March 6-9, 2012

Rancho Mirage, CA

More than any meeting in the lipid field, the Deuel Conference on Lipids provides a collegial and informal setting for close interactions between scientists from industry and academia.

DEUEL CONFERENCE ON LIPIDS

DEUEL Conference on Lipids

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The Deuel Conference on Lipids was organized in 1955 by a small group of eminent West Coast investigators who were interested in lipid metabolism. Their goal was to establish a high-quality conference on lipids within the western part of the country, akin to forums provided by the Gordon Conferences on the east coast. Shortly after the Conference was organized, one of the founders, Dr. Harry Deuel, died—and the conference was named in his memory. The two-and-one-half day conference includes five scientific sessions, with an eminent lipid scientist chairing each session Each session includes three to four original scientific presentations followed by in-depth discussions of the topic.

The relatively small size of the audience, a round-table format, and the absence of video-taping or recording encourage informality and the free interchange of new hypotheses and scientific data. Lively discussions by conference participants are the highlight of the meeting.

We Invite You to Join the

ASBMB Lipid Research Division

Exciting Research News

Forum Discussions

Lipid Events Calendar

www.asbmb.org/lipidcorner

The Havel Lecture

The Havel Lecture was named after Dr. Richard J. Havel because he has done more than anyone else to keep the Deuel Conference going

Richard J. Havel is known by many as "Mr. Lipoprotein, USA." He, more than any other investigator unraveled the complex metabolism of the plasma lipoproteins beginning with his pioneering work in the Anfinsen lab at the National Heart Institute in Bethesda, Maryland, where he was one of the first Clinical Associates from 1953-1956. His manuscript on the ultracentrifulgal separation of lipoproteins is one of the most frequently cited papers, rivaling Lowry's paper on protein measurement.

Richard Havel has published over 300 manuscripts. Their quality is attested to by his election to the National Academy of Sciences in 1983; the Institute of Medicine in 1989; the American Academy of Arts and Sciences in 1992. He has received many other honors including the Bristol-Myers Squibb Award for Distinguished Achievement in Nutrition Research and the Distinguished Achievement Award from the AHA Council on Arteriosclerosis.

Richard J. Havel Lecturers

2012 Gokhan Hotamisligil, Harvard University

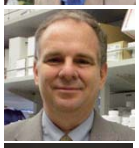
"Inflammation, Endoplasmic Reticulum Stress and Lipids: Emerging Networks Regulating Metabolism"

2011 Christopher K. Glass, University of California San Diego

"Oxysterol regulation of macrophage gene expression"

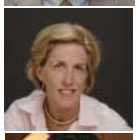
2010 David J. Mangelsdorf, University of Texas Southwestern

"Nuclear receptor control of lipid metabolism"



2009 Stephen G. Young, UCLA School of Medicine

"Adventures in Lipid Metabolism"



2008 Helen H. Hobbs, University of Texas Southwestern Medical Center

"Going to Extremes to Identify Genetic Variations Contributing to Cardiovascular Risk"

2007 Ronald Evans, The Salk Institute for Biological Sciences

"PPARdelta and the Marathon Mouse: Running Around Physiology"

2006 David Russell , University of Texas Southwestern Medical Center

"The Enzymes of Cholesterol Breakdown"

2005 Johann Deisenhofer, HHMI/UTSW Medical Center

"Structure of the LDL receptor"

2004 Jeffrey M. Friedman, Rockefeller University

"The Function of Leptin in Nutrition, Weight and Physiology"

2003 Bruce Spiegelman, Harvard Medical School

"Transcriptional Control of Energy and Glucose Metabolism"

2002 Co-Lecturers Michael S. Brown & Joseph L. Goldstein, UT Southwestern Medical Center,

"SREBPs: Master Regulators of Lipid Metabolism" 2002 - Joseph L. Goldstein, UT Southwestern

Schedule of Events

	Tuesday, March 6	Wednesday, March 7	Thursday, March 8		Friday, March 9
7 AM		Breakfast 7-8:30	Breakfast 7-8:30	Board Mtg. 7:00- 8:30	Breakfast 7-8:30
8 AM					
9 AM		Session I 8:30-10:00	Session 2 8:30-9:50		Session 4 8:30-9:50
10 AM		Coffee Break 9:50	Coffee Break 9:50		Coffee Break 9:50
11 AM		Session I, Continued 10:20-12:00	Session 2, Continued 10:20-12:30		Session 4, Continued 10:20-11:40
12 PM		Free Time			
1 PM			Free Time		
2 PM					
3 PM	Registration 3-6:30				
4 PM					
5 PM			Sponsor Reception 5:00-6:00		
6 PM		Dinner 6:00- 7:30	Dinner 6:00-7:30		
7 PM	Welcome Reception and Dinner	HAVEL LECTURE 7:30-8:30	Session 3 7:30-9:30		
8 PM					
9 PM					
10 PM		Poster Session 8:30			

Meeting Program

2012 Deuel Conference on Lipids, March 6-9, 2012
Silverado Resort, Napa Valley, California

SCHEDULE

Tuesday, March 6

3:00- 6::30pm Registration

6:30- 10:00pm Opening Reception, Posters and Dinner

Wednesday, March 7

Wednesday, March 2, 8:30 AM to 12:00 PM

Session Chair: Joe Witzum

Session 1 **Inflammation and Lipids in Metabolic Disease and Atherosclerosis**

8:30-9:10 "Inflammasomes: The CARD Containing Regulators of Obesity-Related Comorbidities"
Vishwa Deep Dixit, *Louisiana State University*, Baton Rouge, LA

9:10-9:50 "Inflammasomes, Macrophages, and Atherosclerosis"
Eicke Latz, *University of Bonn*, Bonn, Germany

9:50-10:20 Coffee Break

10:20-11:00 "MicroRNAs that Modulate Lipoprotein Metabolism: Transport and Intracellular Regulation "
Alan Remaley, *National Institutes of Health*, Bethesda, MD

11:00-11:40 "A Systems Approach to Dissecting Inflammation"
Alan Aderem, *Institute for Systems Biology*, Seattle, WA

11:40 -12:00 "MicroRNA-144 Regulates Hepatic ABCA1 and Plasma HDL Following Activation of the Nuclear Receptor FXR"
Thomas A. Vallim, *University of California*, Los Angeles

Wednesday, March 2, 7:30 to 8:30 PM

Session Chair: Ira Tabas

The Havel Lecture

"'Inflammation, Endoplasmic Reticulum Stress and Lipids: Emerging Networks Regulating Metabolism"

Gokhan Hotamisligil, *Harvard University*, Boston, MA

Wine Reception and Poster Session

Thursday, March 8

Thursday, March 3, 8:30 AM to 12:00 PM

Session Chair: Bob Farese

Session 2 **Brown Fat, Thermoregulation, and Lipid Metabolism**

8:30-9:10 "Epigenomic regulation of inflammation, energy metabolism, and adipogenesis"
Juro Sakai, *University of Tokyo*

9:10-9:50 "Role of Acyl-CoA Synthetase-1 in Thermoregulation"
Rosalind Coleman, *University of North Carolina Chapel Hill*, NC

9:50-10:20 Coffee Break

10:20-11:00 "Brown Adipose Tissue in Humans"
Sven Enerback, *Goteborg University*, Sweden

The Journal of Lipid Research Lecture

Introduction to the lecture - Steve Young, University of California, Los Angeles, CA

11:00-11:40 "Brown Fat Development and Therapeutics of the Metabolic Syndrome"
Bruce Spiegelman, *Harvard Medical School,* Boston, MA

11:40-12:00 "Lipolysis fuels the nuclear receptor PPARs with ligands: a role for fatty acids in promoting oxidation in brown adipocytes"
Emilio P. Mottillo, *Wayne State University School of Medicine*

Thursday, March 9, 7:30-9:30 PM

Session Chair: Alan Attie

Session 3 Circadian Rhythm and Lipid Metabolism

7:30-8:10 "Clock Genes in Fuel Selection and Energy Homeostasis"
Joe Bass, *Northwestern University*, Chicago, IL

8:10-8:50 "Rev-erb-alpha and the Circadian Control of Lipid Metabolism"
Mitch Lazar, *University of Pennsylvania*, Philadelphia, PA

8:50-9:30 "Cryptochromes mediate rhythmic repression of glucocorticoid signaling"
Katja Lamia, *Salk Institute*, La Jolla, CA

Friday, March 9

Friday, March 9, 8:30 AM to 12:00 PM

Session Chair: Dan Rader

Session 4 Therapeutics and Clinical Studies in Lipoprotein and Lipid Metabolism

8::30-9:10 "New Therapeutic Approaches to the Treatment of Type 2 Diabetes and Obesity"
Nancy Thornberry, *Merck*, Rahway, NJ

9:10-9:50 "Update on PCSK9 Function and Activity"
Jay Horton, *University of Texas-Southwestern,* Dallas, TX

9:50-10:20 Coffee Break

10:20-11:00 "FGF21: From Famine to Feast to Pharmacology"
Steve Kliewer, *University of Texas-Southwestern*, Dallas, TX

11:00-11:40 "Mechanisms underlying nicotinic acid's wanted and unwanted effects"
Stefan Offermanns, *Max-Planck-Institut*, Bad Nauheim, Germany

Poster Presentations

1
Regulation of LDL Uptake by the LDL Receptor

Peter Michaely, Zhenze Zhao, and Shanica Pompey

University of Texas Southwestern Medical Center, Dallas, TX

Abstract:

The LDL receptor (LDLR) internalizes LDL via interaction with apoB100, while internalizing VLDL remnants and other lipoproteins via interaction with apoE. LDL uptake also requires interaction of the FDNPVY sequence of the LDLR with endocytic adaptor proteins, the most important of which is the autosomal recessive hypercholesterolemia (ARH) protein. Here, we show that ARH is nitrosylated and that this nitrosylation is required for LDL uptake. LDL uptake requires ARH nitrosylation because this post-translational modification promotes the interaction of ARH with the AP-2 adaptor and is necessary for ARH to target LDL-LDLR complexes to coated pits. As a consequence, inhibition of nitric-oxide synthases cripples LDL uptake. LDLR-dependent uptake of the VLDL remnant, β-VLDL, does not require ARH and is unaffected by inhibition of nitric-oxide synthases. These findings suggest that cells, such as leukocytes and hepatocytes that rely upon ARH for LDL uptake, regulate the lipoprotein specificity of LDLR-dependent uptake through nitric oxide. Atherosclerotic lesions are rich in reactive oxygen species that eliminate nitric oxide, and loss of ARH activity may help protect leukocytes from LDL. Changes in whole body nitric oxide may also allow liver hepatocytes to better maintain LDL homeostasis.

2

Impaired Cholesterol Efflux in Senescent Macrophages Promotes Macular Degeneration

Rajendra S. Apte1, Abdoulaye Sene1, Douglas Cox1, Rei Nakamura1, Angel Baldan2, Peter Edwards3, John Parks4, Rohini Sidhu1, and Daniel Ory1

1Washington University, St. Louis, MO; 2Saint Louis University, St. Louis, MO; 3University of California, Los Angeles, CA; 4Wake Forest University, Winston-Salem, NC

Abstract:

Pathologic angiogenesis mediated by abnormally polarized macrophages plays a central role in common age-associated diseases such as atherosclerosis, cancer, and macular degeneration. We demonstrate that abnormal polarization in older macrophages is caused by programmatic changes that lead to reduced expression of ATP-binding cassette transporter ABCA1. Down-regulation of ABCA1 impairs the ability of senescent macrophages to efflux intracellular cholesterol effectively. Elevated intracellular lipid polarizes older macrophages to an abnormal phenotype that promotes pathologic vascular proliferation. Mice deficient for Abca1, but not Abcg1, demonstrate an accelerated aging phenotype, whereas restoration of cholesterol efflux using liver X receptor (LXR) agonists reverses it. Monocytes from human patients with age-related macular degeneration showed similar changes. These findings provide an avenue for therapeutic modulation of macrophage function in common age-related diseases.

