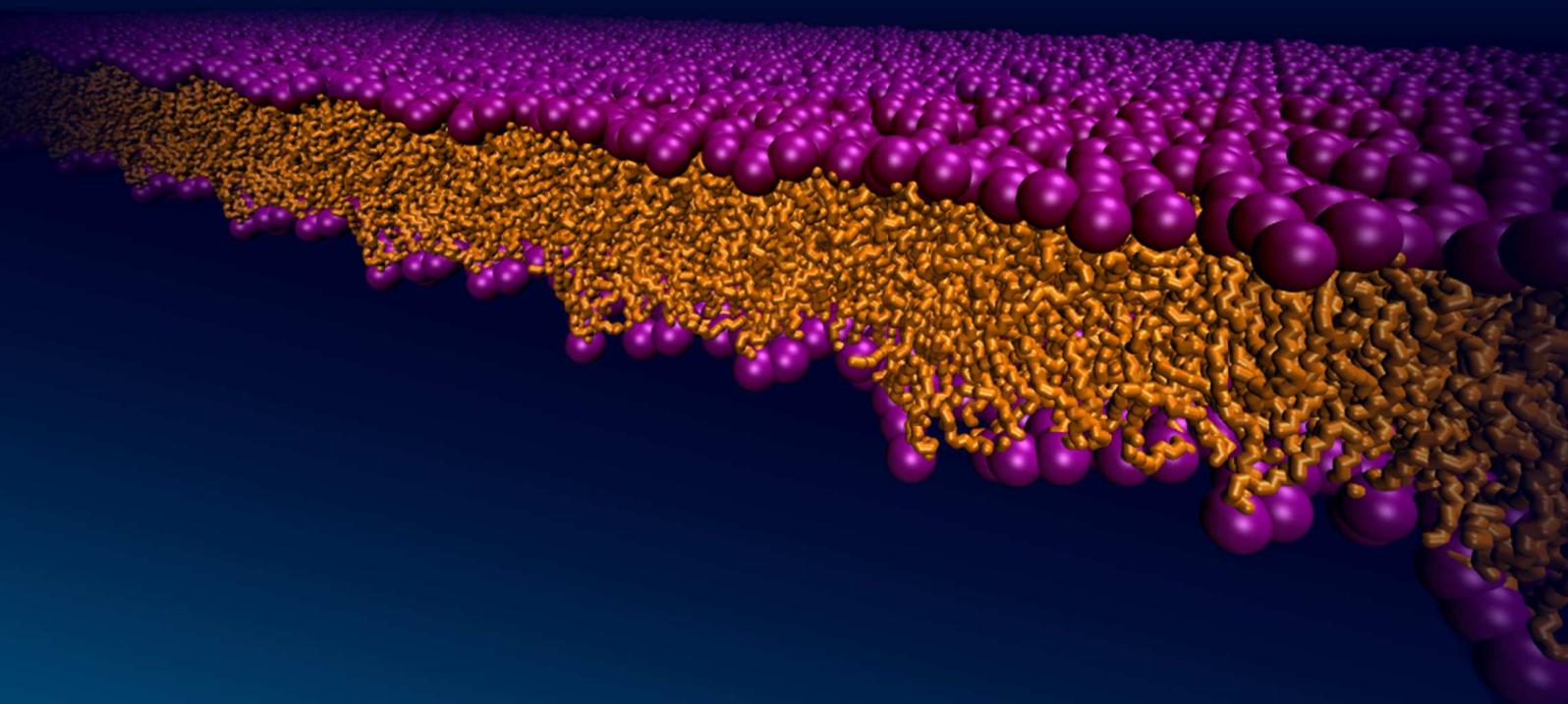


EVOLUTION OF LIPIDS



LIPIDS IN EVOLUTION



NOV. 8 - 10, 2012
RIKEN, JAPAN

Evolution of Lipids – Lipids in Evolution

Nov 8th - Thursday

- 13:15 Opening remarks (**Peter Greimel**)
- 13:15 **Toshihide Kobayashi** *Chair: Howard Riezman*
“Evolution of Lipid – Lipids in Evolution”
- 14:00 **Akihiko Nakano**
“Evolutionary View on the Mechanisms and Pathways of Membrane Traffic”
- 15:00 *Coffee break*
- 15:30 **Haruhiko Yao** *Chair: Toshihide Kobayashi*
“High-resolution calorimetric study of intermediate phases near the main transition in short-chain phosphatidylcholines”
- 16:00 **Toyoshi Fujimoto**
“Distribution of membrane lipids in yeasts and mammals”
- 17:00 **Hui Hui Tan**
“Spectroscopic Evidence of an Endosome-Specific Lipid: Towards Elucidation of the BMP Biosynthetic Pathway”
- 18:00 *Conference mixer (not included in registration fee)*
- 20:30 Round table (invited speakers & organizers only)

Nov 9th - Friday

- 9:30 **Teymuras Kurzchalia** *Chair: Yoshio Hirabayashi*
“Maradolipids, dauer larva specific structural glycolipids in *Caenorhabditis elegans*”
- 10:30 *Coffee break*
- 11:00 **Masato Umeda**
“Lipid biology using *Drosophila melanogaster* as a model animal”
- 12:00 *Lunch break*
- 13:30 **Yeon-Jeong Kim** *Chair: Teymuras Kurzchalia*
“GPRC5B activates obesity-associated adipose inflammatory signaling”
- 14:00 **Yoshio Hirabayashi**
“Evolution and membrane glycolipid synthesis - Conserved roles of glucosylated lipids”
- 15:00 *Coffee break*
- 15:30 **Francoise Hullin-Matsuda** *Chair: Nario Tomishige*
“Limonoid compounds inhibit sphingomyelin biosynthesis in mammal cells by preventing ceramide extraction from the endoplasmic reticulum”
- 16:00 **Kentaro Hanada**
“Co-evolution of SM and CERT: Diverse lipids may require co-evolution of enzymes and trafficking systems”
- 20:30 White board session (invited speakers & organizers only)

