Cfatg

11th SCIENTIFIC DAYS ON AUTOPHAGY

November, 8 - 10 2023
Palais Hirsch, Lyon

4 THEMATIC SESSIONS

- MECHANISM & REGULATION
- PHYSIOPATHOLOGY
- IMMUNITY & INFECTION
- CANCER

INVITED SPEAKERS

Masaaki Komatsu - *Tokyo, Japan*
Claudine Kraft - *Freiburg, Germany*
Lisa Frankel - *Copenhagen, Danemark*
Carmine Settembre - *Naples, Italy*
Harald Wodrich - *Bordeaux, France*

LOCAL ORGANIZATION COMMITTEE

Flavie Strappazzon - *Coordinator, PGNM, Lyon*
Carole Kretz-Remy - *Coordinator, PGNM, Lyon*
Aurore Rozières - *CIRI, Lyon*
Mathias Faure - *CIRI, Lyon*
Fabien Chevalier - *LBTI, Lyon*
Olivier Meurette - *CRCL, Lyon*
Ludivine Walter - *LBMC, Lyon*

BOOK OF ABSTRACTS

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WELCOME TO THE 11TH SCIENTIFIC DAYS ON AUTOPHAGY

The CFATG is a french association that promotes scientific research in the field of autophagy, stimulates exchanges, creates links, supports young researchers, awards grants and organizes meetings.

As members fo the CFATG board, we are proud to organize and welcome you at the 11th scientific days on autophagy in Lyon.

Flavie Strappazzon & Carole Kretz-Remy

SCIENTIFIC COMMITTEE

Sophie Pattingre - *IRCM U1194, Montpellier*
Audrey Esclatine - *I2BC, Gif sur Yvette*
Frédéric Gros - *CRBS, Strasbourg*
Carole Kretz-Remy - *PGNM, Lyon*
Flavie Strappazzon - *PGNM, Lyon*
Iban Seiliez - *INRA/UPPA, St Pée-sur-Nivelle*
Coralie Daussy - *MFP, Bordeaux*
Guillaume Beauclair - *I2BC, Gif sur Yvette*

LOCAL ORGANIZATION COMMITTEE

Fabien Chevalier

Tissue Biology and Therapeutic Engineering Laboratory (LBTI), UCB Lyon1 CNRS UMR 5305 - Team Skin Functional Integrity

Mathias Faure

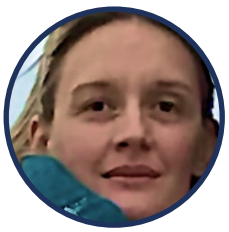
International Research Center in Infectiology (CIRI) - UCB Lyon1, ENS Lyon, CNRS UMR5308, INSERM U1111 – Team Autophagy Infection Immunity

Carole Kretz-Remy

Pathophysiology and Genetics of Neuron and Muscle laboratory (PGNM, INMG) - UCB Lyon1 CNRS UMR5261 INSERM U1315 – Team Muscle Nucleus and Cytoskeleton Architecture

Olivier Meurette

Cancer Research Center of Lyon (CRCL) - UCB Lyon1 CNRS UMR 5286 INSERM 1052 Centre Léon Bérard – Team Apoptosis Cancer and Development.



Aurore Rozière

International Research Center in infectiology - UCB Lyon1, ENS Lyon, CNRS UMR5308, INSERM U1111– Team Autophagy Infection Immunity

Flavie Strappazzon

Pathophysiology and Genetics of Neuron and Muscle laboratory, UCB Lyon1 CNRS UMR5261 INSERM U1315 – Team Energy Metabolism and Neuronal Development

Ludivine Walter

Laboratory of Biology and Modeling of the Cell – UCB Lyon1, ENS Lyon CNRS UMR5239, INSERM U1293 – Team Regulated Cell Death and Genetics of Neurodegeneration.

TABLE OF CONTENTS

SCIENTIFIC PROGRAM

SCIENTIFIC PROGRAM

Wednesday November 8th
Afternoon

01:00pm ***Participants Welcoming & registration***

02:00pm Opening & welcome address
Sophie Pattingre - CFATG president
Carole Kretz & Flavie Strappazzon - Local committee coordinators

02:30pm **Keynote Lecture**
Phase-separation and autophagy co-creating stress response
Pr Masaaki Komatsu
Jutendo University School of medicine, Tokyo, Japan

SESSION 1
MOLECULAR MECHANISMS & SIGNALING
Chair(wo)men: Audrey Esclatine - Fabien Chevalier

03:30pm **Physical properties of cargo determine their degradability through autophagy**
Claudine Kraft
Institute for Biochemistry and Molecular Biology, University of Freiburg, Germany

04:15pm O1* - The autophagy protein WIPI2 governs omegasome biogenesis
Daniele Campisi - Paris, France

04:30pm O2* - Involvement of the protein SH3KBP1 in the modulation of ER architecture and autophagy during myofiber formation
Marine Daura - Lyon, France

04:45pm ***Break with partners***

** Eligible for best Oral Communication or best Flash Talk awards*

SCIENTIFIC PROGRAM

Wednesday November 8th
Afternoon

05:15pm O3* - Characterization of MYTHO, a new player of autophagy that regulates muscle mass integrity and ageing
Anaïs Franco-Romero - Padua, Italy

05:30pm O4 - Membrane localization of LGG-1/GABARAP is dispensable for autophagy in *C. elegans*
Renaud Legouis - Gif-sur-Yvette, France

05:45pm Flash talk Session 1
- FT1* - *Caroline Liénard - Lyon, France*
- FT2* - *Giuliana Cesare - Milan, Italy*
- FT3* - *Puck Norell - Paris, France*
- FT4* - *Melissa Jauquet - Paris, France*
- FT5* - *Claire Allioux - Toulouse, France*
- FT6* - *Aude Lavedrine - Lyon, France*
- FT7* - *Francesco Naso - Rome, Italy*

06:15pm Group Photo

06:30pm Free time

07:30pm Cocktail with partners

** Eligible for best Oral Communication or best Flash Talk awards*

SCIENTIFIC PROGRAM

Thursday November 9th

08:30am Participants Welcoming

SESSION 2
PHYSIOPATHOLOGY
Chairmen: Iban Seiliez - Etienne Morel

09:00am Modulation of autophagy in human disorders
Carmine Settembre
Telethon Institute of Genetics and Medicine, Pozzuoli, Italy

09:45am O5* - Chaperone-Mediated Autophagy safeguards against hyperglycemic stress
Emilio-José Vélez - St Pée-sur-Nivelle, France

10:00am O6* - The role of autophagy in the rare genetic neurodegenerative disease BPAN
Marion Celle- Lyon, France

10:15am Break with partners

11:00am O7* - Mitochondrial respiration and mitophagy in familial sarcoidosis
Thomas El Jammal - Lyon, France

11:15am O8 - A novel pathogenic mutation in the ATP5MC3 gene of ATP synthase is associated with lysosomal-autophagosomal alterations
Camilla Bean - Udine, Italy

11:30am Round-table discussion with associations of patients
Chairwomen: Ludivine Walter - Aurore Rozières

12:00pm Lunch Break with partners & Poster session 1

** Eligible for best Oral Communication or best Flash Talk awards*

SCIENTIFIC PROGRAM

Thursday November 9th

SESSION 3
IMMUNITY & INFECTION
Chairmen: Mathias Faure - Frédéric Gros

02:00pm **Adenovirus entry: A voyage through the autophagy nexus**
Harald Wodrich
Microbiologie Fondamentale et Pathogénicité, Bordeaux, France

02:45pm O9 - Impaired Reprogramming of the Autophagy Flux in Maturing Dendritic Cells from Crohn's Disease Patients with Core Autophagy Gene-Related Polymorphisms
Aurore Rozières - Lyon, France

03:00pm O10* - Role of ATG16L1 partners in B cell receptor trafficking and antigen presentation
Quentin Frenger - Strasbourg, France

03:15pm ***Break with partners***

03:45pm O11* - Role of LC3/GABARAP proteins in the assembly of HIV-1
Marjory Palaric - Paris, France

04:00pm O12 - Interactions between the fungal pathogen Candida albicans and the host's autophagy machinery during the infection of epithelial cells
Pierre Lapaquette - Dijon, France

** Eligible for best Oral Communication or best Flash Talk awards*

SCIENTIFIC PROGRAM

Thursday November 9th

04:15pm Flash talk session 2

- FT8* - *Mathilde Nugue - Paris, France*
- FT9* - *Claudia Cirotti - Rome, Italy*
- FT10* - *Alice Desprairies - Toulouse, France*
- FT11 - *Daniela Trisciuoglio - Rome, Italy*
- FT12* - *Anna M Schläfli - Bern, Switzerland*
- FT13* - *Charlotte Ducau - Toulouse, France*

04:45pm Poster session 2

05:45pm CFATG general assembly

06:30pm Free time

07:30pm Congress dinner in a typical "bouchon" restaurant of Lyon in the historical center & After at The Big White around 10:45pm

** Eligible for best Oral Communication or best Flash Talk awards*

SCIENTIFIC PROGRAM

Friday November 10th

08:30am Participants Welcoming

SESSION 4
CANCER
Chair(wo)men: Olivier Meurette - Valérie Pierrefite-Carle

09:00am **Autophagy-mediated control of ribosome homeostasis in oncogene-induced senescence**
Lisa Frankel
Danish Cancer Institute, University of Copenhagen Copenhagen, Danemark

09:45am O13* - Role of autophagy on intestinal stem cell genome integrity
Caterina Luana Pitasi - Paris, France

10:00am O14* - PD-L1 and the post-transcriptional control of autophagy: molecular mechanisms and role in response and resistance to therapy in head and neck cancers
Axel Arthur - Toulouse, France

10:15am Break with partners

11:00am O15* - Effect on tumor development of Atg5 inactivation in bone microenvironment
Marie-Charlotte Trojani - Nice, France

11:15am O16 - The oncogenic DMTF1β splice variant promotes autophagy-dependent cancer cell motility
Mario Tschan - Bern, Switzerland

11:30am Awards

12:00pm Closing remarks

12:45pm End of the 11th Scientific Days on Autophagy & Lunch boxes before departure

** Eligible for best Oral Communication or best Flash Talk awards*

ORAL COMMUNICATIONS

SESSION 1 MOLECULAR MECHANISMS & SIGNALING

Wednesday November 8th
03:30 - 05:45pm

Chair(wo)men:
Audrey Esclatine - Fabien Chevalier

O1* - MOLECULAR MECHANISMS & SIGNALING

Daniele CAMPISI
Kennedy Bonjour , Thomas Wollert

Membrane Biochemistry and Transport, Department of Cell biology and Infection, INSTITUT PASTEUR, 75015 Paris, France

The autophagy protein WIPI2 governs omegasome biogenesis

Autophagy is a cellular recycling process that degrades damaged or superfluous cytoplasmic components. The formation of autophagosomes occurs at specialized domains of the endoplasmic reticulum (ER), termed omegasomes, from which cup-shaped phagophores emerge (1). Recent data showed that vesicles from different sources merge to generate a hybrid structure called HyPAS (2). However, how omegasomes are generated and how they relate to phagophores remain unknown. We found that targeting the phosphatidylinositol 3 phosphate (PI(3)P) binding protein WIPI2 to the plasma membrane (PM) induces the formation of omegasome-like membranes from which phagophores emerge (3). The process is independent of canonical autophagy inducers including the ULK1 kinase or PI(3)-kinase complexes, suggesting that WIPI2 is a key factor for the induction of omegasomes (3). WIPI2 targeting at the PM allows us to uncouple the formation of omegasomes from canonical autophagy, providing a model system to identify membrane trafficking pathways that contribute lipids for the formation of omegasomes and important molecular regulators of the pathway. Through a combination of correlative light electron microscopy (CLEM), confocal and live cell imaging, we revealed that omegasome-like membranes generated at the PM are formed by fusion of donor vesicles. We found that this process is regulated by the autophagy proteins ATG9A, FIP200 and E-Syt2, as well as canonical trafficking factors VAMP7 and STX17 which are involved in the fusion of vesicles. Our results suggest that in contrast to the current paradigm, omegasomes are generated by fusion of donor vesicles and not by ER membrane remodeling.

1. Dooley et al., 2014. Molecular Cell
2. Kumar et al., 2021. Cell
3. Mohan et al., Under revision

** Eligible for best Oral Communication awards*

O2* - MOLECULAR MECHANISMS & SIGNALING

Marine DAURA
Leslie Andromaque, Vincent Gache, Carole Remy-Kretz

UCB Lyon 1 - CNRS UMR5261 - Inserm U1315

Involvement of the protein SH3KBP1 in the modulation of ER architecture and autophagy during myofiber formation

The formation of mature striated and plurinucleated myofibers occurs from myoblasts that are muscle precursors, in a process called muscle differentiation. During this process, the organization of cellular components such as organelles is essential for the proper functioning of the muscle fiber.

SH3KBP1 is an adaptor protein well described to be involved in membrane trafficking, but its function in muscle cells has never been investigated. In the team, we determined that SH3KBP1 expression is transiently increased during the differentiation of myoblasts into myotubes. We also demonstrated that SH3KBP1 binds to calnexin, a transmembrane chaperone of the endoplasmic reticulum (ER). Moreover, we observed that SH3KBP1 under-expression alters the perinuclear architecture of the ER, during the early phases of muscle fiber formation. Of interest, a well-known process involved in the ER remodeling is the reticulophagy (also called ER-phagy), which is a selective autophagy targeting the ER. During this process, a portion of the ER is specifically targeted for degradation by ER-phagy receptors, which allow the recruitment of the autophagic machinery at ER sites. The ER portion is thus engulfed in autophagosomes that fuse with lysosomes to form autolysosomes, in which the ER is degraded.

We thus asked whether SH3KBP1 could be involved in the maintenance of ER through modulation of bulk autophagy and/or ER-phagy process. Our results indicate that under-expression of SH3KBP1 modulate the bulk autophagic and ER-phagic fluxes. Moreover, we identified that SH3KBP1 possesses many hallmarks of ER-phagy receptors. Thus, we suggest that SH3KBP1 is involved in the maintenance of muscle fiber integrity through ER modulation via autophagic process.

** Eligible for best Oral Communication awards*

O3* - MOLECULAR MECHANISMS & SIGNALING

Anaïs FRANCO-ROMERO
Leduc-Gaudet Jean-Philippe, Morbidoni Valeria, Sartori Roberta, Romanello Vanina, Grumati Paolo, Tooze Sharon A., Gouspillou Gilles, Hussain Sabah NA, Trevisson Eva, Sandri Marco

Department of Biomedical Sciences, University of Padova, Italy

Characterization of MYTHO, a new player of autophagy that regulates muscle mass integrity and ageing

The discovery of new unknown players involved in muscle protein degradation is of potential interest to combat aging sarcopenia and other muscle-related diseases. We identified a novel FoxO-dependent conserved gene, that we named MYTHO (Macroautophagy and YouTH Optimizer), that upregulates in many catabolic conditions such as aging, denervation, cancer, sepsis and fasting. In vitro and in vivo experiments in muscle showed MYTHO interaction with autophagic markers and suggested a potential role in autophagy regulation. As autophagy contributes to protein breakdown, gain and loss of function experiments confirmed that MYTHO modulates muscle fiber size. Indeed, while MYTHO overexpression in skeletal muscle was sufficient to induce atrophy, short term inhibition of MYTHO attenuated muscle atrophy in fasting, cancer-cachexia and sepsis animal models. However, prolonged MYTHO downregulation triggers a progressive apparition of several myopathic features, muscle weakness and many ultrastructural defects as autophagic vacuoles, tubular aggregates, swollen mitochondria, etc. In addition, our recent data showed that the deletion of the ortholog mytho gene in C.elegans blocks autophagy, impairs muscle function and shortened the life span of animals. Our findings contribute to the identification and the characterization of a new FoxO-dependent gene that plays a central role in the autophagy-lysosomal system and that regulates muscle mass integrity and longevity.

** Eligible for best Oral Communication awards*

O4 - MOLECULAR MECHANISMS & SIGNALING

Renaud LEGOUIS
Romane Leboutet, Céline Largeau, Emmanuel Culetto, Christophe Lefebvre

Université Paris-Saclay, CEA, CNRS, Institute for Integrative Biology of the Cell (I2BC) and INSERM U1280, 91198, Gif-sur-Yvette, France

Membrane localization of LGG-1/GABARAP is dispensable for autophagy in *C. elegans*

The ubiquitin-like proteins Atg8/LC3/GABARAP are required for multiple steps of autophagy, such as initiation, cargo recognition and engulfment, vesicle closure and degradation. Most of LC3/GABARAP functions are considered dependent on their post-translational modifications and their association with the autophagosome membrane through a conjugation to a lipid, the phosphatidyl-ethanolamine. Contrarily to mammals, C. elegans possesses single homologs of LC3 and GABARAP families, named LGG-2 and LGG-1. Using site-directed mutagenesis, we inhibited the conjugation of LGG-1 to the autophagosome membrane and generated mutants that express only cytosolic forms, either the precursor or the cleaved protein. LGG-1 is an essential gene for autophagy and development in C. elegans, but we discovered that its functions could be fully achieved independently of its localization to the membrane. This study reveals an essential role for the cleaved form of LGG-1 in autophagy but also in an autophagy-independent embryonic function. Our data question the use of lipidated GABARAP/LC3 as the main marker of autophagic flux and highlight the high plasticity of autophagy.

SESSION 2
PHYSIOPATHOLOGY

Thursday November 9th
09:00 - 11:30am

Chairmen:
Iban Seiliez - Etienne Morel

O5* - PHYSIOPATHOLOGY

Emilio-José VÉLEZ[1]
Simon Schnebert[1], *Maxime Goguet*[1], *Sara Balbuena-Pecino*[1], *Karine Dias*[1], *Linda Beauclair*[1], *Stéphanie Fontagné-Dicharry*[1], *Vincent Véron*[1], *Alexandra Depincé*[2], *Florian Beaumatin*[1], *Amaury Herpin*[2], *Iban Seiliez*[1]

1. INRAE UMR1419 NuMeA, Université de Pau et des Pays de l'Adour, France
2. INRAE UR1037 LPGP, France

Chaperone-Mediated Autophagy safeguards against hyperglycemic stress

Chaperone-Mediated Autophagy (CMA) constitutes a major pathway of lysosomal proteolysis, essential for cellular homeostasis and metabolism, whose dysfunction has been associated with various human pathologies. While extensively characterized in mammals, only recent findings have unveiled functional evidence of CMA in fish. The present study delves into the exploration of CMA in the rainbow trout (RT, Oncorhynchus mykiss), a fish species recognized as a model organism of glucose intolerance and characterized by the presence of two paralogs of the CMA-limiting factor lysosomal-associated membrane protein 2A (Lamp2a). To this end, we validated a fluorescent reporter (KFERQ-PA-mCherry1), previously used to monitor functional CMA in mammalian cells, in an RT hepatoma-derived cell line (RTH-149). We found that exposure of these cells to elevated glucose concentrations (HG, 25 mM) prompted the relocation of the CMA reporter to lysosomes and/or late endosomes in a KFERQ- and Lamp2a-dependent manner, while also diminishing its half-life compared to a lower glucose condition (Control, 5 mM). This unequivocally highlighted an augmented CMA flux under HG levels. Furthermore, we observed that the activation of CMA in response to HG exposure was mediated by the generation of mitochondrial reactive oxygen species, and involved the antioxidant transcription factor nuclear factor erythroid-derived 2, like 2 (Nrf2). Finally, we evidenced the pivotal role of CMA in safeguarding against hyperglycemic stress, predominantly facilitated by one of the two RT Lamp2A paralogs. Collectively, our results provide unequivocal evidence for CMA activity existence in RT and highlight CMA's role and regulation during glucose-related metabolic disorders.

** Eligible for best Oral Communication awards*

O6* - PHYSIOPATHOLOGY

Marion CELLE[1]*
Sahra Aniorte[1], Gaetan Lesca[2], Ludivine Walter[1], Bertrand Mollereau[1]*

1. Laboratory of Biology and Modelling of the Cell -CNRS: UMR5239, INSERM U2110, Université de Lyon, Université Claude Bernard Lyon1, ENS de Lyon, UMS344 Biosciences Lyon Gerland - France
2. Department of Medical Genetics -University Hospital of Lyon -France
**First Authors*

The role of autophagy in the rare genetic neurodegenerative disease BPAN

The Beta-Propeller protein Associated with Neurodegeneration (BPAN) is a rare genetic neurological disease characterized by iron accumulation in the brain of patients. The clinical features are divided in two phases: a neurodevelopmental phase with epilepsy and intellectual deficiency, and a neurodegenerative phase associated with parkinsonism. BPAN disease is caused by mutations of the WDR45 gene, known as a regulator of autophagy processes. The loss of WDR45 protein leads to autophagy defects in various BPAN cellular and animal models. Moreover, iron metabolism and ER-stress response are also dysregulated, and mice models show neurodegeneration and locomotor disorders. However, the molecular events leading to these phenotypes in WDR45 mutants and particularly the possible causal role of autophagy are still largely unknown. To address this question, we have constructed a Drosophila melanogaster mutant for CG11975, the Drosophila WDR45 homolog (dWDR45). We have demonstrated that flies harboring dWDR45 mutation mimic some hallmarks of BPAN, such as locomotors disorder, seizure-like phenotype, autophagy and ER stress response dysregulations. Importantly, the Drosophila BPAN model harbors iron accumulation in the whole body, a phenotype seen for the first time in an animal model. The establishment of this new and original BPAN model allows us to investigate the importance of autophagy in the establishment of the phenotypes associated with loss of dWDR45 functions. Our data will shed light on the biological mechanisms that link genetic mutations in dWDR45 gene to behavioral defects in Drosophila. In the long term, our study will contribute to a better understanding of BPAN and bring valuable knowledge to the development of therapeutic molecules.

