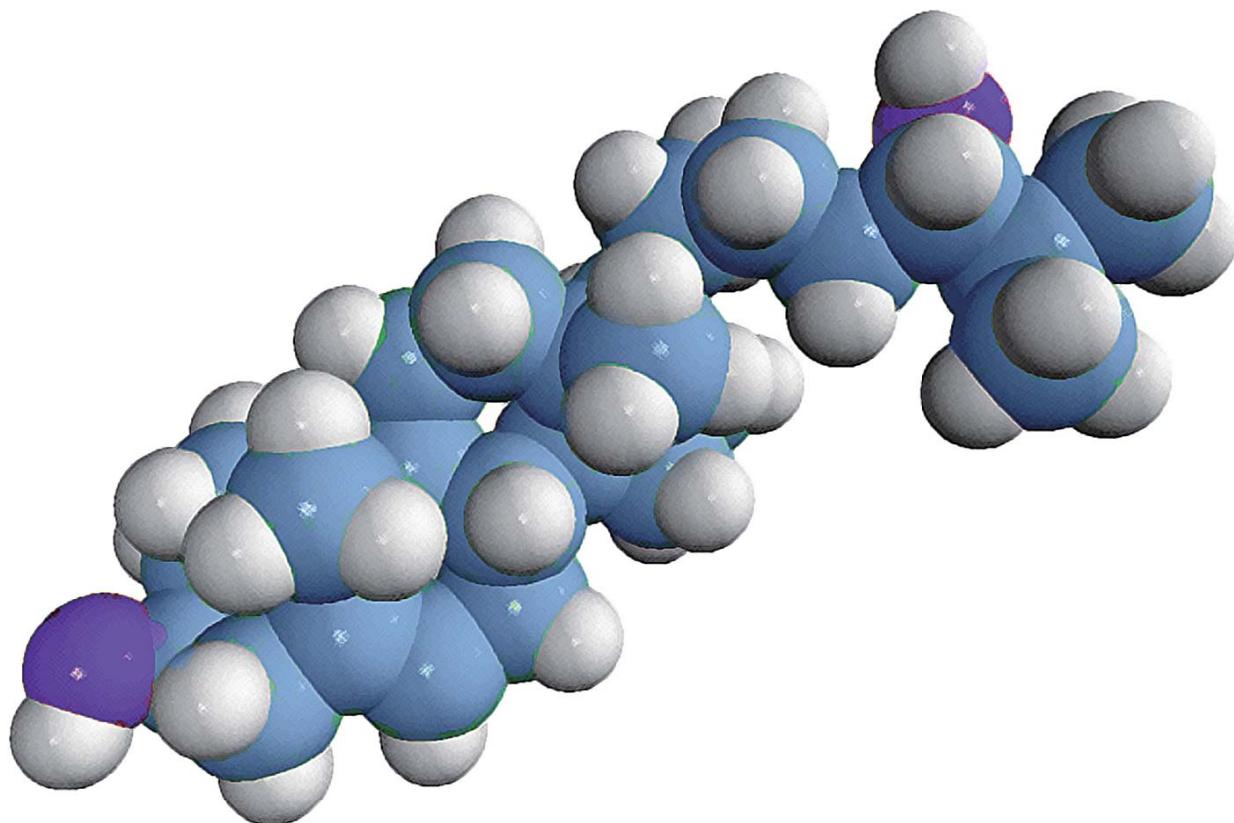


March 3-6, 2009

Borrego Springs, California

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



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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 videotaping 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.

In Memoriam: Roger A. Davis (1945-2008)

On June 17, 2008, the lipid research community lost a beloved friend and scholar, Roger A. Davis. Roger was a major contributor to our understanding of the regulation of lipoprotein production, bile acid metabolism, and atherosclerosis.

Roger gravitated to science at an early age; he loved to tinker and he felt that the truthfulness of science provided a refuge from the conflicting religious orthodoxies between the two sides of his family. During his senior year in high school in Wilmington, Delaware, he befriended Howard Simmons, a prominent chemist at DuPont. Simmons taught Roger how to smoke cigars, drink scotch and love organic chemistry. Simmons' spell determined the trajectory of Roger's education; his undergraduate and graduate degrees were in chemistry.

After earning his doctorate in organic chemistry at Washington State University in Pullman, he studied the biophysical aspects of bile acids in Fred Kern's laboratory at the University of Colorado. But, it was in Dan Steinberg's laboratory at UCSD where he first fell in love with biology and began what would become a lifelong involvement in the assembly and secretion of apoB containing lipoproteins. After leaving UCSD, Roger served on the faculties of Louisiana State University, University of Colorado, and San Diego State University.



