European Lipoprotein Club

42nd Annual Scientific Meeting

September 09-12, 2019

Evangelische Akademie

Tutzing, Germany

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Program Monday Sep 9

12:00 - 14:00	**Arrival and registration**
14:00 - 14:10	**Welcome** Patrick Rensen (Leiden, The Netherlands)
Session:	**Vessel Wall** Chairperson: Nicola Ferri (Padova, Italy)
14:10 - 14:50	**Invited speaker: Kees Hovingh (Amsterdam, The Netherlands)** Genes: guidance in lipid-targeted therapy
14:50 - 15:10	**Fabrizia Bonacina (Milan, Italy)** Engineered regulatory T cell Adoptive Therapy as a novel tool for the treatment of atherosclerosis
15:10 - 15:30	**Bianca Papotti (Parma, Italy) *** The anti-atherogenic role of sphingosine-1-phosphate (S1P) and its receptor S1P3 in the reverse cholesterol transport
15:30 - 15:50	**Sara Oppi (Zurich, Switzerland) *** The nuclear receptor corepressor 1 blocks CD36-mediated foam cell formation in atherogenesis
15:50 - 16:10	**Maria Giovanna Lupo (Padova, Italy) *** PCSK9 induces smooth muscle cell-mediated calcification: in vitro and in vivo evidences
16:10 - 16:40	**Coffee break**
Session:	**Brain & Bugs** Chairperson: Ruth Frikke-Schmidt (Copenhagen, Denmark)
16:40 - 17:00	**Monique Mulder (Rotterdam, The Netherlands)** Dietary Sargassum fusiforme improves memory and reduces amyloid plaque load in an Alzheimer's disease mouse model
17:00 - 17:20	**Emily Button (Vancouver, Canada) *** High-density lipoprotein deficiency in transgenic Alzheimer's disease mice increases global and vascular specific amyloid pathology and neuroinflammation
17:20 - 17:40	**Liv Nordestgaard (Copenhagen, Denmark) *** Genetic inhibition of CETP and risk of ischemic heart disease, cardiovascular mortality, age-related macular degeneration, and dementia

** Eligible for Young Investigator Oral Award*

Program Monday Sep 9

17:40 - 18:00	**Lisanne Blauw (Leiden, The Netherlands) *** The biological function of CETP: modulation of HDL to resolve infections
18:00 - 18:20	**Bart Staels (Lille, France)** Hepatic PPARa is critical in the metabolic adaptation to sepsis
18:30 - 19:30	**Dinner**
20:00 - 21:00	**Keynote Lecture** Chairperson: Patrick Rensen (Leiden, The Netherlands) **Ira Tabas (New York, USA)** Inflammation resolution and efferocytosis in atherosclerosis
21:00	**Bar will be open**

** Eligible for Young Investigator Oral Award*

Program Tuesday Sep 10

07:30 - 08:30	**Breakfast**
Session:	**Lipoproteins** Chairperson: Katariina Öörni (Helsinki, Finland)
08:30 - 08:50	**Pauli Ohukainen (Oulu, Finland)** Multivariate lipoprotein phenotyping supports the culprit role of apolipoprotein B in coronary heart disease
08:50 - 09:10	**Cedric Le May (Nantes, France)** Pharmacological inhibition of circulating PCSK9 but not intestinal deficiency reduces post-prandial lipemia in mice
09:10 - 09:30	**Maija Ruuth (Helsinki, Finland) *** Dietary saturated fats increase and plant stanol esters decrease LDL aggregation
09:30 - 09:50	**Simon Pfisterer (Helsinki, Finland)** Heterogeneity of LDL uptake responses in individual hypercholesterolemia patients
09:50 - 10:10	**Kristian Kølby Kristensen (Copenhagen, Denmark) *** A disordered acidic domain in GPIHBP1 harboring a sulphated tyrosine regulates lipoprotein lipase
10:10 - 10:30	**Vesa Olkkonen (Helsinki, Finland)** The impacts of ANGPTL3 deficiency on serum lipoprotein measures and lipidome – comparison with omics data from ANGPTL3 silenced hepatocytes
10:30 - 11:00	**Coffee break**
Session:	**Lipid & Droplets** Chairperson: Dagmar Kratky (Graz, Austria)
11:00 - 11:40	**Invited speaker: Rosalind Coleman (Chapel Hill, USA)** Cell organization and lipid metabolism
11:40 - 12:00	**Sander Kersten (Wageningen, The Netherlands)** Hypoxia-induced lipid droplet-associated (HILPDA) increases lipid accumulation in macrophages and hepatocytes via ATGL-dependent and -independent mechanisms
12:00 – 12:20	**Melanie Korbelius (Graz, Austria) *** Contribution of neutral lipolysis on the catabolism of cytosolic lipid droplets in the small intestine

** Eligible for Young Investigator Oral Award*

Program Tuesday Sep 10

12:20 – 12:40	**Benedikt Kien (Graz, Austria) *** Establishment of a model to investigate the impact of Perilipin 5 mediated peridroplet mitochondria formation
12:40 – 13:00	**Suzanne van Wouw (Amsterdam, The Netherlands) *** The role of the LXR-EEPD1 axis in cholesterol metabolism
13:00 - 14:00	**Lunch**
14:00 – 15:30	**Networking (and OC Meeting)**
Session:	**Adipose tissue** Chairperson: Ludger Scheja (Hamburg, Germany)
15:30 – 16:10	**Invited speaker: Fredrik Karpe (Oxford, UK)** The link between adiposity, adipose tissue function and CVD
16:10 – 16:30	**Enchen Zhou (Leiden, The Netherlands) *** Anti-PCSK9 treatment enhances beneficial effects of brown fat activation on cholesterol metabolism in APOE*3-Leiden.CETP mice
16:30 – 16:50	**Isabel Reinisch (Graz, Austria) *** p53-driven miRNA-92a expression as potential regulator of BAT activity under fasting
16.50 -17.20	**Coffee break**
17:40 – 18:00	**Maaike Schilperoort (Leiden, The Netherlands) *** Circadian rhythm of glucocorticoids regulates brown adipose tissue activity and is important for maintaining metabolic health
17:40 – 18:00	**Michelle Yvonne Jäckstein (Hamburg, Germany) *** Endothelial lysosomal acid lipase deficiency impairs white adipose tissue browning
18:00 – 18:20	**Bart van de Sluis (Groningen, The Netherlands)** Loss of adipocyte WASH complex reduces brown and white adipose tissue mass
18:30 - 19:30	**Dinner**
19:30 - late	**Wine and Poster Science**

** Eligible for Young Investigator Oral Award*

Program Wednesday Sep 11

07:30 - 08:30	**Breakfast**
Session:	**Fatty liver** Chairpersons: Kevin Jon Williams (Gothenburg, Sweden) and Christina Christoffersen (Copenhagen, Denmark)
08:30 - 09:10	**Invited speaker: Adil Mardinoglu (Stockholm, Sweden)** Use of systems biology in the treatment of fatty liver disease
09:10 - 09:30	**Menno Hoekstra (Leiden, The Netherlands)** Inhibition of PRMT3 activity reduces hepatic steatosis without altering atherosclerosis susceptibility in ApoE knockout mice
09:30 - 09:50	**Jan Kovář (Prague, Czech Republic)** The acute response of hepatic fat content to high-fat load is more pronounced in subjects with non-alcoholic fatty liver disease than in control subjects
09:50 - 10:10	**Alexandre Motte (Paris, France) *** Postprandial changes in circulating lipoprotein-associated microRNAs distribution
10:10 - 10:40	**Coffee break**
10:40 - 11:00	**Noam Zelcer (Amsterdam, The Netherlands)** A mammalian haploid genetic screen identifies the ERAD-associated E3 ubiquitin ligase MARCH6 as a novel determinant of hepatic fatty acid and lipoprotein metabolism
11:00 - 11:20	**Audrey Deprince (Lille, France) *** The role of apolipoprotein F in the control of plasma and hepatic lipid metabolism
11:20 - 11:40	**Wieneke Dijk (Nantes, France) *** Identification of novel regulators of cholesterol metabolism by using a mass-spectrometry-based approach
11:40 - 12:00	**Lorenzo Da Dalt (Milan, Italy) *** Tissue selective PCSK9-KO mice present altered glucose metabolism, pancreatic function and insulin release
12:00 - 13:00	**Lunch**

** Eligible for Young Investigator Oral Award*

Program Wednesday Sep 11

13:00 - 15:00	**Networking**
Session:	**Bile acids** Chairpersons: Mathilde Varret (Paris, France)
15:00 - 15:20	**Ioannis Evangelakos (Hamburg, Germany) *** The role of the alternative pathway-derived bile acids in NAFLD progression
15:20 - 15:40	**Jan Freark de Boer (Groningen, The Netherlands)** A human-like composition of the circulating bile acid pool impacts on plasma LDL-cholesterol in mice
15:40 - 16:00	**Mats Rudling (Stockholm, Sweden)** Mice devoid of murine bile acids display a human-like phenotype
16:00 - 16:20	**Christian Wolfrum (Schwerzenbach, Switzerland)** Atypical bile acid signalling regulating adipocyte formation
16:20 - 16:40	**Yanan Wang (Leiden, The Netherlands)** Δ24-Dehydrocholesterol reductase (DHCR24): a novel target for the treatment of NASH
16:40 - 17:00	**Annual Members' Assembly**
18:40 and 18:55	Bus transfer to Networking dinner
19:00 - 24:00	**Networking dinner and Young Investigator Awards**
23:00, 23:30 and 0:00	Bus transfer to Evangelische Akademie

Program Thursday Sep 12

09:00 - 10:00	**Breakfast**
10:00 - 12.00	**Departure** See you next year - September 07-10, 2020!

** Eligible for Young Investigator Oral Award*

Oral presentations

Eligible for Young Investigator Oral Award:

Bianca Papotti (Parma, Italy)
Sara Oppi (Schlieren, Switzerland)
Maria Giovanna Lupo (Padova, Italy)
Emily Button (Vancouver, Canada)
Liv Nordestgaard (Copenhagen, Denmark)
Lisanne Blauw (Leiden, The Netherlands)
Maija Ruuth (Helsinki, Finland)
Kristian Kølby Kristensen (Copenhagen, Denmark)
Melanie Korbelius (Graz, Austria)
Benedikt Kien (Graz, Austria)
Suzanne van Wouw (Amsterdam, The Netherlands)
Enchen Zhou (Leiden, The Netherlands)
Isabel Reinisch (Graz, Austria)
Maaike Schilperoort (Leiden, The Netherlands)
Michelle Yvonne Jäckstein (Hamburg, Germany)
Alexandre Motte (Paris, France)
Audrey Leprince (Lille, France)
Wieneke Dijk (Nantes, France)
Lorenzo Da Dalt (Milan, Italy)
Ioannis Evangelakos (Hamburg, Germany)

ENGINEERED REGULATORY T CELL ADOPTIVE THERAPY AS A NOVEL TOOL FOR THE TREATMENT OF ATHEROSCLEROSIS

Fabrizia Bonacina[1], Elisa Martini[2], Marco Cremonesi[2], Annalisa Moregola[1], Fabio Pellegatta[3], Alberico Luigi Catapano[1,3], Marinos Kallikourdis[2], Giuseppe Danilo Norata[1,3]

[1]DisFeb, University of Milan, Milan, Italy. [2]IRCCS Humanitas Research Foundation, Rozzano, Italy. [3]SISA Centre for the study of Atherosclerosis, Cinisello Balsamo, Italy

Aim: Loss of anti-inflammatory activity of regulatory Tcells (Treg) is a pathogenic feature of immune mediated-disease, as atherosclerosis. Our aim was to investigate whether Treg functionality was impaired in patients affected by familial hypercholesterolemia (FH) and test Treg-Adoptive Cell Therapy (ACT) as a treatment of atherosclerosis-related inflammation. To achieve selective targeting, we develop plaque-homing Treg-ACT in models of atherosclerosis.

Method: Treg from FH patients (HE for LDLR) and LDLR KO mice were phenotypical and functional characterized by flow cytometry. Then, Treg from WT animals were retrovirally (IRES-EGFP vector) transfected with chemokine receptors or an empty vector and i.v. injected (2x105 GFP+ cells/mouse) in male 8-week WTD LDLR KO. Homing of transfected Treg to atherosclerotic plaque, its progression and composition was analysed by flow cytometry and histology.

Results: Circulating levels of CD4 Teffector memory cells are significantly increased (+23%) in HeFH patients compared to matched CTRL, but paralled by an increased level of Treg(+15%) that show decreased suppressive function ($p<0.05$). This picture is also confirmed in LDLR KO compared to WT littermates. Therefore, we explored the use of functional WT Treg to target atherosclerosis-inflammation. Gene expression of 8-week WTD LDLR KO revealed that the chemokine CX3CL1 is selectively expressed in the aorta ($p<0.05$), but not in other tissues (lymph nodes, spleen and liver). CX3CR1-engineered Treg showed a specific homing to atherosclerotic plaques (2,5% of GFP+/lived cell compared to 0.6%) with similar homing in lymph nodes and spleen 24 hours after the injection. Next we investigated whether CX3CR1-Treg reduce atherosclerosis by performing plaque analysis 4 weeks after ACT in LDLR KO mice under WTD. Although levels of plasma cholesterol were similar, CX3CR1- compared to control-Treg treated mice showed decreased plaque area and pro-inflammatory macrophage infiltration, with increased stability ($p<0.05$).

