March 2016
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ACCELERATING BREAKTHROUGH DISCOVERIES INTO MEDICINES
Geoffrey Pitt, MD, PhD, Associate Editor, is a Professor of Medicine in the Division of Cardiology at Duke University and the Director of the Ion Channel Research Unit. Dr. Pitt was elected to the American Society for Clinical Investigation in 2007 and the Association of American Physicians in 2013. Dr. Pitt’s research explores how ion channels function in physiology and how ion channel dysfunction leads to disease. Current areas of interest in the Pitt laboratory include mechanisms of channel function and dysfunction in inherited cardiac channelopathies, neuropsychiatric disorders, synaptic plasticity, and developmental disorders.

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ART influences HIV persistence in the female reproductive tract and cervicovaginal secretions

Rikke Olesen, Michael D. Swanson, Martina Kovarova, Tomonori Nochi, Morgan Chateau, Jenna B. Honeycutt, Julie M. Long, Paul W. Denton, Michael G. Hudgens, Amy Richardson, Martin Tolstrup, Lars Østergaard, Angela Wahl, and J. Victor Garcia  http://jci.me/64212

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**T regulatory cell chemokine production mediates pathogenic T cell attraction and suppression**
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**Neonatal thymectomy reveals differentiation and plasticity within human naive T cells**

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**Lymphatic endothelial cells are a replicative niche for Mycobacterium tuberculosis**

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Lymphatic endothelial cells are a locus for extrapulmonary tuberculosis infection

*Mycobacterium tuberculosis* infection most commonly occurs in the lungs. In some cases, tissues outside the lung, including the lymph nodes, can also be infected, particularly in immunocompromised patients. In this month’s issue of the *JCI*, a research team led by Maximiliano Gutierrez reports that lymphatic endothelial cells within the lymphatic vascular system harbor *M. tuberculosis* and serve as a site for bacterial replication. In human lymph node tissue from patients diagnosed with tuberculosis, the authors detected *M. tuberculosis* within lymphatic endothelial cells. They subsequently showed, in primary human lymph node–derived endothelial cells cultured in vitro, that *M. tuberculosis* localizes primarily within the cytosol and, to a lesser extent, within membrane-bound compartments, such as phagosomes, lysosomes, and autophagosomes. Moreover, they showed that *M. tuberculosis* was able to grow within autophagosomes. Stimulation of lymphatic endothelial cells with IFN-γ, a cytokine that has been implicated in control of *M. tuberculosis*, restricted bacterial replication in a manner dependent on the presence of the *M. tuberculosis* RD1 virulence locus. The researchers found that IFN-γ stimulates nitric oxide production in lymphatic endothelial cells and that the nitric oxide synthase inhibitor L-NMMA blocked the inhibitory effect of IFN-γ on *M. tuberculosis* growth. Together, these findings provide new evidence that lymphatic endothelial cells can serve as a replicative niche for *M. tuberculosis* and suggest a mechanism for sustained infection in the lymphatic system. The accompanying image shows human primary lymphatic endothelial cells (actin, red; nuclei, blue) infected with mycobacteria expressing EGFP (green).

**Lymphatic endothelial cells are a replicative niche for *Mycobacterium tuberculosis***

[http://jci.me/83379](http://jci.me/83379)
AIDS/HIV

Antiretroviral therapy reduces HIV in the female reproductive tract

A recent HIV prevention clinical trial demonstrated 93% protection against secondary heterosexual transmission when infected partners received early antiretroviral therapy (ART). Rikke Olesen and colleagues tested the hypothesis that ART reduces genital cell–free or genital cell–associated HIV to levels that are too low to support HIV transmission. Using the humanized BM/liver/thymus (BLT) mouse model, they demonstrated that humanized CD4+ T cells were present throughout the female reproductive tract (FRT) and that these cells were shed into cervicovaginal secretions (CVS). HIV infection increased the number of CD4+ and CD8+ T cells in the CVS, and virus was present throughout the FRT (see the accompanying image) and in CVS. ART strongly suppressed CVS viral load; however, HIV-RNA+ cells were present in both the FRT and the CVS, though these cells did not transmit HIV in an in vitro coculture assay.

