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**Featured Editor**

David M. Virshup, M.D., Associate Editor, is the inaugural Director of the Program in Cancer and Stem Cell Biology at the Duke-NUS Graduate Medical School in Singapore. Until 2007, he was an investigator at the Huntsman Cancer Institute and the first Willard Snow Hansen Presidential Professor of Cancer Research at the University of Utah. Dr. Virshup received his medical degree in 1981 from the Johns Hopkins School of Medicine, where he also completed his clinical training in pediatrics and pediatric hematology/oncology. His research training was in the departments of Pediatrics, Cell Biology and Anatomy, and Molecular Biology and Genetics at Johns Hopkins. Currently, his laboratory in Singapore studies the Wnt signaling pathways, with an emphasis on Wnt secretion. A related interest is in protein phosphorylation in the Wnt pathway, and in circadian rhythms.

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Autoimmunity
Edited by Antonio La Cava  Published June 2015

Autoimmune disease encompasses a diverse group of over 80 chronic disorders. Each of these diseases has distinct clinical manifestations that are due to the differences in the cells and organ systems involved; however, these diseases are universally characterized by a loss of self-tolerance, resulting in autoreactive immune cells, autoantibodies, and elevated levels of inflammatory cytokines. Reviews in this series examine mechanisms underlying autoimmunity, including failure of B cell tolerance checkpoints, the generation of autoantibodies, cytokine dysregulation, aberrant T cell signaling, and the loss of immune suppressive cells and functions. They also explore the influence of genetic background, environment, microRNAs, and sex-specific factors on the loss of immune homeostasis.

Enteric nervous system
Edited by Rodger A. Liddle  Published March 2015

The enteric nervous system (ENS) encompasses extrinsic and intrinsic neurons, glia, and sensory epithelial cells that are embedded throughout the gastrointestinal tract. The circuits formed by these cells are responsible for interpreting sensory information in the gut lumen in order to regulate gut motility, secretion, food intake, and immune function. The ENS communicates with the CNS in a bidirectional manner, allowing stimuli in the gut to influence mood, food intake, and other behaviors. Reviews in this series examine the mechanisms by which the ENS develops from neural crest cells, chemosensory mechanisms that allow for the detection of and response to fats and other nutrients within the gut lumen, the role of the enteric glia, regulation of ENS function by the immune system and inflammation, and the impact of surgery and the gut microbiota on ENS communication with the brain.

All JCI review series: jci.org/review_series
Autoimmune type 1 diabetes (T1D) is characterized by the immune infiltration and destruction of pancreatic β cells. Nadine Nagy and colleagues previously reported that extracellular matrix polysaccharide hyaluronan (HA) deposits accumulate within pancreatic islets in patients with T1D with autoimmune insulitis; however, it was unclear whether these deposits are important in disease pathogenesis. In this month’s issue of the JCI, this research team used the DO11.10×RIPmOVA (DORmO) mouse model of T1D to demonstrate that HA deposits promote islet-destructive insulitis by impairing the differentiation of Tregs. Importantly, treatment of DORmO mice after the onset of insulitis with the HA synthase inhibitor 4-methylumbelliferone (4-MU) blocked HA deposition and prevented progression to autoimmune diabetes. These effects were recapitulated in a second model of T1D, NOD mice, in which a single week of 4-MU markedly decreased the number of diabetic mice and provided durable improvements in blood glucose levels. In addition, Nagy and colleagues showed that 4-MU treatment reestablishes a regulatory checkpoint that prevents β cell destruction and promotes the differentiation of Tregs within pancreatic islets. In vitro induction of Tregs was likewise diminished in the presence of HA or antibodies targeting the HA receptor CD44. These findings suggest that 4-MU, which is already used to treat biliary spasm, could potentially also be used therapeutically to prevent T1D progression. The accompanying image shows insulin staining (brown), despite robust insulitis in pancreatic islets from a 15-week-old DORmO mouse treated with 4-MU for 7 weeks.

