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MEETING REPORT

Meeting Report – The 2019 FEBS special meeting on sphingolipid biology: sphingolipids in physiology and pathology

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ABSTRACT

Sphingolipids are a fundamental class of molecules that are involved in structural, organizational and signaling properties of eukaryotic membranes. Defects in their production or disposal lead to acquired and inherited human diseases. A growing community of scientists has embraced the challenge to dissect different aspects of sphingolipid biology using a variety of approaches, and a substantial part of this community met last May in the beautiful town of Cascais in Portugal. Over 200 scientists from 26 countries animated the conference, held in a 15th century citadel, sharing their data and opinions on the current understanding and future challenges in sphingolipid research. Here, we report some of their contributions to provide the readers with a bird's-eye view of the themes discussed at the meeting.

Introduction

Despite progress in the field of sphingolipid biology, at almost 150 years after their discovery, many tools for sphingolipid analysis as well as knowledge of the molecular mechanisms regulating sphingolipid enzymes, the downstream effectors and the compartmentalization of sphingolipid function are largely lacking. The desire to increase the quality and significance of sphingolipid research led to the foundation of the Sphingolipid Club (SLC) under the presidency of Riccardo Ghidoni (University of Milan, Italy) and the international Ceramide Conference (iCC), chaired by Yusuf Hannun (Stony Brook University, USA). The initiation of both these conference series was instrumental in driving the sphingolipid field forward, and, in 2015, the iCC and SLC came together for the first time in Izmir, Turkey. The positive feedback from this meeting spurred the organization of the second joint, and to-date largest, sphingolipid meeting in Cascais, Portugal (6–10 May 2019), organized by the authors with the support of Thierry Levade (INSERM, France) and Yusuf Hannun. The goal of this meeting was not only to look back to where sphingolipid biology is coming from, but also to define where the field needs to be going; this report summarizes the major themes and ideas that emerged from the conference. Such themes included an increased focus on the analysis, regulation and functions of sphingolipids at the level of subcellular compartmentalization, the translation of biophysical lipid studies from the *in vitro* context to the cell, the identification of novel sphingolipid effectors, and the development of sphingolipid enzymes as viable therapeutic targets.

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Innovative tools to study sphingolipid structure and function

Research on lipids has lagged behind that on other biomolecules for a long time due to the paucity of effective tools able to analyze lipid content, distribution, structure and function in biological systems. However, this is changing, and this was represented with a dedicated session on technical novelties for the toolkit of the 21st century sphingolipidologist. The session was chaired by Thorsten Hornemann (University Hospital of Zurich, Switzerland) who emphasized the importance of innovative probes for the assessment of sphingolipid enzyme activity in living cells, and of space-resolved lipid analysis. Accordingly, Gemma Fabrias (Institute for Advanced Chemistry of Catalonia, Spain) presented her work on the development of fluorescence-based chemical sensors for the assessment of ceramidase activity (Ordóñez et al., 2019). Ceramidases are enzymes that hydrolyze ceramide to yield sphingosine and fatty acids. Ceramidases are mutated in human genetic diseases (i.e. Farber disease, spinal muscular atrophy with progressive myoclonic epilepsy, and early childhood leukodystrophy) and their inhibition has been found to reduce tumor growth. She discussed the development of new chemical tools to study ceramidases, including specific sensors that measure enzyme activity in high-throughput formats and detect active enzymes in living cells. Based on the use of these sensors, new inhibitors have been synthesized with increased potency and specificity towards ceramidase isoforms. Along similar lines, Christoph Arenz (Humboldt University of Berlin, Germany) reported on the progress of his laboratory in developing Förster resonance energy transfer (FRET) probes (Mohamed et al., 2018) to measure acid sphingomyelinase activity, which is a lysosomal catabolic enzyme that converts sphingomyelin into ceramide. Deficiency in acid sphingomyelinase activity leads to Niemann–Pick disease types A and B. Arenz presented several synthesized sphingomyelin FRET probes with unique features that can be used for an easy and reliable monitoring of acid sphingomyelinase activities in *in vitro* experiments using purified enzyme or cell homogenates (Mohamed et al., 2018). He further maintained that the possibility of monitoring two colors at the same time not only allows for ratiometric imaging and quantification inside of living cells, but also provides unique features for enzymology and high-throughput screening. Joost Holthuis (University of Osnabruck, Germany) described how the use of novel tools such as photo-activatable ceramide probes and switchable ceramide transfer proteins helped the group to unravel the mechanisms by which ceramides can commit cells to death. Their latest results established the voltage-dependent anion channel 2 (VDAC2) as a critical effector of ceramide-mediated apoptosis (Dadsena et al., 2019). Howard Riezman (University of Geneva, Switzerland) also reported on the development of new tools to manipulate and follow sphingolipid metabolism in cells (Feng et al., 2019) in his EMBO keynote lecture. Specifically, he presented his work on the use of caged sphingolipid precursors with organelle-specific targeting that

