S. Iberg, James D. Nolin, Sarah Abdalla, Dylan T. Casey, Kenneth D. Tew, Danyelle M. Townsend, Colin J. Henderson, C. Roland Wolf, Kelly J. Butnor, Douglas J. Taatjes, Ralph C. Budd, Charles G. Irvin, Albert van der Vliet, Stevenson Flemer, Vikas Anathy, and Yvonne M.W. Janssen-Heininger

<http://jci.me/85717>

Renal rescue of dopamine D2 receptor function reverses renal injury and high blood pressure

Prasad R. Konkalmatt, Laureano D. Asico, Yanrong Zhang, Yu Yang, Cinthia Drachenberg, Xiaoxu Zheng, Fei Han, Pedro A. Jose, and Ines Armando

<http://jci.me/85888>

Distinct activation thresholds of human conventional and innate-like memory T cells

Chloe K. Slichter, Andrew McDavid, Hannah W. Miller, Greg Finak, Brenda J. Seymour, John P. McNevin, Gabriela Diaz, Julie L. Czartoski, M. Juliana McElrath, Raphael Gottardo, and Martin Prlic

<http://jci.me/86292>

A wearable artificial kidney for patients with end-stage renal disease

Victor Gura, Matthew B. Rivara, Scott Bieber, Raj Munshi, Nancy Colobong Smith, Lori Linke, John Kundzins, Masoud Beizai, Carlos Ezon, Larry Kessler, and Jonathan Himmelfarb

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Cyclosporine A immunosuppression drives catastrophic squamous cell carcinoma through IL-22

Melody Abikhair, Hiroshi Mitsui, Valerie Yanofsky, Nazanin Roudiani, Channa Ovits, Teddy Bryan, Tatiana M. Oberyszyn, Kathleen L. Tober, Juana Gonzalez, James G. Krueger, Diane Felsen, and John A. Carucci

<http://jci.me/86434>

Quantitation of circulating satellite RNAs in pancreatic cancer patients

Takahiro Kishikawa, Motoyuki Otsuka, Takeshi Yoshikawa, Motoko Ohno, Keisuke Yamamoto, Natsuyo Yamamoto, Ai Kotani, and Kazuhiko Koike

<http://jci.me/86646>

Paneth cell defects in Crohn's disease patients promote dysbiosis

Ta-Chiang Liu, Bhaskar Gurram, Megan T. Baldrige, Richard Head, Vy Lam, Chengwei Luo, Yumei Cao, Pippa Simpson, Michael Hayward, Mary L. Holtz, Pavlos Bousounis, Joshua Noe, Diana Lerner, Jose Cabrera, Vincent Biank, Michael Stephens, Curtis Huttenhower, Dermot P.B. McGovern, Ramnik J. Xavier, Thaddeus S. Stappenbeck, and Nita H. Salzman

<http://jci.me/86907>

CRIg-expressing peritoneal macrophages are associated with disease severity in patients with cirrhosis and ascites

Katharine M. Irvine, Xuan Banh, Victoria L. Gadd, Kyle K. Wojcik, Juliana K. Ariffin, Sara Jose, Samuel Lukowski, Gregory J. Baillie, Matthew J. Sweet, and Elizabeth E. Powell

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Distal vessel stiffening is an early and pivotal mechanobiological regulator of vascular remodeling and pulmonary hypertension

Fei Liu, Christina Mallarino Haeger, Paul B. Dieffenbach, Delphine Sicard, Izabela Chrobak, Anna Maria F. Coronata, Margarita M. Suárez Velandia, Sally Vitali, Romain A. Colas, Paul C. Norris, Aleksandar Marinković, Xiaoli Liu, Jun Ma, Chase D. Rose, Seon-Jin Lee, Suzy A.A. Comhair, Serpil C. Erzurum, Jacob D. McDonald, Charles N. Serhan, Stephen R. Walsh, Daniel J. Tschumperlin, and Laura E. Fredenburgh

<http://jci.me/86987>

Effect of tolerance versus chronic immunosuppression protocols on the quality of life of kidney transplant recipients

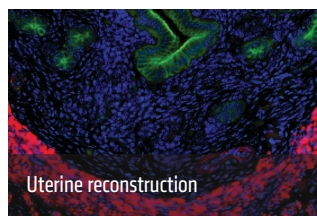
Maria Lucia L. Madariaga, Philip J. Spencer, Kumaran Shanmugarajah, Kerry A. Crisalli, David C. Chang, James F. Markmann, Nahel Elias, A. Benedict Cosimi, David H. Sachs, and Tatsuo Kawai

