

JCI

This Month

JCI

Dysregulated protein phosphorylation associates with insulin resistance **3**

Early response to tuberculosis in HIV coinfection **4**

RAF1 amplification drives a subset of bladder tumors **5**

Protein kinase N2 mediates vascular tone and eNOS **5**

APOL1 risk alleles in kidney transplant recipients **6**

December 2021

JCI **This Month** is a summary of recent articles in **The Journal of Clinical Investigation** and **JCI Insight**

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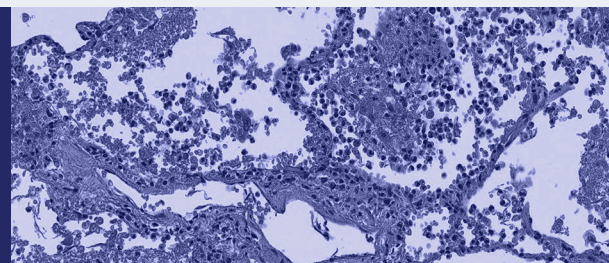


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Phosphodiesterase 9A inhibition for obesity and cardiometabolic syndrome p. 2

Journal of Clinical Investigation

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Angelo M. De Marzo, MD, PhD, Associate Editor

is a Professor of Pathology, Oncology, and Urology at The Johns Hopkins University School of Medicine. He serves as the Associate Director of Cancer Research Pathology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and is a member of the Association of American Physicians. Dr. De Marzo's research interests include the molecular pathology of prostate cancer initiation, specifically, the role of inflammation, epithelial cell injury, and c-MYC

overexpression. His group also studies the downstream sequelae of c-MYC activation, including increased nucleolar activity, altered telomere dynamics, and mitochondrial biogenesis. He also serves on the editorial boards of *The Prostate* and *Cancer Prevention Research*.

Publication highlights

Shrestha E, Coulter JB, Guzman W, Ozbek B, Hess MM, Mummert L, Ernst SE, Maynard JP, Meeker AK, Heaphy CM, Haffner MC, De Marzo AM, Sfanos KS. Oncogenic gene fusions in nonneoplastic precursors as evidence that bacterial infection can initiate prostate cancer. *Proc Natl Acad Sci U S A*. 2021;118(32):e2018976118.

Chen J, Zheng Q, Peiffer LB, Hicks JL, Haffner MC, Rosenberg AZ, Levi M, Wang XX, Ozbek B, Baena-Del Valle J, Yegnasubramanian S, De Marzo AM. An in situ atlas of mitochondrial DNA in mammalian tissues reveals high content in stem and proliferative compartments. *Am J Pathol*. 2020;190(7):1565-1579.

Trabzonlu L, Kulac I, Zheng Q, Hicks JL, Haffner MC, Nelson WG, Sfanos KS, Ertunc O, Lotan TL, Heaphy CM, Meeker AK, Yegnasubramanian S, De Marzo AM. Molecular pathology of high-grade prostatic intraepithelial neoplasia: challenges and opportunities. *Cold Spring Harb Perspect Med*. 2019;9(4):a030403.

Baena-Del Valle JA, Zheng Q, Esopi DM, Rubenstein M, Hubbard GK, Moncaliano MC, Hruszkewycz A, Vaghasia A, Yegnasubramanian S, Wheelan SJ, Meeker AK, Heaphy CM, Graham MK, De Marzo AM. MYC drives overexpression of telomerase RNA (hTR/TERC) in prostate cancer. *J Pathol*. 2018;244(1):11-24.

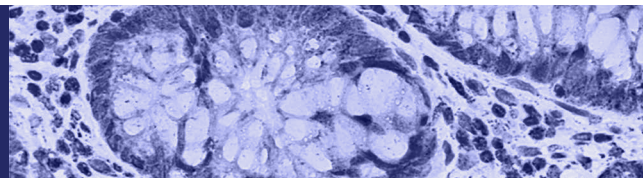
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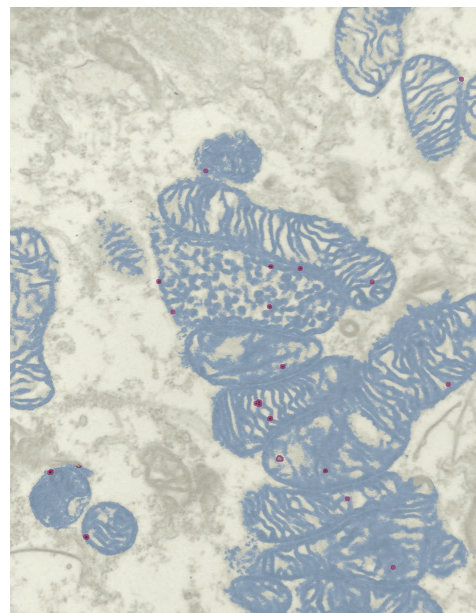


METABOLISM

ON THE JCI COVER

Phosphodiesterase 9A inhibition reduces obesity and cardiometabolic syndrome in mice

Abdominal obesity often associates with cardiometabolic disease, including diabetes and cardiovascular disease. Since current weight loss strategies focus on insulin signaling or appetite suppression with limited efficacy, further therapies are needed. In a recent issue of the *JCI*, Sumita Mishra and colleagues explored the effects of an inhibitor of the cyclic GMP-selective phosphodiesterase 9A (PDE9-I) on obesity and related cardiac pathologies. Female mice, ovariectomized (OVX) mice, and male mice were fed a standard or high-fat diet, and some were subjected to cardiac pressure load to model hypertensive stress. OVX female and male mice treated with PDE9-I showed reduced body, inguinal, hepatic, and myocardial fat, yet food intake and activity were unaffected when compared with placebo controls. PDE9-I also improved cardiac function and suppressed hypertrophic gene expression. The changes were not observed in intact female mice, indicating sexual dimorphism. The authors also found that the PDE9 protein localized to mitochondria and that PDE9-I stimulated lipolysis in multiple cell types and enhanced mitochondrial respiration. PDE9-I signaled through peroxisome proliferator-activated receptor- α (PPAR α) to modulate expression of genes regulating fat metabolism. Notably, the presence of coactivated estrogen receptor- α altered PPAR α chromatin binding away from fat-metabolism genes, suggesting a mechanism for the observed sexual dimorphism. These findings highlight PDE9-I as a potential therapeutic for obesity and cardiometabolic syndrome. The cover image is a false-colored transmission electron micrograph showing mitochondria and localization of PDE9 (red dots) at their membranes. Image credit: Vivek Jani.



Inhibition of phosphodiesterase type 9 reduces obesity and cardiometabolic syndrome in mice

Sumita Mishra, Nandhini Sadagopan, Brittany Dunkerly-Eyring, Susana Rodriguez, Dylan C. Sarver, Ryan P. Ceddia, Sean A. Murphy, Hildur Knutsdottir, Vivek P. Jani, Deepthi Ashok, Christian U. Oeing, Brian O'Rourke, Jon A. Gangoiti, Dorothy D. Sears, G. William Wong, Sheila Collins, and David A. Kass <http://jci.me/148798>

IMMUNOLOGY

The self-peptide repertoire and transplant tolerance induction

Transplanted organs offer lifesaving potential; however, immune complications can cause major medical problems. Alloreactive CD8⁺ T cells act via unknown molecular targets to determine whether allografts are rejected or tolerated. In a recent issue of the *JCI*, Eric Son and colleagues evaluated the role of self-peptides in the induction of skin transplant tolerance. Notably, altering the endogenous peptide repertoire impeded the induction of transplantation tolerance. The authors used peptide-exchange tetramers to screen peptide-MHC complexes for recognition by allospecific T cells and identified 17 strongly immunogenic peptides. Just five of these peptides labeled the majority of alloreactive T cells in rejected skin grafts, suggesting that a small proportion of MHC-peptide complexes dominate the alloresponse. These findings show recognition of endogenous peptides bound to allogeneic MHC as necessary for both transplant tolerance and rejection. In the associated Commentary, Hossam

Abdelsamed and Fadi Lakkis highlight the findings as providing a much-needed tool to study polyclonal alloreactive T cells.

The self-peptide repertoire plays a critical role in transplant tolerance induction

Eric T. Son, Pouya Faridi, Moumita Paul-Heng, Mario L. Leong, Kieran English, Sri H. Ramarathinam, Asolina Braun, Nadine L. Dudek, Ian E. Alexander, Leszek Lisowski, Patrick Bertolino, David G. Bowen, Anthony W. Purcell, Nicole A. Mifsud, and Alexandra F. Sharland <http://jci.me/146771>

► Related Commentary

The role of self-peptides in direct T cell allorecognition

Hossam A. Abdelsamed and Fadi G. Lakkis

<http://jci.me/154096>

METABOLISM

Nonalcoholic fatty liver disease is unaffected by liver-specific cannabinoid signaling inhibition

Nonalcoholic fatty liver disease (NAFLD) is a common liver disease that can progress to cirrhosis but has few treatment options. Cannabinoid receptor 1 (CB-1) has been proposed as a potential target in NAFLD, on the basis of its ability to improve some aspects of metabolic syndrome. However, whether restricting peripheral cannabinoid signaling affects NAFLD remains unknown. In a recent issue of the *JCI*, Simeng Wang and colleagues engineered mice with hepatocyte- or stellate cell-specific CB-1 deficiency. In both models, mice fed a high-fat diet

developed NAFLD, and exposure to the toxic compound carbon tetrachloride induced fibrosis, similar to controls. Analysis of human livers revealed extremely low CB-1 mRNA (*Cnr1*) levels in healthy and NAFLD/nonalcoholic steatohepatitis (NASH) samples (see the associated image). These findings do not support the idea that cannabinoid signaling plays a direct role in the development of NAFLD and fibrosis. In the accompanying Commentary, Beste Mutlu and Pere Puigserver highlight the results in the context of previous contradictory reports.

