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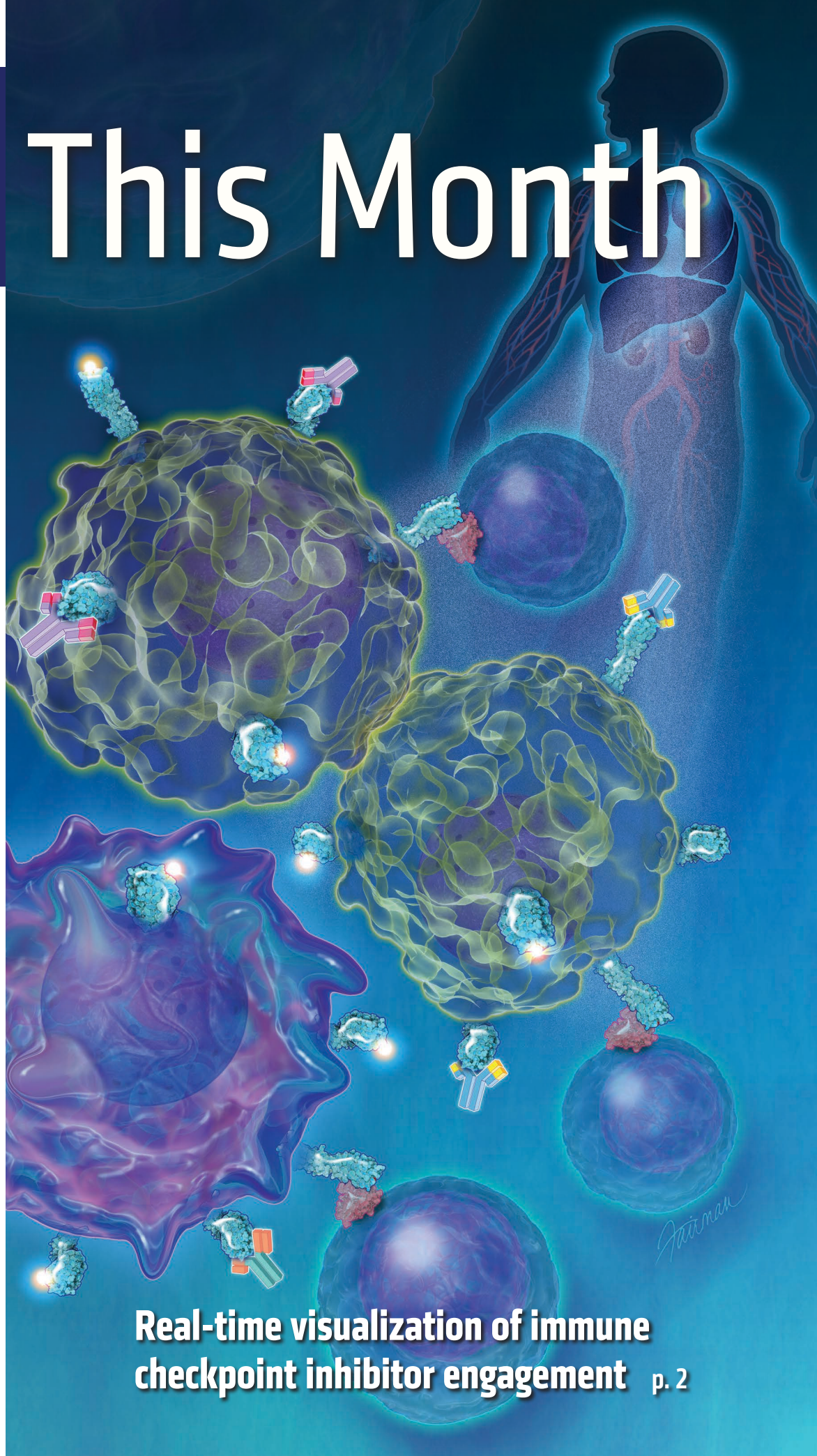
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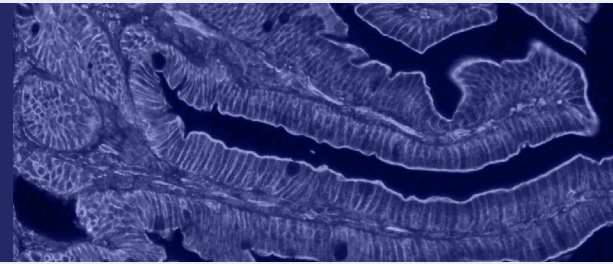
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Journal of Clinical Investigation

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Featured Editor

The JCI's Editorial Board is composed of peer scientists at Johns Hopkins University School of Medicine, the University of Maryland School of Medicine, and the National Institutes of Health. Editorial Board members review and oversee peer review of each manuscript that is submitted to the JCI, and the Board meets weekly to discuss manuscripts undergoing review.



Mary Armanios, MD, Associate Editor,

is a Professor in the Department of Oncology and the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins University School of Medicine. Her research interests have focused on understanding the role of telomeres and telomerase in disease. Dr. Armanios is a member of the American Society for Clinical Investigation. She and Dr. Agata Smogorzewska of the Rockefeller

University served as Series Editors for the reviews featured in this issue, which focus on the biology and genetics underlying familial cancer predisposition syndromes.

Publication highlights

Wagner CL, Hanumanthu VS, Talbot Jr. CC, Abraham RS, Hamm D, Gable DL, Kanakry CG, Applegate CD, Siliciano J, Jackson JB, Desiderio S, Alder JK, Luznik L, Armanios M. Short telomere syndromes cause a primary T cell immunodeficiency. *J Clin Invest*. 2018;128(12):5222–5234.

Popescu I, Mannem H, Winters SA, Hoji A, Silveira F, McNally E, Pipeling MR, Lendermon EA, Morrell MR, Pilewski JM, Hanumanthu VS, Zhang Y, Gulati S, Shah PD, Iasella CJ, Ensor CR, Armanios M, McDyer JF. Impaired CMV immunity in idiopathic pulmonary fibrosis lung transplant recipients with short telomeres [published online ahead of print August 8, 2018]. *Am J Respir Crit Care Med*. doi: 10.1164/rccm.201805-0825OC.

Alder JK, Hanumanthu VS, Strong MA, DeZern AE, Stanley SE, Takemoto CM, Danilova L, Applegate CD, Bolton SG, Mohr DW, Brodsky RA, Casella JF, Greider CW, Jackson JB, Armanios M. Diagnostic utility of telomere length testing in a hospital-based setting. *Proc Natl Acad Sci U S A*. 2018;115(10):E2358–E2365.