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Repurposing tromethamine as inhaled therapy to treat CF airway disease

Mahmoud H. Abou Alaiwa, Janice L. Launspach, Kelsey A. Sheets, Jade A. Rivera, Nicholas D. Gansemer, Peter J. Taft, Peter S. Thorne, Michael J. Welsh, David A. Stoltz, and Joseph Zabner

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STAT3 accelerates uterine epithelial regeneration in a mouse model of decellularized uterine matrix transplantation

Takehiro Hiraoka, Yasushi Hirota, Tomoko Saito-Fujita, Mitsunori Matsuo, Mahiro Egashira, Leona Matsumoto, Hirofumi Haraguchi, Sudhansu K. Dey, Katsuko S. Furukawa, Tomoyuki Fujii, and Yutaka Osuga

<http://jci.me/87591>

CITED4 induces physiologic hypertrophy and promotes functional recovery after ischemic injury

Vassilios J. Bezzerides, Colin Platt, Carolin Lerchenmüller, Kaavya Paruchuri, Nul Loren Oh, Chunyang Xiao, Yunshan Cao, Nina Mann, Bruce Spiegelman, and Anthony Rosenzweig

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Asfotase alfa therapy for children with hypophosphatasia

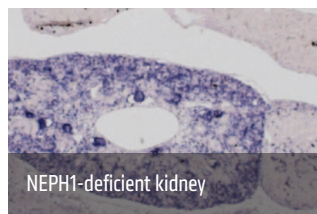
Michael P. Whyte, Katherine L. Madson, Dawn Phillips, Amy L. Reeves, William H. McAlister, Amy Yakimoski, Karen E. Mack, Kim Hamilton, Kori Kagan, Kenji P. Fujita, David D. Thompson, Scott Moseley, Tatjana Odrlić, and Cheryl Rockman-Greenberg

<http://jci.me/85971>

TGF- β and VEGF cooperatively control the immunotolerant tumor environment and the efficacy of cancer immunotherapies

Tristan Courau, Djamel Nehar-Belaid, Laura Florez, Béatrice Levacher, Thomas Vazquez, Faustine Brimaud, Bertrand Bellier, and David Klatzmann

<http://jci.me/85974>



A flexible, multilayered protein scaffold maintains the slit in between glomerular podocytes

Florian Grahammer, Christoph Wigge, Christoph Schell, Oliver Kretz, Jaakko Patrakka, Simon Schneider, Martin Klose, Sebastian J. Arnold, Anja Habermann, Ricarda Bräuniger, Markus M. Rinschen, Linus Völker, Andreas Breggenzer, Dennis Rubbenstroth, Melanie Boerries, Donscho Kerjaschki, Jeffrey H. Miner, Gerd Walz, Thomas Benzing, Alessia Fornoni, Achilleas S. Frangakis, and Tobias B. Huber

<http://jci.me/86177>

Fibulin-1 regulates the pathogenesis of tissue remodeling in respiratory diseases

Gang Liu, Marion A. Cooley, Andrew G. Jarnicki, Alan C.-Y. Hsu, Prema M. Nair, Tatt Jhong Haw, Michael Fricker, Shaan L. Gellatly, Richard Y. Kim, Mark D. Inman, Gavin Tjin, Peter A.B. Wark, Marjorie M. Walker, Jay C. Horvat, Brian G. Oliver, W. Scott Argraves, Darryl A. Knight, Janette K. Burgess, and Philip M. Hansbro

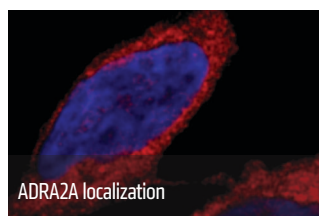
<http://jci.me/86380>

Effects of sphingosine-1-phosphate receptor 1 phosphorylation in response to FTY720 during neuroinflammation

Hsing-Chuan Tsai, Yingxiang Huang, Christopher S. Garriss, Monica A. Moreno, Christina W. Griffin, and May H. Han <http://jci.me/86462>

CNS-directed gene therapy for the treatment of neurologic and somatic mucopolysaccharidosis type II (Hunter syndrome)

Sandra Motas, Virginia Haurigot, Miguel Garcia, Sara Marcó, Albert Ribera, Carles Roca, Xavier Sánchez, Víctor Sánchez, Maria Molas, Joan Bertolin, Luca Maggioni, Xavier León, Jesús Ruberte, and Fatima Bosch <http://jci.me/86696>



Whole-exome sequencing identifies ADRA2A mutation in atypical familial partial lipodystrophy