Nov 10th - Saturday

- 10:00 **Howard Riezman** *Chair: Takuma Kishimoto*
“Sterols and Sphingolipid Homeostasis and Functions in Model Organisms”
- 11:00 **Makoto Ito**
“Lipids in Single Cell Organisms: Unity in Diversity and Diversity in Unity”
- 12:00 Closing remarks

Evolution of Lipids and Lipids in Evolution

Toshihide Kobayashi

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One of the characteristic features of lipids is their diversity. Whereas some lipids are maintained during evolution, some of them are observed only in a subset of organisms.

There are many questions on the lipids in evolution, such as:

1. Why are there so many lipids?
2. Why yeasts contain ergosterol as their main sterol whereas human beings have cholesterol?
3. Why sphingomyelin appears only in higher eukaryotes?
4. Why phosphatidylethanolamine and cardiolipin are observed from bacteria to mammals whereas phosphatidylcholine is detected only in eukaryotes?
5. Why eukaryotes and bacteria contain phospholipids with mainly sn-3 glycerophosphate backbone whereas archaea have sn-1 glycerophosphate backbone?

Of course it is difficult to find simple answers to these questions. However, I would like to take the advantage of having this forum to seriously discuss such fundamental and often ignored questions. Provocative ideas of (mentally) young participants are welcome!

Evolution of Lipids – Lipids in Evolution

Notes

Evolutionary View on the Mechanisms and Pathways of Membrane Traffic

Akihiko Nakano

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Membrane trafficking is one of the fundamental processes well conserved in eukaryotes. Common mechanisms consist of vesicle budding from a donor membrane, and tethering and fusion with a target membrane. However, significant differences exist among fungi (e.g. yeast), animals (e.g. mammals) and plants.