3

Liver X Receptor (LXR)a Is Uniquely Required for Maximal Reverse Cholesterol Transport and Atheroprotection in Apolipoprotein E-deficient Mice

Xin Rong1, Cynthia Hong1, 2, Michele N. Bradley1, Xuping Wang3, Alan Wagner3, Victor Grijalva3, Lawrence W. Castellani3, Jon Salazar1, Susan Realegeno1, Rima Boyadian1, Tamer Sallam3, Alan M. Fogelman3, Brian J. Van Lenten3, Srinivasa T. Reddy3, Aldons J. Lusis3, Rajendra K. Tangirala3, and Peter Tontonoz1, 2

1Department of Pathology and Laboratory Medicine, 2Howard Hughes Medical Institute, and 3David Geffen School of Medicine, University of California, Los Angeles, CA

Abstract:

The liver X receptors (LXRa and LXRb) are cholesterol-responsive transcription factors implicated in sterol homeostasis. Prior studies have established the LXR signaling pathway as an important modulator of atherosclerosis, but the relative importance of the two LXR isotypes in atheroprotection, as well as the contribution of specific cell types to LXR-dependent reverse cholesterol transport, are incompletely understood. We show here that LXRa, the dominant LXR isotype expressed in liver, plays a particularly important role in whole body sterol homeostasis. In the context of the atherogenic ApoE–/– background, deletion of LXRa, but not LXRb, led to prominent increases in atherosclerosis and peripheral cholesterol accumulation. However, combined loss of LXRa and LXRb on the ApoE–/– background led to an even more severe cholesterol accumulation phenotype compared with LXRa–/–ApoE–/– mice, indicating that LXRb does contribute to reverse cholesterol transport but that this contribution is quantitatively less important than LXRa. Unexpectedly, macrophages did not appear to underlie the differential phenotype of LXRa–/–ApoE–/– and LXRb–/–ApoE–/– mice because in vitro assays revealed no difference in the efficiency of cholesterol efflux from isolated macrophages. By contrast, in vivo assays of reverse cholesterol transport using exogenously labeled macrophages revealed a marked defect in fecal sterol efflux in LXRa–/–ApoE–/– mice, but not LXRb–/–ApoE–/– mice compared with ApoE–/– controls. Mechanistically, this defect was linked to a specific requirement for LXRa–/– in the expression of hepatic LXR target genes involved in sterol transport and metabolism. Others tissues and cell types involved in cholesterol homeostasis, including macrophages and intestine, were equally dependent on LXRa and LXRb for LXR target gene expression. These studies reveal a previously unrecognized requirement for hepatic LXRa for optimal reverse cholesterol transport in mice.

4

Alternatively Activated Macrophages Produce Catecholamines to Sustain Adaptive Thermogenesis

Khoa D. Nguyen1, 2, Yifu Qiu1, Xiaojin Cui1, Sharon Goh1, 2, Julia Mwangi1, Tovo David1, Lata Mukundan1, Frank Brombacher3, Richard M. Locksley4, and Ajay Chawla1

1Cardiovascular Research Institute and 4Department of Medicine, University of California, San Francisco, CA; 2Immunology Program, Stanford University, Palo Alto, CA; 3University of Cape Town, Rondebosch, South Africa

Abstract:

All homeotherms (warm-blooded animals) utilize thermogenesis to maintain core body temperature, ensuring that cellular functions and physiologic processes can continue to operate properly in cold environments. In the prevailing model, when the hypothalamus senses cold temperatures, it triggers a sympathetic discharge, resulting in the release of noradrenaline in brown adipose tissue (BAT) and white adipose tissue (WAT). However, the precise nature of all the cell types involved in this efferent loop is not well established. Here, we report an unexpected requirement for the interleukin 4 (IL-4)-stimulated program of alternative macrophage activation in adaptive thermogenesis. Cold exposure rapidly promoted alternative activation of adipose tissue macrophages, which secrete catecholamines to induce thermogenic gene expression in BAT and lipolysis in WAT. The absence of alternatively activated macrophages impaired metabolic adaptations to cold, whereas administration of IL-4 increased thermogenic gene expression, fatty acid mobilization, and energy expenditure, all in a macrophage-dependent manner. We have thus discovered a surprising role for alternatively activated macrophages in the orchestration of an important mammalian stress response, the response to cold.

5

Conserved SREBP-1/Phosphatidylcholine Feedback Circuit Regulates Lipogenesis in Metazoans

Amy K. Walker1, René L. Jacobs2, Jennifer L. Watts3, Lorissa J. Niebergall4, Dennis E. Vance4, and Anders M. Näär5

1Program in Molecular Medicine, University of Massachusetts Medical School, Worcester MA; 2Department of Agricultural, Food and Nutritional Science and 4Department of Biochemistry, University of Alberta, Edmonton, AB, Canada; 3School of Molecular Biosciences, Washington State University, Pullman, WA; 5Massachusetts General Hospital Cancer Center, Charlestown, MA

Abstract:

Sterol regulatory element-binding proteins (SREBPs) activate genes involved in the synthesis and trafficking of cholesterol and other lipids and are critical for maintaining lipid homeostasis. Aberrant SREBP activity, however, can contribute to obesity, fatty liver disease, and insulin resistance, hallmarks of metabolic syndrome. Our studies identify a conserved regulatory circuit in which SREBP-1 controls genes in the one-carbon cycle, which produces the methyl donor S-adenosylmethionine (SAMe). Methylation is critical for the synthesis of phosphatidylcholine (PC), a major membrane component, and we find that blocking SAMe or PC synthesis in Caenorhabditis elegans, mouse liver, and human cells causes elevated SREBP-1-dependent transcription and lipid droplet accumulation. Distinct from negative regulation of SREBP-2 by cholesterol, our data suggest a feedback mechanism where maturation of nuclear, transcriptionally active SREBP-1 is controlled by levels of PC. Thus, nutritional or genetic conditions limiting SAMe or PC production may activate SREBP-1, contributing to human metabolic disorders.

6

Inflammasomes, Macrophages, and Atherosclerosis

Eicke Latz

University of Massachusetts Medical School, Worcester, MA; Institute of Innate Immunity, University of Bonn, Bonn, Germany

Abstract:

Innate immunity evolved to recognize microbial infection and to respond to danger signals that appear under disease conditions. The most recently described innate immune receptor family is the Nod-like receptor (NLR) family. The NLR member NLRP3 and the adaptor apoptosis-associated speck-like (ASC) protein form a multimolecular complex termed the NLRP3 inflammasome. Inflammasomes control the activity of caspase-1, which cleaves and activates the pro-forms of the inflammatory cytokines IL-1β and IL-18. The NLRP3 inflammasome can be activated by various membrane-active bacterial toxins or after phagocytosis of crystalline materials. In addition, various microbes can activate the NLRP3 inflammasome. The mechanisms by which the NLRP3 inflammasome is activated by physico-chemical diverse activators are not well understood. We demonstrated that crystals activate the NLRP3 inflammasome in a process that requires phagocytosis, and we found that crystal uptake leads to lysosomal damage and rupture. Furthermore, sterile lysosomal damage was sufficient to induce NLRP3 activation, and inhibition of phagosomal acidification or inhibition or lack of cathepsins impaired NLRP3 activation. These results indicate that the NLRP3 inflammasome can sense lysosomal damage as an endogenous danger signal. We have recently demonstrated that cholesterol crystals can be recognized by the NLRP3 inflammasomes and contribute to inflammation in atherosclerotic plaques. We are currently developing novel therapeutic approaches for atherosclerotic disease that are based on the solubilization of cholesterol crystals.

7

Ketone Body Secretion from the Liver, a New Node of Lipid Metabolism

Sarah E. Hugo1, Lourdes Cruz-Garzia1, Santhosh Karanth1, Ryan M. Anderson2, Didier Y. Stainier2, and Amnon Schlegel1

1University of Utah School of Medicine, Salt Lake City, UT; 2University of California, San Francisco, CA

Abstract:

To find new genes that influence liver lipid mass we performed a genetic screen for zebrafish mutants with hepatic steatosis, a pathological accumulation of fat. The red moon (rmn) mutant develops hepatic steatosis as maternally deposited yolk is depleted. Conversely, hepatic steatosis is suppressed in rmn mutants by adequate nutrition. Adult rmn mutants show increased liver neutral lipids and induction of hepatic lipid biosynthetic genes when fasted. Positional cloning of the rmn locus reveals a loss-of-function mutation in slc16a6a, a gene that we show encodes a β-hydroxybutyrate transporter. Restoring wild-type zebrafish slc16a6a expression or introducing human SLC16A6 in rmn mutant livers rescues the mutant phenotype. Radiotracer analysis revealed that loss of slc16a6a function causes diversion of liver-trapped ketogenic precursors into triacylglycerol. Underscoring the importance of slc16a6a to normal fasting physiology, previously fed rmn mutants are more sensitive to death by starvation than are wild-type larvae. Our unbiased, forward genetic approach has revealed a heretofore unrecognized critical step in fasting energy metabolism: hepatic ketone body transport. Because β-hydroxybutyrate is both a major fuel and a signaling molecule in fasting, the discovery of this transporter provides a new direction for modulating circulating levels of ketone bodies in metabolic diseases (Hugo, S. E., Cruz-Garcia, L., Karanth, S., Anderson, R. M., Stainier, D. Y. R., and Schlegel, A. (2012) A monocarboxylate transporter required for hepatocyte secretion of ketone bodies during fasting. Genes Dev, in press).

8

Up-regulating Reverse Cholesterol Transport with CETP Inhibition Requires Reduction of Apolipoprotein E-rich HDL Levels in Hyperlipidemic Hamsters

Francois Briand, Quentin Thieblemont, Elodie Muzotte, and Thierry Sulpice

PhysioGenix, Milwaukee, WI

Abstract:

Cholesteryl ester transfer protein (CETP) inhibition increases the levels of enlarged/apolipoprotein E-rich HDL particles (apoE-HDL). Here, we investigated whether these particles are functional in promoting reverse cholesterol transport (RCT). Hamsters were made hyperlipidemic with a 4-week high fat diet, which increased non-HDL-cholesterol levels, CETP activity, liver lipids levels, and induced a 35% reduction in LDL receptor protein expression (all $p < 0.05$ vs. chow fed hamsters). In vivo RCT was measured after an intravenous injection of [3H]cholesteryl oleate-labeled oxidized LDL (3H-oxLDL), which is rapidly cleared from plasma by liver resident macrophages for further 3H-tracer egress in plasma, HDL, liver, and feces. Hyperlipidemic hamsters were treated with vehicle or 30 mg/kg torcetrapib (TOR) over 2 weeks. Compared with vehicle, TOR increased apoE-HDL levels and significantly increased 3H-tracer appearance in HDL by 30% over 72 h after 3H-oxLDL injection. However, TOR did not change 3H-tracer recovery in liver and feces, suggesting that uptake and excretion of cholesterol deriving from apoE-HDL are not stimulated. Because apoE-HDL is a potent ligand for the LDL receptor, we next evaluated the effects of TOR in combination with berberine (a compound known to up-regulate LDL receptor expression), which stimulates both LDL-cholesteryl ester catabolism and LDL-derived cholesterol fecal excretion in the same hyperlipidemic hamster model. Compared with TOR alone, treatment with TOR + 150 mg/kg berberine (TOR+BER) resulted in lower apoE-HDL levels. After 3H-oxLDL injection, TOR+BER significantly increased 3H-tracer appearance in fecal cholesterol by 109%. This effect was confirmed by a significant 97% increase of cholesterol mass excreted in feces with TOR+BER. Overall, our data suggest that reduction of apoE-rich HDL levels is required to up-regulate RCT under CETP inhibition. These findings should be investigated in humans to evaluate the benefits of CETP inhibitors.

