Symposium 7

Lipid Remodeling and Adipocyte Biology in Metabolic Health and Disease

Chairpersons

Yun-Hee Lee
Seoul National University, Korea

Dae Ho Lee
Gachon University, Korea

Speakers

Emilio Mottillo
Henry Ford Hospital, USA

Maria Ulvmar
Uppsala University, Sweden

Dong Wook Choi
Korea University, Korea

Panel Discussion

Ja Hyun Koo
Seoul National University, Korea

Ki Yong Hong
Seoul National University, Korea

Emilio Mottillo

Henry Ford Hospital, USA

• Education

Period	Affiliation	Position
– **2008-2013**	Pathology, Wayne State University School of Medicine, Detroit, MI, USA	Ph.D.
– **2001-2003**	Biological Sciences, University of Windsor, Windsor, ON, Canada	M.Sc.
– **1996-2001**	Biological Sciences, University of Windsor, Windsor, ON, Canada	B.Sc.

• Affiliations / Experience

Period	Affiliation	Position
– **2023-Present**	Henry Ford Hospital, Detroit, MI, USA	Associate Scientist
– **2020-Present**	Physiology, Wayne State University	Assistant Professor Full-time Affiliate
– **2019-2023**	Henry Ford Hospital, Detroit, MI, USA	Assistant Scientist

• Committee Memberships

- Anamika Sharma, Doctoral
- Chisom Onu, Doctoral
- Diabetes Endocrinology and Metabolic Diseases, NIDDK, National Institutes of Health (NIH)

• Publications

- Guohua Chen, Zhou G., Zai L., Bao X., Li J.,Tiwari N., Mottillo E.P. and Jian Wang. Serine catabolism reduces fatty liver but promotes liver inflammation and fibrosis in mice. *Commun*. 12;7(1):173. doi: 10.1038/s42003-024-05861-y
- Rahman A.A., Butcko J.A., Songyekutu E., Granneman J.G., and Mottillo E.P. Direct effects of adipocyte lipolysis on AMPK through intracellular long-chain acyl-CoA signaling. *Scientific Reports*. 2; 14(1):19. doi: 10.1038/s41598-023-50903-w
- Mottillo E.P&, Ljiljana Mladenovic-Lucas, Huamei Zhang, Li Zhou Christopher V. Kelly, Pablo A. Ortiz and James G. Granneman. A FRET sensor for the real-time detection of long chain acyl-CoAs and synthetic ABHD5 ligands. Cell Reports Methods
- Kim H, Wei J, Song Z, Mottillo E.P., Samavati L, Zhang R, Li L, Chen X, Jena BP, Lin JD, Fang D, Zhang K. Regulation of hepatic circadian metabolism by the E3 ubiquitin ligase HRD1-controlled CREBH/PPARα transcriptional program. *Mol Metab*. 49:101192. PMID:33592335; PMCID: PMC7966871. Role: study conception, design, implementation. IF: 8.57 Citations: 11
- Mottillo E.P&, Huamei Zhang, Alexander Yang, Li Zhou and James G. Granneman. Genetically -encoded Sensors to detect fatty acid production and trafficking. *Mol Metab*. 29:55-64. &Corresponding author. PMID: 31668392 IF: 8.57 Citations: 11

Symposium 7

Role of Lipid Droplets in Health and Cardiometabolic Disease

Emilio Mottillo (Henry Ford Hospital, USA)

The balance between the storage and mobilization of triacylglycerol (TAG) is critical for metabolic health. TAG hydrolysis is regulated by the dynamic assembly of protein complexes on the surface of lipid droplets (LDs) in key metabolic tissues such as fat tissue and the liver. As such, Patatin Like Phospholipase Domain Containing 2 (PNPLA2)/Adipose Triglyceride lipase (ATGL), the major TAG lipase, is regulated by the co-lipase α/β hydrolase domain-containing 5 (ABHD5, also known as CGI-58). Importantly, the dysregulation of lipid metabolism is at the heart of cardiometabolic disease which encompasses cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD). Recently we demonstrated that PNPLA3, a close paralogue of PNPLA2 interacts with ABHD5. Of significance, a common human variant of PNPLA3, I148M, is the greatest single genetic risk factor for the development of non-alcoholic fatty liver disease (NAFLD). Notably, PNPLA3 I148M is a gain of function for the interaction with ABHD5 and functions to sequester ABHD5 away from PNPLA2, likely initiating TAG accumulation and subsequent NAFLD. This interaction between ABHD5 and PNPLA3 I148M represents a novel therapeutic target for NAFLD. Surprisingly, patients that carry the I148M mutation are protected from coronary artery disease. Our lab is currently investigating the mechanism by which PNPLA3 I148M causes NAFLD but protects from cardiac disease. Overall, by understanding the fundamental mechanisms of lipid storage and hydrolysis this will lead to novel therapies for treating cardiometabolic disease.

