



HAL
open science

EMBO Workshop: Membrane Contact Sites in Health and Disease

Emmanuelle Maria Bayer, Tito Calì, Francesca Giordano, Anne Hamacher-Brady, Luca Pellegrini

► **To cite this version:**

Emmanuelle Maria Bayer, Tito Calì, Francesca Giordano, Anne Hamacher-Brady, Luca Pellegrini. EMBO Workshop: Membrane Contact Sites in Health and Disease. *Contact*, 2019, 2, 10.1177/2515256419825931 . hal-02368102

HAL Id: hal-02368102

<https://hal.science/hal-02368102>

Submitted on 18 Nov 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

EMBO Workshop: Membrane Contact Sites in Health and Disease

Emmanuelle M. Bayer¹, Tito Cali^{2,3} , Francesca Giordano⁴, Anne Hamacher-Brady⁵  and Luca Pellegrini⁶

Contact
Volume 2: 1–8
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2515256419825931
journals.sagepub.com/home/ctc



The key evolutionary innovation of the Last Eukaryotic Common Ancestor consisted in the formation of physically and functionally specialized organelles that, through the compartmentalization of biological processes and signaling pathways, allowed life to adapt to new challenging and ever-changing environments. Similarly, the basic drive of the evolution of the eukaryotic cell consisted in using sites of contact between organelles as a platform for hosting biological or regulatory processes, thereby allowing life to evolve complexity through tissue and cellular specialization. For this reason, in the past decade, the study of interorganellar associations has attracted great interest and momentum. The emerging picture is one where organelles establish multiple and physically close or direct contacts with each other (Figure 1), through the activity of protein tethering complexes. This association, in turn, creates a spatially and functionally specialized subcellular compartment known as membrane contact sites (MCS); here, dedicated protein complexes allow MCS to execute and coordinate a plethora of physiological, metabolic, and cellular processes.

The discovery of MCS forced cell biologists to profoundly reconsider the way organelles are studied because it introduced the concept that through a network of specialized membranes, organelles can control, and interact and cooperate with each other, thereby allowing for the orchestration of integrated and novel functions that individual organelles would otherwise be unable to perform. It is now clear that complex processes indeed occur at the interface between the endoplasmic reticulum (ER) and mitochondria, Golgi, endosomes, peroxisomes, lipid droplets, and the plasma membrane (PM). Moreover, heterotypic contact sites between other types of organelles also exist; they include, for instance, those between mitochondria and peroxisomes or endosomes/lysosomes (vacuole in yeast) or between PM and endosomes/lysosomes. Their ultrastructural and functional characterization has just started to emerge in the literature and at scientific meetings.

The parallel discovery of new types of MCS and of their role in key physiological and metabolic processes

prompted a new community of cell biologists to emerge and to come together to work on two key objectives. One was that of launching a new scientific journal dedicated to becoming the gold-standard journal in this field: *Contact*. Under the leadership of Tim Levine (University College London, UK), *Contact* aims at addressing how MCS mediate and regulate cellular homeostasis and how impaired MCS biogenesis, regulation, or activity are linked to human diseases and metabolic conditions. The second objective was that of organizing and promoting the MCS field through the organization of world-class scientific meetings. So, under the leadership of Luca Scorrano (University of Padua, Italy), the very first meeting on MCS took place as an EMBO Workshop in Domus Maria, Italy, from September 15 to 18, 2016. Following the immense

¹Laboratory of Membrane Biogenesis, University of Bordeaux, UMR5200 CNRS Villenave d'Ornon, France

²Department of Biomedical Sciences, University of Padua, Padua, Italy

³Padua Neuroscience Center, University of Padua, Padua, Italy

⁴Institute for Integrative Biology of the Cell (I2BC), CEA, CNRS, Univ. Paris-Sud, Université Paris-Saclay, Gif-sur-Yvette cedex, France

⁵W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA

⁶Department of Molecular Biology, Medical Biochemistry and Pathology, Faculty of Medicine, Université Laval, Quebec, Canada

Received December 20, 2018. Revised December 28, 2018. Accepted December 29, 2018.

Corresponding Authors:

Emmanuelle M. Bayer, Laboratory of Membrane Biogenesis, University of Bordeaux, France.

Email: emmanuelle.bayer@u-bordeaux.fr

Tito Cali, University of Padua, Padua, Italy.