One of Roger's most influential discoveries occurred in 1987 when he discovered that although apoB is constitutively synthesized, a substantial fraction of what is synthesized is degraded somewhere in the secretory pathway; in fact, the amount of apoB that is secreted is determined by the amount rescued from degradation (1). These findings preceded the appreciation of proteasomal degradation and the ER-associated degradation pathway, now very active research fields in their own right. In elegant and technically challenging experiments, Roger went on to show that critical segments of the apoB molecule require an interaction with microsomal triglyceride transfer protein (MTP) to be translocated across the ER membrane (2). His work in primary rodent hepatocytes emphasized that apoB secretion is very sensitive to MTP but not to free fatty acids or triglycerides (3).

As early as 1983, Roger showed that, contrary to widespread belief in the field, bile acids do not exert a direct feedback inhibitory effect on bile acid synthesis (4, 5). He also showed, predating the discovery of LXR, that cholesterol is "a positive effector of bile acid synthesis" (5). The work also pre-dated the discovery of FGF-15 and FXR. Recent discoveries clearly establish that bile acids, through FXR, induce the expression of FGF 15 in the intestine and that the feedback effect on hepatic bile acid production is mediated by a signaling pathway involving the interaction of FGF-15 with its receptor and suppression of Cyp7A in the liver, rather than a direct effect of bile acids (6-8). Roger recently wrote commentaries about these findings (9, 10).

One of Roger's interests was to develop new therapeutic approaches. He reasoned that resident macrophages (Kupffer cells) could provide a useful vehicle for delivery of protective genes in the liver, a large organ with unrestricted contact with the blood. In a proof-of-principle study, he created transgenic mice expressing the atherosclerosis-protective enzyme paraoxonase-1, and transplanted their marrow into hyperlipidemic recipient mice. To achieve efficient transplantation, he treated the recipient mice with gadolinium chloride, an agent that destroys endogenous Kupffer cells. This clever strategy resulted in a dramatic reduction of atherosclerotic lesions (11). Roger pursued several ideas that led to inventions.

Roger had an unusually broad view of the important biologic problems. This undoubtedly derived from his insatiable curiosity. Although he liked to refer to himself as a chemist working in biology, his interests encompassed diverse areas of biology, including gene regulation, nutrition, metabolism, immunology, and genetics. He was not afraid to employ techniques from each of these areas. For example, he made use of natural variation among inbred strains of mice to help dissect regulatory pathways involving bile acids (12).

In recent years, Roger focused his attention on the role of thioredoxin interacting protein (txnip) in metabolism. His studies with txnip knockout mice led to the discovery that this gene plays a key role in mitochondrial function and insulin sensitivity in muscle. In a landmark study, which was his last research publication, Roger's research team showed that mice deficient in muscle txnip have a profound defect in fatty acid and ketone body oxidation and a dramatic increase in insulin sensitivity. He showed that the latter phenotype was associated with a suppression of PTEN and argued that this was a consequence of an altered NAD⁺/NADH ratio (13). Roger was passionately excited about this new direction and shortly before his death, obtained a new NIH grant to support this project.

Roger brought his passion for science to his battle with prostate cancer. He was simultaneously fascinated and frightened by his illness. He studied it and devised several novel therapies, all of which were attempted. He lived far longer than his doctors predicted, perhaps because of his own therapeutic interventions. Roger was deeply devoted to his wife of 36 years, Kathy, his daughter, Kimmie, and his son, Harley. He enjoyed having family gatherings with friends and was especially proud of his Louisiana gumbo and jambalaya. He enjoyed sailing, golf, and was a lifelong avid motorcycle rider, with a special fondness for Harley-Davidson bikes.

Roger had an extraordinary capacity for friendship. He developed a wide network of lifelong friends from all walks of life and continually nurtured those friendships with his warmth, wit, companionship, and joie de vivre. He enjoyed traveling with friends and was a wonderful travel companion. Within his scientific milieu, he was deeply appreciated for his razor-sharp judgment, his inclination to stimulate critical discussions, and his ability to speak with scientific authority without ever being pretentious or pedantic. His love of science emanated from his belief in its integrity and authenticity. He had low tolerance for scientists who exaggerated or oversold their data. His sardonic, sometimes corny wit, his hilarious puns, and his ability to make all of us take ourselves less seriously added much-needed levity to scientific conferences, committee meetings, and JLR Editorial Board meetings. We all miss him terribly.

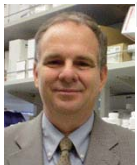


The Havel Lecture

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 Anfinson 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 ultracentrifugal 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

2009 Stephen G. Young, UCLA School of Medicine, Los Angeles, CA

“Adventures in Lipid Metabolism”



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

“Going to Extremes to Identify Genetic Variations Contributing to Cardiovascular Risk”



2007 Ronald Evans, The Salk Institute for Biological Sciences, La Jolla, CA

“PPARdelta and the Marathon Mouse: Running Around Physiology”



2006 David Russell, University of Texas Southwestern Medical Center, Dallas, TX

“The Enzymes of Cholesterol Breakdown”



2005 Johann Deisenhofer, HHMI/UTSW Medical Center, Dallas, TX

“Structure of the LDL receptor”



2004 Jeffrey M. Friedman, Rockefeller University, New York, NY

“The Function of Leptin in Nutrition, Weight and Physiology”