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allows researchers to follow lipid metabolism with high spatial and temporal resolution. This enables metabolic bias in lipid fate linked to different subcellular lipid localization to be revealed, and monitoring, indirectly, of the movement of lipids between organelles. He also reported on the use of systematic lipidomics coupled to genome-wide CRISPR screens for cells resistant or hypersensitive to sphingolipid synthesis inhibition, which led to the discovery of unexpected links between distinct lipid metabolic pathways and membrane trafficking. In all, talks focused in this subject highlighted the significant advances made by the community in devising tools to visualize and manipulate sphingolipid metabolism directly within cells and at the single-cell level. These advances allow us to ask new questions on intracellular sphingolipid trafficking and on the unique physiological functions of specific subcellular pools of bioactive sphingolipids – something that was not possible before.

Sphingolipids in membrane structure and dynamics

The overall recognition of the role of membrane structure, organization and dynamics in cell pathophysiology fostered the growing number of biophysical studies that address these topics. Whereas this has historically been confined to studies in artificial membrane systems, progress in tools and methodologies to investigate lipid structure–function relationships and awareness of the need to integrate the biophysical analysis into the biological context enabled tremendous advance in the field, as highlighted by Alicia Alonso (Institute of Biofisika, University of Basque Country, Spain) who chaired a session dedicated to this topic. She emphasized the importance of combining systematic biophysical studies with lipidomic data and cell biology studies to unravel the molecular mechanisms that determine the biological function of the different sphingolipid species. This was also evidenced by the works presented by the speakers of the session. Galia Staneva (Institute of Biophysics and Biomedical Engineering, Bulgarian Academy of Sciences, Sofia, Bulgaria) and Maria João Sarmento (J. Heyrovský Institute of Physical Chemistry, Prague, Czech Republic) reported on the importance of sphingolipids and sphingolipid-enriched domains in neurodegenerative diseases. Staneva discussed the antagonist effects of sphingosine and sphingosine1-phosphate in modulating the interaction of the amyloid-β peptide (Aβ) with the membrane and the implications of Aβ on the growth rate of lipid raft domains. Her data suggest that impairment in lipid raft dynamics might affect neural signaling events (Staneva et al., 2018). Sarmento uses mimetic membrane systems and a combination of microscopy, spectroscopy, molecular dynamics and Monte Carlo simulations to reveal that physiological concentrations of the ganglioside GM1 do not cause amyloid aggregation (Amaro et al., 2016). In contrast, amyloid oligomerization is enhanced by the presence of sphingomyelin. Her data bring new findings into Alzheimer's disease (AD) research by highlighting that altered ganglioside levels and composition might contribute to the onset of AD. The work presented by Rodrigo de Almeida (Faculdade de Ciências da Universidade de Lisboa, Lisboa, Portugal) brought new insights into the organization of the yeast plasma membrane and into the potential roles of sphingolipid domains in the regulation of the stress response in yeast. He presented his strategy, which includes multiple biophysical methodologies and an integrated experimental approach combining synthetic membranes, isolated plasma membrane, reconstituted lipid extracts and living yeast. In doing so, he showed that sphingolipids form highly rigid and slow diffusing gel domains that might stabilize membrane compartments in yeast (Marquês et al., 2018). He also discussed the importance of fatty acyl chain hydroxylation in the properties and stability of those domains and in the yeast response to antifungal agents and adaptation to hydrogen peroxide. Peter Nagy (University of Debrecen, Debrecen, Hungary) described the biophysical effects of sphingolipid accumulation in a drug-induced cellular model of the most common lysosomal storage disorder – Gaucher disease (GD) (Batta et al., 2018). In his presentation, he showed that the observed decreased membrane fluidity, enhanced formation of membrane nanotubes and decreased endocytic rate of non-raft components upon sphingolipid accumulation during GD suggest a role of altered membrane dynamics in the development of GD. Overall, the works discussed in this session emphasized the importance of the biophysical properties of the membranes in cell physiology and how the impairment in the organization, structure and dynamics of biological membranes can contribute to pathological situations and response to therapeutics. It further underlined that proper membrane structure and function depends on its composition. Therefore, it highlighted that dysregulation of the lipid metabolism can have a tremendous impact at the membrane level and compromise multiple cellular events, reiterating the significance of the physico-chemical properties of membranes in modulating cell pathophysiology.