Email: tito.cali@unipd.it

Francesca Giordano, Université Paris-Saclay, Gif-sur-Yvette cedex, France.

Email: Francesca.GIORDANO@i2bc.paris-saclay.fr

Anne Hamacher-Brady, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA.

Email: abrady9@jhu.edu

Luca Pellegrini, Université Laval, Quebec, Canada.

Email: luca.pellegrini@fmed.ulaval.ca





success of that meeting, under the leadership of Thomas Simmen (University of Alberta, Canada), new exciting insights and key questions about MCS biology were recently discussed at the EMBO Workshop on “Membrane Contact Sites in Health and Diseases.” This conference was co-organized by Jennifer Rieusset (University of Lyon, France), Antonio Zorzano (IRB, Spain), and Stephan Frank (University of Basel, Switzerland) and was held in the beautiful mountains of Arosa, Switzerland, from September 21 to 25, 2018. It gathered more than 120 MCS scholars from all over the world who presented a wealth of mostly still unpublished studies. What follows here is a report of the entirety of the talks, and selected posters, that were presented and discussed at this EMBO Workshop.

The Wilhelm Bernhard Prize and the Keynote Lecture

The meeting opened by awarding Prof. Jean Vance (University of Alberta, Canada) the Wilhelm Bernhard Prize in MCS biology. Jean pioneered the MCS field by discovering and functionally characterizing the mitochondria-associated ER membranes (MAMs), also known as mitochondria-ER contact sites (MERCs), in phospholipids biosynthesis. Indeed, in the 90s, her laboratory successfully isolated this subcellular structure and showed that phosphatidylserine (PS) is imported into mitochondria from the ER via the MAM/MERCs for decarboxylation to phosphatidylethanolamine (PE). Her captivating award lecture thus focused on these and related groundbreaking milestones in the MCS field.

The EMBO Workshop opening keynote was held by Prof. Kai Simons (Max Planck Institute for Molecular Cell Biology and Genetics and Lipotype GmbH, Germany) who presented a fascinating overview of how lipid biology and the use of lipidomics analysis can continue to drive the functional and structural characterization of new types of MCS. Lipids are important building blocks of life. Their main function is to form the matrix of our cell membranes where they support a variety of functions essential for life. It is becoming clear that the lipid composition in cells is tightly regulated and here the membrane contacts must function as a coordinated whole to monitor and adjust lipid transport so that different cell membranes maintain their functional composition. One reason for this tight regulation is that cell membranes have evolved material properties that allow them to sub-compartmentalize the bilayer into dynamic cholesterol-stabilized sphingolipid-protein assemblies that function in membrane trafficking, signaling, and other membrane functions. This capability is a property of cell membranes that are poised close to a phase transition, enabling coalescence into subdomains, that is, lipid composition has to be correctly and constantly balanced. How are the intracellular membrane lipid compositions regulated? Here, MCS are playing an important role to rapidly adjust lipid compositions of the different cellular membrane compartments and govern their dynamic and functional needs. Kai Simons’ team has developed a shotgun mass spectrometry platform that can analyze hundreds of lipids in only a few minutes with absolute quantification. Their data suggest that the plasma lipidome is tightly controlled and seems to reflect the metabolic status of the body. Since the lipids that they are measuring are contained in the plasma lipoproteins, Kai Simons’ team hypothesize that these extracellular lipid carriers function as a surveillance, delivery, and retrieval system that could function generally as nanosensors to regulate cellular lipid homeostasis.

MCS With Mitochondria

Konstanze Winklhofer (Ruhr-University Bochum, Germany) reported her recent research on the role of ubiquitination and E3 ubiquitin ligases/deubiquitinases in the dynamic regulation of ER-mitochondria contact sites under physiological and pathophysiological conditions.

Mike Ryan (Monash University, Australia) presented work on knockout cell lines showing that Dynamin-related protein 1 (Drp1) is essential for both mitochondrial and peroxisomal fission while the other dynamin members play a less critical role in this process. Drp1 was shown to independently constrict and sever preformed membrane tubules *in vitro* in a process dependent on GTP hydrolysis.