Hyaluronan synthase inhibition prevents islet destruction in autoimmune diabetes


http://jci.me/79271

Hyaluronan synthase inhibition prevents islet destruction in autoimmune diabetes


http://jci.me/79271
IDI1 mediates tolerance to clotting factor treatment in hemophilia

Hemophilia A patients have a deficiency in the clotting protein factor VIII. Severe bleeding episodes in these patients require FVIII replacement therapy; however, patients frequently develop neutralizing antibodies or inhibitors to exogenous FVIII, reducing its effectiveness. Davide Matino and colleagues report that inhibitor-positive hemophilia A patients exhibit impaired induction of indoleamine 2,3-dioxygenase (IDO1), an enzyme that mediates peripheral tolerance through suppression of antigen-specific T cells and enhancement of Treg-mediated immune suppression. Using a murine hemophilia model, they found that IDO1-generated tryptophan metabolites prevented the generation of anti-FVIII antibodies. IDO1 is induced by activation of TLR9, and administration of a TLR9 agonist suppressed FVIII-specific B cells through IDO1-dependent induction of Tregs (see the accompanying image). These data identify mechanisms by which IDO1 induces tolerance to exogenous FVIII and suggest strategies to prevent the development of FVIII antibodies and inhibitors.

IDO1 suppresses inhibitor development in hemophilia A treated with factor VIII

Davide Matino, Marco Gargaro, Elena Santagostino, Matteo N.D. Di Minno, Giancarlo Castaman, Massimo Morfini, Angiola Rocino, Maria E. Mancuso, Giovanni Di Minno, Antonio Coppola, Vincenzo N. Talesa, Claudia Volpi, Carmine Vacco, Ciariana Drabona, Rossana Iannitti, Maria G. Mazzucconi, Cristina Santoro, Antonella Testi, Sara Chiappalupi, Guglielmo Sorci, Giuseppe Tagariello, Donata Belvini, Paolo Radossi, Raffaele Landolfi, Dietmar Fuchs, Louis Boon, Matteo Pirro, Emanuela Marchesini, Ursula Grohmann, Paolo Puccetti, Alfonsa Iorio, and Francesca Fallarino

http://jci.me/81859

Related Commentary

The ups and downs of negative (and positive) selection of B cells
Jean-Claude Weill and Claude-Agnès Reynaud

http://jci.me/84009

Wiskott-Aldrich syndrome patients provide insight into B cell tolerance checkpoints

Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency caused by mutations in the WAS protein (WASp). To determine the effects of WASp deficiency on B cell tolerance, Francesca Pala and colleagues tested the reactivity of antibodies isolated from individual B cells in four WAS patients before and after gene therapy. Prior to gene therapy, WAS patients had fewer autoreactive B cells exiting the BM and greater numbers of autoreactive, mature peripheral B cells compared with unaffected individuals. These findings indicate that there is increased negative selection at the central tolerance checkpoint and a defect in the peripheral tolerance checkpoint associated with impaired Treg-mediated suppression. WASp gene therapy corrected alterations in both central and peripheral tolerance. In the accompanying Commentary, Jean-Claude Weill and Claude-Agnès Reynaud discuss how these findings suggest that WASp plays a critical role in the establishment and maintenance of B cell tolerance.

Lentiviral-mediated gene therapy restores B cell tolerance in Wiskott-Aldrich syndrome patients
Francesca Pala, Henner Morbach, Maria Carmine Castiello, Jean-Nicolas Schickel, Samantha Scaramuzzo, Nicolas Chamberlain, Barbara Cassani, Salome Glausy, Neil Romberg, Fabio Cundotti, Alessandro Aiuti, Marita Bosticardo, Anna Villa, and Eric Meffre

http://jci.me/82249

Immunology

Hematology
A pathway to amplify insulin secretion

Insulin secretion from pancreatic β cells is triggered by glucose-stimulated electrical activity and opening of voltage-dependent Ca²⁺ channels to elicit exocytosis; however, this pathway does not account for the entire magnitude of the secretory response. Using isolated human islets and transgenic murine models, Mourad Ferdaoussi, Xiaoqing Dai, and colleagues demonstrate in this issue that cytosolic isocitrate dehydrogenase (ICDc) transfers reducing equivalents to generate NADPH and reduced glutathione (GSH). NADPH and GSH serve as coupling factors that act through sentrin/SUMO-specific protease-1 (SENP1) to amplify Ca²⁺-induced insulin exocytosis (see the accompanying image, in which insulin is labeled green and SENP1 is labeled red). Notably, the glucose-dependent amplification of insulin exocytosis is impaired in human type 2 diabetes (T2D) and an in vitro model of human islet dysfunction. Exocytosis in these models was rescued by supplementation of signaling intermediates in the ICDc/SENP1 pathway. In the accompanying Commentary, Alan Attie discusses how this study elucidates a mechanism linking glucose metabolism to the amplification of insulin secretion that is disrupted in T2D.

Isocitrate-to-SENP1 signaling amplifies insulin secretion and rescues dysfunctional β cells


http://jci.me/82498

Related Commentary

How do reducing equivalents increase insulin secretion?

