Transcription factor BCL6 is a druggable oncoprotein
A designer drug targets diffuse large B cell lymphomas

The BCL6 transcriptional repressor is a master regulator of germinal center formation and antibody affinity maturation. Constitutive expression of BCL6, through either chromosomal translocations or somatic mutations, contributes to the development of germinal center–type diffuse large B cell lymphomas (DLBCLs). While strategies aimed at inhibiting BCL6 are attractive in treating this subset of DLBCLs, transcription factors are notoriously poor pharmacological targets. In this issue of the JCI, a group of researchers led by Ari Melnick describe an in silico drug design functional-group mapping approach to design a small molecule inhibitor with even higher affinity for BCL6 than its endogenous binding partner. The optimized compound, known as FX1, demonstrated superior binding with BCL6 than previously developed molecules, while also exhibiting a high degree of specificity for BCL6 over other BTB domain transcription factors. In mice, treatment with FX1 depleted germinal center B cells and, in 2 DLBCL xenograft models, caused tumor shrinkage. The researchers also found that FX1 inhibited primary tumor cell growth of non–germinal center DLBCLs, suggesting that BCL6 may be a broadly important target in DLBCLs, even in tumors expressing lower levels of the transcription factor. The cover image is a graphic depiction of FX1 (green) interacting with the BCL6 BTB domain lateral groove pocket and displacing its natural ligand. Image credit: Sam Shlomo Spaeth, CMI.

Rationally designed BCL6 inhibitors target activated B cell diffuse large B cell lymphoma

Serine 421 phosphorylation mitigates toxicity of mutant Huntington's protein

In Huntington's disease (HD), a mutant version of the HTT gene leads to neuronal dysfunction and degeneration, most prominently in the striatum, as well as motor, cognitive, and psychiatric dysfunction. Recent studies have shown that manipulations that increase phosphorylation of serine 421 (S421) in fragments of the mutant HTT protein can reduce its toxicity. Ian Kratter and colleagues investigated whether the S421 site regulates progressive neurodegeneration and behavioral deficits in a murine model of HD. They expressed a human HTT that was altered either to mimic continuous S421 phosphorylation or to prevent S421 phosphorylation. Mimicking continuous S421 phosphorylation ameliorated neurodegeneration and behavioral dysfunction by increasing turnover of mutant HTT, leading to a reduction in levels of the toxic protein in striatal neurons (see the accompanying image). These data indicate that S421 is a potential target for therapeutic interventions for HD.

Serine 421 regulates mutant huntingtin toxicity and clearance in mice
Ian H. Kratter, Hengameh Zahed, Alice Lau, Andrey S. Tsvetkov, Aaron C. Daub, Kurt F. Weiberth, Xiaofeng Gu, Frédéric Saudou, Sandrine Humbert, X. William Yang, Alex Osmand, Joan S. Steffan, Eliezer Masliah, and Steven Finkbeiner
http://jci.me/80339

Protein-diluted diet improves glucose homeostasis through liver signaling pathways

Although high-protein diets have been linked to an increased incidence of type 2 diabetes, it is not known whether decreasing protein intake is an effective strategy for lowering the risk of developing obesity-related metabolic disorders. Adriano Maida and coworkers demonstrated that very-low-protein diets can increase metabolic health by improving glucose homeostasis in mice and humans. In nutritional and genetic murine models of obesity, a protein-diluted diet prevented impairments in glucose homeostasis and promoted metabolic inefficiency by inducing the liver integrated stress response–driven nuclear protein 1 (NUPR1) and liver-derived fibroblast growth factor 21 (FGF21). These data indicate that stress response pathways in the liver may mediate the protective effects of low-protein diets on obesity-related metabolic diseases.

A liver stress-endocrine nexus promotes metabolic integrity during dietary protein dilution
Adriano Maida, Annika Zota, Kim A. Sjöberg, Jonas Schumacher, Tjeerd P. Sijmonsma, Anja Pfenninger, Marie M. Christensen, Thomas Gantert, Jessica Fuhrmeister, Ulrike Rothermel, Dieter Schmoll, Mathias Heikenwälder, Juan L. Ivanova, Kerstin Stemmer, Bente Kiens, Stephan Herzig, and Adam J. Rose
http://jci.me/85946

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 2017, will receive an unrestricted grant of $30,000 to advance academic efforts, and will deliver a research talk at the ASCI's April 2018 meeting.