Stanley SE, Gable DL, Wagner CL, Carlile TM, Hanumanthu VS, Podlevsky JD, Khalil SE, DeZern AE, Rojas-Duran MF, Applegate CD, Alder JK, Parry EM, Gilbert WV, Armanios M. Loss-of-function mutations in the RNA biogenesis factor NAF1 predispose to pulmonary fibrosis-emphysema. *Sci Transl Med*. 2016;8(351):251ra107.

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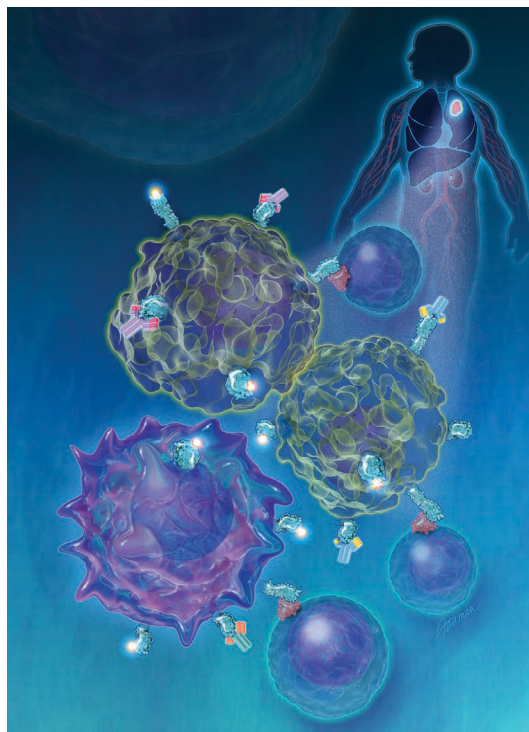
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A peptide-based PET radioligand illuminates immune checkpoint inhibitor dynamics



Therapeutic antibodies targeting immune checkpoints have the potential to dramatically improve cancer treatment, but their outcomes critically depend on adequate engagement with their targets on tumor cells. Physiological variables including tumor vascularity and location can limit drug accumulation, drug-target engagement, and treatment efficacy. Although PET imaging techniques have been used to noninvasively assess the distribution and target engagement of some oncologic drugs, this technique has not yet been applied to studies of immune checkpoint therapies or therapeutic antibodies. In this issue of the *JCI*, Dhiraj Kumar et al. describe a peptide-based PET ligand that quantifies the engagement between anti-PD-L1 therapeutic antibodies and their target. The peptide, WL12, competes for the same PD-L1 binding sites as the FDA-approved therapeutic antibodies atezolizumab, avelumab, and durvalumab, but is unable to bind PD-L1 in their presence. In xenograft-bearing mice, the radiolabeled peptide [^{64}Cu]WL12 illuminated tumor PD-L1 expression and enabled quantitative analysis of PD-L1 levels during treatment, thus providing a real-time readout on target engagement by therapeutic antibodies. This tool has the potential to provide powerful predictions about individual therapeutic responses to diverse checkpoint immunotherapies for selecting efficacious treatment regimens. The cover image illustrates the [^{64}Cu]WL12 ligand and PD-L1-targeting antibodies bound to a patient's tumor cells. Image credit: Jennifer E. Fairman, CMI, FAMI.

Peptide-based PET quantifies target engagement of PD-L1 therapeutics

Dhiraj Kumar, Ala Lisok, Elyes Dahmane, Matthew McCoy, Sagar Shelake, Samit Chatterjee, Viola Allaj, Polina Syta-Shah, Bryan Wharram, Wojciech G. Lesniak, Ellen Tully, Edward Gabrielson, Elizabeth M. Jaffee, John T. Poirier, Charles M. Rudin, Jogarao V.S. Gobburu, Martin G. Pomper, and Sridhar Nimmagadda <http://jci.me/122216>

HEMATOLOGY

Targeting mutant nucleophosmin 1 neoepitopes in acute myeloid leukemia

Although most patients with acute myeloid leukemia (AML) go into remission following standard therapies, they are at high risk of incurable relapse. Mutations in the AML driver gene nucleophosmin 1 (NPM1) are common in AML and represent a potential neoantigen target for immunotherapeutic approaches. Dyantha van der Lee and colleagues isolated a T cell receptor (TCR) specific for a particular mutated NPM1

neoantigen (ΔNMP1) and investigated its potential as a cellular immunotherapy against NPM1-mutant AML. T cells transduced with the ΔNMP1 -targeting TCR were effective in killing AML cells in an immunodeficient mouse model. The accompanying Commentary by Paul Armistead supports ΔNMP1 as a generalizable target for potentially curative cellular immunotherapies against NPM1-mutant AML.

Mutated nucleophosmin 1 as immunotherapy target in acute myeloid leukemia

Dyantha I. van der Lee, Rogier M. Reijmers, Maria W. Honders, Renate S. Hagedoorn, Rob C.M. de Jong, Michel G.D. Kester, Dirk M. van der Steen, Arnold H. de Ru, Christiaan Kweekel, Helena M. Bijen, Inge Jedema, Hendrik Veelken, Peter A. van Veelen, Mirjam H.M. Heemskerk, J.H. Frederik Falkenburg, and Marieke Griffioen <http://jci.me/97482>

► Related Commentary Cellular therapy against public neoantigens

Paul M. Armistead <http://jci.me/126116>

CARDIOLOGY

Ulk1 and Rab9 activate nonconventional cardioprotective mitophagy during ischemia

Cardiac ischemia leads to the production of excessive ROS that damage myocardial mitochondria. Autophagosomes then degrade the damaged mitochondria in a specialized form of autophagy called mitophagy. Toshiro Saito and coworkers report that cardiac ischemia activates mitophagy through a process that is distinct from classical Atg7-, Parkin-, and LC3-dependent autophagy pathways. Under energy starvation conditions, cardiac mitophagy persisted in the absence of cardiac Atg7 and Parkin expression, and was not associated with increases in LC3 proteins. Instead, the researchers found that initiation of mitophagy required interaction of the protein kinase Ulk1 with its target Rab9, a GTPase known to mediate endosome-to-*trans*-Golgi transport. As part of a protein complex, Ulk1 and Rab9 recruited *trans*-Golgi membranes to damaged mitochondria, initiating cardioprotective mitophagy. In an accompanying Commentary, Rimpdy Dhinra, Inna Rabinovich-Nikitin, and Lorrie Kirshenbaum indicate that this distinct activation pathway may reveal important

therapeutic targets for preserving mitophagy during cardiac ischemia and other forms of energy stress.