In this conference I will describe some studies of my group on yeast and plants from an evolutionary point of view and compare them with the knowledge in mammals. In particular, I will discuss 1) diversity and complexity of the post-Golgi network, 2) organization of the Golgi apparatus, and 3) modes of transport from the endoplasmic reticulum to the Golgi apparatus. Regarding this, I would like to speculate on the roles of lipids in membrane curvature formation.

Evolution of Lipids – Lipids in Evolution

Notes

Spectroscopic Evidence of an Endosome-Specific Lipid: Towards Elucidation of the BMP Biosynthetic Pathway

H.H. Tan, A. Makino, F. Hullin-Matsuda, K. Sudesh, P. Greimel, T. Kobayashi

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The endosome-specific lipid bis(monoacylglycero)phosphate (BMP) is a structural isomer of phosphatidylglycerol (PG), featuring two glycerol subunits linked via a phosphodiester bond. Unlike other mammalian phospholipids, it has been proposed that BMP exhibits an unusual stereochemical configuration, where the phosphodiester moiety is linked to position *sn*-1 and *sn*-1' of the glycerol subunits. Despite the intriguing roles of this lipid in both structural and functional aspects of late endosomes, the exact stereochemical configuration of the glycerol phosphate backbone and its biosynthetic pathway have remained elusive.

To determine the stereoconfiguration of BMP, D-camphor ketals were introduced as chemical shift reagents to directly probe the backbone configuration of BMP. As a first step, all possible configurations of the BMP backbone were enantiomerically pure synthesized as reference material, namely *sn*-1-glycerophospho-*sn*-1'-glycerol backbone, *sn*-3-glycerophospho-*sn*-3'-glycerol backbone and *sn*-1-glycerophospho-*sn*-3'-glycerol backbone. Subsequently, these backbones were converted to their corresponding D-camphor bisketals to facilitate their identification by NMR. Thereafter, a suitable protocol was developed to convert natural BMP isolated from BHK cells into the corresponding D-camphor bisketal. Direct comparison of ¹H-NMR spectra of the reference material and the D-camphor bisketal of natural BMP revealed that natural BMP exhibits the unusual *sn*-1-glycerophospho-*sn*-1'-glycerol backbone.

While the *sn*-1 phosphorylation of BMP is unique among phospholipids from the eukarya domain, it is the exclusive phosphorylation pattern in phospholipids from the archaea domain. Thus, identification and isolation of the enzymes involved in the biosynthetic pathway of BMP will provide a new approach to advance the discussion on the origin and early development of the eukarya domain.

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High-Resolution Calorimetric Study of Intermediate Phases Near the Main Transition in Short-Chain Phosphatidylcholines

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High-resolution calorimetric measurements have been carried out on the phospholipids, diundecanoyl phosphatidylcholine (DC₁₁PC), dilauroyl phosphatidylcholine (DLPC), ditridecanoyl phosphatidylcholine (DC₁₃PC), dimyristoyl phosphatidylcholine (DMPC), dipentadecanoyl phosphatidylcholine (DC₁₅PC) and dipalmitoyl phosphatidylcholine (DPPC). It was found that the L_x phase reported in DLPC exists also in DC₁₁PC and DC₁₃PC. The existing temperature range of the L_x phase becomes narrower with increasing the chain length. The L_x phase does not appear in DMPC, however, pretransitional heat capacity wing above the main transition temperature is larger than that below the transition temperature. Thus, we propose that the anomalous swelling observed in phosphatidylcholines is caused by the appearance of the L_x phase and that the L_x phase is the liquid-ordered(ℓ_o) phase observed in phosphatidylcholine-cholesterol system because the heat capacity anomaly of the L_x-L _{α} transition has common features with the liquid-ordered(ℓ_o) to liquid-disordered(ℓ_d) transition.