Cannabinoid receptor 1 signaling in hepatocytes and stellate cells does not contribute to NAFLD

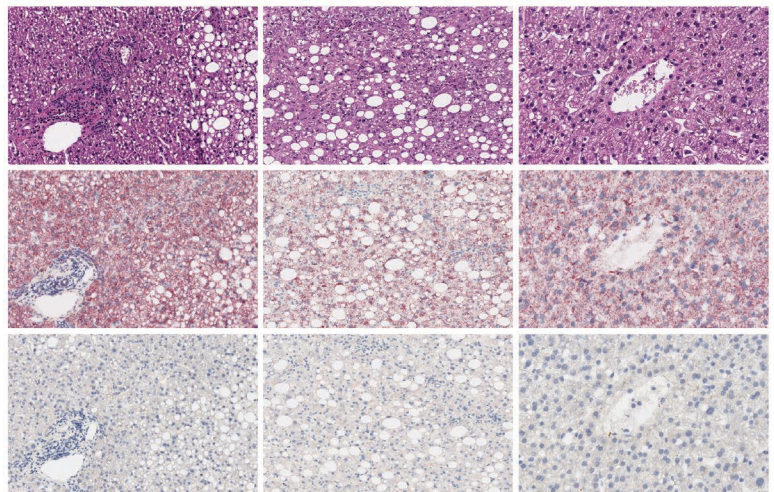
Simeng Wang, Qingzhang Zhu, Guosheng Liang, Tania Franks, Magalie Boucher, Kendra K. Bence, Mingjian Lu, Carlos M. Castorena, Shangang Zhao, Joel K. Elmquist, Philipp E. Scherer, and Jay D. Horton <http://jci.me/152242>

► Related Commentary

Controversies surrounding peripheral cannabinoid receptor 1 in fatty liver disease

Beste Mutlu and Pere Puigserver

<http://jci.me/154147>



Sex modifies cell-autonomous determinants of insulin resistance

Insulin resistance is prevalent in the general population and associates with type 2 diabetes (T2D), cardiovascular disease, and metabolic disease. Although insulin resistance is well studied on a systems level, the muscle cell properties that determine insulin resistance remain elusive. In a recent issue of the *JCI*, Nida Haider, Jasmin Lebastchi, and colleagues generated induced pluripotent stem cell–derived myoblasts (iMyos) from healthy individuals that possessed varying insulin sensitivities, and also evaluated previously acquired T2D iMyos data. iMyos derived from the most insulin-resistant individuals showed protein phosphorylation and signaling differences when compared with those with insulin sensitivity. Key proteins with dysregulated phosphorylation included IRS1, AKT, mTOR, and TBC1D1. Notably, there were major sex-specific phosphorylation and signaling differences. In the accompanying Commentary, Victoria Tokarz, Paul Delgado-Olguín, and Amira Klip highlight the broad phosphorylation

networks and a sex-specific phosphoproteomic fingerprint as advances in identifying the universal causes of insulin resistance.

Signaling defects associated with insulin resistance in nondiabetic and diabetic individuals and modification by sex

Nida Haider, Jasmin Lebastchi, Ashok Kumar Jayavelu, Thiago M. Batista, Hui Pan, Jonathan M. Dreyfuss, Ivan Carcamo-Orive, Joshua W. Knowles, Matthias Mann, and C. Ronald Kahn <http://jci.me/151818>

► Related Commentary

Deprogram and reprogram to solve the riddle of insulin resistance

Victoria L. Tokarz, Paul Delgado-Olguín, and Amira Klip

<http://jci.me/154699>

ENDOCRINOLOGY

CREBH clears circulating remnant lipoproteins to improve atherosclerosis in diabetes

Diabetes accelerates atherosclerosis and cardiovascular disease. However, targetable molecular mechanisms for the treatment and prevention of diabetes-related atherosclerosis measures remain ill defined. In a recent issue of the *JCI*, Masami Shimizu-Albergine and colleagues investigated the role of the transcription factor CREBH in the pathogenesis of atherosclerosis in type I diabetes mellitus (T1DM). In a T1DM mouse model, expression of liver-specific CREBH induced genes involved with clearing remnant lipoproteins, reduced plasma lipids and apolipoprotein E, and prevented atherosclerosis progression when compared with control mice (see the associated image). Genetic models and human studies indicated that triglyceride-rich lipoprotein remnants were cleared in the liver via a lipoprotein lipase-independent and APOE-dependent mechanism. These findings reveal that impaired remnant lipoprotein clearance promotes atherosclerosis in diabetes. In the accompanying Commentary, Alan Attie discusses the possible mechanism underlying the atherogenicity of remnant lipoproteins and highlights CREBH expression in the liver as a plausible path for preventing or treating atherosclerosis in diabetes.

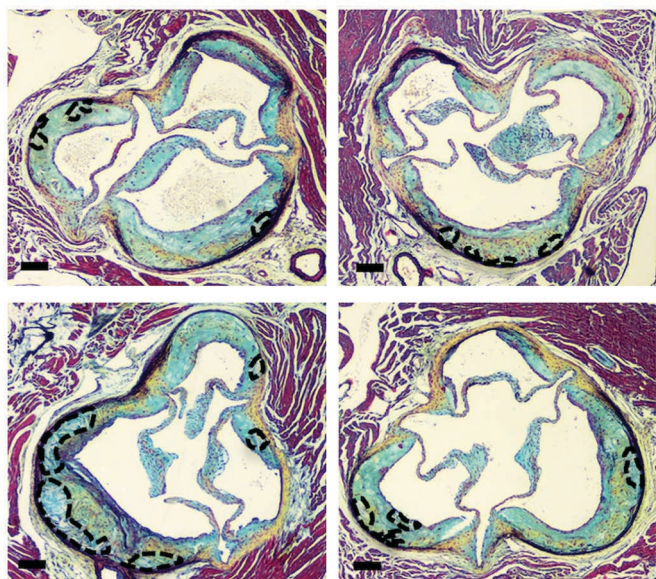
CREBH normalizes dyslipidemia and halts atherosclerosis in diabetes by decreasing circulating remnant lipoproteins

Masami Shimizu-Albergine, Debapriya Basu, Jenny E. Kanter, Farah Kramer, Vishal Kothari, Shelley Barnhart, Carissa Thornock, Adam E. Mullick, Noemie Clouet-Foraison, Tomas Vaisar, Jay W. Heinecke, Robert A. Hegele, Ira J. Goldberg, and Karin E. Bornfeldt <http://jci.me/153285>

► Related Commentary

Recruiting a transcription factor in the liver to prevent atherosclerosis

Alan D. Attie <http://jci.me/154677>



INFECTIOUS DISEASE

Alveolar macrophages from individuals with HIV have impaired antimycobacterial response

People living with HIV (PLWH) have increased susceptibility to tuberculosis (TB) despite receiving antiretroviral therapy (ART). Although alveolar macrophages (AMs) engulf *Mycobacterium tuberculosis* in the first stages of infection, the influence of HIV and ART on the AM response remains unknown. In a recent issue of the *JCI*, Wilian Correa-Macedo, Vinicius Fava, and colleagues collected AMs from control subjects, PLWH who received ART, and those without HIV who received ART as a preexposure prophylaxis. The AMs were exposed to *M. tuberculosis* in vitro. Notably, AMs from PLWH and individuals who received ART prophylactically showed blunted transcriptomic changes in response to *M. tuberculosis* compared with control subjects. Further, the epigenetic profile of AMs from both groups that received ART remained unchanged in response to *M. tuberculosis*, which contrasted with the remodeling noted for AMs from control subjects. These findings suggest that ART diminishes the AM response to *M. tuberculosis*. In the accompanying Commentary, Eileen Scully and Bryan Bryson highlight the AM phenotype at the first point of *M. tuberculosis* contact as a guide for future studies.

Alveolar macrophages from persons living with HIV show impaired epigenetic response to *Mycobacterium tuberculosis*

Wilian Correa-Macedo, Vinicius M. Fava, Marianna Orlova, Pauline Cassart, Ron Olivenstein, Joaquín Sanz, Yong Zhong Xu, Anne Dumaine, Renata H.M. Sindeaux, Vania Yotova, Alain Pacis, Josée Girouard, Barbara Kalsdorf, Christoph Lange, Jean-Pierre Routy, Luis B. Barreiro, and Erwin Schurr <http://jci.me/148013>

► Related Commentary

Unlocking the complexity of HIV and *Mycobacterium tuberculosis* coinfection

Eileen P. Scully and Bryan D. Bryson <http://jci.me/154407>

ONCOLOGY

Bladder tumors with *RAF1* amplification and MAPK-targeted agent sensitivity

Multiple genetic alterations associate with bladder cancer, but few agents are effective in treating metastatic or muscle-invasive bladder cancer (MIBC). In a recent issue of the *JCI*, Raie Bekele et al. screened The Cancer Genome Atlas for cancers that showed *RAF1* amplification. *RAF1* amplification was present in 12% of bladder

cancers but rarely occurred in other cancers. *RAF1*-amplified bladder cancer cell lines targeted with *RAF1* siRNA showed decreased RAF/MEK/ERK signaling and underwent cell death. Further, cell lines and in vivo models were sensitive to RAF inhibitors alone or in combination with MEK inhibitors (see the associated image). Notably,

bladder tumors harboring *HRAS* and *NRAS* mutations were also sensitive to RAF and MEK inhibition. These findings reveal *RAF1* as a driver in nearly 20% of MIBCs. In the accompanying Commentary, Sean Clark-Garvey and William Kim propose differential targeting of the MAPK pathway in the treatment for bladder cancer.

***RAF1* amplification drives a subset of bladder tumors and confers sensitivity to MAPK-directed therapeutics**

Raie T. Bekele, Amruta S. Samant, Amin H. Nassar, Jonathan So, Elizabeth P. Garcia, Catherine R. Curran, Justin H. Hwang, David L. Mayhew, Anwesha Nag, Aaron R. Thorner, Judit Börcsök, Zsófia Sztupinszki, Chong-Xian Pan, Joaquim Bellmunt, David J. Kwiatkowski, Guru P. Sonpavde, Eliezer M. Van Allen, and Kent W. Mouw

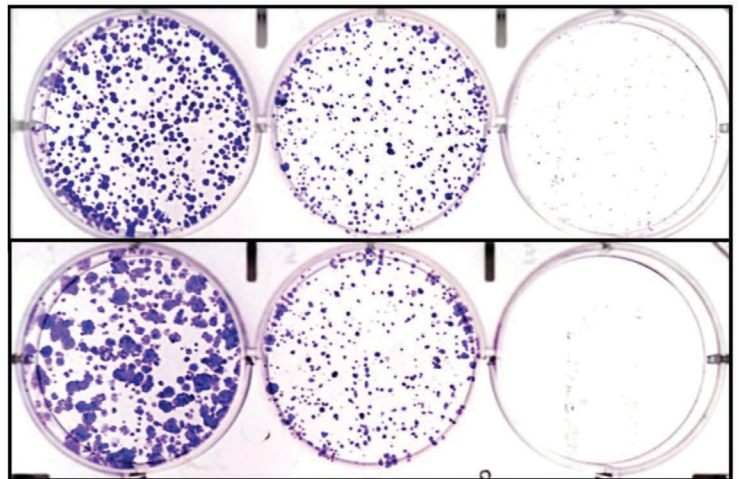
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► **Related Commentary**

***RAF1* amplification: an exemplar of MAPK pathway activation in urothelial carcinoma**

Sean Clark-Garvey and William Y. Kim

<http://jci.me/154095>



VASCULAR BIOLOGY

Protein kinase N2 regulates vascular tone via endothelial NOS phosphorylation

Blood pressure and vascular tone are regulated by nitric oxide (NO) production via endothelial NO synthase (eNOS) activation that occurs in response to force exerted by blood flow against vessel walls. However, the mechanism by which fluid shear stress stimulates eNOS phosphorylation remains unknown. In a recent issue of the *JCI*, Young-June Jin and colleagues examined the role of protein kinase N2 (PKN2) in the regulation of flow-induced eNOS. PKN2 phosphorylated eNOS indirectly via AKT at serine 1177 and directly at the less-characterized serine 1179 site, and phosphorylation at both sites additively induced eNOS activity. Mice deficient in PKN2 in endothelial cells showed reduced eNOS activity and reduced flow-induced vasodilation and developed arterial hypertension. In the accompanying Commentary, David Fulton and David Stepp highlight PKN2 as having a key role in shear stress response, NO production, and vascular functions, including blood pressure.