9

MicroRNA-144 Regulates Hepatic ABCA1 and Plasma HDL Following Activation of the Nuclear Receptor Farnesoid X Receptor (FXR)

Thomas A. Vallim1, Elizabeth J. Tarling1, Tammy J. Kim1, Mete Civelek1, Christy Esau2, and Peter A. Edwards1

1University of California, Los Angeles, CA; 2Regulus Therapeutics, San Diego, CA

Abstract:

ABCA1 is regulated by transcriptional and post-transcriptional mechanisms and is a major determinant of plasma HDL-cholesterol. We now show that treatment of mice with a specific FXR agonist results in increased hepatic levels of miR-144. We identify two complementary sequences to miR-144 in the 3'-untranslated region of Abca1 mRNA and show that they are necessary for miR-144-dependent repression. Consistent with these results, we report that overexpression of miR-144 in vitro decreased both ABCA1 protein and cholesterol efflux to apoA-I. Studies in mice show that whereas hepatic overexpression of miR-144 reduces ABCA1 protein and plasma HDL-cholesterol, antisense oligonucleotide silencing of miR-144 results in increases in both ABCA1 protein and HDL-cholesterol. In conclusion, the current studies identify a signaling pathway linking FXR to HDL-cholesterol levels via the up-regulation of miR-144 and subsequent repression of ABCA1. These results suggest that decreasing hepatic miR-144 may represent an alternative approach to raise HDL.

10

Macrophage Proteoglycans: Decrease in Sulfation Results in Accentuated Atherosclerosis

Philip Gordts1, Erin Foley1, Joseph Witztum2, and Jeffrey Esko1

Departments of 1Cellular and Molecular Medicine and 2Medicine, University of California, San Diego, La Jolla, CA

Abstract:

Atherogenesis initiates by retention of atherogenic lipoproteins within the vessel wall. Macrophage uptake of these atherogenic lipoproteins subsequently triggers the formation of foam cells and plaque deposition. To examine the role of macrophage heparan sulfate proteoglycans (HSPGs) in atherogenesis and foam cell formation, we inactivated the biosynthetic gene GlcNAc N-deacetylase/N-sulfotransferase 1 (Ndst1) selectively in macrophages by crossing Ndst1f/f mice with LysMCre+ mice. When bred onto an Ldlr–/– background and placed on an atherogenic diet, Ndst1f/fLysMCre+Ldlr–/– mice demonstrated increased atherosclerosis compared with Ldlr–/– mice. Preliminary plaque analysis also revealed significantly increased macrophage content in lesions from Ndst1f/fLysMCre+Ldlr–/– mice. Diminished sulfation of HSPGs in bone marrow-derived macrophages (BMDMs) from Ndst1f/fLysMCre+ mice also resulted in significantly increased aggregated LDL-induced foam cell formation compared with BMDMs from wild-type mice. Binding and uptake of aggregated LDL were not affected, but reduction of sulfation of HSPGs reduced HDL-mediated cholesterol efflux, suggesting that heparan sulfate participates in reverse cholesterol transport. These findings indicate that one or more HSPGs participate in macrophage foam cell formation possibly through regulation of cholesterol efflux pathways, with adverse effects on cardiovascular disease when changes in heparan sulfate composition occur.

11

Role of AMP-activated Protein Kinase (AMPK)-mediated Cryptochrome 1 (CRY1) Phosphorylation in Organismal Metabolism

Sabine D. Jordan and Katja A. Lamia

The Scripps Research Institute, La Jolla, CA

Abstract:

Circadian clocks are widely distributed in mammalian tissues and coordinate behavioral and physiological processes with day-night cycles. The transcriptional regulators BMAL1 and CLOCK activate expression of many genes including their own inhibitors period (Per1-3) and cryptochrome (CRY1 and 2), resulting in oscillating expression of target genes. The emerging evidence that dysregulation of circadian rhythms can contribute to obesity and diabetes suggests that circadian regulation is intimately linked to metabolic homeostasis. The recent demonstration that AMPK, a central mediator of metabolic signaling, phosphorylates and thereby destabilizes CRY1 provides a molecular mechanism by which metabolic signals can reset the timing of circadian clocks. Moreover, this finding suggests that in addition to its role in clock function, CRY1 may be crucial in mammalian energy sensing and metabolic regulation. We are generating mice in which the phosphoacceptor serine 71 in CRY1 is mutated to alanine, a nonphosphorylatable amino acid. CRY1 protein levels in these mice are expected to be constitutively high in both the central nervous system and in peripheral organs. Moreover, activation of AMPK is predicted to no longer induce CRY1 protein degradation. Given the recent finding that CRY1 also modulates the transcriptional activity of the glucocorticoid receptor, a nuclear hormone receptor with key roles in mammalian metabolism, we expect that these animals will exhibit altered metabolic function attributable to the loss of a specific substrate of AMPK. The in-depth analysis of these mice will likely contribute to a better understanding of cryptochromes as metabolic sensors and provide overall insight into their role in the cross-talk between circadian regulation and metabolic signaling. Moreover, this mouse model will provide a useful tool to analyze whether AMPK-mediated regulation of CRY1 is implicated in further circadian clock and/or AMPK functions that are not yet fully understood.

12

ABCG1 Is an Intracellular Sterol Transporter

Elizabeth J. Tarling and Peter A. Edwards

Departments of Biological Chemistry and Medicine, University of California, Los Angeles, CA

Abstract:

Four members of the mammalian ATP-binding cassette (ABC) transporter G subfamily are thought to be involved in the transmembrane (TM) transport of sterols. The mechanism of action of ABCG1 is controversial, and it has been proposed to act at the plasma membrane to facilitate the efflux of cellular sterols to exogenous high density lipoprotein (HDL). Here, we show that ABCG1 function is dependent on localization to intracellular endosomes. Importantly, localization to the endosomal pathway distinguishes ABCG1 and/or ABCG4 from all other mammalian members of this superfamily, including other sterol transporters. We have identified critical residues within the TM domains of ABCG1 that are essential for sterol transport. Our conclusions are based on studies in which (i) biotinylation of mouse peritoneal macrophages showed that endogenous ABCG1 is intracellular and undetectable at the cell surface, (ii) a chimeric protein containing the TM of ABCG1 and the cytoplasmic domains of the nonsterol transporter ABCG2 is both targeted to endosomes and functional, and (iii) ABCG1 co-localizes with multiple proteins that mark late endosomes and recycling endosomes. Mutagenesis studies identify critical residues in the TM domains that are important for ABCG1 to alter sterol efflux, induce sterol regulatory element-binding protein-2 (SREBP-2) processing, and selectively attenuate the oxysterol-mediated repression of SREBP-2 processing. Our data demonstrate that ABCG1 is an intracellular sterol transporter that localizes to endocytic vesicles to facilitate the redistribution of specific intracellular sterols away from the endoplasmic reticulum.

13

Anti-oxidized LDL Antibodies: Novel Treatment for Nonalcoholic Steatohepatitis

Tim Hendrikx1, Veerle Bieghs1, Patrick J. van Gorp1, Sofie Walenbergh1, Marion J. Gijbels1, 2, Fons Verheyen3, Wim A. Buurman4, David E. Briles5, Marten H. Hofker6, Christoph J. Binder7, 8, and Ronit Shiri-Sverdlov1

Departments of 1Molecular Genetics, 2Pathology, 3Electron Microscopy Unit, Department of Molecular Cell Biology, and 4Department of Surgery, Maastricht University, Maastricht, The Netherlands; 5Departments of Microbiology and Pediatrics, University of Alabama at Birmingham, Birmingham, AL; 6Department of Pathology and Laboratory Medicine, University Medical Center Groningen, Groningen, The Netherlands; 7Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria; 8Center for Molecular Medicine, Austrian Academy of Sciences, Vienna, Austria

Abstract:

Nonalcoholic steatohepatitis (NASH) is known as the hepatic event of the metabolic syndrome and is characterized by hepatic lipid accumulation combined with inflammation, which can ultimately progress into cirrhosis. Recently, we demonstrated that deletion of scavenger receptors (SR) CD36 and SR-A in hematopoietic cells reduced hepatic inflammation. In addition to uptake of modified lipoproteins, CD36 and SR-A are also involved in other functions that can activate the inflammatory response. Therefore, the actual trigger for SR activation during NASH is unclear. Here, we hypothesized that hepatic inflammation is triggered by recognition of oxidized LDL (oxLDL) by Kupffer cells (KCs). To inhibit the recognition of oxLDL by KCs, female Ldlr–/– mice were immunized with heat-inactivated pneumococci, which were shown to induce the production of anti-oxLDL IgM antibodies, due to molecular mimicry with oxLDL. During the last 3 weeks the mice received a high fat cholesterol (HFC) diet to induce NASH. To investigate whether these autoantibodies against oxLDL also affect hepatic inflammation in humans, plasma from patients with fatty liver disease was examined. Immunization with pneumococci increased anti-oxLDL IgM levels and led to a reduction in hepatic inflammation, as shown by reduced macrophage, neutrophil and T cell infiltration, and reduced gene expression of TNF, Il-6, Il-1β, MCP1, and fibrosis-related genes. In immunized mice, KCs were smaller and showed less formation of cholesterol crystals compared with nonimmunized mice. Furthermore, NASH patients showed lower levels of these protective IgM antibodies to oxLDL compared with subjects with a healthy liver or steatosis alone. We conclude that antibodies to oxLDL play an important role in NASH, and pneumococcal immunization could represent a strategy toward therapy for NASH.

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Coding Synonymous Single Nucleotide Polymorphisms (SNPs) in the LDL Receptor Gene Modulates LDL Uptake in Hepatocytes

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Abstract:

Mutations in the LDL receptor (LDLR) gene can cause familial hypercholesterolemia and increased risk of cardiovascular disease. Three coding synonymous single nucleotide polymorphisms (SNPs), rs2228671 (C->T), rs5930 (G->A), and rs688 (C->T), have been shown to be strongly associated with LDL cholesterol levels. rs2226871 is located in the ligand binding domain of LDLR whereas both rs5930 and rs688 are located in the □-propeller region, involved in LDLR intracellular trafficking through the late endosome/lysosome. These SNPs are not in linkage disequilibrium (r2<0.5). Based on their predicted effects on mRNA secondary structures, these three SNPs may increase (rs2228671) or decrease (rs5930/rs688) LDLR transcript translational efficiency, resulting in altered form and/or function of the LDLR protein. Hence, we hypothesize that these three SNPs may modulate LDL uptake by increasing LDL binding (rs2228671) or increasing the accumulation of LDLR in lysosome and/or endosome (rs5930 and rs688). pCMV-LDLR-FLAG plasmids containing either wild-type or mutant LDLR with SNPs rs2228671, rs5930, and rs688 were transfected into HepG2 (n = 8) or Huh7 cells (n = 8) and incubated with DiI-LDL. Both rs2228671 (C 171.7±6.3; T 204.5±6.3; p < 0.0001) and rs688 (C 193.1±6.6; T 183.1±6.9; p = 0.049) were found to have statistically significant associations with DiI-LDL uptake in HepG2 cells, whereas the association with rs5930 did not achieve statistical significance (G 193.0±6.5; A 183.2±6.9; p = 0.075). Similar trends were found for Huh7 cells. No SNP-SNP interactions were observed between these SNPs, suggesting that rs2228671 and rs688 function independently. We have demonstrated that both rs2228671 and rs688 directly alter the rate of receptor-mediated LDL uptake, proving that these SNPs produce functionally relevant changes in LDLR activity. Thus, rs2228671 and rs688 are suitable candidates for future mechanistic studies.