Evolution of Lipids – Lipids in Evolution

Notes

Distribution of Membrane Lipids in Yeasts and Mammals

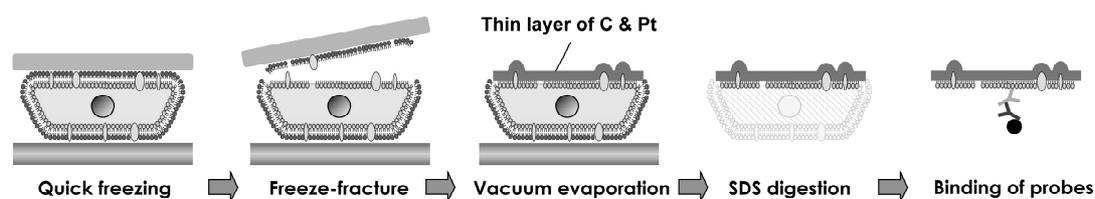
Toyoshi Fujimoto

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To understand various molecular events in the membrane, it is critical to define the local heterogeneity of membrane composition. High-resolution microscopy enabled observation of membrane proteins at a very small scale, but fine distribution of membrane lipids are largely unknown because most of the techniques used for proteins cannot be applied to lipids for various reasons.

We have developed an electron microscopic method that can observe distribution of membrane lipids at the nanometer scale. The method consists of quick freezing, freeze-fracturing to reveal the hydrophobic interface of two membrane leaflets, physically stabilizing membrane molecules by deposition of platinum and carbon layers, and labelling of target molecules with specific probes, and data acquisition by electron microscopy. This method is unique in that it can define the membrane asymmetry unambiguously.

By use of this methodology, we have been able to observe the distribution of phosphatidylinositol 4,5-bisphosphate, phosphatidylinositol 3-phosphate, and several other membrane lipids at the nanoscale and found that they distribute in characteristic patterns, which had not been detectable by other techniques. Interestingly, budding yeast (*Saccharomyces cerevisiae*) and mammals show clear difference in some aspects. The result indicated that hitherto unknown mechanisms should work to give rise to membranes and membrane domains.



Evolution of Lipids – Lipids in Evolution

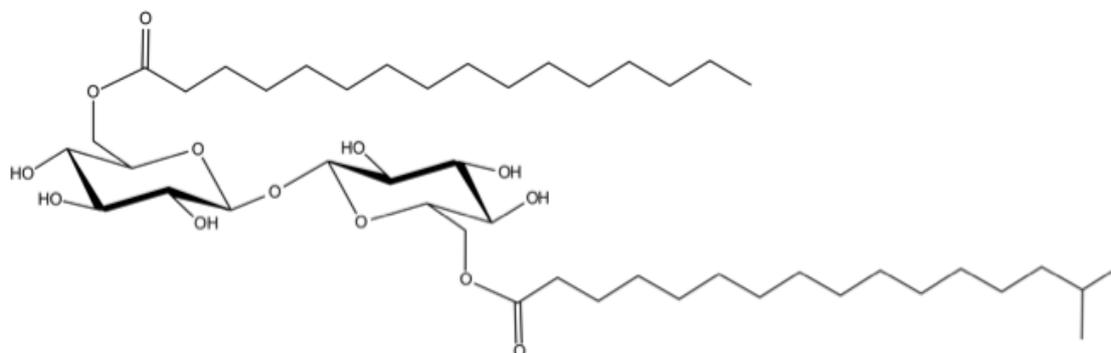
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Maradolipids, Dauer Larva Specific Structural Glycolipids in *Caenorhabditis Elegans*

Teymuraz V. Kurzchalia, Sider Penkov, Fanny Mende, Vyacheslav Zagoriy, Cihan Erkut, René Martin, Ulrike Pässler, Kai Schuhmann, Dominik Schwudke, Margit Gruner, Jana Mäntler, Thomas Müller-Reichert, Andrej Shevchenko, Hans-Joachim Knölker

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Dauer stage, a specialized non-feeding larva of *Caenorhabditis elegans*, is formed under unfavorable conditions and is resistant to metabolic stress. We present a peculiarity of dauer lipidome: dauer larvae synthesize a class of stage-specific structural glycolipids, that we name maradolipids. Chemical analysis revealed that maradolipids are 6,6'-diacyltrehaloses, a large fraction of which contains monomethyl branched chain fatty acid moieties. Such lipids have not been found before in metazoans. Maradolipids, however, display similarity to the cord factor of *Mycobacterium tuberculosis* that is part of the outer cell wall and is essential for its virulence. We show that maradolipids are required for structuring the apical surface of the gut by forming a lipid layer. Maradolipid content is strongly reduced in dehydrated dauers, suggesting a role of these lipids in the protection against desiccation stress possibly as a local deposit of trehalose.