Alan D. Attie  http://jci.me/84011
Research | Editor’s picks

Perhexiline reduces atherosclerosis via Krüppel-like factor 14

Genetic variants in Krüppel-like factor 14 (KLF14) are strongly associated with elevated plasma HDL levels, metabolic syndrome, and coronary artery disease. Yanhong Guo and colleagues found that KLF14 is reduced in murine models of hepatic dyslipidemia. Mice with liver-specific KLF14 deficiency had decreased plasma HDL, while overexpression of KLF14 in the liver increased plasma HDL and cholesterol efflux capacity. Mechanistically, KLF14 regulates plasma HDL and cholesterol efflux capacity by modulating hepatic production of apolipoprotein A-I (ApoA-I). To identify pharmacological interventions that enhance KLF14 activity, Guo and colleagues screened a chemical library for compounds that increase KLF14 expression. They found that perhexiline, which is approved for treatment of angina and heart failure, increases KLF14 expression, plasma HDL levels, and ApoA-I levels in mice. Additionally, perhexiline attenuated the development of atherosclerosis in a murine model of the disease (see the accompanying image).

Perhexiline activates KLF14 and reduces atherosclerosis by modulating ApoA-I production


Noninvasive prenatal diagnosis of recessive monogenic disease

Noninvasive prenatal genetic testing (NIPGT) is a method of examining cell-free fetal DNA in the maternal bloodstream that is currently used for the diagnosis of chromosomal abnormalities. As discussed in this issue, David Zeevi and colleagues developed an NIPGT method to diagnose monogenic disorders caused by autosomal recessive mutations. Zeevi and colleagues collected blood samples from eight couples of Ashkenazi Jewish heritage that were at risk of passing on type I Gaucher disease—causing alleles of acid β-glucosidase (GBA) as well as from mutation carrier family members and unrelated individuals who were homozygous for disease-causing mutations. The samples were subjected to high-throughput sequencing of GBA-flanking SNPs and fine mapped to establish a consensus disease-associated haplotype. Zeevi and colleagues then used this haplotype to diagnose six unrelated fetuses. This study establishes a method for the rapid, prenatal diagnosis of recessive disease-causing mutations.

Proof-of-principle rapid noninvasive prenatal diagnosis of autosomal recessive founder mutations

David A. Zeevi, Cheona Altarescu, Ariella Weinberg-Shukron, Fouad Zahdeh, Tama Dinur, Gaya Chicco, Yair Herskovitz, Paul Renbaum, Deborah Elstein, Ephrat Levy-Lahad, Arndt Rolfs, and Ari Zimran http://jci.me/79322
Tracing the origins of hepatocellular carcinoma

Many cancers originate from the stem or progenitor compartment of a given organ; however, the liver does not have a defined stem cell population, and the cellular origin of hepatocellular carcinoma (HCC) is not clear.

Importantly, HCCs with a progenitor signature carry a worse prognosis. Xueru Mu, Regina Español-Suñer, and colleagues used complementary fate-tracing strategies to label the progenitor/biliary compartment and hepatocytes in genotoxic and genetic models of murine hepatocarcinogenesis. They found that HCCs arose exclusively from hepatocytes in both models. Additionally, cells with a progenitor signature within HCCs were derived from hepatocytes, suggesting that these cells result from dedifferentiation of hepatocytes. The accompanying image shows HCC in a murine HCC model in which hepatocytes were labeled with GFP.

An activatable fluorescent reporter for whole animal imaging

Noninvasive imaging of whole living animals is a powerful method for monitoring tumor growth, immune responses, vascularization, and treatment effects in longitudinal studies. Such studies rely upon the ability to tag specific tissues and cells with interest with labels that generate signals that are detectable through tissue. Ming Zhang and colleagues report the development of a fluoromodule-based reporter/probe system consisting of a fluorogenic dye, SC1, which is dark in solution but becomes highly fluorescent when bound to its cognate reporter, Mars1. Notably, these fluorogens maximally absorb and emit light at a wavelength that is minimally absorbed by tissue. The accompanying image shows fluorescence imaging of a nude mouse implanted with Mars1-expressing cells labeled with SC1.