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Lipolysis Fuels Nuclear Receptor PPARs with Ligands: Role for Fatty Acids in Promoting Oxidation in Brown Adipocytes

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Abstract:

Adult humans have functional brown adipose tissue (BAT), a thermogenic organ, whose function is to maintain body temperature. BAT is activated by β-adrenergic receptors (β-ARs) that promote the mobilization and oxidation of fatty acids and the induction of genes involved in oxidative metabolism. Whereas β-AR activation increases gene expression by elevating cAMP, the role of lipolytic products is not known. This study examined the role that adipose triglyeride lipase (ATGL) and hormone-sensitive lipase (HSL) play in the induction of gene expression. In brown adipocytes, β-AR activation or stimulation with 8-bromo-cAMP increased the expression of PPARγ coactivator (PGC)1α, pyruvate dehydrogenase kinase (PDK)4, peroxisome proliferator-activated receptor (PPAR)α, uncoupling protein (UCP)1, and neuron-derived orphaned receptor (NOR)1, whereas inhibition of HSL reduced the induction of PGC1α, PDK4, PPARα, and UCP1, but not NOR1. In BAT of mice, β3-AR activation increased the expression of genes, whereas gene expression was reduced by pharmacological or genetic inhibition of HSL. Stable knockdown of ATGL also reduced the induction of genes by β-AR activation. Conversely, treatments that increase fatty acids elevated gene expression. These data suggest that lipolysis augments gene transcription, possibly by providing ligands for nuclear receptors. Nuclear receptor antagonists and siRNA knockdown demonstrate that PPARα and δ modulated the induction of genes by β-AR activation. Using a live fluorescent reporter assay of PPAR activation, we demonstrate that ligands for PPARα and δ, but not γ, are generated on the lipid droplet surface during lipolysis. Furthermore, luciferase reporter assays demonstrate that lipolysis can transcriptionally activate PPARα and δ. Knockdown of ATGL reduced cAMP-mediated induction of genes involved in fatty acid oxidation and oxidative phosphorylation. Consequently, ATGL knockdown reduced mitochondrial biogenesis and the maximal activation of fatty acid oxidation in response to cAMP stimulation. Overall, results indicate that lipolysis can activate PPARα and δ in brown adipocytes, thereby further promoting an oxidative phenotype.

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Increased Secretion of Apolipoprotein B-100 from Calcium-independent Phospholipase A2 (iPLA2β)-deficient Mice That Are Resistant to Hepatosteatosis under Lipid-rich Conditions

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Abstract:

Increasing experimental evidences have suggested that hepatic phospholipid metabolism is intimated linked to triglyceride (TG) metabolism as well as assembly and secretion of very low density lipoproteins (VLDL). Cell culture studies with the use of calcium-independent phospholipase A2 (iPLA2β) inhibitor bromoenol lactone or antisense oligonucleotides suggested iPLA2β is involved in TG-rich VLDL assembly and secretion. To determine the role of iPLA2β in vivo, we generated a C57BL/6J mouse model with targeted inactivation of iPLA2β. The iPLA2β–/– mice (fed chow diet) showed no change in fasted or postprandial plasma TG at young (12-15 weeks) or old (40-44 weeks) age compared with wild-type littermates. Feeding a high fat diet (HFD) for 2-4 weeks resulted in increased (by 2- to 3-fold) plasma apolipoprotein (apo)B-100 in iPLA2β–/– mice, and the increased apoB-100 was mainly associated with VLDL when lipolysis was blocked by injection with poloxamer 407 (P407). In vivo metabolic labeling experiments (by injecting [35S]methionine together with P407) showed increased secretion of apoB-100 as did VLDL in HFD-fed iPLA2β–/– mice. Secretion of 35S-labeled apoB-100 as VLDL was also increased (by 2-fold) from cultured primary hepatocytes of iPLA2β–/– mice. Pulse-chase experiments revealed that secretion of [3H]palmitic acid-labeled TG from iPLA2β–/– cells was increased (by 2-fold) in the presence of exogenous oleic acid or palmitic acid during chase. Moreover, the iPLA2β–/– livers were resistant to HFD-induced steatosis, probably through enhanced VLDL secretion. These data reveal a novel function of iPLA2β in hepatic VLDL assembly and secretion and suggest that iPLA2β may be considered as a therapeutic target for the prevention and treatment of high fat-induced hepatic steatosis.

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ACSL1 Multitissue Knock-out Mice Are Resistant to Diet- and Age-induced Obesity and Have Altered Tissue Insulin Sensitivity

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Abstract:

Long chain acyl-CoA synthetase 1 (ACSL1) is the major activator of long chain fatty acids in heart, adipose tissue, and skeletal muscle. To understand the functional role of ACSL1, we studied mice with a temporally induced knock out of ACSL1 in multiple tissues (Acsl1T–/–), including heart, skeletal muscle, and kidney. Compared with littermate controls (tamoxifen-injected ACSL1flox/flox), lack of ACSL1 caused 80-90% lower oxidation of palmitate in heart and adipose. Compared with controls, hearts that lacked ACSL1 took up 75% less [1-14C]bromopalmitate and 10-fold more [2-14C]deoxyglucose. Compared with controls, chow-fed Acsl1T–/– mice had higher rates of glycogen degradation in liver and heart. When fed a high fat diet (HFD; 45% of kcal from lard and soybean oil), Acsl1T–/– male mice failed to become obese. HFD-fed Acsl1T–/– and control mice had similar food intake, respiratory quotients, and heat production, but Acsl1T–/– mice were significantly more active at night. HFD-fed control mice had abnormal glucose and insulin tolerance tests, whereas HFD-fed Acsl1T–/– mice retained normal whole body insulin sensitivity. With the HFD, skeletal muscle from control mice showed lower insulin-stimulated Akt phosphorylation, indicating impaired insulin signaling. In contrast, Acsl1T–/– skeletal muscle retained normal insulin-stimulated Akt phosphorylation. In hearts, however, lower insulin-stimulated Akt phosphorylation was observed in HFD-fed Acsl1T–/– mice than in controls, indicating a defect in insulin signaling. Compared with aged controls, 14-month-old chow-fed Acsl1T–/– female mice had a lower fat mass and higher Akt phosphorylation in skeletal muscle. Thus, Acsl1T–/– mice were protected from HFD- and age-induced obesity and had increased and decreased insulin sensitivity in skeletal muscle and heart, respectively.

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Macrophage-specific Transgenic Expression of Cholesteryl Ester Hydrolase-induced Changes in Macrophage Phenotype: Increased M2 Polarization, Decreased Apoptosis, and Increased Efferocytosis

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Abstract:

We have demonstrated earlier that macrophage-specific transgenic over expression of human macrophage CE hydrolase (CEH) in LDLR–/– mice resulted in attenuation of atherosclerosis and lesion necrosis as well as reduced systemic and adipose tissue inflammation leading to improved insulin sensitivity. The objective of the present study was to systematically characterize the phenotypic differences in macrophages isolated from LDLR–/– and LDLR–/–CEHTg mice. Peritoneal macrophages (MPMs) from either chow- or Western diet-fed mice were used for these studies, and staining for specific markers was analyzed by FACS. MPMs from LDLR–/–CEHTg mice showed increased polarization toward an anti-inflammatory M2 phenotype as determined by Ly6C staining; a significant increase in Ly6Clo population was observed. Significantly less TUNEL-positive macrophages are associated with lesions in LDLR–/–CEHTg mice, and apoptosis/necrosis of MPMs from chow- as well as Western diet-fed mice was monitored. Compared with MPMs from LDLR–/– mice, a significant decrease in F4/80+/annexin V+/7AAD+ population was noted with LDLR–/–CEHTg mice (28% decrease in chow-fed, $p = 0.005$, and 54% decrease in Western diet-fed, $p = 0.017$), demonstrating decreased apoptosis/necrosis of LDLR–/–CEHTg MPMs. Consistently, there was a significant increase in F4/80+/annexin V–/7AAD– live cells. In vivo phagocytosis of apoptotic cells (efferocytosis) was examined by monitoring the uptake of CFDA-SE-labeled apoptotic macrophages by phagocytic macrophages in the peritoneal cavity. At comparable viability, increased uptake of apoptotic cells was observed in LDLR–/–CEHTg mice (F4/80+/resorufin+/CFDA-SE+). Collectively, these data suggest that CEH-mediated intracellular CE mobilization significantly and beneficially alters macrophage phenotype. Targeted decrease in macrophage CE content therefore represents a common mechanism to attenuate atherosclerosis, lesion necrosis, and inflammation-associated diseases such as diabetes.

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Molecular Basis of Circadian Desynchrony in Cardiometabolic Disease

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Abstract:

The circadian system is a key integrator of behavior and metabolism that synchronizes physiological process to anticipate and respond to recurrent daily changes in the environment. Studies from our laboratory have shown that, in addition to disruption in circadian activity rhythm and sleep-related pathologies, perturbation of normal circadian gene function leads to diet-induced obesity and cardiometabolic syndrome. Conversely, high fat diet (HFD) disrupts sleep, feeding, and locomotor activity rhythms. These observations raise interest in uncovering signaling mechanisms intersecting nutrient flux and dietary lipid composition to circadian homeostasis, at both the behavioral and gene regulatory levels. Here, we show that mice fed a diet high in saturated fat display increased activity during the normal rest (light) period in contrast to mice provided control diet (i.e. regular chow). In addition, saturated and unsaturated fat diets show opposite effects on circadian activity rhythm: HFD containing mainly saturated fatty acid (SFD) lengthened circadian period whereas an isocaloric diet containing unsaturated fatty acids (UFD) shortened the period. The effects of each diet were examined at the level of isolated live cultures of suprachiasmatic nuclei (SCN) in genetic reporter mouse, mPer2Luc, to compare the effects of saturated versus unsaturated fat master pacemaker neurons. Remarkably, the overt behavioral effects of HFD on locomotor activity were recapitulated in live-cell cultures of SCN from mPer2Luc mice. These observations delineate a relationship between dietary fatty acid composition per se on behavioral and molecular circadian rhythms in mice. Genetic and nutritional manipulations provide a new entry point to probe the reciprocal relationship between obesogenic diet and circadian disruption.