The nomination deadline is October 14, 2016. 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.
Calpain-6 mediates atherosclerotic accumulation of LDL in macrophages

In atherosclerosis, macrophages form foam cells to deposit LDL cholesterol on vascular walls, leading to the formation of the plaques that cause lethal cardiovascular events. Although scavenger receptors mediate LDL uptake into macrophages, recent work suggests that independent mechanisms may also contribute to LDL accumulation. Takuro Miyazaki and coworkers investigated the role of calpain-6, an unconventional nonproteolytic isoform in the calpain protease family, in driving pinocytotic LDL uptake in atherogenic macrophages. Calpain-6 was required for LDL cholesterol uptake into macrophages as well as macrophage recruitment into atherosclerotic lesions, and calpain-6 deficiency in mice produced an atheroprotective phenotype in the aorta (see the accompanying image). Finally, evidence of calpain-6 induction in advanced human atherosclerotic vessels suggests that this molecule may be responsible for LDL uptake and deposition in advanced atherosclerosis.

Calpain-6 confers atherogenicity to macrophages by dysregulating pre-mRNA splicing

Takuro Miyazaki, Kazuo Tamami, Shoji Hata, Yoshihito Aiuchi, Kaji Ohnishi, Xiao-Feng Lei, Joo-ri Kim-Kaneyama, Motohiro Takeya, Hiroyuki Itobe, Hiroyuki Sorimachi, Hiroki Kurihara, and Akira Miyazaki

http://jci.me/85880

Angiopoietin and Tie signaling drive vascular remodeling in inflammation

Blood vessel remodeling is a central feature of developmental angiogenesis and plays key roles in inflammation and tumor growth. These changes in blood vessels depend on complex signaling through angiopoietins (ANG) and Tie receptors. ANG1 and ANG2 promote interactions between Tie1 and Tie2 that regulate changes in vessel structure, but the pathways that govern vessel stability or remodeling are not well understood. This month in the JCI, two studies investigate how ANG and Tie signaling control blood vessel homeostasis. Emilia Korhonen, Anita Lampinen, and colleagues determined that Tie1 acts as an intermediate in determining the effects of ANG1 and ANG2 on Tie2 signaling. Tie1 deficiency impaired the agonist action of ANG2 on Tie2 under normal conditions, leading to decreased Tie2 phosphorylation that resembled its response to inflammatory states. Minah Kim and coworkers investigated the mechanisms enabling ANG2 to activate or inhibit Tie2. In normal conditions, ANG2 activated Tie2 to promote stable enlargement of blood vessels. However, in an infection-induced inflammatory state, ANG2 acted as an antagonist that drove vascular remodeling. Both studies found that cleavage of Tie1's ectodomain during inflammation was associated with the switch of ANG2 from Tie2 agonist to antagonist. In the accompanying Commentary, Sarah Mueller and Christopher Kontos discuss ANG2/Tie1 interactions as an important control point in blood vessel remodeling under inflammatory conditions.

Related Research

Tie1 controls angiopoietin function in vascular remodeling and inflammation

Emilia A. Korhonen, Anita Lampinen, Hemant Giri, Andrey Anisimov, Minah Kim, Breanna Allen, Shentong Fang, Gabriela D’Amico, Tuomas J. Sipilä, Marja Lohela, Tomas Strandin, Antti Vaheri, Seppo Ylä-Herttuala, Gou Young Koh, Donald M. McDonald, Kari Alitalo, and Pipsa Saharinen

http://jci.me/84923

Opposing actions of angiopoietin-2 on Tie2 signaling and FOXO1 activation

Minah Kim, Breanna Allen, Emilia A. Korhonen, Maximilian Nitschké, Hee Won Yang, Peter Boluk, Pipsa Saharinen, Kari Alitalo, Christopher Daly, Gavin Thurston, and Donald M. McDonald

http://jci.me/84871

Related Commentary

Tie1: an orphan receptor provides context for angiopoietin-2/Tie2 signaling

Sarah B. Mueller and Christopher D. Kontos

http://jci.me/89963
Aminoglycoside-induced hair cell death is driven by mitochondrial oxidation