Protein kinase N2 mediates flow-induced endothelial NOS activation and vascular tone regulation

Young-June Jin, Ramesh Chennupati, Rui Li, Guozheng Liang, ShengPeng Wang, András Iring, Johannes Graumann, Nina Wettschureck, and Stefan Offermanns

<http://jci.me/145734>

► **Related Commentary**

Protein kinase N2 connects blood flow with NO production in a double AKT

David J.R. Fulton and David W. Stepp

<http://jci.me/154256>

TRANSPLANTATION

Recipient APOL1 risk alleles associate with death-censored renal allograft loss

Kidney transplants in people of African ancestry are reported to associate with poorer outcomes. Although donor kidneys carrying exonic *APOL1* risk variants (which are exclusively present in individuals of African ancestry) are well known to influence allograft survival, the influence of *APOL1* variants in recipients remains unknown. In a recent issue of the *JCI*, Zhongyang Zhang, Zeguo Sun, and colleagues correlated *APOL1* genotypes with outcomes using the Genomics of Chronic Allograft Rejection (GOCAR) and Clinical Trials in Organ Transplantation (CTOT) kidney transplant cohorts. Recipient G1 or G2 variants associated with death-censored allograft loss and T cell-mediated rejection. *APOL1* was expressed in PBMCs. Notably, among healthy controls and pretransplant patients, individuals with a G1 or G2 genotype had a transcriptomic signature of immune activation in PBMCs when compared with those with a G0 genotype. These studies highlight *APOL1* risk variants as affecting immune pathways to negatively affect kidney transplant outcomes. In the accompanying Commentary, Andrew Malone discusses

the intrinsic and extrinsic mechanisms by which *APOL1* risk variants influence kidney outcomes.

Recipient APOL1 risk alleles associate with death-censored renal allograft survival and rejection episodes

Zhongyang Zhang, Zeguo Sun, Jia Fu, Qisheng Lin, Khadija Banu, Kinsuk Chauhan, Marina Planoutene, Chengguo Wei, Fadi Salem, Zhengzi Yi, Ruijie Liu, Paolo Cravedi, Haoxiang Cheng, Ke Hao, Philip J. O'Connell, Shuta Ishibe, Weijia Zhang, Steven G. Coca, Ian W. Gibson, Robert B. Colvin, John Cijiang He, Peter S. Heeger, Barbara Murphy, and Madhav C. Menon

<http://jci.me/146643>

► Related Commentary

APOL1 risk variants in kidney transplantation: a modulation of immune cell function

Andrew F. Malone <http://jci.me/154676>

CONVERSATIONS WITH GIANTS IN MEDICINE

A conversation with Katalin Karikó

Biochemist Katalin Karikó's work on nucleoside modifications able to suppress the immunogenicity of RNA is among the key advances that made rapid development of mRNA-based vaccines against SARS-CoV-2 possible. Dr. Karikó, now Senior Vice President at BioNTech SE, shares the 2021 Lasker~DeBakey Clinical Medical Research Award with Dr. Drew Weissman for their contributions to technology underlying the lifesaving and highly effective COVID-19 mRNA vaccines. In a recent interview with *JCI*'s Editor at large Ushma Neill, Dr. Karikó discussed her early career and the years of work that led to her transformative discoveries.

<http://jci.me/155559>



COVID-19

NK cell receptor and ligand composition influences the clearance of SARS-CoV-2

Wan-Chen Hsieh, En-Yu Lai, Yu-Ting Liu, Yi-Fu Wang, Yi-Shiuan Tzeng, Lu Cui, Yun-Ju Lai, Hsiang-Chi Huang, Jia-Hsin Huang, Hung-Chih Ni, Dong-Yan Tsai, Jian-Jong Liang, Chun-Che Liao, Ya-Ting Lu, Laurence Jiang, Ming-Tsan Liu, Jann-Tay Wang, Sui-Yuan Chang, Chung-Yu Chen, Hsing-Chen Tsai, Yao-Ming Chang, Gerlinde Wernig, Chia-Wei Li, Kuo-I Lin, Yi-Ling Lin, Huai-Kuang Tsai, Yen-Tsung Huang, and Shih-Yu Chen <https://jci.me/146408>

Metabolic imbalance of T cells in COVID-19 is hallmarked by basigin and mitigated by dexamethasone

Peter J. Siska, Sonja-Maria Decking, Nathalie Babl, Carina Matos, Christina Bruss, Katrin Singer, Jana Klitzke, Marian Schön, Jakob Simeth, Josef Kostler, Heiko Siegmund, Ines Ugele, Michael G. Paulus, Alexander Dietl, Kristina Kolodova, Louisa Steines, Katharina Freitag, Alice Peuker, Gabriele Schönhammer, Johanna Raithe, Bernhard Graf, Florian Geismann, Matthias Lubnow, Matthias Mack, Peter Hau, Christopher Bohr, Ralph Burkhardt, Andre Gessner, Bernd Salzberger, Ralf Wagner, Frank Hanes, Florian Hitzebichler, Daniel Heudobler, Florian Lüke, Tobias Pukrop, Wolfgang Herr, Daniel Wolff, Rainer Spang, Hendrik Poeck, Petra Hoffmann, Jonathan Jantsch, Christoph Brochhausen, Dirk Lunz, Michael Rehli, Marina Kreutz, and Kathrin Renner <https://jci.me/148225>

Seasonal coronavirus-specific B cells with limited SARS-CoV-2 cross-reactivity dominate the IgG response in severe COVID-19

Muriel Aguilar-Bretones, Brenda M. Westerhuis, Matthijs P. Raadsen, Erwin de Bruin, Felicity D. Chandler, Nisreen M.A. Okba, Bart L. Haagmans, Thomas Langerak, Henrik Endeman, Johannes P.C. van den Akker, Diederik A.M.P.J. Gommers, Eric C.M. van Gorp, Corine H. Geurts van Kessel, Rory D. de Vries, Ron A.M. Fouchier, Barry H.G. Rockx, Marion P.G. Koopmans, and Gijsbert P. van Nierop <https://jci.me/150613>

ENDOCRINOLOGY

Identification of direct transcriptional targets of NFATC2 that promote β cell proliferation

Shane P. Simonett, Sunyoung Shin, Jacob A. Herring, Rhonda Bacher, Linsin A. Smith, Chenyang Dong, Mary E. Rabaglia, Donnie S. Stapleton, Kathryn L. Schueler, Jee Choi, Matthew N. Bernstein, Daniel R. Turkewitz, Carlos Perez-Cervantes, Jason Spaeth, Roland Stein, Jeffery S. Tessem, Christina Kendzior, Sündüz Keleş, Ivan P. Moskowitz, Mark P. Keller, and Alan D. Attie <https://jci.me/144833>

CREBH normalizes dyslipidemia and halts atherosclerosis in diabetes by decreasing circulating remnant lipoproteins ▶ p. 4

Masami Shimizu-Albergine, Debapriya Basu, Jenny E. Kanter, Farah Kramer, Vishal Kothari, Shelley Barnhart, Carissa Thornock, Adam E. Mullick, Noemie Clouet-Foraison, Tomas Vaisar, Jay W. Heinecke, Robert A. Hegele, Ira J. Goldberg, and Karin E. Bornfeldt <https://jci.me/153285>

IMMUNOLOGY

The self-peptide repertoire plays a critical role in transplant tolerance induction ▶ p. 2

Eric T. Son, Pouya Faridi, Moumita Paul-Heng, Mario L. Leong, Kieran English, Sri H. Ramarathnam, Asolina Braun, Nadine L. Dudek, Ian E. Alexander, Leszek Lisowski, Patrick Bertolino, David G. Bowen, Anthony W. Purcell, Nicole A. Mifsud, and Alexandra F. Sharland <https://jci.me/146771>

CD146 bound to LCK promotes T cell receptor signaling and antitumor immune responses in mice

Hongxia Duan, Lin Jing, Xiaoqing Jiang, Yanbin Ma, Daji Wang, Jianquan Xiang, Xuehui Chen, Zhenzhen Wu, Huiwen Yan, Junying Jia, Zheng Liu, Jing Feng, Mingzhao Zhu, and Xiyun Yan <https://jci.me/148568>

INFECTIOUS DISEASE

sEH promotes macrophage phagocytosis and lung clearance of *Streptococcus pneumoniae*

Hong Li, J. Alyce Bradbury, Matthew L. Edin, Joan P. Graves, Artiom Gruzdev, Jennifer Cheng, Samantha L. Hoopes, Laura M. DeGraff, Michael B. Fessler, Stavros Garantziotis, Shepherd H. Schurman, and Darryl C. Zeldin (ASCI) <https://jci.me/129679>

Early reduction in PD-L1 expression predicts faster treatment response in human cutaneous leishmaniasis

Nidhi S. Dey, Sujai Senaratne, Vijani Somaratne, Nayani P. Madarasinghe, Bimalka Seneviratne, Sarah Forrester, Marcela Montes de Oca, Luiza Campos Reis, Srijia Moullick, Pegine B. Walrad, Mitali Chatterjee, Hiro Goto, Renu Wickremasinghe, Dimitris Lagos, Paul M. Kaye, and Shalindra Ranasinghe <https://jci.me/142765>