Sphingolipids in cell physiology: signaling, trafficking and metabolism

Cellular sphingolipids are signaling mediators, and much effort focuses on understanding their regulation as well as on deciphering their cellular functions. Sarah Spiegel (Virginia Commonwealth University, USA) and Yasuyuki Igarashi (Hokkaido University, Japan) co-chaired this session and the former identified major challenges in this area, most notably understanding the mechanisms by which sphingolipid enzymes and metabolism are coordinately regulated, with additional emphasis on their subcellular compartmentalization. Spiegel also noted that a key future challenge is to determine the molecular mechanisms of action of specific sphingolipids, which is particularly relevant for our understanding of functions of various ceramide species. Konrad Sandhoff (University of Bonn, Germany) gave a detailed description of how microenvironmental factors – particularly membrane lipid composition – influences sphingolipid catabolism in the late endosomes and lysosomes. For example, disruption of cholesterol trafficking in Niemann–Pick disease type C leads to secondary accumulation of sphingolipids and, conversely, defects in lysosomal sphingomyelinase activity disrupt cholesterol transport. Furthermore, accumulation of chondroitin sulfate in mucopolysaccharidoses – Hurler, Hunter, Sanfilippo and Sly disease – disrupts ganglioside GM2 catabolism (Anheuser et al., 2019). At a more mechanistic level, Sebastien Granier (Montpellier University, France) reported on the structure of alkaline ceramidase 3 and its similarity to adiponectin receptor, which also exhibits intrinsic ceramidase activity (Vasiliauskaité-Brooks et al., 2018). He maintains that solving the structure of alkaline ceramidase 3 has led to the understanding of important details in its catalytic mechanism, such as the fact that it hydrolyses ceramide directly from within the membrane bilayer. At the *in vivo* level, Annarita Di Lorenzo (Weill Cornell Medical College, USA) explores the role of the *de novo* sphingolipid pathway in endothelial dysfunction – a key event in many cardiovascular diseases (Sasset et al., 2016). She reported how targeted disruption of *de novo* sphingolipid synthesis resulted in high-blood pressure through impairment of specific vasodilatory pathways. Most strikingly, these effects were able to be rescued through supplementation of some but

not all ceramide species – consistent with the idea of distinct lipid species having distinct roles. In his presentation, Fikadu Tafesse (Oregon Health and Science University, USA) discussed how pathogens such as the Zika virus co-opt the host lipid metabolism to secure invasion, persistence and propagation (Leier et al., 2018). Analyses by his research group suggest alterations in sphingolipids are among the most striking changes induced by Zika infection and that targeting specific sphingolipid pathways could disrupt viral replication. Kentaro Hanada (National Institute of Infection Diseases, Japan) gave updates on the development of new ceramide-non-mimetic inhibitors of the lipid transfer protein CERT. He discussed potent new compounds that are effective at disrupting ceramide transport but without the obvious concerns of ceramide mimetics, which is the potential targeting of other ceramide-binding proteins. Paola Signorelli (University of Milan, Italy) presented research focused on the regulation and role of ceramide synthesis in myocardial ischemia-reperfusion injury. She suggested that activation of the *de novo* sphingolipid pathway occurs during ischemia-reperfusion and disruption of sphingosine biosynthesis using the antibiotic myriocin is effective at limiting injury by modulating inflammation and lipid metabolism (Reforgiato et al., 2016). Focusing on protein sorting at the trans-Golgi network (TGN) of plants, Yohann Boutte (University of Bordeaux, France) discussed how modifying TGN sphingolipids influenced secretory sorting pathways without affecting endocytic recycling and sorting, and described how interplay between phosphoinositides and sphingolipids could play a role in polar protein sorting to these pathways (Boutté, 2018). Remaining at the interplay between sphingolipid trafficking and metabolism and phosphoinositides, Antonella De Matteis (Telethon Institute of Genetics and Medicine, Naples, Italy) articulated on the structure and function of endoplasmic reticulum–Golgi complex membrane contact sites (ER-Golgi MCS) in her keynote lecture. ER–Golgi MCS are sites where the ER membranes approach those of the trans Golgi, leaving an interstitial space of 10 to 30 nm. It is there that ceramide and possibly non-vesicular glucosylceramide transport takes place. This is mediated by the lipid transfer proteins CERT and phosphatidylinositol-four-phosphate adapter protein 2 (FAPP2) that use the phosphoinositide PtdIns(4)*P* as a Golgi-targeting signal (Venditti et al., 2019a,b). De Matteis reported on her meticulous dissection of the molecular machinery required for the maintenance of ER–Golgi MCS and on its importance in the regulation of PtdIns(4)*P* levels at the trans Golgi complex. Collectively, this session highlighted the importance of the bilayer microenvironment as a regulatory factor of sphingolipid enzymes, with particular insight into interplay between phosphoinositides and sphingolipids. These sessions also began to highlight downstream *in vitro* and *in vivo* effectors of sphingolipid signaling in important cell physiologies.