Conclusions: Our data suggest that the increased immuno-inflammatory burden observed in FH patients is also contributed by dysfunctional Treg. Engineered Treg overexpressing CX3CR1 appears a promising ACT to promote selective homing of Treg into the plaque thus limiting atherosclerosis progression.

THE ANTI-ATHEROGENIC ROLE OF SPHINGOSINE 1-PHOSPHATE (S1P) AND ITS RECEPTOR S1P3 IN THE REVERSE CHOLESTEROL TRANSPORT

Enrica Scalera[1], Bianca Papotti[1], Ilaria Zanotti[1], Daniela Greco[1], Simone Battista[1], Franco Bernini[1], Jerzy-Roch Nofer[2], Manuela Simoni[3], Francesco Potì[4]

[1]Department of Food and Drug, University of Parma, Parma, Italy. [2]Center for Laboratory Medicine, University Hospital of Münster, Münster, Germany. [3]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy. [4]Department of Medicine and Surgery, Unit of Neurosciences, University of Parma, Parma, Italy

Aim: Sphingosine 1-phosphate plays a crucial role in atherosclerosis, even though the molecular mechanisms underlying its anti-atherogenic effects are still partially known. S1P exerts its biological activity by binding to its G protein-coupled receptors, such as S1P3. To date, we have no direct evidence connecting S1P3 role in cellular and systemic cholesterol handling. This study aims to investigate whether the anti-atherogenic activity of S1P is related to the modulation of lipid metabolism.

Method: The role of S1P3 receptor was studied in a transgenic mouse model overexpressing S1P3 in myeloid lineage (S1P3-Lyz). ABCA1 and ABCG1 expression in MPM were quantified through RT-qPCR and Western Blot analysis. ABCA1- and ABCG1-mediated cholesterol efflux was evaluated in control (C57BL/6) and S1P3-Lyz MPM through a radioisotope technique, using different mouse plasma concentration (0.1% and 2% v/v) and HDL (12.5 mg/ml) as cholesterol acceptors. *In vivo* RCT was measured through a radioisotope technique by injecting [^{3}H]cholesterol-enriched MPM isolated from both C57BL/6 and S1P3-Lyz mice in C57BL/6 recipient.

Results: S1P3-Lyz MPM displayed an increased ABCG1 expression compared to C57BL/6, while no differences were observed in ABCA1. Accordingly, ABCG1-mediated cholesterol efflux to mouse plasma was higher in S1P3-Lyz MPM compared to C57BL/6 MPM; similarly, acetylated LDL-loaded S1P3-Lyz MPM displayed an higher cholesterol efflux to plasma acceptors compared to C57BL/6 MPM. Finally, S1P3-Lyz MPM incubated with plasma together with a selective S1P3 antagonist (TY52156, 10 μM) displayed a reduced cholesterol efflux compared to non-treated S1P3-Lyz MPM. *In vivo* total RCT resulted higher in S1P3-Lyz group, as ^{3}[H]-Cholesterol found in plasma, liver and faeces was higher compared to C57BL/6 group.

Conclusions: These results showed that endogenous S1P, through the interaction with its receptor S1P3 on myeloid cells, positively modulates cholesterol metabolism by improving RCT. For these reasons, S1P-S1P3 axis may represent a potential pharmacological target for the modulation of cholesterol homeostasis.

Eligible for Young Investigator Oral Award

THE NUCLEAR RECEPTOR COREPRESSOR 1 BLOCKS CD36-MEDIATED FOAM CELL FORMATION IN ATHEROGENESIS

Sara Oppi[1], Stefanie Nusser-Stein[1], Vincenzo Marzolla[1], Elena Osto[2], Zoran Rancic[3], Lüscher Thomas F.[1], Maaike H. Oosterveer[4], Sokrates Stein[1]

[1]University of Zurich, Schlieren, Switzerland. [2]ETH Zürich, Zurich, Switzerland. [3]University Hospital Zurich, Zurich, Switzerland. [4]University of Groningen, Groningen, The Netherlands

Aim: Nuclear receptors and their cofactors regulate the expression of various target genes in different tissue and organs to orchestrate downstream (patho) physiological processes. Although the function of several nuclear receptors in atherosclerosis has been studied, very little is known about the role of nuclear receptor cofactors in atherosclerosis. Given its important role to suppress inflammatory processes, we speculated that macrophage nuclear receptor corepressor 1 (NCOR1) plays a protective function in atherosclerosis development.

Method: To evaluate the contribution of macrophage NCOR1 in atherosclerosis we exposed 8-week-old male and female myeloid cell-specific *Ncor1* knockout mice to a high high-cholesterol diet for 12 weeks and assess atherosclerosis development.

Results: Our findings demonstrate that the lack of macrophage *Ncor1* leads to a severe atherosclerotic phenotype in both sexes. These mice show a higher content of plaques along the thoraco-abdominal aortae as well as at the aortic sinus, which were characterized by larger necrotic cores and thinner fibrous caps, a typical signature of unstable plaques. Moreover, we found that the pro-atherogenic effects of the *Ncor1* deletion are mediated via derepression of peroxisome proliferator-activated receptor gamma (PPARγ) target genes in mouse and human macrophages, especially the enhanced expression of the CD36 scavenger receptor and the subsequent rise in oxLDL uptake. Interestingly, while the expression of NCOR1 is reduced, the PPARγ signature is increased in human atherosclerotic plaques, and this signature is further pronounced in ruptured compared to stable carotid plaques.

Conclusions: Our findings suggest that macrophage NCOR1 blocks the pro-atherogenic functions of PPARγ in atherosclerosis and prevents the disease development.

Eligible for Young Investigator Oral Award

Vessel wall

PCSK9 INDUCES SMOOTH MUSCLE CELL-MEDIATED CALCIFICATION: IN VITRO AND IN VIVO EVIDENCES

Maria Giovanna Lupo[1], Paolo Poggio[2], Marina Camera[2,3], Elisabetta Faggin[4], Marcello Rattazzi[4,5], Nicola Ferri[1]

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Aim: Vascular calcification represents a main risk factor of cardiovascular events in patients with chronic kidney disease (CKD). Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) levels correlates with the presence of calcific aortic valve stenosis and carriers of the PCSK9 R46L loss-of-function variant have a low calcific aortic valve stenosis. We investigated a possible role of PCSK9 on aortic calcification by using a uremic rat model of vascular calcification and *in vitro* cultured human smooth muscle cells (hSMCs) overexpressing PCSK9.

Method: Sprague-Dawley rats were fed a standard diet (n=10) or uremic diet containing 0.5% adenine (n=10) for 6 weeks. Urine volumes have been measured every two weeks by leaving rats in metabolic cages for 24h. At sacrifice, abdominal aortas, plasma, livers and kidneys have been collected. Hydroxyapatite deposition into the media has been measured by a calcium colorimetric assay and visualized by von Kossa staining. Plasma creatinine and phosphate levels have been evaluated by clinical standardized methods. PCSK9 expression in kidneys and liver has been visualized by Western Blotting. The overexpression of PCSK9 in hSMCs has been realized through retroviral infection. Both control and PCSK9-overexpressing hSMCs have been cultured with low-FCS/high-phosphate media (0.4% FCS *plus* 2.0 mM or 2.4 mM of NaH_2PO_4) for 7 days, changing media every two days. Hydroxyapatite deposition by cells has been measured by a calcium colorimetric assay.

Results: The uremic condition was documented by increased urine volume (26 ml/day vs 58 ml/day), plasma creatinine (25.7 µM vs 208 µM) and phosphate levels (2.64 µM vs 6.11 µM). High phosphate concentration was associated to aortic calcification determined by measuring aorta Ca^{2+} concentrations (0.34 mg/g tissue vs 2.48 mg/g tissue) and by Von Kossa staining. This pathological condition was associated to a significant increase of total cholesterol (from 75.3 mg/dL to 107.6 mg/dL) and PCSK9 levels (from 40.1 ng/ml to 109.7 ng/ml). Higher expression of PCSK9 was also observed in kidney (+4.8 fold) and liver (+1.5 fold). The overexpression of PCSK9 in hSMCs (from 0.02 ng/ml to 11.3 ng/ml) induced a significant increase of extracellular calcification in response to 5 days exposure to 2.4 mM NaH_2PO_4 (+39% compared to control hSMCs), while NaH_2PO_4 reduced the release of PCSK9 from hSMCs (-33.6%) and the mRNA expression levels (-43%).

Conclusions: The present study indicates a direct role of PCSK9 on vascular calcification associated to a CKD condition. Further analysis will attempt to identify the molecular mechanism of this action and to study the effect of monoclonal antibodies anti PCSK9.

Eligible for Young Investigator Oral Award

DIETARY SARGASSUM FUSIFORME IMPROVES MEMORY AND REDUCES AMYLOID PLAQUE LOAD IN AN ALZHEIMER'S DISEASE MOUSE MODEL

Jeroen Bogie[1], Cindy Hoeks[2], Melissa Schepers[2], Assia Tiane[2], Ann Cuypers[2], Frank Leijten[3], Yupyn Chintapakorn[4], Dicky Struik[5], Hong-bing Liu[6], Niels Hellings[2], Pilar Martinez-Martinez[7], Johan Jonker[5], Ilse Dewachter[1], Jochen Walter[8], Jerome Hendriks[1], Albert Groen[9], Bart Staels[10], Dieter Lutjohann[8], Tim Vanmierlo[1], Monique Mulder[3]

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Aim: Activation of liver X receptors (LXRs) by synthetic agonists was found to improve cognition in Alzheimer's disease (AD) mice. However, these LXR agonists induce hypertriglyceridemia and hepatic steatosis, hampering their use in the clinic. We hypothesized that phytosterols as LXR agonists enhance cognition in AD without affecting plasma and hepatic triglycerides.

Method & Results: Phytosterols previously reported to activate LXRs were tested in a luciferase-based LXR reporter assay. Using this assay, we found that phytosterols commonly present in a Western type diet in physiological concentrations do not activate LXRs. However, a lipid extract of the 24(S)-Saringosterol-containing seaweed *Sargassum fusiforme* did potently activate LXRβ. Dietary supplementation of crude *Sargassum fusiforme* or a *Sargassum fusiforme*-derived lipid extract to AD mice significantly improved short-term memory and reduced hippocampal Aβ plaque load by 81%. Notably, none of the side effects typically induced by full synthetic LXR agonists were observed. In contrast, administration of the synthetic LXRa activator, AZ876, did not improve cognition and resulted in the accumulation of lipid droplets in the liver. Administration of *Sargassum fusiforme*-derived 24(S)-Saringosterol to cultured neurons reduced the secretion of $A\beta_{42}$. Moreover, conditioned medium from 24(S)-Saringosterol-treated astrocytes added to microglia increased phagocytosis of Ab.

Conclusions: Our data show that *Sargassum fusiforme* improves cognition and alleviates AD pathology. This may be explained at least partly by 24(S)-Saringosterol-mediated LXRb activation.

HIGH-DENSITY LIPOPROTEIN DEFICIENCY IN TRANSGENIC ALZHEIMER'S DISEASE MICE INCREASES GLOBAL AND VASCULAR SPECIFIC AMYLOID PATHOLOGY AND NEUROINFLAMMATION

Emily Button[1], Guilaine Boyce[1], Anna Wilkinson[1], Sophie Stukas[1], Arooj Hayat[1], Jianjia Fan[1], Brennan Wadsworth[1], Jerome Robert[1], Kris Martens[2], Cheryl Wellington[1]

[1]University of British Columbia, Vancouver, Canada. [2]West Virginia University, Morgantown, USA

Aim: Alzheimer's disease (AD) is defined by amyloid beta (Aβ) plaques and neurofibrillary tangles and characterized by neurodegeneration and memory loss. Most AD patients also have Aβ deposition in cerebral vessels known as cerebral amyloid angiopathy (CAA), microhemorrhages, and vascular co-morbidities, suggesting cerebrovascular dysfunction contributes to AD etiology. Promoting cerebrovascular resilience may therefore be a promising therapeutic or preventative strategy for AD. Plasma high-density lipoproteins (HDL) have several vasoprotective functions, are associated with reduced AD risk in some epidemiological studies, improve pathology and memory in AD model mice, and prevent CAA in 3D bioengineered arteries. Here we investigate the interaction of HDL, amyloid, and inflammation on the cerebrovasculature in AD model mice.

Method: APP/PS1 mice, with human transgenes causing them develop brain Aβ plaques, were bred with apoA-I-deficient mice and aged to 12 months. Plasma lipids, amyloid plaque deposition, Aβ protein levels, protein and mRNA markers of neuroinflammation, and astrogliosis were assessed using ELISA, qRT-PCR, and immunofluorescence.

Results: APP/PS1 mice without apoA-I had worse amyloid pathology and neuroinflammation both globally and specifically on cerebral vessels. Specifically, apoA-I-deficient mice had increased parenchymal amyloid beta in the cortex and increased total brain levels of intercellular adhesion molecule 1 (ICAM-1) and of the reactive astrocyte marker glial fibrillary acidic protein (GFAP). Additionally, apoA-I-deficient mice had significantly elevated cortical vascular amyloid as well as cortical and hippocampal ICAM-1 and GFAP specifically associated with endothelial cells. Loss of apoA-I also increased the reactivity of astrocytes to parenchymal and vascular amyloid beta.