Aminoglycoside antibiotics can cause irreversible damage to the hair cells of the inner ear. Although the mechanism of aminoglycoside-induced hair cell death is currently unknown, degeneration frequently occurs when reactive oxygen species (ROS) rise to toxic levels within the cochlea. Robert Esterberg and colleagues studied hair cells in the zebrafish lateral line to determine the origin of aminoglycoside-induced ROS and observed that oxidation levels in the mitochondria and cytoplasm of dying cells correlated strongly with mitochondrial calcium uptake (see the accompanying image). Inhibition of mitochondrial calcium uptake protected hair cells against aminoglycoside-induced death. These findings further implicate ROS in aminoglycoside’s toxic effects and suggest that targeting mitochondrial calcium transporters may be an effective strategy for reducing aminoglycoside-induced hair cell damage.

Mitochondrial calcium uptake underlies ROS generation during aminoglycoside-induced hair cell death
Robert Esterberg, Tor Linbo, Sarah B. Pickett, Patricia Wu, Henry C. Ou, Edwin W. Rubel, and David W. Raible
http://jci.me/84939

Lung-resident eosinophils have a homeostatic function in allergic disease

Eosinophil production is increased in allergic diseases, and the inflammatory, Th2-associated actions of these immune cells can cause pathogenic tissue damage. However, increasing evidence suggests that eosinophils may also play a noninflammatory role in regulating homeostatic immune functions. Claire Mesnil, Stéfanie Raulier, and colleagues characterized a subset of lung-resident eosinophils that display a regulatory profile and can inhibit the proallergic function of allergen-loaded DCs. Mice deficient for lung-resident eosinophils exhibited increased Th2 immunity in response to low doses of inhaled allergens, demonstrating a role for this subtype in the regulation of lung immune homeostasis. In the accompanying Commentary, Marc Rothenberg discusses how the identification of this lung-resident population adds to our understanding of eosinophils as an immunoregulatory cell population.

Lung-resident eosinophils represent a distinct regulatory eosinophil subset
Claire Mesnil, Stéfanie Raulier, Geneviève Paulissen, Xue Xiao, Mark A. Birrell, Dimitri Pirottin, Thibaut Janss, Philipp Starkl, Eve Ramery, Monique Henket, Florence N. Schleich, Marc Radermecker, Kris Thielemans, Laurent Gillet, Marc Thiry, Maria G. Belvisi, Renaud Louis, Christophe Desmet, Thomas Marichal, and Fabrice Bureau
http://jci.me/85664

Related Commentary
A hidden residential cell in the lung
Marc E. Rothenberg
http://jci.me/89768
**Ghrelin cell β₁-adrenergic receptors regulate ghrelin secretion to prevent hypoglycemia**

The peptide hormone ghrelin is known to stimulate appetite and increase preference for calorie-dense foods. Ghrelin also increases blood glucose through multiple mechanisms, including modulation of insulin and glucagon secretion. Bharath Mani and coworkers observed that activation of β₁-adrenergic receptors (β₁ARs) on ghrelin-producing cells drives ghrelin secretion during caloric restriction. Ghrelin cell–specific β₁AR-deficient mice exhibited impairments in ghrelin secretion and exaggerated hypoglycemia upon caloric restriction, which was reversed by ghrelin administration. Inhibition of β₁AR activity with beta blockers similarly reduced ghrelin secretion and increased the incidence of hypoglycemia in calorie-restricted adolescent WT mice. These findings highlight a critical role for β₁AR signaling in ghrelin secretion and its requirement in the maintenance of blood glucose levels, indicating a potential therapeutic use for ghrelin replacement in treating beta blocker–induced hypoglycemia.