Fluoromodule-based reporter/probes designed for in vivo fluorescence imaging

The trouble with tribbles-1 in hepatic lipid metabolism

Genetic variants near tribbles-1 (TRIB1) are associated with alterations in plasma lipid profiles and liver enzymes, and in coronary artery disease in humans. Robert Bauer and colleagues investigated the role of TRIB1 in hepatic lipid metabolism by generating mice with a liver-specific Trib1 KO (Trib1_LSKO). These mice exhibited increased total plasma cholesterol and triglycerides, as well as greater hepatic lipogenesis, steatosis (see the accompanying image), and markedly dysregulated hepatic gene expression. Gene expression analysis of Trib1_LSKO livers revealed increased expression of genes downstream of C/EBPα. TRIB1 deficiency was associated with elevated levels of C/EBPα protein but decreased levels of transcript. C/EBPα overexpression in WT mice phenocopied the Trib1_LSKO liver phenotype, while C/EBPα deficiency in Trib1_LSKO mice decreased hepatic lipogenesis to WT levels. Importantly, Trib1_LSKO mice had increased DNA-bound C/EBPα near lipogenic genes and the Trib1 gene, indicating that C/EBPα and TRIB1 are part of a feedback loop regulating hepatic lipogenesis.

Tribbles-1 regulates hepatic lipogenesis through posttranscriptional regulation of C/EBPα
Robert C. Bauer, Makoto Sasaki, Daniel M. Cohen, Jian Cui, Mikhaila A. Smith, Batuhan O. Yenilmez, David J. Steger, and Daniel J. Rader
http://jci.me/77095

Understanding the anticonvulsant effects of valproic acid

Valproic acid (VPA) is commonly used to treat epilepsy; however, its mechanism of action is not well understood. Hee Yeon Kay, Derek Greene, and colleagues report that the anticonvulsant effects of VPA are mediated through preservation of the M-current during seizures. The M-current is a low-threshold, noninactivating current mediated by delayed rectifier potassium channels (KCNO); suppression of the M-current induces neuronal hyperexcitability through the activation of various Gq-coupled GPCRs, including the M1 muscarinic acetylcholine receptor (M1R). Using primary neurons, cell lines, and a murine seizure model, Kay, Greene, and colleagues found that VPA reduced palmitoylation of the signaling scaffold A-kinase anchoring protein 150 (AKAP150), thereby disrupting M1R-mediated M-current suppression. These studies demonstrate that M-current suppression contributes to seizures, and they elucidate the mechanism by which VPA acts as an anticonvulsant.

M-current preservation contributes to anticonvulsant effects of valproic acid
Hee Yeon Kay, Derek L. Greene, Seungwoo Kang, Anastasia Kosenko, and Naoto Hoshi
http://jci.me/79727

A bacterial impostor helps streptococci evade neutrophils

Neutrophils are critical for the acute inflammatory response to control pathogens; thus, microbes must evade neutrophils in order to successfully infect a host. Christopher Hergott and colleagues report that the leading respiratory pathogen Streptococcus pneumoniae utilizes molecular mimicry to disable neutrophils. The exterior of S. pneumoniae is decorated with phosphorylcholine (ChoP) moieties, a structure also found on the host-derived inflammatory phospholipid platelet-activating factor (PAF). This mimicry allows S. pneumoniae to utilize a ChoP-remodeling enzyme, Pce, to deplete PAF from the airway, thereby reducing the viability, activation, and bactericidal capacity of neutrophils. Neutrophils rapidly cleared Pce-deficient S. pneumoniae, but abrogation of PAF signaling allowed Pce-deficient bacteria to persist. These data identify a mechanism by which bacteria evade the acute inflammatory response to establish stable infection.

Bacterial exploitation of phosphorylcholine mimicry suppresses inflammation to promote airway infection
Christopher B. Hergott, Aoife M. Roche, Nikhil A. Naidu, Clementina Mesaros, Ian A. Blair, and Jeffrey N. Weiser
http://jci.me/81888
VASCULAR BIOLOGY

FOXC2 promotes lymphatic vessel homeostasis

As vessels mature, a complex signaling network provides cues to arrest endothelial cell proliferation, stabilize cell-cell junctions, and induce mural cell coverage. In this issue, Amélie Sabine and colleagues examine the factors that maintain lymphatic vessel homeostasis, which has been poorly understood. They show that the transcription factor FOXC2 acts under conditions of disturbed fluid flow to induce quiescence in lymphatic endothelial cells and increase the integrity of cell-cell junctions. Using conditional Foxc2 knockout mice, they demonstrate that these effects are mediated by the Hippo pathway and that inducible loss of Foxc2 causes lymphatic vascular dysfunction. The accompanying image shows that a FOXC2+ cell has continuous cell-cell junctions (arrows), while neighboring knockdown cells having zigzag junctions (arrowheads).