Conclusions: ApoA-I-containing HDL can reduce amyloid pathology, cerebrovascular inflammation, and astrocyte reactivity to parenchymal and vascular amyloid in amyloid beta expressing mice.

Eligible for Young Investigator Oral Award

GENETIC INHIBITION OF *CETP* AND RISK OF ISCHEMIC HEART DISEASE, CARDIOVASCULAR MORTALITY, AGE-RELATED MACULAR DEGENERATION, AND DEMENTIA

Liv Tybjærg Nordestgaard[1,2], Bo Kobberø Lauridsen[3,2], Mette Christoffersen[1,2], Shoaib Afzal[4,2], Børge Nordestgaard[5,2], Ruth Frikke-Schmidt[1,2], Anne Tybjærg-Hansen[1,2]

[1]Department of Clinical Biochemistry, Rigshospitalet, Copenhagen, Denmark. [2]University of Copenhagen, Copenhagen, Denmark. [3]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark. [4]Deparment of Clinical Biochemistry, Herlev-Gentofte Hospital, Herlev, Denmark. [5]Department of Clinical Biochemistry, Herlev-Gentofte Hospital, Herlev, Denmark

Aim: Raising high-density lipoprotein (HDL) cholesterol has been heralded as a potential therapeutic to reduce the residual risk of cardiovascular disease after optimal treatment of low-density lipoprotein (LDL) cholesterol. One of the most prominent drug classes explored when attempting to raise HDL cholesterol, have been inhibitors of cholesteryl ester transfer protein (CETP). CETP facilitates the exchange of triglycerides for cholesteryl esters between triglyceride-rich lipoproteins and HDL particles. Thus, inhibition of CETP would result in an overall favorable lipid profile of high levels of potentially beneficial HDL cholesterol and low levels of non-HDL cholesterol. However, this strategy has fueled several failed randomized controlled trials, and side effects such as age-related macular degeneration (AMD) and dementia have been suggested. Our aim was to test whether genetic inhibition of *CETP*, mimicking treatment with CETP inhibitors, was associated with risk of ischemic heart disease (IHD), cardiovascular mortality, age-related macular degeneration, vascular dementia, and Alzheimer's dementia.

Method: We genotyped 8 common variants in *CETP* in two general population studies (n=103,000 combined) and created a weighted allele score (WAS) based on the non-HDL cholesterol-lowering effects of the individual variants. We then investigated the association between the WAS and risk of IHD, cardiovascular mortality, AMD, vascular dementia and Alzheimer's dementia.

Results; The WAS associated with 2.3% lower non-HDL cholesterol levels and 11.3% higher HDL cholesterol for highest versus lowest tertile of non-HDL cholesterol. The corresponding hazard ratios (95% confidence intervals) were 0.92(0.87-0.97) for IHD, 0.90(0.83-0.97) for cardiovascular mortality, 1.32(1.17-1.48) for AMD, 0.74(0.58-0.96) for vascular dementia, and 1.03(0.96-1.12) for Alzheimer's dementia.

Conclusions; Genetic inhibition of *CETP*, mimicking treatment with CETP inhibitors, was associated with lower risk of IHD, cardiovascular mortality, and vascular dementia, but with an even higher risk of AMD. This suggests that AMD is a likely, long term side-effect of pharmacological CETP inhibition.

Eligible for Young Investigator Oral Award

THE BIOLOGICAL FUNCTION OF CETP: MODULATION OF HDL TO RESOLVE INFECTIONS

Lisanne Blauw[1], Mark Trinder [2], Yanan Wang[1], Raymond Noordam[1], Sebastian Soidinsalo[3], Peter Würtz[3], Ko Willems van Dijk[1], John Boyd[2], Liam Brunham[2], Patrick Rensen[1]

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Aim: CETP is primarily produced by hepatic resting macrophages and bacterial LPS rapidly decreases CETP expression and raises HDL. Since HDL-C declines during sepsis, and lower HDL-C levels are associated with worse survival, we hypothesized that LPS sensing by hepatic macrophages elevates HDL to combat the underlying infection. Here, we aimed to evaluate the effects of CETP on HDL composition and sepsis outcome.

Method: First, we used a genetic score for serum CETP concentration to estimate causal effects of CETP on 159 metabolic biomarkers (NMR; Nightingale platform) in the Netherlands Epidemiology of Obesity (NEO) study, to show that higher CETP concentrations were casually associated with less large HDL (largest effect XL-HDL-C, $P=6\times10^{-22}$). Next, we identified a rare missense variant in the CETP gene (rs1800777-A) that was associated with significant reductions in HDL-C levels during sepsis in 200 patients admitted to an emergency department (Early Infection cohort).

Results; We next examined the association of this genetic variant with 28-d survival and organ dysfunction. Carriers of the A allele (n=10) had decreased survival and more organ failure compared to non-carriers. We replicated this finding in the VASST (n=632) and SPHICU2 (n=302) cohorts, in which carriers of the A allele (n=35 and n=12, respectively) had significantly reduced 28-day survival. Mendelian randomization was consistent with genetically reduced HDL levels being a causal factor for decreased sepsis survival. Finally, pretreatment of APOE*3-Leiden.CETP mice with the CETP inhibitor anacetrapib increased HDL and markedly reduced the murine clinical assessment score for sepsis during endotoxemia, compared to vehicle.

Conclusions: Although CETP has been targeted to increase HDL-C and thereby lower CVD risk, we now identify CETP as a critical regulator of HDL to modulate clinical outcomes during sepsis. It is thus intriguing to propose that CETP inhibitors may be repurposed as drugs to promote clearance of bacterial infection.

Eligible for Young Investigator Oral Award

HEPATIC PPARa IS CRITICAL IN THE METABOLIC ADAPTATION TO SEPSIS

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Aim: Although the role of inflammation to combat infection is known, the contribution of metabolic changes in response to sepsis is poorly understood. Sepsis induces the release of lipid mediators, many of which are activators of nuclear receptors such as the peroxisome proliferator-activated receptor (PPAR)a, which controls both lipid metabolism and inflammation. However, the metabolic role of hepatic PPARa in the response to sepsis is unknown.

Method: Sepsis was induced by intraperitoneal injection of *Escherichia coli* in total, non-hematopoietic and hepatocyte-specific PPARa-deficient and WT mice. The systemic and hepatic metabolic response was analysed using biochemical, transcriptomic and mitochondrial respiration assays. PPARa expression was analysed in livers from elective surgery and critically ill patients and correlated with hepatic gene expression and blood parameters.

Results: Both total and non-hematopoietic PPARa-deficiency decreases survival upon bacterial infection in mice. Livers of septic PPARa-deficient mice displayed an impaired metabolic shift from glucose to lipid utilization resulting in more severe hypoglycemia, less pronounced hyperketonemia and increased steatosis due to lower expression of genes involved in fatty acid catabolism and ketogenesis, associated to decreased mitochondrial fatty acid utilization. Hepatocyte-specific deletion of PPARa was sufficient to decrease survival upon bacterial infection and impaired the metabolic response to sepsis. Hepatic PPARa expression was lower in critically ill patients and correlated positively with expression of the lipid metabolism genes, but not with the systemic inflammatory response.

Conclusions: These data demonstrate that metabolic control by PPARa in hepatocytes plays a key role in the host defense to infection.

Lipoproteins

MULTIVARIATE LIPOPROTEIN PHENOTYPING SUPPORTS THE CULPRIT ROLE OF APOLIPOPROTEIN B IN CORONARY HEART DISEASE

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Aim: To investigate the potential of lipoprotein data-driven population subgrouping in coronary heart disease (CHD) risk prediction.

Method: We used a multivariate artificial intelligence (AI) algorithm to define subgroups within a population-based cohort (N=5,789) based on their detailed lipoprotein profile (14 NMR-measured subclasses with particle counts, cholesterol and triglyceride content from each class). Subgroups were replicated in an independent cohort (N=7607) where the relative cardiovascular risk of groups was estimated using a cox proportional hazard model. The predictive power of the AI-based subgrouping was compared to subgrouping based on apoB quartiles.

Results: The AI algorithm identified four subgroups of individuals with various differences in their lipoprotein profiles as well as CHD risk. Subgroup characterized by the highest values for all non-HDL measures (particle, cholesterol and triglyceride) and apoB concentrations also represented the highest risk for CHD. Conversely, the subgroup characterized by the lowest values for these measures represented the lowest risk. Interestingly, the subgroup with elevated triglycerides and the subgroup with elevated cholesterol had substantially different VLDL and LDL subclass profiles, yet a comparable concentration of apoB and overlapping event curves. Thus, even though multidimensional and comprehensive data on lipoprotein subclass profiles were used, the apoB concentrations in the population subgroups appeared to be directly related to the CHD risk, with no apparent contribution from the assorted lipoprotein subclass-related cholesterol and triglyceride concentrations. By comparison, when the population was subgrouped simply by apoB quartiles, it stratified the groups even more distinctly into dose-dependent risk categories.

Conclusions: Our conclusions are twofold: 1) majority of lipoprotein-mediated CHD risk is driven by apoB and 2) we challenge the notion that more advanced lipoprotein profiling would improve risk prediction.

PHARMACOLOGICAL INHIBITION OF CIRCULATING PCSK9 BUT NOT INTESTINAL DEFICIENCY REDUCES POST-PRANDIAL LIPEMIA IN MICE

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Aim: Postprandial lipemia (PPL) is associated with atherosclerosis development and cardiovascular diseases. PCSK9 reduces plasma cholesterol by promoting LDLR degradation. We previously showed that PCSK9-deficiency reduced PPL by altering the intestinal chylomicron production and by increasing their hepatic catabolism. Our study aims: i) to assess the relative importance of intestinal PCSK9 in PPL regulation; ii) to assess the efficacy of an anti-PCSK9 monoclonal antibody on PPL in C57BL/6J and LDLR$^{-/-}$ mice; iii) to determine whether PCSK9-deficiency also reduced PPL in insulinopenic streptozotocin (STZ)-induced diabetic mice.

Method: PPL was measured in overnight fasted mice after a olive oil gavage. Insulinopenic diabetes was induced by a single high dose STZ injection (150 mg/kg) in PCSK9$^{+/+}$ & PCSK9$^{-/-}$ mice.

Results: By contrast with PCSK9$^{-/-}$ mice, intestinal-PCSK9$^{-/-}$ mice do not exhibit a reduced PPL compared to control PCSK9 floxed mice. Anti-PCSK9 monoclonal antibody injection (alirocumab, 10mg/kg) in 10-weeks-old C57BL/6J mice induced a significant reduction of the plasma cholesterol levels (-21%, P<0,001) and of postprandial TG levels. By contrast, alirocumab injection had no effect on plasma cholesterol or PPL in LDLR$^{-/-}$ mice. Finally, STZ induced severe hyperglycemia in PCSK9$^{+/+}$ and PCSK9$^{-/-}$ mice (respectively: 390.5±39.8 *vs* 425.2±38 mg/dL). Interestingly, PPL was highly increased in STZ-treated PCSK9$^{+/+}$ mice but not in STZ-treated PCSK9$^{-/-}$ mice.

Conclusions: PPL is significantly altered by full but not intestinal PCSK9-deficiency. PCSK9 monoclonal antibody mimics the effect of PCSK9-deficiency on PPL suggesting that circulating PCSK9 rather than intestinal PCSK9 is a critical regulator of PPL. Finally, we showed that PCSK9-deficiency protects against the PPL induced by insulinopenic diabetes.

Lipoproteins

DIETARY SATURATED FATS INCREASE AND PLANT STANOL ESTERS DECREASE LDL AGGREGATION

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Aim: We recently showed that LDL aggregation susceptibility predicts future cardiovascular deaths and depends on LDL surface lipid composition (Ruuth M, et al., Eur Heart J 2018). Now we examined if excess intake of macronutrients from saturated fats, unsaturated fats, or sugars affect LDL lipidomics and aggregation susceptibility. In addition, we studied if cholesterol-lowering plant stanol esters have an effect on LDL aggregation susceptibility.

Method: In overfeeding study participants (age: 48±2 y, BMI: 31±1 kg/m^2) consumed 1000 extra kcal/day for 3 weeks. Extra calories consisted of saturated fats (n=13), monounsaturated fats (n=11), or simple sugars (n=12). In the plant stanol ester study, subjects (age: 50.8±1 y, BMI: 25.2±0.4 kg/m^2) consumed plant stanol ester-enriched rapeseed oil-based spread (3.0 g of plant stanols/d) in intervention group (n=46) or the same spread without plant stanols (control group, n=46) for 6 months. Plasma samples were collected at baseline and at the end of the studies, LDL particles were isolated, and LDL aggregation was detected by dynamic light scattering. LDL lipidomics were analyzed with lipid mass spectrometry.