**β₁-Adrenergic receptor deficiency in ghrelin-expressing cells causes hypoglycemia in susceptible individuals**

Bharath K. Mani, Sherri Osborne-Lawrence, Prasanna Vijayaraghavan, Chelsea Hepler, and Jeffrey M. Zigman

http://jci.me/86270

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**Disruptions in Gpr45 dysregulate POMC expression in murine obesity**

*Many of the genetic markers* that have been linked to obesity risk involve neuropeptides that control food intake and energy expenditure, suggesting that dysfunctions in the pathways that regulate energy homeostasis may underlie some individuals’ predisposition to weight gain. Using a genetic screen for obesity-linked mutations in mice, Jing Cui and colleagues identified that disruptions in the gene encoding GPR45, a G protein–coupled receptor, lead to increased adiposity, body mass, glucose intolerance, and hepatic steatosis (see the accompanying image). They determined that GPR45 drives expression of the peptide POMC, which acts as a signal to regulate energy balance. These findings indicate that developing therapeutics to target GPR45 signaling could be an effective approach for combating obesity.

**Disruption of Gpr45 causes reduced hypothalamic POMC expression and obesity**

Jing Cui, Yi Ding, Shu Chen, Xiaoying Zhu, Yichen Wu, Mingliang Zhang, Yaxin Zhao, Tong-Ruei R. Li, Ling V. Sun, Shimin Zhao, Yuan Zhuang, Weiping Jia, Lei Xue, Min Han, Tian Xu, and Xiaohui Wu

http://jci.me/85676

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http://jci.me/85676

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http://jci.me/85676
**Gastroenterology**

EGFR signaling drives macrophage-mediated chronic inflammation in bacterial infection

Chronic inflammation induced by *H. pylori* infection creates a cycle of tissue and DNA damage that can lead to gastric cancer. This inflammation is driven in part by the activation of macrophages, which can mediate both proinflammatory and antiinflammatory responses to infection. Dana Hardbower and colleagues determined that macrophage activation and function during infection depend on signaling through the EGFR. EGFR deficiency exacerbated bacterial burden in mice infected with *H. pylori* and led to decreases in cytokine, chemokine, and NO production. Moreover, EGFR-deficient macrophages displayed impaired adaptive immune responses to infection, leading to a decrease in chronic inflammation (see the accompanying image). These findings suggest that targeting EGFR signaling is a potential intervention for chronic inflammation and carcinogenesis associated with *H. pylori* infection.

EGFR regulates macrophage activation and function in bacterial infection


http://jci.me/83585

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**Angiogenesis**

Local lymphatic remodeling determines immune responses to murine melanoma

Tumor-associated lymphatic vessels facilitate metastasis, yet they are also implicated in the immune cell trafficking that underlies antitumor adaptive immune responses. Amanda Lund, Marek Wagner, and colleagues determined that lymphatic vessels and their drainage are required for initiation of inflammation and immune responses against melanoma tumors. Unlike in normal mice, where melanoma growth occurs with leukocyte infiltration and suppressive cytokines, mice lacking dermal lymphatic vessels exhibited robust melanoma growth with marked reductions in cytokine expression and immune infiltrates. Without local lymphatics, metastasis was prevented (see the accompanying image), and adoptively transferred T cells were more effective. These findings imply that lymphatics regulate both pro- and antitumor immune responses and suggest that the pathways regulating local lymphatic vessel remodeling and drainage may be potential therapeutic targets for improving responses to tumor-targeting immunotherapies.

Lymphatic vessels regulate immune microenvironments in human and murine melanoma


http://jci.me/79434
Kaposi sarcoma: understanding latency, infection, and reactivation

**Kaposi sarcoma (KS)** is the most prevalent type of cancer affecting individuals living with HIV and AIDS, but the disease also occurs in HIV-negative adults and children. All cases of KS are linked to prior infection with the KS-associated herpesvirus (KSHV), a virus that can persist in a latent reservoir for many years before reactivating and producing cancerous lesions. In spite of its lifelong persistence, only a small fraction of KSHV-infected individuals develop KS, usually in response to therapeutic or disease-related immune system suppression. In this issue of the *JCI*, Dirk Dittmer and Blossom Damania review ongoing progress toward understanding the molecular mechanisms of KSHV infection, latency, and reactivation (see the accompanying image), as well as the insights this research provides about future clinical strategies for treating and preventing KS.