Maradolipid (C16:0; isoC17:0)

Evolution of Lipids – Lipids in Evolution

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Lipid Biology Using *Drosophila Melanogaster* as a Model Animal

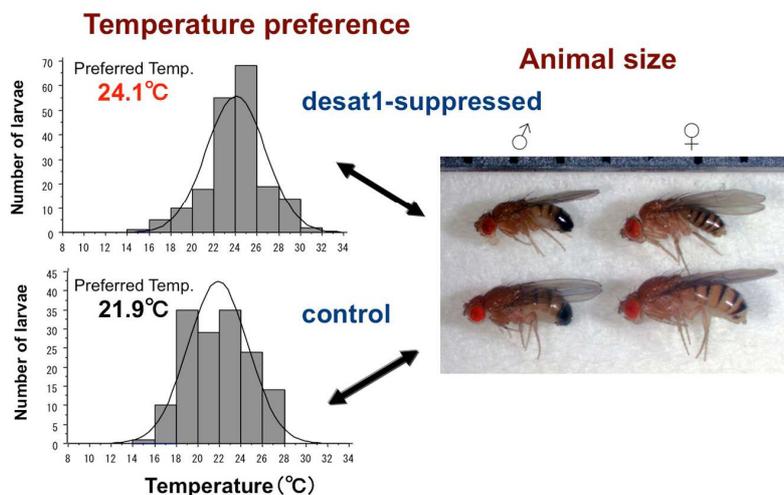
Masato Umeda

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Insects such as *Drosophila melanogaster* have a unique lipid metabolism pathways compared to those of mammals; for instance, flies do not have enzymes responsible for synthesizing polyunsaturated fatty acids, cholesterol, and sphingomyelin, and have a delta-9 fatty acid desaturase, called *desat1*, as the only desaturase for acyl-CoA. This unique feature of the lipid metabolism in *Drosophila* provides a useful opportunity to explore the *in vivo* function of lipids and their synthesizing enzymes.

During the course of studying the biochemical processes that underlie the thermoregulatory behavior of *Drosophila* (*Science* **323**:1740, 2009), we have found that *desat1* plays a pivotal role in controlling thermoregulatory behavior as well as mitochondrial energy metabolism. Tissue-specific manipulation of *desat1* revealed that the level of *desat1* expressed in the fat body, a tissue equivalent to mammalian adipose tissue and liver, is critical in controlling the thermoregulatory behavior and energy metabolism. Induced expression of delta-12 fatty acid desaturase (*Caenorhabditis elegans* Fat-2) in the fat body also significantly affects the thermoregulatory behavior. These results suggest that the remodeling of fatty acyl chains coordinately regulates mitochondrial energy metabolism and thermoregulatory behavior in *Drosophila*. Signaling cascades that link the fatty acid remodeling to mitochondrial energy metabolism will be discussed.

Fat body-specific manipulation of *desat1* affects thermoregulatory behavior and body size of *Drosophila*



Evolution of Lipids – Lipids in Evolution

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GPRC5B Activates Obesity-Associated Adipose Inflammatory Signaling

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A recent genome-wide association study identified a strong correlation between body mass index and the human *GPRC5B* gene. Nevertheless, the functional role of *GPRC5B* in obesity remains unknown. Here we report that *GPRC5B*-deficient mice are protected from diet-induced obesity and insulin resistance because of reduced inflammation in white adipose tissue. GPRC5B is a lipid-raft-associated transmembrane protein that contains multiple phosphorylated residues at its C terminus. Importantly, Fyn-mediated tyrosine phosphorylation of GPRC5B and subsequent direct interaction with Fyn through the Fyn-SH2 domain are critical for the initiation and progression of adipose inflammatory signaling. We demonstrated that a GPRC5B mutant lacking the direct binding site for Fyn failed to reciprocal activation of the IKK ϵ -NF- κ B signaling axis. These findings suggest that GPRC5B is a major node in adipose signaling systems linking diet-induced obesity to type 2 diabetes and may open new avenues for therapeutic approaches to diabetic progression.