ART influences HIV persistence in the female reproductive tract and cervicovaginal secretions

Rikke Olesen, Michael D. Swanson, Martina Kovařová, Tamanori Nochi, Morgan Chateau, Jenna B. Honeycutt, Julie M. Long, Paul W. Denton, Michael G. Hudgens, Amy Richardson, Martin Tolstrup, Lars Østergaard, Angela Wahl, and J. Victor Garcia

http://jci.me/64212

IMMUNOLOGY

Tregs produce chemokines to attract and suppress adaptive immune cells

Regulatory T cells (Tregs) prevent inappropriate responses to self and nonharmful foreign antigens, and modulation of Treg activity is a potential strategy to treat immune-mediated disease. Scott Patterson, Anne Pesenacker, and colleagues demonstrate that Tregs produce the chemokines CCL3 and CCL4 to attract CD4+ and CD8+ T cells via the receptor CCR5, drawing these cell populations close, possibly increasing proximity-dependent regulation of their activity. WT and Ccl3-deficient Tregs were comparable in their activation phenotypes and ability to suppress T cell proliferation in vitro, while Ccl3-deficient Tregs were unable to attract CD4+ and CD8+ T cells. Using murine models of multiple sclerosis and islet allograft rejection, Patterson, Pesenacker, and colleagues demonstrate that Tregs produce the chemokines CCL3 and CCL4 to attract CD4+ and CD8+ T cells via the receptor CCR5, drawing these cell populations close, possibly increasing proximity-dependent regulation of their activity. WT and Ccl3-deficient Tregs were comparable in their activation phenotypes and ability to suppress T cell proliferation in vitro, while Ccl3-deficient Tregs were unable to attract CD4+ and CD8+ T cells. Using murine models of multiple sclerosis and islet allograft rejection, Patterson, Pesenacker, and colleagues demonstrate that Tregs produce the chemokines CCL3 and CCL4 to attract CD4+ and CD8+ T cells via the receptor CCR5, drawing these cell populations close, possibly increasing proximity-dependent regulation of their activity. WT and Ccl3-deficient Tregs were comparable in their activation phenotypes and ability to suppress T cell proliferation in vitro, while Ccl3-deficient Tregs were unable to attract CD4+ and CD8+ T cells. Using murine models of multiple sclerosis and islet allograft rejection, Patterson, Pesenacker, and colleagues demonstrate that Tregs produce the chemokines CCL3 and CCL4 to attract CD4+ and CD8+ T cells via the receptor CCR5, drawing these cell populations close, possibly increasing proximity-dependent regulation of their activity. WT and Ccl3-deficient Tregs were comparable in their activation phenotypes and ability to suppress T cell proliferation in vitro, while Ccl3-deficient Tregs were unable to attract CD4+ and CD8+ T cells. Using murine models of multiple sclerosis and islet allograft rejection, Patterson, Pesenacker, and colleagues demonstrate that Tregs produce the chemokines CCL3 and CCL4 to attract CD4+ and CD8+ T cells via the receptor CCR5, drawing these cell populations close, possibly increasing proximity-dependent regulation of their activity. WT and Ccl3-deficient Tregs were comparable in their activation phenotypes and ability to suppress T cell proliferation in vitro, while Ccl3-deficient Tregs were unable to attract CD4+ and CD8+ T cells.

T regulatory cell chemokine production mediates pathogenic T cell attraction and suppression

Scott J. Patterson, Anne M. Pesenacker, Adele Y. Wang, Jana Gillies, Majid Mojibian, Kim Morishita, Rusung Tan, Timothy J. Kieffer, C. Bruce Verchere, Constadina Panagiotopoulos, and Megan K. Levings

http://jci.me/83987
Lysine-specific demethylase 2B regulates hematopoietic lineage commitment

Transcriptional and epigenetic networks regulate hematopoietic lineage specification, and these networks are frequently dysregulated in hematopoietic malignancies. Jaclyn Andricovich and colleagues investigated the role of lysine-specific demethylase 2B (KDM2B) in lineage commitment by analyzing hematopoietic stem and progenitor cells (HSPCs) from mice that were engineered to conditionally ablate or overexpress KDM2B in the hematopoietic system. They found that KDM2B was required for embryonic development and definitive hematopoiesis. RNA sequencing revealed that KDM2B regulates developmental pathways by binding repressed and activated chromatin through interactions with polycomb and trithorax group complexes, respectively. Additionally, they demonstrate that KDM2B functions as either a tumor suppressor or an oncogene, depending on the cellular context. The accompanying image shows accelerated Kras-driven myeloid transformation in KDM2B-deficient peripheral blood.