Results: Excess intake of saturated fats increased LDL aggregation susceptibility ($p<0.005$), and LDL-sphingomyelin content. Overfeeding unsaturated fats or simple sugars had no effect on LDL aggregation susceptibility, and only minor effects on LDL lipids. However, consumption of unsaturated fats decreased the amount of oxLDL and decreased the binding of LDL to human aortic proteoglycans. Consumption of plant stanol esters decreased LDL aggregation susceptibility ($p<0.001$) when compared to baseline, while control spread did not affect LDL aggregation susceptibility.

Conclusions: Excess consumption of saturated fats increases LDL aggregation susceptibility by affecting LDL lipids, while unsaturated fats decreases oxLDL and LDL binding to proteoglycans, sugars had no effect. Consumption of plant stanol ester-enriched spread decreases LDL aggregation susceptibility. Taken together, these dietary changes appear to influence, in addition to LDL levels, also LDL quality, and potentially the future risk of cardiovascular disease.

Eligible for Young Investigator Oral Award

HETEROGENEITY OF LDL UPTAKE RESPONSES IN INDIVIDUAL HYPERCHOLESTEROLEMIA PATIENTS

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Aim: Despite widespread genetic analyses, we understand little of how hypercholesterolemia evolves differently in individual patients. Cellular LDL receptor (LDLR) expression, translocation to the cell surface and ultimately LDL internalization governs clearance of blood LDL. Currently, we cannot readily measure these parameters from individual patients due to high cost and long turnaround times. We set up an automated platform that allows dissection of these cellular pathways in primary human cells with improved efficiency.

Method: We established a multi-parametric imaging platform for primary human peripheral blood mononuclear cells. This allows us to quantify LDLR mRNA and protein expression combined with LDLR cell surface abundance, LDL uptake and lipid storage at the single cell level from the same samples. We studied individuals with verified LDLR mutations from the METSIM (METabolic Syndrome In Men) cohort as well as hypercholesterolemic individuals lacking LDLR mutations from the FINRISK 2012 cohort. Up to date, we have analysed >60 patient samples.

Results: First, we show that our analysis of primary cells is superior to their immortalized counterparts, which display altered cellular lipid metabolism. For each patient we can quantify multiple cell populations with different LDL internalization rates under basal and stimulated conditions. We observe substantial differences in LDL internalization and LDLR surface abundance in individuals bearing identical mutations in the LDLR gene. Additionally, we demonstrate that individuals without LDLR mutations may have decreased LDL uptake. Reduced LDL uptake is often accompanied by increased cellular lipid storage, indicative of reprogrammed lipid metabolism.

Conclusions: Our automated profiling of primary blood cells enables an unprecedented quantitative characterization of functional defects in hypercholesterolemia patients. This provides novel insights into the underlying disease mechanisms for individual patients and has the potential to improve diagnosis and clinical care in the future.

Lipoproteins

A DISORDERED ACIDIC DOMAIN IN GPIHBP1 HARBORING A SULFATED TYROSINE REGULATES LIPOPROTEIN LIPASE

Kristian Kølby Kristensen[1], Søren Midtgaard[2], Simon Mysling[3], Oleg Kovrov[4], Lars Hansen[5], Anne Beigneux[6], Birthe Kragelund[7], Gunilla Olivecrona[4], Stephen Young[6], Thomas Jørgensen[3], Loren Fong[6], Michael Ploug[1]

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Aim: Lipoprotein lipase (LPL) is the rate-limiting enzyme of intravascular lipolysis. As the gate-keeping enzyme of energy-rich FFAs, LPL is tightly regulated by both intrinsic (enzyme instability) and extrinsic (ANGPTLs and Apolipoproteins) factors. To reach LPLs site of action in the capillary lumen LPL needs to be transported by the small endothelial protein, GPIHBP1. GPIHBP1 is a two domain protein consisting of a folded LU-domain and a negatively charged intrinsically disordered acidic region (IDR).

Method: In this study we investigated the role of the acidic domain of GPIHBP1 on its different biological functions and identified a tyrosyl-O-sulfation in the acidic domain using advanced biophysical methods (SPR, SAXS, HDX-MS) as well as biochemical experiments (LPL activity assays).

Results: First, we found that the IDR of GPIHBP1 increases the affinity for LPL by >250 fold and that the tyrosyl-O-sulfation adds to this affinity. Second, we found that the protecting effects of GPIHBP1 against ANGPTL4-catalyzed unfolding of LPL critically depends on its acidic IDR, and that the tyrosyl-O-sulfate assist in this process ensuring that LPL activity remains focalized on the cell surface. Third, we show that the acidic IDR of GPIHBP1 is indispensable for mobilization of LPL from a HSPG bound pool, and that the tyrosine sulfation potentiates this effect. Fourth, we generated a model of GPIHBP1 based on SAXS analysis, where the acidic domain structure occupies a large space.

Conclusions: Combined this study present an extensive characterization of the functional properties of the acidic domain of GPIHBP1, providing a detailed molecular understanding of the dynamic regulation of LPL activity in the capillary unit, which could assist future studies on intervention strategies regulating elevated TG levels.

Eligible for Young Investigator Oral Award

THE IMPACTS OF ANGIOPOIETIN-LIKE PROTEIN 3 DEFICIENCY ON SERUM LIPOPROTEIN MEASURES AND LIPIDOME – COMPARISON WITH OMICS DATA FROM ANGPTL3 SILENCED HEPATOCYTES

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Aim: Loss-of-function (LOF) variants in angiopoietin-like 3 (*ANGPTL3*) are associated with low levels of plasma lipoproteins (Lp) and decreased CAD risk. We aimed to determine serum Lp profiles and lipid compositions of genetic ANGPTL3 deficiency in human subjects, and whether these can be correlated with gene expression and lipid metabolism of ANGPTL3-depleted immortalized human hepatocytes (IHH).

Method: *ANGPTL3* S17X mutation carriers (6 homozygous and 32 heterozygous) and 38 controls were studied. NMR metabolomics was employed to quantify Lp measures. VLDL, LDL and HDL from 5 homozygous LOF subjects and 10 controls, and ANGPTL3-depleted IHH were subjected to ESI-MS/MS lipidomics and GC fatty acid (FA) analysis. NG-RNA sequencing was carried out on the IHH.

Results: Under fasting, ANGPTL3 deficiency was characterized by a reduction in LDL cholesterol (0.74 SD-units lower concentration per LOF allele) and many triglyceride(TG)-rich lipoprotein (TRL) measures, including VLDL cholesterol (0.75 SD units). Within TRLs and their remnants, the relative proportion of cholesterol was reduced. Homozygous LOF carriers showed essentially no postprandial increase in TRLs and FA. Saturated FA were enriched and polyunsaturated FA (PUFA) reduced in the VLDL and LDL of *ANGPTL3* LOF carriers. In the ANGPTL3-depleted IHH, in contrast, PUFA were evelated, mainly in cholesterol esters (CE), phosphatidyl-cholines, -ethanolamines and –inositols. Of note, total CE and CE synthesis were reduced, coinciding with a drastic downregulation of *SOAT1* mRNA.

Conclusions: ANGPTL3 deficiency results in a reduction of the proportion of cholesterol within TRLs and their remnants. The Lp lipidome of ANGPTL3 deficient subjects differs from that of ANGPTL3-depleted hepatocytes, suggesting that most of the changes arise from altered Lp metabolism in circulation. The reduction of CE in TRL could reflect a dampening of hepatic CE synthesis, impaired synthesis by LCAT due to altered substrate quality, or altered CETP function. The results support a cardioprotective effect of therapeutic ANGPTL3 inhibition.

HYPOXIA-INDUCED LIPID DROPLET-ASSOCIATED (HILPDA) INCREASES LIPID ACCUMULATION IN MACROPHAGES AND HEPATOCYTES VIA ATGL-DEPENDENT AND -INDEPENDENT MECHANISMS

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Aim: Lipid droplets are very dynamic organelles that can rapidly expand or shrink, driven by fluctuations in the rate of triglyceride synthesis and degradation. The synthesis of triglycerides, their storage in lipid droplets, and the subsequent breakdown of triglycerides into fatty acids are governed by a complex set of enzymes and lipid droplet-associated proteins. A relatively novel lipid droplet-associated protein that is abundant in macrophages and hepatocytes is HILPDA. Here we aimed to better characterize the physiological role and mechanism of action of HILPDA in macrophages and hepatocytes.

Method: Biochemical and microscopic analyses in Hilpda-deficient primary macrophages and hepatocytes, and metabolic analyses in macrophage and hepatocyte-specific Hilpda-deficient mice.

Results: In both cultured macrophages and hepatocytes, expression of Hilpda was highly induced by fatty acids. HILPDA deficiency in bone marrow-derived macrophages markedly reduced intracellular lipid levels and accumulation of fluorescently-labeled fatty acids in lipid droplets. Decreased lipid storage in HILPDA-deficient macrophages could be almost completely rescued by inhibition of adipose triglyceride lipase (ATGL) and was associated with increased oxidative metabolism. HILPDA deficiency in mouse precision cut liver slices and primary hepatocytes reduced lipid storage and accumulation of fluorescently-labeled fatty acids in lipid droplets, respectively, which was independent of ATGL. Real-time fluorescence imaging indicated that Hilpda preferentially localizes to active lipid droplets that are being remodelled.

Conclusions: Our data indicate that HILPDA is highly induced by lipids, preferentially associates with active lipid droplets, and promotes lipid storage in macrophages and hepatocytes via ATGL-dependent and independent mechanisms.

CONTRIBUTION OF NEUTRAL LIPOLYSIS ON THE CATABOLISM OF CYTOSOLIC LIPID DROPLETS IN THE SMALL INTESTINE

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Aim: Systemic lipid levels are mainly determined by dietary lipid absorption and lipoprotein secretion by enterocytes of the small intestine (SI). Excessive triglycerides (TGs), originating from apical (diet) or basolateral (lipoprotein remnants) lipid uptake, are transiently stored in form of cytosolic lipid droplets (cLDs). Mobilization of this intracellular lipid pool is believed to sustain peripheral lipid supply in interprandial periods, however, the underlying mechanism(s) and enzyme(s) involved are still elusive. As mice lacking adipose TG lipase (ATGL) in the gut displayed massive accumulation of cLDs, we hypothesize that the enzymatic pathway accountable for the catabolism of intestinal cLDs involves ATGL and its co-activator CGI-58.

Method: To prevent systemic effects of ATGL/CGI-58 deficiency, we generated mice lacking both proteins exclusively in the SI (Atgl/Cgi-58 iDKO).

Results: Loss of intestinal ATGL/CGI-58 resulted in cLD accumulation within enterocytes, independent of the diet. Alimentary lipids failed to accumulate in the SI of iDKO mice in the early phase of absorption, but got incorporated into cLDs 2 h post-gavage. These findings together with persistent cLD accumulation after restriction to endogenous lipids (fat-free diet feeding, prolonged fasting) indicated the existence of a secretion/reuptake cycle in enterocytes. In line, accumulation of intravenously applied VLDL particles in the proximal SI of iDKO mice highlighted the role of intestinal ATGL/CGI-58 in the hydrolysis of a basolaterally-derived lipid pool.

Conclusions: This study identified ATGL and CGI-58 as critical players in the catabolism of an intestinal lipid storage pool, consisting of lipids re-absorbed basolaterally rather than alimentary lipids. Furthermore, fatty acids released by ATGL/CGI-58-mediated hydrolysis in the SI are not destined for chylomicron synthesis but more likely used for energy production and PPARa signaling.

Eligible for Young Investigator Oral Award

ESTABLISHMENT OF A MODEL TO INVESTIGATE THE IMPACT OF PERILIPIN 5 MEDIATED PERIDROPLET MITOCHONDRIA FORMATION

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Aim: Perilipin 5 (PLIN5) decorates lipid droplets (LD) in oxidative tissues and regulates triacylglycerol (TG) mobilization by interaction with adipose triglyceride lipase (ATGL) and its co-activator comparative gene identification 58 (CGI-58). Furthermore, PLIN5 tethers mitochondria to LDs via its C-terminus. Such peridroplet mitochondria (PDM) were recently identified as a mitochondrial subpopulation with increased ATP synthase capacity, facilitating incorporation of acyl-CoA into the TG pool. We hypothesize that PLIN5-mediated PDM formation is crucial to maintain cellular lipid and redox homeostasis. Enhanced fatty acid (FA) activation and esterification via PDM may protect mitochondria from excessive FA influx and oxidative damage. Therefore, we aimed to characterize the PLIN5 interaction with ATGL, CGI-58 and mitochondria in detail, to establish an adequate cell culture model for further studies.

Method: We generated C2C12 myoblasts stably expressing PLIN5 to investigate its impact on lipid homeostasis and respiration. Next, we studied the interaction of C-terminally truncated PLIN5 variants with mitochondria by fluorescence microscopy. Furthermore, we characterized the interaction of wild type or mutant PLIN5 with ATGL or CGI-58, respectively, by co-immunoprecipitation (IP).

Results: PLIN5 overexpression elevated cellular TG levels by 52%, reduced TG hydrolysis during serum starvation and significantly increased maximal respiratory rate upon stimulation. Microscopy analysis revealed that truncation of the last three amino acids (AA) of PLIN5 was sufficient to prevent PDM formation. Moreover, we found that AA 423-443 of murine PLIN5 are essential for interaction with ATGL. At last, a PLIN5(S155E) mutant mimicking phosphorylation of a crucial PKA target site exhibited decreased binding affinity for CGI-58 but not ATGL.