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Compensatory Regulation of Toll-like Receptors 2 and 4 in Adipocytes and Mice

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Abstract:

Obesity is associated with insulin resistance and chronic low grade inflammation. The closely related toll-like receptors 2 (TLR2) and 4 (TLR4) are indicated to be key candidates for participation in the cross-talk between inflammatory and metabolic signals. Studies in mice and in cultured cells show conflicting results regarding the role of TLR4 or TLR2 alone in obesity-induced inflammation. To test whether TLR2 and TLR4 are regulated in a dependent manner, we studied TLR2/4-silenced adipocytes and TLR4-deficient mice fed a diabetogenic diet (DD). TLR4 and LDL receptor double knock-out (Tlr4–/–Ldlr–/–) mice and Ldlr–/– mice were fed either chow or DD for 24 weeks. On chow diet, TLR4 deficiency did not alter the mRNA level of TLR2 expression; however, TLR2 expression was significantly increased in Tlr4–/–Ldlr–/– mice fed DD compared with obese Ldlr–/– mice in both intra-abdominal adipose tissue and liver. TLR4-siRNA-transfected 3T3-L1 adipocytes were used to measure TLR2 expression in response to palmitate exposure in both 5 and 25 mmol/liter glucose, and vice versa. Similar to what we found in the in vivo experiment, the mRNA level of TLR2 was increased significantly only in palmitate-treated TLR4-silenced cells. However, TLR4 expression was not up-regulated in differentiated adipocytes with a TLR2-specific siRNA. Moreover, enhanced SAA and MCP-1 expression in 3T3-L1 adipocytes in response to palmitate was TLR4-dependent, but not TLR2-dependent. In conclusion, TLR4 deletion leads to a compensatory increase of TLR2 expression in vivo and in vitro, which could in part contribute to the mixed findings regarding the role of TLR4 in current literature. The effect of TLR2 on diet-induced inflammation might be to a lesser extent than TLR4. Our findings suggest that both TLR4 and TLR2 are required for increased monocyte chemotaxis, adipose tissue inflammation, and insulin resistance in obesity.

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Electron Microscopy Reveals GPIHBP1- and Lipoprotein Lipase-dependent Margination of Chylomicrons to the Surface of Endothelial Cells

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Abstract:

Dietary lipids are packaged into chylomicrons and delivered to peripheral tissues, principally adipose tissue and striated muscle. There, along the surface of capillaries, the triglycerides within the core of chylomicron particles are hydrolyzed by lipoprotein lipase (LPL). LPL is synthesized by adipocytes and myocytes and secreted into the interstitial spaces, but it is bound by GPIHBP1, a GPI-anchored protein of capillary endothelial cells and transported to its site of action along the capillary lumen. What has been unclear is why chylomicrons marginate along capillaries (so that lipolysis can take place), and how the products of lipolysis move across endothelial cells. To gain insights into these issues, we used a combination of transmission electron microscopy and dual-axis electron tomography to examine the ultrastructure of LPL-mediated lipolysis in cultured endothelial cells and in the tissues of mice. We documented close interactions between chylomicrons and GPIHBP1-expressing endothelial cells, both in cultured cells and tissues, when LPL was present. In the absence of GPIHBP1, or in the absence of LPL, chylomicrons did not bind to endothelial cells. GPIHBP1, LPL, and chylomicrons were generally found at the necks of invaginations on the surface of cells. In the presence of LPL, we were able to visualize chylomicron lipids "emptying" into the invaginations (which morphologically resemble caveolae). We conclude that GPIHBP1 and LPL, concentrated within invaginations on the surface of endothelial cells, play vital roles in binding chylomicrons. We are currently working on determining whether these invaginations contain caveolin-1 and whether the absence of caveolin-1 has a significant impact on the GPIHBP1- and LPL-containing invaginations on the surface of endothelial cells.

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Perilipin 5 Creates an Oxidative Compartment in Striated Muscles

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Abstract:

Perilipin 5 (P5) is a lipid droplet (LD) coat protein that is highly expressed in oxidative tissue including skeletal muscle and heart. In cultured cells, P5 overexpression increases cellular triglyceride (TG). P5 binds adipose triglyceride lipase (ATGL) and its co-activator CGI-58. These observations led us to hypothesize that P5 forms a scaffold that binds appropriate partners and regulates flux in and out of LDs in a physiologically appropriate manner. To examine the physiological role of P5 we developed a mouse line (MCK-P5) that overexpresses P5 in skeletal muscle. Our preliminary results reveal that MCK-P5 are more glucose-tolerant than their nontransgenic (NTG) littermates. MCK-P5 mice accumulate more TG in uniform 1- to 2-mm LDs, but not the metabolically disruptive diglyceride (DG) compared to NTGs. Recently, two groups reported that P5 transient overexpression recruits mitochondria to the LD surface. Consistent with these reports, imaging MCK-P5 muscle reveals linear arrays of P5-coated lipid droplets enveloped by mitochondria. This organellar arrangement is also seen in heart muscle which has high endogenous levels of P5 and is not evident in P5 poor NTG skeletal muscle. We hypothesize that these mitochondria-enveloped LDs form oxidative organellar systems within the muscle and that the muscle preferred fuel is fatty acids from these LDs. In support of this hypothesis, we observed that enzymes that control flux through glycolysis are down-regulated in MCK-P5 muscle. We are comparing the respiratory exchange ratio of MCK-P5 and NTG mice to determine how much fatty acid is being used as fuel. Because endurance training increases intramyocellular mitochondria-enveloped LDs, we are comparing the exercise capacity of these mice. Finally, we are comparing MCK-P5 and NTG response to over nutrition by high fat feeding and tracking body weight, insulin sensitivity and glucose tolerance.

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Blockade of IL-6 Trans-signaling Prevents Adipose Tissue Inflammation and Attenuates Insulin Resistance in Obese Mice

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Abstract:

IL-6 signaling usually occurs through a trans-membrane complex consisting of an IL-6 receptor-α homodimer and gp130 receptor-β, but IL-6 may also signal by binding a soluble receptor (sIL-6R) termed "IL-6 trans-signaling." The pro-inflammatory effects of IL-6 are due to trans-signaling because mice overexpressing a soluble form of the gp130 protein (sgp130Fc) are protected during an air pouch model of local inflammation (Rabe, et al. (2008) Blood 111, 1021-1028). We determined whether IL-6 trans-signaling contributes to adipose tissue inflammation and insulin resistance in obesity. Sgp130Fc and littermate (WT) mice were fed a chow or high fat diet (HFD) for 12 weeks. The HFD increased fat mass equally when comparing sgp130Fc with WT mice. As expected, EmR1 mRNA expression in white adipose tissue (WAT), the percentage of adipocytes surrounded by macrophages (F4/80+ staining) in crown-like structures, and the percentage of macrophages in WAT staining positive for F4/80 and CD11c were all elevated in WT mice fed a HFD. Strikingly, however, despite the equivalent fat mass compared with WT on HFD, no such increases in these measures were observed in sgp130Fc mice. Next, we performed euglycemic, hyperinsulinemic clamp experiments in mice fed a HFD. The glucose infusion rate during the clamp was ~2-fold higher in sgp130Fc compared with WT mice. This difference was due to an enhanced glucose disposal rate, because the percent suppression of hepatic glucose production during the clamp did not differ between genotypes. Furthermore, glucose uptake during the clamp was elevated in several hindlimb muscles of the sgp130Fc compared with WT mice. These data demonstrate that blocking IL-6 trans-signaling can prevent inflammation and attenuate insulin resistance in obese mice. Because sgp130Fc protein has been intended for use as a drug to treat human inflammatory bowel diseases, these data suggest that sgp130Fc may be a viable therapeutic treatment for human type 2 diabetes.

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Assessing Mechanisms of GPIHBP1 and Lipoprotein Lipase Movement across Endothelial Cells

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Abstract:

Lipoprotein lipase (LPL) is secreted into the interstitial spaces by parenchymal cells (adipocytes and myocytes) but needs to reach the capillary lumen to hydrolyze the triglycerides within plasma lipoproteins. GPIHBP1, a glycosylphosphatidylinositol-anchored protein of capillary endothelial cells, is essential for transporting LPL from the interstitial spaces to the capillary lumen, but the mechanisms underlying GPIHBP1 and LPL movement across endothelial cells remain mysterious. For example, whether the movement of GPIHBP1 and LPL across cells is unidirectional or bidirectional is unknown. Also, it is unclear whether GPIHBP1 and LPL transport across cells involves transcytotic vesicles and whether this process requires the caveolar protein caveolin-1. We addressed each of these issues. In cultured endothelial cells, LPL moves bidirectionally (both basolateral-to-apical and apical-to-basolateral). Also, GPIHBP1 moves bidirectionally across capillary endothelial cells in the brown adipose tissue of mice. Electron microscopy revealed that GPIHBP1 and LPL are located in vesicles and within invaginations of the plasma membrane. Also, the movement of LPL across endothelial cells could be inhibited by dynasore and genistein, supporting a vesicular transport process. GPIHBP1 and LPL transport did not depend on caveolin-1. Movement of GPIHBP1 across cells was efficient in the absence of caveolin-1, as was the internalization of LPL by GPIHBP1-expressing endothelial cells. By electron microscopy, GPIHBP1 and LPL were located within the transcytotic vesicles of caveolin-1–deficient endothelial cells. These studies clarify the mechanisms by which GPIHBP1 and LPL move across endothelial cells.

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Lack of Ces3/TGH Reduces atherosclerosis in Ldlr–/– Mice

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Abstract:

Carboxylesterase 3 (Ces3)/triacylglycerol hydrolase (TGH) has been shown to participate in hepatic very low density lipoprotein (VLDL) assembly and adipose lipolysis. Deficiency of TGH in mice lowers hepatic VLDL secretion and plasma lipids without inducing hepatic steatosis. To examine the hypothesis that the loss of TGH has protective effect on atherosclerosis, Tgh–/– mice were crossed into Ldlr–/– background (Tgh–/– Ldlr–/– mice) and fed with the Western-type diet for 12 weeks. Tgh–/–/Ldlr–/– mice showed a significant reduction (54%, *p* less than 0.01) of the high fat, high cholesterol diet-induced atherosclerotic plaques compared with Tgh+/+/Ldlr–/– mice in the cross-sectional aortic root analysis. The attenuation of atherosclerosis in TGH deficiency is consistent with the atheroprotective plasma lipoprotein profile of Tgh–/–/Ldlr–/– mice observed by FPLC analysis, which showed decreased cholesterol and triglyceride in the VLDL and the low density lipoprotein (LDL) fractions, concomitant with elevated high density lipoprotein (HDL)-cholesterol. The liver lipid profile indicated that the TGH deficiency did not cause further liver steatosis. Tgh–/–/Ldlr–/– mice also showed significantly improved plasma lipid levels and decreased ApoB levels. Decreased hepatic expression of genes involved in lipogenesis and increased insulin sensitivity in TGH-deficient Tgh–/– mice may also contribute to the improved lipid profile and the reduced atherosclerotic lesion. In conclusion, our data suggested that inhibition of TGH ameliorates atherosclerosis development.

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Canonical and Noncanonical Inflammasomes in Obesity-associated Insulin Resistance

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Abstract:

It is recognized that the pro-inflammatory state driven by aberrant immune cell activation is one of the mechanisms that contributes to the development of insulin resistance and type 2 diabetes. IL-1β is a cytokine that plays an important role in initiating and sustaining inflammation induced organ dysfunction in type 2 diabetes. Canonical inflammasome signaling occurs via the NLRP3 inflammasome, and we previously demonstrated that NLRP3–/– mice have improved insulin and glucose tolerance, insulin signaling, and reduced caspase-1 activation during high fat feeding. Caspase-11 has recently been identified as a noncanonical inflammasome pathway leading to caspase-1 activation. Our hypothesis is that caspase-11 contributes to inflammasome activation and IL-1 β production during obesity and contributes to obesity-associated co-morbidities. Preliminary data indicate that caspase-11–/– subjects have no differences in body weight, body composition, and glucose tolerance, and they have reduced insulin tolerance. Our preliminary data indicate that caspase-11 has a limited role in obesity-associated inflammation.