An alternative mitophagy pathway mediated by Rab9 protects the heart against ischemia

Toshiro Saito, Jihoon Nah, Shin-ichi Oka, Risa Mukai, Yoshiya Monden, Yasuhiro Maejima, Yoshiyuki Ikeda, Sebastiano Sciarretta, Tong Liu, Hong Li, Erdene Baljinnyam, Diego Fraidenraich, Luke Fritzky, Peiyong Zhai, Shizuko Ichinose, Mitsuaki Isobe, Chiao-Po Hsu, Mondira Kundu, and Junichi Sadoshima (ASCI)

<http://jci.me/122035>

► Related Commentary Ulk1/Rab9-mediated alternative mitophagy confers cardioprotection during energy stress

Rimpdy Dhinra, Inna Rabinovich-Nikitin, and Lorrie A. Kirshenbaum

<http://jci.me/125980>

Ca_v1.2 β subunits mediate β -adrenergic stimulation of cardiac output

The fight-or-flight response to acute stress triggers adrenaline release that, among other outcomes, increases cardiac contractility. Signaling through β -adrenergic receptors on cardiomyocytes enhances calcium influx to increase heart output, but the molecular pathways involved remain unclear. A study led by Steven Marx identifies the β subunit of the voltage-dependent calcium channel Ca_v1.2 as a critical effector of the cardiac fight-or-flight response and challenges fundamental assumptions that the β subunit's interactions with pore-forming α subunits are the basis for all Ca_v1.2 trafficking. Researchers observed that Ca_v1.2 α subunits continued to traffic to the cardiomyocyte's plasma membrane and form functional pores even when α subunits were modified by mutations that prevented binding to the β subunit. In the accompanying Commentary, Brooke Ahern and Jonathan Satin outline the essential role of α and β subunit interactions in adrenaline-mediated enhancement of both calcium channel conductance and cardiac contractility but not in basal Ca_v1.2 trafficking.

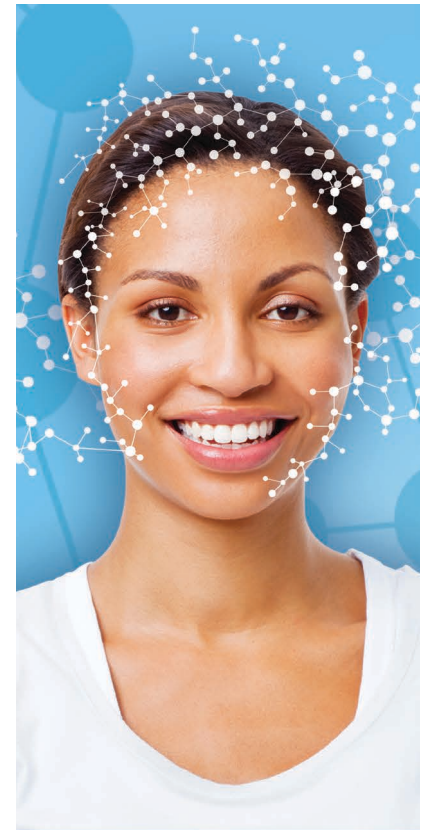
Cardiac Ca_v1.2 channels require β subunits for β -adrenergic-mediated modulation but not trafficking

Lin Yang, Alexander Katchman, Jared Kushner, Alexander Kushnir, Sergey I. Zakharov, Bi-xing Chen, Zunaira Shuja, Prakash Subramanyam, Guoxia Liu, Arianne Papa, Daniel Roybal, Geoffrey S. Pitt, Henry M. Colecraft, and Steven O. Marx (ASCI) <http://jci.me/123878>

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The L-type calcium channel current modulation mechanism: the plot thickens and fogs

Brooke M. Ahern and Jonathan Satin <http://jci.me/125958>



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AGING

Endothelial progerin accumulation accelerates cardiac fibrosis and dysfunction

The premature aging disease **Hutchinson-Gilford progeria syndrome (HGPS)** is caused by *LMNA* mutations that lead to the production of progerin, a truncated splice variant of the structural protein lamin A. HGPS patients commonly experience very early-onset cardiovascular disease (CVD), but progerin's role in its pathogenesis remains unknown. Selma Osmanagic-Myers and colleagues investigated endothelial contributions to HGPS-linked CVD in mice expressing progerin selectively in endothelial cells (*Prog-Tg* mice). *Prog-Tg* mice displayed left ventricular dysfunction and early mortality that the researchers linked to aberrant profibrotic responses. Mechanistically, progerin accumulation impaired mechanoresponses that promote eNOS production in endothelial cells, thereby enhancing a profibrotic program that contributes to CVD. As Charles Lowenstein and J. Allen Bennett describe in the accompanying Commentary, this work provides a foundation for studying endothelium-specific processes in both normal and HGPS-associated vascular aging. The associated images show progerin expression in the intimal layers of coronary arteries and within the cardiac microvasculature.

Endothelial progerin expression causes cardiovascular pathology through an impaired mechanoresponse

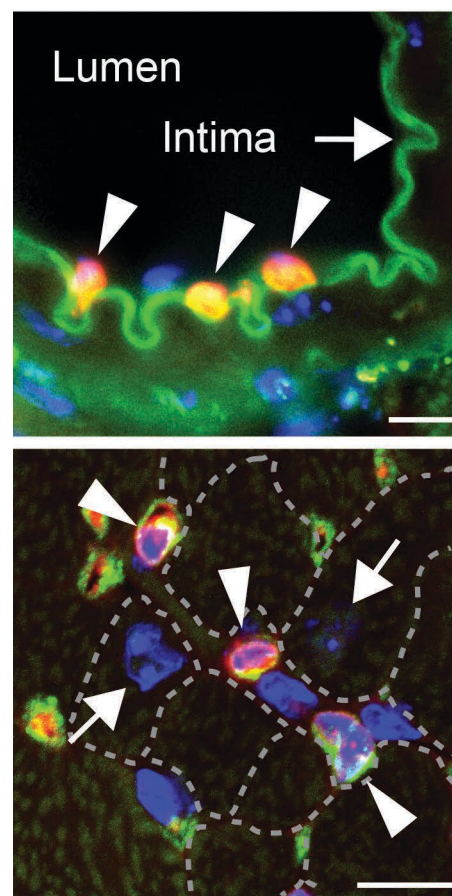
Selma Osmanagic-Myers, Attila Kiss, Christina Manakanatas, Ouafa Hamza, Franziska Sedlmayer, Petra L. Szabo, Irmgard Fischer, Petra Fichtinger, Bruno K. Podesser, Maria Eriksson, and Roland Foisner
<http://jci.me/121297>

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New vascular insights into premature aging

Charles J. Lowenstein and J. Allen Bennett

<http://jci.me/125616>



INFECTIOUS DISEASE

Identification of group A streptococcus genes that facilitate necrotizing myositis infection

Necrotizing fasciitis and myositis are rare, deadly bacterial infections characterized by rapid and severe tissue and muscle necrosis. The infections are commonly linked to the human-specific pathogen group A streptococcus (GAS), and lack of an established animal model has hindered insights into their molecular pathogenesis. Luchang Zhu, Randall Olsen, and colleagues used a nonhuman primate (NHP) model to identify the GAS virulence factors required for necrotizing myositis infection. They generated transposon insertion mutant libraries in the genetically representative GAS serotypes M1 and M28 and screened the libraries for fitness during necrotizing myositis in the NHP model. The researchers identified 13 transport proteins that contribute substantially to GAS-mediated necrotizing myositis infection and confirmed their roles in pathogenesis by infecting NHPs with isogenic mutant strains. Harry Hill's accompanying Commentary asserts that these insights into GAS pathogenicity provide a basis for further research into interventions that can treat or prevent necrotizing infections.