**Bioactive fragments of the lung extracellular matrix**

The extracellular matrix (ECM) serves as a cellular scaffold and plays a critical role in the maintenance of organ structure, the regulation of tissue development, cellular signaling, and mediation of cell-cell interactions. It undergoes continuous remodeling, with both synthesis of ECM components and proteolytic degradation. The fragments resulting from ECM degradation, known as matrikines, have been shown to promote immune cell infiltration, progressive tissue damage, and wound healing. In this issue, Amit Gaggar and Nathaniel Weathington review the role of matrikines in lung biology, focusing on fragments derived from collagen, hyaluronan, elastin, and laminin. Notably, several of these matrikines have been linked to lung disease and could potentially serve as biomarkers or therapeutic targets.

**Bioactive extracellular matrix fragments in lung health and disease**

Amit Gaggar and Nathaniel Weathington
[http://jci.me/83147](http://jci.me/83147)
ANGIOGENESIS

Lymphatic vessels regulate immune microenvironments in human and murine melanoma ➤ p. 6


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Tyrosine kinase FYN negatively regulates NOX4 in cardiac remodeling

Shouji Matsushima, Junya Kuroda, Peiyong Zhai, Tong Liu, Shohei Ikeda, Narayani Nagarajan, Shin-ichi Oka, Takashi Yokota, Shintaro Kinugawa, Chiao-Po Hsu, Hong Li, Hiroyuki Tsutsui, and Junichi Sadoshima  http://jci.me/85624

ENDOCRINOLOGY

Recurrent EZH1 mutations are a second hit in autonomous thyroid adenomas


Disruption of Gpr45 causes reduced hypothalamic POMC expression and obesity ➤ p. 5

Jing Cui, Yi Ding, Shu Chen, Xiaojiang Zhu, Yichen Wu, Mingliang Zhang, Yaxin Zhao, Tong-Ruei R. Li, Ling V. Sun, Shimin Zhao, Yuan Zhuang, Weiping Jia, Lei Xue, Min Han, Tian Xu, and Xiaohui Wu  http://jci.me/85676

β1-Adrenergic receptor deficiency in ghrelin-expressing cells causes hypoglycemia in susceptible individuals ➤ p. 5

Bharath K. Mani, Sherri Osborne-Lawrence, Prasanna Vijayaraghavan, Chelsea Hepler, and Jeffrey M. Zigman  http://jci.me/86270

Insulin and IGF-1 receptors regulate FoxO-mediated signaling in muscle proteostasis


GASTROENTEROLOGY

EGFR regulates macrophage activation and function in bacterial infection ➤ p. 6


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Posttranscriptional manipulation of TERC reverses molecular hallmarks of telomere disease

Baris Boyraz, Diane H. Moon, Matthew Segal, Maud Z. Muosieyiri, Asli Aykanat, Albert K. Tai, Patrick Cahan, and Suneeat Agarwal  http://jci.me/87547

Biallelic inactivation of REV7 is associated with Fanconi anemia


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Lung-resident eosinophils represent a distinct regulatory eosinophil subset ➤ p. 4

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BET bromodomain inhibition enhances T cell persistence and function in adoptive immunotherapy models

Yuki Kagoya, Munehide Nakatsugawa, Yuki Yamashita, Toshiki Ochi, Tingxi Guo, Mark Anczurowski, Kayoko Saso, Marcus O. Butler, Cheryl H. Arrowsmith, and Naoto Hirano  http://jci.me/86437
INFLAMMATION

**Loss of ABCG1 influences regulatory T cell differentiation and atherosclerosis**
Hsin-Yuan Cheng, Dalia E. Gaddis, Runpei Wu, Chantel McSkimming, LaTeira D. Haynes, Angela M. Taylor, Coleen A. McNamara, Mary Sorci-Thomas, and Catherine C. Hedrick  http://jci.me/83136