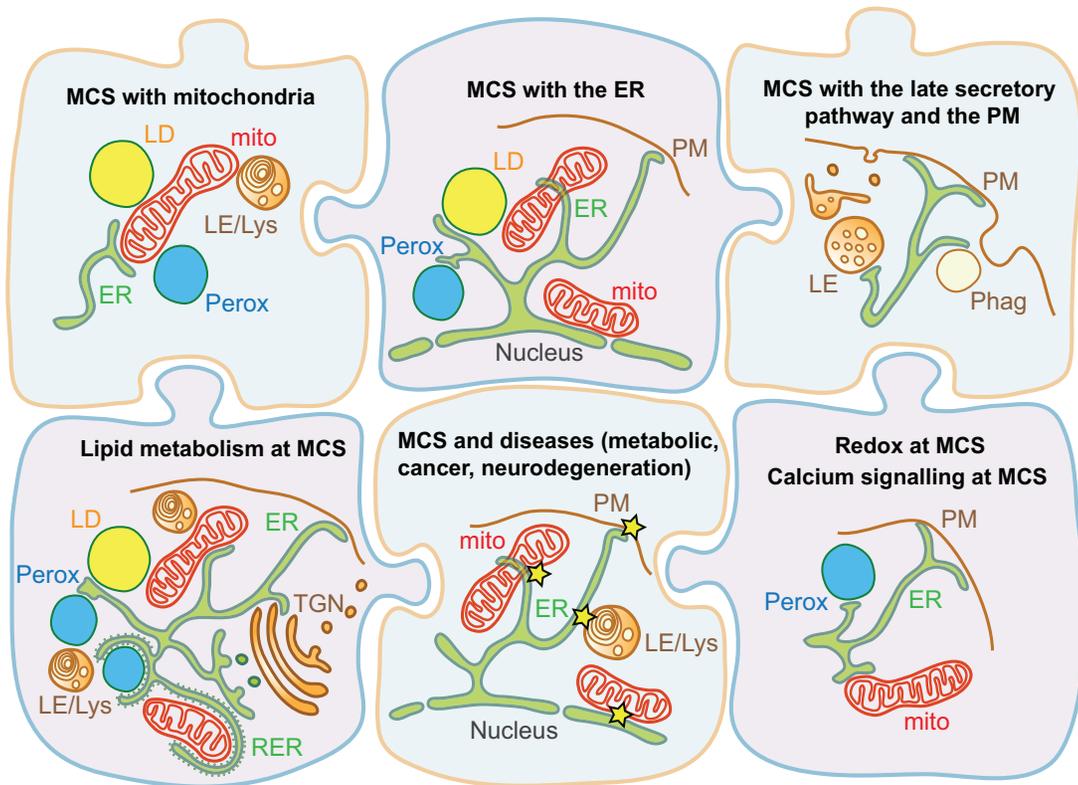


Figure 1. Schematic cartoon illustrating select mammalian interorganellar MCS and related functions. ER = endoplasmic reticulum; mito = mitochondria; LE = late endosomes; Lys = lysosomes; Perox = peroxisomes; LD = lipid droplets; PM = plasma membrane; Phag = phagosome; TGN = trans-Golgi network; RER = rough endoplasmic reticulum.

Luca Scorrano (University of Padova, Italy) presented the results of a genome-wide screening for ER-mitochondria contact modulators. By using a Föerster resonance energy transfer (FRET) probe, his group screened a library containing five different shRNAs per each of the approximately 13,000 genes targeted. To refine the list of identified modulators, they ran isobaric tag for relative and absolute quantitation (iTRAQ) mass spectrometry on MAM samples from brain and MEFs, in collaboration with Ivan Dikic's group (Goethe University, Germany). The intersection of the two lists was further curated to identify potential tethers and spacers. Subscreening identified three previously uncharacterized ER-mitochondria contact modulators. Interestingly, most of these modulators are involved in disease and are alternatively spliced in variants targeted on the two opposing membranes.

Thomas Langer (CECAD, University of Cologne, Germany) reported research on membrane contacts that facilitate lipid transport between the mitochondrial outer and inner membranes, which is facilitated by lipid transfer proteins of the Ups/PRELI family. These conserved proteins exhibit high lipid specificity whose structural basis is not understood. Combining new X-ray structures with gain-of-function genetic screens in

yeast, his work demonstrates that head group recognition and flexible loop regions regulating lipid binding confer specificity to lipid transfer proteins of the Ups/PRELI family.