** Eligible for best Oral Communication awards*

O7* - PHYSIOPATHOLOGY

Thomas EL JAMMAL[1]
S. Ferraro-Couturier[1], *T. Barthélemy*[1], *Y. Pacheco*[1], *P. Sève*[2], *A. Calender*[3], *F. Chevalier*[1]

1. Laboratoire de Biologie Tissulaire et Ingénierie thérapeutique, Institut de Biologie et Chimie des Protéines (IBCP), Lyon
2. Médecine interne, Hôpital de la Croix-Rousse, Lyon
3. Génétique, Centre de Biologie Est, Bron

Mitochondrial respiration and mitophagy in familial sarcoidosis

Sarcoidosis is a systemic inflammatory disorder characterized by granuloma formation in various organs, mostly the lungs and the intrathoracic lymph nodes. Although its etiology is still unknown, sarcoidosis is thought to be due to a defective elimination of environmental antigens in genetically predisposed individuals. Using whole exome sequencing data, we evidenced the potential implication of autophagy and mitophagy in familial sarcoidosis patients. We next focused on a particular variant of the TBK1 gene, displaying a putative deleterious in-frame mutation. We used patient-derived lymphoblastoid cell lines from a family of five individuals (3 with sarcoidosis, 2 healthy controls) and one external control, and found a defective mitochondrial respiration using Seahorse technology. Glycolysis and ATP synthesis were also different between sarcoidosis and control patients. Electron microscopy demonstrated ultrastructural abnormalities in some mitochondria. PINK1-dependent mitophagy protein abundances were also found to be different between sarcoidosis and control patients. An accumulation of mitochondrial DNA in response to a chemical stress was also observed. Those findings suggest that defective mitophagy in sarcoidosis patients may lead to altered metabolism and ineffective immune response, driving the granuloma formation. Both impaired mitophagy and autophagy have already been associated with increased inflammation through loss of inhibition of NLRP3 and IL1a or b in response to an accumulation of oxidized mtDNA or ROS within the cytosol. We are now investigating the interaction of TBK1 with multiple partners involved in the mitophagy signaling. Better deciphering of sarcoidosis pathophysiology is of utmost importance for future targeted therapies in order to improve patient care.

** Eligible for best Oral Communication awards*

Camilla BEAN
Clarissa Gissi, Marina Comelli, Francesca D'Este, Federico Caicci, Michela Carraro, Paolo Bernardi, Michael Zech, Bruno Grassi, Giovanna Lippe*

University of Udine, University of Padova, Technical University of Munich
**First Author*

A novel pathogenic mutation in the ATP5MC3 gene of ATP synthase is associated with lysosomal-autophagosomal alterations

Dystonia is one of the most frequent movement disorder in childhood and numerous disease-causing genes have been described. Because of this genetic heterogeneity associated with an enormous phenotypic variability, the full comprehension of the pathophysiology of dystonias is necessary to find effective therapeutic strategies. We recently reported a new pathogenic variant in the nuclear gene ATP5MC3 that encodes for the c3 subunit of the mitochondrial complex V/ATP synthase. As ATP synthase provides the most energy of the cell via the oxidative phosphorylation, mitochondrial- and energy-homeostasis dysfunction has been expectedly revealed in patient-derived fibroblasts. Here we show that the reduced ATPase activity and mitochondrial respiration are associated with altered ATP synthase complex assembly, resulting in ROS overproduction and in the cytoplasmic mislocalization of the subunit c. Notably, we found great cellular trafficking alterations with accumulation of aberrant autophagy-lysosome structures. Consistently, the levels of key autophagic markers were found increased. Our results suggest that the mutation in the ATP5MC3 gene impairs ATP synthase assembly and stability. However, the way in which this finally compromises lysosomal function supporting the selective packaging of mitochondrial parts into multivescicular (MVB) bodies remains to be completely understood, but pave the way for future therapeutic treatments.

SESSION 3
IMMUNITY & INFECTION

Thursday November 9th
02:00 - 04:15pm

Chairmen:
Mathias Faure - Frédéric Gros

O9 - IMMUNITY & INFECTION

Aurore ROZIÈRES[1#]
Gaëlle Quiniou, Leslie Andromaque[1], Rémi Duclaux-Loras[1,2], Océane Dinet[1], Ornella Cervantes[1], Mallorie Verdet[1], Camille Meunier[1,2], Gilles Boschetti[1,3], Christophe Viret[1], Stéphane Nancey[1,3], Mathias Faure[1],*,#*

1. CIRI, Centre International de Recherche en Infectiologie, Université de Lyon, Inserm U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, ENS de Lyon, F-69007, Lyon, France
2. Department of Pediatric Hepatology, Gastroenterology and Nutrition, Femme-Mère-Enfant Hospital, Hospices Civils de Lyon, Bron, France
3. Department of Gastroenterology, Lyon-Sud university hospital, Hospices Civils de Lyon, Lyon, France
 # Equal contribution
** First Author*

Impaired Reprogramming of the Autophagy Flux in Maturing Dendritic Cells from Crohn's Disease Patients with Core Autophagy Gene-Related Polymorphisms

Crohn's disease (CD) is an inflammatory bowel disease whose pathogenesis involves inappropriate
immune responses towards gut microbiota on genetically predisposed backgrounds. Notably, CD is associated with single-nucleotide polymorphisms affecting several genes involved in autophagy, the catabolic process that ensures the degradation and recycling of cytosolic components and microorganisms. In a clinical translation perspective, monitoring the autophagic activity of CD patients will require some knowledge on the intrinsic functional status of autophagy. Here, we focused on monocyte-derived dendritic cells (DCs) to characterize the intrinsic quantitative features of the autophagy flux. Starting with DCs from healthy donors, we documented a reprogramming of the steady state flux during the transition from the immature to mature status: both the autophagosome pool size and the flux were diminished at the mature stage while the autophagosome turnover remained stable. At the cohort level, DCs from CD patients were comparable to control in term of autophagy flux reprogramming capacity. However, the homozygous presence of ATG16L1 rs2241880 A>G (T300A) and ULK1 rs12303764 (G/T) polymorphisms abolished the capacity of CD patient DCs to reprogram their autophagy flux during maturation. This effect was not seen in the case of CD patients heterozygous for these polymorphisms, revealing a gene dose dependency effect. In contrast, the NOD2 rs2066844 c.2104C>T (R702W) polymorphism did not alter the flux reprogramming capacity of DCs. The data, opening new clinical translation perspectives, indicate that polymorphisms affecting autophagy-related genes can differentially influence the capacity of DCs to reprogram their steady state autophagy flux when exposed to proinflammatory challenges.

O10* - IMMUNITY & INFECTION

Quentin FRENGER[1,2]
Julie Lucas[1,2], *Nadège Wadier*[1], , *Sabine Depauw*[1], *Pascal Kessler*[3], *Oliver Lefebvre*[1], *Julie Blagojevic*[4], *Lauriane Kuhn*[4], *Johana Chicher*[4], *Philippe Hammann*[4], *Frédéric Gros*[1,2]

1. *Immuno-Rhumatologie Moléculaire UMR_S 1109 Institut National de la Santé et de la Recherche Médicale, Université de Strasbourg Centre de Recherche de Biomedecine de Strasbourg 1 rue Eugène Boeckel 67000 Strasbourg - France*
2. *Faculté des Sciences de la Vie Université de Strasbourg 28 Rue Goethe, 67000 Strasbourg -France*
3. *PIC-STRA Imaging Patform Institut National de la Santé et de la Recherche Médicale : UMS38, Université de Strasbourg Centre de Recherche de Biomedecine de Strasbourg 1 rue Eugène Boeckel 67000 Strasbourg - France*
4. *Proteomic Facility University of Strasbourg, Centre National de la Recherche Scientifique - CNRS : FR1589 Insitute of Molecular and Cell Biology 2, Allée Konrad Roentgen 67000 Strasbourg - France*

Role of ATG16L1 partners in B cell receptor trafficking and antigen presentation

Antigen presentation is a key mechanism in vertebrate immunity. Professional antigen presenting cells, including dendritic cells, macrophages and B cells are responsible for presentation of exogenous antigens after internalization, processing and loading of peptides on major histocompatibility class II complexes. Autophagy related (ATG) proteins members of the LC3-conjugation machinery perform macroautophagy and participate in LC3-associated phagocytosis, two degradative pathways generating MHC-II peptides. Our lab showed that deletion of ATG5 in B cells disrupts B cell polarization during the formation of the immune synapse and the trafficking of the internalized B cell receptor-antigen complex. This negatively impacts B cells ability to present surface-tethered antigens. Using CRISPR/Cas9 mediated knock-out in human B cell lines, we confirmed the implication of ATG5 and discovered the involvement of ATG16L1 for B cell polarization after B cell receptor engagement by surface-tethered antigens. Using other genetically modified human B cell lines and proteomic analysis, we unveiled novel ATG16L1 partners enriched after B cell receptor engagement. Among them, synaptosome associated protein 23 (SNAP23) is an interesting candidate because it is involved in lysosome exocytosis, a key mechanism in optimizing antigen extraction by B cells. SNAP23 is also involved in the maturation of LC3-coated phagosomes. We are now monitoring SNAP23 localization and behavior before and after B cell receptor engagement. Using antigen presentation assays, we aim to decipher the relevancy of ATG16L1 and its identified partners in B-cell mediated antigen presentation.

** Eligible for best Oral Communication awards*

O11* - IMMUNITY & INFECTION

Marjory PALARIC
Margaux Versapuech, Delphine Judith, Sarah Gallois-Montbrun, Clarisse Berlioz-Torrent

Université Paris Cité, Institut Cochin, INSERM, CNRS, F-75014 PARIS, France

Role of LC3/GABARAP proteins in the assembly of HIV-1

HIV-1 infection remains a major public health problem. It is therefore essential to understand the molecular mechanisms that control viral replication in order to define potential strategies to control and eradicate this virus.
Here, we aim to identify new cellular factors required for HIV morphogenesis. To this end, we developed an unbiased mass spectrometry approach and define the protein composition of HIV-1 virions. Gene ontology annotation revealed an enrichment for terms linked to protein translation, intracellular trafficking, mRNA stability and regulation of macroautophagy. Autophagy is a highly conserved degradative pathway that maintains cellular homeostasis, responds to disease processes and fights infection. The autophagy proteins (ATG) regulate this pathway, but are also implicated in other cellular functions, such as phagocytosis of pathogens, membrane remodelling, vesicle and virus secretion. Interestingly, amongst the ATG proteins enriched in purified viral particles, we discovered 4 of the 6 ATG proteins belonging to the LC3/GABARAP family. Present in a non-lipidated cytoplasmic form or in a lipidated and membrane-anchored form, LC3/GABARAP proteins control the elongation and closure of autophagic vesicles, but also the selection of cargos to be degraded by these vesicles. Their enrichment was confirmed by western blot on purified virions produced by HeLa and primary CD4+ T cells. The non-lipidated and lipidated forms of these LC3/GABARAP proteins were found associated with viruses. Importantly, their association are not dependent on any of the auxiliary viral proteins (Vpu, Vif, Vpr or Nef). Through CRISPR-Cas9 approaches and virological assays, we next revealed that GABARAP proteins are necessary for the production of full infectious virions. Indeed, we showed that knockout of GABARAP proteins led to the release of a large quantity of viral particles that were nonetheless less infectious. This low infectivity correlates with an accumulation of intracellular viral genomic RNA (gRNA) and a decrease of the viral gRNA quantity found in virus-containing supernatants. Collectively, our data support a role of GABARAP proteins in the encapsidation of viral gRNA in virions. Additional experiments are underway to characterize this new non-canonical function of GABARAP proteins in the selection and packaging of the viral genome in virions.
This work is supported by the FRM, the ANRS and the "French Ministry of Higher Education and Research".

** Eligible for best Oral Communication awards*

O12 - IMMUNITY & INFECTION

Pierre LAPAQUETTE
Amandine Ducreux, Louise Basmaciyan, Fabienne Bon, Amandine Bataille, Bernhard Hube, Christophe d'Enfert and Frédéric Dalle

Univ. Bourgogne Franche-Comté, Agrosup Dijon, UMR PAM A 02.102, Dijon, France
Laboratoire de Parasitologie-Mycologie, Plateforme de Biologie Hospitalo-Universitaire Gérard Mack, Dijon France
CellImaP corefacility, INSERM LNC-UMR1231, Dijon, France
Department of Microbial Pathogenicity Mechanisms, Leibniz Institute for Natural Product Research and Infection Biology, Hans Knoell Institute, Jena, Germany
Unité Biologie et Pathogénicité Fongiques, Institut Pasteur, USC2019 INRA, Paris, France

Interactions between the fungal pathogen Candida albicans and the host's autophagy machinery during the infection of epithelial cells

Candida albicans (C. albicans) is an opportunistic fungal pathogen causing infections ranging from superficial to life-threatening disseminated infections. In a susceptible host, C. albicans can translocate through the gut barrier, promoting its dissemination into deeper organs. C. albicans hyphae can invade human epithelial cells. On host side, autophagy is a lysosomal degradation pathway that is essential to prevent the spreading of intracellular pathogens by promoting their clearance. Beyond this degradative role of autophagy, autophagy machinery contributes to the regulation of cell membrane dynamics, including membrane repair in response to pathogen attack. We recently published a study demonstrating the massive recruitment of several autophagy-related proteins (ATGs: ATG5, ATG16L1, WIPI2 and LC3A/B) at C. albicans-active penetration sites into epithelial cells. This event, likely linked to noncanonical autophagy processes, is associated with host plasma membrane damages and contributes to plasma membrane repair mediated by lysosomal membrane exocytosis. Our latest unpublished findings unveil that Candidalysin, a pore forming toxin secreted by C. albicans, appears to limit this protective ATGs response at plasma membrane during invasion. Furthermore, Candidalysin appears capable of inhibiting basal autophagy flux in infected cells and hindering xenophagy against Staphylococcus aureus in a co-infection model. Altogether these results suggest that C. albicans, through the secretion of the Candidalysin toxin within the invasion pocket, can dampen autophagy and autophagy-related processes within the host's infected cell.

SESSION 4
CANCER

Friday November 10th
02:00 - 04:15pm

Chair(wo)men:
Olivier Meurette - Valérie Pierrefite-Carle

O13* - CANCER

Caterina Luana PITASI[1]

Alessia Rubiola[1], *David Cune*[1], *Cédric Broussard*[1], *Virginie Salnot*[1], *Pierre Sohier*[1], *Pierre-Francois Roux*[2], *Islem Toumi*[2], *Nicolas Minc*[3], *Laurent Le Cam*[2], *Delphine Delacour*[3], *Béatrice Romagnolo*[1]

1. University of Paris, Cochin Institute, Inserm U1016-CNRS UMR8104-Université de Paris, Romagnolo team «Self-renewal and tumorigenesis of the intestinal epithelium», 24 rue du Fb Saint-Jacques, 75014 Paris, France
2. IRCM -Inserm U1194, 208 Avenue des Apothicaires, 34298 Montpellier, France
3 Jacques Monod Institute, UMR7592, 15 rue Hélène Brion, 75013 Paris, France

Role of autophagy on intestinal stem cell genome integrity

Intestinal stem cells (ISC) has been described as the cell of origin of colorectal cancer. It is therefore essential to better understand the mechanisms that preserve its genomic integrity. We have shown that (macro)autophagy plays a key role in homeostasis of ISC. Autophagy inhibition, via inactivation of Atg7 gene in intestinal epithelium, causes several functional defects that induces p53 activation and ISCs death. The double invalidation of the Atg7 and p53 genes in intestinal epithelial cells promotes tumorigenesis. These findings revealed the causal relationship between autophagy failure and oncogenesis but the mechanisms have still to be described.

We performed proteomic studies of autophagy-deficient and autophagy-proficient ISCs. Analyzes by Ingenuity have revealed that Atg7KO ISCs exhibit dysregulation of important proteins in centrosome structure and in the attachment of kinetochores to microtubules. We cultured intestinal organoids from Atg7KO and Atg7KOp53KO mice and generated Atg5KO organoids, using a CRISPR-Cas9 strategy. Intestinal organoids deficient in autophagy present destructured and multipolar mitotic spindles, that are associated with abnormalities in cell division and the presence of lagging chromosomes. These defects are amplified in Atg7KOp53KO organoids. In order to identify the driver mutations of intestinal oncogenic transformation, we kept these organoids in culture for six months and we studied their DNA at early, intermediate and late times point. Whole genome sequencing analyses reveals LOH of chromosome 13 in p53KO organoids, which occurs earlier Atg7KOp53KO organoids where it is also associated with other DNA abberations. Importantly, these genetic abnormalities are similar to those founded in polyps from Atg7p53KO mice.

Our data show that autophagy is essential to ensure normal division of ICS. The tumor initiation observed in Atg7KOp53KO mice is certainly related to the accumulation of aberrant mitoses following the loss of p53. Taken together, our data underscore the importance of autophagy and p53 in maintaining the integrity of ICS genome.

** Eligible for best Oral Communication awards*

O14* - CANCER

Axel ARTHUR[1,2]
Sanae Nejmi[1,2], *Erik Dassi*[3], *Stefania Millevoi*[1,2]*, *Estelle Espinos*[1,2]

1. Cancer Research Center of Toulouse, UMR1037 Inserm, Toulouse
2. University Toulouse III, Paul Sabatier, Toulouse
3. Laboratory of RNA Regulatory Networks, Department of Cellular, Computational and Integrative Biology (CIBIO), University of Trento, Trento, Italy
**Co-First Author*

PD-L1 and the post-transcriptional control of autophagy: molecular mechanisms and role in response and resistance to therapy in head and neck cancers

The recent elucidation of the RNA-binding proteome has highlighted new RNA-Binding Proteins (RBP) already known to play a role in several cellular pathways. Among them, the immune checkpoint inhibitor, PD-L1 (Programmed Death-Ligand 1) has been shown to interact with specific mRNAs, resulting in increased stability. Furthermore, accumulating evidence demonstrates that PD-L1 is involved in stress response in particular by regulating autophagy but the mechanism is not still deciphered. Autophagy is a highly conserved catabolic process that plays a major role in the maintenance of homeostasis and it is implicated in tumor initiation and progression but also in resistance to treatments. We propose here an original model in which PD-L1 is a post-transcriptional regulator of autophagy playing a crucial role in resistance to treatments in cancer cells. We focus our study on Head and Neck Squamous Cell Carcinoma (HNSCC), a heterogeneous type of tumor that displays an increase of PD-L1 levels in response to treatment, marked chemo/radio-resistance and a modest response to immunotherapy.

Using a combination of molecular/cellular biology and bioinformatics (including large-scale transcriptomic/proteomic analysis), we found that PD-L1 regulates mRNAs translation and bind autophagy-related mRNAs. We also showed that PD-L1 is able to regulate the basal autophagic flux and that PD-L1 is up-regulated in response to chemotherapy treatment. Further experiments should clarify the role of PD-L1 in autophagy-induced by genotoxic stress.

This project will lead to a better comprehension of therapy failures in HNSCC and may pave the way for new treatment combinations.

Key words: PD-L1, RNA, Post-transcription, Autophagy, HNSCC

** Eligible for best Oral Communication awards*

O15* - CANCER

Marie-Charlotte TROJANI[1,2]
Marie Nollet[1], *Olivier Camuzard*[1,3], *Sabine Santucci-Darmanin*[1], *Chantal Cros*[1], *Fanny Burel-Vandenbos*[4], *Dominique Heymann*[5], *Véronique Breuil*[1,2], *Georges F Carle*[1] *et Valérie Pierrefite-Carle*[1]

1. MATOs UMR E4320 CEA UCA
2. Service de Rhumatologie, CHU de Nice
3. Institut Universitaire Locomoteur et Sport, CHU de Nice
4. Laboratoire Central d'Anatomie Pathologique, Hôpital Pasteur, CHU Nice
5. INSERM UMR 957, Université de Nantes, Equipe labellisée Ligue Nationale Contre le Cancer 2012, Nantes

Effect on tumor development of Atg5 inactivation in bone microenvironment

Bone is a dynamic tissue, composed of a mineralized extracellular matrix, specialized cells as osteoblasts responsible for matrix synthesis, and osteoclasts responsible for matrix resorption. Autophagy is a ubiquitous cellular process, dedicated to degradation and recycling of damaged proteins and organelles. It has recently been shown that autophagy plays a key role in the crosstalk between the tumor and its microenvironment, and that inactivation of autophagy in an osteosarcoma model leads to changes in bone microenvironment. The aim of our work was to study, in reverse, the effect of autophagy inactivation in bone microenvironment on tumor development. We performed intra-tibial injections of syngeneic AXT and MOS-J osteosarcoma cell in a mouse model of Atg5 inactivation in osteoblasts (mutant mice) and control littermates. We observed an increase in tumor growth and metastatic potential in mutant mice. These results were extended to a bone metastatic model of breast cancer. To understand the modifications induced by Atg5 deficiency in osteoblasts, a proteomic analysis of control and mutant bone matrix was performed. It revealed a decrease in a large number of proteins involved in translation machinery and suggested stress granules formation. As Atg5 inactivation was recently shown to induce lysosome hypersensitivity, leading to lysosomal exocytosis and stress granule formation, we are presently analyzing those 3 parameters in our model. In this context, microenvironment acidification could be a favorable soil for tumor growth and could explain the tumor supportive effect observed in mutant mice. This work should ultimately lead to the development of new compounds, stimulating bone autophagy, thus increasing the therapeutic arsenal already available to fight against bone tumoral lesions development.