**Local TNF causes NFATc1-dependent cholesterol-mediated podocyte injury**
Christopher E. Pedigo, Gloria Michelle Ducasa, Farah Leclercq, Alexis Sloan, Alla Mitrofanova, Tahreem Hashmi, Judith Molina-David, Mengyuan Ge, Mariann I. Lassenius, Carol Forsblom, Markku Lehto, Per-Henrik Groop, Matthias Kretzler, Sean Eddy, Sebastian Martini, Heather Reich, Patricia Wahl, GianMarco Ghiglieri, Christian Faul, George W. Burke III, Oliver Kretz, Tobias B. Huber, Armando J. Mendez, Sandra Merscher, and Alessia Fornoni  http://jci.me/85939

**Granulocyte macrophage colony-stimulating factor induces CCL17 production via IRF4 to mediate inflammation**
Adrian Achuthan, Andrew D. Cook, Ming-Chin Lee, Reem Saleh, Hsu-Wei Khiew, Melody W.N. Chang, Cynthia Louis, Andrew J. Fleetwood, Derek C. Lacey, Anne D. Christensen, Ashlee T. Frye, Pui Yeng Lam, Hitoshi Kusano, Koji Nomura, Nancy Steiner, Irmgard Förster, Stephen L. Nutt, Moshe Olshansky, Stephen J. Turner, and John A. Hamilton  http://jci.me/87828

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**MondoA coordinately regulates skeletal myocyte lipid homeostasis and insulin signaling**

MUSCLE BIOLOGY

**PIK3C2B inhibition improves function and prolongs survival in myotubular myopathy animal models**

NEPHROLOGY

**Urea impairs β cell glycolysis and insulin secretion in chronic kidney disease**
Laetitia Koppe, Elsa Nyam, Kevin Vivot, Jocelyn E. Manning Fox, Xiao-Qing Dai, Bich N. Nguyen, Dominique Trudel, Camille Attané, Valentine S. Moulé, Patrick E. MacDonald, Julien Ghislain, and Vincent Poitout  http://jci.me/86181

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**ZEB1 drives epithelial-to-mesenchymal transition in lung cancer**

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**Mechanistically distinct cancer-associated mTOR activation clusters predict sensitivity to rapamycin**
Jianing Xu, Can G. Pham, Steven K. Albanese, Yiyu Dong, Yoshio Oyama, Chung-Han Lee, Vanessa Rodrik-Outmezguine, Zhan Yao, Song Han, David Chen, Daniel L. Parton, John D. Chodera, Neal Rosen, Emily H. Cheng, and James J. Hsieh  
[http://jci.me/86120](http://jci.me/86120)

**Phase I trials using Sleeping Beauty to generate CD19-specific CAR T cells**
[http://jci.me/86721](http://jci.me/86721)

**Tumor immune profiling predicts response to anti–PD-1 therapy in human melanoma**
[http://jci.me/87324](http://jci.me/87324)

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**Mitochondrial calcium uptake underlies ROS generation during aminoglycoside-induced hair cell death**  
Robert Esterberg, Tor Linbo, Sarah B. Pickett, Patricia Wu, Henry C. Ou, Edwin W. Rubel, and David W. Raible  
[http://jci.me/84939](http://jci.me/84939)

**STEM CELLS**

**BRPF1 is essential for development of fetal hematopoietic stem cells**
Linya You, Lin Li, Jinping Zhou, Kezhi Yan, Jinhua Zhao, Anastasia Nijnik, Edwin Wang, and Xiang-Jiao Yang  
[http://jci.me/80711](http://jci.me/80711)

**TRANSPLANTATION**

**A colitogenic memory CD4+ T cell population mediates gastrointestinal graft-versus-host disease**
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**Opposing actions of angiopoietin-2 on Tie2 signaling and FOXO1 activation**  
Minah Kim, Breanna Allen, Emilia A. Korhonen, Maximilian Nitschke, Hee Won Yang, Peter Baluk, Pipsa Saharin, Kari Alitalo, Christopher Daly, Gavin Thurston, and Donald M. McDonald  
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**Tie1 controls angiopoietin function in vascular remodeling and inflammation**  
Emilia A. Korhonen, Anita Lamminen, Hemant Giri, Andrey Anisimov, Minah Kim, Breanna Allen, Shentong Fang, Gabriela D’Amico, Tuomas J. Sipilä, Marja Lohela, Tomas Strandin, Antti Vaheer, Seppe Ylä-Herttuala, Gou Young Koh, Donald M. McDonald, Kari Alitalo, and Pipsa Saharin  
[http://jci.me/84923](http://jci.me/84923)