Alveolar macrophages from persons living with HIV show impaired epigenetic response to *Mycobacterium tuberculosis* ▶ p. 4

Willian Correa-Macedo, Vinicius M. Fava, Marianna Orlova, Pauline Cassart, Ron Olivenstein, Joaquín Sanz, Yong Zhong Xu, Anne Dumaine, Renata H.M. Sindeaux, Vania Yotova, Alain Pacis, Josée Girouard, Barbara Kalsdorf, Christoph Lange, Jean-Pierre Routy, Luis B. Barreiro, and Erwin Schurr <https://jci.me/148013>

Ribonuclease 7 polymorphism rs1263872 reduces antimicrobial activity and associates with pediatric urinary tract infections

Keith Pierce, Tad Eichler, Claudia Mosquera Vasquez, Andrew L. Schwaderer, Aaron Simoni, Steven Creacy, David S. Hains, and John D. Spencer <https://jci.me/149807>

INFLAMMATION

Skin inflammation activates intestinal stromal fibroblasts and promotes colitis

Tatsuya Dokoshi, Jason S. Seidman, Kellen J. Cavagnero, Fengwu Li, Marc C. Liggins, Bryn C. Taylor, Jocelyn Olvera, Rob Knight, John Chang, Nita H. Salzman, and Richard L. Gallo (ASCI) <https://jci.me/147614>

METABOLISM

TRIB1 regulates LDL metabolism through CEBP α -mediated effects on the LDL receptor in hepatocytes

Katherine Quiroz-Figueroa, Cecilia Vitali, Donna M. Conlon, John S. Millar, John W. Tobias, Robert C. Bauer, Nicholas J. Hand, and Daniel J. Rader (ASCI) <https://jci.me/146775>

Inhibition of phosphodiesterase type 9 reduces obesity and cardiometabolic syndrome in mice ► p. 2

Sumita Mishra, Nandhini Sadagopan, Brittany Dunkerly-Eyring, Susana Rodriguez, Dylan C. Sarver, Ryan P. Ceddia, Sean A. Murphy, Hildur Knutsdottir, Vivek P. Jani, Deepthi Ashok, Christian U. Oeing, Brian O'Rourke, Jon A. Gangoi, Dorothy D. Sears, G. William Wong, Sheila Collins, and David A. Kass (ASCI) <https://jci.me/148798>

Signaling defects associated with insulin resistance in nondiabetic and diabetic individuals and modification by sex ► p. 3

Nida Haider, Jasmin Lebastchi, Ashok Kumar Jayavelu, Thiago M. Batista, Hui Pan, Jonathan M. Dreyfuss, Ivan Carcamo-Orive, Joshua W. Knowles, Matthias Mann, and C. Ronald Kahn (ASCI) <https://jci.me/151818>

Cannabinoid receptor 1 signaling in hepatocytes and stellate cells does not contribute to NAFLD ► p. 3

Simeng Wang, Qingzhang Zhu, Guosheng Liang, Tania Franks, Magalie Boucher, Kendra K. Bence, Mingjian Lu, Carlos M. Castorena, Shangang Zhao, Joel K. Elmquist, Philipp E. Scherer, and Jay D. Horton (ASCI) <https://jci.me/152242>

NEUROSCIENCE

Candesartan prevents arteriopathy progression in cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy model

Taisuke Kato, Ri-ichiroh Manabe, Hironaka Igarashi, Fuyuki Kametani, Sachiko Hirokawa, Yumi Sekine, Natsumi Fujita, Satoshi Saito, Yusuke Kawashima, Yuya Hatano, Shoichiro Ando, Hiroaki Nozaki, Akihiro Sugai, Masahiro Uemura, Masaki Fukunaga, Toshiya Sato, Akihide Koyama, Rie Saito, Atsushi Sugie, Yasuko Toyoshima, Hirotohi Kawata, Shigeo Murayama, Masaki Matsumoto, Akiyoshi Kakita, Masato Hasegawa, Masafumi Ihara, Masato Kanazawa, Masatoyo Nishizawa, Shoji Tsuji, and Osamu Onodera <https://jci.me/140555>

Macrophage monocarboxylate transporter 1 promotes peripheral nerve regeneration after injury in mice

Mithilesh Kumar Jha, Joseph V. Passero, Atul Rawat, Xanthe Heifetz Ament, Fang Yang, Svetlana Vidensky, Samuel L. Collins, Maureen R. Horton, Ahmet Hoke, Guy A. Rutter, Alban Latremoliere, Jeffrey D. Rothstein, and Brett M. Morrison <https://jci.me/141964>

Hyperexcitable interneurons trigger cortical spreading depression in an *Scn1a* migraine model

Eva Aufferberg, Ulrike B.S. Hedrich, Raffaella Barbieri, Daniela Miely, Bernhard Groschup, Thomas V. Wuttke, Niklas Vogel, Philipp Lühns, Ilaria Zanardi, Sara Bertelli, Nadine Spielmann, Valerie Gailus-Durner, Helmut Fuchs, Martin Hrabě de Angelis, Michael Pusch, Martin Dichgans, Holger Lerche, Paola Gavazzo, Nikolaus Plesnila, and Tobias Freilinger <https://jci.me/142202>

Initiation of migraine-related cortical spreading depolarization by hyperactivity of GABAergic neurons and Na_v1.1 channels

Oana Chever, Sarah Zerimech, Paolo Scalmani, Louisiane Lemaire, Lara Pizzamiglio, Alexandre Loucif, Marion Ayrault, Martin Krupa, Mathieu Desroches, Fabrice Duprat, Isabelle Léna, Sandrine Cestèle, and Massimo Mantegazza <https://jci.me/142203>

Exceptionally potent human monoclonal antibodies are effective for prophylaxis and treatment of tetanus in mice

Marco Pirazzini, Alessandro Grinzato, Davide Corti, Sonia Barbieri, Oneda Leka, Francesca Vallese, Marika Tonellato, Chiara Silacci-Fregni, Luca Piccoli, Eaazhisai Kandiah, Giampietro Schiavo, Giuseppe Zanotti, Antonio Lanzavecchia, and Cesare Montecucco <https://jci.me/151676>

ONCOLOGY

CHI3L1 regulates PD-L1 and anti-CHI3L1-PD-1 antibody elicits synergistic antitumor responses

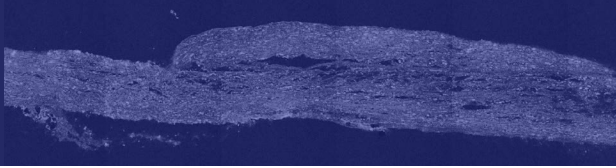
Bing Ma, Bedia Akosman, Suchitra Kamle, Chang-Min Lee, Chuan Hua He, Ja Seok Koo, Chun Geun Lee, and Jack A. Elias (ASCI) <https://jci.me/137750>

U2af1 is a haplo-essential gene required for hematopoietic cancer cell survival in mice

Brian A. Wadugu, Sridhar Nonavinkere Srivatsan, Amanda Heard, Michael O. Alberti, Matthew Ndonwi, Jie Liu, Sarah Grieb, Joseph Bradley, Jin Shao, Tanzir Ahmed, Cara L. Shirai, Ajay Khanna, Dennis L. Fei, Christopher A. Miller, Timothy A. Graubert, and Matthew J. Walter (ASCI) <https://jci.me/141401>

Folliculin impairs breast tumor growth by repressing TFE3-dependent induction of the Warburg effect and angiogenesis

Leeanna El-Houjeiri, Marco Biondini, Mathieu Paquette, Helen Kuasne, Alain Pacis, Morag Park, Peter M. Siegel, and Arnim Pause <https://jci.me/144871>



Dual role of allele-specific DNA hypermethylation within the *TERT* promoter in cancer

Donghyun D. Lee, Martin Komosa, Sumedha Sudhaman, Ricardo Leão, Cindy H. Zhang, Joana D. Apolonio, Thomas Hermanns, Peter J. Wild, Helmut Klocker, Farshad Nassiri, Gelareh Zadeh, Bill H. Diplas, Hai Yan, Steven Gallinger, Trevor J. Pugh, Vijay Ramaswamy, Michael D. Taylor, Pedro Castelo-Branco, Nuno Miguel Nunes, and Uri Tabori <https://jci.me/146915>

RAF1 amplification drives a subset of bladder tumors and confers sensitivity to MAPK-directed therapeutics ► p. 5

Raie T. Bekele, Amruta S. Samant, Amin H. Nassar, Jonathan So, Elizabeth P. Garcia, Catherine R. Curran, Justin H. Hwang, David L. Mayhew, Anwesha Nag, Aaron R. Thorner, Judit Börcsök, Zsófia Sztupinszki, Chong-Xian Pan, Joaquim Bellmunt, David J. Kwiatkowski, Guru P. Sonpavde, Eliezer M. Van Allen, and Kent W. Mouw <https://jci.me/147849>

Inflammatory cytokine-regulated tRNA-derived fragment *tRF-21* suppresses pancreatic ductal adenocarcinoma progression

Ling Pan, Xudong Huang, Zexian Liu, Ying Ye, Rui Li, Jialiang Zhang, Guandi Wu, Ruihong Bai, Lisha Zhuang, Lusheng Wei, Mei Li, Yanfen Zheng, Jiachun Su, Junge Deng, Shuang Deng, Lingxing Zeng, Shaoping Zhang, Chen Wu, Xu Che, Chengfeng Wang, Rufu Chen, Dongxin Lin, and Jian Zheng <https://jci.me/148130>

Therapeutic implications of activating noncanonical *PIK3CA* mutations in head and neck squamous cell carcinoma

Nan Jin, Bhumsuk Keam, Janice Cho, Michelle J. Lee, Hye Ryun Kim, Hayarpi Torosyan, Natalia Jura, Patrick K.S. Ng, Gordon B. Mills, Hua Li, Yan Zeng, Zohar Barbash, Gabi Tarcic, Hyunseok Kang, Julie E. Bauman, Mi-Ok Kim, Nathan K. VanLandingham, Danielle L. Swaney, Nevan J. Krogan, Daniel E. Johnson, and Jennifer R. Grandis (ASCI) <https://jci.me/150335>

RBMS1 regulates lung cancer ferroptosis through translational control of *SLC7A11*