Maria Ulvmar

Uppsala University, Sweden

• Education

Period	Affiliation	Position
– **2009**	Karolinska Institute, Sweden	Ph.D.
– **2001**	Stockholm University, Sweden	M.Sc.

• Affiliations / Experience

Period	Affiliation	Position
– **2022-Present**	Uppsala University, (IMBIM), Sweden	Senior Lecturer Associate Professor
– **2017-2022**	Uppsala University, (IGP), Sweden	Group leader, Assistant Professor
– **2013-2017**	Uppsala University, Department of Immunology, Genetics and Pathology (IGP), Sweden	Senior Postdoctoral Fellow
– **2010-2013**	Birmingham University, Centre for Immune Regulation, United Kingdom	Marie Curie Postdoctoral Fellow (IEF FP7)

• Committee Memberships

- The Swedish Cancer Foundation, microbiology and immunology division
- Medical Research Council in the United Kingdom, Grant committee
- Auckland Medical Research Foundation, New Zealand, Grant committee
- U-CAN (Uppsala-Umeå Comprehensive Cancer Consortium) diagnosis-specific group breast cancer U-CAN (Uppsala-Umeå Comprehensive Cancer Consortium) diagnosis-specific group pancreatic and liver cancer
- European Vascular Biology Organisation (EVBO)

• Publications

- Bekkhus T, Olofsson A, Sun Y, Magnusson PU, Ulvmar M.H. Stromal transdifferentiation drives lipomatosis and induces extensive vascular remodeling in the aging human lymph node The Journal of Pathology. 259(3):236-253. doi: 10.1002/path.6030. Cover article
- Bekkhus T, Avenel C, Hanna S, Franzén Boger M, Klemm A, Bacovia DV, Wärnberg F, Wählby C, Ulvmar M.H.. Automated detection of vascular remodeling in tumor-draining lymph nodes by the deep-learning tool HEV-finder. *The Journal of Pathology*. 258(1):4-11. doi: 10.1002/path.5981. Cover article
- Bekkhus T., Martikainen T., Olofsson A., Franzen Boger M., Vasiliu Bacovia D., Warnberg F., Ulvmar M.H.: Remodeling of the Lymph Node High Endothelial Venules Reflects Tumor Invasiveness in Breast Cancer and is Associated with Dysregulation of Perivascular Stromal Cells. Cancers (Basel), doi: 10.3390/cancers13020211. Senior corresponding author. Selected as editors choice
- Xiang M., Adrián Grosso R., Takeda A., Pan J., Bekkhus T., Brulois K., Dermadi D., Nordling S., Vanlandewijck M., Jalkanen S., Ulvmar M.H.* and Butcher E.C.* A single-cell transcriptional roadmap of the mouse and human lymph node lymphatic vasculature. *Frontiers in Cardiovascular medicine* 7(52) doi: 10.3389/fcvm.00052 *Co-senior and corresponding author
- Ulvmar M.H., Werth K., Braun A., Kelay P., Hub E.,Eller K., Chan L., Lucas B., Novitzky-Basso I., Nakamura K., Rülicke T., Nibbs R.J., Worbs T., Förster R., Rot A. The atypical chemokine receptor CCRL1 shapes functional CCL21 gradients in lymph nodes. *Nature Immunology*, (7); 623-630. doi: 10.1038/ni.2889. Cover article

Symposium 7

Stromal Transdifferentiation Drives Lipomatosis and Induces Extensive Vascular Remodeling in the Aging Human Lymph Node

Maria Ulvmar (Uppsala University, Sweden)