FOXC2 and fluid shear stress stabilize postnatal lymphatic vasculature
http://jci.me/80454

TRANSPLANTATION

Treg-secreted IL-34 teaches tolerance

The induction and maintenance of immune tolerance of transplanted tissues involves multiple mechanisms, including Treg-mediated suppression of graft-specific T cells. In this issue, Séverine Bézie and colleagues demonstrate that Treg secretion of the cytokine IL-34 promotes graft tolerance. Using a rodent heart transplant model, they observed that IL-34 levels were markedly increased in the spleens and grafts of tolerated heart transplant recipients, but that IL-34 was decreased in rats with graft rejection. Overexpression of IL-34 prolonged graft survival on its own and had synergistic effects in combination with the immunosuppressant rapamycin. Moreover, adoptive transfer of Tregs from tolerant animals induced tolerance in sublethally irradiated naive animals. Using blood from healthy human volunteers, Bézie and colleagues demonstrated that IL-34 induces differentiation of macrophages into a phenotype that potentiates the suppressive capacity of Tregs. In the accompanying Commentary, James Kim and Laurence Turka discuss additional experiments that will be required to understand the interactions between Tregs and macrophages.

IL-34 is a Treg-specific cytokine and mediates transplant tolerance
Séverine Bézie, Elodie Picarda, Jason Ossart, Laurent Tesson, Claire Usal, Karine Renaudin, Ignacio Anegon, and Carole Guillonneau
http://jci.me/81227

Related Commentary
Transplant tolerance: a new role for IL-34
James I. Kim and Laurence A. Turka
http://jci.me/84010
A blueprint for building the physician-scientist workforce

In this month’s JCI, Dianna Milewicz and colleagues on the Executive Committee of the National Association of MD-PhD Programs provide their perspective on specific action items that can be taken to improve retention of trainees in the physician-scientist workforce pipeline. Their proposal calls for better integration of research into clinical training programs, early career grants designated specifically for physician-scientists, promotion of diversity in physician-scientist training programs, and the establishment of centralized offices at individual institutions to support and facilitate mentorship of new physician-scientists. They also call for an improved national dialogue on postgraduate physician-scientist training to share effective training strategies across institutions. Such strategies are geared toward shortening the time for investigators to achieve independence by 5 years and reducing attrition during the long training period, particularly during the extended postgraduate training period.

Rescuing the physician-scientist workforce: the time for action is now

Dianna M. Milewicz, Robin G. Lorenz, Terence S. Dermody, Lawrence F. Brass, and the National Association of MD-PhD Programs Executive Committee

http://jci.me/84170

Helen Hobbs

Helen Hobbs is an investigator of the Howard Hughes Medical Institute and a professor of Internal Medicine and Molecular Genetics at the University of Texas Southwestern Medical Center. Additionally, she is the director of the Dallas Heart Study, a longitudinal, multiethnic population-based study of more than 6,000 adults that aims to identify genetic, protein, and imaging biomarkers for early detection of cardiovascular disease as well as social, behavioral, and environmental factors that contribute to cardiovascular disease risk. By studying outliers in this population, Dr. Hobbs identified a genetic defect in PCSK9 that is responsible for low plasma LDL levels. In an interview with JCI Editor-at-Large Ushma Neill, Dr. Hobbs discusses her early scientific training at Parkland Memorial Hospital in Dallas under the direction of Donald Seldin, who guided her to scientific bench training. She also discusses the initiation of the Dallas Heart Study and the development of a therapeutic inhibitor of PCSK9 for lowering LDL.

http://jci.me/84086

CALL FOR NOMINATIONS

The DONALD SELDIN–HOLLY SMITH AWARD FOR PIONEERING RESEARCH

The American Society for Clinical Investigation seeks nominations of outstanding early-stage physician-scientists who have demonstrated exceptional creativity and accomplishments in biomedical research. The recipient of this high-level recognition will be announced at the ASCI’s annual meeting in April 2016, will receive an unrestricted grant of $30,000 to advance academic efforts, and will deliver a research talk at the ASCI’s April 2017 meeting.

The nomination deadline is October 15, 2015. Details are available at: www.the-asci.org/seldin-smith-award

The American Society for Clinical Investigation

Founded in 1908, the ASCI seeks to support the scientific efforts, educational needs, and clinical aspirations of physician-scientists to improve human health.

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Published February 2014  [http://jci.me/71691](http://jci.me/71691)  Times cited: 20

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