Anne Hamacher-Brady (Johns Hopkins University, USA) discussed findings on direct interactions between mitochondria and endosomes/lysosomes during apoptosis signaling. Quantitative, high-resolution *live* cell fluorescence microscopy revealed that mitochondria are globally and dynamically targeted by endosomes/lysosomes during apoptosis-related mitochondrial membrane permeabilization. Molecular dissection and perturbation strategies indicate a regulatory role of these interorganellar interactions on functional mitochondrial apoptosis signaling.

Tito Cali (University of Padova, Italy) presented an extended palette of split green fluorescent protein-based MCS sensors (SPLICS) for *in vitro* and *in vivo* narrow and wide heterotypic MCS monitoring. An improved single-vector-based SPLICS probe (SPLICSS/L-P2A) revealed the dynamic nature of the ER-mitochondria interface under basal conditions and upon cell stimulation, *in vivo*. A novel YFP-based single-vector SPLICS probe (PM-SPLICSS/L-P2A) to monitor changes in the ER-PM interface was also discussed. The extended palette of SPLICS probes could allow for simultaneous

monitoring of the ER-mitochondria and the ER-PM contacts within the same cell.

MCS With the ER

Luca Pellegrini (Laval University, Canada) presented the first *in vivo* structural and functional characterization of a new cellular compartment, which he christened WrappER. Using electron tomography and 3D reconstruction analysis, he showed that the WrappER is composed by rough-ER that extensively wraps around most of the mitochondria and of the peroxisomes of the mouse liver hepatocyte. Using unbiased parallel proteomic, transcriptomic, and lipidomics analysis on isolated mouse liver WrappER, he showed that this new type of ER is functionally linked to lipoprotein biogenesis.

Maria Livia Sassano (Patricia Agostinis lab; KU Leuven, Belgium) reported on work unraveling that the ER stress sensor PERK interacts with the lipid binding and trafficking protein Extended synaptotagmin 1 (E-Syt1), which they found enriched at MAM. PERK-E-Syt1 interaction occurs at ER-mitochondria contacts. Through loss-of function studies coupled to subcellular lipidomics, they found that PERK and E-Syt1 remodel the ER-mitochondria phospholipids redistribution.

Ivan Robert Nabi (University of British Columbia, Canada) presented work on the role of the ER-associated protein degradation (ERAD)-associated Gp78 E3 ubiquitin ligase in the regulation of rough ER-mitochondria contacts and mitophagy. Data were presented showing that Gp78 induced mitophagy of both undamaged and damaged mitochondria.

Maya Schuldiner (Weizmann Institute of Science, Israel) described the recent efforts of her lab to map the proteome of all yeast contact sites by systematic colocalization assays. To do this, they have taken split Venus fluorophore sensors of many different MCS and have colocalized their signal with thousands of yeast proteins tagged with a red-fluorophore. For each MCS, they have discovered a myriad of new proteins, many of which have unknown functions and have never before been studied. Among those are new members of a family of lipid transfer proteins that are distributed amongst multiple cellular contacts.

Pietro De Camilli (Yale University, USA) focused on VPS13, a very large protein encoded by four genes in humans. He reported that VPS13 is a lipid transport protein that contains a very large hydrophobic cavity in its N-terminal region. VPS13A and VPS13C localize at contacts of the ER with mitochondria and lysosomes, respectively, but both proteins also localize at ER-lipid droplet contacts. Loss-of-function mutations of VPS13A and VPS13C result in chorea-acanthocytosis and Parkinson's disease, respectively, suggesting that these neurodegenerative conditions are due to defects in

interorganelle lipid transport. Most interestingly, VPS13 has homology to the autophagy protein ATG2, pointing to a lipid transport function of this protein as well.

Ruben Fernandez-Busnadiego (Max Planck Institute of Biochemistry, Germany) uses cryo-electron tomography to understand the molecular organization of MCS. His team showed how some of the tethers of ER-PM MCS are involved in generating high curvature on the ER membrane to presumably facilitate lipid transport to the PM.

Julien Prudent (University of Cambridge, UK) emphasized the new role of phosphatidylinositol-4-phosphate (PI(4)P) in the late stage of mitochondrial division. His work showed that PI(4)P, generated by phosphatidylinositol 4-kinase III β , the effector of the small GTPase Arf1, accumulates at ER-mitochondria MCS and is required for mitochondrial fission, downstream of Drp1 recruitment.