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Dynamics of Endoplasmic Reticulum in Liver in Response to Nutrients

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Abstract:

The endoplasmic reticulum (ER) is the main site for protein and lipid synthesis, trafficking, and the storage of cellular calcium and plays a significant role in adaptation to metabolic fluctuations. Therefore, the ER needs to be dynamically regulated to accommodate the functional needs of individual cells. However, understanding the compositional and functional regulation of the ER has been limited beyond the realms of the unfolded protein response (UPR) and cholesterol metabolism. Here, we have taken a systematic approach to study how the different components of the ER (lipids, proteins, and calcium) act together to accommodate physiological dynamics and nutritional fluctuations in vivo. Through the systematic use of lipomic, proteomic, and transcriptomic platforms, we identified rapid and integrated responses of the ER during fasting and refeeding. In particular, we identified profound differences in ER lipid composition in response to diet of different lipid compositions and corresponding reprogramming of nuclear transcriptional activity and ER client composition. In summary, our work for the first time established a three-dimensional (lipomic, proteomic, and transcriptomic) characterization of the ER, and we identified novel, integrated mechanisms of ER regulation in response to its physiological environment.

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Metformin Improves Insulin Sensitivity through AMP-activated Protein Kinase (AMPK) Regulation of Lipid Metabolism

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Abstract:

Metformin is the most commonly prescribed medication used to treat type 2 diabetes and has been shown to stimulate AMP-activated protein kinase (AMPK), a multifaceted protein kinase that influences various branches of cellular metabolism. With more than 30 substrates identified, it is difficult to determine the molecular mechanisms by which AMPK maintains metabolic homeostasis. Acetyl-CoA carboxylase 1 (ACC1) and ACC2 were among the first identified AMPK substrates, and in vitro studies have demonstrated that phosphorylation of Ser-79 on ACC1 (equivalent site on ACC2, Ser-212) inhibits enzyme activity and reduces the production of malonyl-CoA, an important determinant of fatty acid metabolism. Here, we report on the metabolic phenotype of mice with ACC1 S79A and ACC2 S212A knock-in mutations (ACC DKI). In hepatocytes, phosphorylation of both ACC1 and ACC2 by AMPK is required to inhibit enzyme activities, liver malonyl-CoA levels, and fatty acid synthesis, as well as to increase fatty acid oxidation, thus demonstrating that the individual ACC isoforms do not have distinct metabolic functions. Unlike wild-type control, metformin was unable to reduce malonyl-CoA levels and fatty acid synthesis in ACC DKI cells despite AMPK activation. In vivo, when fed a normal chow diet, ACC DKI mice do not develop obesity but are glucose-intolerant and have hepatic insulin resistance characterized by increased liver lipids and protein kinase Cε activation. When mice were placed on a high fat diet and treated with metformin, only wild-type mice had reduced liver lipids and improvements in hepatic insulin sensitivity. Therefore, we demonstrate that AMPK phosphorylation/inhibition of both ACC isoforms is essential for the control of hepatic fatty acid metabolism and in maintaining euglycemia in lean mice, whereas with obesity metformin-induced improvements in insulin sensitivity are dependent on AMPK signaling and subsequent reductions in ACC activity and liver-lipid content.

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Ancient Drug Salicylate Directly Activates AMP-activated Protein Kinase

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Abstract:

The medicinal effects of willow bark have been known since the time of Hippocrates. The active component is salicylate, a hormone produced by plants in response to pathogen infection. For medicinal use it was largely replaced by aspirin (acetylsalicylate), which is rapidly broken down to salicylate in vivo. Salicylate can also be administered as salsalate, which shows promise for treatment of insulin resistance and type 2 diabetes. Salsalate and high dose aspirin increase fatty acid oxidation and reduce circulating lipids in obese rats and humans with type 2 diabetes. Importantly, changes in lipid metabolism occur before improvements in insulin sensitivity; however, the mechanisms mediating these effects are unknown. We show that at concentrations reached in plasma following administration of salsalate, or aspirin at high doses, salicylate activates adenosine monophosphate-activated protein kinase (AMPK), a central regulator of cell growth and metabolism. Unlike most activators of AMPK, such as metformin, which increase AMPK activity indirectly by inhibiting mitochondrial respiration and altering the adenylate charge of the cell, salicylate directly activates AMPK via a mechanism dependent on Ser-108 within the β1 subunit. This mechanism of action appears to be identical to the synthetic activator, A-769662, causing allosteric activation and inhibition of dephosphorylation of the activating phosphorylation site, Thr-172. Importantly, in AMPK β1 knock-out mice, effects of salicylate to increase fat utilization and lower plasma fatty acids are eliminated. Our results suggest that AMPK activation could explain some of the beneficial effects of salicylate-based drugs in humans.

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Adipose-Specific Deletion of ARV1 Results in a Lipodystrophic Phenotype Accompanied by Improved Glucose Tolerance

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Abstract:

ACAT-related enzyme 2 required for viability 1 (ARV1) was identified as a gene required for viability in yeast in the absence of cholesterol esterification. ARV1 encodes a putative lipid transporter believed to be important in trafficking of lipids from the endoplasmic reticulum (ER) to the Golgi. ARV1-deficient yeast exhibit profound alterations in cholesterol, phospholipid, and sphingolipid metabolism, accompanied by a constitutively activated unfolded protein response and impaired glycosylphosphatidylinositol (GPI) anchor synthesis. To study the role of ARV1 in mammalian lipid metabolism, we have generated mice with an adipose-specific deletion of ARV1 using Cre/loxP technology with Cre expression driven by the AP2 promoter. ARV1 adipose-specific knockout (ASKO) mice exhibited significant reductions in plasma total cholesterol (down 21%, $p < 0.05$), HDL cholesterol (down 25%, $p < 0.01$), and phospholipid (down 17.6%, $p < 0.05$) levels, while fasting triglyceride levels were unaffected. ARV1 ASKO mice also had substantial reductions in epididymal adipose (WT 0.41 ± 0.07 g versus KO 0.10 ± 0.07 g, $p = 0.0002$) and subcutaneous adipose tissue mass (WT 0.32 ± 0.03 g versus KO 0.11 ± 0.08 g; $p= 0.0002$) on a chow diet. ARV1 KO adipocytes were far smaller than WT adipocytes (~200 μm2 versus ~1,200 μm2) and often contained multiple lipid droplets per cell. In contrast to nearly every other lipodystrophic mouse model, the reduced fat mass in these animals was paradoxically accompanied by improved glucose tolerance (WT AUC 32,055 versus KO AUC 21,470 mg/dl*minutes, $p<0.05$). Insulin levels were not altered in the ARV1 ASKO mice, but these animals had an apparent increase in insulin sensitivity in insulin tolerance tests. Hyperinsulinemic euglycemic clamp studies indicate that this is due to reduced hepatic glucose production. These data identify mammalian ARV1 as an important player in adipose tissue biology, fat storage, and glucose metabolism.

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Fiber Type-specific Distribution of Lipid Droplets in Skeletal Muscles of Inbred Berlin Fat Mice (BFMI) Lines

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Abstract:

Skeletal muscle plays an essential role in glucose homeostasis, and elevated intramyocellular lipid (IMCL) accumulation directly correlates with insulin resistance in skeletal muscle in metabolic disorders. This study aims to quantify the lipid droplet (LD) content in the longissimus and quadriceps muscles of standard and high fat diet fed control (DBA/J2) and two inbred obese (BFMI860, BFMI861) mouse lines using confocal microscopy. Serial muscle cross-sections were stained for myosin heavy chain type I, IIa, and IMCL, and viewed with confocal microscopy. A new neutral lipid stain, namely LD540, was used for staining IMCL. The results revealed a fiber type-specific accumulation of LDs in both skeletal muscles, where more total lipid content was observed in IIa fibers. The lipid content expressed as area fraction was found to be higher in both BFMI lines compared with the control. Furthermore, LD content was increased in high fat diet-fed groups in longissimus muscles, whereas no significant difference was observed between the groups in quadriceps muscle. BFMI861 line which has higher blood glucose levels and a slower clearance of glucose from blood upon injection of insulin was found to has the highest lipid content in longissimus muscle.

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Diabetes Results in an Increase in Inflammatory Monocytes and Atherosclerosis in LDL Receptor-deficient Mice

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Abstract:

Diabetes is associated with an increased risk of cardiovascular disease. Monocytes are important cells in all stages of atherogenesis. We, and others, have demonstrated that monocytes from mice and humans with diabetes express elevated levels of inflammatory markers. Two main populations of monocytes have been described in humans and mice. In mice, the classical Ly6Chi population is considered to be more readily recruited to sites of inflammation than the nonclassical Ly6Clo population. To investigate whether diabetes affects these two populations and associated atherosclerosis, we collected blood from streptozotocin-diabetic (D) LDL receptor-deficient mice and nondiabetic controls (ND) and analyzed the cells with flow cytometry. Importantly, in this model diabetes results in hyperglycemia (419 ± 38 mg/dl in D versus 171 ± 14 mg/dl in ND mice, n = 5-6, $p < 0.001$) but no elevation in blood cholesterol (332.5 ± 6 mg/dl in D versus 308 ± 26 mg/dl in ND, p = not significant). Interestingly, diabetes results in an increased percentage of CD11b+Ly6hi monocytes (73.5 ± 3% in D versus 58.5± 2% in ND, $p < 0.01$) at the expense of the CD11b+Ly6Clo monocyte population (17.5 ± 2% in D versus 26.4 ± 1% in ND, $p < 0.01$) without affecting total monocyte numbers (CD115+ cells). Monocytes from diabetic mice express elevated levels of TLR4, TNFα, and ACSL1 (acyl-CoA synthetase 1) mRNA (all $p < 0.05$), the latter two endotoxin-inducible gene products. Furthermore, diabetes elevates plasma endotoxin levels to 1.1 ± 0.2 EU/ml compared with 0.58 ± 0.03 EU/ml in ND mice ($p < 0.05$, n = 10-11), similar to what has been reported in humans with type 1 diabetes. Finally, 12 weeks of diabetes is associated with a doubling of atherosclerosis in the aorta, as determined by Sudan IV staining en face (1.0 ± 0.3 mm2 in ND versus 2.1 ± 0.3 mm2 in D, n = 8-10, $p < 0.05$). Together, these results suggest that an increased inflammatory monocyte phenotype, perhaps due to increased endotoxin levels, contributes to diabetes-accelerated atherosclerosis.

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Regulation of Autophagy-induced Cholesterol Efflux by Atherogenic Lipoproteins

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Abstract:

Cholesterol clearance from arterial macrophages is critical for the prevention and treatment of atherosclerosis. Mobilization of lipid droplet (LD) cholesterol, the rate-limiting step for cholesterol efflux from macrophage foam cells, was recently described as a process dependent on both neutral and acid lipolysis. Specifically, a role for autophagy in macrophage LD lipolysis has emerged and thus represents a new target for modulating cholesterol efflux. Here, we sought to elucidate the mechanism of autophagy induction by atherogenic lipoproteins. Additionally, while autophagy inhibition reduces cholesterol efflux from foam cells, we hypothesized that positive autophagy modulators promote efflux to reverse lipid accumulation. We found that lipoprotein-induced autophagy in macrophages does not operate via a canonical autophagy pathway and instead is triggered via a nutrient-insensitive mechanism. Because pattern recognition receptors (PPRs) that internalize modified lipoproteins cooperate with Toll-like receptors (TLRs) to initiate TLR signaling, and TLR4 signaling has been linked to autophagy induction, we investigated whether autophagy activation in foam cells requires TLR4. Unexpectedly, we found that basal autophagy in TLR4–/– macrophages was elevated compared with WT and that modified lipoproteins triggered autophagy in the absence of TLR4. Elevated autophagic activity in lipid-loaded macrophages enhanced cholesterol efflux, suggesting that promoting arterial macrophage autophagy may be anti-atherogenic. Finally, we detected elevated levels of an autophagy marker in human atherosclerotic lesions, particularly in macrophages located in the rupture-prone "shoulder region" of the lesions and found evidence of altered autophagic activity in macrophages faced with a prolonged lipogenic challenge in vitro. Together, these data suggest that defective autophagy in arterial macrophages during prolonged lipogenic challenge contributes to atherosclerosis progression.