Evolution of Lipids – Lipids in Evolution

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Evolution and Membrane Glycolipid Synthesis - Conserved Roles of Glucosylated Lipids

Yoshio Hirabayashi

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Today, glucose is the most important component for living organisms. During chemical evolution the prevailing heat and the energy from the sun were stored in chemical bonds, leading to the formation of carbohydrates, such as glucose and mannose. Glucose, one of the most stable carbohydrates, was selected as a key molecule by ancestral primitive microorganisms (Hirabayashi J, 1996) for energy supply. This is further corroborated by the fact, that also today the energy of the sun is stored as chemical energy in glucose during photosynthesis and later released via the Krebs Cycle generating ATP to meet the energy demand of the cell.

The brain, metabolically the most expensive tissue, depends on glucose as its fuel source. Hence, a specific glucose transporter system (SLC2A1 and SLC2A4) to cross the blood brain barrier evolved during evolution. Noteworthy, during brain development, glia cells (radial glia) produce amino acids, such as *L*-serine, via the phosphate pathway (3-phosphoglycerate). During this process α -ketoglutarate is produced, which in turn might be utilized for energy production (Locasale JW, et al 2011).

Despite the importance of glucose as energy source, it not only plays a pivotal role as signaling molecule, but is also utilized as lipid head group. So far, three glucosylated lipids, namely glucosylceramide, cholesterylglucoside, and phosphatidylglucoside, have been identified in mammals. Intriguingly, all of these glucosylated lipids are enriched in lipid rafts and lipid microdomains, indicating the fundamental importance of lipid glucosylation in life. This is further highlighted for example by the presence of UDP-glucose ceramide glucosyltransferase (UGCG), the key enzyme in glucosylceramide synthesis, in essentially all animal tissue. Additionally, the high degree of UGCG gene conservation across multi-cellular organisms further corroborates the biological significance of glucosylated lipids. For example, glucosylceramide acts as the key precursor for the biosynthesis of over 300 glycosphingolipids, an important lipid class in the brain.

Recently it has been shown that glucosylceramide acts as a glucose donor for cholesterylglucoside synthesis (Akiyama et al., 2011). Moreover model animal studies on *Drosophila* demonstrated (Kohyama et al 2011) that glycolipid synthesis regulates accumulation and release of stored lipids, such as triglycerides, in fat bodies - the equivalent to mammalian adipose tissue. This regulatory role of glucosylceramide on energy homeostasis is not a surprise, taking into consideration that the basic building blocks of glucosylceramide synthesis, namely UDP-glucose, palmitoyl-CoA and serine (derived from glucose), are directly related to energy metabolism.

Consequently, better understanding of the cellular glucosylation machinery, especially involved in the synthesis of cholesterylglucoside and phosphatidylglucoside, will open up new perspectives on the fundamental role of glucosylated lipids during evolution.

Evolution of Lipids – Lipids in Evolution

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Limonoid Compounds Inhibit Sphingomyelin Biosynthesis in Mammal Cells by Preventing Ceramide Extraction from the Endoplasmic Reticulum

Françoise Hullin-Matsuda^{1,2}, Nario Tomishige¹, Kumiko Ishii¹, Reiko Ishitsuka¹, Shota Sakai¹, Peter Greimel¹, Asami Makino¹, Mitsuhiro Abe¹, Elad L. Laviad³, Kentaro Hanada⁴, Anthony H. Futerman³ and Toshihide Kobayashi^{1,2}