Peroxisomes and Redox at MCS

György Hajnoczky (Thomas Jefferson University, USA) discussed the structure and signaling function of the ER-mitochondria MCS. He described the development of synthetic interorganellar linkers for the measurement and perturbation of the physical parameters and Ca²⁺ and reactive oxygen species (ROS) signaling functions of these contacts. Lastly, he showed propagation of mitochondrial ROS production to the adjoining ER for stimulation of ER Ca²⁺ mobilization.

Michael Schrader (University of Exeter, UK) talked about peroxisome-ER MCS. His group showed that ACBD5, a peroxisomal acyl-CoA binding membrane protein, directly interacts with ER-resident VAPB and regulates peroxisome-ER interactions. First patients with ACBD5 deficiency have been identified, who present with white matter disease, ataxia, and retinal dystrophy. Loss of ACBD5, which combines tethering and fatty acid capturing properties, has metabolic consequences for peroxisome-ER cooperation in ether lipid (myelin) biosynthesis and metabolism of very long-chain fatty acids. In addition, it impacts on phospholipid transfer from ER to peroxisomes for peroxisomal membrane expansion, on peroxisome positioning and movement within the cell.

Peter Kim (Hospital for Sick Children, University of Toronto, Canada) reported on the role of the oxysterol-binding protein-related proteins (ORPs), which are involved in the trafficking of cholesterol and other lipids, at peroxisomal MCS, a still largely unexplored field. An siRNA screen of all 12 ORPs revealed a novel role of a number of ORPs in peroxisomes biogenesis and function.

György Csordas (Thomas Jefferson University, USA) reported on studies of the effect of the environmental

pollutant arsenic (As(III)) on local Ca^{2+} and ROS communication at ER MCS. They found ROS-dependent killing of hepatocytes involved enhanced local ER-to-mitochondria Ca^{2+} transfer (required IP3Rs and MCU) despite suppressed IP3R-mediated Ca^{2+} release, owing to ER MCS tightening and mitochondrial Ca^{2+} uptake sensitization.

Barbara Knoblach (Richard Rachubinski lab; University of Alberta, Canada) described work on yeast Pex3p, a membrane protein of peroxisomes and ER, and Inp1p, a connector linking peroxisomes to the ER. They defined regions in Inp1p required for tether assembly and maintenance and showed that proteins that interact with Inp1p, but localize primarily outside of ER-peroxisome tethers, affect peroxisome dynamics. Their findings suggest the presence of regulatory cues acting on ER-peroxisome tethers and the existence of MCS between peroxisomes and organelles other than the ER.

Lipid Metabolism and Roles at MCS

Tim Levine (UCL Institute of Ophthalmology, UK) identified widespread tubular lipid transfer domains (TULIPs) in bacteria, some of which share an N-terminal hydrophobic scoop with TamB, implicating TamB in lipid traffic to the bacterial outer membrane. His team has also attempted to map all potential FFAT-like motifs in yeast.

Will Prinz (NIH, NIDDK, USA) showed that lipid droplet and peroxisome biogenesis can occur at the same domains in the ER. These domains are marked by proteins that contain reticulon-like domains, Pex30 in yeast and MCTP2 in mammals. The Pex30/MCTP2 ER domains often remain associated with mature lipid droplets and peroxisomes, suggesting an unexpected link between organelle biogenesis in the ER and subsequent contacts between the ER and organelles that form there.

Mark McNiven (Mayo Clinic, USA) presented observations focused on the catabolism of cytoplasmic lipid droplets in hepatocytes, a central fat storing cell in the body. Digital recordings of live hepatocytes, and electron microscopy of fixed cells, demonstrated an active and transient exchange of both surface proteins and lipids from lipid droplets to lysosomes. This process was termed *nanolipophagy*.

Chris Loewen's group (University of British Columbia, Canada) identified a pH biosensing role for PI(4)P in the trans-Golgi network (TGN) in yeast and showed that this regulates the recruitment of Osh1 to ER-TGN membrane contacts. Osh1 TGN recruitment regulates trafficking at the TGN in response to glucose availability, a major signal regulating intracellular pH. Thus, intracellular pH is a factor regulating protein recruitment to membrane contacts.

Francesca Giordano (Institute for Integrative Biology of the Cell, France) presented work on the identification of the oxysterol binding protein (OSBP)-related proteins ORP5 and ORP8 as the lipid transport machinery mediating phosphatidylserine transport at ER-mitochondria MCS. They have also found that ORP5/8 are physically and functionally linked to the components of the MICOS complex that bridge outer and inner mitochondrial membranes to increase the efficiency of lipid transport between ER and mitochondria.