** Eligible for best Oral Communication awards*

O16 - CANCER

Mario TSCHAN
*Anna M. Schläfli, Nicolas J. Niklausa, Igor Tokarchuk, Federico la Manna, Ramin Radpour, Marianna Kruithof-De Julio, Jörn Dengjel, Mario P. Tschan, Ju Xu**

Institute of Tissue Medicine and Pathology, University of Bern, Bern, Switzerland
Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland
Department of Biomedical Research, Division of Urology, University of Bern, Bern, Switzerland
Department of Biomedical Research, Division of Tumor immunology, University of Bern, Bern, Switzerland
Department of Biology University of Fribourg, Fribourg, Switzerland
**First Author*

The oncogenic DMTF1β splice variant promotes autophagy-dependent cancer cell motility

The oncogenic isoform DMTF1β, which is generated by alternative splicing of the DMTF1 gene is associated with increased cell proliferation and tumorigenesis. Despite these correlative findings little is known about the mechanism of action of DMTF1β. To unravel oncogenic DMTF1β signaling pathways, we performed RNA sequencing analysis of DMTF1β depleted prostate cancer cells and determined the DMTF1β specific protein interactome in cancer cells. Interestingly, autophagy genes such as ULK1, PIK3C3 and WIPI1 were significantly downregulated in DMTF1β knockdown cancer cells as confirmed by qPCR. Furthermore, DMTF1β protein interacted with several autophagy proteins including the ULK1 complex members ULK1 and ATG13. These interactions were confirmed by Co-IP and/or proximity ligation assays.
Since published data show an important role for autophagy in migration and invasion of cancer cells, we next investigated whether DMTF1β is regulating these cellular processes. Indeed, DMTF1β depletion lowers wound closure and trans-well invasion of MDA-MB231 breast and PCMPRO4 prostate cancer cells. Importantly, pharmacological, or genetic inhibition of autophagy initiation but not later stages decreases DMTF1β-mediated migration in MCF-7 cells. In summary our data suggests that DMTF1β regulates migration most probably via autophagy activation. Ongoing research will uncover whether DMTF1β regulates autophagy via the ULK1 complex and how DMTF1β-induced autophagy or related pathways support cancer cell motility.

FLASH TALKS SESSION 1

Wednesday November 8th
05:45 - 06:15pm

LISTING FLASH TALK SESSION 1

#	LAST NAME	FIRST NAME	TITLE
FT1*	LIENARD	Caroline	Gigaxonin regulates autophagosome dynamics in neurons
FT2*	CESARE	Giuliana	Characterization of the function of Hecw in TFEB/Mitf-mediated autophagy
FT3*	NORELL	Puck	LC3 proteins in autophagy, very similar yet different
FT4*	JAUQUET	Melissa	NMDA Receptors trigger neuronal autophagy in an in vitro stroke model and prevent IGF1 receptors-mediated neuroprotection
FT5*	ALLIOUX	Claire	A non-canonical role of LC3B in HEV-infected polarized hepatocytes
FT6*	LAVEDRINE	Aude	Measles virus-induced targeting of cellular cargoes toward autophagic degradation
FT7*	NASO	Francesco	miR-218-5p and doxorubicin combination enhances anticancer activity in breast cancer cells through Parkin-dependent mitophagy inhibition

** Eligible for best Flash Talk award*

FT1* - MOLECULAR MECHANISMS & SIGNALING

Caroline LIÉNAR
Leticia Arias, Camille Bonnet and Pascale Bomont

Institut NeuroMyoGene -PGMN, Inserm U1315, UCBL, UMR 5261, University of Lyon, Lyon

Gigaxonin regulates autophagosome dynamics in neurons

Autophagy is a major cellular degradation pathway, particularly essential in neurons due to their post-mitotic nature and specific functions. A dysregulation of the autophagic pathway can lead to various neurodevelopmental and neurodegenerative diseases. In neurons, the autophagy pathway is compartmentalized. Best known is the formation of autophagosomes in the distal portion of the axon, with maturation and fusion with lysosomes occurring in the soma. In the laboratory, we study giant axonal neuropathy (GAN) as a pathological model to investigate the spatial regulation of autophagy in neurons. This disease is caused by mutations in the gene encoding for gigaxonin, an E3 ligase we showed to control the degradation of ATG16, a key protein in membrane elongation of autophagosome formation. In GAN neurons, gigaxonin loss of function induces an accumulation of ATG16L1, an impairment of LC3 lipidation, leading to a decreased production of autophagosomes. Here, we explore autophagy compartmentalization using GAN as an interesting biological model due to the unexpected accumulation of ATG16L1 in the soma and the axon. Combining immunofluorescence and live imaging with autophagic probe, we investigated the spatial dynamics of autophagy in GAN. Altogether, our data reveal an alteration of the identity and dynamics of autophagic vesicles in different compartments of GAN neurons. Our study suggests a fundamental role of gigaxonin in the spatial regulation of neuronal autophagy.

** Eligible for best Flash Talk award*

Giuliana CESARE
Valentina Fajner, Elena Maspero, Shiyao Ma, Simona Polo, Thomas Vaccari

IFOM (Istituto Fondazione di Oncologia Molecolare ETS), Università degli Studi di Milano

Characterization of the function of Hecw in TFEB/Mitf-mediated autophagy

Autophagy is a crucial catabolic process aiming to recycle cytosolic material to maintain cellular homeostasis. During autophagy, dysfunctional organelles and macromolecules are captured by newly formed double-membrane organelles, named autophagosomes, and delivered to lysosomes for degradation. Impairments in the autophagic pathway are associated with a wide number of pathologies, including cancer and neurodegeneration. Nonetheless, despite the wide effort in finding new components of this pathway, we are far from fully elucidating the molecular mechanisms behind autophagy. Recent studies support a role for E3 ubiquitin ligases in autophagy, highlighting the importance of ubiquitination in tightly controlling the progression of this pathway. We recently characterized the function of Hecw, the Drosophila melanogaster ortholog of human HECW1. Hecw is essential to maintain the liquid-like state of ribonucleoprotein particles (RNPs). In its absence, flies show defective oogenesis as well as neurodegenerative-like phenotypes. While it is possible that the function of Hecw in RNPs biology might support both egg development and prevent neurodegeneration, the onset of the neurodegeneration-like phenotypes in flies lacking Hecw remains unexplained. Our data indicates Hecw may act in TFEB/Mitf mediated-autophagy as we find that Hecw is essential for the correct engagement of starvation-induced autophagy in larval and adult tissues. Moreover, aging Hecw mutant flies present a strong reduction of TFEB/Mitf protein levels, possibly leading to impaired autophagy as shown by reduced levels of the autophagic marker Ref2P. Furthermore, Hecw interacts in vivo with the autophagy chaperone mediators 14-3-3, that bind phosphorylated TFEB/Mitf in the cytoplasm and to escort it to degradation. Since neuronal cells strongly rely on autophagy for their survival, these results might be important to find new actors in the autophagic process and elucidate the genetics of neurodegeneration.

** Eligible for best Flash Talk award*

FT3* - MOLECULAR MECHANISMS & SIGNALING

Puck NORELL
Jagan Doreswamy, Thomas Wollert

Institut Pasteur, Paris, France

LC3 proteins in autophagy, very similar yet different

The LC3 (LC3A, -B and -C) proteins are key players in (macro)autophagy, a cellular degradation pathway removing damaged cytoplasmic material. Autophagy either non-selectively degrades bulk cytosol as a response to cellular stress, or selectively degrades cargo such as protein aggregates. An early step in the autophagic process is the formation of the phagophore, a membrane that encloses cargo forming the autophagosome. The autophagosome delivers the cargo to lysosomes for degradation.

LC3 proteins are present on both leaflets of the phagophore membrane. The luminal pool of LC3 proteins tethers cargo to the membrane, ensuring its selective sequestration. The cytoplasmic pool of LC3 is thought to mainly serve as binding partner for other proteins, but the molecular functions of LC3A, -B and -C are still unknown. Previous findings in our laboratory revealed a division of labour between LC3B and LC3C, indicating that both variants evolved to fulfil distinct molecular functions in autophagy.

A major difference between both proteins is a proline-rich motif in the N-terminus of LC3C which is not present in LC3B. We have shown that by adding the proline motif in the N-terminus of LC3B, and deleting it from LC3C, there are significant differences between puncta formation in control, non-selective and selective autophagy compared to their wild-types.

** Eligible for best Flash Talk award*

Melissa JAUQUET
Triniac H, Pelleter C, Lechevallier C, Vivien D, Lemarchand E, Roussel BD

INSERM U1237, Caen, France

NMDA Receptors trigger neuronal autophagy in an in vitro stroke model and prevent IGF1 receptors-mediated neuroprotection

Background and aims
Ischemic stroke induces multiple signaling pathways that contribute to neuronal death. We previously demonstrated the importance of neuronal autophagy during oxygen and glucose deprivation (OGD), an in vitro stroke model (Thiebaut et al 2021). Autophagy is important for the trafficking of NMDAR, especially in the context of long-term potentiation and long-term depression. We have recently shown that the activation of the Insulin Growth Factor 1 receptor (IGF1R) during ischemic stroke protects neurons from autophagy-mediated death (Thiebaut et al 2021). Here, we highlight the importance of the NMDA receptor in the induction of autophagy-mediated neuronal death during ischemia, probably by inhibiting the phosphorylation of IGF1 receptor.

Methods
Mouse cortical neurons were subjected to OGD (in a hypoxic chamber) or to NMDA stimulations. Cell death was evaluated by LDH release. Autophagy and IGFR-1 phosphorylation were assessed by western blot.

Results
In cortical neurons, OGD following by reoxygenation (OGDreox) and NMDA stimulations, increase both cell death and autophagic flux, showed by autophagosome accumulation (increased levels of LC3-II) and enhanced degradation of the autophagy receptor SQSTM1/p62. We found that NMDA decreases IGF1-R phosphorylation induced by IGF-1.These effects were reversed by the NMDA receptor antagonist MK-801. However, blockage of autophagy by E64d/PepA partially reverses NMDA-induced death, suggesting that neuronal death induced by NMDA is not only excitotoxic, but also autophagic.

Conclusions
We show here that NMDA receptors stimulation are enough to trigger autophagy-mediated neuronal death, and are central in an in vitro model of ischemia. This is accompanied by a NMDAR-dependent inhibition of the IGF1R induced neuroprotection.

** Eligible for best Flash Talk award*

FT5* - IMMUNITY & INFECTION

Claire ALLIOUX[1]
Olivia Paronetto[1], *Mélanie Pucelle*[2], *Isabelle Da Silva*[2], *Sébastien Lhomme*[1,2], *Jacques Izopet*[1,2], *Sabine Chapuy-Regaud*[1,2]

1. *Toulouse Institute for Infectious and Inflammatory Diseases (Infinity), INSERM UMR1291, CNRS UMR 5051, Université Toulouse III, Toulouse*
2. *Laboratoire de Virologie, CHU Toulouse*

A non-canonical role of LC3B in HEV-infected polarized hepatocytes

Hepatitis E virus (HEV) is a common cause of acute hepatitis worldwide. Most infections are asymptomatic but some genotypes can lead to chronic infections in immunocompromised patients. HEV is a small non-enveloped RNA virus. However, it is released from infected cells in a lipid-associated form. The different stages of HEV cycle are not fully known. In polarized hepatocytes, we found that the ORF2 capsid protein colocalized with LC3B, an essential protein of the autophagosome formation. (Macro)autophagy is a conserved pathway in the host cell defense against pathogens. Autophagosomes are double membrane vesicles that trap cytosolic content and deliver it to the lysosome for degradation or participate to secretion pathways. Their formation involves LC3B anchoring in the phagophore membrane. Selective autophagy involves receptors recognized by LC3B via a LC3-interacting region (LIR) motif.
To investigate the links between autophagy and the HEV life cycle, we infected the polarized hepatocarcinoma cell line HepG2/C3A/F2 in conditions of autophagy activation or inhibition. This pharmacological modulation of the initial steps of autophagy did not influence HEV RNA production. LC3B labeling showed a basal level of LC3B nucleation in uninfected cells, that did not increase upon a 6-hour rapamycin treatment. This LC3B nucleation was inhibited by wortmannin in uninfected cells but not in HEV-infected cells at 6 hours post-infection (pi). LC3B nucleation was maintained during 7 days pi in HEV-infected cells treated during the first 6 hours pi. These results suggest that HEV induces LC3B nucleation independently of the first steps of the autophagy pathway. Using a coimmunoprecipitation assay, we detected that ORF2 interacted with the LC3B-I form in polarized hepatocytes. Further experimentation could help unravel the role of the LIR domain in ORF2-LC3B-I interaction and would advance understanding of the HEV life cycle. Our study highlights a non-classical role of LC3B in HEV-infected polarized hepatocytes.

** Eligible for best Flash Talk award*

FT6* - IMMUNITY & INFECTION

Aude LAVEDRINE[1]
Franck Mortreux[2], *Lucile Espert*[3], *Christian Behrends*[4], *Christophe Viret*[1], *Mathias Faure*

1. CIRI, Centre International de Recherche en Infectiologie - Inserm U1111, CNRS UMR5308, ENS de Lyon, UCB Lyon 1, Lyon, France
2. LBMC - INSERM U1210 CNRS UMR 5239, ENS de Lyon, UCB Lyon 1, Lyon, France
3.IRIM, University of Montpellier, UMR 9004 CNRS, Montpellier, France
4. Munich Cluster for Systems Neurology, Medical Faculty, Ludwig-Maximilians-Universität München, Munich, Germany

Measles virus-induced targeting of cellular cargoes toward autophagic degradation

Autophagy is a potent process for controlling and containing infection in a cell-autonomous manner. However, some pathogens succeed in evading autophagic degradation by inhibiting specific steps of this cellular process. Extensive efforts have been made to gain deeper insight into this phenomenon. On the other hand, much less is known regarding pathogens that utilize the autophagic pathway to their own advantage. Among them, Measles virus has been shown to induce a complete and a degradative autophagy, benefiting from it to enhance its replication. Nevertheless, the precise mechanisms by which this virus exploits this pathway remain unclear. Given that autophagy receptors play pivotal roles in measles virus infection, identifying cellular cargoes targeted toward the autophagic degradation could shed light on how the virus divert this cellular pathway. In this study, using a proteomic approach, we have, for the first time, characterized change in autophagosomal content between a homeostatic state and a viral infection. We were thus able to identify cellular candidates that may explain the pro-viral effect of autophagy on mealses virus infection.

** Eligible for best Flash Talk award*

FT7* - CANCER

Francesco NASO[1]
Krenare Bruqi[1,2], *Valeria Manzini*[3], *Valerio Chiurchiù*[1,4], *Mara D'Onofrio*[3], *Ivan Arisi*[3], *Flavie Strappazzon*[1,2]

1. IRCCS Santa Lucia Foundation, Via del Fosso di Fiorano 64/65, 00143, Rome, Italy
2. Institut NeuroMyogène, CNRS UMR5261-INSERM U1315, Université Claude Bernard Lyon1, Lyon, France
3. European Brain Research Institute (EBRI) «Rita Levi-Montalcini», Viale Regina Elena 295, 00161, Rome, Italy
4. Institute of Translational Pharmacology, CNR, Via del Fosso del Cavaliere, 100, 00133, Rome, Italy

miR-218-5p and doxorubicin combination enhances anticancer activity in breast cancer cells through Parkin-dependent mitophagy inhibition

Breast Cancer (BC), is one of the most common tumour, and is unfortunately known for its ability to develop resistance to chemotherapeutic treatments. Autophagy has been linked to chemotherapeutic response in several types of cancer, such as BC, highlighting its contribution to the development of drug resistance. However, the role of mitophagy, a selective form of autophagy, responsible for damaged mitochondria degradation, in the response to therapies in BC is still unclear. In order to investigate this point, we analysed the role of mitophagy in the treatment of the most common anticancer drug, doxorubicin (DXR), in different models of BC, such as a luminal A subtype-BC cell line MCF7 cells, cultured in 2D or 3D, and the triple negative BC cell line MDA-MB-231. Through a microarray analysis, we identified a relationship between mitophagy gene expressions related to the canonical PINK1/Parkin-mediated pathway and DXR treatment in BC cells. We next demonstrated that the PINK1/Parkin-dependent mitophagy is indeed induced following DXR treatment, suggesting that this process could be a pro-survival pathway stimulated by the DXR treatment. In order to address this point, we took advantage of the exogenous expression of a microRNA, miRNA-218-5p, that targets Parkin mRNA , and consequently inhibits mitophagy. We found that both MCF7 cultured in 2D or grown as mammospheres and MDA-MB-231 cells expressing miRNA-218-5p were unable to remove their damaged mitochondria following DXR treatment and consequently, their vitality were reduced compared to DXR treatment alone. Our work highlights a relationship between DXR therapy and mitophagy in BC context, and that combining mitophagy inhibition and chemotherapy could represent a new strategy for clinical practice. Altogether, our results enhance our knowledge on the mitophagic process related to BC cells and provide a novel tool for therapeutic intervention.

** Eligible for best Flash Talk award*

FLASH TALKS SESSION 2

Thursday November 9th
04:15 - 04:45pm

LISTING FLASH TALK SESSION 2

#	LAST NAME	FIRST NAME	TITLE
FT8*	NUGUE	Mathilde	Modulation of autophagy affects ADCC in a tissue-specific manner
FT9*	CIROTTI	Claudia	NRF2 connects Src tyrosine kinase to ferroptosis resistance in glioblastoma
FT10*	DESPRAIRIES	Alice	RNA G-quadruplexes couples mRNA translation to autophagy
FT11	TRISCIUOGLIO	Daniela	α-Tubulin N-acetyltransferase 1 promotes autophagy and oxidative stress in non-small cell lung cancer cell lines
FT12*	SCHLÄFLI	Anna M	ATG16L2, but not L1 is crucial for ATRA-induced differentiation of APL cells
FT13*	DUCAU	Charlotte	Autophagy as a critical mediator of drug resistance in Acute Myeloid Leukemia

** Eligible for best Flash Talk award*

FT8* - IMMUNITY & INFECTION

Mathilde NUGUE
Eva Boisel, Despoina Koumantou, Sophie Lotersztajn, Loredana Saveanu

Centre de Recherche sur l'Inflammation, Inserm U1149

Modulation of autophagy affects ADCC in a tissue-specific manner

Fc immunoglobulin G receptor (FcyRs) are essential to mediate the antibody-dependent cellular cytotoxicity (ADCC) induced by therapeutical antibodies. Recent data have shown that after their cross-linking by immune complexes, FcyRs are internalized in endosomes, from where they continue to signal for longer time periods, up to 2 hours after receptor internalization. We showed in vitro that FcyR endosomal signaling is necessary and essential to mediate different effector functions, such as pro-inflammatory cytokines secretion or ADCC.
Considering that ensodomal and autophagosomal pathway are inherently linked at multiple steps, we hypothesized that the autophagic flux modulation will affect the FcyRs endosomal signaling and, consequently, FcyRs effector functions. To investigate this hypothesis, we performed 2 different models of ADCC in vivo: B cell depletion in spleen and tumor cell depletion in the peritoneum. These 2 ADCC models were applied tos mice genetically modified for autophagy in macrophages: ATG5LysM-Cre+ mice, which have a defective autophagy and Rubicon LysM-Cré+ mice, in which autophagy induction and flux are facilitated. In the B cell depletion model, we observed that autophagy is required for ADCC function in splenic macrophages. On the contrary, in an intraperitoneal model of ADCC, autophagy is not involved.
These results indicate that, according to their tissular localization, the mechanisms involved in ADCC function are different. Although this may be surprising, our results are in agreement with the concept of "tissues-specificity of macrophages", recently described in the literature. We also observed tissue-specificity for particular phenotypes induced by autophagy modulation, such as a more inflammatory phenotype for autophagy-deficient peritoneal macrophages. However, this pro-inflammatory phenotype does not lead to a more efficient ADCC function of autophagy-deficient peritoneal macrophages. By undergoing RNAseq analyses, we explore the mechanisms underlying tissue-specific involvement of autophagy in ADCC function of mouse macrophages.