Gene fitness landscape of group A streptococcus during necrotizing myositis

Luchang Zhu, Randall J. Olsen, Stephen B. Beres, Jesus M. Eraso, Matthew Ojeda Saavedra, Samantha L. Kubiak, Concepcion C. Cantu, Leslie Jenkins, Amelia R. L. Charbonneau, Andrew S. Waller, and James M. Musser (ASCI) <http://jci.me/124994>

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Fitness genes of group A streptococci in necrotizing fasciitis and myositis

Harry R. Hill <http://jci.me/126482>

INFLAMMATION

Neutrophil-derived microRNAs exacerbate genomic instability and delay intestinal epithelial repair

In inflammatory bowel disease (IBD), polymorphonuclear neutrophils (PMNs) that migrate to inflamed intestinal mucosa release soluble mediators and ROS that potentiate epithelial damage. Recent observations suggest that PMN-derived microparticles deliver microRNAs that also exacerbate DNA damage and intestinal inflammation. Veronika Butin-Israeli and colleagues reveal that microparticle-mediated delivery of the proinflammatory microRNAs miR-23a and miR-155 contributes to PMN-mediated damage to the intestinal epithelium. They observed that PMN-derived microparticles induced S-phase cell-cycle arrest and DNA double-strand breaks in intestinal epithelial cells. Mechanistically, microparticle-mediated delivery of miR-23a and miR-155 stalled replication forks and impaired homologous recombination by downregulating lamin B1 and RAD51, respectively, leading to genomic instability and impaired wound healing. Eóin McNamee suggests that inhibition of these microRNAs could potentially mitigate aspects of PMN-mediated pathology in IBD and other inflammatory conditions in an accompanying Commentary.

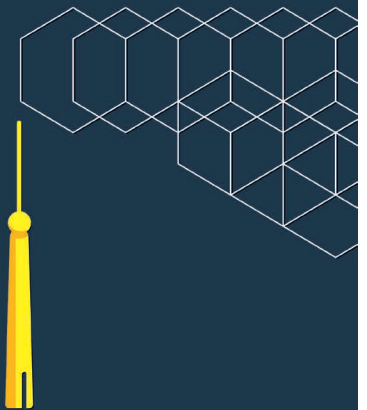
Neutrophil-induced genomic instability impedes resolution of inflammation and wound healing

Veronika Butin-Israeli, Triet M. Bui, Hannah L. Wiesolek, Lorraine Mascarenhas, Joseph J. Lee, Lindsey C. Mehl, Kaitlyn R. Knutson, Stephen A. Adam, Robert D. Goldman, Arthur Beyder, Lisa Wiesmuller, Stephen B. Hanauer, and Ronen Sumagin <http://jci.me/122085>

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Neutrophil-derived microRNAs put the (DNA) breaks on intestinal mucosal healing

Eóin N. McNamee <http://jci.me/125779>



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CONVERSATIONS WITH GIANTS IN MEDICINE



Mary-Claire King

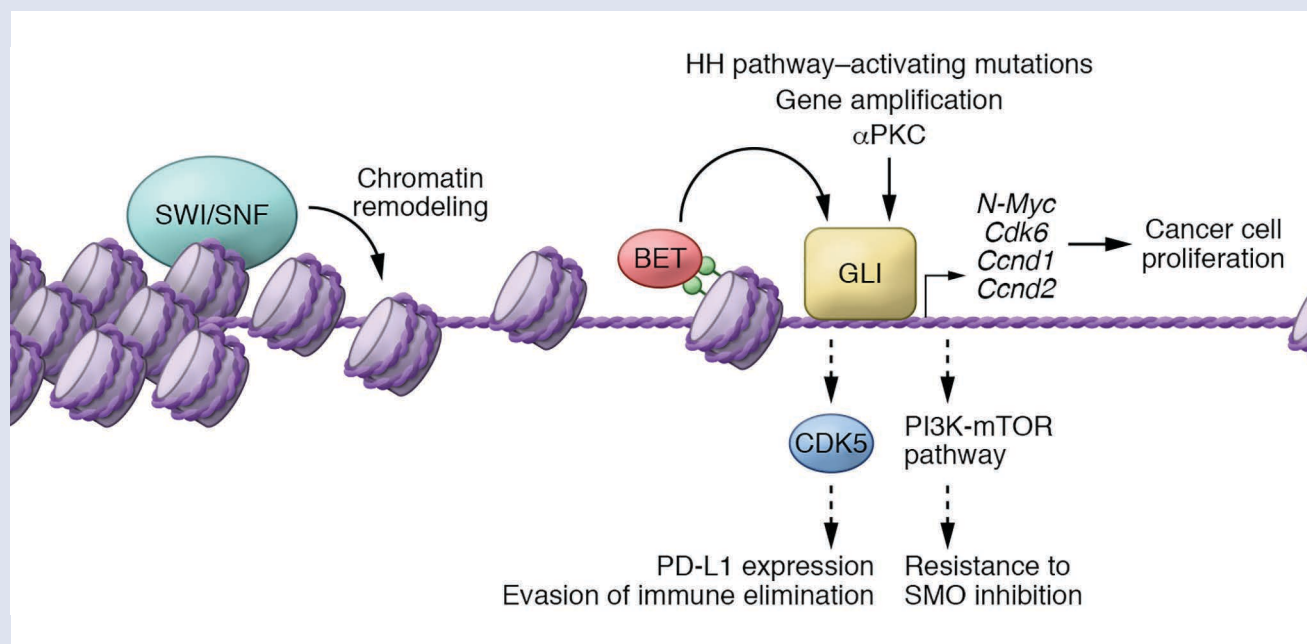
Mary-Claire King, a renowned geneticist at the University of Washington, is well known for her demonstration that the protein-coding DNA sequences of human and chimpanzees are 99% identical as well as the important discovery that *BRCA1* mutations underlie a familial risk for breast cancer. In addition to her groundbreaking scientific work, King is recognized for her lifelong involvement in social justice causes. She discusses the stories behind her accomplishments and more in an engaging interview with JCI's Editor-at-Large Ushma Neill. <http://jci.me/126050>

JCI REVIEW SERIES

BIOLOGY OF FAMILIAL CANCER PREDISPOSITION SYNDROMES

Series Editors: Mary Armanios and Agata Smogorzewska

Familial cancer predisposition syndromes spur insights into cancer biology and treatment



Heritable germline mutations are estimated to drive 10% of all cancers. These inherited cancers are manifested in pediatric as well common adult cancers. This series, curated by series editors Agata Smogorzewska and JCI Associate Editor Mary Armanios, unravels how the biology and genetics underlying familial cancer

predisposition syndromes inform our understanding of cancer etiology and biology. The Reviews focus on cancer-driving mutations in transcription factors, in developmental and metabolic signals, and in pathways that control genetic stability and provide insights linking mechanistic studies with ongoing clinical

research. An enhanced understanding of the biological basis for these familial cancers may inform the treatment of cancers driven by both germline and somatic mutations. The accompanying image from David Raleigh and Jeremy Reiter's Review depicts misregulation of the Hedgehog transcriptional program in cancer.