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Perilipin 2 (PLIN2) Is a Safe Target to Prevent Foam Cell Formation

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Abstract:

The lipid-laden foam cell is fundamental to the formation and progression of atherosclerosis. Therefore, certain interventions aiming to slow down atherogenesis by preventing foam cell formation have been studied. The best characterized is the inhibition of ACAT1, an endoplasmic reticulum (ER)-resident enzyme that re-esterifies cholesterol. However, ACAT1 inhibition led to toxic effects caused by free cholesterol (FC) accumulation in the ER. Previously we showed that targeting perilipin-2 (PLIN2, also known as ADFP, ADRP, or adipophilin), a major lipid droplet (LD)-associated protein in macrophages, prevents foam cell formation and protects against atherosclerosis. Here, we have assessed the tolerance of PLIN2-deficient bone marrow-derived macrophages (BMM) to several lipid-loading conditions that mimic the environment found within atherosclerotic lesions. The culture conditions included acetylated low density lipoprotein (acLDL, 50 μg/ml) in the presence or absence of an ACAT1 inhibitor (Sandoz 58-035, 10 μg/ml) and 7-ketocholesterol (7-KC, 50 μM), an oxidized FC metabolite. BMM were cultured in media with or without 10% FBS to allow or prevent cholesterol efflux, respectively. We tested apoptosis (TUNEL and cleaved caspase-3), ER stress (CHOP induction and XBP1 splicing) and inflammation (TNF-α and interlukin-6 mRNA levels) in BMM that do or do not express PLIN2. PLIN2 deficiency markedly reduced LD buildup in BMM. Culture conditions that are known to induce ER stress and apoptosis (i.e. acLDL+ACAT1 inhibitor or 7-KC) increased ER stress and apoptosis markers to comparable levels in BMM of both genotypes. Furthermore, conversely to what happens under ACAT1 inhibition, acLDL treatment did not induce apoptosis, ER stress, or synthesis of inflammatory cytokines in PLIN2-deficient BMM regardless of the presence or absence of FBS. Taken together, the data support that PLIN2 may be a safe target to prevent foam cell formation and atherosclerosis.

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Asymmetrical Flow Field-flow Fractionation for Size Characterization of Lipoprotein Subclasses: Comparison with Gel Electrophoresis

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Abstract:

According to recent data, half of coronary artery disease patients have normal lipid cholesterol levels and one third of heart attacks occur in spite of normal LDL/HDL cholesterol ratios. At the same time, numerous clinical studies support the consensus that assessment of cardiovascular risk is more successful by sub-HDL and sub-LDL size/density profile characterization coupled with measurement of lipoprotein particle number, which should be based on directly measured structural apolipoprotein concentration (apoA-I and apoB-100). The most important barrier to the widespread application of these measurements in US clinical laboratories is the lack of a standardization program that is based on an accurate reference method and the availability of well characterized reference materials. We used asymmetric flow field-flow fractionation (AF4) for lipoprotein size profile characterization. The AF4 retention time of lipoprotein particles was converted into lipoprotein particle size measurements. The AF4 size fractionation was coupled with multiangle and dynamic light-scattering measurements, providing direct verification of AF4 retention time-derived size measurements. We implemented an integrated flow-through system with continuous on-line measurement of cholesterol content as a function of lipoprotein size. Because of the highly controllable flow-through nature of the AF4 technique, it also allows automated fraction collection. AF4 is a gentle separation technique; preparative fractionation can be achieved without destroying the lipid particles in the process. The lipid particle concentration in the fractions was high enough to be able to perform chemical characterization including direct quantitative measurement of apoB-100 concentration. This AF4 method was compared with the Lipoprint (Quantimetrix) tube gel electrophoresis system. Excellent correlation between the two techniques was found for quality control materials and clinical samples.

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Amelioration of Type 2 Diabetes by Antibody-mediated Activation of Fibroblast Growth Factor Receptor 1

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Abstract:

Clinical use of recombinant fibroblast growth factor 21 (FGF21) for the treatment of type 2 diabetes and other disorders linked to obesity has been proposed; however, its therapeutic development is challenging because of its poor pharmacokinetics and the difficulties in producing long acting variants. As an alternative strategy to gain FGF21-like clinical benefits, we have generated agonistic anti-FGFR1 antibodies that mimic the metabolic effects of FGF21. Remarkably, after a single injection of anti-FGFR1 into db/db mice at a low dose, blood glucose was normalized for 2 weeks and maintained at reduced levels for more than a month. Anti-FGFR1 activates the mitogen-activated protein kinase (MAPK) pathway in adipose tissues and pancreas, but not in the liver, and neither FGF21 nor anti-FGFR1 improved glucose clearance in lipoatrophic aP2-SREBP-1c transgenic mice, suggesting that adipose tissues play a central role in the observed metabolic effects. In brown adipose tissues, anti-FGFR1 induces phosphorylation of cAMP-responsive element-binding protein (CREB) and mRNA expression of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) and the downstream genes associated with oxidative metabolism. Collectively, our work defines adipose FGFR1 as a major functional receptor for FGF21, as an upstream regulator of PGC-1α, and as a compelling target for antibody-based therapy for type 2 diabetes and other obesity-associated disorders.

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Bistable Switch Driven by Multiple Positive Feedbacks Triggers Commitment to Adipocyte Fate

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Abstract:

Regulation of the conversion of preadipocytes to adipocytes is an important part of the vertebrate weight maintenance program. It is not yet understood whether a bistable switch mechanism exists that commits preadipocytes to the adipocyte fate. Here, we use image-based, multiparameter analysis of single cells together with selective reaction monitoring (SRM) mass spectrometry to show that an all-or-none decision is made early in differentiation, well before lipid accumulation occurs. The process starts with glucocorticoid and cAMP signaling raising CCAT enhancer-binding protein (C/EBP)γ and bringing preadipocytes above a critical threshold. Bistable commitment then results from reinforced activation of peroxisome proliferator-activated receptor γ (PPARγ) and C/EBPγ, followed by a second positive feedback that links PPARγ back to C/EBPγ. Experiments and model calculations show that both feedback loops are necessary to generate a differentiated state independent of glucocorticoids and cAMP. Markedly, in differentiated cells, the amount of fat storage is controlled by insulin in a graded fashion. Thus, preadipocytes commit to the adipocyte fate by undergoing an early irreversible switch that is independent of insulin signaling and fat accumulation.

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Mice with Adipocyte-specific Deletion of JAK2 Develop Obesity in Response to Growth Hormone

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Abstract:

Growth hormone (GH) decreases adiposity ostensibly through modulating lipolysis; however, the mechanism by which GH regulates fat mass is unknown. To determine the importance of GH signaling in adipocytes, we generated mice with adipocyte-specific disruption of the GH signaling mediator, Janus kinase 2A (JAK2A). GH treatment of WT and JAK2A mice decreased epididymal/inguinal fat and increased plasma free fatty acids in WT but not JAK2A mice, indicating disrupted GH-stimulated lipolysis. Previously, we showed that mice with liver-specific disruption of JAK2 (JAK2L) develop severe fatty liver (FL) that was dependent on increased circulating GH. To determine the importance of GH-stimulated lipolysis on FL development in JAK2L mice, we crossed JAK2A with JAK2L to generate JAK2L/A mice. Like JAK2L, JAK2L/A mice have high circulating GH; however, the amount of liver lipid was significantly reduced in JAK2L/A versus JAK2L. JAK2L mice are slightly leaner than WT whereas JAK2A have increased epididymal/inguinal fat pad mass and percentage fat by dual-energy x-ray absorptiometry (DEXA). Paradoxically, JAK2L/A mice have even larger gains in adiposity than JAK2A, despite high circulating GH. In vitro, the direct effect of GH on adipocyte lipolysis is minimal; however, GH is thought to inhibit the lipogenic/antilipolytic actions of insulin via activation of JAK2. In adipose tissue explants, insulin inhibits basal lipolysis; this effect is partially blocked by GH in WT, but not in JAK2A samples. JAK2A mice also have increased insulin sensitivity in vivo versus WT, indicating that deletion of JAK2 in adipocytes enhances insulin response. Further, JAK2L/A mice have greater circulating insulin versus JAK2A, allowing for greater lipogenic/antilipolytic insulin action and fat accumulation. In summary, these data indicate that direct GH signaling in adipocytes is necessary for GH-stimulated lipolysis via the anti-insulin actions of GH. Disrupting GH signaling in adipocytes has important consequences on fat metabolism leading to paradoxical obesity in response to GH.

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MicroRNA-27b Is a Lipid-sensitive Post-transcriptional Regulatory Hub in Lipid Metabolism

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Abstract:

MicroRNAs (miRNAs) are post-transcriptional regulators of gene expression and have emerged as critical mediators of metabolism and disease. As such, specific miRNAs likely play key regulatory roles in cellular and global lipid homeostasis; however, this has yet to be systematically investigated. In this study, we performed high throughput small RNA sequencing and detected approximately 150 miRNAs in mouse liver. Using a novel unbiased in silico strategy, we identified miR-27b as the strongest candidate regulatory hub in lipid metabolism. Overexpression of miR-27b in human hepatocytes (Huh7) resulted in the significant (corrected $p < 0.05$) down-regulation (>1.5-fold) of 177 genes, including key lipid-regulating genes: PPARγ, ANGPTL3, NDST1, and GPAM. All four of these genes harbor putative miR-27b target sites, and gene reporter (luciferase) assays were used to validate the direct targeting of the GPAM 3′-untranslated region. Inhibition of endogenous miR-27b activity resulted in a significant increase in PPARγ, ANGPTL3, and GPAM mRNA levels. Furthermore, loss of endogenous miR-27b significantly increased cellular GPAM protein, secreted ANGPTL3 protein, and PPARγ transcriptional activity. Strikingly, miR-27b was found to be highly sensitive to plasma hyperlipidemia and hepatic lipid content, as evidenced by its ~3-fold up-regulation in the livers of mice on a high fat diet (in vivo) and ~400-fold increase in human hepatocytes incubated with 10% fat emulsion (in vitro). Finally, hepatic levels of miR-27b (up) and its target genes, Pparg, Angptl3, and Gpam (down), were inversely regulated in apoE–/– mice on a high fat/high cholesterol diet, which represents a mouse model of severe dyslipidemia and atherosclerosis. We conclude that miR-27b serves as a post-transcriptional regulatory hub controlling lipid metabolism and likely mediates a systemic response to hyperlipidemia by antagonizing triglyceride biogenesis (GPAM) and promoting triglyceride catabolism (ANGPTL3).

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Cluster of Lymphocyte Antigen-6 Genes in Mice Affects Body Weight and Fuel Metabolism

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Abstract:

Lymphocyte antigen-6 (Ly6) proteins contain one or more ~80–amino acid segments containing 10 cysteines, all arranged in a characteristic spacing pattern. Each cysteine is disulfide-bonded, generating a three-fingered structural motif. More than 30 Ly6 proteins exist in mammals, nine of which are encoded by genes in close proximity to Gpihbp1. GPIHBP1 is a well characterized Ly6 protein, expressed exclusively by capillary endothelial cells, that transports lipoprotein lipase (LPL) from the subendothelial spaces to the capillary lumen. An absence of GPIHBP1 causes mislocalization of LPL and severe hypertriglyceridemia. The functions of most Ly6 family members are unknown. Here, we assessed phenotypes in knock-out mice for three Ly6 genes neighboring Gpihbp1 (Slurp1, Slurp2, and Lypd2). We demonstrate that Slurp1, Slurp2, and Lypd2 knock-out mice exhibit striking phenotypes: complete protection from obesity on a high fat diet, lower glucose and insulin levels, and increased oxygen consumption. These mice also exhibit a thickened epidermis on the palms and soles (palmoplantar keratoderma), similar to the skin abnormality in patients with Mal de Meleda (a recessive skin disease caused by SLURP1 mutations). We conclude that Slurp1, Slurp2, and Lypd2 are relevant to body weight and fuel metabolism, but work is required to define the functions of these genes.