** Eligible for best Flash Talk award*

Claudia CIROTTI[1]
I. Taddei[1,2], *C. Contadini*[1,2], *G. Pepe1, M. De Bardi*[3], *G. Borsellino*[3], *M. Helmer-Citterich1, D. Barilà*[1,2]*

1. Department of Biology, University of Rome «Tor Vergata», 00133 Rome, Italy
2. Laboratory of Cell Signaling, IRCCS-Fondazione Santa Lucia, 00179 Rome, Italy
3. Neuroimmunology Unit, Experimental Neuroscience, IRCCS Fondazione Santa Lucia, Via Ardeatina 306-354, 00179 Rome, Italy
**Co-First Author*

NRF2 connects Src tyrosine kinase to ferroptosis resistance in glioblastoma

Glioblastoma (GBM) is a severe brain tumor characterized by an extremely poor survival rate of patients. GBM cancer cells escape to standard therapeutic protocols consisting of combination of ionizing radiation (IR) and temozolomide that trigger DNA damage, by rewiring of signaling pathways. In recent years, the upregulation of factors that counteract ferroptosis, among which NRF2 transcription factor, has been highlighted as a major driver of cancer resistance to IR, although the molecular connection between the activation of oncogenic signaling and the modulation of ferroptosis has not been clarified yet.
Here we provide the first evidence for a molecular connection between the constitutive activation of tyrosine kinases and resistance to ferroptosis. We demonstrate that Src tyrosine kinase - central hub on which Receptor Tyrosine Kinases deregulated signaling converge in cancer - unambiguously sustains the constitutive activation of NRF2. We identify the molecular mechanism behind this new signaling axis focusing on the deregulated interaction between p62 and KEAP1, two important players of NRF2 non-canonical regulation. We show that Src hyperactivation in GBM promotes mTORC1-dependent phosphorylation of p62 on Ser349, required for KEAP1 sequestration by p62. As a consequence, Src activity sustains p62-KEAP1 interaction in aggregates resulting in the stabilization and activation of NRF2 and its dependent pathway, thus promoting resistance to IR-induced ferroptosis. These data suggest that the upregulation of Src-NRF2 axis may represent a vulnerability for combined strategies that, by targeting ferroptosis resistance, enhance radiation sensitivity in glioblastoma.

** Eligible for best Flash Talk award*

Alice DESPRAIRIES[1,2]
Pauline Herviou[1,2]*, *Léa Février*[2], *Erik Dassi*[3], *Stefania Millevoi*[1,2,#] *and Anne Cammas*[1,2,#]

1. Cancer Research Center of Toulouse, UMR1037 Inserm, Toulouse
2. Université Paul Sabatier, Toulouse
3. Laboratory of RNA Regulatory Networks, Department of Cellular, Computational and Integrative Biology (CIBIO), University of Trento, Trento, Italy
**These authors contributed equally to this work*
#Co-senior authors

RNA G-quadruplexes couples mRNA translation to autophagy

The role of autophagy in cell survival in response to stress condition put this catabolic process at the heart of resistance to cancer treatments. A better understanding of the molecular mechanisms controlling autophagy is required in order to consider its targeting as a novel therapeutic option. While current knowledge is mainly centered on transcriptional regulation and post-translational modification of autophagy factors, accumulating evidences showed that alteration in mRNA translation impacts autophagy, but the molecular determinants governing this link remain poorly characterized. Our project addresses the gap of knowledge in RNA-mediated regulation of autophagy by focusing on RNA G-quadruplexes (RG4s), non-canonical RNA structures playing a critical role in mRNA translation of factors involved in the stress response and resistance to treatments in glioblastoma, a highly aggressive cerebral tumours with bad prognosis. Our results identified RG4s as important regulators of basal and stress-induced autophagy, revealed their function in regulating translation of autophagy-related factors, and uncovered the underlying molecular mechanisms involving the RNA helicase DDX3X. We showed the biological relevance for the RG4-dependent translation in maintaining the expression of autophagy factors in response to chemotherapy which contribute to resistance to antitumoral treatments in glioblastoma cells. Since RG4 structures are targetable by small molecule ligands, the control of autophagic protein synthesis via RG4 structures appears as promising therapeutic avenue in glioblastoma cells.

** Eligible for best Flash Talk award*

Daniela TRISCIUOGLIO
FR Pellegrini,A. Iuzzolino, F. Ambrosio, A. Paone, S. Rinaldo, F. Crutruzzolà, F. Degrassi, V. Stagni, D. Trisciuoglio*

CNR-IBPM
**First Author*

α-Tubulin N-acetyltransferase 1 promotes autophagy and oxidative stress in non-small cell lung cancer cell lines

Tubulin acetylation plays a pivotal role in a plethora of cellular activities. α-tubulin-N-acetyltransferase-1 (ATAT1) has recently been identified as the writer of α -tubulin acetylation on lysine-40 (K40), but still little is known about its relevance in cancer. It has recently been discovered that tubulin acetylation contributes to control the autophagic pathway, however ATAT1 involvement in this process remains unknown. To fill this gap, we employed a panel of non-small cell lung cancer (NSCLC) cell lines in which we transiently or stably silenced the enzyme. ATAT1 silencing results in the induction of the autophagic flux and the modulation of several autophagic markers, under basal conditions and in response to starvation. Indeed, ATAT1 silencing promotes the ATG7 dependent autophagic pathway. Interestingly, ATAT1 silenced cells were also found to have a significantly higher number of reactive oxygen species (ROS) compared to control cells and to be significantly more sensitive to H2O2 treatment. In support of these findings, we found a damaged mitochondrial respiration and glycolysis in ATAT1 silenced cells when compared to parental cells. Other experiments are in progress to define the functional role of ATAT1 dependent autophagy and the possible connection with oxidative stress and cell metabolism. We believe that the successful completion of this study will provide a detailed mechanistic understanding of the role of ATAT1 in autophagy and in cancer progression.

FT12* - CANCER

Anna M. SCHLÄFLI
Yasmeen Mady, Jing Jin, Sreoshee Rafiq, Magali Humbert and Mario P. Tschan

Institute of Tissue Medicine and Pathology, Division of Experimental Pathology, University of Bern, Bern, Switzerland
Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland

ATG16L2, but not L1 is crucial for ATRA-induced differentiation of APL cells

Acute promyelocytic leukemia (APL) is hallmarked by an accumulation of granulocyte precursors in bone marrow, blood, and tissue due to a blockage in differentiation. In clinics, APL is successfully treated with a combination of differentiation therapy using all-trans-retinoic acid (ATRA) and chemotherapy. Current data shows an important role for autophagy in ATRA-induced granulocytic differentiation of APL cells and that genetic or pharmacological inhibition of various autophagy genes blocks ATRA-differentiation. Interestingly, Beclin-1 is dispensable for ATRA-induced autophagy and differentiation. This suggests that ATRA does not trigger a classical autophagy pathway as it is described during starvation. We therefore set out to better characterize the type of autophagy acting during granulocytic differentiation of APL cells. To this end, we first checked expression levels of different autophagy genes in APL patient samples and found that ATG16L2 but not L1 mRNA was significantly low in immature APL cells from patients if compared to granulocytes of healthy donors. In agreement, more differentiated polymorph nuclear cells express higher levels of ATG16L2 but not L1 if compared to hematopoietic stem cells. In agreement with an upregulation of ATG16L2 in more differentiated cells, knocking-down ATG16L2 in NB4 cells significantly disrupts ATRA differentiation as determined by CD11b surface levels, GCSFR and CEBPE mRNA levels and nitro blue tetrazolium assay (NBT). In contrast, depletion of ATG16L1 by CRISPR CAS9 technology or shRNAs did not inhibit ATRA differentiation of NB4 cells. Importantly, ATG16L1 knock-out NB4 cells show a significant reduction in autophagy upon mTOR inhibition by Torin1 excluding that ATG16L1 is dispensable for autophagy in NB4 cells. Currently, we are performing rescue experiments with different ATG16L1 or L2 domains spanning either the N-Terminus, the middle region, or the C-terminus to further characterize the contribution of macroautophagy and/or related pathways, such as conjugation of ATG8 to single membranes (CASM) to ATRA-differentiation of APL cells.

** Eligible for best Flash Talk award*

FT13* - CANCER

Charlotte DUCAU
Marjorie Fanjul, Loïc Platteeuw, Alexandre Boudet, Ambrine Sahal, Estelle Saland, Jean-Emmanuel Sarry, Laura Poillet and Carine Joffre

Centre de Recherches en Cancérologie de Toulouse (CRCT), Inserm UMR1037, Université Toulouse III Paul Sabatier, CNRS ERL 5294

Autophagy as a critical mediator of drug resistance in Acute Myeloid Leukemia

Acute myeloid leukemias (AML) are hematologic malignancies characterized by an uncontrolled proliferation of immature hematopoietic cells. Despite a high rate of complete remission after conventional chemotherapies and the recent development of targeted therapies, their outcome remains relatively poor. Indeed, the persistence of therapy-resistant leukemic cells in the organism frequently leads to relapses. AML cells resistance to cytarabine (AraC) relies on their capacity to adapt and increase their mitochondrial metabolism. We hypothesized that this metabolic adaptation is controlled by autophagy, a catabolic process involved in cell metabolism regulation that exhibits ambivalent roles in tumor progression. We recently showed that, in AML cells, autophagy supplies free fatty acids to sustain mitochondrial activity, required to support their proliferation in vitro and in vivo (Bosc et al., 2020 Nat Comm). However, data about the role of autophagy in AML resistance to therapy remain sparse and often incomplete, especially in vivo.

Here we show that autophagy inhibition enhances AraC cytotoxicity in vitro and in vivo in a mouse model of leukemic development, indicating that AraC induces a cytoprotective autophagy in AML cells. Surprisingly, despite an increase in autophagy, AraC treatment does not modify mitophagy levels. Moreover, autophagy inhibition alters the mitochondrial metabolism adaptation observed upon AraC treatment by affecting mitochondrial functions and increasing ROS production. Altogether, our results suggest that the metabolic adaptation driven by AraC is controlled, at least partially, by autophagy and link autophagy, metabolism and resistance.

Collectively, this study will lead to the establishment of promising therapeutic strategies intended to curtail the autophagy-associated malignant properties of AML, thereby leading to long-term patient remission.

** Eligible for best Flash Talk award*

POSTERS SESSION 1

Thursday November 9th
12:00 - 02:00pm

LISTING POSTERS SESSION 1

#	LAST NAME	FIRST NAME	TITLE
P1*	ABUAMMAR	Hussein	Short-term activation of TRPML1 promotes autophagic flux through lysosomal maturation
P2*	ALEMANY	Carla	Rab11 endomembranes and phosphoinositides turnover interplay in response to stresses
P3	BULTEAU	Anne-Laure	Induction of mitophagy by Biofermented Aframomum angustifolium extract: A potential anti-aging mechanism
P4	CULETTO	Emmanuel	The endoplasmic reticulum protein PDZD-8 could mediate a LGG-2/LC3-dependent functional interaction of the ER with autophagosome
P5*	DE GRAÇA	Juliane	Lipid Transfer Proteins and endosomal dynamics associated with nutritional stress
P6*	FABRIZI	Lucie	New function(s) of chk1 kinase in the autophagy process
P7*	LAMIRAL	Guénaëlle	Identification of a new regulator of autophagy receptors-mediated autophagy maturation
P8	MERABET	Samir	Regulation of developmental autophagy by a novel HOX/LAmC partnership in the Drosophila larval fat body
P9	MULLER	Alexandra	Regulation of lysosome by CISD2
P10*	ROJAS	Maria Laura	Unraveling the role of ER-contact sites and VMP1 protein in the autophagic response to shear stress
P11*	VAUCOURT	Mathilde	Selective autophagy in X-linked centronuclear myopathy: molecular mechanisms and pathophysiological relevance
P12*	ANTUÑA	Eduardo	Muscle dependence is associated with autophagy blockade in the elderly

** Eligible for best Poster awards*

LISTING POSTERS SESSION 1

#	LAST NAME	FIRST NAME	TITLE
P13	CLAUDE-TAUPIN	Aurore	The AMPK-Sirtuin 1-YAP axis is regulated by fluid flow intensity and controls autophagy flux in kidney epithelial cells.
P14	DUCLAUX-LORAS	Rémi	Alteration of S. typhimurium degradation in a MYO5B loss-of-function model
P15*	GROSSI	Noëlla	Identificaton of compensatory mechanisms involved in the pathophysiology of LGMD R2
P16*	LABRANA	Honora	Hyperglycemia exacerbates smooth muscle foam cell formation through PI3Kγ-dependent defective autophagy
P17	LAPAQUETTE	Pierre	Membrane vesicles of the food grade bacteria Lactobacillus helveticus stimulate autophagy in vitro and in vivo in aged mice.
P18	LENOIR	Olivia	Autophagy protein 5 controls flow-dependent endothelial functions
P19*	MATTIONI	Anna	A natural variant of the autophagic receptor NDP52 as a new target for Alzheimer's Disease
P20	PROCHAINTZ	Alain	The expression of autophagosome p62/SQSTM1 protein is regulated by paracrine ENGRAILED-1 homeoprotein transcription factor in mouse spinal cord α-motoneurons
P21	STAGNI	Venturina	ACVR1/Alk2-R206H mutant receptor signalling promotes acceleration of chondrogenic differentiation through dyregulation of autophagy

** Eligible for best Poster awards*

P1* - MOLECULAR MECHANISMS & SIGNALING

Hussein ABUAMMAR
Arindam Bhattacharya, Aladar Pettko-Szandtner, Gábor Juhász

Biological Research Centre, Szeged, Hungary

Short-term activation of TRPML1 promotes autophagic flux through lysosomal maturation

Autophagy is a degradation process of intracellular compartments that is highly conserved in eukaryotes. Autophagosome-lysosome fusion and regulation of acidic lysosomal pH (4.5-5.0) are critical steps for proper autophagic degradation of cargo by lysosomes. Defects in those two steps were associated with neurodegenerative lysosomal storage disorders (LSD). Mucolipidosis type IV (MLIV), one such LSD, is characterized by delayed development and vision impairment due to a massive accumulation of unfused autophagosomes. MLIV is caused by mutations in MCOLN1/TRPML1 encoding Transient Receptor Potential Mucolipin channel subfamily 1, leading to lysosomal dysfunction. TRPML1 is a lysosomal cation channel that releases Ca2+ from the lysosomes during amino acid starvation. TRPML1 function is implicated in lysosomal pathways including its formation, positioning and tubulation and exocytosis; but consequences of the short-term TRPML1 Ca2+ release in context of autophagy are much less known. Here, we show that short-term TRPML1 activation by its agonist ML-SA, promotes autophagosome-lysosome fusion and lysosome acidification. ML-SA1-induced acidification, remained through the involvement of v-ATPase and Ca2+. To understand these mechanisms in more detail, we used lysosomal proteomics in TRPML activated cellsand identified lysosomal enrichment of candidates in the fusion machinery: the SNARE proteins STX7, VAMP7, and the small GTPase Rab2a/b. Furthermore, TRPML1 overexpression or activation rescued STX7 recycling observed in PI(3,5)P2 deficient enlarged, non-fusogenic lysosomes. Finally, we identified that lysosomal fusion is important for TRPML-activated acidification of lysosomes. Taken together, we highlight an important early step in lysosomal activation regulated by this channel.

** Eligible for best Poster awards*

P2* - MOLECULAR MECHANISMS & SIGNALING

Carla ALEMANY[1]
Juliane Da Graça[1], *Jean-Baptiste Brault*[2], *Nadia Naffakh*[2] *and Etienne Morel*[1]

1. Institut Necker-Enfants Malades (INEM), INSERM U1151-CNRS UMR 8253, Université Paris Descartes-Sorbonne Paris Cité, Paris, F-75993 France
2. Institut Pasteur, Unité Biologie des ARN et Virus Influenza, CNRS UMR3569, Paris, France

Rab11 endomembranes and phosphoinositides turnover interplay in response to stresses

Mammalian cells are facing different type of stresses, and to overcome changes in homeostasis situations, they have to adapt acutely. Beside the classical autophagy pathway initiation, one of the cellular mechanisms to adapt is dedicated organelles and endomembranes mobilization. In this work, I investigated the molecular mechanisms by which mammalian cells utilize their endosomal arsenal to cope with homeostasis alteration, by comparing nutritional, mechanical and infectious stresses. Both nutritional and mechanical stresses adaptations are at the benefit of the host (recycling to survive nutritional stress and cell differentiation upon shear stress in the kidney). On the contrary, infectious stress adaptations are at the benefit of the pathogen which could lead to a different activation of the same machinery. I particularly focused on endosomal subpopulation positive for the small GTPase Rab11, in putative association with dynamic levels of endosomal phosphoinositides PI3P and PI4P. It was previously shown in the lab that Rab11 positive structures display increased tubulation upon starvation, a situation associated with autophagy induction. I then investigated further what mechanisms were involved in this mobilization of membranes.
We show that following stress induction, there is a change in phosphoinositides homeostasis. Here we suggest that one of the mechanisms leading to Rab11-positive membranes mobilization is a switch of phosphoinositides which takes places on, or at the vicinity of Rab11-positive membranes.

** Eligible for best Poster awards*

Anne-Laure BULTEAU[1]
Philippe Schaeffer , Seyta Ley-Ngardigal, Philippe Mangeot, Tanesha Naiken, Elodie Bossard, Emmanuelle Leblanc, Ryo Niwa, Miyuki Ono, Fabian Oceguera-Yanez, Lorène Gourguillon, Carine Nizard

1. LVMH recherche
Department of Life Science Frontiers, Center for iPS Cell Research and Application (CiRA), Kyoto University
Centre International de Recherche en Infectiologie, CIRI, Lyon

Induction of mitophagy by Biofermented Aframomum angustifolium extract: A potential anti-aging mechanism

Skin aging is a multifaceted process resulting from the accumulation of molecular damage caused by various environmental and intrinsic cell-related stresses. One significant contributor to this process is the production of cellular energy through oxidative phosphorylation, which can generate harmful reactive oxygen species (ROS). These ROS negatively impact protein quality, lead to DNA mutations, and affect mitochondrial respiration, as observed in the study by Dezest et al. (2017, Scientific Reports).

Prior research conducted by LVMH Recherche established a connection between aging and a decline in respiratory parameters, utilizing induced pluripotent stem cells (iPSCs) derived from normal Caucasian fibroblasts of different ages (20 and 40 years old, Moreau et al. 2022, Scientific Reports).

Age-related accumulation of mutations in mitochondrial DNA (mtDNA) has been linked to aging in various tissues, including the skin (as seen in studies like Eshaghian et al. 2006, J. Invest. Dermatol. and Kang et al. 2016, Cell Stem Cell). This led to the hypothesis that mtDNA mutations found in somatic cells might persist or be favored during iPSC reprogramming and differentiation, potentially affecting respiratory function.

Collaborating with The Woltjen Lab at CiRA and using a bank of iPSCs derived from diverse Japanese donors of different ages (ranging from 24 to 83 years old), along with customized protocols for differentiating iPSCs into keratinocyte-like cells, we established a system for analyzing respiration in iPSCs and iPSC-derived keratinocytes. The goal was to identify mtDNA mutations that correlated with the age of the donor and determine their potential to disrupt respiration or differentiation in these cells.

Emmanuel CULETTO[1]
Alexandre POUGET[1]*, *Christophe Lefebvre*[1], *Céline Largeau*[1] *and Renaud Legouis*[2]

1. Université Paris-Saclay, CEA, CNRS, Institute for Integrative Biology of the Cell (I2BC), 91198, Gif-sur-Yvette, France
2. INSERM U1280, 91198, Gif-sur-Yvette, France
**First Author*

The endoplasmic reticulum protein PDZD-8 could mediate a LGG-2/LC3-dependent functional interaction of the ER with autophagosome

We aim to better understand the biogenesis and maturation steps of the autophagosome using the animal model Caenorhabditis elegans. We performed a yeast two-hybrid screen to characterise the interactome of two key C. elegans autophagy proteins, LGG-1/GABARAP and LGG-2/LC3. We show that the PDZ domain containing 8 protein (PDZD-8) interacts with LGG-2. Using AlphaFold, we obtained a predictive model of LGG-2 in complex with PDZD-8. This model suggests that PDZD-8 contains an LC3-interacting region (LIR) that interacts with hydrophobic residues of LGG-2/LC3. Furthermore, mutation of the PDZD-8 LIR abolished the interaction with LGG-2. We raised antibodies against PDZD-8 and used a CRISPR-Cas9-engineered C. elegans strain expressing PDZD-8::mNeonGreen to analyse its expression and subcellular localisation. PDZD-8 localises to the endoplasmic reticulum and is expressed early during embryogenesis and throughout the life cycle of C. elegans, including adulthood, mainly in the epidermis and in some neurons.
Taken together, these results suggest the existence of an interaction between PDZD-8 and LGG-2/LC3 that could mediate contact sites between the endoplasmic reticulum and autophagosomes.
To assess the effect of PDZD-8 inactivation on autophagy, we generated a CRISPR-Cas9-mediated pdzd-8 KO C. elegans. We then stimulated autophagy by subjecting the worms to acute heat stress. We observed an increase in autophagy flux in both control and mutant animals. Interestingly, we found that the size of LGG-2/LC3-positive structures increased transiently in pdzd-8 mutant animals. Furthermore, most of the enlarged autophagosomes were in close contact with lysosomes, suggesting an alteration in autophagosome-lysosome fusion. We will soon investigate whether the PDZD-8 synaptotagmin-like mitochondrial lipid-binding protein (SMP) domain, which could transfer phosphoinositides from one membrane to another, is involved in the autophagosome-lysosome fusion step.
Taken together, these results could provide new data on the interaction between the endoplasmic reticulum and autophagosomes and how it influences autophagosome formation and maturation steps.