Misactivation of Hedgehog signaling causes inherited and sporadic cancers

David R. Raleigh and Jeremy F. Reiter <http://jci.me/120850>

Transcription factor mutations as a cause of familial myeloid neoplasms

Jane E. Churpek and Emery H. Bresnick <http://jci.me/120854>

Hypoxia, angiogenesis, and metabolism in the hereditary kidney cancers

John C. Chappell, Laura Beth Payne, and W. Kimryn Rathmell <http://jci.me/120855>

PTEN-opathies: from biological insights to evidence-based precision medicine

Lamis Yehia, Joanne Ngeow, and Charis Eng <http://jci.me/121277>

AGING

Endothelial progerin expression causes cardiovascular pathology through an impaired mechanoresponse ▶ p. 4

Selma Osmanagic-Myers, Attila Kiss, Christina Manakanatas, Ouafa Hamza, Franziska Sedlmayer, Petra L. Szabo, Irmgard Fischer, Petra Fichtinger, Bruno K. Podesser, Maria Eriksson, and Roland Foisner <http://jci.me/121297>

CARDIOLOGY

An alternative mitophagy pathway mediated by Rab9 protects the heart against ischemia ▶ p. 3

Toshiro Saito, Jihoon Nah, Shin-ichi Oka, Risa Mukai, Yoshiya Monden, Yasuhiro Maejima, Yoshiyuki Ikeda, Sebastiano Sciarretta, Tong Liu, Hong Li, Erdene Baljinnyam, Diego Fraidenraich, Luke Fritsky, Peiyong Zhai, Shizuko Ichinose, Mitsuki Isobe, Chiao-Po Hsu, Mondira Kundu, and Junichi Sadoshima (ASCI) <http://jci.me/122035>

Cardiac Ca_v1.2 channels require β subunits for β -adrenergic-mediated modulation but not trafficking ▶ p. 3

Lin Yang, Alexander Katchman, Jared Kushner, Alexander Kushnir, Sergey I. Zakharov, Bi-xing Chen, Zunaira Shuja, Prakash Subramanyam, Guoxia Liu, Arianne Papa, Daniel Roybal, Geoffrey S. Pitt, Henry M. Colecraft, and Steven O. Marx (ASCI) <http://jci.me/123878>

GENETICS

A nonhuman primate model of inherited retinal disease

Ala Moshiri, Rui Chen, Soohyun Kim, R. Alan Harris, Yumei Li, Muthuswamy Raveendran, Sarah Davis, Qingnan Liang, Ori Pomerantz, Jun Wang, Laura Garzel, Ashley Cameron, Glenn Yiu, J. Timothy Stout, Yijun Huang, Christopher J. Murphy, Jeffrey Roberts, Kota N. Gopalakrishna, Kimberly Boyd, Nikolai O. Artemyev, Jeffrey Rogers, and Sara M. Thomasy <http://jci.me/123980>

Rescue of recurrent deep intronic mutation underlying cell type-dependent quantitative NEMO deficiency

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HEMATOLOGY

In vivo hematopoietic stem cell gene therapy ameliorates murine thalassemia intermedia

Hongjie Wang, Aphrodite Georgakopoulou, Nikoletta Psatha, Chang Li, Chrysi Capsali, Himanshu Bhusan Samal, Achilles Anagnostopoulos, Anja Ehrhardt, Zsuzsanna Izsvák, Thalia Papayannopoulou, Evangelia Yannaki, and André Lieber (ASCI) <http://jci.me/122836>

Mutated nucleophosmin 1 as immunotherapy target in acute myeloid leukemia ▶ p. 2

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HEPATOLOGY

STING-mediated inflammation in Kupffer cells contributes to progression of nonalcoholic steatohepatitis

Yongsheng Yu, Yu Liu, Weishuai An, Jingwen Song, Yuefan Zhang, and Xianxian Zhao <http://jci.me/121842>

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Subdominance and poor intrinsic immunogenicity limit humoral immunity targeting influenza HA stem

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Genetic reduction of eEF2 kinase alleviates pathophysiology in Alzheimer's disease model mice

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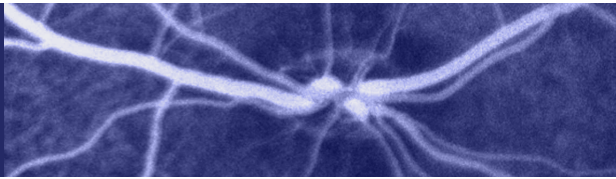
ONCOLOGY

Splicing factor SRSF1 promotes gliomagenesis via oncogenic splice-switching of MYO1B