2003 Bruce Spiegelman, Harvard Medical School, Boston, MA

“Transcriptional Control of Energy and Glucose Metabolism”



2002 Co-Lecture Michael S. Brown, University of Texas Southwestern Medical Center, Dallas, TX

“SREBPs: Master Regulators of Lipid Metabolism”

Schedule of Events

	Tuesday, March 3	Wednesday, March 4	Thursday, March 5	Friday, March 6
7 AM		Breakfast 7-8:45	Breakfast 7-8:45	Breakfast 7-8:45
8 AM				
9 AM		Session I 8:45-10:15	Session 2 8:45-10:15	Session 4 8:30-10:10
10 AM		Coffee Break 10:15	Coffee Break 10:15	Coffee Break 10:10
11 AM		Session I, Continued 10:45-12:05	Session 2, Continued 10:45-12:30	Session 4, Continued 10:30-12
12 PM		Free Time	Free Time	
1 PM				
2 PM				
3 PM	Registration 3-6:30			
4 PM				
5 PM		DEUEL Board Meeting 5-6 Exec. Conf. Center #2		
6 PM	Welcome Reception and Dinner 6:30-10	Dinner 6:00- 7:30	Dinner 6:00-7:30	
7 PM				
8 PM		HAVEL LECTURE 7:30-8:45	Session 3 7:30-9:30	
9 PM		Wine Reception/Poster Session Dinner		
10 PM		8:45		

All meals will be held in the Rosegarden Room
 Session lectures will be held in the DeAnza Ballroom

Meeting Program

2009 Deuel Conference on Lipids, March 3-6, 2009

La Casa del Zorro, Borrego Springs, CA

Tuesday, March 3

3:00 PM to 6:30 PM - Registration

6:30 PM- Reception & Dinner

Wednesday, March 4

8:45 AM to 12:30 PM- Session 1: Transcriptional Regulation of Lipid Metabolism

8:45-9:30 - "Macrophage Subtypes and Diabetes Mellitus"

Chris Glass, *University of California, San Diego, CA*

9:30-10:15- "Transcriptional Control of Hepatic Lipid Metabolism"

Marc Montminy, *Salk Institute, La Jolla, CA*

10:15-10:35 Coffee Break

10:35 – 11:20 - "PGC-1 and SIRT1 Interactions"

Pere Puigserver, *Harvard, Boston, MA*

11:20 – 12:05- "Functional Roles of Nuclear Receptors in the Adipocyte"

Mitch Lazar, *University of Pennsylvania, Philadelphia, PA*

7:30 to 8:45 PM- **The Havel Lecture**

"Adventures In Lipid Metabolism"

Stephen Young, *University of California, Los Angeles, CA*

8:45 PM- Wine reception and Trainees' Poster Session to Follow

Thursday, March 5

8:45 AM to 12:30 PM- Session 2: Proteins and Lipids

8:45 – 9:30- "Phospholipids and Protein Folding"

William Dowhan, *University of Texas Health Science Center, Houston, TX*

9:30 – 10:15- "Sterol Binding to INSIGS and Regulation of Cholesterol Metabolism"

Arun Radhakrishnan, *Cornell Medical School, New York, NY*

10:15 – 10:25- "How ER stress triggers cell death: a novel link between CHOP and calcium-induced apoptosis."

Ira Tabas, *Columbia University Medical School, New York, NY*

10:25 – 10:45 Coffee Break

10:45 – 11:30- “The Crystal Structure of the Sterol Binding Domain of NPC1”

Rodney Infante, *UT Southwestern Medical Center, Dallas, TX*

11:30 – 12:15- “Insights into the Function and Regulation of PCSK9”

Nabil Seidah, *IRCM, Montreal, Canada*

12:15 -12:25- “Heparan Sulfate Proteoglycans Mediate Clearance of Triglyceride-Rich Lipoproteins In Vivo”

Jeff Esko, *University of California San Diego, California*

7:30-9:30 PM- Session 3: Lipid Metabolizing Enzymes

7:30 – 8:10 - **JLR 50th Anniversary Lecture**

“Metabolite Profiling to Identify New Lipid Metabolizing Enzymes”

Benjamin Cravatt, *Scripps Research Institute, La Jolla, CA*

8:10 – 8:50- “Crystal Structures of Bile Acid Biosynthetic Enzymes”

Trevor Penning, *University of Pennsylvania, Philadelphia, PA*

8:50 – 9:30- “Intestinal Bile Acid Transport Mediated by OST”

Paul Dawson, *Wake Forest, Winston-Salem, NC*

Friday, March 6

8:30 AM to 12:00 PM- Session 4: New Drugs Affecting Lipid Metabolism

8:30 – 9:15 - “CETP Inhibitors”

Molly Ranaletta, *Merck Research Laboratories, Rahway, NJ*

9:15 – 10:00 - “Development of Lipid Lowering Therapeutics”