P5* - MOLECULAR MECHANISMS & SIGNALING

Juliane DE GRAÇA
Emmanuelle Marjault, Etienne Morel

Institut Necker-Enfants Malades (INEM), INSERM U1151-CNRS UMR 8253, Université de Paris Cité, Paris, France.

Lipid Transfer Proteins and endosomal dynamics associated with nutritional stress

Nutrients deprivation ("starvation") is a major catabolic stress faced by mammalian cells in both pathological and physiological situations, resulting in the activation of the autophagic pathway. Recently we reported that starvation induces early endosome mobilization and promotes endosomal membrane rewiring toward ER sub-regions fostering autophagosome assembly. This process is dependent on a cooperation between SNX1 protein, which promotes endosomal tubulation, and SNX2 which regulates endosomal tubules tethering towards VAPB positive ER subdomains involved in autophagosome biogenesis (Da Graça et al., Life Sci. Alliance 2022). This type of connection directly plays a role in the formation of autophagosome since knocking down SNX1 reduces the autophagic response, while its overexpression increases the number of autophagosomes. As a follow up, we are now investigating the molecular contribution of these dynamic endosomal tubules to these processes. We observed that some lipid transfer proteins (LTP, proteins specialized in inter-membrane non-vesicular lipid transfer) are recruited to this specialized region under starvation. Therefore, we hypothesized that endosomal membranes mobilized by nutritional stress could actively fuel the expanding phagophore with lipids. Our ongoing work focuses on the characterization of the local functions of LTP proteins, including VPS13 subfamily, in the context of phagophore biogenesis from ER/endosome membrane interface.

** Eligible for best Poster awards*

P6* - MOLECULAR MECHANISMS & SIGNALING

Lucie FABRIZI
Lisa Penchede, Stefania Millevoi, Stéphane Manenti

Centre de Recherches en Cancérologie, Université Toulouse III - Paul Sabatier

New function(s) of chk1 kinase in the autophagy process

DNA damage response (DDR) is a complex signalling network activated upon different kinds of genotoxic events. Activation of this pathway, which implicates the phosphorylation and activation of the CHK1 kinase by the ATR kinase, leads to cell cycle arrest and DNA repair to preserve genomic integrity. Autophagy is a biological process activated in response to different types of metabolic stress, including DNA damage. It is a highly conserved self-eating process during which cells digest some of their structural components to maintain cell homeostasis and metabolic equilibrium.
Both autophagy and DDR are therefore essential for survival and maintenance of cellular homeostasis in response to different categories of stress. Several studies report that autophagy can be activated by different types of DNA damage, and that it is involved in cellular responses such as DNA repair, senescence or cell death. Although functional links exist between DDR and autophagy, few studies have reported the implication of CHK1 in this cross-talk.
The hypothesis of this project is that CHK1 is by itself an actor of autophagy. The aim of my project is to demonstrate the existence of this new CHK1 function, and to decipher the molecular elements of this pathway. Our first results suggest that CHK1 is involved into autophagy induction in response to different types of metabolic stress independently of DNA damage. Also, we observe a modification of the CHK1 phosphorylation status (Serine 280) and the CHK1 localisation in response to different types of non-genotoxic stress. In addition, our preliminary data suggest that the role of CHK1 in the survival of leukemic cells during metabolic stress is dependent on an "autophagic" function of the kinase. We are currently trying to identify new CHK1 substrates that could account for these functions in the autophagy process. Altogether, we propose that CHK1 participates to the autophagy process induced in response to different types of stress, and that targeting CHK1 in the cancer field should be considered in light of these data.

** Eligible for best Poster awards*

P7* - MOLECULAR MECHANISMS & SIGNALING

Guénaëlle LAMIRAL[1]
Pauline Verlhac[1], *Aurore Rozières*[1], *Rémi Duclaux-Loras*[1], *Richard J. Youle*[2], *Christophe Viret*[1], *Mathias Faure*[1]

1. *CIRI, Centre International de Recherche en Infectiologie - Inserm U1111, CNRS UMR5308, ENS de Lyon, UCB Lyon 1, Lyon, France*
2. *Biochemistry Section, Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA*

Identification of a new regulator of autophagy receptors-mediated autophagy maturation

Autophagy is a ubiquitous lysosomal degradative process essential for maintaining cellular homeostasis. Autophagy also serves as a major cell-autonomous immune mechanism, playing a crucial role in intracellular pathogens clearance. To this end, during the autophagy maturation step, the fusion of newly formed autophagic vesicles, known as autophagosomes, with lysosomes, results in the formation of an acidic degradative compartment. We previously reported that, beyond their function in targeting cargos towards growing autophagosomal membrane, several autophagy receptors have a dual function in regulating the fusion of autophagosomes with lysosome. We have now identified an autophagy receptor upstream potent regulator essential for facilitating this fusion process. Our research demonstrates that cells depleted of this protein exhibit autophagosomes accumulation and seem no longer capable of efficiently restraining Salmonella Typhimurium intracellular growth. We are currently characterizing the molecular mechanism through which this regulator modulates autophagy receptors-mediated autophagy maturation, which may rely on post-translational events.

** Eligible for best Poster awards*

Samir MERABET
Vanderperre Solene, Ajura Leiore, Duffraisse Marilyne, Forect Christelle, Carnesecchi Julie, Paul Rachel*

IGFL
**First Author*

Regulation of developmental autophagy by a novel HOX/LAmC partnership in the Drosophila larval fat body

Autophagy is an evolutionary conserved catabolic pathway involved in diverse physiological processes such as energy homeostasis or tissue remodelling during development. Autophagy results from the expression of a core set of autophagy-related genes (atg) and its deregulation is associated with a number of pathologies, highlighting the importance of understanding its underlying regulatory mechanisms. Surprisingly, very little is known about the molecular mechanisms that keep autophagy in a silent state. Developmental autophagy is repressed by Hox proteins in the Drosophila larval fat body. Hox proteins constitute one of the rare transcription factor family described as repressors of atg genes' expression, but their underlying molecular mode of action is not known. By using genetics, high resolution imaging and Bimolecular Fluorescence Complementation, we show that the nuclear membrane scaffolding protein Lamin-C (LamC) interacts with Hox proteins and is required for autophagy repression in the Drosophila larval fat body. Remarkably, Hox-LamC interactions preferentially occur on atg loci and in nuclear foci that are reminiscent of nuclear microenvironments. Altogether our results reveal a novel mechanism of transcriptional repression of autophagy, whereby Hox proteins act as anchoring molecules to target atg loci in a LamC-rich repressive environment.

Alexandra MULLER
Lucille Ferret, Karla Alvarez-Valadez, Allan Sauvat, Guido Kroemer, Mojgan Djavaheri-Mergny

Inserm UMRS 1138 - Centre de Recherche des Cordeliers, Paris, France

Regulation of lysosome by CISD2

Type 2 Wolfram Syndrome is a neurodegenerative disease characterized by mutations on the CISD2 gene. The encoded protein, CISD2, is located at Mitochondrial Associated Membranes (MAM) where it plays a critical role in regulating iron and calcium homeostasis, managing ROS levels, maintaining mitochondrial integrity and respiratory chain as well as modulating apoptosis and autophagy. As several studies described the interaction and communication between mitochondria and lysosomes, we aimed to elucidate the potential role of CISD2 in lysosomal regulation. Indeed, recent finding suggest that dysregulation of the interplay between mitochondria and lysosomes plays a role in the development of neurodegenerative diseases. Interestingly, we found that loss of CISD2 rendered cells more susceptible to lysosomotropic agents (such as chloroquine and lys05) as compared to WT cells. As the latter agents are known to induce Lysosomal Membrane Permeabilization (LMP), we then analysed LMP in the presence and absence of CISD2 using a Galectin-3 puncta assay. We found that lys05-induced LMP was markedly increased in CISD2 KO cells as compared to WT cells suggesting the critical role of CISD2 in regulating lysosomal membrane integrity. We are currently investigating the mechanisms underlying the regulation of lysosome by CISD2.

P10* - MOLECULAR MECHANISMS & SIGNALING

Maria Laura ROJAS
Etienne Morel

Institut Necker-Enfants Malades (INEM), INSERM U1151-CNRS UMR 8253, Université de Paris, Paris, France.

Unraveling the role of ER-contact sites and VMP1 protein in the autophagic response to shear stress

At the cellular level, shear stress induced by fluid flow is sensed by the primary cilium located at the apical membrane of most epithelial cells. Previous data from our lab have shown that fluid flow stimulates mobilization of autophagic machinery in kidney epithelial cells (KECs), promoting lipid metabolism reprogramming through lipid droplets (LDs) catabolism and mitochondrial biogenesis, highlighting the importance of autophagic arsenal recruitment to allow cellular adaptation.

The vacuole membrane protein 1 (VMP1) is an autophagy-related protein located in contact sites between the ER-mitochondria, ER-LDs or ER-endosomes. Recent data suggest that VMP1 also plays an active role in neutral lipids mobilization as well as in the biogenesis of de novo organelles via a dedicated lipid-scramblase activity.

Based on these observations, my project aims to decipher the function of VMP1 in the molecular cross-talk between ER, LDs, mitochondria, and the autophagic machinery during metabolic adaptation to mechanical stress.

Here, we show that under shear stress (1dyn/cm fluid flow) during 24h, 48h or 72h VMP1 levels were increased in KECs. To clarify the importance of VMP1 in lipophagy-associated fatty acid transfer from lipid droplets to mitochondria during shear stress we knocked-down the protein expression using a pool of siRNAs against VMP1 and we are now quantifying mitochondria and LDs content after 48h of fluid flow. Our preliminary results suggest that autophagy-associated VMP1 mobilization and stabilization at ER-contact sites necessary for LDs turnover during shear stress metabolic adaptation.

** Eligible for best Poster awards*

P11* - MOLECULAR MECHANISMS & SIGNALING

Mathilde VAUCOURT
Karim Hnia, Marie Vandromme*, Nesrine Hifdi*

Co-Authors

Selective autophagy in X-linked centronuclear myopathy: molecular mechanisms and pathophysiological relevance

X-linked centronuclear myopathy (XLCNM) is a neonatal myopathy characterized by severe hypotonia, general skeletal muscle weakness at birth leading to premature death. MTM1, the mutated gene in XLCNM encodes Myotubularin/MTM1 a phosphoinositide (PIs) 3-phosphatase with two known substrates: PI3P and PI(3,5)P2. PIs are involved in cellular processes including the function of proteolytic organelles such as the lysosome and the autophagosome. However, there is a lack of knowledge about the molecular and pathophysiological outputs of lipid deregulation in XLCNM. Also, the functional connection between MTM1, its substrates and autophagosome/lysosome proteolytic systems remain to be addressed. Ensemble of previous and preliminary data from host team indicate that loss of MTM1 leads to dysfunctional degradation system including autophagy. Notably, muscle and cells from XLCNM models displayed accumulation of altered mitochondria supporting a defective mitophagy, a highly specialized processes required mitochondria quality control and for muscle development and function. Therefore, my PhD project main goal is to address the molecular connection between MTM1 and mitophagy and how this process is involved in the pathophysiology of XLCNM. Finally, in view of therapeutic perspectives I will boost mitochondrial biogenesis and function to improve the defective muscle differentiation observed in XLCNM cell and animal models.

* Eligible for best Poster awards

P12* - PHYSIOPATHOLOGY

Eduardo ANTUÑA[1,2,3]
González-Blanco L.[1,2,4], *Potes Y.*[1,2,3], *García-González C.*[1,2,3], *Cachán-Vega C.*[1,2,3], *Menéndez-Coto N.*[1,2], *Caballero B.*[1,2,3], *Gutierrez-Rodriguez J.* [1,2,5], *López E.*[1,2,5], *Vega-Naredo I.* [1,2,3], *Coto-Montes A.*[1,2,3]

1. University of Oviedo, Morphology and Cell Biology Department, Oviedo, Spain
2. Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Av. Hospital Universitario, Oviedo, Spain
3. Instituto de Neurociencias del Principado de Asturias (INEUROPA), Faculty of Psychology, Oviedo, Spain
4. Servicio Regional de Investigación y Desarrollo Agroalimentario (SERIDA), Villaviciosa, Spain;
5. Àrea de Gestión Clínica de Geriatría, Hospital Monte Naranco, Oviedo, Spain.

Muscle dependence is associated with autophagy blockade in the elderly

Dependency is one of the features evidenced in the elderly population suffering from sarcopenia. This geriatric syndrome is a multifactorial process based on increased alterations in the main homeostatic mechanisms and an imbalance between the synthesis and degradation of macromolecules. This imbalance causes an early onset of aging. Autophagy is the cellular mechanism responsible for the degradation of macromolecules and damaged or dysfunctional organelles to maintain proper cellular functioning, thus ensuring survival. However, the molecular alterations that favor the loss of muscle mass and strength, observed in the development of sarcopenia-related dependency, are still unknown. Therefore, the search for alterations in the autophagy pathway in the aging population is the main objective of this work.
Thirty randomized patients from the HIPA cohort (Principality of Asturias Hip Fracture cohort) were selected for the study. This cohort includes patients older than 70 years who underwent hip fracture surgery. Patients of both sexes were divided into two study groups according to the Barthel Index (BI): fifteen individuals were functionally severely dependent patients (DP; BI 0-40) and fifteen individuals were independent (IP; BI 90-100). The results show a decreased expression of macroautophagic markers (Beclin1 and LC3) and p62 in DP muscle. Only the marker LAMP2A (chaperone-mediated autophagy, CMA) showed a significant increase in DP compared with the IP group. This implies that CMA is, in DP, a macroautophagy-independent pathway. Similarly, the results suggest that in DP there is a blockage of the autophagy pathway from the early signaling, preventing the increase of p62 and causing fatal effects on cell survival. This work shows that the autophagic state could provide a promising new therapeutic target to be unblocked to delay dependency in the elderly population.
Acknowledments: FI22/00286, PRE2019-091053, AYUD/2021/58477, IDI/2021/000033, FISS-14-PI13/02741 and PI21/01596.

** Eligible for best Poster awards*

P13 - PHYSIOPATHOLOGY

Aurore CLAUDE-TAUPIN[1]
Pierre Isnard[1], *Alessia Bagattin*[1], *Nicolas Kuperwasser*[2], *Federica Roccio*[1], *Biagina Ruscica*[1], *Nicolas Goudin*[2], *Meriem Garfa-Traoré*[2], *Alice Regnier*[1], *Lisa Turinsky*[1], *Martine Burtin*[1], *Marc Foretz*[3], *Marco Pontoglio*[1], *Etienne Morel*[1], *Benoit Viollet*[3], *Fabiola Terzi*[1], *Patrice Codogno*[1], *Nicolas Dupont*[1]

1. Université Paris Cité, INSERM UMR-S1151, CNRS UMR-S8253, Institut Necker Enfants Malades, F-75015 Paris, France
2. Structure Fédérative de Recherche Necker, US24-UMS3633, Paris, France
3. Institut Cochin, Inserm U1016 - CNRS UMR8104 -Université Paris Cité, 75014, Paris, France

The AMPK-Sirtuin 1-YAP axis is regulated by fluid flow intensity and controls autophagy flux in kidney epithelial cells.

Shear stress generated by urinary fluid flow is an important regulator of renal function. Its dysregulation is observed in various chronic and acute kidney diseases. Previously, we demonstrated that primary cilium-dependent autophagy allows kidney epithelial cells to adapt their metabolism in response to fluid flow. Here, we show that nuclear YAP/TAZ negatively regulates autophagy flux in kidney epithelial cells subjected to fluid flow. This crosstalk is supported by a primary cilium-dependent activation of AMPK and SIRT1, independently of the Hippo pathway. We confirmed the relevance of the YAP/TAZ-autophagy molecular dialog in vivo using a zebrafish model of kidney development and a unilateral ureteral obstruction mouse model. In addition, an in vitro assay simulating pathological accelerated flow observed at early stages of chronic kidney disease (CKD) activated YAP, leading to a primary cilium-dependent inhibition of autophagic flux. We confirmed this YAP/autophagy relationship in renal biopsies from patients suffering from diabetic kidney disease (DKD), the leading cause of CKD. Our findings demonstrate the importance of YAP/TAZ and autophagy in the translation of fluid flow into cellular and physiological responses. Dysregulation of this pathway is associated with the early onset of CKD.

P14 - PHYSIOPATHOLOGY

Rémi DUCLAUX-LORAS[1]
Juliette Bardet[1,*], *Josephine Maes*[1], *Gilles Boschetti*[1], *Stéphane Nancey*[1], *Christophe Viret*[1], *Marianna Parlato*[2], *Mathias Faure*[1]

1. CIRI, INSERM U1111, CNRS UMR 5308, ENS de Lyon, UCBL Lyon 1
2. Université Paris-Cité, Institut Imagine, Laboratory of Intestinal Immunity, INSERM U1163, Paris, France
**First Author*

Alteration of S. typhimurium degradation in a MYO5B loss-of-function model

Background and Aim:
Congenital Diarrheal Disorders (CDDs) are a heterogeneous group of inherited diseases affecting the digestive system and are frequently life-threatening if left untreated. More than 50 genes have been reported to target different functions of intestinal cells, the immune system, or both. MYO5B LOF (Loss of Function) is responsible for a complete disorganization of enterocyte structure; however, the precise role of MYO5B in intestinal homeostasis is scarce. Therefore, we aimed to evaluate the role of MYO5B in the autophagic dynamic process, a complex intracellular mechanism of catabolism that allows the degradation of intracellular elements through lysosomes.

Methods:
We evaluated autophagic flux in Caco2 MYO5B KO (Knockout) cells in comparison to the control after blocking autophagosome-lysosome fusion using bafilomycin A1 at different time points. Then, we evaluated the intracellular degradation of Salmonella typhimurium after 2 hours, 4 hours, and 6 hours of infection. Finally, we performed confocal microscopy on Caco2 MYO5B KO cells infected by S. typhimurium at similar periods after infection.

Results:
We first demonstrated that the autophagic flux was similar in Caco2 MYO5B KO and control cells after blocking autophagosome-lysosome fusion by bafilomycin A1. CFU counts were significantly higher in Caco2 MYO5B KO cells compared to the wild type (WT) after 6 hours of infection. Finally, confocal microscopy confirmed the higher level of S. typhimurium replication in Caco2 MYO5B KO cells.

Conclusion:
The defect in MYO5B did not impact autophagic flux in our model. However, we pinpointed an increased level of S. typhimurium replication after 2 hours of infection in the context of MYO5B deficiency.

P15* - PHYSIOPATHOLOGY

Noëlla GROSSI[1]

Céline Bruge, Emilie Pellier, Gorka Fernandez, Tanya Stojkovic, Teresinha Evangelista and Xavier Nissan

1. CECS, INSERM U861, I-STEM, AFM, Institute for Stem Cell Therapy and Exploration of Monogenic Diseases, 28 Rue Henri Desbruères, 91100, Corbeil-Essonnes, France
2. Institute of myology, Hôpital Pitié-Salpêtrière, Bâtiment Babinski, 47-83 Boulevard de l'Hôpital, 75013, Paris, France

Identificaton of compensatory mechanisms involved in the pathophysiology of LGMD R2

Limb Girdle muscular dystrophies are a heterogeneous group of genetic diseases leading to progressive loss of the limb girdle muscles. Caused by mutations in the gene encoding dysferlin, limb girdle myopathy type R2 (or LGMDR2, formerly known as LGMD2B) is a rare disease affecting less than 1 in 100,000 people for which there is no treatment. The particularity of this dystrophy is the variability in the clinic and the age of onset of symptoms between patients. Because this difference is not correlated to patient's genotypes, recent in vitro findings have suggested the expression of compensatory mechanism in late onset patients. To identify these compensatory mechanisms, we have have compared gene expression profiles of muscular biopsies obtained from late onset and early onset patients. Several pathways have been identified including autophagy, a lysosomal degradation pathway, which seems to play an important role in the disease, especially in the ability to preserve fibers from stress and damage. The discovery of such pathological or compensatory mechanisms involved in dysferlinopathies may lead to the development of therapeutic procedures by pharmacology or gene transfer.