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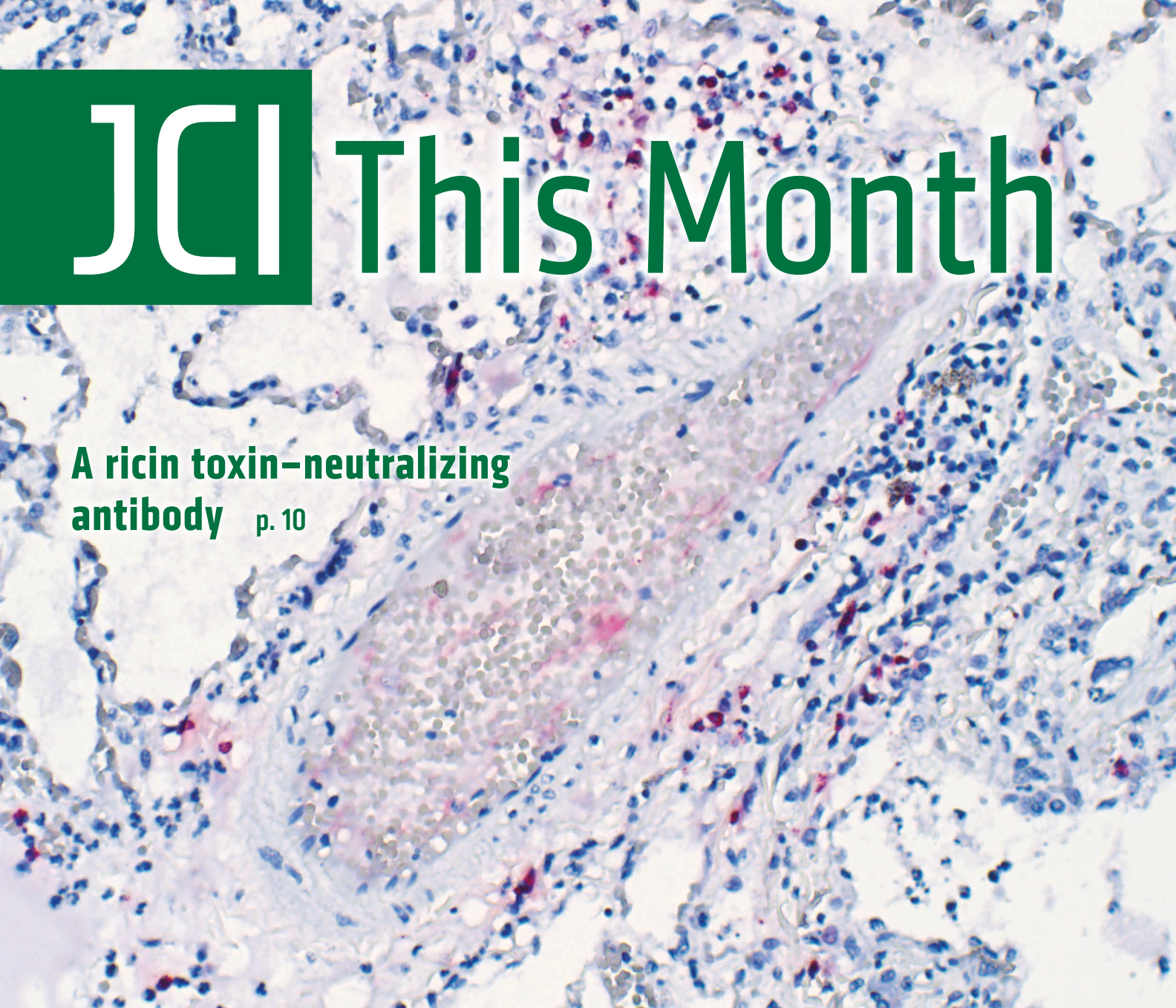
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Lineage-specific events underlie aortic root aneurysm pathogenesis in Loeys-Dietz syndrome

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JCI

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February 2019

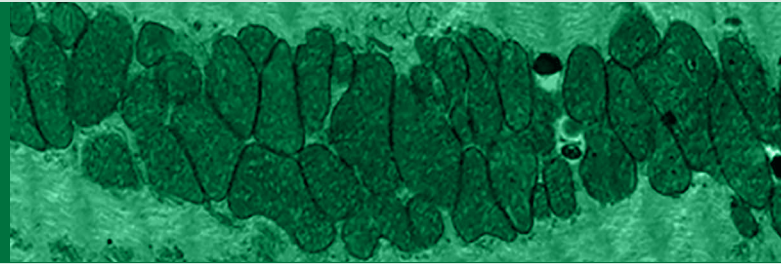
JCI **This Month** is a summary of the
most recent articles in
The Journal of Clinical Investigation
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jci.org/this-month

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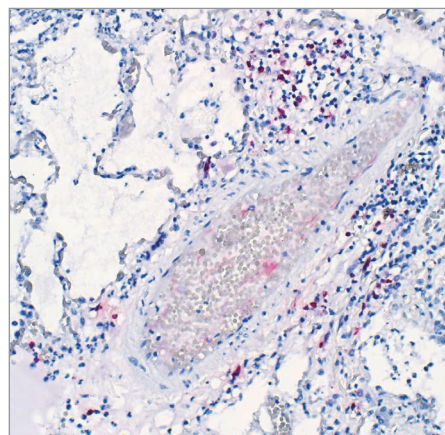
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ON THE JCI INSIGHT COVER

Rescue of rhesus macaques from the lethal effects of aerosolized ricin toxin



Ricin toxin (RT), which is derived from castor beans, is considered a high-priority biothreat due to its extreme toxicity, stability, and accessibility. When inhaled, aerosolized RT triggers acute respiratory distress characterized by pulmonary edema, alveolar cell death, accumulation of proinflammatory cytokines, and an often-lethal influx of inflammatory cells. Measures to counteract this toxin are lacking, further amplifying

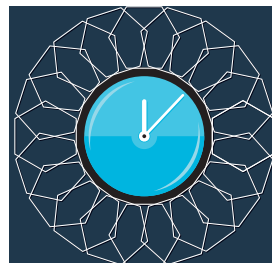
the potential of RT to be deployed as a bioweapon. In this issue, Chad Roy et al. used a rhesus macaque model to evaluate the efficacy of a humanized mAb (huPB10) that targets an immunodominant epitope on the toxin's enzymatic A chain (RTA) against RT challenge. Compared with untreated monkeys that were exposed to a lethal dose of aerosolized RT, those that received i.v. huPB10 4 hours after exposure survived. One of 5 rhesus macaques given huPB10 12 hours after RT challenge survived. Evaluation of bronchial lavage fluid from RT-challenged monkeys revealed differential expression of proinflammatory cytokines, chemokines, and growth factors in survivors compared with those that succumbed to RT. These results demonstrate that huPB10 is protective against RT exposure when given within a few hours of exposure, and they identify biomarkers that stratify the response to RT and intervention with huPB10. The cover image shows lung tissue from an RT-treated animal, with infiltrating eosinophils stained with eosinophil major basic protein antibody (crimson).

Rescue of rhesus macaques from the lethality of aerosolized ricin toxin

Chad J. Roy, Dylan J. Ehrbar, Natasha Bohorova, Ognian Bohorov, Do Kim, Michael Pauly, Kevin Whaley, Yinghui Rong, Fernando J. Torres-Velez, Ellen S. Vitetta, Peter J. Didier, Lara Doyle-Meyers, Larry Zeitlin, and Nicholas J. Mantis

<http://jci.me/124771>

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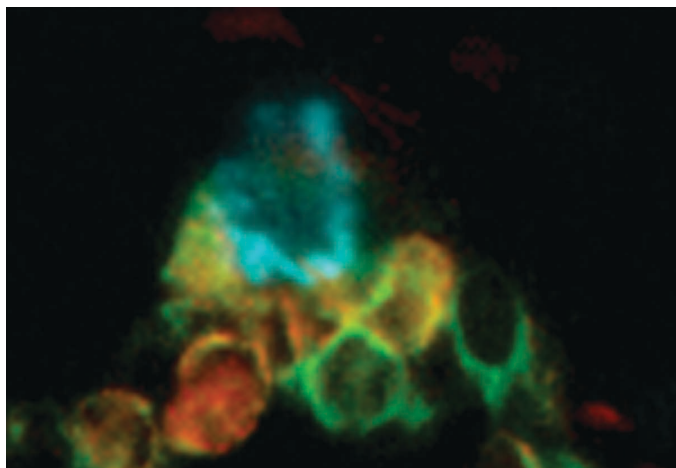
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DERMATOLOGY