**Calpain-6 confers atherogenicity to macrophages by dysregulating pre-mRNA splicing**  
Takuro Miyazaki, Kazuo Tonami, Shoji Hata, Toshistihiro Ouchi, Koji Ohnishi, Xiao-Feng Lei, Joo-ri Kim-Kaneyama, Motonburo Takeya, Hiroshi Itabe, Hiroshi Sorimachi, Hiroki Kurihara, and Akira Miyazaki  
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**Dasatinib induces lung vascular toxicity and predisposes to pulmonary hypertension**
Christophe Guignabert, Carole Phan, Andrei Seferian, Alice Huertas, Ly T, Raphael Thuillot, Caroline Sattler, Morane Le Hiress, Yuchi Tamura, Etienne-Marie Jutant, Marie-Camille Chaumais, Stéphane Bouchet, Benjamin Manéglier, Mathieu Molimard, Philippe Rousselot, Olivier Sitbon, Gérald Simonneau, David Montani, and Marc Humbert  
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**Vascular stiffness mechanoactivates YAP/TAZ-dependent glutaminolysis to drive pulmonary hypertension**
[http://jci.me/86387](http://jci.me/86387)
Heart-resident macrophages drive neutrophil trafficking in cardiac ischemia-reperfusion injury

Myocardial ischemia-reperfusion injury, such as occurs after cardiopulmonary bypass operations or heart transplant, triggers cardiomyocyte death, resulting in impaired heart function. Neutrophil infiltration of the heart is known to promote damage, but the underlying mechanisms governing neutrophil trafficking are unclear. Using a murine model of cardiac transplant ischemia-reperfusion and two-photon microscopy, Wenjun Li, Hsi-Min Hsiao, and colleagues show that tissue-resident CCR2+ macrophages mediate neutrophil recruitment (see the accompanying image). Mechanistically, cardiac cell death results in the release of damage-associated molecular patterns, which activate a TLR9/MyD88 pathway in CCR2+ macrophages. This pathway mediates the release of the chemoattractants CXCL2 and CXCL5, which induce neutrophil adhesion and crawling, respectively, ultimately leading to extravasation and migration into the heart.

Aldehyde dehydrogenase mediates ocular mucosa fibrosis

Fibrotic scarring of the ocular mucosa causes blindness and is associated with ocular pemphigoid, trachoma, and allergic eye disease (AED). Two independent research groups led by Daniel Saban and John Dart demonstrate that the aldehyde dehydrogenase (ALDH) metabolite retinoic acid (RA) mediates ocular mucosal fibrosis. Using a murine model of AED, Saban and colleagues demonstrated that DCs directly induce fibrosis through ALDH production of RA, which activates the retinoid X receptor (RXR) in conjunctival fibroblasts. RXR stimulation rapidly induced ocular mucosal fibrosis, while inhibition of ALDH activity or depletion of DCs markedly reduced fibrosis in mice. Dart and colleagues found that ALDH1 family members were upregulated in the conjunctiva of patients with ocular mucous membrane pemphigoid (OMMP), as well as in cultured patient fibroblasts. Treatment of cultured patient fibroblasts with the ALDH1 inhibitor disulfiram reduced collagen production, increased matrix contraction and proliferation, and altered actin organization. Moreover, topical disulfiram treatment attenuated ocular inflammation and fibrosis in a murine AED model. Taken together, these findings delineate mechanisms mediating ocular fibrosis and identify potential therapeutic targets.