Histone demethylase KDM2B regulates lineage commitment in normal and malignant hematopoiesis
Jaclyn Andricovich, Yan Kai, Weiqun Peng, Adlen Foudi, and Alexandros Tzatsos  
http://jci.me/84014

Chemokine receptor expression on lymphocytes influences melanoma spread

The abundance, trafficking, and characteristics of tumor-infiltrating lymphocytes (TILs) strongly influence the prognosis of human malignancies including metastatic melanoma (MMel). Lymphocyte trafficking into the tumor is largely determined by the expression of chemokine receptors on peripheral T cells (peripheral blood mononuclear cells [PBMCs]). Nicolas Jacquelot and colleagues analyzed PBMCs and TILs from MMel patients to determine whether chemokine receptor expression correlated with intratumoral accumulation, metastatic progression, or overall survival (OS). They found that T cell chemokine receptor expression was strongly correlated with MMel dissemination and that the expression of specific chemokine receptors was associated with metastases at different sites, such as the skin, lymph nodes, or lungs. Importantly, expression of CCR9 on naïve CD8+ peripheral T cells correlated with increased OS in patients, while inhibition of CCR9 signaling stimulated tumor progression in mice. Taken together, these results suggest that specific chemokine receptor expression patterns could help guide diagnostic and therapeutic approaches.

Chemokine receptor patterns in lymphocytes mirror metastatic spreading in melanoma
Nicolas Jacquelot, David P. Enot, Caroline Flamant, Nadège Vimond, Carolin Blattner, Jonathan M. Pitt, Takahiro Yamazaki, Maria Paula Roberti, Romain Daillère, Marie Vétizou, Vinclou Poirier-Colame, Michèla Sbemara, Anne Caignard, Craig L. Slingluff Jr., Federica Sallusto, Sylvie Rusakiewicz, Benjamin Weide, Aurélien Marabelle, Holbrook Kohrt, Stéphane Dalle, Andréa Cavalcanti, Guido Kroemer, Anna Maria Di Giacomo, Michele Maio, Phillip Wong, Jianda Yuan, Jedd Wolchok, Viktor Umansky, and Laurence Zitvogel  
http://jci.me/80071

Neoantigen quality determines T cell receptor gene therapy effectiveness

Immunotherapy-induced melanoma regression is associated with increased frequencies of neoantigen-specific T cells; however, the fate and function of these cells are unclear. Matthias Leisegang and colleagues generated T cells expressing a transgenic T cell receptor (TCR) recognizing two different naturally occurring immunogenic mutations in the same position in cyclin-dependent kinase 4 (CDK4). Using a murine model of large, established tumors, they demonstrate that these T cells produced an effective antitumor response when the tumor expressed the CDK4R24L mutation, but failed when the tumor expressed the CDK4R24C mutation. These results suggest that neoantigen quality, which is not always measurable by in vitro assays, may underlie differences in patient responses to immunotherapy.

Targeting human melanoma neoantigens by T cell receptor gene therapy
Matthias Leisegang, Thomas Kammertoens, Wolfgang Uckert, and Thomas Blankenstein  
http://jci.me/83465
Jumonji domain–containing protein JMJD1C regulates leukemia stem cell self-renewal

Both hematopoietic stem cells (HSCs) and leukemia stem cells (LSCs) are capable of self-renewal. Identification of mechanisms underlying LSC but not HSC self-renewal could be therapeutically exploited to reduce the toxicity of leukemia treatment. Nan Zhu and colleagues performed an in vivo shRNA screen and identified the jumonji domain–containing protein JMJD1C as a critical regulator of LSC self-renewal in MLL-AF9– and HOXA9-driven leukemias. Loss of JMJD1C decreased LSC frequency (see the accompanying image), drove differentiation of leukemic cells, and prolonged survival, but caused only minor defects in HSC self-renewal and blood homeostasis. Zhu and colleagues show that JMJD1C interacted with HOXA9 to modulate gene expression. These data demonstrate that JMJD1C selectively modulates LSC self-renewal in MLL-AF9– and HOXA9-driven leukemias.

Bone homeostasis in men is primarily regulated by estradiol

Severe gonadal steroid deficiency induces bone loss in adult men; however, the specific roles of androgens and estrogens in male bone homeostasis are unclear. Joel S. Finkelstein and colleagues conducted a clinical study in which healthy men were treated with the gonadotropin-releasing hormone agonist goserelin to induce severe gonadal steroid deficiency. The trial subjects also received either placebo testosterone or one of a range of doses of testosterone gel. Half the men also received the aromatase inhibitor anastrozole to inhibit the conversion of testosterone to estradiol. Decreasing doses of testosterone were inversely correlated with serum C-telopeptide, a marker of bone turnover. Moreover, anastrozole treatment increased bone turnover and decreased bone mineral density, indicating that estradiol is required to maintain bone homeostasis. In the accompanying Commentary, Thomas J. Weber discusses how this study reveals a dominant effect of estradiol in suppressing bone resorption.