Benign T cells take the lead in mycosis fungoides



Mycosis fungoides (MF) is a subtype of cutaneous T cell lymphoma (CTCL) in which malignant T cells are confined to inflammatory skin lesions. Psoralen plus UVA therapy (PUVA) is highly effective for MF, although how PUVA confers long-term remission is poorly understood. Pablo Vieyra-Garcia and colleagues analyzed the T cell and immune responses to PUVA in a small cohort of MF patients. Overall, PUVA markedly reduced skin inflammation and disease burden. However, the frequency of malignant T cell clones after treatment was variable and associated with the initial malignant T cell burden. Clinical improvement was not dependent on malignant T cell reduction but was linked to turnover of benign T cells and a switch from Th2 to Th1. Areas of skin inflammation were rich with c-Kit⁺ DCs, which formed a proinflammatory synapse with benign and malignant T cells (see the accompanying image), resulting in activation and secretion of inflammatory cytokines. These results identify benign T cells as mediators of CTCL-associated skin inflammation and as the cells primarily affected by PUVA.

Benign T cells drive clinical skin inflammation in cutaneous T cell lymphoma

Pablo Vieyra-Garcia, Jack D. Crouch, John T. O'Malley, Edward W. Seger, Chao H. Yang, Jessica E. Teague, Anna Maria Vromans, Ahmed Gehad, Thet Su Win, Zizi Yu, Elizabeth L. Lowry, Jung-Im Na, Alain H. Rook, Peter Wolf, and Rachael A. Clark (ASCI)

<http://jci.me/124233>

ONCOLOGY

Interrogation of hepatic cancer patient-derived organoids reveals heterogeneity

Liver cancer has a high rate of mortality due to a lack of effective therapeutic options. Heterogeneity within hepatic tumors has been proposed to contribute to treatment resistance; however, the prevalence of intratumor diversity has not been fully explored. Ling Li and colleagues employed patient-derived organoids (PDOs) from primary liver cancers, with multiple PDOs generated from distinct regions of a single tumor, to evaluate response to a variety of FDA-approved cancer drugs. The drug

response was variable between organoids, even those from the same tumor, indicative of intratumor and interpatient heterogeneity. Most of the drugs were ineffective or effective for only a few PDOs; however, a subset of the tested drugs was at least moderately effective in the majority of PDOs. Cumulatively, these results reveal high intratumor heterogeneity in liver cancer, support multi-region biopsy for complete tumor profile, and demonstrate the utility of PDOs for personalized drug testing.

Human primary liver cancer organoids reveal intratumor and interpatient drug response heterogeneity

Ling Li, Hildur Knutsdottir, Ken Hui, Matthew J. Weiss, Jin He, Benjamin Philosophie, Andrew M. Cameron, Christopher L. Wolfgang, Timothy M. Pawlik, Gabriel Ghiaur, Andrew J. Ewald, Esteban Mezey, Joel S. Bader, and Florin M. Selaru

<http://jci.me/121490>

CARDIOLOGY

Insulin resistance–related lipoprotein alterations prevalent in pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH)

often goes undetected until the presence of overt symptoms, such as shortness of breath and chest pain. Patients with PAH have a high prevalence of insulin resistance (IR); however, the links between these conditions are not fully understood. Anna Hemnes and colleagues evaluated IR in metabolically similar individuals with and without PAH by measuring indices of glucose homeostasis and insulin-sensitive lipoproteins. While glucose tolerance was similar between those with and without PAH, lipoprotein indices were different, with PAH patient plasma exhibiting more IR-associated alterations, including an increase in long-chain acylcarnitine, phosphatidylcholines, proteins related to insulin metabolism, and oxidized LDL receptor 1 (OLR1), findings that were validated in a second cohort. Finally, lung

tissue from PAH patients had enhanced OLR1 staining and accumulation of oxidized LDL within macrophages, suggesting that oxidized LDL may contribute to PAH-associated pulmonary inflammation.

Human PAH is characterized by a pattern of lipid-related insulin resistance

Anna R. Hemnes, J. Matthew Luther, Christopher J. Rhodes, Jason P. Burgess, James Carlson, Run Fan, Joshua P. Fessel, Niki Fortune, Robert E. Gerszten, Stephen J. Halliday, Rezzan Hekmat, Luke Howard, John H. Newman, Kevin D. Niswender, Meredith E. Pugh, Ivan M. Robbins, Quanhu Sheng, Cyndya A. Shibao, Yu Shyr, Susan Sumner, Megha Talati, John Wharton, Martin R. Wilkins, Fei Ye, Chang Yu, James West, and Evan L. Brittain

<http://jci.me/123611>

INFLAMMATION

Host microbiota and myeloid progenitor cell crosstalk exacerbates systemic inflammation

Dysfunctional regulation of the immune response following inflammatory injury or infection results in a devastating cytokine storm that can irreparably damage healthy tissues and lead to death. TLRs on innate immune cells drive proinflammatory responses, and sustained TLR signaling is thought to amplify inflammatory cytokine production during cytokine storm. Lehn Weaver and colleagues now reveal that host microbiota-dependent stimulation of myelopoiesis potentiates production of proinflammatory cytokines in response to repeated TLR stimulation and subsequent cytokine storm. The host microbiota primed JAK signaling in myeloid progenitor cells, thereby enhancing myelopoiesis and accumulation of TLR-responsive monocytes. Moreover, germ-free and antibiotic-treated mice were protected from TLR-induced cytokine storm, and this protection was associated with the absence of TLR-enhanced monocytopoiesis. Together, these results identify an important interaction between the host microbiota and the hematopoietic system that sustains pathological inflammation.

Microbiota-dependent signals are required to sustain TLR-mediated immune responses

Lehn K. Weaver, Danielle Minichino, Chhanda Biswas, Niansheng Chu, Jung-Jin Lee, Kyle Bittinger, Sabrin Albeituni, Kim E. Nichols, and Edward M. Behrens (ASCI) <http://jci.me/124370>

AUTOIMMUNITY

Mycophenolate mofetil targeting of STAT3 underlies benefit in lupus

One of the more severe complications of the autoimmune disease systemic lupus erythematosus (SLE)

is the development of lupus nephritis. The drug mycophenolate mofetil (MMF) reduces lupus nephritis-associated mortality; however, the effects of the drug that confer benefit are poorly understood. Samantha Slight-Webb and colleagues analyzed immune cell populations and effectors in peripheral blood of SLE patients taking MMF or not taking MMF. Compared with those not taking MMF, those taking the drug had reduced numbers of transitional B cells, plasmablasts, and T cells, along with a marked decrease in soluble mediators, including chemokines and growth factors, associated with STAT3 and B cell pathways. Moreover, treatment of healthy PBMCs with SLE-associated cytokine IL-6 and the active metabolite of MMF reduced STAT3 phosphorylation and signaling, supporting STAT3 as the effective target of MMF.