** Eligible for best Poster awards*

P16* - PHYSIOPATHOLOGY

Honora LABRANA
Wahart Amandine, Cormier Kévin, Solinhac Romain, Swiader Audrey, Smirnova Natalia, Malet Nicole, Salvayre Anne, Gayral Stéphanie, Ramel Damien, Auge Nathalie., Laffargue Muriel

Inserm

Hyperglycemia exacerbates smooth muscle foam cell formation through PI3Kγ-dependent defective autophagy

Diabetic patients are particularly susceptible to post-stenting complications in part due to hyperglycemia as elevated levels of glycated hemoglobin have been linked to the development of neo-atherosclerosis. Smooth Muscle Cell (SMC) phenotype switch drives atherosclerotic and neo-atherosclerotic lesions as they may contribute to lesion formation and stability. They can migrate, proliferate or adopt a macrophage-like phenotype that allows them to engulf lipids to turn foam SMC that represent more than 60% of all the foamy cells presented in atherosclerotic lesions. The presence of foam SMC in neo-atherosclerotic lesions is poorly documented. Moreover, the role of high glucose (HG) in foam SMC formation has not been fully demonstrated, particularly during post-angioplasty recurrence in diabetic patients. The formation of foam cells is linked to an imbalance between the influx of atherogenic lipoproteins and efflux processes. During atherogenesis, autophagy could be limited, potentiating the development of the lesion. Moreover, activators of autophagy appear to limit the formation of atheromatous lesions and foam SMC. So, lipid dedicated autophagy, Lipophagy, a major process involved in cholesterol efflux through lipid droplet degradations, may be deregulated during foamy SMC formation. The links between HG, lipophagy and foam SMC formation are still largely unknown. To investigate the underlying mechanism of this process, we explored in vivo and in vitro the impact of HG on foam smooth muscle cell formation through autophagy and cholesterol efflux processes. This SMC homeostasis disruption could in part explain complications of atherosclerosis treatment in diabetic patients and suggest novel therapeutic approaches for the treatment of neo-atherosclerosis in these high-risk populations.

** Eligible for best Poster awards*

Pierre LAPAQUETTE
Bringer MA., Al Azzaz J., Buteau B., Proukhnitzky L., Aumeunier A., Bermúdez-Humarán LG., Chain F., Daniel C., Acar N., Guzzo J., Rieu A*

Centre des Sciences du Goût et de l'Alimentation, AgroSup Dijon, CNRS, INRA, University of Bourgogne Franche-Comté, Eye and Nutrition Research Group, Dijon, F-21000, France
UMR A 02.102 Procédés Alimentaires et Microbiologiques (PAM), AgroSup Dijon, Université de Bourgogne Franche-Comté, 21000 Dijon, France
**First Author*

Membrane vesicles of the food grade bacteria Lactobacillus helveticus stimulate autophagy in vitro and in vivo in aged mice

Autophagy plays a well-recognized role in longevity and age-related diseases. The activity of autophagy decreases with age and this reduced autophagy is blamed to contribute to the accumulation of cell damages and increase susceptibility to several infectious, inflammatory, neurodegenerative, and metabolic disorders. By contrast, chronic autophagy stimulation can increase lifespan in healthy model organisms, supporting the idea that chronic stimulation of autophagy can be beneficial for healthy aging. Designing nutritional approaches aimed at enhancing autophagy represents an attractive strategy to prevent autophagy defects associated with aging and human diseases. Several lines of evidence show that gut microbes modulate host autophagy at the gut mucosa and in distant organs. Microbial-derived products are among promising candidates to induce autophagy since some of them modulate it through regulation of Pathogen Recognition Receptor (PRR)-associated signaling and metabolic pathways. The aim of this study was to investigate the potential of ferments and probiotics to stimulate autophagy at the gut mucosa and in distant organs. For that purpose, we first screened 11 bacterial food-grade and/or probiotic strains from the lactobacilli and bifidobacteria families for their ability to stimulate autophagy in vitro in human epithelial cell lines (Hela and HCT116 cells) by using complementary biochemical and microscopy approaches. We selected the Lactobacillus helveticus strain VEL12193 as being the best candidate for stimulating autophagy in vitro. In a second step, we analyzed the ability of this strain to stimulate autophagy in vivo (mouse model) both at the gut mucosa and in distant organs, using retina as a proof of concept. We showed that long-term consumption (6 months) of a diet supplemented with L. helveticus VEL12193 by aging mice resulted in the stimulation of basal autophagy both at the gut mucosa and in the retina. In another experiment, we also showed that short term administration of L. helveticus by oral gavage alleviated some of the symptoms of dextran sulfate sodium (DSS)-induced colitis in mice, indicating that, in addition to stimulate autophagy, this bacterial strain has anti-inflammatory potential in vivo. Finally, in an attempt to identify L. helveticus factor(s) involved in autophagy activation, different L. helveticus-derived fractions/products were tested for their ability to stimulate autophagy in vitro. Interestingly, we identified membrane vesicles (MVs) released by L. helveticus as effective inducers of autophagy. Altogether these results show the potential of the food grade bacteria L. helveticus to promote autophagy, opening avenue for the research and development of innovative microbial-based functional food.

P18 - PHYSIOPATHOLOGY

Olivia LENOIR[1]

Nivoit P[1], Mathivet T[1], Wu J[2,3], Salemkour Y[1], Sankar DS[4], Baudrie V[1], Bourreau J[5], Guihot AL[5], Vessieres E[5], Lemitre M[1], Bocca C[5,6], Teillon J[7], Le Gall M[8], Chipont A[1], Robidel E[1], Dhaun N[1,2], Camerer E[1], Reynier P[5,6], Roux E[9], Couffinhal T[9], Hadoke PWF[2], Silvestre JS[1], Guillonneau X[10], Bonnin P[11], Henrion D[5], Dengjel J[4], Tharaux PL[1], Lenoir O[1]

1. Inserm, Université Paris Cité, PARCC, 56 Rue Leblanc, 75015, Paris, France
2. Centre for Cardiovascular Science, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, EH16 4TJ, UK
3. Department of Biomedical Engineering, University of Strathclyde, Glasgow, G4 ONW, UK
4. Department of Biology, University of Fribourg, 1700, Fribourg, Switzerland
5. MITOVASC, CNRS UMR 6015, Inserm U1083, Université d'Angers, 49500, Angers, France
6. Département de Biochimie et Biologie Moléculaire, Centre Hospitalier Universitaire d'Angers, 49500, Angers, France
7. CNRS, Inserm, Bordeaux Imaging Center, BIC, UMS 3420, US 4, Université de Bordeaux, 33000, Bordeaux, France
8. Plateforme Protéomique 3P5-Proteom'IC, Institut Cochin, INSERM U1016, CNRS UMR8104, Université Paris Cité, 75014, Paris, France
9. Inserm, Biologie Des Maladies Cardiovasculaires, U1034, Université de Bordeaux, 33600, Pessac, France
10. Institut de La Vision, INSERM, CNRS, Sorbonne Université, 75012, Paris, France
11. AP-HP, Hôpital Lariboisière, Physiologie Clinique - Explorations Fonctionnelles, Hypertension Unit, Université Paris Cité, 75010, Paris, France

Autophagy protein 5 controls flow-dependent endothelial functions

Dysregulated autophagy is associated with cardiovascular and metabolic diseases, where impaired flow-mediated endothelial cell responses promote cardiovascular risk. The mechanism by which the autophagy machinery regulates endothelial functions is complex. We applied multi-omics approaches and in vitro and in vivo functional assays to decipher the diverse roles of autophagy in endothelial cells. We demonstrate that autophagy regulates VEGF-dependent VEGFR signaling and VEGFR-mediated and flow-mediated eNOS activation. Endothelial ATG5 deficiency in vivo results in selective loss of flow-induced vasodilation in mesenteric arteries and kidneys and increased cerebral and renal vascular resistance in vivo. We found a crucial pathophysiological role for autophagy in endothelial cells in flow-mediated outward arterial remodeling, prevention of neointima formation following wire injury, and recovery after myocardial infarction. Together, these findings unravel a fundamental role of autophagy in endothelial function, linking cell proteostasis to mechanosensing.

P19* - PHYSIOPATHOLOGY

Anna MATTIONI[1]
C Carsetti[2], *V Caputo*[3], *V Cianfanelli*[4,5,6], *C Gabelli*[7], *E Giardina*[3,8], *GL Cestra*[2], *F Strappazzon*[1,9]

1. Lab of Cellular and Molecular Neurosciences Santa Lucia Foundation
2. Institute of Molecular Biology and Pathology (IBPM), National Research Council (CNR), 00185 Rome, Italy
3. IRCCS Fondazione Santa Lucia, Rome, Italy
4. Department of Pediatric Hemato-Oncology and Cell and Gene Therapy, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
5. Department of Science, University «ROMA TRE», 00146, Rome, Italy
6. Department of Woman and Child Health and Public Health, Gynecologic Oncology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
7. Clinical Center for the Aging Brain, Dept of Medicine, University of Padua, Via Giustiniani 2, 35128 Padova, Italy
8. Department of Biomedicine and Prevention, Tor Vergata University, Rome, Italy
9. Univ Lyon, Univ Lyon 1, CNRS, INSERM, Physiopathologie et Génétique du Neurone et du muscl, UMR5261, U1315, Institut Neuromyogène, Lyon, France.

A natural variant of the autophagic receptor NDP52 as a new target for Alzheimer's Disease

Neurofibrillary tangles caused by abnormally phosphorylated Tau protein is one of the classic pathological hallmarks of Alzheimer disease (AD) that contributes to neurodegeneration. It is thus important to develop therapeutic approaches that may favour their elimination. Pathological Tau can be degraded through selective autophagy thanks to a direct binding to NDP52 (Nuclear dot protein 5), a well-known autophagy receptor. We recently characterized a natural variant of NDP52 (NDP52GE), with a point mutation "G140E" that favours its autophagic activity by increasing the binding to the autophagy machinery (LC3C binding). We here anticipated that the variant NDP52GE may be able to mitigate AD disease by clearing more efficiently Tau protein compared to the wild-type (WT) form of NDP52, and this through its higher capacity to bind LC3C. In line with this notion, our data demonstrate that NDP52GE binds more efficiently LC3C compared to NDP52WT in neuronal-like cells. Furthermore, by using an in vitro model that mimics the formation of pathological Tau-related AD, we show that NDP52GE blocks the accumulation of hyperphosphorylated Tau more efficiently than NDP52WT. Moreover, we provide evidence that NDP52GE may be beneficial in an in vivo Drosophila model of Tau-related AD. Finally, through a genetic case-control study, we discovered that NDP52 G140E variant is a protective factor for AD patients. Altogether, our work highlights NDP52GE as a new target for AD patients.

** Eligible for best Poster awards*

Alain PROCHAINTZ
Mélanie Lebœuf, Stephanie E. Vargas-Abonce, Eugénie Pezé-Hedsieck, Edmond Dupont, Lucia Jimenez-Alonso, Kenneth L. Moya

Collège de France, CNRS, INSERM, BrainEver SAS

The expression of autophagosome p62/SQSTM1 protein is regulated by paracrine ENGRAILED-1 homeoprotein transcription factor in mouse spinal cord α-motoneurons

Several homeoprotein transcription factors transfer between cells and regulate gene expression, protein translation, and chromatin organization in recipient cells. ENGRAILED-1 is one such homeoprotein expressed in spinal cord V1 interneurons that synapse on α-motoneurons. Neutralizing extracellular ENGRAILED-1 by expressing a secreted single-chain antibody blocks its capture by spinal motoneurons resulting in α-motoneuron loss and limb weakness. A similar but stronger amyotrophic lateral sclerosis-like (ALS-like) phenotype is observed in the Engrailed-1 heterozygote mouse, confirming that ENGRAILED-1 exerts a paracrine neurotrophic activity on spinal cord α-motoneurons. Following a single intrathecal injection, ENGRAILED-1 reaches the spinal cord parenchyma where it is specifically internalized by spinal motoneurons and has long-lasting protective effects against neurodegeneration and weakness. Midbrain dopaminergic neurons also express Engrailed-1 and, similarly to spinal cord α-motoneurons, degenerate in the heterozygote. We identified genes expressed in spinal cord motoneurons whose expression changes in mouse Engrailed-1 heterozygote midbrain neurons, among which the autophagy gene p62/SQSTM1. Accordingly, p62/SQSTM1 shows increased expression during aging in wild-type spinal cord α-motoneurons, in the Engrailed-1 heterozygote and upon extracellular ENGRAILED-1 neutralization. Conversely, ENGRAILED-1 gain of function through intrathecal injection in the Engrailed-1 heterozygote brings back p62/SQSTM1 to control values, in parallel with its long-lasting therapeutic activity. We conclude (i) that p62/SQSTM1 increase - due to autophagy decrease - is an age marker in spinal cord α-motoneurons, (ii) that a single ENGRAILED-1 injection has a long-lasting anti-aging therapeutic activity in the Engrailed-1 heterozygote ALS-like model and (iii) that this therapeutic activity involves an increase in autophagy. The latter hypothesis, is supported by the disappearance of TDP-43 aggregates in the cytoplasm of Engrailed-1 heterozygote α-motoneurons, following ENGRAILED-1 injection.

Venturina STAGNI[1,2]
Laura Coculo[1,2,*], *Marius Wits*[3], *Rosario Luigi Sessa*[1,2], *Elisabetta Volpe*[2], *Serena Ciolfi*[2], *Serena Rinaldo*[4], *Francesca Cutruzzolà*[4], *Daniela Trisciuoglio*[1], *Gonzalo Sanchez-Duffhues*[3]

1. Institute of Molecular Biology and Pathology, National Research Council (CNR), 00185, Rome, Italy
2. Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Fondazione Santa Lucia, Rome
3. Department of Cell & Chemical Biology, Leiden University Medical Center, 2333, ZC Leiden, The Netherlands
4. Department of Biochemical Sciences, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185, Rome, Italy
**First Author*

ACVR1/Alk2-R206H mutant receptor signalling promotes acceleration of chondrogenic differentiation through dyregulation of autophagy

Heterotopic Ossification (HO) within soft connective tissues occurs sporadically in response to trauma, or by genetic mutation in the rare, autosomal dominant disorder, Fibrodysplasia Ossificans Progressiva (FOP; MIM 135100) [1]. FOP is caused by a recurrent heterozygous activating mutation of activin receptor A, type I/activin-like kinase 2 (ACVR1/ALK2), a bone morphogenetic protein (BMP) type I receptor . The canonical FOP mutation (R206H) exhibits loss of auto inhibition of BMP signalling, that results in constitutive active ACVR1 signalling and correlates with enhanced chondrogenic differentiation. Although gain-of-function ACVR1 mutations are identified as the sole genetic cause of HO in FOP, the molecular mechanism involved in the effect of the mutant ACVR1 is still under investigation. Auotophagy is an essential pathway necessary to maintain cartilage homeostasis, in particular in the hypoxic environment necessary for chondrocytes growth in vivo . Interestingly, hypoxia or Activin A stimulation might enhance BMP signalling in FOP . Herein, we provide, for the first time, evidence of a dysregulation of autophagy signalling in ATCD5 cells expressing mutant FOP receptor. Notably, we discovered that autophagic signalling is impaired in ATCD5 cells exogenously expressing mutant ACVR1 Receptor (ACVR1-R206H), and that this correlates with enhancement of chondrocyte differentiation. Interestingly, we confirmed these data on cells derived from FOP patients, supporting the idea that autophagic flux is impaired in FOP cells, and that drugs that could induce autophagy could be beneficial for FOP patients. At the molecular level, we hypothesize that autophagy is necessary for degradation of receptor during differentiation in a hypoxic environment. Overall, this study could contribute to find new molecular "actors" involved in FOP progression, and so could lead to the design new molecular target therapies for FOP.

POSTERS SESSION 2

Thursday November 9th
04:45 - 05:45pm

LISTING POSTERS SESSION 2

#	LAST NAME	FIRST NAME	TITLE
P22*	ANDROMAQUE	Leslie	Impaired adaptation of the autophagy flux in mature dendritic cells of Crohn's disease patients expressing ATG16L1 T300A polymorphisms
P23*	CAMUS	Guillaume	Bordetella pertussis induces canonical autophagy and LC3-associated phagocytosis in alveolar macrophages
P24*	LUCAS	Julie	Involvement of LC3-conjugation to single membrane in B-cell antigen receptor trafficking
P25*	PRADEL	Baptiste	Nanomechanical forces mediated by AFM-probe can induce localized ATG8ylation
P26	VERGNE	Isabelle	Autophagy as a target for BCG vaccine improvement in the fight against tuberculosis
P27*	FERRET	Lucille	Inhibition of the autophagy/lysosomal pathway exacerbates the anti-cancer effects of RNA Polymerase I inhibitors
P28	MARCHETTI	Sandrine	Unraveling the role of mitophagy during lung cancer progression
P29*	NEJMI	Sanae	PD-L1 mediated post-transcriptional regulation of autophagy : implications for treatment resistance in head and neck cancer
P30*	PLATTEEUW	Loïc	The role of autophagy-dependent signaling in the development of therapeutic resistance mechanisms in acute myeloid leukemia (AML).
P31*	RODRIGUEZ	Aida	Loss of USP10 from the ribosome interactome triggers ribophagy in Oncogene-Induced Senescence
P32*	ROLLAND	Léo	The cell cycle inhibitor p27kip1 controls cell metabolism
P33*	RUGGIERO	Sonia	Characterizing the role of the arginine methyltransferase CARM1 during autophagy in triple-negative breast cancer cells
P34*	SAAD BOUZID	Rima	Breast cancer: Epidemiological, pathological and biological profile
P35	VILLARES	Marie	Pexophagy is induced in the first steps of HIV-1 infection in CD4+ T lymphocytes

P22* - IMMUNITY & INFECTION

Leslie ANDROMAQUE[1]
Gaëlle Quiniou[1], *Rémi Duclaux-Loras*[1,2], *Gilles Boschetti*[1,2], *Christophe Viret*[1], *Mathias Faure*[1], *Stéphane Nancey*[1,2], *Aurore Rozières*[1]

1. CIRI, Centre International de Recherche en Infectiologie, Université de Lyon, Inserm U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, ENS de Lyon, F-69007, Lyon, France
2. Department of Gastroenterology, Hospices Civils de Lyon, Lyon, France

Impaired adaptation of the autophagy flux in mature dendritic cells of Crohn's disease patients expressing ATG16L1 T300A polymorphisms

Crohn's disease (CD) is a chronic disabling immune-mediated intestinal inflammatory disorder resulting in an aberrant immune response to the gut microbiota. Genome-wide association studies have revealed a significant association between CD and various gene polymorphisms, especially ATG16L1 T300A which is intricately linked to autophagy. Autophagy is essential for maintaining cellular homeostasis through the degradation and recycling of cytoplasmic components and microorganisms. However, our knowledges of the mechanism of autophagy in CD patients remains fragmentary, particularly concerning dendritic cells (DC), which mediate major functions in both gut homeostasis and disease. Our aim is to assess the impact of ATG16L1 T300A polymorphisms on dynamic of the autophagy flux in DC from a cohort of CD patients. This dynamic process was assessed quantitatively, by evaluating 3 quantitative parameters: the size of the autophagosome pool, the flux and the turnover. We report here that DCs from CD patients homozygous for ATG16L1 T300A exhibit a strong defect to adapt their autophagy flux to the mature status. Interestingly, this effect was not detected in heterozygous CD patients suggesting a gene dose-dependent influence. Importantly, thanks using a HeLa cell model ATG16L1 knocked out expressing only the T300A polymorphism, we identified that the sole presence of ATG16L1 T300A was sufficient to modulate the dynamics of autophagy flux.
In conclusion, by characterizing with precision the autophagy flux, these findings uncover a previously unknown effect of autophagy-related gene polymorphisms on the autophagy status of DC in Crohn's disease . More specifically, their defective capacity to adjust the dynamic of the flux during maturation, driving their immune functions could be a critical mechanism involved into disease pathogenesis.

** Eligible for best Poster awards*

P23* - IMMUNITY & INFECTION

Guillaume CAMUS
Fethi Khiter, Ghaffar Muharram, Stéphanie Slupek, Nicolas Barois, Emmanuelle Petit, Franck Lafont, Carine Rouanet, Nathalie Mielcarek

Centre d'Infection et d'Immunité de Lille

Bordetella pertussis induces canonical autophagy and LC3-associated phagocytosis in alveolar macrophages

Bordetella pertussis is the main causative agent of whooping cough, a highly contagious respiratory disease that can be fatal in infants. B. pertussis colonizes the airways where alveolar macrophages play an important role in the early innate immune response. These macrophages have also been described as a potential niche for bacterial persistence. Despite that, the fate of B. pertussis and the mechanisms of bacterial degradation in alveolar macrophages remain poorly understood. The induction of autophagy has, for example, never been explored. We studied this mechanism in a cellular model phenotypically and functionally very similar to alveolar macrophages, the MPI (Max Planck Institute) cells, which we infected with B. pertussis. Using confocal microscopy, we first highlighted the induction of LC3 in B. pertussis-infected MPI cells, and its codistribution with bacteria. By analyzing the kinetic of expression of autophagy markers by immunoblotting, we showed that B. pertussis infection of MPI cells induces both canonical autophagy and LC3-associated phagocytosis (LAP). Using transcription electron microscopy, we observed B. pertussis most of the time engulfed in simple-membrane vacuoles and less frequently in double-membrane vacuoles. Our study also suggests a differential role for autophagy receptors p62 and TAX1BP1. Using small interfering RNA (siRNA) to silence rubicon and/or atg13, we demonstrated that autophagy pathways play a role in intracellular B. pertussis clearance.