Related Research

Aldehyde dehydrogenase inhibition blocks mucosal fibrosis in human and mouse ocular scarring

Classical dendritic cells mediate fibrosis directly via the retinoic acid pathway in severe eye allergy
Nephrology

Metalloprotease ADAM17 mediates profibrotic factor release in the kidney

Kidney fibrosis is a frequent consequence of kidney injury or disease and can result in nephron loss and eventual kidney failure. Eirini Kefaloyianni and colleagues demonstrate that the metalloprotease ADAM17 is upregulated after kidney injury and mediates the release of pro-TNFα and the EGFR ligand amphiregulin in the proximal tubule. Deletion of Adam17 within the proximal tubule or treatment with an ADAM17 inhibitor protected against fibrosis after acute kidney injury (AKI; see the accompanying image) or unilateral ureter obstruction (UUO) in mice. Importantly, soluble amphiregulin levels were elevated in urine samples from patients with AKI or chronic kidney disease, and ADAM17 and amphiregulin expression in kidney biopsies strongly correlated with markers of fibrosis, indicating that ADAM17 drives fibrosis in human kidney fibrosis.

ADAM17 substrate release in proximal tubule drives kidney fibrosis

Eirini Kefaloyianni, Muthu Lakshmi Muthu, Jakob Kaeppler, Xiaoming Sun, Venkata Sabbisetti, Athena Chalaris, Stefan Rose-John, Eitan Wong, Irit Sagi, Sushrut S. Waikar, Helmut Rennke, Benjamin D. Humphreys, Joseph V. Bonventre, and Andreas Herrlich

http://jci.me/87023

Oncology

PAX8/chromatin interactions are dramatically altered in serous ovarian carcinomas

Most high-grade serous ovarian carcinomas (HGSOCs) arise from fallopian tube secretory epithelial cells (FTSECs). PAX8 is a lineage-restricted transcription factor (TF) of the Müllerian epithelium. It gives rise to the female reproductive tract and is retained in nearly all HGSOCs. Kevin Elias and colleagues investigated alterations in the epigenetic behavior of PAX8 between FTSECs and HGSOCs. Using whole transcriptome shotgun sequencing (RNA-seq) and ChIP-seq, Elias and colleagues showed that the cistromes between FTSEC and HGSOC lines are radically altered. Additionally, genes that were significantly altered between FTSECs and HGSOCs were clustered around PAX8 binding sites. The differentially regulated genes were also near binding sites for the TEAD family of transcription factors, which mediate YAP-dependent gene induction and have been implicated in FTSEC/HGSOC transformation. Coimmunoprecipitation and proximity ligation assays confirmed that PAX8 and TEAD TFS physically interact in Müllerian cells. These results suggest that the development of HGSOC is linked to PAX8/TEAD-mediated interactions with chromatin.

Epigenetic remodeling regulates transcriptional changes between ovarian cancer and benign precursors

Kevin M. Elias, Megan M. Emori, Thomas Westerling, Henry Long, Anna Budina-Kolomet, Fugen Li, Emily MacDuffie, Michelle R. Davis, Alexander Holman, Brian Lawney, Matthew L. Freedman, John Quackenbush, Myles Brown, and Ronny Drapkin

http://jci.me/87988
IL4 receptor-α deficiency impairs T cell egress in murine systemic sclerosis

Systemic sclerosis (SSc) is a fatal autoimmune disease characterized by inflammation and fibrosis of internal organs and the skin. Because mice deficient in IL4 receptor-α (IL4RA) are protected in a murine model of SSc (sclerodermatous graft versus host disease), Katia Urso and colleagues examined the mechanisms underlying this protection. They found that IL4RA deficiency resulted in decreased levels of the sphingosine-1 phosphate–producing (S1P-producing) enzyme sphingosine kinase 1 (SPHK1) in the lymphatic endothelial cells of the draining lymph nodes (dLNs). Impaired S1P production altered the efferent lymphatics morphology and resulted in retention of effector T cells in skin dLNs (see the accompanying image). Intravenous injection of effector T cells, which bypasses the efferent lymphatics, induced SSc-like symptoms in IL4RA-deficient mice. These findings reveal a role for IL4RA in T cell egress that could potentially serve as a therapeutic target in SSc.

IL4RA on lymphatic endothelial cells promotes T cell egress during sclerodermatous graft versus host disease
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