Conclusions: We established a PLIN5 mutant variant that interacts normally with ATGL and CGI-58 but does not trigger PDM formation. This allows us to investigate the impact of PDM on cellular lipid and redox homeostasis in a model, where lipolysis is not compromised by altered interaction with lipolytic proteins.

Eligible for Young Investigator Oral Award

THE ROLE OF THE LXR-EEPD1 AXIS IN CHOLESTEROL METABOLISM

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Aim: We have recently reported that Endonuclease/Exonuclease/Phosphatase family Domain containing 1 (EEPD1) is a target of the sterol responsive nuclear Liver X Receptor (LXR) in macrophages (Nelson et al, ATVB, 2017). In both human and rodent macrophage-like cell lines EEPD1 was required for maximal ABCA1-mediated cholesterol efflux towards ApoAI. The aim of this study is to further characterize the physiological role of EEPD1 in lipid metabolism.

Method: To study the physiological role of EEPD1 we used CRISPR/Cas9-based methodology to generate EEPD1-KO mice. We are evaluating the function of EEPD1 specifically in bone marrow-derived macrophages (BMDM), and also in whole-body lipid metabolism. In BMDMs we studied cholesterol efflux and distribution, the inflammatory response, and profiled the transcriptional landscape using RNAseq. To investigate the role of EEPD1 in systemic lipid and energy metabolism EEPD1-KO and control mice are being challenged with a high fat diet (HFD).

Results: In BMDMs we found that EEPD1-deficient macrophages have decreased maximal cholesterol efflux to ApoA1, supporting our previous report. Furthermore, we observed that intracellular distribution of cholesterol in EEPD1-deficient macrophages is distinct from that observed in control macrophages. This observation may be related to our finding using RNAseq that the expression of cholesterol biosynthetic genes was reduced in EEPD1-deficient macrophages. Our *in vivo* results from the HFD experiment suggest that EEPD1 KO mice are more susceptible to weight gain than WT mice following a HFD and the existence of a difference in the levels of plasma triglyceride levels between these two mouse lines.

Conclusions: Our ongoing experiments further support a role for EEPD1 in regulation of cellular and systemic lipid homeostasis.

Eligible for Young Investigator Oral Award

Adipose tissue

ANTI-PCSK9 TREATMENT ENHANCES BENEFICIAL EFFECTS OF BROWN FAT ACTIVATION ON CHOLESTEROL METABOLISM IN APOE*3-LEIDEN.CETP MICE

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Aim: Brown fat activation-mediated lipolytic processing of VLDL promotes the clearance of the cholesterol-enriched remnants via hepatic LDLR and increases HDL levels and functionality, thus improving dyslipidemia and ameliorating atherosclerosis development in mice. We hypothesized that LDLR-mediated remnant clearance is rate-limiting in the beneficial cardiometabolic effects of brown fat activation. Since proprotein convertase subtilisin/kexin type 9 (PCSK9) targets the LDLR for degradation, we now aimed to investigate effects of anti-PCSK9 treatment on top of brown fat activation on cholesterol metabolism and atherosclerosis development.

Method: *APOE*3-Leiden.CETP* mice were fed a Western-type diet and treated with or without the anti-PCSK9 antibody Alirocumab weekly. After two weeks, both groups of mice were randomized and received either the selective β3-adrenergic receptor (AR) agonist CL316,243 or saline for another 3 weeks to assess effects on [^{14}C]cholesteryl ester and [^{3}H]phospholipid double-labeled VLDL-like particle clearance or 12 weeks to assess atherosclerosis development in the aortic root.

Results: Compared to placebo treatment, the β3-AR agonist, the anti-PCSK9 antibody and their combination caused a step-wise decrease in plasma total cholesterol and non-HDL-cholesterol (up to -42% and -48%; P<0.001), explained by a step-wise increase in the hepatic uptake of [^{14}C]cholesteryl ester (up to +36%, P<0.001). In addition, β3-AR agonism alone promoted the transfer [^{3}H]phospholipid to HDL (approx. +30%) which was further accelerated by anti-PCSK9 antibody (approx. +45%), both of which increased plasma HDL-C levels (+26% and +36%, P<0.01). Furthermore, anti-PCSK9 treatment on top of β3-AR agonism further reduced atherosclerotic lesion area (-68%; P<0.001) and lesion severity as compared to β3-AR agonism alone.

Conclusions: Anti-PCSK9 treatment on top of brown fat activation further accelerates the hepatic clearance of cholesterol-enriched remnants and promotes HDL remodeling, thus further improving dyslipidemia and reducing atherosclerosis development. We anticipate that the combination of brown fat activation and anti-PCSK9 treatment is a promising strategy to reduce atherosclerosis development.

Eligible for Young Investigator Oral Award

p53-DRIVEN miRNA-92a EXPRESSION AS POTENTIAL REGULATOR OF BAT ACTIVITY UNDER FASTING

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Aim: Our body's ability to adapt to varying metabolic demands is a crucial determinant of health span. Brown adipose tissue (BAT) dissipates energy to drive thermogenesis under cold-stress, through sympathetic activation and by taking up large amounts of fatty acids and glucose from circulation. The aim of this study was to elucidate molecular mechanisms that prevent futile energy dissipation of BAT under fasting, when energy substrates need to be conserved and directed to the brain.

Method: We investigated BAT from mice fasted for 24 hours and kept below thermo-neutrality using transcriptomics, miRNA-sequencing and bioinformatics analyses.

Results: Bioinformatics analyses of the BAT transcriptome of fasted mice revealed p53 signalling as top upregulated pathway while oxidative phosphorylation (OXPHOS) was downregulated. From p53 binding site predictions and miRNA-sequencing results, we identified miRNA-92a-1-5p as possible p53 target upregulated under nutrient deprivation. Circulating miRNA-92a-1-5p was previously described as marker for BAT activity in humans and has predicted seed matches in mRNAs of Pgc1a and Pgc1β, two master regulators of mitochondrial biosynthesis, providing a potential link between p53 activation and reduced OXPHOS under starvation. Indeed, in a mouse brown adipocyte cell line, overexpression of miRNA-92a-1-5p via miRNA mimics modulates Pgc1 and Glut expression.

Conclusions: Our data suggest p53 as a possible activator of miRNA-92-1-5p expression in fasted BAT, leading to a reduction of OXPHOS and glucose uptake via regulation of Pgc1 and Glut mRNA levels. Thus we propose a potential mechanism to curtail energy dissipation in BAT in times of nutrient scarcity.

Eligible for Young Investigator Oral Award

Adipose tissue

CIRCADIAN RHYTHM OF GLUCOCORTICOIDS REGULATES BROWN ADIPOSE TISSUE ACTIVITY AND IS IMPORTANT FOR MAINTAINING METABOLIC HEALTH

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Aim: Circulating levels of glucocorticoids display diurnal fluctuations, and are known to act as an internal synchronizer of many peripheral tissues. Interestingly, the primary glucocorticoid in mice, corticosterone (CORT), is known to influence brown adipose tissue (BAT) activity. In this study, we explored whether the circadian rhythm of CORT determines rhythmic BAT activity and metabolic health in mice.

Method: At regular intervals over a 24 h period, plasma was collected from C57Bl/6J mice to measure CORT levels, and tissue-specific uptake of radiolabeled fatty acids was determined to evaluate BAT activity. To investigate whether CORT rhythm dictates BAT activity rhythm, mice were subcutaneously implanted with pellets releasing a continuous low dose of CORT. These CORT pellets were implanted in both wildtype and APOE*3-Leiden.CETP mice, the latter being a model for hyperlipidemia and metabolic syndrome.

Results: We found that the rhythmicity in plasma CORT levels closely coincides with rhythmic activity of BAT, i.e. highest uptake of fatty acids for combustion at the start of the wakeful period. Implantation of CORT pellets flattened the circulating levels of CORT (i.e. similar morning and evening levels intermediate to those found normally at the circadian peak). Strikingly, flattened CORT rhythm was accompanied by a loss of circadian rhythm in BAT. In APOE*3-Leiden.CETP mice, flattened CORT increased fat mass (+2.8 g, $P<0.05$), and induced lipid accumulation in white adipose tissue (+65%, $P<0.01$) and BAT (+43%, $P<0.05$), which was accompanied by delayed plasma clearance and reduced uptake of fatty acids by BAT (-51%, $P<0.001$) after 5 weeks of intervention.

Conclusions: Collectively, these results indicate that CORT rhythmicity dictates BAT activity, and that disturbance of this rhythm decreases BAT activity and adversely affects metabolic health. As many individuals use synthetic glucocorticoids, which affects the physiological glucocorticoid rhythm, this justifies further research on the interplay between glucocorticoids, BAT rhythm, and metabolic health in humans.

Eligible for Young Investigator Oral Award

ENDOTHELIAL LYSOSOMAL ACID LIPASE DEFICIENCY IMPAIRS WHITE ADIPOSE TISSUE BROWNING

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Aim: Brown adipose tissue (BAT) is able to combust fatty acids and other substrates to produce heat. Lipid uptake into BAT is not restricted to lipoprotein lipase (LPL)-mediated hydrolysis of triglyceride-rich lipoproteins (TRL), but also includes whole particle uptake by endothelial cells. The relevance for BAT function of endothelial TRL uptake and subsequent lysosomal processing is still unknown. We investigated the impact of impaired lipoprotein handling in endothelial-specific lysosomal acid lipase (LAL)-deficient mice with regard to BAT functionality and thermogenesis.

Method: Tamoxifen-inducible endothelial-specific LAL knockout ($Lipa^{-/-}Cdh5^{Tam\text{-}cre}$) mice were fed chow or Western-type diet and exposed to a cold environment. Magnetic-activated cell sorting (MACS) was used for cell type-specific analyses. Gene and protein expression in WAT and BAT, metabolic turnover studies and indirect calorimetry were employed to examine thermogenic adipose function. Cell culture experiments with primary cells were conducted to investigate the LAL-dependent signaling mechanisms involved in thermogenic differentiation.

Results: MACS confirmed the specific LAL knockout in endothelial cells. Lipid uptake studies with radiotracers showed an accumulation of cholesterol and triolein in LAL-deficient endothelial cells indicating delayed lipid processing. *In vivo*, $Lipa^{-/-}Cdh5^{Tam\text{-}cre}$mice displayed only minor differences in BAT lipid uptake and beta3-adrenergic induced thermogenesis, what might be due to the compensatory induction of LPL and UCP1. Cold acclimation resulted in impaired thermogenic capacity accompanied by reduced browning of white adipose tissue (WAT), in WTD, but not chow-fed mice. While BAT appears unaltered, LAL activity is essential for differentiation of beige adipocytes in WAT depots. The impaired browning was reproduced in primary adipocytes during differentiation in cell culture.

Conclusions: Our data show the relevance of endothelial lipoprotein handling in thermogenic adipose tissue function. Lysosomal lipoprotein processing is necessary for proper cold adaptation, since endothelial LAL-deficiency leads to impaired browning of WAT depots.

Eligible for Young Investigator Oral Award

Adipose tissue

LOSS OF ADIPOCYTE WASH COMPLEX REDUCES BROWN AND WHITE ADIPOSE TISSUE MASS

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Aim: Metabolic syndrome (MetS) is a serious consequence of diet-induced obesity characterized by increased cardiovascular risk factor such as hypertension, dyslipidemia and glucose intolerance. Therefore, it is crucial to understand the mechanism by which dietary fat causes obesity. We recently uncovered that the WASH complex – a component of the endosomal sorting machinery – is crucial for the endosomal recycling of the members of the LDLR family, including LRP1. LRP1 is essential for adipose triglyceride-rich lipoproteins (TGLR) uptake, glucose metabolism, and energy expenditure, but whether adipose LRP1 functioning also depends on WASH remains unclear. Here, we investigated the contribution of adipose WASH in lipid and glucose metabolism.

Method: The WASH complex was depleted in adipocytes by crossing *Washc1*$^{flox/flox}$ mice with *aP2-Cre* mice (*ad-Washc1*), mice were fed a chow diet and body weight gain was determined. At an age of 22 weeks, mice were sacrificed, adipose tissue mass was determined and glucose, total cholesterol and triglyceride (TG) levels were measured. The expression of the WASH components, LRP1 and GLUT4 were determined on RNA and protein level.

Results: Successful ablation of WASHC1 in adipocytes resulted in reduced body weight gain due to a reduction in total fat mass. Brown adipose tissue (BAT) mass was decreased by ±20% in *Ad-Washc1* mice compared with wild-type (WT) litter-mates. Histological analysis of fat tissues revealed smaller-sized and fewer lipid droplets in brown adipocytes. The size of adipocytes in WAT of *ad-Washc1* was also reduced. Blood glucose, total cholesterol and triglyceride levels were not affected in *Ad-Washc1* mice after 4 hours fasting. The decrease of fat mass was not due to differences in *Upc1* expression in BAT. Immunoblot analysis showed that loss of WASH reduced the protein expression of LRP1, but not GLUT4, in BAT.

Conclusions: Although additional experiments are currently being performed, our preliminary data suggest that WASH is essential for adipocyte energy homeostasis, likely through regulating the functioning of LRP1 in adipocytes.