Lymph node (LN) lipomatosis is a common but rarely discussed phenomenon associated with aging that involves a gradual exchange of the LN parenchyma into adipose tissue. The mechanisms behind these changes and the effects on the LN are unknown. We show that LN lipomatosis starts in the medullary regions of the human LN and link the initiation of lipomatosis to transdifferentiation of LN fibroblasts into adipocytes. The latter is associated with a downregulation of lymphotoxin beta expression. We also show that isolated medullary and CD34+ fibroblasts, in contrast to the reticular cells of the T-cell zone, display an inherently higher sensitivity for adipogenesis. Progression of lipomatosis leads to a gradual loss of the medullary lymphatic network, but at later stages, collecting-like lymphatic vessels are found inside the adipose tissue. The stromal dysregulation includes a dramatic remodeling and dilation of the high endothelial venules associated with reduced density of naïve T-cells. Abnormal clustering of plasma cells is also observed. Thus, LN lipomatosis causes widespread stromal dysfunction with consequences for the immune contexture of the human LN. Our data warrant an increased awareness of LN lipomatosis as a factor contributing to decreased immune functions in the elderly and in disease.

Dong Wook Choi

Korea University, Korea

• Education

Period	Affiliation	Position
– **2014**	Department of Biological Sciences, Sungkyunkwan University	Ph.D.
– **2010**	Department of Biological Sciences, Sungkyunkwan University	M.S.
– **2004-2008**	Department of Biological Sciences, Sungkyunkwan University	B.S.

• Affiliations / Experience

Period	Affiliation	Position
– **2023-Present**	Department of Biotechnology, College of Life Sciences and Biotechnology, Korea University	Associate Professor
– **2021**	Department of Biochemistry, College of Natural Sciences, Chungnam National University	Assistant Professor
– **2016**	Division of Metabolic Diseases, Department of Cancer Biology, Dana Farber Cancer Institute, Harvard Medical School	Research Fellow
– **2014**	Department of Biological Sciences, Sungkyunkwan University	Postdoctoral Fellow

• Committee Memberships

- KSBMB, Energy Metabolism Subcommittee
- KSBMB YSP, Committee / FAOBMB exhibition committee
- The Korean Association for Laboratory Science (KALAS) Webzine
- Korean Society for The Study of Obesity
- Korean Diabetes Association

• Publications

- Hepatic stellate cells facilitate ammonia detoxification via GPT1-driven alanine synthesis in hepatocellular carcinoma. *Under Review at Nature Metabolism*. *Co-corresponding Author
- A microbiota-derived metabolite, 3-phenyllactic acid, prolongs healthspan by enhancing mitochondrial function and stress resilience via SKN-1/ATFS-1. *Minor revision at Nature Communications*. *Co-corresponding Author
- MsrB1-regulated GAPDH oxidation plays programmatic roles in shaping metabolic and inflammatory signatures during macrophage activation. *Cell Reports*. 2022 Nov 8;41(6):111598. *Co-corresponding author
- Mitochondrial morphology controls fatty acid utilization by changing CPT1 sensitivity to malonyl-CoA. *EMBO Journal*. 2023 Mar 14;e111901 Co-first author
- HCF-1 regulates de novo lipogenesis through a nutrient sensitive complex with ChREBP. *Molecular Cell*. 2019 Jul 25;75(2):357-371 *Co-first author

Symposium 7

The Functional Relevance of a Microbiome-Derived SCFA in Reprogramming Hepatic Lipid Metabolism

Dong Wook Choi (Korea University, Korea)

A hepatocyte is the primary cell responsible for the metabolism of de novo synthesized, dietary, and microbiome-derived fuels to maintain systemic metabolic homeostasis. In this presentation, I will introduce a robust platform, stable isotope-based metabolic flux analysis, which enables the mapping and tracing of nutrient utilization within cellular metabolic processes. Specifically, I will discuss the hepatic alterations following propionate (Prop) treatment, a three-carbon short-chain fatty acid predominantly produced by the gut microbiome in mammals. Propionate-treated hepatocytes exhibit a distinctive metabolic profile, including the significant reprogramming of TCA cycle carbon flux into amino acids, facilitating the synthesis of phosphatidylcholine (PC). This rerouted carbon flux into PC is potentially significant for driving hepatic lipoprotein clearance. Additionally, this metabolic reprogramming, coupled with the hepatic regulation of adipose tissues, may play a vital role in enhancing systemic lipid metabolism, as demonstrated in an in vivo mouse model of propionate administration. In summary, our study comprehensively mapped the hepatic remodeling induced by propionate, elucidating its intricate regulatory mechanisms underlying the beneficial effects of a microbiome-derived metabolite on host metabolism.