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Method to Purify ApoB-100 Particles from ApoB-48 Particles in Triglyceride-rich Lipoproteins (TRL) Isolated by Ultracentrifugation

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Abstract:

The determination of kinetics of apoB lipoprotein particles as well as their respective triglyceride (TG) content kinetic is important to understanding the mechanisms by which dietary or pharmacological interventions modify particles size, lipid profile, and cardiovascular risk. Ultracentrifugation cannot separate remnant chylomicrons from large VLDL particles because they have overlapping densities. We devised an immunoaffinity method to separate apoB-100 particles from apoB-48 particles in TG-rich lipoproteins (TRLs) obtained by ultracentrifugation. We developed an apoB-100 affinity matrix, using a goat antibody against a chimeric protein containing apoB-100 epitopes and lacking apoB-48 epitopes, purified with a human LDL (apoB-100) column. The anti-apoB-100 was bound to a protein G column. The separation of apoB-100 from lipoprotein-fractionated serum was performed by incubating TRL fractions on fresh affinity columns, overnight at 4 °C. The resin/sample mixture was centrifuged, resulting in a flow-through (FT), which was reapplied to fresh resin. This process was repeated for two consecutive passes. The columns were then washed (high salt) and eluted (low pH). All steps were followed by centrifugation. ApoB-100 was removed sequentially after two passes over fresh resin. Samples were taken at each step and analyzed by Silver Stain and by apoB-specific ELISA. The silver-stained gels showed a depletion of apoB-100 in the sequential FTs with little or no apoB-100 in FT 2. The gel showed the specific elution of apoB-100, again with little or no apoB-100 in the last pass. The apoB-48-specific ELISA showed that the elution fractions contain no apoB-48. The apparent capacity of the apoB-100 affinity resin was approximately 100-140 µg/ml, calculated from the combined elute of passes 1 and 2. These results demonstrate that we have developed and validated a method that allows us to isolate apoB-48 particles from apoB-100 particles in human TRL samples.

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Critical Role of Lymphocytes on Lipid Metabolism in Mouse Liver and Human Hepatocytes

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Abstract:

Obesity is a chronic, active inflammatory disease. The significance of activated macrophages in the pathogenesis of obesity-associated insulin resistance and the metabolic syndrome has been well described. Recent studies in diet-induced obese mice have demonstrated a critical role for lymphocytes in the development of insulin resistance and inflammation in the adipose tissue. The aim of this study was to elucidate further the role of lymphocytes in the pathogenesis of obesity with an emphasis in the development of nonalcoholic fatty liver disease, NAFLD. We compared the responses of the lymphocyte-deficient rag1–/– and wild-type mice to high fat diet-induced obesity with particular emphasis in liver pathology. After 8-10 weeks of HFD we found similar body weight changes in both genotypes and comparable serum glucose levels, but rag1–/– mice exhibited increased insulin sensitivity, as assessed by the insulin tolerance test. Importantly, rag1–/– mice showed no histological signs of liver steatosis in contrast to the significant infiltration detected in the wild-type mice. Genomic and proteomic analyses of liver and adipose tissues from both groups revealed significant differences in the expression of genes involved in lipid synthesis and oxidation, in agreement with the histological picture. In vitro studies assessing the role of primary human lymphocytes in lipid metabolism in the human cell line, HepG2, confirmed the in vivo mouse data. These findings provide evidence for a critical role of lymphocytes in hepatic lipid metabolism in human and mouse experimental models. Ongoing studies aim at demonstrating the exact metabolic pathways and the particular factors mediating the above effects of lymphocytes on lipid metabolism.

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Zbtb16 Has a Role in Brown Adipocyte Bioenergetics: Implications for Obesity

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Abstract:

A better understanding of the processes influencing energy expenditure could provide new therapeutic strategies for reducing obesity. The metabolic activity of brown adipose tissue (BAT) and skeletal muscle is an important determinant of overall energy expenditure and adiposity. In a screen for genes that are induced in both BAT and skeletal muscle during acute adaptive thermogenesis in the mouse, we identified the transcription factor Zbtb16 (also known as Plzf and Zfp145). In vitro, Zbtb16 expression was induced during differentiation of brown adipocytes as well as by a β-adrenergic agonist and dexamethasone, consistent with a role in brown adipocyte function. Zbtb16 overexpression in brown adipocytes led to the induction of many genes of the thermogenic program, including genes involved in fatty acid oxidation, glycolysis, and mitochondrial function. Furthermore, enhanced Zbtb16 expression increased mitochondrial number, ATP-linked respiration, and maximal respiratory capacity. These effects were accompanied by decreased triglyceride content and increased carbohydrate utilization in brown adipocytes. Natural variation in Zbtb16 mRNA levels in multiple tissues across a panel of more than 100 mouse strains was inversely correlated with body weight and body fat content. In addition, ZBTB16 expression was significantly lower in obese diabetic women compared with normal glucose-tolerant controls. Our results implicate Zbtb16 as a novel determinant of substrate utilization in brown adipocytes and of adiposity in vivo.

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Resolvin D1 Blocks Leukotriene B4 Formation by Regulating 5-Lipoxygenase

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Abstract:

Inflammation plays major roles in metabolic disorders and atherosclerosis. A key feature of physiologic inflammation is the resolution phase, which actively suppresses inflammation and yields tissue repair. It is becoming increasingly evident that defective inflammation resolution underlies chronic inflammatory diseases, such as obesity and atherosclerosis. An important mechanism of regulation of inflammation resolution is the balance of fatty acid-derived pro-resolving versus pro-inflammatory lipid mediators, such as lipoxin A4 (LXA4) and leukotriene B4 (LTB4), respectively. 5-Lipoxygenase (5-LOX) can produce both pro-resolving and pro-inflammatory mediators from arachidonic acid (AA) depending on the context. Another mechanism of regulation may occur through microRNAs, and a recent report showed that overexpression of the microRNA miR-219 in human macrophages decreased 5-LOX expression and LTB4 production (Recchiuti et al. (2011) FASEB J.). Here, we report that stimulation of macrophages with the pro-resolving mediator resolvin D1 (RvD1) decreases endogenous miR-219 by ~50% while increasing 5-LOX expression. Despite this increase in 5-LOX, RvD1 blocked AA-stimulated LTB4 formation. The ability of 5-LOX to synthesize LTB4 involves the translocation of 5-LOX to the nuclear membrane. We hypothesize that RvD1 modulates both 5-LOX expression and its substrate utilization profile which allows AA to be converted primarily into lipoxins to modulate resolution of inflammation.

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Endothelial Acyl-CoA Synthetase 1 Does Not Mediate Inflammatory Effects of a Diet High in Saturated Fatty Acids in Blood Vessels

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Abstract:

Diets high in saturated fatty acids induce endothelial dysfunction, measured as increased expression of adhesion molecules and inflammatory mediators. Fatty acids must be converted into their acyl-CoA derivatives before exerting many of their biological effects in cells. Acyl-CoA synthetase 1 (ACSL1) is one of the ACSL isoforms that catalyze the conversion of fatty acids, such as palmitate (16:0) and stearate (18:0), to acyl-CoAs in endothelial cells. We therefore investigated the role of ACSL1 in endothelial cells in vitro and in vivo. ACSL1 was stably overexpressed in cultured human umbilical vein endothelial cells (HUVECs). Mouse heart CD45-negative-CD31-positive endothelial cells (MHECs) were isolated by fluorescence-activated cell sorting. Exposure of MHECs to 16:0 and 18:0 resulted in a greater than 300-fold increase in the release of the soluble adhesion molecule sICAM-1 ($p < 0.01$), a 30-fold increase in sVCAM-1 ($p < 0.01$), and a 3.5-fold increase in release of the chemokine CCL2 ($p < 0.05$). Overexpression of ACSL1 enhanced CCL2 release from HUVECs exposed to 5% serum by 2-fold ($p < 0.01$). To evaluate the role of endothelial ACSL1 in vivo, a mouse model deficient in endothelial ACSL1 was generated. Male C57BL/6 mice with endothelial ACSL1 deficiency and wild-type littermate controls were fed a chow diet or a diet rich in saturated fatty acids for 20 weeks. Fat feeding resulted in a 2.5-fold increase in aortic VCAM-1 mRNA levels ($p < 0.05$) and increased accumulation of macrophages in adipose tissue, but endothelial ACSL1 deficiency had no effect. Endothelial ACSL1 deficiency also did not affect circulating plasma levels of sIVAM-1 or sICAM-1 in chow-fed or fat-fed mice. Thus, endothelial ACSL1 expression does not seem to mediate detrimental effects of saturated fat feeding in blood vessels.

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Triacylglycerol Storage Modulates Fatty Acid-Induced ER Stress in Murine Macrophages

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Abstract:

Saturated dietary fatty acids (palmitic acid; PA) are toxic to myeloid cells (MCs; macrophages and dendritic cells), inducing inflammatory (M1) activation and the unfolded protein response (UPR), while monounsaturates (oleic acid; OA) are comparatively inert. We showed that increasing expression of the triacylglycerol (TG) synthesis enzyme DGAT1 enhances PA storage within TG and mitigates M1 activation. Here we explore the role of TG storage in the UPR. As with M1 activation, PA treatment induced the UPR (expression of Bip, Chop, spliced Xbp1, and activity of an Xbp1-coupled luciferase reporter [ERAI-luc]). PA-induction of M1 activation was partially abrogated by deletion of the endotoxin receptor Toll-like receptor 4 (TLR4) whereas induction of the UPR was relatively insensitive to this, indicating that PA-induced lipotoxicity has TLR4-dependent and independent components. Interestingly, both components were induced by PA but not OA treatment. For example, PA treatment increased ERAI-luc activity (dose-dependent from 100μM-1mM), whereas OA did not. To explore where PA acts to cause lipotoxicity, we treated MCs with sulfo-n-succinimidyl oleate (SSO), a blocker of fatty acid uptake. SSO co-treatment abolished PA-induced ERAI-luc activity, indicating that PA-induction of the UPR requires intracellular PA uptake. We next focused on TG storage. PA treatment did not alter cellular TG whereas OA treatment increased it 2-fold. Interestingly, treatment with 200μM each of OA and PA increased TG to levels similar to or higher than those reached by treatment with 400 μM OA, indicating that OA, like increasing DGAT1 expression, facilitates incorporation of PA into TG. Moreover, pre- or co-treatment of MCs with OA (100 μM) fully protected against PA (600 μM)-induction of ERAI-luc activity, though OA could not reverse the UPR once initiated. We also tested the extent to which DGAT activity modulates the PA-induced UPR. Like OA co-treatment, genetically increasing DGAT1 expression protected against PA-induction of the UPR, whereas pharmacologic inhibition of DGAT activity potentiated it. Unlike OA, myriocin co-treatment could not lessen PA-induced ERAI-luc activity, suggesting a mechanism independent of ceramide biosynthesis. Our findings indicate that induction of the UPR in MCs by intracellular PA is counteracted by factors promoting its storage within TG and does not require ceramide biosynthesis, pointing to the importance of other metabolic pathways. The work has implications for metabolic diseases of lipid excess.

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