Wenjing Zhang, Yu Sun, Lu Bai, Lili Zhi, Yun Yang, Qingzhi Zhao, Chaoqun Chen, Yangfan Qi, Wenting Gao, Wenxia He, Luning Wang, Dan Chen, Shujun Fan, Huan Chen, Hai-Long Piao, Qinglong Qiao, Zhaochao Xu, Jinrui Zhang, Jinyao Zhao, Sirui Zhang, Yue Yin, Chao Peng, Xiaoling Li, Quentin Liu, Han Liu, and Yang Wang <https://jci.me/152067>

Micropeptide ASAP encoded by *LINC00467* promotes colorectal cancer progression by directly modulating ATP synthase activity

Qiwei Ge, Dingjiacheng Jia, Dong Cen, Yadong Qi, Chengyu Shi, Junhong Li, Lingjie Sang, Luo-jia Yang, Jiamin He, Aifu Lin, Shujie Chen, and Liangjing Wang <https://jci.me/152911>

Cul4A-*DDB1*-mediated monoubiquitination of phosphoglycerate dehydrogenase promotes colorectal cancer metastasis via increased *S*-adenosylmethionine

Yajuan Zhang, Hua Yu, Jie Zhang, Hong Gao, Siyao Wang, Shuxian Li, Ping Wei, Ji Liang, Guanzhen Yu, Xiongjun Wang, Xinxiang Li, Dawei Li, and Weiwei Yang <https://jci.me/146187>

LIN28B alters ribosomal dynamics to promote metastasis in *MYCN*-driven malignancy

Pavlos Missios, Edroaldo Lummertz da Rocha, Daniel S. Pearson, Julia Philipp, Maria M. Aleman, Mehdi Pirouz, Dorian Farache, Joseph W. Franses, Caroline Kubaczka, Kaloyan M. Tsanov, Deepak K. Jha, Brian Pepe-Mooney, John T. Powers, Richard I. Gregory, Amy S.Y. Lee, Daniel Dominguez, David T. Ting, and George Q. Daley (ASCI) <https://jci.me/145142>

PULMONOLOGY

Machine learning-driven identification of early-life air toxic combinations associated with childhood asthma outcomes

Yan-Chak Li, Hsiao-Hsien Leon Hsu, Yoojin Chun, Po-Hsiang Chiu, Zoe Arditi, Luz Claudio, Gaurav Pandey, and Supinda Bunyavanich (ASCI) <https://jci.me/152088>

TRANSPLANTATION

Recipient *APOL1* risk alleles associate with death-censored renal allograft survival and rejection episodes ► p. 6

Zhongyang Zhang, Zeguo Sun, Jia Fu, Qisheng Lin, Khadija Banu, Kinsuk Chauhan, Marina Planoutene, Chengguo Wei, Fadi Salem, Zhengzi Yi, Ruijie Liu, Paolo Cravedi, Haoxiang Cheng, Ke Hao, Philip J. O'Connell, Shuta Ishibe, Weijia Zhang, Steven G. Coca, Ian W. Gibson, Robert B. Colvin, John Cijiang He, Peter S. Heeger, Barbara Murphy, and Madhav C. Menon <https://jci.me/146643>

Transcription factor *FOXF1* identifies compartmentally distinct mesenchymal cells with a role in lung allograft fibrogenesis

Russell R. Braeuer, Natalie M. Walker, Keizo Misumi, Serina Mazzoni-Putman, Yoshiro Aoki, Ruohan Liao, Ragini Vittal, Gabriel G. Kleer, David S. Wheeler, Jonathan Z. Sexton, Carol F. Farver, Joshua D. Welch, and Vibha N. Lama (ASCI) <https://jci.me/147343>

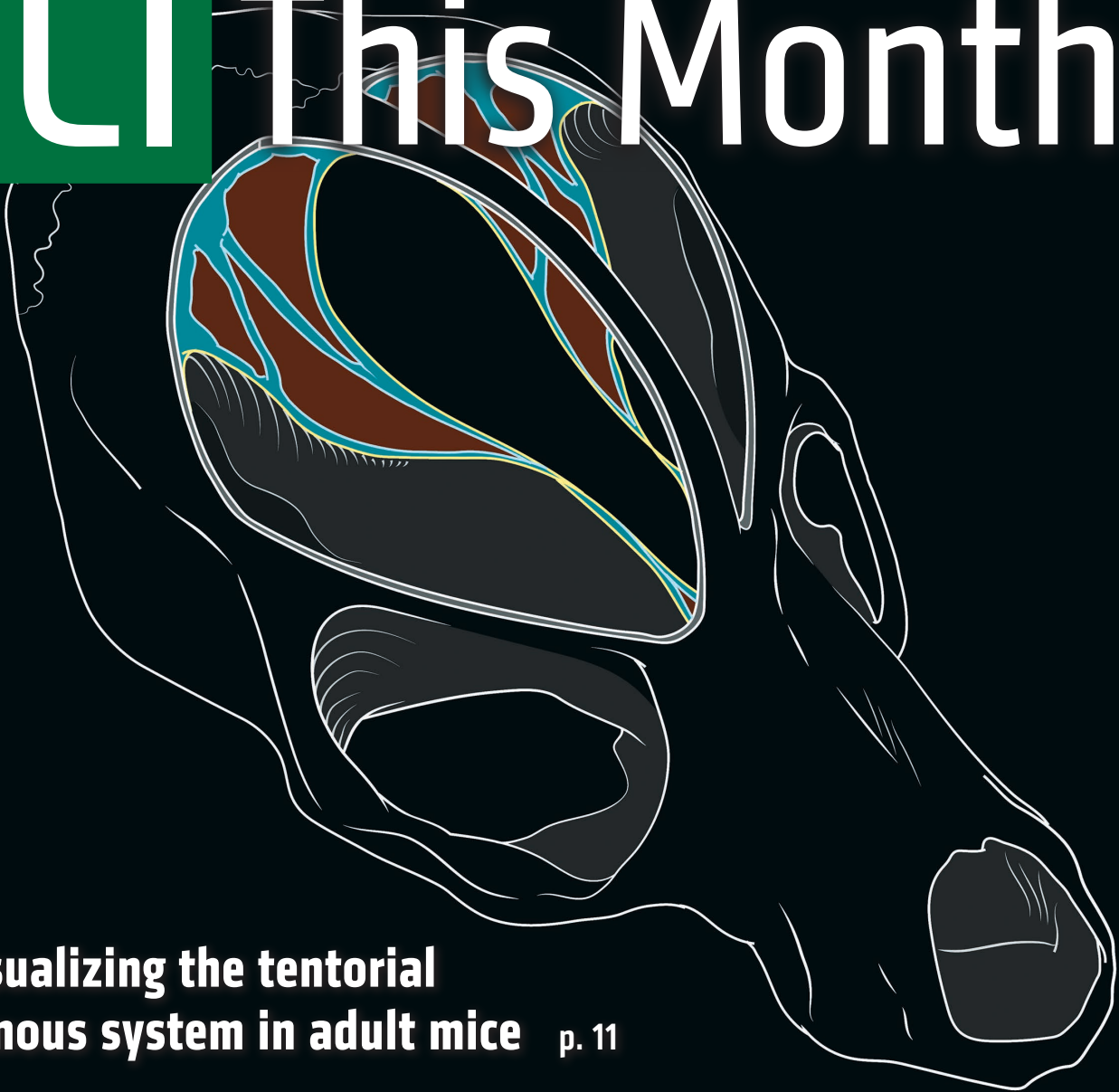
VASCULAR BIOLOGY

Protein kinase *N2* mediates flow-induced endothelial *NOS* activation and vascular tone regulation ► p. 5

Young-June Jin, Ramesh Chennupati, Rui Li, Guozheng Liang, ShengPeng Wang, András Iring, Johannes Graumann, Nina Wettschureck, and Stefan Offermanns <https://jci.me/145734>

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JCI This Month



**Visualizing the tentorial
venous system in adult mice** p. 11

December 2021

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jci.org/this-month

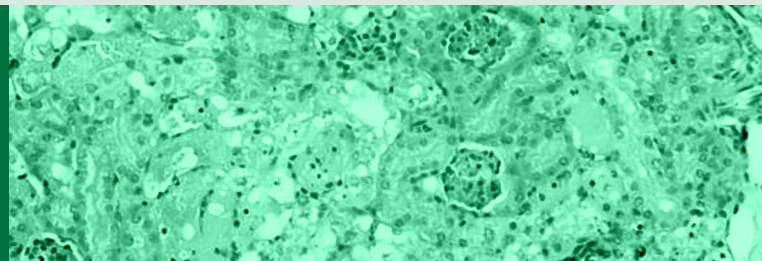
JCI insight

Ozone-activated mast cells drive airway hyperresponsiveness **13**

SPINK1 expression marks radioresistance-promoting tumor hypoxia **13**

IL-33-decorated NETs stimulate lupus-like IFN pathology **12**

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Publication highlights

Coleman DM, Wang Y, Yang ML, Hunker KL, Birt I, Bergin IL, Li JZ, Caridi J, Ganesh SK. Molecular genetic evaluation of pediatric renovascular hypertension due to renal artery stenosis and abdominal aortic coarctation in neurofibromatosis type 1 [published ahead of print September 2, 2021]. *Hum Mol Genet*. <https://doi.org/10.1093/hmg/ddab241>.

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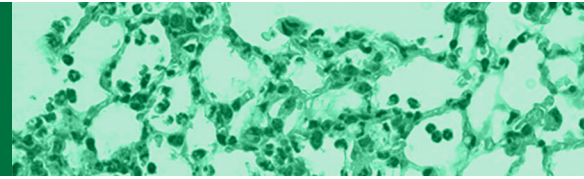
Kim E, Saw J, Kadian-Dodov D, Wood M, Ganesh SK. Fibromuscular dysplasia and spontaneous coronary artery dissection: Sex-biased arterial diseases with clinical and genetic pleiotropy. *Circ Res*. 2021;128(12):1958–1972.

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(ASCI) indicates corresponding authors who are ASCI members.