INHIBITION OF PRMT3 ACTIVITY REDUCES HEPATIC STEATOSIS WITHOUT ALTERING ATHEROSCLEROSIS SUSCEPTIBILITY IN APOE KNOCKOUT MICE

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Aim: The nuclear receptor liver X receptor (LXR) impacts on cholesterol metabolism as well as hepatic lipogenesis via transcriptional regulation. It is proposed that inhibition of the protein arginine methyltransferase 3 (PRMT3) uncouples these two transcriptional pathways in vivo by acting as a specific lipogenic coactivator of LXR. Here we validated the hypothesis that treatment with the allosteric PRMT3 inhibitor SGC707 will diminish the hepatic steatosis extent, while leaving global cholesterol metabolism, important in cholesterol-driven pathologies like atherosclerosis, untouched.

Method: Twelve-week old hyperlipidemic apolipoprotein E knockout mice were fed a Western-type diet for six weeks to induce both hepatic steatosis and atherosclerosis. The mice received 3 intraperitoneal injections with SGC707 or solvent control per week.

Results: Mice chronically treated with SGC707 developed less severe hepatic steatosis as exemplified by the 51% reduced ($P < 0.05$) liver triglyceride levels. In contrast, the extent of in vivo macrophage foam cell formation and aortic root atherosclerosis was not affected by SGC707 treatment. Interestingly, SGC707-treated mice gained 94% less body weight ($P < 0.05$), which was paralleled by changes in white adipose tissue morphology, i.e. reduction in adipocyte size and browning.

Conclusions: We have shown that through PRMT3 inhibitor treatment specific functions of LXR involved in respectively the development of fatty liver disease and atherosclerosis can be uncoupled, resulting in an overall diminished hepatic steatosis extent without a negative impact on atherosclerosis susceptibility. As such, our studies highlight that PRMT3 inhibition may constitute a novel therapeutic approach to limit the development of fatty liver disease in humans.

Fatty liver

THE ACUTE RESPONSE OF HEPATIC FAT CONTENT TO HIGH-FAT LOAD IS MORE PRONOUNCED IN SUBJECTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE THAN IN CONTROL SUBJECTS

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Aim: The excessive consumption of fat contributes to current epidemics of non-alcoholic fatty liver disease (NAFLD). However, the role of dietary fat in development of hepatosteatosis has not been fully elucidated. Therefore, using ^{3}H-magnetic resonance spectroscopy (MRS) we studied the acute response of hepatic fat content (HFC) to high-fat load in healthy control subjects and in non-obese subjects with hepatosteatosis.

Method: Ten male healthy volunteers (BMI: 26.9±2.7 kg/m^2; HFC 1.8±0.8 %) and 7 non-obese male subjects with NAFLD (BMI: 27.4±2.3 kg/m^2; HFC 12.3±5.7%) underwent 2 experiments lasting 8 hours. HFC was determined using MRS three times in each experiment – after overnight fast and three (T=3h) and six hours (T=6h) after consumption of 150 g of fat (dairy cream) at T=0 h. In control experiment subjects fasted. Plasma triglyceride (TG), non-esterified fatty acids (NEFA), glucose, and insulin were monitored throughout the experiments.

Results: There was no difference in baseline TG, NEFA, glucose, and insulin concentrations between groups. HFC increased six hours after consumption of 150 g of fat in both groups. Importantly, the increase was 3.5 times higher in steatotic than in control subjects: 0.90±0.42% (from 12.60±8.13% to 13.50±8.00%, p=0.001) versus 0.26±0.27% (from 1.99±1.28% to 2.25±1.34%, p=0.013), p=0.006. There was no difference in the response of triglyceridemia and glycemia to fat load, however NAFLD subjects had higher response of NEFA evaluated as an area under increment curve (NEFA AUIC) and also higher insulin AUIC. It remains to be clarified whether ineffective suppression of lipolysis in adipose tissue play a role in higher accrual of liver fat in subjects with steatosis.

Conclusions: The subjects with hepatosteatosis accrue more liver fat immediately after high-fat load than control subjects.

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POSTPRANDIAL CHANGES IN CIRCULATING LIPOPROTEIN-ASSOCIATED MICRORNAS DISTRIBUTION

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Aim: After meal intake, a transient elevation of triglycerides reflecting the appearance of triglyceride-rich lipoprotein particles (TRL) is observed. We recently identified that postprandial phase is associated with significant increase in plasma levels of various miR candidates (miR-Cand). Circulating miRs can be found associated with lipoproteins, mainly HDL particles. The aim of the study was to identify preferential intravascular lipoprotein-associated postprandial miRs.

Method: Lipoproteins were isolated from plasma by sequential ultracentrifugation. Then, miRs were extracted and expression levels were determined by real time PCR. Lipoprotein-miR levels were reported as relative quantitative value normalized by housekeeping RNU6 gene ($2^{-\Delta Ct}$). MiR levels were equally expressed per mg of lipoprotein mass.

Results: We observed a significant increase in postprandial TRL-miR-Cand levels as compared to fasting state (4.1-fold, $p=0.04$; 5.7-fold, $p<0.05$ and 5.1-fold, $p=0.02$ for miR-Cand 1, miR-Cand 2 and miR-Cand 3, respectively). Such increase was significantly correlated ($p<0.03$) with postprandial elevation in plasma TG levels. Expression of miR-Cand levels relative to mg of TRL mass revealed a significant increased content of miR-Cand 1 (3.7-fold, $p=0.018$) and miR-Cand 3 (9-fold, $p=0.009$) per postprandial TRL particles. We equally observed a specific reduction in miR-Cand 1 levels per mg of postprandial HDL mass (-80%; $p=0.004$), thus suggesting that postprandial phase is associated with an intravascular redistribution of miR-Cand 1 from HDL towards TRL. In fasting state, approximately 15% of lipoprotein associated-miR-Cand 1 or miR-Cand 3 levels were detected within TRL whereas postprandial TRL were identified as the preferential carriers of both miR-Cand 1 and miR-Cand 3, accounting for at least 65% of total circulating lipoprotein-associated miR-Cand 1 and miR-Cand-3 levels.

Conclusions: For the first time our study reveals association of miRs with postprandial TRL particles and indicate that postprandial phase is characterized by a specific lipoprotein-associated miRs signature. We are currently deciphering molecular mechanisms underlying relationship between miR-Cand and TRL metabolism.

Eligible for Young Investigator Oral Award

Fatty liver

A MAMMALIAN HAPLOID GENETIC SCREEN IDENTIFIES THE ERAD-ASSOCIATED E3 UBIQUITIN LIGASE MARCH6 AS A NOVEL DETERMINANT OF HEPATIC FATTY ACID AND LIPOPROTEIN METABOLISM

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Aim: Disturbed lipid metabolism is a key feature of cardiovascular and hepatic diseases. To identify new genes and elucidate cellular mechanisms that govern lipid homeostatic pathways we developed lipid-focused haploid mammalian genetic screens. We employed this approach to follow native and tagged endogenous proteins associated with lipid-regulating pathways, and identified the ER-resident E3 ubiquitin ligase MARCH6 as a post-transcriptional regulator of the rate-limiting enzyme in cholesterol biosynthesis SQLE. The physiological role of MARCH6 in lipid and lipoprotein metabolism is unknown.

Method: To study the *in vivo* physiological role of MARCH6 we developed mouse models with constitutive or conditional ablation of *March6*. Metabolic parameters were followed during physiological aging or a challenge with a high fat-containing diet (HFD). To identify altered metabolic processes we combined global transcriptomic and lipidomic analysis, and studies in primary hepatocytes.

Results: *March6*$^{(-/-)}$mice were born at a sub-Mendelian ratio precluding their study. We therefore studied mice with liver-specific ablation of *March6* (M6-LIV) and their control counterparts (WT-LIV). In two metabolic settings, physiological aging and a HFD challenge, no marked differences were seen in body-weight and glucose handling. Yet we observed a dramatic increase in abundance of lipid droplets and TG accumulation in livers of M6-LIV mice. Circulating plasma TGs were reduced in M6-LIV mice even though production and secretion of hepatic VLDL particles remained unchanged. RNAseq analysis of the hepatic transcriptome coupled with an unbiased lipidomic screen identified alterations in fatty acid saturation and synthesis. Most notably, *March6*loss led to activation of the SREBP1-mediated fatty acid synthesis program *in vivo*and in isolated primary hepatocytes, in line with enhanced SQLE-dependent production of endogenous LXR ligands.

Conclusions: Our results identify a MARCH6-SREBP1 axis as a central determinant of hepatic lipid metabolism, and further highlight the potential of haploid mammalian genetics to study lipid metabolism.

THE ROLE OF APOLIPOPROTEIN F IN THE CONTROL OF PLASMA AND HEPATIC LIPID METABOLISM

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Aim: NAFLD (Non-Alcoholic Fatty Liver Disease) is a chronic, progressive liver disease evolving from steatosis to steatohepatitis (NASH) and is associated with increased risk of mortality from cardiovascular disease (CVD). However, the molecular mechanisms of NAFLD development and its links to CVD remain poorly understood. We recently identified Apolipoprotein F (ApoF), a minor apolipoprotein present on LDL and HDL, whose hepatic expression is inversely correlated with steatosis and reduced by half in patients with NASH. Moreover, previous literature suggests ApoF overexpression in mice enhances reverse cholesterol transport. These results suggest ApoF may play a role in NAFLD or associated CVD development.

Method: To assess the role of ApoF in the control of plasma and hepatic lipid metabolism, we employed adenovirus mediated strategies to acutely overexpress or knockdown ApoF expression in the livers of C57Bl/6J mice.

Results: ApoF overexpression in mice reduces plasma TG levels, especially VLDL-TG. To test whether this was due to altered TG production or clearance, we measured hepatic VLDL-TG secretion and found, surprisingly, it was increased in mice overexpressing ApoF compared to controls. Likewise, ApoF reduction was associated with increased plasma VLDL-TG and decreased hepatic VLDL-TG production. Because we observed increased VLDL production but decreased plasma VLDL-TG in mice overexpressing ApoF, we hypothesize that TG clearance is also increased. To assess the effects of ApoF expression on TG clearance, we measured post-prandial TG excursion and *in vitro* lipase activity in post-heparin plasma from mice overexpressing ApoF. While post-prandial TG clearance was faster in ApoF overexpressing mice, we observed no change in either total or hepatic lipase activity, suggesting that ApoF may favor receptor-mediated TG removal from circulation by the liver or other peripheral tissues.

Conclusions: Because hypertriglyceridemia is an independent risk factor for CVD development, these results suggest ApoF may link NAFLD and altered lipoprotein metabolism.

Eligible for Young Investigator Oral Award

Fatty liver

IDENTIFICATION OF NOVEL REGULATORS OF CHOLESTEROL METABOLISM BY USING A MASS-SPECTROMETRY-BASED APPROACH

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Aim: Elevated plasma cholesterol levels majorly contribute to the development of cardiovascular disease. A main regulator of plasma cholesterol levels is the protein PCSK9 that lowers the levels of the LDL receptor. PCSK9 is now being targeted by new therapeutics to lower plasma cholesterol levels. Many aspects of PCSK9 biology - especially on the intracellular level - remain, however, ill defined. Therefore, the aim of this project is to identify interacting partners of PCSK9 by using a technique called BioID and to identify novel proteins implicated in PCSK9 biology and cholesterol metabolism.

Method: We overexpressed BirA-tagged PCSK9-WT in immortalized human hepatocytes (IHH) and promoted the biotinylation of proteins in close proximity of or interacting with PCSK9. Upon isolation of biotinylated proteins, we subjected these proteins to LC-MS/MS for identification. To determine the functional relevance of the identified proteins, we used a custom-made siRNA library to individually knockdown all identified proteins. Upon knockdown, we determined the secretion of PCSK9 and apolipoprotein B (APOB) from these cells. We further characterized a smaller number of proteins using western blot, immunoprecipitation, ELISA and FACS to determine, among others, their interaction with PCSK9 and their impact on LDL internalization in IHH.

Results: By using BioID we identified 110 proteins that were significantly enriched in IHH over-expressing PCSK9-BirA. Following the knockdown of all identified proteins, we selected 5 proteins that significantly impacted PCSK9 and/or APOB secretion for a more extensive characterization. The characterization of these proteins is currently on going.

Conclusions: We successfully identified 5 putative PCSK9 partners that could impact cholesterol metabolism. Further characterization is needed to clarify the exact function of the identified proteins. We anticipate that this characterization might help to better understand intracellular PCSK9 biology and could provide novel clues for the therapeutic lowering of plasma cholesterol levels.

Eligible for Young Investigator Oral Award

TISSUE SELECTIVE PCSK9-KO MICE PRESENT ALTERED GLUCOSE METABOLISM PANCREATIC FUNCTION AND INSULIN RELEASE

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Aim: *PCSK9* genetic polymorphisms are associated with lower LDL-Cholesterol levels but also with higher plasma glucose levels and increased risk of developing T2D while therapy against PCSK9 did not show any correlation on increased risk of New onset diabetes. We investigated the molecular mechanisms beyond this association.