Margrit Schwarz, *Amgen, South San Francisco, CA*

10:00 – 10:10- “Nur77 deletion impairs systemic glucose metabolism”

Lilly Chao, *UCLA School of Medicine, Los Angeles, CA*

10:10 – 10:30 Coffee Break

10:30 – 11:15- “Genetic Approaches to Defining Lipid Metabolism Genes”

Sekar Kathiresan, *Massachusetts General Hospital, Cambridge, MA*

11:15 – 12:00- “RNAi Approaches to Modifying Lipid Levels”

Kevin Fitzgerald, *Alnylam Therapeutics, Cambridge, MA*

Poster Presentations

Anne Beigneux	University of California, Los Angeles
Dragana Bojanic	University of California, Los Angeles
Michael Breen	Boston University School of Medicine
Lilly Chao	University of California, Los Angeles
Ruchi Chaube	University of Windsor
Meng-Yun Chou	University of California, San Diego
Hai Li	VA Palo Alto Health Care System
Kristin I. Stanford	University of California, San Diego
Claudio Villanueva	HHMI – University of California, Los Angeles
Michael M. Weinstein	University of California, Los Angeles

1

Elucidation of the Posttranscriptional Regulatory Mechanism for LDL Receptor Expression

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2. Department of Medicine, Stanford University, Stanford, CA 94305

Abstract:

Regulation of hepatic LDL receptor (LDLR) expression occurs at the transcriptional, posttranscriptional, and translational levels. While the mechanisms that control its transcription through the SREBP pathway and translation through PCSK9-mediated degradation have been extensively studied, currently little is known regarding the mechanism that regulates the rapid decay of LDLR mRNA in liver cells. We have taken a systematic approach that integrated different lines of investigation, including siRNA library construction and screening, reporter gene transfection, biotinylated RNA pull-down, mass spectrometry (MS) analysis, and functional assays to identify LDLR mRNA binding proteins (MBPs) and their interacting cis-acting elements on the 3'untranslated region (UTR) of LDLR mRNA. Through these comprehensive studies we now demonstrate that LDLR mRNA stability is regulated by at least 11 MBPs, among which are 3 AU-rich elements (ARE)-binding proteins (hnRNP D, hnRNP I, and KSRP). We show that hnRNP D, hnRNP I, and KSRP interact with AREs of the LDLR 3'UTR with sequence specificity. Silencing the expression of these proteins increased LDLR mRNA and protein levels. We further demonstrate that hnRNP I and KSRP are also involved in a pharmacological agent berberine-induced mRNA stabilization, as their cellular depletion abolished the stabilizing effect of berberine on LDLR mRNA and berberine treatment reduced the binding of hnRNP I and KSRP to the LDLR mRNA 3'UTR. These new findings provide a molecular basis for the understanding of the regulatory mechanism in a cell culture model. To begin to explore the posttranscriptional regulatory mechanism of LDLR in vivo, we have made transgenic mouse strains that carry a CMV-driven luciferase reporter construct. This construct contains the LDLR mRNA 3'UTR sequence at the end of the luciferase coding region. Examination of luciferase activities in tissues of both young (7-8 days) and adult mice (2-3 months) showed a low expression level of the reporter gene in liver as compared to that in other tissues such as intestine, muscle, heart and skin. Utilizing bioluminescent imaging technology, we further showed that the reporter activity is increased after berberine treatment in the transgenic mice in a dose-dependent manner. Taken together, our studies in vivo and in vitro suggest that LDLR mRNA stability is regulated by a network of mRNA binding proteins and possibly the tissue specific expression of some of these regulatory proteins may affect LDLR mRNA stability differentially in different tissues.

2

ER Stress mediated effects on Plasma Membrane cholesterol and the Nitric Oxide Synthase Activity

Bulent Mutus, 1 Ruchi Chaube, 1

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Abstract:

In a recent study in our lab we have shown that increase in plasma membrane (PM) cholesterol leads to attenuation of Nitric Oxide (NO) diffusion and NO-mediated signaling (*J. Biol. Chem.*, Vol. 283, 18513-18521). In parallel with this study, we now have evidence that endoplasmic reticulum (ER) stress, a common occurrence in the pathology of many diseases including diabetes, cardiovascular and neurological disorders, leads to elevation in PM-cholesterol which in addition to its effects on NO-diffusion and reactivity, attenuates endothelial nitric oxide synthase (eNOS) activity and its intracellular distribution. In our attempts to discover potential pathological mechanisms that can lead to elevations in PMcholesterol we have observed that during ER stress, neutral sphingomyelinase (NSmase) becomes dysfunctional via S-nitrosation, thus disrupting the plasma membrane cholesterol-sphingomyelin balance and making the plasma membrane susceptible to elevations in cholesterol levels. Furthermore, we have also observed that as the ER stress is prolonged there is an increase in the expression of Sterol Regulatory Element Binding Protein (SREBP) transcription factors upregulating cholesterol biosynthesis. These results have led us to propose a mechanism by which ER-stress can lead to endothelial dysfunction through elevation of PM-cholesterol.