Robin Klemm (University of Zurich, Switzerland) presented the discovery of a mechanism that controls the spatial organization of organelles during adipocyte differentiation. His group found that the outer mitochondrial membrane protein MIGA2 tethers mitochondria to the ER and lipid droplets and this is important for efficient de novo biosynthesis of triacylglycerols from nonlipid precursors. Lipid droplets are formed during starvation, likely to prevent lipotoxicity by excess fatty acids formed upon autophagic degradation.

Mitsuo Tagaya (Tokyo University of Pharmacy and Life Sciences, Japan) reported that in addition to autophagosome formation, Syntaxin 17 mediates lipid droplet formation by interacting with acyl-CoA synthetase 3, a critical enzyme for lipid droplet formation.

Carmelina Petrunaro (Benoît Kornmann lab; ETH Zurich, Switzerland) presented a new strategy to monitor phospholipid transport in vivo using an enzyme-mediated lipid modification approach. This method enables for the first time the analysis of distinct transport routes between organelles of choice.

Calcium Signaling at MCS

Franck Polleux's group (Columbia University, USA) recently identified PDZD8 as an ER protein present at ER-mitochondria MCS and showed using gene replacement strategies in yeast that its SMP domain is functionally related to the SMP domain found in yeast Mmm1. Using 3D FIB-SEM in a Pdzd8 knockout cell line, they found that PDZD8 is required for the formation of ER-mitochondria contacts. In cortical pyramidal neurons, PDZD8 is required for Ca^{2+} uptake by mitochondria following synaptically induced Ca^{2+} -release from the ER and thereby regulates cytoplasmic Ca^{2+} dynamics in dendrites of pyramidal neurons in vitro. These results identify PDZD8 as a novel ER-mitochondria tethering protein in metazoan cells and uncover a critical role for ER-mitochondria coupling in the regulation of dendritic Ca^{2+} dynamics in mammalian neurons.

Paola Pizzo (University of Padova, Italy) found two unsuspected proteins, known to participate in different cellular processes, to be enriched at the ER-mitochondria interface and able to modulate their functional crosstalk. The first one, the TOM70

component of the mitochondrial translocase of the outer membrane, binds and recruits IP3Rs at ER-mitochondria contact sites, sustaining interorganelle Ca^{2+} transfer, mitochondrial respiration, and ATP production in a translocase-independent way. Similarly, the ER protein Presenilin-2 (PS2), especially its mutant forms linked to familial Alzheimer's disease (FAD), is also able, independently from its gamma secretase activity, to modulate mitochondrial function and bioenergetics, by a different mechanism: FAD-PS2 decreases both ER Ca^{2+} content, and thus, the amount of Ca^{2+} taken up by mitochondria upon physiological stimulations, and Hexokinase I mitochondrial association, altering organelle metabolites availability.

MCS With the Late Secretory Pathway and PM

Elizabeth Conibear's group (University of British Columbia, Canada) identified two adaptor proteins that recruit yeast Vps13 to different membrane contacts and showed that all known adaptors bind Vps13 via a related motif. These results support a competition-based model for regulating the dynamic localization of Vps13.

Efficient cross-presentation of phagocytosed antigens is vital for anti-cancer immunity and requires ER proteins, yet its mechanisms remain poorly understood. Paula Nunes-Hasler (University of Geneva, Switzerland) described a novel mechanism regulating cross-presentation where the ER-SNARE protein Sec22b tethers ER-phagosome MCS, facilitating PI(4)P/PS exchange.

Christian Ungermann (University of Osnabrueck, Germany) showed recent progress on the constituents and function of vacuole and mitochondria patch (vCLAMP) contact sites. He showed that the vacuolar HOPS subunit Vps39 and the mitochondrial outer membrane protein Tom40 form the principle tether of this contact site. Furthermore, his group identified separation-of-function alleles in both proteins that specifically impaired vCLAMPs, while maintaining their additional function on mitochondria and vacuoles. Based on this, he showed that vCLAMPs are critical for growth and proliferation of yeast cells.