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In order to identify novel inhibitors of sphingolipid metabolism, a new and selective high-throughput microscopy screening based on the toxicity of the sphingomyelin (SM)-specific toxin, lysenin, was developed. Out of a library of 2011 natural compounds, the limonoid, 3-chloro-8 α -hydroxycarapin-3,8-hemiacetal (CHC), rendered cells resistant to lysenin by decreasing cell surface SM. CHC treatment selectively inhibited the *de novo* biosynthesis of SM in mammal cells, but not biosynthesis of sphingolipids in yeast.. Pretreatment with brefeldin A abolished the limonoid-induced inhibition of SM synthesis suggesting that the transport of ceramide (Cer) from the endoplasmic reticulum (ER) to the Golgi apparatus is affected. Like the Cer transporter (CERT) inhibitor HPA-12, CHC inhibited the conversion of *de novo* synthesized Cer to SM. We show that CHC specifically inhibited the CERT-mediated extraction of Cer from ER membranes *in vitro*. Subsequent biochemical screening of 21 limonoids revealed that some of them, such as gedunin which exhibits anti-cancer and anti-malaria activity, inhibited SM biosynthesis and CERT-mediated extraction of Cer from membranes. Model membrane studies suggest that the active limonoids reduced the miscibility of Cer with membrane lipids and thus induced the formation of Cer-rich membrane domains. Our study shows that certain limonoids are novel inhibitors of SM biosynthesis and suggests that some biological activities of these limonoids are related to their effect on the ceramide metabolism.

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Co-evolution of SM and CERT: Diverse Lipids May Require Co-evolution of Enzymes and Trafficking Systems

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Lipids are key components of biomembrane in all living organisms. Barrier against hydrophilic solutes and generation of fluid matrix are two major essential functions of lipids for biomembrane. For these two functions and more other functions including bioactive mediators, energy deposition, and chemical modifications of proteins, tremendous diversities in the structure of natural lipids have appeared along with evolution of life.

Sphingomyelin (SM), cholinephospho ceramide, is ubiquitous membrane phospholipids in vertebrates and also exists in some invertebrates. Multicellular lower animals lacking SM have ethanolaminephospho ceramide (EPC), a structurally close relative of SM, instead. Inositolphospho ceramide (IPC), another relative of SM, exists in fungi, plant and protozoa (single-cellular animals), but, to my knowledge, these organisms have not SM nor EPC. Surprisingly, although SM and IPC are synthesized by enzymes classified to the same family, bulk EPC in fly is likely to be produced by a different enzyme type despite of the presence of an SM synthase/IPC synthase member in the fly genome.

CERT is a cytosolic soluble protein to mediate non-vesicular trafficking of ceramide from the ER to the Golgi apparatus for SM synthesis. CERT consists of, at least, two functional domains and a short-peptide motif: PH domain recognizing PtdIns(4)P, FFAT motif recognizing the ER membrane protein VAP, and START domain catalyzing inter-membrane transfer of ceramide. These functional domains and motif are encoded by different exons in the human genome.

PH domains and FFAT motives are widely present in eukaryotes, while START domains seem to exist only in metazoan and plant. Known partners of CERT, namely PtdIns(4)P and VAP (SCS2), also widely exist in eukaryotes.

Metazoan (multicellular animals) have CERT orthologs, while protozoa, plant and fungi have not. In the yeast *Saccharomyces cerevisiae*, which has IPC not glucosylceramide (GlcCer), a sec18-dependent vesicular pathway is likely the major pathway to transport ceramide from the ER to the Golgi. The pathogenic fungus *Cryptococcus neoformans* produces both GlcCer and IPC, indicating two-way anabolism of ceramide is compatible with the absence of CERT.

Based on these pieces of information, I'd here like to propose that CERT appeared after module-arrangements in metazoan genomes to overcome a difficulty in regulated delivery of the same precursor ceramide to different sites for two different metabolites by only one vesicular system. I consider that the short-range non-vesicular delivery system at organelle membrane contact sites is a quite smart product in evolution of life.