3

The Heparan Sulfate Proteoglycan Syndecan-1 Clears Plasma Lipoproteins in the Liver Independently of LDL Receptor Family Members

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1. Department of Cellular and Molecular Medicine, University of California, San Diego

2. Biomedical Sciences Graduate Program, University of California, San Diego

3. Department of Medicine, University of California, San Diego

Abstract:

We previously provided genetic evidence that alterations in hepatic heparan sulfate results in accumulation of plasma triglyceride-rich lipoproteins (MacArthur et al, *J. Clin. Invest.* 117:153, 2007). In this study, we determined the heparan sulfate proteoglycan (HSPG) that mediates clearance, and examined the contribution of HSPG to clearance of other lipoprotein particles. Analysis of available proteoglycan-deficient mice showed that syndecan-1 mutants (*Sdc1*^{-/-}) accumulated plasma triglycerides (95 + 11 mg/dl vs. 44 + 19 mg/dl in wild-type). *Sdc1*^{-/-} mice also exhibited prolonged circulation of injected human VLDL and intestinally derived chylomicrons, and adenovirus containing syndecan-1 corrected the clearance defect in vivo. Crossbreeding mutants defective in syndecan-1 and *Ndst1f/fAlbCre*⁺ (the latter reduces sulfation of heparan sulfate on all HSPGs) did not accentuate triglyceride accumulation, indicating that syndecan-1 is the primary proteoglycan mediating clearance. Immunoelectron microscopy showed expression of syndecan-1 on the microvilli of hepatocyte basal membranes facing the space of Disse where lipoprotein uptake occurs. Syndecan-1 receptors are abundant on hepatocytes, exhibit saturable binding and inhibition by heparin, and facilitate degradation of VLDL. Adenovirus containing syndecan-1 corrected the clearance defect in vivo and restored binding, uptake, and degradation of VLDL in isolated hepatocytes. To study the relative contribution of HSPGs, LDL receptors (LDLR) and LDL receptor related protein-1 (LRP1), in clearance, double and triple mutants were generated and characterized. Combining *Ldlr*^{-/-} with *Lrp1f/fAlbCre*⁺ or *Ndst1f/fAlbCre*⁺ with *Lrp1f/fAlbCre*⁺ did not result in additional accumulation of triglyceride-rich lipoproteins compared to *Ldlr*^{-/-} or *Ndst1f/fAlbCre*⁺ mice, respectively. In contrast, combining *Ndst1f/fAlbCre*⁺ and *Ldlr*^{-/-} resulted in greatly enhanced accumulation of triglyceride- and cholesterol-rich particles (triglycerides 205 + 26 mg/dl vs. 43 + 3 mg/dl in wild-type; cholesterol 216 + 15 mg/dl vs. 67 + 3 mg/dl in wild-type). Mice deficient in all three receptors (*Ldlr*^{-/-}*Lrp1f/fNdst1f/fAlbCre*⁺) further accentuated accumulation of triglyceride- and cholesterol-rich lipoprotein particles (triglyceride 629 + 122; cholesterol 1088 + 80). These findings provide the first genetic evidence showing that syndecan-1 is the primary hepatocyte proteoglycan receptor mediating the clearance of both hepatic and intestinally derived triglyceride-rich lipoproteins. Furthermore, they show that HSPGs can mediate clearance of both triglyceride and cholesterol rich particles independently of LDLR and LRP1.

4

Chylomicronemia Associated with a Mutant GPIHBP1 (Q115P) That Cannot Bind Lipoprotein Lipase

Peter Gin, 1 André Bensadoun, 2 Remco Franssen, 3 John J Kastelein, 3 Loren G Fong, 1 Geesje M Dallinga-Thie, 3 Stephen G Young, 1 Anne P Beigneux, 1
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2. Cornell University, Ithaca, NY 14853
3. Amsterdam Medical Center, Amsterdam, The Netherlands

Abstract:

PIHBP1 is an endothelial cell protein that binds lipoprotein lipase (LPL) and chylomicrons. Since GPIHBP1 deficiency causes severe chylomicronemia in mice, we sought to determine if some cases of chylomicronemia in humans are due to functionally important GPIHBP1 mutations. Patients with severe hypertriglyceridemia (n = 60, with plasma triglycerides above the 95th percentile for age and gender) were screened for mutations in GPIHBP1. A homozygous GPIHBP1 mutation (c.344A>C) that changed the highly conserved glutamine at residue 115 to a proline (p.Q115P) was identified in a 33-year-old patient with lifelong chylomicronemia. He had failure to thrive as a child but there was no history of pancreatitis. He had no mutations in LPL, APOC2, or APOA5. The Q115P substitution did not affect the ability of GPIHBP1 to reach the cell surface. However, unlike wild-type GPIHBP1, GPIHBP1-Q115P lacked the ability to bind LPL or chylomicrons (d < 1.006 g/ml lipoproteins from *Gpihbp1*^{-/-} mice). Mouse GPIHBP1 with the corresponding mutation (Q114P) also did not bind LPL.