MCS and Metabolic Diseases

Cancer cells dying in response to immunogenic cell death (ICD) stimulate anti-tumor immunity. Patrizia Agostinis' group (KU Leuven, Belgium) unraveled that during ICD, the extracellular exposure/emission of key danger signals by the dying cancer cells requires a PERK-Filamin A axis. This PERK-mediated module governs the spatial organization of ER-PM appositions

and store operated Ca^{2+} entry, through the dynamic rearrangement of the cytoskeleton.

Proper coordination of metabolism and its integration with immune response is paramount for the function and survival of cells. Gokhan Hotamisligil's group (Harvard University, Harvard-MIT Broad Institute, USA) in the past decade uncovered a critical role for the ER in this coordinated response and metabolic adaptation and in the pathogenesis of metabolic diseases such as obesity and diabetes. This new role of the ER involves specialized molecules involved in metabolic adaptation as well as interactions with other organelles, particularly the contacts between the ER and mitochondria. The details of these interactions during nutrient fluctuations and under obesity, and the application of advanced imaging technologies to quantitatively document these complex interactions were discussed. In conclusion, ER-mitochondria interactions were found to be highly dynamic and dramatically regulated during feeding cycles and disrupted in obesity in the liver tissue.

Emine Korkmaz (FEI/Thermo, The Netherlands) presented an integrated Cryo-Tomography Workflow aiming at determining structures directly within cellular environments.

MCS and Cancer

Anti-apoptotic Bcl-2-family members, including Bcl-2 and Bcl-X_L, reside at ER-MCS, thereby directly targeting IP3Rs and VDAC1, both Ca^{2+} -transport systems. Geert Bultynck (KU Leuven, Belgium) discussed work identifying the molecular determinants underlying IP3R/Bcl-2-complex formation, pointing to a unique role for Bcl-2's BH4 domain. This work also yielded novel peptide tools that can either antagonize or mimic Bcl-2's function in IP3R modulation. Bcl-2-inhibiting peptides targeting Bcl-2's BH4 domain are able to elicit pro-apoptotic Ca^{2+} signals in a variety of Bcl-2-dependent cancer cell models, causing cell death. Bcl-2-derived peptides corresponding to its BH4 domain are able to prevent pathophysiological Ca^{2+} signals that underlie disease burden in models of acute pancreatitis.

David Bernard (Université de Lyon, France) presented the work of his laboratory showing that ITPR2 (also known as IP3R2) promotes cellular senescence through increased levels of mitochondrial Ca^{2+} . They now reveal that ITPR2 plays a role in regulating cancer, some other aging hallmarks and lifespan in mice, and this could be linked to MERCs and cellular senescence.

Michelangelo Campanella's group (The Royal Veterinary College, University of London, UK) discovered that stressed mitochondria gather on the nucleus establishing cholesterol-rich contact sites to facilitate the retrograde response. This first evidence of tethering

between mitochondria and nucleus is regulated by the outer mitochondrial membrane-based protein TSPO and implicated in aggressive forms of breast cancer.

Nina Bonekamp (Nils-Göran Larsson lab; Max Planck Institute for Biology of Ageing, Germany) presented recent work on specific inhibitors of the mitochondrial RNA polymerase. Treatment of certain tumor cell lines with the inhibitors led to a reduction of cancer cell proliferation *in vitro* as well as *in vivo* without acute toxicity.

MCS and Neurodegeneration

Estela Area Gomes (Columbia University, USA) presented work showing that the 99 aa C-terminal domain of the amyloid precursor protein (APP-C99), a protein associated to Alzheimer's disease (AD), is involved in the regulation of MAM activity. In AD, the accumulation of APP-C99 at the MAM alters MAM function in the regulation of lipid homeostasis and mitochondrial functionality. This work suggests that lipid deregulation is an early feature of AD triggered by MAM dysfunction.

The TMEM16 family of proteins have recently been identified as evolutionarily conserved but functionally diverse modulators of cellular physiology and human pathology. While their yeast homolog Ist2 was shown to act as an MCS tether, no such function was attributed to mammalian counterparts. Maja Petkovich (Lily and Yuh-Nung Jan lab; University of California San Francisco, USA) showed that the spinocerebellar ataxia gene TMEM16K acts at ER-endolysosomal contact sites and is essential for proper endolysosomal function, opening the possibility that physiological functions of this important family of proteins in mammals are linked with interorganelle communication.