Sphingolipids in health and disease

A major step forward in recent years has been the appreciation that dysregulation of sphingolipid metabolism is associated with pathogenesis of multiple diseases. This has led to increased interest, not only in targeting the sphingolipid network for therapeutics, but in potentially utilizing the level of sphingolipids in blood plasma as a biomarker of diseases. This was summarized by co-chairs Antonio Gomez-Munoz (University of the Basque Country, Spain) and Thierry Levade (CRCT, INSERM, France), who highlighted how a deeper understanding of the roles of specific sphingolipids in health and disease is needed if effective therapeutic approaches that target sphingolipid metabolism are to be developed. Yoshio Hirabayashi (RIKEN, Japan) discussed data about the interplay of the orphan receptor G-protein coupled receptor family C group 5 member B (GPRC5B) and plasma membrane sphingomyelin synthesis and its contribution to high-fat-induced insulin resistance (Kim et al., 2018). In addition to providing insight into sphingomyelin synthase 2 (SMS2) regulation by phosphorylation, Hirabayashi also presented evidence that SMS2-driven diacylglycerol generation is the crucial lipid for insulin resistance. Joo-Won Park (Ewha Womans University, South Korea) investigates the role of ceramide in non-alcoholic fatty liver disease (NAFLD) and showed that ceramides of different acyl chain length have opposing protective and aggravating roles for NAFLD, through interactions with ER stress pathways and lipogenesis. Along similar lines, Jin-Ichi Inokuchi (Tohoku University, Japan) talked about the pro- and anti-inflammatory roles of different GM3 ganglioside species through regulating toll-like receptor 4 (TLR4) signaling. He also discussed the pathological implications of an imbalance in GM3 species levels in promoting the pathogenesis of metabolic disorders through chronic inflammation. Alice Yu (University of California in San Diego, USA and Chang Gung University, Taiwan) reported on the progress to enhance efficacy of dinutuximab – a chimeric anti-GD2 antibody that she pioneered to become the first agent targeting a glycosphingolipid molecule – by combining it with chemotherapy and other immune modulators (Yu et al., 2010). Yu also discussed ongoing research on a vaccine against Globo-H-ceramide (GHCer) – a prevalant cancer-associated antigen in most epithelial cancers – as well as early preclinical and clinical efforts to develop a next-generation GHCer vaccine combined with an immunostimulatory α-galactosylceramide analog. Bruno Ségui (CRCT, INSERM, France) continued the theme of sphingolipid interaction with the adaptive immune system, discussing mechanisms of how altered sphingolipid metabolism promotes immune escape in melanoma, and how effective targeting of the sphingolipid network could promote the anti-tumor immune response and overcome resistance to immune checkpoint blockade therapy (Garandeau et al., 2018). Chiara Luberto (Stony Brook University, USA) presented further insight into the transcriptional regulation of sphingomyelin synthases by the Bcr-Abl oncogene in chronic myelogenous leukemia. In this, Luberto described a novel oncogene-driven mechanism of protein upregulation through alternative transcriptional start sites that has potential implications for other cancers (Moorthi et al., 2018). Addressing the challenge of effective targeting of sphingolipid enzymes, Susan Pyne (University of Strathclyde, UK) discussed recent collaborative efforts with Nigel Pyne (University of Strathclyde, UK) and David Adams (Heriot-Watt University, UK) to develop isoform-specific sphingosine kinase inhibitors that have nanomolar potency. By analyzing crystal structures, they have pinpointed subtle structural variations between the two isoforms, which have enabled them to produce new compounds with 100-fold selectivity for each isoform. In addition to being valuable tools for research, such inhibitors are excellent starting points for targeting sphingosine kinases, which have been implicated in a variety of pathologies (Adams et al., 2019). Overall, the talks of this session demonstrated the strong steps that have been made to advance sphingolipid metabolism as a therapeutic target – particularly in emerging areas such as immunotherapy – as well as the advancing of existing and new inhibitors as potential therapeutics of interest. These talks also emphasized the importance of identifying the key sphingolipid mediators for the pathologies being studied, in order to achieve the maximal therapeutic efficacy.