All together these data strongly suggest that the p.Q115P homozygous missense mutation in GPIHBP1 caused the patient's chylomicronemia.

5

Role of Sterol Transporters ABCG1 and ABCG4 During Development and Beyond

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5. Division of Clinical Chemistry, Karolinska University Hospital, Huddinge, S-14186, Sweden.

6. Department of Neurobiology, David Geffen School of Medicine, University of California, Los Angeles, CA 90095

7. Brain Research Institute, David Geffen School of Medicine, University of California, Los Angeles, CA 90095

Abstract:

Co-expression of ABCG1 and ABCG4, two highly homologous members of the ATP binding cassette (ABC) transporter family that are involved in cellular cholesterol homeostasis, is reportedly limited to neurons and astrocytes of the adult brain. Herein, we report on the expression of these genes during development utilizing *Abcg1*^{-/-}-LacZ, *Abcg4*^{-/-}-LacZ knock-in and double knockout (DKO) mice. Surprisingly, these studies demonstrate that ABCG4, but not ABCG1, is highly expressed both in hematopoietic cells in the developing fetal liver and in enterocytes that line the developing ileum. However, expression of ABCG4 is lost in the corresponding cells of adult mice. We also show that ABCG1 and ABCG4 are highly co-expressed in the dorsal root ganglion and motor neurons of the CNS, as early as E12.5. In addition, we utilized a combination of beta-galactosidase staining and in situ hybridization to demonstrate that *Abcg1* and *Abcg4* have an overlapping pattern of expression in both developing and adult retina. Despite the particularly abundant expression of both genes in the neurons of the photoreceptor layer of the retina, electromicrographs of *Abcg1*^{-/-} or *Abcg4*^{-/-} retinas indicate normal structures. Electroretinograms identify a mild impairment of cone visual function in 15-month old *Abcg1*^{-/-} and *Abcg4*^{-/-} mice. Finally we show that expression of selected LXR target genes, that include *Abca1*, are induced in the retinas and brains obtained from single KO or DKO mice. Importantly, the retinas and brains of the DKO mice have elevated levels of the stress-induced gene *Egr1*, consistent with the accumulation of number of specific sterols and oxysterols. A series of behavioral tests identify changes in the response to contextual fear, although this is limited to the *Abcg4*^{-/-} mouse. Together, these data suggest that loss of ABCG1 and ABCG4 in cells of the CNS result in a stress response despite the increased expression of ABCA1 that presumably is insufficient to maintain normal sterol homeostasis.

6

Caveolae and Caveolar Associated Proteins Play a Role in Lipid Storage and Release.

Tova Meshulam, 1 Libin Liu, 1 Mark P Jedrychowski, 1 Paul F Pilch, 1 Michael R Breen, 1
1. Boston University School of Medicine

Abstract:

Caveolae are small invaginations of the plasma membrane, which play a role in several important physiological processes, notably, lipid flux in adipocytes where caveolae are present in particular abundance. Until recently, Caveolin-1 was thought to be the only protein constituent necessary for caveolae formation, but recent data from our lab (Liu et al, Cell Metabolism, 2008) and that of Robert Parton (Hill et al, Cell, 2008) have demonstrated an absolute requirement of PTRF (Polymerase I and Transcript Release Factor)/Cavin expression for caveolae formation. Mice lacking the gene for this protein have no detectable caveolae, are hyperlipidemic and insulin resistant, which is a phenotype resembling that recently described for humans with Caveolin-1 deficiencies. In light of this, we have re-examined adipocyte caveolae composition and found two additional protein constituents, SDR (Serum deprivation response) and SRBC (SDR-related gene that binds PKC), which appear to be members of the PTRF family. When 3T3-L1 fibroblasts are induced to differentiate into adipocytes, Caveolin-1 and Cavin are coordinately induced, with SDR being expressed highly only after Caveolin-1 and Cavin levels are maximal, while SRBC changes very little. When mice are subjected a high-fat diet, Caveolin-1, Cavin, and SDR expression is increased several fold. Similarly, animals subjected to a prolonged fast, which causes a massive release of fatty acids from adipose tissue, exhibit a significant increase in the expression of Caveolin-1, Cavin, SDR, and SRBC. When MEFs derived from Caveolin-1 null mice are differentiated into adipocytes, they have a higher rate of lipolysis with no apparent change in lipogenic or lipolytic enzymes. Taken together these data strongly support a role for caveolae and caveolar associated proteins in lipid storage and handling. We are currently exploiting SiRNA-mediated knockdowns as well as pharmacological strategies to dissect the biochemical roles of the individual caveolae component proteins and lipids.