Mycophenolate mofetil reduces STAT3 phosphorylation in systemic lupus erythematosus patients

Samantha Slight-Webb, Joel M. Guthridge, Eliza F. Chakravarty, Hua Chen, Rufe Lu, Susan Macwana, Krista Bean, Holden T. Maecker, Paul J. Utz, and Judith A. James (ASCI)

<http://jci.me/124575>

GENETICS



Pilot study of oral nitisinone in patients with oculocutaneous albinism

Oculocutaneous albinism (OCA) is characterized by reduced melanin pigment in the eyes, hair, and skin, and individuals with OCA are at increased risk of skin malignancies and developmental eye abnormalities. In a tyrosine hypomorphic mouse model of OCA-1B albinism, oral administration of nitisinone increased fur and eye pigmentation. Now, David Adams and colleagues have reported on an open-label study of nitisinone in 5 adults with OCA-1B. While ocular melanin did not increase in these individuals, visual acuity as well as skin and hair pigmentation increased over the 12-month study (see the accompanying image). These promising results support further evaluation of oral nitisinone for OCA.

Effects of nitisinone on melanin in patients with OCA-1B: results of a 1-year pilot study

David R. Adams, Supriya Menezes, Ramon Jauregui, Zaheer M. Valivullah, Bradley Power, Maria Abraham, Brett G. Jeffrey, Angel Garced, Ramakrishna P. Alur, Denise Cunningham, Edythe Wiggs, Melissa A. Merideth, Pei-Wen Chiang, Shanna Bernstein, Shosuke Ito, Kazumasa Wakamatsu, Rhona M. Jack, Wendy J. Inrone, William A. Gahl, and Brian P. Brooks (ASCI)

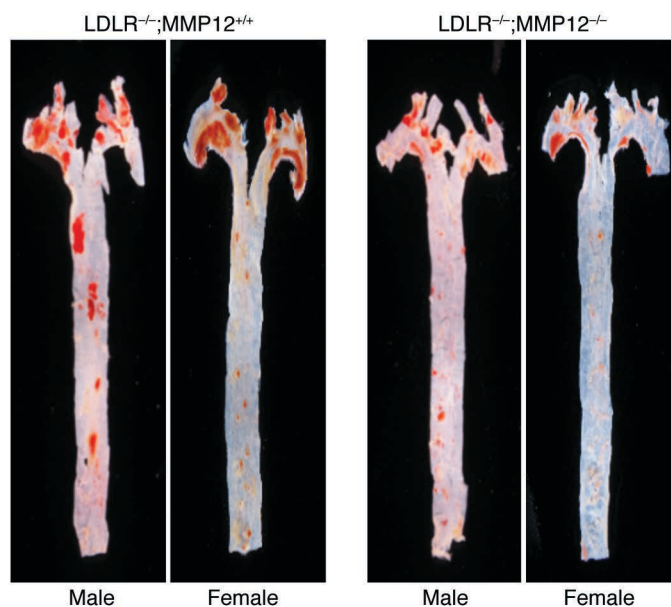
<http://jci.me/124387>

VASCULAR BIOLOGY

Sex-specific differences in atherosclerosis risk linked to MMP12 expression

Arterial stiffening is a cholesterol-independent risk factor for cardiovascular disease (CVD) that naturally occurs with age. Men are more susceptible than women to arterial stiffening and subsequent CVD; however, factors that underlie this sex bias are poorly understood. Shu-lin Liu, Anamika Bajpai, and colleagues used the LDLR-null mouse model of atherosclerosis to investigate sex-specific contributions to disease development and determined that the expression of matrix metalloproteinase-12 (MMP12) is higher in LDLR-deficient

male versus female mice on a high-fat diet. Deletion of *Mmp12* in LDLR-deficient males attenuated arterial stiffness and atherosclerosis (see the accompanying image), even in the presence of high cholesterol. In both human and murine macrophages, oxidized LDL stimulated MMP12 secretion; however, the presence of estrogen downregulated MMP12 expression. Together, these results indicate that estrogen-mediated suppression of MMP12 underlies sex-specific differences in arterial stiffening and atherosclerosis.



Cardiovascular protection in females linked to estrogen-dependent inhibition of arterial stiffening and macrophage MMP12

Shu-lin Liu, Anamika Bajpai, Elizabeth A. Hawthorne, Yongho Bae, Paola Castagnino, James Monslow, Ellen Puré, Kara L. Spiller, and Richard K. Assoian <http://jci.me/122742>

Exercise promotes a cardioprotective gene program in resident cardiac fibroblasts

Janet K. Lighthouse, Ryan M. Burke, Lisette S. Velasquez, Ronald A. Dirkx Jr., Alessandro Aiezza II, Christine S. Moravec, Jeffrey D. Alexis, Alex Rosenberg, and Eric M. Small <http://jci.me/92098>

SIRT3 diminishes inflammation and mitigates endotoxin-induced acute lung injury

Deepali Kurundkar, Ashish R. Kurundkar, Nathaniel B. Bone, Eugene J. Becker Jr., Wanqu Liu, Balu Chacko, Victor Darley-Usmar, Jaroslaw W. Zmijewski, and Victor J. Thannickal <http://jci.me/120722>

Transcriptome network analysis identifies protective role of the LXR/SREBP-1c axis in murine pulmonary fibrosis

Shigeyuki Shichino, Satoshi Ueha, Shinichi Hashimoto, Mikiya Otsuji, Jun Abe, Tatsuya Tsukui, Shungo Deshimaru, Takuya Nakajima, Mizuha Kosugi-Kanaya, Francis H.W. Shand, Yutaka Inagaki, Hitoshi Shimano, and Kouji Matsushima <http://jci.me/122163>

Organoid single cell profiling identifies a transcriptional signature of glomerular disease

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Combined functional genomic and chemical screens identify SETD8 as a therapeutic target in MYC-driven medulloblastoma

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Magnesium supplementation improves diabetic mitochondrial and cardiac diastolic function

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BACE2, a conditional β -secretase, contributes to Alzheimer's disease pathogenesis

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A recombinant human IgG1 Fc multimer designed to mimic the active fraction of IVIG in autoimmunity

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Carbon irradiation overcomes glioma radioresistance by eradicating stem cells and forming an antiangiogenic and immunopermissive niche

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Resident macrophages reprogram toward a developmental state after acute kidney injury

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