Julien Licchesi (University of Bath, UK) discussed preliminary data regarding the identification of a novel E3 ubiquitin ligase at MAM in brain cells. Moreover, his data suggest that MAM are dynamic microenvironments where the ubiquitin system might have important regulatory functions.

Yannik Poirier (Anne Eckert's lab; Psychiatric University Clinics Basel, University of Basel, Switzerland) presented that amyloid- β and tau-overexpressing cells have a highly activated unfolded protein response (UPR) and dysregulated mitochondrial bioenergetics, phenotypes which were found to increase upon an additional ER stress. These findings lend further evidence for the interplay between the UPR of the ER and mitochondrial dysregulation and provide new insights into the diverse pathways involved in AD pathology.

Poster Prize Winners

The winners of the Poster Sessions were as follows: Rishi Agrawal (Columbia University, USA), Yves Gouriou (INSERM U1060, France), and Florian Dingreville (University of Lyon, France). The Neuroscience Award (funded by Dementia Discovery Fund) was won by Elizabeth Sun (Yale University, USA).

Rishi Agrawal observed increased functionality of MAM-localized lipid biosynthetic enzymes in a mouse model of traumatic brain injury, possibly as a mechanism for repairing damaged membranes; these findings recapitulate their previous work in AD and suggest a molecular link between traumatic brain injury and AD. Yves Gouriou showed that MFN2 knock-down is associated with a Warburg-like mechanism increasing the glycolytic metabolism and the cytosolic ATP importation into mitochondria through ANT2. This study suggested that this metabolic reprogramming confers resistance to hypoxic injury. Florian Dingreville demonstrated that glucotoxicity-associated beta cell dysfunction is associated with increased ER-mitochondria interactions, disruption of Ca^{2+} homeostasis, and mitochondria fission in rat and human pancreatic beta cells. Elizabeth Sun reported on TMEM24 (CDC2L), a lipid transfer protein predominantly expressed in neurons and neuroendocrine cells. TMEM24 functions as a tether between the ER and the PM, resides near Kv2.1 channels, and is regulated by cytosolic Ca^{2+} .

Concluding Remarks

On behalf of the MCS community, we would like to thank Thomas Simmen and his co-organizers Jennifer Rieusset, Antonio Zorzano, and Stephan Frank, for securing the funding and the organization of a truly inspiring and highly educating scientific meeting. The MCS community gathered in Arosa elected the authors of this report to carry the torch and organize a new edition of this EMBO Workshop in 2020.

Acknowledgments

We would like to extend our thanks to the following sponsors for supporting the exchange of the results of the studies done in our field: EMBO (w18/38), Swiss National Fund (IZSEZ0_177581), Canadian Institutes for Health Research (155310), Swiss Industry Science Fund (Novartis, Roche), The Company of Biologists (EMBO105), JCB, FEI (Thermo Scientific), SAGE press (Contact), EMBO Press, Graubündner Kantonalbank. We thank the presenters for their support in the preparation of this report.



Authors' Note

This work was presented at the *EMBO Workshop: Membrane Contact Sites in Health and Disease*, Arosa, Switzerland, September 21–25, 2018.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The meeting was sponsored by: EMBO (w18/38), Swiss National Fund (IZSEZ0_177581), Canadian Institutes for Health Research (155310), Swiss Industry Science Fund (Novartis, Roche), The Company of Biologists (EMBO105), JCB, FEI (Thermo Scientific), SAGE press (Contact), EMBO Press, Graubündner Kantonalbank.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/ or publication of this article: E.B. is supported by the European Research Council

(ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No 772103-BRIDGING). T.C. is supported by grants from the Ministry of University and Research (Bando SIR 2014 no RBS114C65Z) and from the Università degli Studi di Padova (Progetto Giovani 2012 no GRIC128SP0 to T.C. and Progetto di Ateneo 2016 no CALI_SID16_01 to T.C.). F.G. is supported by an ATIP-Avenir Program (project: R16071LS, grant number: RSE17006LSA) and by a dotation "Fondation Schlumberger pour l'Éducation et la Recherche", FSER, 2019. A.H.-B. is supported by start-up funds #1606500086 of the W. Harry Feinstone Department of Molecular Microbiology & Immunology, Johns Hopkins University Bloomberg School of Public Health. L.P. is supported by the Canadian Institutes of Health Research Operating Grant 201603PJT-365052.

ORCID iD

Anne Hamacher-Brady  <http://orcid.org/0000-0001-5042-1338>