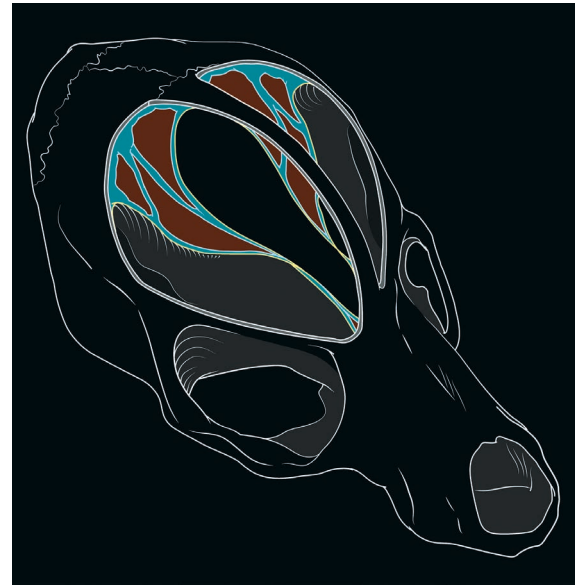


VASCULAR BIOLOGY

ON THE JCI INSIGHT COVER

Visualizing the tentorial venous system in adult mice

The tentorium is a fold of the dura mater that separates the cerebrum and cerebellum. Understanding tentorial anatomy is important when planning surgical approaches, as venous regions of the tentorium must be avoided to prevent complications. In a recent issue of *JCI Insight*, Pashayar Lookian et al. follow up on their recent description of a functionally relevant transtentorial venous system (TTVS) connecting venous drainage of distant regions of the brain in adult humans with similarities to embryonic cerebral venous drainage systems. The present study characterizes an analogous TTVS in adult mice using vascular casting and ex vivo micro-CT. High-resolution MRI confirmed that the transition of the tentorial venous plexus from the embryonic to adult configuration in mice corresponded to the human developmental timeline, further supporting the suitability of mice as a translational model for studying intracranial pathologies related to the TTVS, such as arteriovenous malformations. In the cover image, the lateral, medial, and intermediate veins of the adult mouse TTVS originating from the dural sinuses are overlaid in blue atop the tentorium (maroon, with its edges shown in yellow). Image credit: Erina He.



Tentorial venous anatomy of mice and humans

Pashayar P. Lookian, Vikram Chandrashekar, Anthony Cappadona, Jean-Paul Bryant, Vibhu Chandrashekar, Jessa M. Tunacao, Danielle R. Donahue, Jeeva P. Munasinghe, James G. Smirniotopoulos, John D. Heiss, Zhengping Zhuang, and Jared S. Rosenblum

<http://jci.me/151222>

COVID-19

Comparing upper airway cellular responses to influenza A and SARS-CoV-2

Immune and epithelial responses in the upper airway are a first line of defense against influenza A virus and SARS-CoV-2 infections. Kevin Gao, Alan Derr, Zhiru Guo, and colleagues collected nasal wash samples from adults presenting with acute COVID-19 ($n = 7$ individuals) or acute influenza A ($n = 8$ individuals), as well as adults without respiratory viral infection ($n = 6$ individuals), and compared the transcriptional responses in

epithelial and immune cells. Compared with influenza A, COVID-19 was associated with decreases in IFN-associated transcripts in neutrophils, macrophages, and epithelial cells. Although epithelial cell responses to COVID-19 appeared relatively limited, macrophage interactions were intact and distinct from those documented in individuals with influenza A. These divergent cellular responses in the upper airway provide insights into the origins of

COVID-19-associated hyperinflammation in the early stages of disease.

Human nasal wash RNA-Seq reveals distinct cell-specific innate immune responses in influenza versus SARS-CoV-2

Kevin M. Gao, Alan G. Derr, Zhiru Guo, Kerstin Nündel, Ann Marshak-Rothstein, Robert W. Finberg, and Jennifer P. Wang

<http://jci.me/152288>

AUTOIMMUNITY

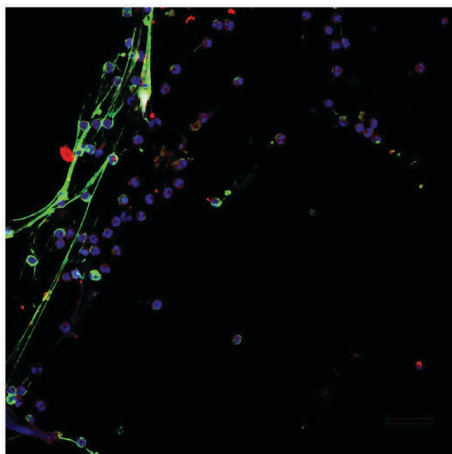
NETs complexed with bioactive IL-33 stimulate lupus-like IFN overproduction

In systemic lupus erythematosus (SLE), dysregulation in both innate and adaptive arms of the immune system drives autoimmune pathology in skin, kidneys, and other tissues. A key feature of SLE pathobiology is plasmacytoid dendritic cells (pDCs) overproducing IFN- α , which appears to be incited by neutrophil extracellular traps (NETs). Spiros Georgakis and colleagues identified increased levels of NETs complexed with the alarmin IL-33 in the peripheral blood, skin, and kidney biopsies from patients with active SLE. These patient-derived NETs were particularly enriched in bioactive isoforms of IL-33. Through a series of ex vivo and in vitro experiments using human samples, they show that IL-33-decorated NETs recapitulate lupus-like IFN- α production in pDCs. The findings link neutrophil activation with IFN pathology and suggest that targeting NET-derived IL-33 may have beneficial effects in SLE. The accompanying image represents patient-derived NETs (green) decorated with IL-33 (red).

NETs decorated with bioactive IL-33 infiltrate inflamed tissues and induce IFN- α production in patients with SLE

Spiros Georgakis, Katerina Gkirtzimanaki, Garyfalia Papadaki, Hariklia Gakiopoulou, Elias Drakos, Maija-Leena Eloranta, Manousos Makridakis, Georgia Kontostathi, Jerome Zoidakis, Eirini Baira, Lars Rönnblom, Dimitrios T. Boumpas, Prodromos Sidiropoulos, Panayotis Verginis, and George Bertias

<http://jci.me/147671>



ENDOCRINOLOGY

Tie2⁺ endothelial and hematopoietic cells mediate hepatic benefits of semaglutide

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) like semaglutide were developed as type 2 diabetes and obesity therapeutics that reproduce the glucose-stimulating effect of endogenous GLP-1. GLP-1RAs have antiinflammatory, cardioprotective, and atheroprotective benefits that appear to be independent of their effects on glucose homeostasis, but the mechanisms underlying these benefits remain unclear. Brent McLean and colleagues interrogated the role of GLP-1R expression in Tie2⁺ endothelial and hematopoietic cells, which are not directly associated with glucose control. Inactivation of *Glp1r* in Tie2⁺ cells substantially reduced *Glp1r* expression in aorta, spleen, blood, gut, and liver, including intrahepatic $\gamma\delta$ T cells. Although Tie2-specific loss of *Glp1r* did not affect the antiatherogenic outcome of semaglutide treatment, GLP-1R expression in either endothelial or hematopoietic Tie2⁺ cells did mediate semaglutide's antiinflammatory effects in the liver. The results indicate that, beyond the effects of weight loss, a distinct subset of cells contributes to the hepatic benefits of GLP-1Rs.

Differential importance of endothelial and hematopoietic cell GLP-1Rs for cardiometabolic versus hepatic actions of semaglutide

Brent McLean, Chi Kin Wong, Kiran Deep Kaur, Randy J. Seeley, and Daniel J. Drucker

<http://jci.me/153732>

NEUROSCIENCE

A microglial endosomal-lysosomal pathway regulates brain progranulin levels

Genetic variations causing reduced expression of the secreted glycoprotein progranulin (PGRN, encoded by *GRN*) are linked to several neurodegenerative diseases in humans. PGRN is produced by both neurons and activated microglia, but the mechanisms that control PGRN levels are not well understood. Tingting Dong, Leon Tejwani, and colleagues examined the role of Nemo-like kinase (Nlk) in modulating PGRN levels and PGRN-linked pathogenesis. In mouse models and cultured cells, they found that reducing Nlk in microglia, but not neurons, enhanced endosomal-lysosomal trafficking of PGRN, enhancing PGRN degradation. Moreover, *Nlk* heterozygosity interacted with *Grn* haploinsufficiency to promote neurodegenerative pathology in a mouse model. The results highlight a microglial pathway regulating PGRN levels that may be relevant to the pathophysiology of multiple human neurodegenerative diseases.

Microglia regulate brain progranulin levels through the endocytosis/lysosomal pathway

Tingting Dong, Leon Tejwani, Youngseob Jung, Hiroshi Kokubu, Kimberly Luttik, Terri M. Driessen, and Janghoo Lim

<http://jci.me/136147>

IMMUNOLOGY

ATP-activated mast cells contribute to ozone-induced bronchial hyperresponsiveness

Individuals with asthma and other underlying lung diseases are particularly prone to bronchial hyperresponsiveness (BHR) in the presence of ozone, an oxidant produced when motor vehicle emissions react with sunlight. Xiaomei Kong, Stephen Tilley, and colleagues identified mast cells as important mediators of ozone-induced BHR. In mice, ozone-induced ATP release from airway epithelial cells triggered mast cell degranulation via the P2X7 purinergic receptor. Ozone-stimulated BHR was attenuated in both mast cell-deficient and P2X7-deficient mice. Mast cell-deficient mice reconstituted with P2X7-deficient mast cells developed weaker ozone-induced BHR than did mice reconstituted with WT mast cells, further supporting the important contribution of mast cells and extracellular ATP to the adverse pulmonary effects of ozone.

Identification of an ATP/P2X7/mast cell pathway mediating ozone-induced bronchial hyperresponsiveness

Xiaomei Kong, William C. Bennett, Corey M. Jania, Kelly D. Chason, Zachary German, Jennifer Adouli, Samuel D. Budney, Brandon T. Oby, Catharina van Heusden, Eduardo R. Lazarowski, Ilona Jaspers, Scott H. Randell, Barry A. Hedgspeth, Glenn Cruse, Xiaoyang Hua, Stephen A. Schworer, Gregory J. Smith, Samir N.P. Kelada, and Stephen L. Tilley

<http://jci.me/140207>

Tregs adapt to IL-2-independent survival in the small intestine epithelium

Immunosuppressive Tregs play an important role in limiting autoimmunity in peripheral tissues. Although the molecular pathways that differentiate naive CD4⁺ T cells into Tregs in the periphery have not been fully characterized, the majority of peripheral Tregs express the high-affinity IL-2 receptor (IL-2R) and require signaling by the cytokine IL-2. In a recent issue of *JCI Insight*, Praveen Prakhar and colleagues describe a population of Foxp3⁺ Tregs in the small intestine (SI) epithelium that lack CD25 (IL-2R α), a subunit of the IL-2R complex. Surprisingly, such SI epithelial Tregs displayed robust suppressor function and produced copious amounts of CTLA-4 and IL-10, without a requirement for IL-2. Adoptive transfer of GFP-tagged Foxp3⁺ Tregs indicated that peripheral Tregs were able to adapt their phenotype and survival requirements to the specific environment of the SI epithelium. Further work to uncover the pathways that enable this adaptation may shed light on molecular mechanisms that establish and maintain Treg identity.

