Wednesday May 21, 2025

Olympic Museum | Quai d'Ouchy 1, 1006 Lausanne

LIMNA
LAUSANNE INTEGRATIVE METABOLISM & NUTRITION ALLIANCE

LIMNA SYMPOSIUM

INTER-ORGANELLE METABOLISM AND SIGNALLING

Speakers

Heidi McBride, Montreal Neurological Institute and Hospital, Canada

A. Phillip West, The Jackson Laboratory, USA

Benoit Kornmann, University of Oxford, UK

Stefanie-Kristin Wculek, IRB Barcelona, Spain

Wanda Kukulski, University of Berne, Switzerland

Lluis Fajas Coll, University of Lausanne, Switzerland

+++ Short talks and posters selected from submitted abstracts +++

Organizing committee:
Francesca Amati, Carles Canto, Giovanni D'Angelo, Ping-Chih Ho, Alexis Jourdain, Marlen Knobloch & Ulrike Toepel

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CHUV EPFL UNIL | Université de Lausanne

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8h30-8h55 Welcome coffee and badge distribution

9h00 Opening
Chair: Francesca Amati

Session I

9h05 Wanda Kukulski, University of Berne, Switzerland
The architecture of membrane contact sites
9h40 Benoit Kornmann, University of Oxford, UK
A Journey on the Interorganelle Lipid Transportation Network
10h15 Juliane Da Graça, Université Paris Cité, Paris, France.
ER-endosomes contacts generate a local environment promoting phagophore formation

10h30 Coffee Break

Session II

Chair: Marlen Knobloch
11h00 Stefanie-Kristin Wculek, Institute for Research in Biomedicine (IRB) Barcelona, The Barcelona Institute of Science and Technology (BIST), Barcelona, Spain
How innate immune cells adapt to environment and function: diverse tales of mitochondria
11h35 Lluis Fajas Coll, University of Lausanne, Switzerland
CDK4 remodels cytoskeleton and mitochondria- ER contacts to promote apoptosis and decrease migration in cancer cells
12h10 Simone Crivelli, University of Lausanne, Switzerland
Astrocytes transfer mitochondria to neurons for metabolic support

12h25 Lunch & Poster session & Coffee
13h15-14h Presentation of posters with even numbers
14h00-14h45 Presentation of posters with odd numbers
Please remove your posters

Session III

Chair: Carles Cantó
15h00 A. Phillip West, The Jackson Laboratory, USA
Mitochondrial control of innate immune and inflammatory signaling
15h35 Patricia Boya, University of Fribourg, Switzerland
Mitophagy at the crossroads of neuroinflammation during aging and disease
15h50 Juan C. Landoni, École Polytechnique Fédérale de Lausanne (EPFL), Switzerland
Mitochondrial pearling mediates mtDNA nucleoid and microdomain distribution
16h05 Heidi McBride, Montreal Neurological Institute and Hospital, Canada
New insights into the mechanisms and functions of mitochondrial derived vesicles

16h40 Concluding remarks and award distribution
Chair: Francesca Amati

TALK ABSTRACTS

Session I

The architecture of membrane contact sites

Wanda Kukulski, University of Berne, Switzerland

Organelles interact through close apposition of their membranes. Such contact sites serve the exchange of lipid molecules, calcium transport and organelle biogenesis. The mechanisms by which molecules are transferred at membrane contact sites are poorly understood because little is known about the underpinning supramolecular organisation. We aim to reveal and dissect the architecture composed of proteins and apposing bilayers and thereby shed light on how functional microenvironments between the membranes of two organelles are formed. Towards this goal, we employ correlative light and electron microscopy approaches, which we complement with live fluorescence imaging, biochemical and cell biological experiments.

A Journey on the Interorganelle Lipid Transportation Network

Benoit Kornmann, University of Oxford, UK

How lipids are transported from their site of synthesis – the endoplasmic reticulum – to all other cellular membranes is a question that has defied understanding for years. The last two decades have shown fulgurant progress in this fundamental aspect of cell biology. The discovery of lipid transport proteins at membrane contact sites have provided an elegant mechanism to transport hydrophobic molecules across the aqueous cytosol, to reach all organelle membranes, including those that do not participate in intracellular exchange by vesicular ways. Nevertheless, our understanding of lipid transport is hampered by two plagues; the extensive redundancies in lipid transport routes and the dearth of methods to assess intracellular lipid fluxes. I will discuss our progress towards understanding lipid transport to mitochondria in yeast, and how it can be generalised to other membranes as well, I will describe the technologies that we developed to address redundancies and lipid flux measurements, and I will discuss our view of an integrated intracellular lipid trafficking network.