** Eligible for best Poster awards*

P24* - IMMUNITY & INFECTION

Julie LUCAS[1,2]
Quentin Frenger[1,2], *Sabine Depauw*[1], *Nadège Wadier*[1], *Fabrice Augé*[3], *Pascal Kessler*[4], *Lauriane Kuhn*[4], *Johana Chicher*[5], *Philippe Hammann*[5], *Frédéric Gros*[1,2]

1. *Immuno-Rhumatologie Moléculaire UMR_S 1109 Institut National de la Santé et de la Recherche Médicale, Université de Strasbourg Centre de Recherche de Biomedecine de Strasbourg 1 rue Eugène Boeckel 67000 Strasbourg - France*
2. *Faculté des Sciences de la Vie Université de Strasbourg 28 Rue Goethe, 67000 Strasbourg - France*
3. *Animal Facility FRC1589, Institut de Biologie Moléculaire de Strasbourg, 67000 Strasbourg - France*
4. *PIC-STRA Imaging Patform Institut National de la Santé et de la Recherche Médicale : UMS38, Université de Strasbourg Centre de Recherche de Biomedecine de Strasbourg 1 rue Eugène Boeckel 67000 Strasbourg - France*
5. *Proteomic Facility University of Strasbourg, Centre National de la Recherche Scientifique - CNRS : FR1589 Insitute of Molecular and Cell Biology 2, Allée Konrad Roentgen 67000 Strasbourg - France*

Involvement of LC3-conjugation to single membrane in B-cell antigen receptor trafficking

Antigen presentation by B cells is central in the humoral immune response. B cells present antigens to helper T cells which stimulate their differentiation into plasma cells or memory cells. Autophagy-related (ATG) proteins participate in antigen presentation, but their precise contribution is still unclear. We previously demonstrated a preponderant role for ATG5, being involved in immobilized antigen processing after engagement by the B cell receptor (BCR) through polarized endocytosis. We aim now at precising how ATG proteins participate in BCR trafficking and antigen processing.
We firstly intended to define if LC3-conjugation to single membranes is involved in BCR trafficking. We therefore studied the impact of RUBCN depletion, protein essential for LC3 associated phagocytosis/endocytosis. We stimulated primary B cells isolated from a Rubcn-/- mice, with microbeads-tethered antigens. Upon RUBCN depletion, super-resolution imaging show polarization defects of internalized BCR-containing vesicles. This suggests the involvement of RUBCN-dependent processes in BCR endocytosis. We are now investigating whether RUBCN participates in antigen presentation.
We are also addressing the question of the in vivo role of ATG5 in the processing of BCR captured antigen. We generated ATG5-deficient transgenic mouse models, expressing a BCR specific for a model antigen. After immunization we are investigating by flow cytometry the impact of ATG5 deletion on class switching, and affinity maturation. We are also following B cell capacity to acquire tagged antigen. We will thus be able to evaluate the role of ATG5 in the acquisition of the antigen and investigate whether a selective advantage is provided to B cells by the expression of ATG5, in the long term of the humoral response.
Altogether, we showed that ATG proteins are potentially involved in RUBCN-dependent pathways in BCR endocytosis. We are now validating the in vivo role of this pathway in antigen-driven B cell differentiation.

** Eligible for best Poster awards*

P25* - IMMUNITY & INFECTION

Baptiste PRADEL
Lyonnais Sébastien, Espert Lucile

CEMIPAI UAR3725 ; IRIM UMR9004

Nanomechanical forces mediated by AFM-probe can induce localized ATG8ylation

Cells are constantly subjected to a wide variety of external stimuli. Mechanical forces, such as tension or pressure, triggers cellular responses. Among those, the autophagic pathway has been shown to be induced by several forces leading to the emergence of a new field named the mechanoautophagy1.
Atomic Force Microscopy (AFM) uses local probe with a nanometer resolution to sense sample surface topography. In addition, the AFM probe can be used to apply a localized force on a specific surface, such as cellular plasma membrane. Interestingly, a recent work2 has shown that an AFM-probe driven pressure induces autophagy in a force-dependent manner. Nevertheless, in this study, the use of epifluorescence microscopy does not allow to obtain precise spatiotemporal information about this induction.
To study those aspects, we used a CRISPR Cas9-based approach to generate HEK 293T cells expressing endogenous levels of a GFP tagged LC3B. We followed the distribution of GFP-LC3B by confocal microscopy, in real-time, after the application of an AFM-probe driven force. Our preliminary results show a rapid induction of GFP-LC3B dots that are localized at the site of the AFM-probe contact, suggesting a localized ATG8ylation in response to a mechanical force. In the future, the aim of this project is to decipher the molecular cues involved in this response and the precise function of ATG8ylation in mechanoautophagy.

References :
1. Hernández-Cáceres, M. P. et al. Mechanobiology of Autophagy: The Unexplored Side of Cancer. Front. Oncol. 11, 632956 (2021).
2. Li, B. et al. Nanomechanical Induction of Autophagy-Related Fluorescence in Single Cells with Atomic Force Microscopy. Advanced Science 8, 2102989 (2021).

** Eligible for best Poster awards*

Isabelle VERGNE
Héctor Mayoral Reyes, Aïcha Bah, Claude Gutierrez, Denis Hudrisier, Jérôme Nigou, Olivier Neyrolles*

IPBS, Université de Toulouse, CNRS, UT3, Toulouse, France
**First Author*

Autophagy as a target for BCG vaccine improvement in the fight against tuberculosis

Autophagy is an eukaryotic lysosomal degradative process implicated in intracellular pathogen elimination, modulation of cytokine production and antigen presentation. Recent studies indicate that autophagy activation plays a major role in vaccine efficacy. Thus, enhancing cellular autophagic response has emerged as a novel and promising strategy to improve the BCG vaccine used against tuberculosis. The challenge in designing such improved vaccine is to limit toxicity associated with autophagy induction and/or to target specifically the autophagy pathway. Thankfully, new autophagy inducers have been recently reported especially from peptide design. Here, we propose an innovative approach to enhance BCG vaccine effectiveness by producing recombinant BCG strains engineered to secrete autophagy-inducing peptides (rBCG). To allow efficient secretion, the sequence of the pro-autophagic peptide is flanked at its N-terminus by a signal peptide originating from a natural BCG-secreted protein (a-antigen). Our preliminary data indicate that these rBCG strains can secrete pro-autophagic peptides in culture media. Furthermore, our data show a higher autophagic response in macrophages infected with rBCG than with wild-type (WT). Future work will aim to compare the immune responses in macrophages and dendritic cells as well as safety and protection efficacy against Mycobacterium tuberculosis infection in mice vaccinated with rBCG or WT BCG. Overall, this work should bring new understandings on the impact of a specific and localized autophagy boost during vaccination against tuberculosis. This study was supported by the European Union's Horizon 2020 Research and Innovation Program (grant 643381TBVAC2020). HMR is a recipient of a CONACYT Mexican Scholarship.

P27* - CANCER

Lucille FERRET[1]
Allan Sauvat[1,2], *Gautier Stoll*[1,2], *Karla Alvarez-Valadez*[1,2,3], *Alexandra Muller*[1,2], *Felix Peyre*[1,2], *Harald Wodrich*[4], *Jonathan Pol*[1,2], *Guido Kroemer*[1,2] *and Mojgan Djavaheri-Mergny*[1,2]

1. Centre de Recherche des Cordeliers (CRC), Université de Paris, Sorbonne Université, INSERM U1138, Institut Universitaire de France, Paris, France.
2. Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Campus, Villejuif, France
3. Faculté de Médecine, Université Paris Saclay, Le Kremlin-Bicêtre, France
4. CNRS UMR 5234, Fundamental Microbiology and Pathogenicity, Université de Bordeaux, Bordeaux, France

Inhibition of the autophagy/lysosomal pathway exacerbates the anti-cancer effects of RNA Polymerase I inhibitors

Lysosomes are an intracellular platform that coordinates cellular anabolic and catabolic processes, cell signaling, and transcriptional programs. They contribute to the development of drug resistance through the activation of various processes. These include drug sequestration within lysosomal compartment and activation of adaptive pathways such as autophagy and Transcription Factor-EB (TFEB). Yet little is known about the role of lysosomes in the anticancer effect of RNA Polymerase (POL) I inhibitors. In this study, we investigated the potential effect of two RNA Pol I inhibitors, CX-3543 (Quarfloxin) and CX-5461, on lysosome regulation to identify pathways for enhancing their efficacy and potentially overcoming therapy resistance.

The primary mode of action of CX-3543 (Quarfloxin) and CX-5461 is attributed to the inhibition of RNA polymerase I through specifically targeting guanine quadruplex (G4) structures in ribosomal DNA.

First, we found that CX-3543 not only induced nucleolar disruption but also triggered lysosomal membrane permeabilization (LMP) through its accumulation within lysosomes. As a result of LMP induction, TFEB and autophagy were activated to cope with lysosomal stress. Disruption of either adaptive process led to increased cell death triggered by CX-3543. Moreover, we found that CX-3543 triggered a p53-independent non-apoptotic cell death that depends on BAX and BAK. Inhibiting lysosomal functions using chloroquine derivatives enhanced LMP and significantly amplified nucleolar disruption and cell death induced by CX-3543. Similar results were obtained with another RNA POL I inhibitor, CX-5461. Finally, we observed that the combination of CX-3543 and the chloroquine derivative, DCC61, markedly reduced tumor growth in an immunocompetent mice fibrosarcoma model.
This study uncovers an unanticipated mechanism in which inhibition of lysosomal functions links LMP to nucleolar disruption and cell death induced by the RNA POL I inhibitors, CX-3543 and CX-5461. These findings strongly support future clinical trials combining CX-3543 or CX-5461 with chloroquine derivatives.

** Eligible for best Poster awards*

P28 - CANCER

Sandrine MARCHETTI
Sonia Nunez-Vasquez, Emma Guilbaud, Diogo Gonçalves, Rachel Paul, Johanna chiche, Jean-Ehrland Ricci

Université Côte d'Azur, INSERM, C3M, 06204 Nice, France

Unraveling the role of mitophagy during lung cancer progression

Lung cancer is a leading cause of death worldwide. While recent major advances were made in the treatment of this disease, the overall 5-year survival rate is only 15%, reinforcing the need of innovative and more efficient therapeutic strategies.
Mitophagy, a selective form of autophagy involved in the elimination of damaged mitochondria, is a major process that enables cancer cells to resist both environmental stress and chemotherapeutic agents. It has also recently been established that mitophagy plays an essential role in the regulation of inflammatory responses.
Knowing both the importance of autophagy in cancer initiation and progression, and that lung cancer is highly dependent on mitochondrial metabolism, we first analyzed the level of mitophagy in a genetically engineered mouse models of lung adenocarcinoma to study mitophagy in vivo. We therefore breed KrasLSL-G12D deficient or not for p53 (KP and K model respectively) with Mito-QC mice, which express a pH-sensitive fluorescent mitochondrial tandem, allowing assessment of mitophagy and mitochondrial architecture. Using this unique model, we monitored mitophagy upon lung cancer development by measuring Mito-QC fluorescence at different stages of lung tumor (healthy, pre-malignant lesions or established tumors). Our data indicate that mitophagy is increased in all pre-neoplastic lesions, whereas this induction is more heterogenous at the adenocarcinoma (ADK) stage, even though the oncogenic driver mutations are the same. Finally, we used an innovative intratracheal injection of Cre recombinase-expressing lentivirus with a specific guide RNA to invalidate the expression of two key auto/mitophagy genes (ATG7 or Pink1) in vivo. Overall, our study highlights the impact of mitophagy on lung cancer development and immune cell infiltration.

P29* - CANCER

Sanae NEJMI[1]
Axel Arthur[2], *Erik Dassi*[2], *Stefania Millevoi*[2], *Estelle Espinos*[2]

1. Université Toulouse III - Paul Sabatier
2. Cancer Research Center of Toulouse, UMR1037 Inserm, Toulouse

PD-L1 mediated post-transcriptional regulation of autophagy : implications for treatment resistance in head and neck cancer

Autophagy, a process of cellular self-digestion, plays a vital role in maintaining cellular homeostasis at the basal level and in response to various types of stress. While the impact of this catabolic mechanism on oncogenesis is well established, its precise involvement in tumour initiation, progression, response to treatment and the underlying regulatory mechanisms remain elusive. Although the transcriptional and post-translational regulation of key autophagy genes has been extensively studied, recent investigations have revealed the importance of post-transcriptional regulation by RNA-binding proteins (RBPs), but the molecular mechanisms governing this phenomenon remain largely unknown. So-called «non-canonical» RBPs, i.e those that bind RNA in unconventional ways and are known to exert functions beyond RNA metabolism, could be involved in this regulation. We focus on one of these RBPs, PD-L1 (Programmed Death-Ligand 1), known for its role as an inhibitory immune checkpoint that enables cancer cells to evade immune surveillance. Interestingly, recent studies highlight PD-L1's ability to interact with RNA, giving it the ability to modulate the stability of specific mRNAs encoding stress response-related proteins. In the context of Head and Neck Squamous Cell Carcinoma (HNSCC), in which an inverse correlation between PD-L1 expression and patient survival has been observed, and in which altered expression of autophagy genes has prognostic value, we showed that PD-L1 binds to some autophagy-related mRNAs and influences their translation, thereby impacting the overall autophagic process. Furthermore, our studies have confirmed the role of PD-L1 in conferring resistance to chemotherapy. This led us to propose a novel model in which PD-L1 orchestrates the post-transcriptional regulation of autophagy, thereby contributing to treatment resistance and providing an innovative avenue for therapeutic intervention.

** Eligible for best Poster awards*

P30* - CANCER

Loïc PLATTEEUW[1,2]
Charlotte Ducau[1,2], *Alexandre Boudet*[1,2], *Laura Poillet*[1,2], *Jean-Emmanuel Sarry*[1,2], *Véronique-De Mas*[1,2,3], *Carine Joffre*[1,2]

1. *Centre de Recherches en Cancérologie de Toulouse (CRCT), INSERM UMR1037, CNRS UMR 5071, Université de Toulouse, Toulouse, France*
2. *Equipe labellisée La Ligue contre le Cancer 2018, Toulouse, France*
3. *Laboratoire d'Hématologie, Centre Hospitalier Universitaire de Toulouse, Institut Universitaire du Cancer de Toulouse-Oncopole, Université de Toulouse III Paul Sabatier, Toulouse, France*

The role of autophagy-dependent signaling in the development of therapeutic resistance mechanisms in acute myeloid leukemia (AML).

My project aims to investigate the role of autophagy as a regulator of cellular signaling in treatment resistance in acute myeloid leukemia (AML). Numerous studies have identified pathways and proteins required for autophagy, but few have focused on its influence on cellular signaling pathways.
To do so, we generated AML cell lines deficient in autophagy using an inducible shRNA targeting ATG5. These human cell lines expressed the FLT3-ITD mutant, an oncogenic tyrosine kinase receptor frequently found in AML patients. Thanks to these models, we confirmed unpublished findings from our team, showing that inhibiting autophagy decreased STAT5 phosphorylation, a specific FLT3-ITD mediated signaling, without affecting other pathways. Since STAT5-dependent FLT3-ITD signaling is known to occur mainly from intracellular compartments, we thus hypothesized that a portion of this mutated receptor localizes on autophagosomes. Therefore, the inhibition of autophagosomes formation in cells depleted for ATG5 inhibits STAT5 signaling that occurs from this specific location. These results suggest that autophagy qualitatively regulates FLT3-ITD-dependent signaling. We will perform co-immunofluorescence staining for FLT3 and LC3B, as well as proximity ligation assay to confirm their physical proximity.
In parallel, to identify autophagy-modulated signaling pathways contributing to AML resistance, we are developing two unbiased approaches. Both will compare autophagy-competent and -deficient cells +/- chemotherapy. The first one assesses simultaneously the phosphorylation status of multiple protein kinases using PamStation® (PamGene), a phosphoarray method for kinase activity profiling. The second will identify by mass spectrometry (LC-MS/MS) total cellular protein content as well as proteins present on autophagosomes after their purification thanks to an antibody-based FACS mediated method (here anti-LC3B), that we are currently setting up.
This project aims to establish a potential link between autophagosomal signaling, leukemic development and therapeutic resistance. It will also help identify new players and therapeutic targets controlling AML's oncogenic capabilities regulated by autophagy.

** Eligible for best Poster awards*

P31* - CANCER

Aida RODRIGUEZ

Maria H. Jørgensen[1], Jesper Havelund[2], Frederic S. Arendrup[3], Srinivasa Prasad Kolapalli[1], Thorbjørn M Nielsen[1], Eva Pais[1], Carsten Jörn Beese[1], Ahmad Abdul-Al[1], Anna Constance Vind[4], Jiri Bartek[1,5], Simon Bekker-Jensen[4], Marta Montes[3], Panagiotis Galanos[1], Nils Faergeman[2], Lotta Happonen[6] and Lisa B. Frankel[1,3]

1. Danish Cancer Institute, Copenhagen, Denmark
2. Department of Biochemistry and Molecular Biology, University of Southern Denmark, Odense, Denmark.
3. Biotech Research and Innovation Centre, University of Copenhagen, Copenhagen, Denmark.
4. Center for Healthy Aging, Department of Cellular and Molecular Medicine, University of Copenhagen, Copenhagen, Denmark.
5. Department of Medical Biochemistry and Biophysics, Division of Genome Biology, Science for Life Laboratory, Karolinska Institute, Stockholm, Sweden.
6. Division of Infection Medicine, Department of Clinical Sciences Lund, Faculty of Medicine, Lund University, Lund, Sweden.

Loss of USP10 from the ribosome interactome triggers ribophagy in Oncogene-Induced Senescence

The overexpression of certain oncogenes can lead to Oncogene-Induced Senescence (OIS), a condition of permanent cell cycle arrest that is also a barrier against tumorigenesis. While OIS cells are well known to exhibit an active metabolism and unique secretory features, the mechanisms underlying this remain elusive. Autophagy is a key pathway that regulates cellular homeostasis and although it is intricately linked to senescence, its role in OIS remains poorly understood. Here, we use a model system of BRAF-induced OIS in human fibroblasts, to investigate the regulation of ribophagy, the selective degradation of ribosomes by autophagy. By using the pH-sensitive fluorophore mKeima tagged to several ribosomal proteins, we uniquely identify an increase in the ribophagic flux in OIS cells. Performing ribosome pull-downs coupled to mass spectrometry analysis in OIS or proliferating cells, we reveal the deubiquitinase USP10 as a key player that safeguards ribosomes from lysosomal degradation. While present in the ribo-interactome of proliferating cells, we find that USP10 is released from OIS ribosomes leading to enhanced ribosomal ubiquitination and subsequent increase of ribophagy. We show that the ubiquitinated ribosomes are recognized by the cargo receptor p62 for their subsequent degradation. Moreover, we identify a single lysine in the ribosomal protein RPS2 (K275) as a key residue susceptible of ubiquitination, which can trigger the lysosomal degradation of both the small and large ribosomal subunits. Finally, we observe how the ribophagic flux of OIS cells is related to the metabolic demands of OIS cells and contributes to the altered secretory phenotype of these cells. Our results uniquely show ribophagy in OIS cells as a mechanism that supports the metabolic and secretory profile of senescent cells.

** Eligible for best Poster awards*

P32* - CANCER

Léo ROLLAND[1]
Marion Aguirrebengoa, Ivan Nemazanyy, Anastassia Hatzoglou, Arnaud Besson

1. Centre de Biologie Intégrative - Toulouse
2. Institut Necker Enfants Malades - Paris

The cell cycle inhibitor p27kip1 controls cell metabolism

The cell cycle regulator p27kip1 (p27), acts as a tumor suppressor by binding and inhibiting cyclin-dependent-kinases (CDKs) that allow cell cycle progression. This role of p27 is linked to its nuclear localization, and in cancer cells p27 is often cytoplasmic, losing its role of cell cycle inhibitor and thus participating to the relentless cell division. Furthermore, p27 regulates other cellular functions, such as cytoskeleton dynamics, transcriptional regulation and autophagy.
We have recently shown that p27 plays a critical role under metabolic stress, such as amino acid or glucose starvation. Indeed, under amino acid starvation p27 promotes autophagy flux and controls mTORC1 signaling. Interestingly, p27+/+ cells are more sensitive to an amino acid starvation than p27-/- cells, which survive by maintaining elevated mTORC1 activity. In contrast, p27-/- cells are more sensitive to a glucose starvation than p27+/+ cells, which survive by promoting autophagy.
Given the role of p27 on autophagy, mTORC1 signaling and transcription regulation, we hypothesized that p27 may participate in rewiring cellular metabolic programs upon stress. Using cell lines with different p27 status, we performed :
I) RNA sequencing to understand how p27 controls gene expression during metabolic stress.
II) Metabolomic studies to investigate whether p27 induces metabolic reprogramming upon metabolomic stress.
Our data clearly indicates that p27 modulates cell metabolism during metabolic stress. Metabolomics analysis show that many metabolites are impacted by the p27 status. Transcriptomics analyses reveal that p27 also controls gene expression during metabolic stress and shows that p27 plays a role in mitochondria homeostasis, cell death, autophagy and metabolic processes. Furthermore, our data indicates that mitochondria dynamics is modified which could lead to mitophagy defect.
Given that p27 status is often deregulated in cancer cells and that p27 status confers resistance to cell death during metabolic stresses, we want to determine if p27 could be used to sensitize cancer cells to apoptosis by targeting specific metabolic pathways.