The small intestine epithelium exempts Foxp3⁺ Tregs from their IL-2 requirement for homeostasis and effector function

Praveen Prakhar, Jaylene Alvarez-DelValle, Hilary Keller, Assiatu Crossman, Xuguang Tai, Yoo Kyoung Park, and Jung-Hyun Park

<http://jci.me/149656>

ONCOLOGY

SPINK1 linked to tumor hypoxia and radiotherapy resistance

Solid tumors are prone to regions of hypoxia that result from imbalances between vascular oxygen supply and tumor demand. Hypoxic tumors display approximately 3-fold greater resistance to radiotherapy, and effective strategies to restore sensitivity are needed. Tatsuya Suwa and colleagues have identified serine protease inhibitor Kazal type 1 (SPINK1) as a potential target to

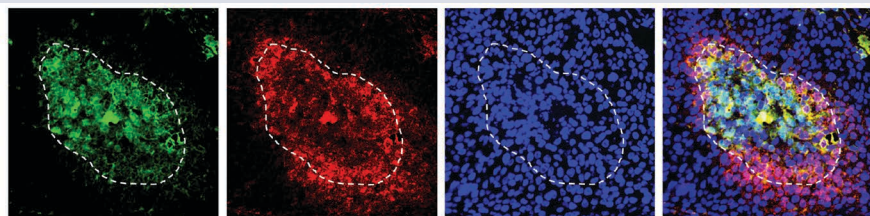
combat radioresistance in hypoxic tumors. They demonstrated that, in xenografted and clinical tumor tissues, SPINK1 mainly colocalized with hypoxic regions but diffused to the relatively oxygenated regions, too (the representative images show a hypoxic region in green and SPINK1 expression in red). Paracrine secretion of SPINK1 enhanced cancer cell radioresistance, even under

normoxic conditions. Targeting SPINK1 with a neutralizing antibody improved radiosensitivity, supporting further investigation of SPINK1 as a target for improving solid tumor responses to radiotherapy.

SPINK1 as a plasma marker for tumor hypoxia and a therapeutic target for radiosensitization

Tatsuya Suwa, Minoru Kobayashi, Yukari Shirai, Jin-Min Nam, Yoshiaki Tabuchi, Norihiko Takeda, Shusuke Akamatsu, Osamu Ogawa, Takashi Mizowaki, Ester M. Hammond, and Hiroshi Harada

<http://jci.me/148135>



Identification of an ATP/P2X7/mast cell pathway mediating ozone-induced bronchial hyperresponsiveness ► p. 13

Xiaomei Kong, William C. Bennett, Corey M. Jania, Kelly D. Chason, Zachary German, Jennifer Adouli, Samuel D. Budney, Brandon T. Oby, Catharina van Heusden, Eduardo R. Lazarowski, Ilona Jaspers, Scott H. Randell, Barry A. Hedgespeth, Glenn Cruse, Xiaoyang Hua, Stephen A. Schworer, Gregory J. Smith, Samir N.P. Kelada, and Stephen L. Tilley <http://jci.me/140207>

$\alpha_v\beta_8$ integrin targeting to prevent posterior capsular opacification

Mahbubul H. Shihan, Samuel G. Novo, Yan Wang, Dean Sheppard, Amha Atakilit, Thomas D. Arnold, Nicole M. Rossi, Adam P. Faranda, and Melinda K. Duncan <http://jci.me/145715>

Detection of diabetes from whole-body MRI using deep learning

Benedikt Dietz, Jürgen Machann, Vaibhav Agrawal, Martin Heni, Patrick Schwab, Julia Dienes, Steffen Reichert, Andreas L. Birkenfeld, Hans-Ulrich Häring, Fritz Schick, Norbert Stefan, Andreas Fritsche, Hubert Preissl, Bernhard Schölkopf, Stefan Bauer, and Robert Wagner <http://jci.me/146999>

NETs decorated with bioactive IL-33 infiltrate inflamed tissues and induce IFN- α production in patients with SLE ► p. 12

Spiros Georgakis, Katerina Gkirtzimanaki, Garyfalia Papadaki, Hariklia Gakiopoulou, Elias Drakos, Maija-Leena Eloranta, Manousos Makridakis, Georgia Kontostathi, Jerome Zoidakis, Eirini Baira, Lars Rönblom, Dimitrios T. Boumpas, Prodromos Sidiropoulos, Panayotis Verginis, and George Bertisias <http://jci.me/147671>

HuR/Cx40 downregulation causes coronary microvascular dysfunction in type 2 diabetes

Rui Si, Jody Tori O. Cabrera, Atsumi Tsuji-Hosokawa, Rui Guo, Makiko Watanabe, Lei Gao, Yun Sok Lee, Jae-Su Moon, Brian T. Scott, Jian Wang, Anthony W. Ashton, Jaladanki N. Rao, Jian-Ying Wang, Jason X.-J. Yuan, and Ayako Makino <http://jci.me/147982>

SPINK1 as a plasma marker for tumor hypoxia and a therapeutic target for radiosensitization ► p. 13

Tatsuya Suwa, Minoru Kobayashi, Yukari Shirai, Jin-Min Nam, Yoshiaki Tabuchi, Norihiko Takeda, Shusuke Akamatsu, Osamu Ogawa, Takashi Mizowaki, Ester M. Hammond, and Hiroshi Harada <http://jci.me/148135>

Complement-containing small extracellular vesicles from adventitial fibroblasts induce proinflammatory and metabolic reprogramming in macrophages

Sushil Kumar, Maria G. Frid, Hui Zhang, Min Li, Suzette Riddle, R. Dale Brown, Subhash Chandra Yadav, Micaela K. Roy, Monika E. Dzieciatkowska, Angelo D'Alessandro, Kirk C. Hansen, and Kurt R. Stenmark <http://jci.me/148382>

CD47 antibody blockade suppresses microglia-dependent phagocytosis and monocyte transition to macrophages, impairing recovery in EAE

Huan Wang, Gail Newton, Liguu Wu, Lih-Ling Lin, Amy S. Miracco, Sridaran Natesan, and Francis W. Luscinskas <http://jci.me/148719>

Chitinase 3-like-1 is a therapeutic target that mediates the effects of aging in COVID-19

Suchitra Kamle, Bing Ma, Chuan Hua He, Bedia Akosman, Yang Zhou, Chang-Min Lee, Wafik S. El-Deiry, Kelsey Huntington, Olin Liang, Jason T. Machan, Min-Jong Kang, Hyeon Jun Shin, Emiko Mizoguchi, Chun Geun Lee, and Jack A. Elias (ASCI) <http://jci.me/148749>

The small intestine epithelium exempts Foxp3⁺ Tregs from their IL-2 requirement for homeostasis and effector function ► p. 13

Praveen Prakhhar, Jaylene Alvarez-DelValle, Hilary Keller, Assiatu Crossman, Xuguang Tai, Yoo Kyoung Park, and Jung-Hyun Park <http://jci.me/149656>

Machine learning implicates the IL-18 signaling axis in severe asthma

Matthew J. Camiolo, Xiuxia Zhou, Qi Wei, Humberto E. Trejo Bittar, Naftali Kaminski, Anuradha Ray, and Sally E. Wenzel <http://jci.me/149945>

Basophil-derived IL-4 promotes cutaneous *Staphylococcus aureus* infection

Juan-Manuel Leyva-Castillo, Mrinmoy Das, Jennifer Kane, Maria Strakosha, Sonal Singh, Daniel Sen Hoi Wong, Alexander R. Horswill, Hajime Karasuyama, Frank Brombacher, Lloyd S. Miller, and Raif S. Geha <http://jci.me/149953>

Early IL-10 promotes vasculature-associated CD4⁺ T cells unable to control *Mycobacterium tuberculosis* infection

Catarina M. Ferreira, Ana Margarida Barbosa, Palmira Barreira-Silva, Ricardo Silvestre, Cristina Cunha, Agostinho Carvalho, Fernando Rodrigues, Margarida Correia-Neves, António G. Castro, and Egidio Torrado <http://jci.me/150060>

Antibody effector analysis of prime versus prime-boost immunizations with a recombinant measles-vectored chikungunya virus vaccine

Roland Tschismarov, Raphaël M. Zellweger, Min Jie Koh, Yan Shan Leong, Jenny G. Low, Eng Eong Ooi, Christian W. Mandl, Katrin Ramsauer, and Ruklanthi de Alwis <http://jci.me/151095>

The small RNA mascRNA differentially regulates TLR-induced proinflammatory and antiviral responses

Tao Sun, Chunxue Wei, Daoyong Wang, Xuxu Wang, Jiao Wang, Yuqing Hu, and Xiaohua Mao <http://jci.me/150833>

IL-6 receptor blockade does not slow β cell loss in new-onset type 1 diabetes

Carla J. Greenbaum, Elisavet Serti, Katharina Lambert, Lia J. Weiner, Sai Kanaparthi, Sandra Lord, Stephen E. Gitelman, Darrell M. Wilson, Jason L. Gaglia, Kurt J. Griffin, William E. Russell, Philip Raskin, Antoinette Moran, Steven M. Willi, Eva Tsalikian, Linda A. DiMeglio, Kevan C. Herold, Wayne V. Moore, Robin Goland, Mark Harris, Maria E. Craig, Desmond A. Schatz, David A. Baidal, Henry Rodriguez, Kristina M. Utzschneider, Hendrik J. Nel, Carol L. Soppe, Karen D. Boyle, Karen Cerosaletti, Lynette Keyes-Elstein, S. Alice Long, Ranjeny Thomas, James G. McNamara, Jane H. Buckner, Srinath Sanda, and the ITN058AI EXTEND Study Team <http://jci.me/150074>

Tentorial venous anatomy of mice and humans ► p. 11

Pashayar P. Lookian, Vikram Chandrashekhar, Anthony Cappadona, Jean-Paul Bryant, Vibhu Chandrashekhar, Jessa M. Tunacao, Danielle R. Donahue, Jeeva P. Munasinghe, James G. Smirniotopoulos, John D. Heiss, Zhengping Zhuang, and Jared S. Rosenblum <http://jci.me/151222>

From circRNAs to fusion circRNAs in hematological malignancies

Loelia Babin, Elissa Andraos, Steffen Fuchs, Stéphane Pyronnet, Erika Brunet, and Fabienne Meggetto <http://jci.me/151513>