Method: *Pcsk9*KO, WT, albumin (*Alb)Cre+/Pcsk9*$^{LoxP/LoxP}$(liver selective *Pcsk9*-KO mice) and Pdx1 (*Pdx1)Cre+/Pcsk9*$^{LoxP/LoxP}$(pancreas selective *Pcsk9*-KO mice) were used and fed for 20 week with chow diet and Standard Fed Diet. GTT, ITT, insulin and C-peptide plasma levels, pancreas morphology and cholesterol and triglycerides accumulation in pancreatic islets were studied in all different animal models.

Results: Glucose clearance was impaired in PCSK9 KO mice compare to WT and in (*Pdx1)Cre+/PCSK9fl/fl*compare to(*Pdx1)Cre-/PCSK9fl/fl*while no difference were observed in insulin tolerance. Glucose tolerance was not impaired in (*Alb)Cre+*mice fed with standard fat diet compared to WT animals; insulin sensitivity was not affected; both animal models showed a similar decrease in plasma glucose levels during ITT. A detailed analysis on (*Alb)Cre+*pancreas morphology revealed no difference in islets. (*Pdx1)Cre+*presented a similar phenotype observed in full PCSK9 KO mice.

Conclusions: The PCSK9/LDLr axis affects beta cell function and insulin secretion. Our current findings confirm our previous observation that this effect is related to local PCSK9 and support the observations available that anti-PCSK9 antibodies or liver specific therapies, such as siRNAs, have a limited impact on glucose metabolism as opposed to statins.

Eligible for Young Investigator Oral Award

Bile acids

THE ROLE OF THE ALTERNATIVE PATHWAY-DERIVED BILE ACIDS IN NAFLD PROGRESSION

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Aim: Brown adipose tissue (BAT) activation by cold exposure induces hepatic *Cyp7b1* expression, hence triggering the conversion of cholesterol to bile acids (BA) mainly through the alternative synthesis pathway. Increased BAT activity inversely correlates with NAFLD disease score and since BA exert anti-inflammatory properties we aim to investigate the potential role of Cyp7b1 derived-BA during NAFLD to NASH progression.

Method: *Cyp7b1*$^{-/-}$ and wild type (WT) mice were fed a choline-deficient high-fat diet (CD-HFD) for 8 months - an experimental model of diet-induced NASH - and were housed either at 30°C (thermoneutral conditions, control) or at 22°C (mild cold exposure) to stimulate BAT and the alternative BA synthesis pathway. Metabolic parameters, histology, gene expression and protein levels were analyzed. BA and oxysterol species were determined using an LC-MS/MS-based method.

Results: Prolonged mild cold exposure induced *Cyp7b1* expression in WT mice and attenuated NAFLD development compared to thermoneutral conditions in both genotypes, since plasma lipids and ALT activity as well as hepatic inflammation and fibrosis are reduced. Conversely, *Cyp7b1*$^{-/-}$ mice housed at 30°C have an aggravated NAFLD phenotype compared to WT, estimated by elevated expression of inflammatory and fibrotic gene markers, increased ALT activity, hyperlipidemia, hyperinsulinemia, hepatic steatosis and fibrosis. However, mild cold exposed *Cyp7b1*$^{-/-}$ mice show increased hepatic expression of *Cyp27a1* and *Ldlr* and seem to have an ameliorated disease phenotype, similar with their WT littermates.

Conclusions: Deletion of the alternative BA synthesis pathway seems to augment NAFLD progression, especially in 30°C, suggesting that the respective BA exert beneficial features during the manifestation of this disease in thermoneutral conditions. Upon mild cold exposure and BAT activation we observe a compensatory hepatic upregulation of *Cyp27a1* in the *Cyp7b1*$^{-/-}$ mice which, together with the increased *Ldlr* expression, could suggest an enhanced lipid metabolism, explaining some features leading to an improved disease phenotype.

Eligible for Young Investigator Oral Award

A HUMAN-LIKE COMPOSITION OF THE CIRCULATING BILE ACID POOL IMPACTS ON PLASMA LDL-CHOLESTEROL IN MICE

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Aim: Despite advances made with LDLc-lowering therapies, atherosclerotic cardiovascular disease (CVD) remains a major cause of death. Bile acids (BAs) affect cholesterol and lipid metabolism, inflammation, and insulin sensitivity by various means and serve as orchestrators of major CVD risk factors. However, translation of promising mechanistic pre-clinical data is hampered by marked species differences in BA metabolism. Unlike humans, mice produce muricholic acids (MCAs), which exert entirely different actions on the BA receptors FXR and TGR5 compared to the BA species present in humans. To allow evaluation of the interconnections between BAs and CVD risk factors, we have recently generated mice with a humanized BA metabolism.

Method: *Cyp2c70*, the gene encoding the enzyme proposed to be responsible for the production of MCAs in mice, was inactivated and parameters of BA, cholesterol and lipid metabolism were investigated.

Results: *Cyp2c70*-KO mice displayed a human-like BA composition with a high abundance of chenodeoxycholic acid, a prominent BA in humans, and undetectable MCAs. Bodyweight and plasma triglycerides were not affected but plasma cholesterol levels were significantly elevated in *Cyp2c70*-KO mice. Lipoprotein fractionation revealed that LDL-c was 2-fold higher in *Cyp2c70*-KO mice, while HDL-c remained unaltered. Hepatic cholesterol levels were increased, while triglycerides were decreased in livers of *Cyp2c70*-KO mice. Cholesterol synthesis was unchanged in *Cyp2c70*-KO mice, but biliary cholesterol secretion rates were higher compared to wild-type littermates.

Conclusions: *Cyp2c70*-deficiency induces a human-like BA pool composition in mice and has clear impact on cholesterol and lipoprotein metabolism. Our 'humanized' mice represent a unique new model to establish the interconnections between BAs and CVD risk.

Bile acids

MICE DEVOID OF MURINE BILE ACIDS DISPLAY A HUMAN-LIKE PHENOTYPE

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Aim: Mice and rats have higher cholesterol and bile acid (BA) synthesis than humans and faster clearance and lower levels of serum LDL cholesterol. Another species difference is that mice produce large amounts of hydrophilic 6-hydroxylated muricholic acids (MCAs) reported to antagonize FXR-agonistic BA-responses. Acute cholestasis in mice and rats, in contrast to humans, paradoxically increase BA synthesis and MCAs. We hypothesized that elevated antagonistic MCAs are responsible for these species differences and therefore studied the effects of deletion of the Cyp2c70 gene, postulated to catalyze their formation.

Method: Cyp2c70-KO mice were developed using CRISPR-Cas9 engineering. The phenotype was identified and bile duct ligation performed in WT and KO mice.

Results: Cyp2c70-KO mice were devoid of MCAs, and displayed >50% reduced BA and cholesterol syntheses and hepatic LDL receptor numbers while serum LDL increased. Despite the absence of intestinal FGF15 mRNA in both groups following bile duct ligation, the strong stimulation of BA synthesis observed in WT animals was abolished in KO mice.

Conclusions: We conclude that MCAs are of major importance for the WT mouse phenotype and suggest that the human-like Cyp2c70-KO model may be a useful tool in studies exploring compounds aimed at human therapy.

ATYPICAL BILE ACID SIGNALLING REGULATING ADIPOCYTE FORMATION

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Aim: Obesity has reached epidemic proportions and by association an increase in obesity associated co-morbidities is observed worldwide. Interestingly, not all obese individuals develop these co-morbidities for so far unknown reasons. One possible reason for this might be adipose tissue quality, which is dependent on various factors. Even though the number of adipocytes in adult humans is tightly controlled, it is nowadays accepted that in obese individuals adipose tissue mass increases as a consequence of an increase in the number of adipocytes (adipose tissue hyperplasia) as well as an increase in adipocyte size (adipose tissue hypertrophy). It has recently been shown that loss of *ROR-gamma* in mice protects from the development of diet-induced insulin resistance, due to increased adipocyte hyperplasia and reduced hepatic gluconeogenesis. Based on these findings and the fact that ROR-gamma is classified as an orphan receptor, we aimed to identify putative endogenous ligands, which could modulate its activity and thus be used to affect systemic energy metabolism by modulating adipose tissue and liver function.

Method: Through the analysis of ROR-gamma isolated from preadipocytes we were able to identity 1b-hydroxy-cholic acid as a putative ligand. Binding affinity was quantified using radiolabeled 1b-hydroxy-cholic acid, while repression of ROR-gamma was measured using a luciferase activity assay. To determine, whether adipose tissue formation can be regulated to affect systemic energy metabolism, we used a model of constitutive and inducible global ablation of ROR-gamma together with the newly identified ligand. Furthermore, 1b-hydroxy-cholic acid was used in different prevention and treatment models of diet induced obesity in mice.

Results: Through a lipidomic-based approach, we identified a 1b-hydroxy-cholic acid as a new natural ligand of ROR-gamma in adipose tissue and liver. We demonstrate that 1b-hydroxy-cholic acid is an inverse agonist of ROR-gamma with nM affinity and affects adipocyte formation as well as hepatic gluconeogenesis by regulating ROR-gamma target gene expression. Supplementation with 1b-hydroxy-cholic acid in vivo prevents the development of systemic insulin resistance by increasing adipocyte hyperplasia and improves diet-induced insulin resistant by lowering blood glucose and insulin. In humans, serum 1b-hydroxy-cholic acid plasma was reduced in obese diabetic patients and its levels inversely correlated with adipocyte size, indicating that 1b-hydroxy-cholic acid might contribute beneficially to metabolic control.

Conclusions: Our studies identify 1b-hydroxy-cholic acid as a novel ligand for ROR-gamma. While the exact mechanism how this ligand is formed in vivo remains unknown we demonstrate here that modulation of this receptor can restore metabolic control at least in part by improving adipose tissue quality. This is underscored by the association of circulating levels of 1b-hydroxy-cholic acid with diabetes in humans. Even though we excluded TGR5 and FXR as targets for 1b-hydroxy-cholic acid, it is possible that this ligand acts via other signaling pathways. Of interest is the physiological regulation of ROR-gamma activity, which to date remains elusive. Intermediates of cholesterol biosynthesis as well as oxysterols have been described as potent agonists of the ROR-gamma-T isoform and mediators of TH17 cell development indicating that endogenous metabolites are more likely to act as ligands of ROR-gamma rather than absorbed agents. In summary, we report the identification of a naturally occurring ROR-gamma inverse agonist, which regulates adipocyte formation and hepatic glucose output. 1b-hydroxy-cholic acid might thus serve as a nutritional intervention to prevent the development of metabolic disorders.

Bile acids

Δ24-Dehydrocholesterol reductase (DHCR24): a novel target for the treatment of NASH

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Aim: Δ24-Dehydrocholesterol reductase (DHCR24) is a crucial terminal enzyme in cholesterol biosynthesis converting the ultimate intermediate desmosterol into cholesterol. Desmosterol is an endogenous liver X receptor (LXR) ligand with anti-inflammatory properties and reduces cholesterol and fatty acid biosynthesis by suppressing signaling via sterol regulatory element binding protein 1c. We hypothesized that increasing desmosterol levels obtained via inhibiting DHCR24 reduces hepatic steatosis and inflammation, the two most important hallmarks of nonalcoholic steatohepatitis (NASH). Thus, by using the novel DHCR24 inhibitor SH42, characterized by high potency and selectivity, we aimed to investigate the therapeutic effects of DHCR24 inhibition on NASH development.

Method: *APOE*3-Leiden.CETP* mice, a well-established translational model for lipoprotein metabolism that develops diet-induced human-like NASH characteristics, were fed a high fat and cholesterol diet (HFCD) with or without simultaneous SH42 treatment. After 8 weeks, liver steatosis and inflammation were assessed. Lipidomics, lipid mediators and cholesterol biosynthesis analyses were carried out on plasma and liver.

Results: DHCR24 inhibition via SH42 treatment markedly increased plasma desmosterol levels (+5,600%), without influencing food intake nor affecting body weight and body composition during the whole time-frame of intervention. SH42 decreased plasma cholesterol esters (-24%) and fatty acid (-19%) levels whilst not affecting diacylglycerol (DAG) and triacylglycerol (TAG) levels. Notably, SH42 largely increased plasma 19,20-epoxydocosapentaenoic acid (19,20-EpDPA) levels (+210%), a well described and potent anti-inflammatory/pro-resolving lipid mediator. In the liver, SH42 reduced the neutral lipid content, namely DAG (-21%), TAG (-38%) and cholesteryl esters (-26%). Moreover, liver histological assessment showed that SH42 prevented HFCD-induced hepatic steatosis, inflammation, ballooning and crown-like structure formation.

Conclusions: Inhibition of DHCR24 by SH42 increases plasma desmosterol, accompanied by reduction of hepatic steatosis, inflammation and damage. We anticipate that DHCR24 inhibition is a potential novel therapeutic strategy for the treatment of NASH by killing two birds with one stone, i.e. inflammation as well as hepatic fat accumulation.