ER-endosomes contacts generate a local environment promoting phagophore formation

Juliane Da Graça, Université Paris Cité, Paris, France.

Autophagy is a cellular process initiated by the de novo formation of a double membrane vesicle called autophagosome, which emanate from a transient structure termed phagophore. Phagophore biogenesis requires phase transition and occurs at the immediate vicinity of endoplasmic reticulum (ER) subdomains which can be engaged in membrane tethering with other organelles such as mitochondria and plasma membrane. Recently, we demonstrated a dynamic recruitment of early endosomal membranes toward sites of phagophore biogenesis. Our present work shows that the number of endosomes-ER contact sites (EERCS) increase during acute response of starvation and are mobilized in early steps of autophagy pathway.
To relevantly tackle the implication of EERCS during phagophore biogenesis, we optimized different cutting-edge technologies specific for contact sites studies (i.e. expansion microscopy, machine learning-

based analysis, split-turboID, biochemical purification). Deeper analyzes on the nature and the dynamics of EERCS unveiled their implication in the creation of a local environment with specific biochemical properties. These include phase transition and Ca2+ confined release, events that could support de novo membrane generation. Here, we identify a novel role for ER-endosomes membrane contact sites during early response to nutrients deprivation. We propose that dynamic mobilization of EERCS enable transient confinement of cytoplasm which in turns favors the local enrichment of proteins, lipids and ions required for phagophore biogenesis initiation.

Session II

How innate immune cells adapt to environment and function: diverse tales of mitochondria

Stefanie-Kristin Wculek, IRB Barcelona, Spain

My lab investigates tissue-specific adaptations of dendritic cells, neutrophils and macrophages in health and non-infectious conditions with a focus on immunometabolism. I will present how mitochondria and an active electron transport chain regulate the context-dependent functions of macrophages and dendritic cells via entirely distinct molecular mechanisms.

CDK4 remodels cytoskeleton and mitochondria- ER contacts to promote apoptosis and decrease migration in cancer cells

Lluis Fajas Coll, University of Lausanne, Switzerland

Cyclin-dependent kinase 4 (CDK4) is a pivotal regulator of cell cycle progression, traditionally recognized for its role in driving cell proliferation. Emerging evidence suggests additional, non-canonical functions for CDK4, including the regulation of cytoskeletal dynamics and metabolism. This presentation shows data about these novel roles of CDK4 in triple-negative breast cancer (TNBC). Using genetic and pharmacological approaches, we found that CDK4 deletion minimally impacts TNBC proliferation yet significantly enhances resistance to apoptosis by impairing mitochondrial apoptosis pathways. CDK4 inhibition was shown to reduce mitochondria-ER contact sites (MERCs) and disrupt mitochondrial dynamics, causing mitochondrial dysfunction and diminished metabolic flexibility. Moreover, phosphoproteomic analyses revealed that CDK4 regulates Protein Kinase A (PKA) activity at MERCs, essential for mitochondrial fission and calcium signaling. Additionally, we demonstrated that CDK4 modulates TNBC cell migration by attenuating RhoA activation through phosphorylation of Myo9b. Collectively, these findings highlight CDK4's broader regulatory role in TNBC progression, linking metabolic sensitivity, apoptosis resistance, and cellular migration. Targeting the CDK4-driven Myo9b-RhoA and MERC-associated pathways presents promising therapeutic opportunities to overcome TNBC aggressiveness and treatment resistance.

Astrocytes transfer mitochondria to neurons for metabolic support

Simone Crivelli, University of Lausanne, Switzerland

Mitochondria are secreted by astrocytes via large vesicles during stressful events, such as hypoxia, to support neurons. However, the mechanisms governing this process and the range of stressors triggering mitochondrial release remain unclear. Additionally, it is debated whether mitochondria are transferred directionally from astrocytes to neurons under physiological conditions.
Using a co-culture system of astrocytes with fluorescently labeled mitochondria and fluorescently labeled neurons, we tracked mitochondrial transfer under various conditions. To investigate physiological transfer

in vivo, we developed an adeno-associated virus (AAV) for astrocyte-specific expression of green fluorescent protein (GFP) in mitochondria, co-injected with an AAV labeling neurons, into the hippocampus of wild-type mice. This enabled visualization of donor (astrocytes) and recipient (neurons) cells via fluorescence microscopy.
We observed directional mitochondrial transfer from astrocytes to neurons under physiological conditions, with the transfer rate doubling within 20 minutes upon exposure to a stressor like glutamate. In vivo data corroborated mitochondrial movement from astrocytes to neurons.
In conclusion, our preliminary findings suggest that directional mitochondrial transfer from astrocytes to neurons occurs in vivo under physiological conditions and intensifies under stressors like glutamate, potentially to provide metabolic support.