Characterization of comorbidity heterogeneity among 13,667 patients with hidradenitis suppurativa

Vivian J. Hua, James M. Kilgour, Hyunje G. Cho, Shufeng Li, and Kavita Y. Sarin <http://jci.me/151872>

NK and CD8⁺ T cell phenotypes predict onset and control of CMV viremia after kidney transplant

Harry Pickering, Subha Sen, Janice Arakawa-Hoyt, Kenichi Ishiyama, Yumeng Sun, Rajesh Parmar, Richard S. Ahn, Gema Sunga, Megan Llamas, Alexander Hoffmann, Mario Deng, Suphamai Bunnapradist, Joanna M. Schaanman, David W. Gjertson, Maura Rossetti, Lewis L. Lanier, Elaine F. Reed, and CMV Systems Immunobiology Group <http://jci.me/153175>

Therapeutic radiation exposure of the abdomen during childhood induces chronic adipose tissue dysfunction

Xiaoqing Huang, Olivia A. Maguire, Jeanne M. Walker, Caroline S. Jiang, Thomas S. Carroll, Ji-Dung Luo, Emily Tonorez, Danielle Novetsky Friedman, and Paul Cohen (ASCI) <http://jci.me/153586>

Role of endothelial cells in pulmonary fibrosis via SREBP2 activation

Marcy Martin, Jiao Zhang, Yifei Miao, Ming He, Jian Kang, Hsi-Yuan Huang, Chih-Hung Chou, Tse-Shun Huang, Hsiao-Chin Hong, Shu-Han Su, Simon S. Wong, Rebecca L. Harper, Lingli Wang, Rakesh Bhattacharjee, Hsien-Da Huang, Zhen Bouman Chen, Atul Malhotra, Marlene Rabinovitch (ASCI), James S. Hagood, and John Y.-J. Shyy <http://jci.me/125635>

Microglia regulate brain progranulin levels through the endocytosis/lysosomal pathway ► p. 12

Tingting Dong, Leon Tejwani, Youngseob Jung, Hiroshi Kokubu, Kimberly Luttik, Terri M. Driessen, and Janghoo Lim <http://jci.me/136147>

DNA damage is overcome by TRIP13 overexpression during cisplatin nephrotoxicity

Taketsugu Hama, Prashanth K.B. Nagesh, Pallabita Chowdhury, Bob M. Moore II, Murali M. Yallapu, Kevin R. Regner, and Frank Park <http://jci.me/139092>

Growth factors with valproic acid restore injury-impaired hearing by promoting neuronal regeneration

Takahiro Wakizono, Hideyuki Nakashima, Tetsuro Yasui, Teppei Noda, Kei Aoyagi, Kanako Okada, Yasuhiro Yamada, Takashi Nakagawa, and Kinichi Nakashima <http://jci.me/139171>

Blocking hyaluronan synthesis alleviates acute lung allograft rejection

Jewel Imani, Kaifeng Liu, Ye Cui, Jean-Pierre Assaker, Junwen Han, Auyon J. Ghosh, Julie Ng, Shikshya Shrestha, Anthony M. Lamattina, Pierce H. Louis, Anne Hentschel, Anthony J. Esposito, Ivan O. Rosas, Xiaoli Liu, Mark A. Perrella, Jamil Azzi, Gary Visner, and Souheil El-Chemaly (ASCI) <http://jci.me/142217>

The TGF- β /HDAC7 axis suppresses TCA cycle metabolism in renal cancer

Hyeyoung Nam, Anirban Kundu, Suman Karki, Garrett J. Brinkley, Darshan S. Chandrashekar, Richard L. Kirkman, Juan Liu, Maria V. Liberti, Jason W. Locasale, Tanecia Mitchell, Sooryanarayana Varambally, and Sunil Sudarshan (ASCI) <http://jci.me/148438>

Irreversible depletion of intestinal CD4⁺ T cells is associated with T cell activation during chronic HIV infection

Osaretin E. Asowata, Alveera Singh, Abigail Ngoepe, Nicholas Herbert, Rabiah Fardoos, Kavidha Reddy, Yenzekile Zungu, Faith Nene, Ntombifuthi Mthabela, Dirhona Ramjit, Farina Karim, Katya Govender, Thumbi Ndung'u, J. Zachary Porterfield, John H. Adamson, Fusi G. Madela, Vukani T. Manzini, Frank Anderson, Alasdair Leslie, and Henrik N. Kløverpris <http://jci.me/146162>



High FODMAP diet causes barrier loss via lipopolysaccharide-mediated mast cell activation

Prashant Singh, Gintautas Grabauskas, Shi-Yi Zhou, Jun Gao, Yawen Zhang, and Chung Owyang <http://jci.me/146529>

Tumor-propagating side population cells are a dynamic subpopulation in undifferentiated pleomorphic sarcoma

Yuning Jackie Tang, Vijitha Puviindran, Yu Xiang, Yasuhiro Yahara, Hongyuan Zhang, Puviindran Nadesan, Yaru Diao, David G. Kirsch, and Benjamin A. Alman <http://jci.me/148768>

YY1 regulation by miR-124-3p promotes Th17 cell pathogenicity through interaction with T-bet in rheumatoid arthritis

Jinpiao Lin, Jifeng Tang, Junyu Lin, Yujue He, Ziqing Yu, Renquan Jiang, Bin Yang, and Qishui Ou <http://jci.me/149985>

Circulating autoreactive proteinase 3⁺ B cells and tolerance checkpoints in ANCA-associated vasculitis

Alvise Berti, Sophie Hillion, Amber M. Hummel, Young Min Son, Nedra Chriti, Tobias Peikert, Eva M. Carmona, Wayel H. Abdulahad, Peter Heeringa, Kristina M. Harris, E. William St. Clair, Paul Brunetta, Fernando C. Fervenza, Carol A. Langford, Cees G.M. Kallenberg, Peter A. Merkel, Paul A. Monach, Philip Seo, Robert F. Spiera, John H. Stone, Guido Grandi, Jie Sun, Jacques-Olivier Pers, Ulrich Specks, Divi Cornec, and the RAVE-ITN Research Group <http://jci.me/150999>

Autoreactive T cell receptors with shared germline-like α chains in type 1 diabetes

Peter S. Linsley, Fariba Barahmand-pour-Whitman, Elisa Balmas, Hannah A. DeBerg, Kaitlin J. Flynn, Alex K. Hu, Mario G. Rosasco, Janice Chen, Colin O'Rourke, Elisavet Serti, Vivian H. Gersuk, Keshav Motwani, Howard R. Seay, Todd M. Brusko, William W. Kwok, Cate Speake, Carla J. Greenbaum, Gerald T. Nepom, and Karen Cerosaletti <http://jci.me/151349>

Airway antibodies emerge according to COVID-19 severity and wane rapidly but reappear after SARS-CoV-2 vaccination

Alberto Cagigi, Meng Yu, Björn Österberg, Julia Svensson, Sara Falck-Jones, Sindhu Vangeti, Eric Åhlberg, Lida Azizmohammadi, Anna Warnqvist, Ryan Falck-Jones, Pia C. Gubisch, Mert Ödemis, Farangies Ghafoor, Mona Eisele, Klara Lenart, Max Bell, Niclas Johansson, Jan Albert, Jörgen Sälde, Deleah D. Pettie, Michael P. Murphy, Lauren Carter, Neil P. King, Sebastian Ols, Johan Normark, Clas Ahlm, Mattias N. Forsell, Anna Färnert, Karin Loré, and Anna Smed-Sörensen <http://jci.me/151463>

Clinical trial of ABCB5⁺ mesenchymal stem cells for recessive dystrophic epidermolysis bullosa

Dimitra Kiritsi, Kathrin Dieter, Elke Niebergall-Roth, Silvia Fluhr, Cristina Daniele, Jasmina Esterlechner, Samar Sadeghi, Seda Ballikaya, Leoni Erdinger, Franziska Schauer, Stella Gewert, Martin Laimer, Johann W. Bauer, Alain Hovnanian, Giovanna Zambruno, May El Hachem, Emmanuelle Bourrat, Maria Papanikolaou, Gabriela Petrof, Sophie Kitzmüller, Christen L. Ebens, Markus H. Frank, Natasha Y. Frank, Christoph Ganss, Anna E. Martinez, John A. McGrath, Jakub Tolar, and Mark A. Kluth <http://jci.me/151922>

Benign tumors in TSC are amenable to treatment by GD3 CAR T cells in mice

Ancy Thomas, Saurav Sumughan, Emilia R. Dellacecca, Rohan S. Shivde, Nicola Lancki, Zhussipbek Mukhatayev, Cristina C. Vaca, Fei Han, Levi Barse, Steven W. Henning, Jesus Zamora-Pineda, Suhail Akhtar, Nikhilesh Gupta, Jasmine O. Zahid, Stephanie R. Zack, Prathyaya Ramesh, Dinesh Jaishankar, Agnes S.Y. Lo, Joel Moss, Maria M. Picken, Thomas N. Darling, Denise M. Scholtens, Daniel F. Dilling, Richard P. Junghans, and I. Caroline Le Poole <http://jci.me/152014>

Human nasal wash RNA-Seq reveals distinct cell-specific innate immune responses in influenza versus SARS-CoV-2 ► p. 11

Kevin M. Gao, Alan G. Derr, Zhiru Guo, Kerstin Nündel, Ann Marshak-Rothstein, Robert W. Finberg, and Jennifer P. Wang <http://jci.me/152288>

Peritransplant glucocorticoids redistribute donor T cells to the bone marrow and prevent relapse after haploidentical SCT

Takayuki Inoue, Motoko Koyama, Katsuji Kaida, Kazuhiro Ikegame, Kathleen S. Ensby, Luke Samson, Shuichiro Takahashi, Ping Zhang, Simone A. Minnie, Satoshi Maruyama, Shinichi Ishii, Takashi Daimon, Takahiro Fukuda, Hirohisa Nakamae, Takahide Ara, Yumiko Maruyama, Ken Ishiyama, Tatsuo Ichinohe, Yoshiko Atsuta, Bruce R. Blazar, Scott N. Furlan, Hiroyasu Ogawa, and Geoffrey R. Hill <http://jci.me/153551>

Differential importance of endothelial and hematopoietic cell GLP-1Rs for cardiometabolic versus hepatic actions of semaglutide ► p. 12

Brent McLean, Chi Kin Wong, Kiran Deep Kaur, Randy J. Seeley, and Daniel J. Drucker (ASCI) <http://jci.me/153732>