Poster presentations

Eligible for Young Investigator Poster Award:

Posters

01 Yara Abou Khalil (Paris, France) *

FROM FATTY STREAKS TO CULPRIT LESIONS, THE IMPACT OF PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9) ON HUMAN ATHEROSCLEROSIS LESIONS THROUGH SMOOTH MUSCLE CELL FUNCTIONS

02 Núria Amigó (Reus, Spain)

TYPE 1 DIABETES: ASSOCIATION BETWEEN ^{1}H-NMR PLASMA GLYCOPROTEINS AND SUBCLINICAL ATHEROSCLEROSIS

03 Lorenzo Arnaboldi (Milan, Italy)

SEPARATION, LIPID CHARACTERIZATION AND PHARMACOLOGICAL MODIFICATION OF EXTRACELLULAR VESICLES TO UNRAVEL THEIR FUNCTION. IN VITRO STUDIES FROM A LYMPH-NODE METASTATIC CELL LINE

04 Franco Bernini (Parma, Italy)

HIGH DENSITY LIPOPROTEIN FUNCTION IS REDUCED IN PATIENTS AFFECTED BY GENETIC OR IDIOPATHIC HYPOGONADISM

05 Anna Borup (Copenhagen, Denmark) *

EFFECTS OF APOM DEFICIENCY IN STREPTOZOTOCIN-INDUCED DIABETES

06 Rachel Byrne (Dublin, Ireland) *

COMPRENHENSIVE INVESTIGATION OF HIGH-DENSITY LIPOPROTEIN (HDL) FUNCTION AND COMPOSITION IN PRE-MENOPAUSAL WOMEN WITH TYPE 1 DIABETES MELLITUS (T1DM) VERSE TYPE 2 DIABETES MELLITUS (T2DM)

07 Emma Börgeson (Gothenburg, Sweden)

THERAPEUTIC POTENTIAL OF LIPOXINS IN HUMAN CARDIOMETABOLIC DISEASE

08 Oscar Chávez-Talavera (Lille, France) *

THE FUNCTIONAL RELEVANCE OF BILE ACIDS IN THE IMPROVEMENT OF HDL-MEDIATED ENDOTHELIAL PROTECTION AFTER BARIATRIC SURGERY

09 Christina Christoffersen (Copenhagen, Denmark)

EFFECT OF MENOPAUSE AND EXERCISE TRAINING ON PLASMA APOLIPOPROTEIN M AND SPHINGOSINE-1-PHOSPHATE

10 Veronica Cocetta (Padova, Italy)

LIPID-METABOLIC REPROGRAMMING IN OVARIAN CARCINOMA CELL LINE RESISTANT TO CISPLATIN

11 Nagila Damasceno (Sao Paulo, Brazil)

DEVELOPMENT OF SCORE OF FUNCTIONALITY OF HIGH-DENSITY LIPOPROTEIN (HDL-SCORE) AND ITS ASSOCIATION WITH CARDIOVASCULAR RISK FACTORS AND SUBCLINICAL ATHEROSCLEROSIS

12 Flavia De Conti Cartolano (Sao Paulo, Brazil) *

IMPACT OF OMEGA 3 INCORPORATION ON THE FUNCTIONALITY OF HIGH-DENSITY LIPOPROTEIN IN BRAZILIAN INDIVIDUALS

13 Thibaut Duparc (Toulouse, France)

ADDITIONAL PROTECTIVE EFFECT OF P2Y13 PURINERGIC RECEPTOR IN CARDIOMETABOLIC DISEASES : ROLE IN NON-ALCOHOLIC FATTY LIVER DISEASE

** Eligible for Young Investigator Oral Award*

14 Tereza Dusilová (Prague, Czech Republic) *

THE RESPONSE OF HEPATIC FAT CONTENT DETERMINED *IN VIVO* TO GLUCOSE ADMINISTRATION IS DYSREGULATED IN MEN WITH NON-ALCOHOLIC FAT LIVER DISEASE (NAFLD)

15 Anouk Feitsma (Amersfoort, The Netherlands)

MILK FORMULA WITH DIFFERENT GLYCATION PROFILE AND FAT BLENDS INFLUENCES GASTROINTESTINAL OUTCOMES IN CHINESE INFANTS: RESULTS FROM TWO CROSS-SECTIONAL STUDIES

16 Youmna Ghaleb (Paris, France) *

IMPLICATION OF LRP6 VARIANTS IN FAMILIAL HYPERCHOLESTEROLEMIA

17 Isabella Giacomini (Padova, Italy)

NATURAL COMPOUNDS AS POSSIBLE MODULATORS OF LIPID METABOLISM IN CISPLATIN-RESISTANT CANCER CELLS

18 Monica Gomaraschi (Milan, Italy)

HDL INHIBIT LDL-INDUCED PROLIFERATION OF PROSTATE CANCER CELLS: ROLE OF ABCA1

19 Gernot Grabner (Graz,Austria)

BIS(MONOACYLGLYCERO)PHOSPHATE (BMP) IN PHYSIOLOGY AND PATHOPHYSIOLOGY

20 Thomas Grewal (Sydney, Australia)

OBESITY COMPROMISES ANTI-CANCER DRUG EFFICACY IN BREAST CANCER

21 Stefan Hajny (Copenhagen, Denmark) *

ELEVATED PLASMA APOLIPOPROTEIN M LEVELS IMPAIR TRIGLYCERIDE TURNOVER IN MICE

22 Hiroaki Ikezaki (Fukuoka, Japan)

SMALL DENSE LOW DENSITY LIPOPROTEIN CHOLESTEROL PREDICT CAROTID INTIMAL MEDIAL THICKNESS PROGRESSION

23 Ida Juul Rasmussen (Copenhagen, Denmark) *

TEN YEAR ABSOLUTE DEMENTIA RISK SCORE FOR IMPROVED RISK STRATIFICATION IN THE POPULATION - A TOOL FOR STRATIFIED CLINICAL TRIALS AND TARGETED PREVENTION

24 Vasily Kudinov (Moscow, Russian Federation)

EFFECTS OF A NEW PHARMACOLOGICAL AGENT BASED ON ULTRA-SMALL PHOSPHOLIPID NANOPARTICLES (MICELLES) IN THE TREATMENT OF COMBINED HYPERLIPIDEMIA

25 Folkert Kuipers (Groningen, The Netherlands)

ALTERED BILE ACID KINETICS CONTRIBUTE TO POSTPRANDIAL HYPOGLYCEMIA AFTER ROUX-EN-Y GASTRIC BYPASS SURGERY

26 Laurent Martinez (Toulouse, France)

LIRAGLUTIDE IMPROVES HEPATIC STEATOSIS AND METABOLIC DYSFUNCTIONS IN A 3-WEEK DIETARY MOUSE MODEL OF NON-ALCOHOLIC STEATOHEPATITIS

27 Borja Martinez-Tellez (Leiden, The Netherlands) *

THE EFFECT OF MIRABEGRON ON ENERGY EXPENDITURE, BROWN ADIPOSE TISSUE AND THE LIPIDOMIC PROFILE IN HEALTHY LEAN SOUTH ASIAN AND WHITE CAUCASIAN MEN

** Eligible for Young Investigator Oral Award*

Posters

28 Manabu Niimi (Chuo, Japan)

ENDOTHELIAL LIPASE ATTENUATES CHOLESTEROL DIET-INDUCED HYPERCHOLESTEROLEMIA AND PROTECTS AGAINST ATHEROSCLEROSIS IN TRANSGENIC RABBITS

29 Polyxeni Papadea (Patras, Greece) *

DEVELOPMENT OF RELIABLE CLINICAL RISK INDICATORS FOR ATHEROSCLEROTIC DISEASES BASED ON OXIDISED LDL

30 Mira Pauly (Hamburg, Germany) *

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31 Matteo Pedrelli (Huddinge, Sweden)

GENERATION OF A NEW HEPATOCYTE MODEL FOR STUDIES OF HUMAN LIPID METABOLISM

32 Aashley Sardjoe Mishre (Leiden, The Netherlands) *

MRI AS A NOVEL TOOL FOR NON-INVASIVE IMAGING OF BROWN ADIPOSE TISSUE

33 Tina Schönberger (Essen, Germany) *

ROLE OF HYPOXIA ON LIPID SIGNALING

34 Mahnaz Shariatzadeh (Rotterdam, The Netherlands) *

IMPACT OF LIPOPROTEIN(a) ON *IN VITRO* ANGIOGENESIS

35 Olga Snip (Leiden, The Netherlands) *

REDUCED SYSTEMIC INFLAMMATION AND INCREASED REVERSE CHOLESTEROL TRANSPORT TOGETHER DRIVE LEUKOCYTE ABCA1-MEDIATED PROTECTION AGAINST ATHEROSCLEROSIS

36 Herbert Stangl (Vienna, Austria)

INTERACTION OF LIPOPROTEIN PARTICLES WITH LIPID BILAYERS

37 Line Stattau Bisgaard (Copenhagen, Denmark) *

KIDNEY DERIVED APOM AND ITS ROLE IN ACUTE KIDNEY INJURY

38 Vasily Sukhorukov (Moscow, Russian Federation) *

THE ROLE OF GENES ASSOCIATED WITH ENDOPLASMIC RETICULUM STRESS AND INFLAMMATION IN THE FOAM CELL FORMATION

39 Vasily Sukhorukov (Moscow, Russian Federation)

GENES POTENTIALLY RESPONSIBLE FOR INTRACELLULAR CHOLESTEROL ACCUMULATION CAUSED BY ATHEROGENIC MODIFIED LDL

40 Anne Tailleux (Lille, France)

PLASMA BILE ACIDS DO NOT PREDICT THE CONVERSION FROM PREDIABETES TO TYPE 2 DIABETES: RESULTS FROM A PROSPECTIVE STUDY IN THE IT-DIAB COHORT

41 Ko Willems van Dijk (Leiden, The Netherlands)

GENETICS OF POSTPRANDIAL PLASMA METABOLITE CONCENTRATIONS

42 Robin van Eenige (Leiden, The Netherlands) *

GIPR/GLP1R DUAL AGONISM STIMULATES VLDL-TRIGLYCERIDE TURNOVER AND HEPATIC REMNANT CLEARANCE

** Eligible for Young Investigator Oral Award*

43 Dongdong Wang (Zurich, Switzerland)

S1PRS REGULATE THE ACTIVITY OF SR-B1 IN ENDOTHELIAL CELLS ON BOTH THE TRANSCRIPTIONAL AND POST-TRANSLATIONAL LEVELS

44 Zhixiong Ying (Leiden, The Netherlands) *

DEVELOPMENT OF A NEW LIPID-BASED GOLD STANDARD TO QUANTIFY BROWN FAT ACTIVITY

45 Veronica Zampoleri (Milan, Italy) *

POST-PRANDIAL LIPEMIA AND CD36 EXPRESSION IN CIRCULATING CELLS

46 Qiaoqing Zhong (Changsha, China)

HIGH-DENSITY LIPOPROTEIN INCREASE THE UPTAKE OF OXIDIZED LOW DENSITY LIPOPROTEIN VIA PPARγ/CD36 PATHWAY IN INFLAMMATORY ADIPOCYTES

47 Katariina Öörni (Helsinki, Finland)

PHOSPHOPLIPASE A_2-MODIFIED LDL TRIGGERS WEIBEL PALADE BODY EXOCYTOSIS FROM ENDOTHELIAL CELLS

** Eligible for Young Investigator Oral Award*

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Mission of ELC

The European Lipoprotein Club (ELC) was established in 1977 in order to "promote active participation, collaboration and exchange of ideas concerning basic and clinical research on the structure, function and metabolism of lipoproteins in health and disease".

The ELC currently includes more than 500 scientists from about 40 countries, and the number grows every year. ELC is thus a Europe-wide network of basic scientists and clinicians, with world-wide collaborations with colleagues actively involved in lipoprotein research. The network is strengthened and expanded by contacts established at the ELC meetings, and fostered by the exchange of ideas, clinical material, techniques, and young visiting investigators.

The ELC organizes one scientific meeting every year in September, with particular emphasis on an active participation and in-depth discussion in an informal atmosphere. The meetings have been hosted since 1980 at the Evangelische Akademie in Tutzing, Germany. An organizing committee comprising 11 members, representing as many different European countries as possible, arranges the meetings. These representatives are elected by the members and serve for 5 years. One representative acts as the chairman of the ELC, and has the major responsibility for the meeting organization. From 1980 to 2011, the local organization was in the hands of the late Dr. Joachim Ziegenhorn and his colleagues from Boehringer Mannheim/Roche. From 2012 to 2018 the local organization has been undertaken by Dr. Joachim Siedel.

The current chairman is Prof. Patrick Rensen, Leiden, The Netherlands. Prof. Dagmar Kratky, Graz, Austria, acts as the treasurer. Several topics, selected by the organizing committee, are discussed at each meeting, in working sessions spread over 4 days. Anyone interested and involved in research in the lipoprotein field is invited to submit an abstract for the meeting. Participating individuals are selected for oral or poster presentation based on the relevance and scientific merit of their abstracts. Because of the size of the auditorium, and in order to maintain an atmosphere conducive to active discussion, participants are limited to approximately 100.

For many years, the ELC has been generously supported by Boehringer Mannheim, to the extent that all housing, dining and other conference facilities were being taken care of. At the 1998 meeting, after the take-over of Boehringer Mannheim by Hoffmann-LaRoche, representatives from Roche have generously continued the support of the ELC until 2012. Since 2013 the European Atherosclerosis Society (EAS) has been a sustained and major sponsor of the meeting, which has also been supported generously by the Deutsche Forschungsgemeinschaft (DFG) approximately every other year. A limited participation fee - covering registration, housing, and full board throughout the meeting - is required provided acceptance of participation.

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