Abhimanyu Garg, Shireesha Sankella, Chao Xing, and Anil K. Agarwal

<http://jci.me/86870>

B cells from African American lupus patients exhibit an activated phenotype

Laurence C. Menard, Sium Habte, Waldemar Gonsiorek, Deborah Lee, Dana Banas, Deborah A. Holloway,

Nataly Manjarrez-Orduno, Mark Cunningham, Dawn Stetsko, Francesca Casano, Selenia Kansal, Patricia M. Davis, Julie Carman, Clarence K. Zhang, Ferva Abidi, Richard Furie, Steven G. Nadler, and Suzanne J. Suchard <http://jci.me/87310>

A clinical measure of DNA methylation predicts outcome in de novo acute myeloid leukemia

Marlise R. Luskin, Phyllis A. Gimotty, Catherine Smith, Alison W. Loren, Maria E. Figueroa, Jenna Harrison, Zhuoxin Sun, Martin S. Tallman, Elisabeth M. Paietta, Mark R. Litzow, Ari M. Melnick, Ross L. Levine, Hugo F. Fernandez, Selina M. Luger, Martin Carroll, Stephen R. Master, and Gerald B.W. Wertheim <http://jci.me/87323>

Synergy of radiotherapy and PD-1 blockade in Kras-mutant lung cancer

Grit S. Herter-Sprie, Shohei Koyama, Houari Korideck, Josephine Hai, Jiehui Deng, Yvonne Y. Li, Kevin A. Buczkowski, Aaron K. Grant, Soumya Ullas, Kevin Rhee, Jillian D. Cavanaugh, Neermala Poudel Neupane, Camilla L. Christensen, Jan M. Herter, G. Mike Makrigiorgos, F. Stephen Hodi, Gordon J. Freeman, Glenn Dranoff, Peter S. Hammerman, Alec C. Kimmelman, and Kwok-Kin Wong <http://jci.me/87415>

PRL3-zumab, a first-in-class humanized antibody for cancer therapy

Min Thura, Abdul Qader Omer Al-Aidaroos, Wei Peng Yong, Koji Kono, Abhishek Gupta, You Bin Lin, Kousaku Mimura, Jean Paul Thiery, Boon Cher Goh, Patrick Tan, Ross Soo, Cheng William Hong, Lingzhi Wang, Suling Joyce Lin, Elya Chen, Sun Young Rha, Hyun Cheol Chung, Jie Li, Sayantani Nandi, Hiu Fung Yuen, Shu-Dong Zhang, Yeoh Khay Guan, Jimmy So, and Qi Zeng

<http://jci.me/87607>

PIK3CA-associated developmental disorders exhibit distinct classes of mutations with variable expression and tissue distribution

Ghayda Mirzaa, Andrew E. Timms, Valerio Conti, Evan August Boyle, Katta M. Girisha, Beth Martin, Martin Kircher, Carissa Olds, Jane Juusola, Sarah Collins, Kaylee Park, Melissa Carter, Ian Glass, Inge Krägeloh-Mann, David Chitayat, Aditi Shah Parikh, Rachael Bradshaw, Erin Torti, Steve Braddock, Leah Burke, Sondhya Ghedia, Mark Stephan, Fiona Stewart, Chitra Prasad, Melanie Napier, Sulagna Saitta, Rachel Straussberg, Michael Gabbett, Bridget C. O'Connor, Catherine E. Keegan, Lim Jjin Yin, Angeline Hwei Meeng Lai, Nicole Martin, Margaret McKinnon, Marie-Claude Addor, Luigi Boccuto, Charles E. Schwartz, Agustina Lanoel, Robert L. Conway, Koenraad Devriendt, Katrina Tatton-Brown, Mary Ella Pierpont, Michael Painter, Lisa Worgan, James Reggin, Raoul Hennekam, Karen Tsuchiya, Colin C. Pritchard, Mariana Aracena, Karen W. Gripp, Maria Cordisco, Hilde Van Esch, Livia Garavelli, Cynthia Curry, Anne Goriely, Hulya Kayserilli, Jay Shendure, John Graham Jr., Renzo Guerrini, and William B. Dobyns

<http://jci.me/87623>

Cardiac myosin-Th17 responses promote heart failure in human myocarditis

Jennifer M. Myers, Leslie T. Cooper, David C. Kem, Stavros Stavrakakis, Stanley D. Kosanke, Ethan M. Shevach, DeLisa Fairweather, Julie A. Stoner, Carol J. Cox, and Madeleine W. Cunningham <http://jci.me/85851>

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