ISN symposium on sphingolipids in neural pathologies

The International Society of Neurochemistry (ISN) generously sponsored a symposium in the meeting dedicated to the role of sphingolipids in neural pathologies. Sphingolipids are, indeed, very abundant in neural tissue and they have a fundamental role in neural development and brain function (Olsen and Færgeman, 2017; van Echten-Deckert and Alam, 2018). Chair Elisabetta Albi (University of Perugia, Italy) highlighted recent progresses of sphingolipid neurobiology and Einat Vitner (Israel Institute of Biological Research, Ness Ziona, Israel) discussed her data on the accumulation of glucosylceramide in the brain in Gaucher disease mouse models (Vardi et al., 2016) and its protective effect towards Sindbis and West Nile virus infections. She finds that glucosylceramide accumulation due to knockout of the glucosylceramidase GBA1 leads to the induction of a type I interferon response that counteracts viral infection, which now leads her to want to study whether asymptomatic Gaucher disease individuals are more resistant to develop central nervous system (CNS) pathology in response to viral infection. Dagmar Wachten (University of Bonn, Germany) reported on her results on the role of the non-lysosomal glucosylceramidase (GBA2) on locomotion. Mutations of GBA2 in humans have been associated with hereditary spastic paraplegia, autosomal recessive cerebellar ataxia and Marinesco–Sjögren like syndrome, whereas GBA2 gene ablation in mice does not recapitulate the severity of these syndromes (Woeste et al., 2019). Nonetheless, Wachten showed how inhibition of GBA2 activity in isolated cerebellar mouse neurons dramatically affects F-actin cytoskeleton dynamics and reduces neurite outgrowth, which has been associated with the development of neurological disorders. Thus, in spite of the species-specific differences in GBA2 defects *in vivo*, the role of this enzyme in controlling neuronal function is conserved across species. Erich Gulbins (University Hospital Essen, Germany) spoke about the role of sphingolipids in depression. His data indicate that commonly used antidepressants inhibit acid sphingomyelinase and that sphingomyelinase inhibition is required for the antidepressant efficacy. According to Gulbins, sphingomyelin accumulation in the lysosomes and of ceramide in the ER induce autophagy in hippocampal neurons and this autophagic process is the key mode of action of antidepressants; this thus suggests that sphingolipid-controlled autophagy could be an important target for antidepressive treatments (Gulbins et al., 2018). Vittorio Maglione (Neuromed, Pozzilli, Italy) discussed the involvement of sphingolipids and sphingolipid-targeting drugs in the treatment of Huntington disease (Di Pardo et al., 2019). He reported on the use of drugs impacting sphingosine 1-phosphate metabolism and on their effects on the maintenance of the blood–brain barrier integrity and on Huntington manifestations in a well-accepted mouse model. Whereas the relevance of sphingolipids in brain function has been known for decades, the molecular details of their roles has remained elusive. The contributions from this session illustrated the efforts that the sphingolipid community has made towards solving this issue and revealed the big potential for treatment of neurological conditions by pharmacological manipulation of sphingolipid metabolism.

Conclusions

In summary, the 2019 FEBS Special Meeting on Sphingolipid Biology has been a precious opportunity for people interested in these lipids to have a comprehensive overview of the field and to meet some of the most active investigators on the topic. The conference has also been a privileged viewpoint on the most recent advancements of sphingolipid research and a valuable occasion of exposure for young scientists and rising personalities in the field. Scientifically, a number of topics emerged from the sessions as particularly relevant areas of focus for future research. This includes the study of sphingolipid metabolic dynamics and signaling functions at a subcellular resolution, the study of physical properties of sphingolipid-rich membranes in living cells, identifying and understanding the function of atypical and pathological sphingolipids, and the development of new pharmacology to modulate sphingolipid metabolism for the treatment of human diseases. As the SLC and iCC conferences approach the end of their second decade, the FEBS Special Meeting offered a unique chance to reflect on progress made as well as new inspiration to tackle the challenges ahead. As we look forward to the future with a growing community, we are sure that the next iCC/SLC joint conference in 2023 will easily replicate the excitement and vibrant atmosphere experienced in Cascais.

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Competing interests

The authors declare no competing or financial interests.

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