Gonadal steroid–dependent effects on bone turnover and bone mineral density in men


http://jci.me/84137

Related Commentary

Battle of the sex steroids in the male skeleton: and the winner is...

Thomas J. Weber

http://jci.me/85006
TLR9 is activated by hepatocyte mitochondrial DNA in nonalcoholic steatohepatitis

Nonalcoholic steatohepatitis (NASH) is a progressive liver disease that can lead to cirrhosis, cancer, and death, but there are currently no approved treatments. Animal models of NASH require TLR9 signaling, but it is unclear how TLR9 contributes to disease pathogenesis. Irma Garcia-Martinez and colleagues demonstrated that plasma from mice and patients with NASH contained high levels of mitochondrial DNA (mtDNA), which activates TLR9. Notably, the majority of the mtDNA was contained in hepatocyte-derived microparticles (MPs), and MP-depleted plasma had a decreased capacity to activate TLR9. Moreover, deletion of Tlr9 in lysozyme-expressing cells or pharmacological inhibition of TLR9 blocked the development of NASH in mice fed a high-fat diet (see the accompanying image). These data demonstrate that NASH-associated metabolites contribute to disease pathogenesis via TLR9.

Hepatocyte mitochondrial DNA drives nonalcoholic steatohepatitis by activation of TLR9
Irma Garcia-Martinez, Nicola Santoro, Yonglin Chen, Rafaz Hoque, Xinshou Ouyang, Sonia Caprio, Mark J. Shlomchik, Robert Lee Coffman, Albert Candia, and Wajahat Zafar Mehal
http://jci.me/83885
Chronic kidney disease–associated FGF23 elevation impairs host defense

Chronic kidney disease (CKD) is associated with impaired host immune defense and an increased susceptibility to infection; however, the mechanisms underlying this impairment are not clear. Jan Rossaint and colleagues report that elevated FGF23 levels in patients and mice with CKD inhibit leukocyte recruitment to inflamed tissues. Neutralization of FGF23 restored neutrophil recruitment and host defense in mice with CKD after induction of pneumonia. Mechanistically, Rossaint and colleagues demonstrated that FGF23 blocks slow rolling, arrest, and transendothelial migration of neutrophils by stimulating a FGFR2/PKA pathway that counteracts selectin- and chemokine-stimulated activation of β2-integrins. These data suggest that FGF23 may be a suitable therapeutic target for inflammation control in patients with CKD.

FGF23 signaling impairs neutrophil recruitment and host defense during CKD
Jan Rossaint, Jessica Oehmichen, Hugo Van Aken, Stefan Reuter, Herrann J. Pavenstädt, Melanie Meersch, Mark Unruh, and Alexander Zarbock http://jci.me/83470

Schwann cell mitochondrial calcium leak triggers nerve demyelination

Demyelination is associated with a number of acquired and hereditary peripheral neuropathies, but the molecular mechanisms that trigger demyelination are unknown. In this issue, Sergio Gonzalez and colleagues used fluorescent probes and in vivo multiphoton time-lapse microscopy to document changes in myelinating Schwann cells (SCs) in a murine sciatic nerve crush model. They found that SC demyelination is induced by mitochondrial voltage-dependent anion channel 1–mediated (VDAC1-mediated) calcium release, which activates ERK1/2-, p38-, JNK-, and c-jUN–mediated demyelination pathways. Further, they demonstrated a VDAC1-mediated calcium leak in mitochondria of murine diabetes models, which primes SCs for demyelination, suggesting a mechanism for diabetic peripheral neuropathy. Finally, blocking VDAC1-mediated calcium release prevented demyelination and improved nerve conduction and neuromuscular performance in rodent models of diabetic neuropathy and of Charcot-Marie-Tooth disease (see the accompanying image).
Mitochondria are essential for energy production via oxidative phosphorylation and also play a key role in nutrient and oxygen sensing as well as cell death and inflammation. Mitochondrial dysfunction is increasingly linked to disease pathogenesis. In this issue, Suzanne Cloonan and Augustine Choi review the role of mitochondrial dysfunction in lung diseases, including chronic obstructive pulmonary disease, pulmonary hypertension, asthma, cystic fibrosis, and lung cancer. At the molecular level, alterations in mitophagy, mitochondrial DNA (mtDNA), second messenger signaling, and the production of mitochondrial damage–associated molecular patterns (mtDAMPs) are features of lung pathogenesis. Such mitochondrial disease signatures are potential targets for diagnosis and therapy for lung diseases.

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**Dynamic dual-isotope molecular imaging elucidates principles for optimizing intrathecal drug delivery**
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