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Sterols and Sphingolipid Homeostasis and Functions in Model Organisms

Kyohei Umebayashi, Thomas Hannich, Aline Santos, Isabelle Riezman, Auxiliadora Aguilera-Romero, Andreas Zumbuehl and Howard Riezman

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Previous experiments using lipidomic approaches to study sterol biosynthesis mutants in yeast have shown that changes in sterol composition provoke specific adaptations in sphingolipid profiles and imply that there is a sensor that can detect the quality of sterols in the membrane. Furthermore, genetic experiments have proven that sterols and sphingolipids work together in many biological processes¹. These studies and the distribution of sterols and sphingolipid species among species imply a co-evolution of these two lipid classes. We have recently undertaken studies to understand how sterols are detected and the reasons behind their pleiotropic phenotypes. We will discuss our recent approaches to identify the sterol sensor and how sterol sensing causes changes in so many phenotypes and controls the transcriptional program. Boosted by the findings on the sterol mutants we have performed lipidomics analysis now on over 600 yeast mutants covering approximately one tenth of the genome, including most of the protein kinases. These results show how the environment can influence lipid metabolism, but also suggested how cells can respond to disturbances in their plasma membrane².

Functions of sphingolipids will also be discussed. Previously, we have shown that *C. elegans* mutants in ceramide synthases affect how the worms respond to anoxia³. Shotgun lipidomics approaches have shown that deoxyceramide accumulation could correlate with the hypersensitivity to anoxia. Therefore, we have synthesized and examined the effects of the worm C17 isobranched deoxysphinganine. A human disease, hereditary sensory autonomous neuropathy I, seems to be caused by synthesis of deoxysphinganine⁴. Similarly, in worms, we have seen that feeding of deoxysphinganine causes neurological phenotypes including defects in moving towards chemoattractants and other behaviors. This suggests a conserved function of deoxysphinganine or its products in evolution even though the exact structure of the sphingoid base is different and specific as the differences in sphingoid base structures in yeast and worms are crucial for survival.

(1) Guan, X. L.; Souza, C. M.; Pichler, H.; Dewhurst, G.; Schaad, O.; Kajiwara, K.; Wakabayashi, H.; Ivanova, T.; Castillon, G. A.; Piccolis, M.; Abe, F.; Loewith, R.; Funato, K.; Wenk, M. R.; Riezman, H. *Mol Biol Cell* **2009**, *20*, 2083.

(2) Berchtold, D.; Piccolis, M.; Chiaruttini, N.; Riezman, I.; Riezman, H.; Roux, A.; Walther, T. C.; Loewith, R. *Nat Cell Biol* **2012**, *14*, 542.

(3) Menuz, V.; Howell, K. S.; Gentina, S.; Epstein, S.; Riezman, I.; Fornallaz-Mulhauser, M.; Hengartner, M. O.; Gomez, M.; Riezman, H.; Martinou, J. C. *Science* **2009**, *324*, 381.

(4) Penno, A.; Reilly, M. M.; Houlden, H.; Laura, M.; Rentsch, K.; Niederkofler, V.; Stoeckli, E. T.; Nicholson, G.; Eichler, F.; Brown, R. H., Jr.; von Eckardstein, A.; Hornemann, T. *J Biol Chem* **2010**, *285*, 11178.

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Lipids in Single Cell Organisms: Unity in Diversity and Diversity in Unity

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Cellular lipids function as cellular membrane components, an energy reservoir, and signaling molecules. These lipid functions are fairly well conserved from single cell organisms to higher animals, including humans. On the other hand, lipid molecules and/or molecular machinery involved in the metabolism of lipids show diversity in structure and function depending on the organism; however, unity in diversity is also observed among organisms evolved from a different ancestor. The discussion of how or why organisms acquire diversity in lipids and maintain unity during evolution will help to understand the biological significance of lipids. To discuss the issue in this symposium, the author will provide data on two subjects; glucosylceramide metabolism in fungus and lipid droplet formation in thraustochytrids.

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