7

Nur77 Deletion Impairs Systemic Glucose Metabolism

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Abstract:

Nur77 is an orphan nuclear receptor with pleiotropic functions. Previous studies have identified Nur77 as a transcriptional regulator of glucose utilization genes in skeletal muscle and gluconeogenesis in liver. However, the net functional impact of these pathways is unknown. To examine the consequence of Nur77 signaling for glucose metabolism in vivo, we challenged Nur77 null mice with high-fat feeding. We report here that mice with genetic deletion of Nur77 exhibited increased susceptibility to diet-induced obesity and insulin resistance. Hyperinsulinemic-euglycemic clamp studies revealed worsened insulinsensitivity in both skeletal muscle and liver of Nur77 null mice compared to controls. Loss of Nur77 expression in skeletal muscle impaired insulin signaling and markedly reduced Glut4 protein expression. Muscles lacking Nur77 also exhibited increased triglyceride content and evidence of incomplete β oxidation. In the liver, Nur77 deletion led to hepatic steatosis and enhanced expression of lipogenic genes. However, as acute expression of Nur77 in primary hepatocytes and HepG2 cells did not suppress lipogenic gene expression, hepatic steatosis of Nur77 null mice may be attributable to the lipogenic effect of hyperinsulinemia. Collectively, these data demonstrate that loss of Nur77 impacts systemic glucose metabolism and highlight the physiological contribution of muscle Nur77 to this regulatory pathway.

8

Ezetimibe Worsens the Hypertriglyceridemia in *Gpihbp1*^{-/-} Mice

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1. Department of Medicine, University of California, Los Angeles, CA 90095

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Abstract:

GPIHBP1 is required for the lipolytic processing of triglyceride-rich lipoproteins. We suspect that GPIHBP1 plays a key role in the entry of lipoprotein lipase (LPL) into the capillaries of adipose tissue and striated muscle. GPIHBP1-deficient suckling mice (*Gpihbp1*^{-/-}) exhibit mild hypertriglyceridemia (plasma triglyceride levels of ~200 mg/dl), but adult chow-fed *Gpihbp1*^{-/-} mice have severe hypertriglyceridemia (triglyceride levels >2000 mg/dl). We suspect that the lower triglyceride levels in the suckling mice relates to high levels of LPL expression in the livers of those mice. In adult *Gpihbp1*^{-/-} mice fed a high-fat, highcholesterol diet, plasma triglyceride levels initially increase to >20,000 mg/dl (after 1 week on diet), but then fall to 5000–10,000 mg/dl. We suspect that the fall in plasma triglyceride levels after 1 week on the high-fat diet is due to induction of LPL expression in the liver (from LXR activation). When *Gpihbp1*^{-/-} mice are given ezetimibe, the fall in plasma triglyceride levels after 1 week is attenuated and plasma triglyceride levels remain >15,000 mg/dl. Interestingly, ezetimibe significantly reduces LPL expression in the liver. ABCA1, ABCG5, and ABCG8 expression levels are also reduced, suggesting that the reduced expression of LPL is due to decreased LXR activation.

Why would the plasma triglyceride levels in *Gpihbp1*^{-/-} mice be responsive to changes in hepatic LPL expression levels? We suspect that GPIHBP1 is absolutely required for the entry of LPL into the capillaries of heart, skeletal muscle, and adipose tissue. Thus, when GPIHBP1 is absent, lipolysis in those tissues is virtually abolished. However, the capillaries of the liver are fenestrated, and we suspect that the small amount of LPL produced by the liver readily enters capillaries—even in the absence of GPIHBP1. Thus, in contrast to the LPL produced by extrahepatic tissues, we believe that the LPL produced by the liver is accessible to lipoproteins—even in the absence of GPIHBP1. We suspect that the reduced hepatic LPL expression levels in ezetimibe-treated *Gpihbp1*^{-/-} mice explains their more severe hypertriglyceridemia. On the other hand, we suspect that plasma triglyceride levels in *Gpihbp1*^{-/-} mice are lower when hepatic LPL expression levels are increased (i.e., suckling pups and adult mice fed a high-fat diet).

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Heparin Ameliorates the Severe Hypertriglyceridemia Caused by GPIHBP1 Deficiency

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Abstract:

GPIHBP1-deficient mice (*Gpihbp1*^{-/-}) exhibit chylomicronemia, strongly suggesting that GPIHBP1 plays an important role in lipoprotein lipase (LPL)-mediated processing of triglyceride-rich lipoproteins. GPIHBP1 is located on the luminal surface of capillaries in heart, skeletal muscle, and adipose tissue, where lipolysis occurs. Studies with transfected cells have shown that GPIHBP1 binds LPL avidly. However, there is little evidence that GPIHBP1 actually interacts with LPL *in vivo*. Heparin is known to release LPL from its *in vivo* binding sites, allowing it to enter the plasma. We hypothesized that *Gpihbp1*^{-/-} mice have little LPL within their intravascular compartment (i.e., little LPL bound within capillaries). We further hypothesized that LPL bound to GPIHBP1 inside capillaries would be released into the plasma extremely quickly in *Gpihbp1*^{+/+} mice, and that LPL release into the plasma would be delayed in *Gpihbp1*^{-/-} mice (as a result of reduced amounts of LPL in capillaries). Indeed, this was the case. Plasma LPL levels peaked rapidly (within 1–3 min) after heparin in wild-type mice. In contrast, plasma LPL levels in *Gpihbp1*^{-/-} mice were much lower 1–3 min after heparin and increased gradually over 15 min. Also, an injection of Intralipid (a triglyceride emulsion with very large particles) released LPL into the plasma of wild-type mice, but failed to release LPL into the plasma of *Gpihbp1*^{-/-} mice. These differences between *Gpihbp1*^{-/-} and wild-type mice cannot be ascribed to differences in tissue stores of LPL, as LPL mass levels in the two groups of mice were similar. The slow LPL release after intravenous heparin and failure of Intralipid to release LPL are consistent with the notion that *Gpihbp1*^{-/-} mice have very little (if any) LPL within capillaries. Although LPL levels within capillaries are probably low in *Gpihbp1*^{-/-} mice, heparin treatment of *Gpihbp1*^{-/-} mice does release significant amounts of enzymatically active LPL into the plasma (presumably this LPL is released into plasma from extravascular binding sites), suggesting that the administration of heparin to *Gpihbp1*^{-/-} mice should ameliorate their severe hypertriglyceridemia. This prediction was upheld; heparin lowered plasma triglycerides in *Gpihbp1*^{-/-} mice by >80% in less than 3 hours.

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Identification of a Transcriptional Regulator of PPAR γ Activity by High Throughput Adipogenic Screening.

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Abstract:

Adipocytes are specialized cells that store lipids during times of caloric excess, mobilize them as free fatty acids during energy deficiency, and secrete endocrine factors to regulate systemic energy metabolism. Dysregulation of adipocyte development and function plays a critical role in metabolic diseases, such as obesity, where adipocyte size and number are increased. Peroxisome proliferator-activated receptor gamma (PPAR γ), a ligand-activated transcription factor, is the master regulator of adipocyte differentiation. In an effort to identify additional factors involved in adipogenesis, we conducted highthroughput cDNA screening using reporter cells expressing a PPAR γ -dependent luciferase reporter. We identified several genes whose function has been previously described in adipogenesis, including PPAR γ , C/EBP α , C/EBP β , C/EBP δ , MAPKK6, and COE1, validating our screening strategy. However, we also identified several novel factors, including TLE3, a nuclear protein whose function had not been previously described in adipogenesis. TLE3 is expressed in adipocytes and belongs to a family of transcriptional corepressors that work in concert with transcription factors to regulate gene expression. TLE3 promotes adipocyte differentiation by increasing the activity of PPAR γ . Conversely, loss of function studies show that adipogenesis and expression of PPAR γ target genes are reduced in the absence of TLE3. Our studies point to TLE3 as a novel regulator of PPAR γ activity and adipocyte differentiation.

11

Oxidation-Specific Epitopes are Dominant Targets of Innate Immunity

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Abstract:

Oxidized low density lipoprotein (OxLDL) is an immunogen present in atherosclerotic plaques that leads to a marked rise in plasma levels of immunoglobulin M (IgM). In uninfected mice, IgMs are thought mainly to represent natural antibodies (NABs), which are germ-line encoded antibodies secreted by B-1 cells. A variety of oxidation-specific epitopes are formed in abundance not only on OxLDL, but also on apoptotic cells and under inflammatory conditions in general. Here we present multiple lines of evidence suggesting that oxidation-specific epitopes are a major target of innate NABs for both mice and humans. For example, using B-1 cell reconstituted Rag1^{-/-} mice expressing solely IgM NABs, we showed that about 30% of all NABs bind to model oxidation-specific epitopes, as well as to atherosclerotic lesions and apoptotic cells. IgMs in human umbilical cord blood, the human equivalent of NABs, also bound prominently to OxLDL as well as apoptotic cells, suggesting that oxidation-specific epitopes are an important target of NABs in humans as well. Because oxidative processes are ubiquitous, we hypothesize that these epitopes exert selective pressure to expand NABs, which in turn play an important role in mediating homeostatic functions consequent to inflammation and cell death. Indeed, we demonstrated that B-1 cell derived NABs can facilitate apoptotic cell uptake by macrophages in vivo. In conclusion, oxidation-specific epitopes constitute a dominant, previously unrecognized but important target of NABs in both mice and human. NABs to oxidation-specific epitopes may be beneficial in identifying altered self that occur as a result of oxidative stress under inflammatory events. Our findings may provide novel insights into the function of NABs in mediating host homeostasis, and into their roles in health and disease, such as chronic inflammatory diseases and atherosclerosis.

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Notes

Save the Date

**2010 DEUEL Conference on Lipids
March 2 – 5, 2010**

Laguna Cliffs Marriott Resort

Peter Tontonoz, Program Chair



2009 DEUEL Conference on Lipids
March 3-6, 2009
Borrego Springs, California