Session III

Mitochondrial control of innate immune and inflammatory signaling

Phillip West, The Jackson Laboratory, USA

Dr. Phillip West received his PhD in Immunobiology from Yale University in 2011 and performed postdoctoral training at Yale School of Medicine with Gerald Shadel. His research group at The Jackson Laboratory studies how mitochondria regulate the mammalian immune system in health and disease. In this seminar, Dr. West will discuss his team's ongoing efforts to define how mitochondrial dysfunction and metabolic rewiring impact innate immune signaling nodes. He will share findings from new mouse models and discuss how differential alterations in mitochondrial homeostasis impinge on inflammatory signaling and cellular innate immunity.

Mitophagy at the crossroads of neuroinflammation during aging and disease

Patricia Boya, University of Fribourg, Switzerland

Loss of proteostasis and dysregulated mitochondrial function are recognized as core hallmarks of aging, with recent revisions also highlighting impaired macroautophagy and chronic inflammation. Mitophagy, a crucial process in mitochondrial quality control, lies at the nexus of these aging-related phenomena; however, its age-associated perturbations have been largely unexplored. In our recent study, we conducted a comprehensive analysis of mitolysosome levels in mice and discovered that, contrary to the established decline in non-selective macroautophagy, mitophagy either remains stable or increases with age across all examined tissues. This upregulation is mediated by the PINK1-PRKN-dependent pathway. Further investigation revealed a simultaneous increase in mitochondrial DNA (mtDNA) leakage into the cytosol and activation of the CGAS-STING1 inflammation axis, phenomena that were also observed in primary fibroblasts from older human donors. We propose that mitophagy may be selectively upregulated during aging to enhance mitochondrial function and mitigate mtDNA-induced inflammation. Notably, treatment with the mitophagy inducer urolithin A alleviates age-related neurological decline, evidenced by improved synaptic connectivity, cognitive memory, and visual function. In alignment with our hypothesis, urolithin A decreases cytosolic mtDNA levels, reduces CGAS-STING1 activation, and diminishes neuroinflammation. Additionally, using an in vitro model of mitochondrial membrane permeabilization, we confirmed that PINK1-PRKN-mediated mitophagy is vital for resolving cytosolic mtDNA-triggered inflammation. These findings suggest a novel integrative approach to addressing aging and enhancing healthspan through the induction of mitophagy.

Mitochondrial pearling mediates mtDNA nucleoid and microdomain distribution

Juan C. Landoni, École Polytechnique Fédérale de Lausanne (EPFL), Switzerland

The mitochondrial network carries an essential multi-copy genome packaged in nucleoids. These are regularly spaced along mitochondria and confined by cristae invaginations, enabling the regionalized distribution of mitochondrial function along the network and the peripheral ejection of damaged material. Mechanistically, however, it is unclear how such a constrained system with seemingly static nucleoids can dynamically manage its contents, segregate and distribute nucleoids, and sense and isolate damaged regions.
The mitochondrial tubule can spontaneously and reversibly collapse into highly regular compartments, a process known as "pearling". Using adaptive super-resolution microscopy and pharmacological and genetic modulation of its occurrence, we identified pearling as a major driver of nucleoid splitting and regular distribution along the tubule, regulated by calcium and fission-adjacent molecular mechanisms. Additionally, we further investigate its putative role in aiding the acute local biochemical changes required for subsequent mitochondrial fission and quality control.

New insights into the mechanisms and functions of mitochondrial derived vesicles

Heidi McBride, Montreal Neurological Institute and Hospital, Canada

The generation of mitochondrial derived vesicles (MDVs) is a tightly regulated process to select mitochondrial contents for removal in vesicular profiles that are delivered to either the endomembrane system or peroxisomes. Our lab pioneered our understanding of these pathways within the context of quality control and peroxisomal biogenesis. More recently we have been investigating the contribution of MDV transport during immune signaling pathways, where they play key roles in the transition between innate and adaptive immune pathways, and in the regulation of pyroptotic cell death. I will present our findings on the mechanisms, signaling, and functional impact of MDV transport within immune pathways.