** Eligible for best Poster awards*

P33* - CANCER

Sonia RUGGIERO[1]
Solène Huard[1], *Samyuktha Suresh*[1], *Damarys Loew*[2], *Nicolas Servant*[3], *Didier Meseure*[4], *and Thierry Dubois*[1]

1. *Breast Cancer Biology Group, Translational Research Department & CNRS UMR144, Institut Curie-PSL Research University, 75005 Paris, France*
2. *Mass-spectrometry platform, Institut Curie-PSL Research University, 75005 Paris, France*
3. *Bionformatics platform, Institut Curie-PSL Research University, 75005 Paris, France*
4. *Experimental pathology platform, Institut Curie-PSL Research University, 75005 Paris, France*

Characterizing the role of the arginine methyltransferase CARM1 during autophagy in triple-negative breast cancer cells

Triple-negative breast cancer (TNBC) is the most aggressive breast cancer subtype, for which finding new therapeutic strategies is still a priority in oncology. A family of enzymes called PRMTs, which methylate arginines on histones and non-histone substrates, emerged as promising therapeutic targets for TNBC. PRMTs play different roles in the cell; for example, they are involved in transcriptional regulation, alternative splicing and immune response. Recent studies revealed that PRMT4, also known as CARM1, regulates autophagy by acting as transcriptional co-activator for TFEB, leading to the expression of lysosomal and autophagy-related genes under stress conditions. We found that CARM1 is overexpressed in TNBC compared to normal breast tissues and is required for the survival of TNBC cell lines, suggesting that CARM1 could be an attractive target for TNBC.
To better understand CARM1 functions in TNBC cells, we have characterized its interactome after immunoprecipitation and mass spectrometry analyses. TFG (TRK-fused gene) and ATG9A, which are both involved in the maturation of autophagosomes during autophagy, were found to interact with CARM1 in several TNBC cell lines. I validated these interactions by co-immunoprecipitation experiments. These results suggest that CARM1 may regulate autophagy also in the cytosol, in addition to its nuclear role as a TFEB co-activator. My project now aims to characterize the functional interplay between CARM1, ATG9A and TFG during autophagy in TNBC cells. More specifically, I would like to examine whether CARM1 regulates autophagy particularly during autophagosome maturation, and whether this happens through the interaction and/or the methylation of ATG9A and TFG.
Since autophagy can act as a pro-survival strategy in tumour cells and its inhibition improved the treatment of certain cancers, understanding the role of CARM1 in autophagy could shed the light on novel mechanisms promoting tumour growth in TNBC.

** Eligible for best Poster awards*

P34* - CANCER

Rima SAAD BOUZID[1]
Radhia Bouzid[1,2], *Donia Hellal*[3], *Hachani Khadraoui*[1,3,5], *Ghania Belaaloui*[1,3]

1. Laboratory of Acquired and Constitutional Genetic Diseases (MAGECA), Department of Medicine, Faculty of Medicine, Batna 2 University, Ezzouhour, Batna 05000, Algeria
2. Faculty of Nature and Life Sciences, Batna 2 University, Batna, Algeria
3. Faculty of Medicine, Batna 2 University, Batna, Algeria
4. Physicien, pathology Department CLCC Batna, Algeria
5. Chief Physicien, pathology Department CLCC Batna, Algeria

Breast cancer: Epidemiological, pathological and biological profile

Breast cancer is the most frequently diagnosed cancer and the second cause of death worldwide and in Algeria. We can distinguish different histological and molecular entities in breast cancer. The objective of this work is to report the preliminary results of a molecular and histological characterization of breast cancer in CLCC Batna center during the period from 2018 to 2023.
Clinical and pathological characteristics of 573 breast cancer cases were collected from the archives of the pathology department of CLCC Batna. To analyze their characteristics, age, histological type, SBR grade, hormone receptor status, HER2 status were taken in account, and molecular phenotypes were compared.
The results revealed that the mean age of the selected population is 50 years with a predominance of the age group 50 to 59 years. The proportions of luminal A, luminal B, TNBC and HER2 breast cancer subtypes were 23.4%, 48,9%, 17.3% and 10.5%, respectively. The invasive ductal carcinoma (IDC) was the most common histological type (85.5%) followed by the invasive lobular carcinoma (9.4%).
The SBR grade II was the most common in the population. We noticed a higher frequency of IDC in the young [40 - 49 y] and middle aged groups [50 -59 y], while all the IDC were of Luminal B molecular type.
Although our results are preliminary, some of them are concordant with other Algerian studies. A more extended molecular and immunohistological characterization is ongoing.
Key words: Breast Cancer, Histological type, sub-molecular type, Aures region, immunohistochemistry

** Eligible for best Poster awards*

Marie VILLARES
Aurélie Rivault, Baptiste Pradel, Véronique Hebmann, Lucile Espert

IRIM - CNRS Montpellier

Pexophagy is induced in the first steps of HIV-1 infection in CD4+ T lymphocytes

Autophagy is an intrinsic immunity mechanism that allows the degradation of pathogens after their entry into target cells. In addition, it can also degrade several innate immunity sensors allowing a return to a basal state of the immune system after its activation following an infection. Consequently, pathogens have developed strategies to block autophagy or to use it for their own benefit in order to promote their replication. In this context, numerous studies show that viruses use autophagy to block the IFN response.

Infection of CD4+ T lymphocytes by HIV-1 leads to an extremely low production of IFN, which does not allow sufficient activation of the antiviral response, suggesting that the virus is able to dampen this response which would be harmful for its replication.

Our results indicate that autophagy is induced in the early step of the HIV-1 replication cycle in CD4+ T lymphocytes. Interestingly, we have shown that peroxisomes are targeted by this process (pexophagy). Peroxisomes are cellular organelles involved in homeostasis, mainly by protecting cells from oxidative stress. However, it is worth noting that they harbor MAVS (Mitochondrial AntiViral Signaling proteins) at their surface, making them innate immunity mediators. Even if the function of peroxisomes in innate immunity is not well characterized, it has been demonstrated that it participates in IFN antiviral response during infection. We are now identifying the selective autophagy mechanisms involved in HIV-1 induced pexophagy and its effect on cellular homeostasis, innate immune response.

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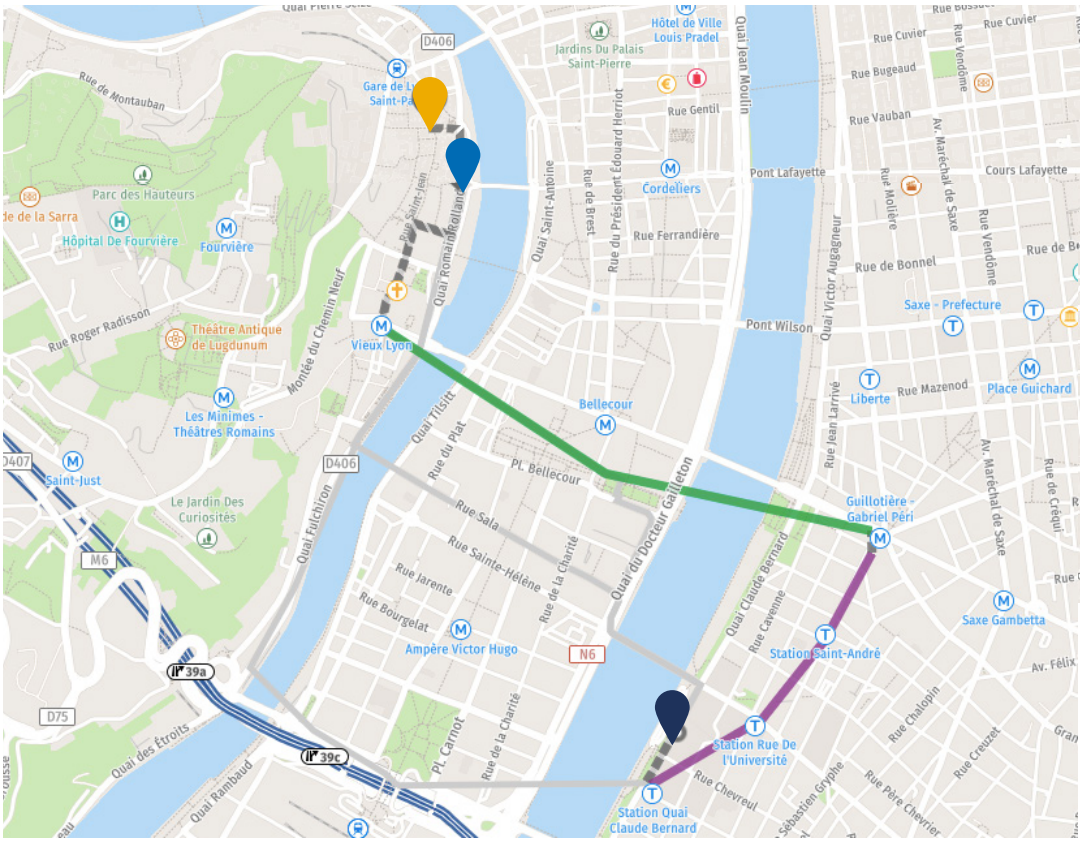

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THE BIG WHITE - 22 Rue Lainerie, Lyon

- Take the Tram T1: 22, rue de l'université *(purple line on the map)*
- Metro D « direction gare de Vaise » *(green line on the map)*
- Stop at vieux-Lyon
- Walk in the Renaissance area of Lyon (10 minutes) *(see map with the «traboules»).*

WHAT TO VISIT IN LYON

Basilique de Fourvière-View of Lyon

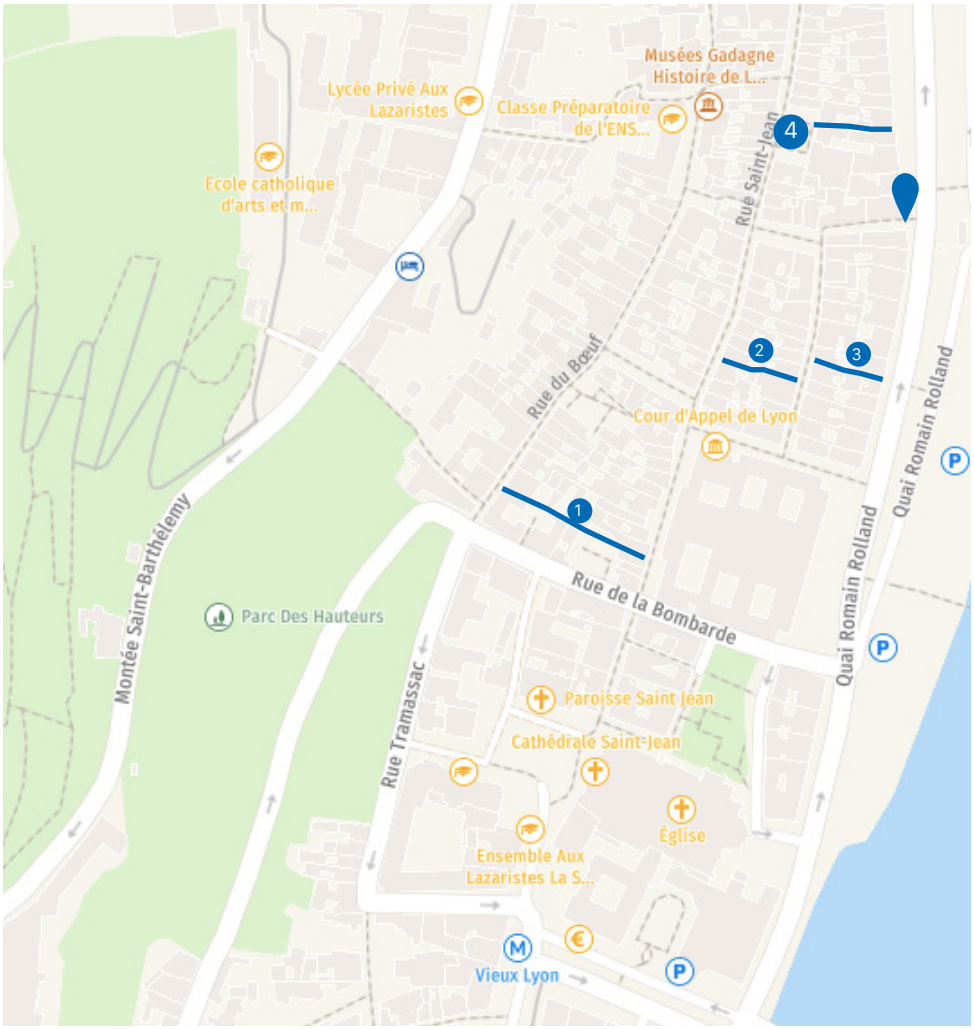
From Vieux-Lyon station (Metro D): take the « funiculaire » to Fourvière

« Trabouler » on the way from vieux Lyon station to the restaurant

« Traboule » are a type of secret covered passageways

1. 54 Rue St Jean connecting with 27 Rue de Boeuf
2. 27 Rue St Jean connecting with 6 Rue des Trois Maries
3. 9 Rue des Trois Maries with 17 Quai Romain Rolland
4. 2 Place du Gouvernement with 10 Quai Romain Rolland

CHEZ CHABERT
13 - 14 Quai Romain Rolland, Lyon



LIST OF PARTICIPANTS

LAST NAME	FIRST NAME	PROFESSIONAL E-MAIL
ABUAMMAR	Hussein A. H.	husammar@brc.hu
AKROUF	Inès	i.akrouf@institut-myologie.org
ALEMANY	Carla	carla.alemany@inserm.fr
ALLIOUX	Claire	claire.allioux@inserm.fr
ANDROMAQUE	Leslie	leslie.andromaque@inserm.fr
ANIORTE	Sahra	sahra.aniorte@ens-lyon.fr
ANTUÑA	Eduardo	edugan.97@gmail.com
ARTHUR	Axel	axel.arthur@inserm.fr
BEAN	Camilla	camilla.bean@uniud.it
BEAUCLAIR	Guillaume	guillaume.beauclair@universite-paris-saclay.fr
BENKHELIFA-ZIYYAT	Sofia	s.ziyyat@institut-myologie.org
BESSON	Arnaud	arnaud.besson@univ-tlse3.fr
BINET	Mathilde	mathilde.binet@i2bc.paris-saclay.fr
BLANC	Jules	jules.blanc1@ens-lyon.fr
BOMONT	Pascale	pascale.bomont@inserm.fr
BOUTONNET	Lauréline	laureline.boutonnet@gmail.com
BRUQI	Krenare	krenare.bruqi@gmail.com
BULTEAU	Anne-Laure	abulteau@research.lvmh-pc.com
CAMPISI	Daniele	daniele.campisi@pasteur.fr
CAMUS	Guillaume	guillaume.camus.etu@univ-lille.fr
CANTALOUBE	Guilhem	guilhem.cantaloube@irim.cnrs.fr
CELLE	Marion	marion.celle@ens-lyon.fr
CESARE	Giuliana	giuliana.cesare@unimi.it
CHAPUY-REGAUD	Sabine	chapuy-regaud.s@chu-toulouse.fr
CHEVALIER	Fabien	fabien.chevalier@univ-lyon1.fr
CIROTTI	Claudia	claudiacirotti89@gmail.com
CLAUDE-TAUPIN	Aurore	aurore.claude-taupin@inserm.fr
COCULO	Laura	lauracoc6@gmail.com
CULETTO	Emmanuel	emmanuel.culetto@i2bc.paris-saclay.fr
DA GRAÇA	Juliane	juliane.da-graca@inserm.fr
DA SILVA	Tristan	tristan.da-silva@etu.univ-lyon1.fr
DAURA	Marine	marine.daura@univ-lyon1.fr
DAUSSY	Coralie	coralie.f.daussy@gmail.com

LIST OF PARTICIPANTS

LAST NAME	FIRST NAME	PROFESSIONAL E-MAIL
DESPRAIRIES	Alice	alice.desprairies@inserm.fr
DJAVAHERI-MERGNY	Mojgan	mojgan.mergny@inserm.fr
DJEBALI	Eva	eva.hernandez@universite-paris-saclay.fr
DOKUDOVSKAYA	Svetlana	svetlana.dokudovskaya@igr.fr
DUCAU	Charlotte	charlotte.ducau@inserm.fr
DUCLAUX-LORAS	Rémi	remi.duclaux-loras@chu-lyon.fr
DUPONT	Nicolas	nicolas.dupont@inserm.fr
EL JAMMAL	Thomas	thomas.el-jammal@ibcp.fr
EL MANSSOURI	Hanane	hanane.el_manssouri@ens-lyon.fr
ESCLATINE	Audrey	audrey.esclatine@u-psud.fr
ESPERT	Lucile	lucile.espert@irim.cnrs.fr
FABRIZI	Lucie	lucie.fabrizi@inserm.fr
FAURE	Mathias	mathias.faure@inserm.fr
FERRET	Lucille	lucille.ferret@universite-paris-saclay.fr
FORCET-VAUCHEL	Christelle	christelle.forcet@ens-lyon.fr
FRANCO-ROMERO	Anaïs	anais.franco@unipd.it
FRANKEL	Lisa	lisa.frankel@bric.ku.dk
FRENGER	Quentin	qfrenger67@gmail.com
GARGANO	Deborah	d.gargano@studenti.unimol.it
GONÇALVES	Diogo	diogo.jumel-goncalves@etu.unice.fr
GROS	Frédéric	f.gros@unistra.fr
GROSSI	Noëlla	ngrossi@istem.fr
JAUQUET	Melissa	jauquet@cyceron.fr
JOLLIVET	Florence	florence.jollivet@ens-lyon.fr
JOURNO	Chloé	chloe.journo@ens-lyon.fr
JUDITH	Delphine	delphine.judith@inserm.fr
KAESER-PEBERNARD	Stéphanie	stephanie.kaeser-pebernard@unifr.ch
KOMATSU	Masaaki	mkomatsu@juntendo.ac.jp
KRAFT	Claudine	claudine.kraft@biochemie.uni-freiburg.de
KRETZ-REMY	Carole	carole.kretz@univ-lyon1.fr
LABRANA	Honora	labrana.honora@inserm.fr
LAMHENE	Sara	sara.lamhene@etu.univ-lyon1.fr
LAMIRAL	Guénaëlle	guenaelle.lamiral@inserm.fr

LIST OF PARTICIPANTS

LAST NAME	FIRST NAME	PROFESSIONAL E-MAIL
LAPAQUETTE	Pierre	pierre.lapaquette@u-bourgogne.fr
LAVEDRINE	Aude	aude.lavedrine@inserm.fr
LE LAY	Emelyne	emelyne.lelay@i2bc.paris-saclay.fr
LEGOUIS	Renaud	renaud.legouis@i2bc.paris-saclay.fr
LIENARD	Caroline	caroline.lienard@univ-lyon1.fr
LOMONTE	Patrick	patrick.lomonte@univ-lyon1.fr
LUCAS	Julie	julie.lucas@etu.unistra.fr
LUSSIGNOL	Marion	marion.lussignol@universite-paris-saclay.fr
MARCHETTI	Sandrine	sandrine.marchetti@univ-cotedazur.fr
MATTIONI	Anna	anna.mattioni@gmail.com
MERABET	Samir	samir.merabet@ens-lyon.fr
MEURETTE	Olivier	olivier.meurette@lyon.unicancer.fr
MOREL	Étienne	etienne.morel@inserm.fr
MORIS	Arnaud	arnaud.moris@i2bc.paris-saclay.fr
MULLER	Alexandra	alexandra.muller@inserm.fr
NANCEY	Stéphane	stephane.nancey@chu-lyon.fr
NASO	Francesco	francesco.naso33@gmail.com
NEJMI	Sanae	sanae.nejmi@inserm.fr
NISSAN	Xavier	xnissan@istem.fr
NORELL	Puck	puck.nasman-norell@pasteur.fr
NUGUE	Mathilde	mathilde.nugue@inserm.fr
NUNEZ-VAZQUEZ	Sonia	snunez@unice.fr
PALARIC	Marjory	marjory.p@orange.fr
PATTINGRE	Sophie	sophie.pattingre@inserm.fr
PELLEGRINI	Francesca Romana	francescaromana.pellegrini@uniroma1.it
PIERREFITE-CARLE	Valérie	valerie.pierrefite@univ-cotedazur.fr
PITASI	Caterina Luana	caterina.pitasi@inserm.fr
PLATTEEUW	Loïc	loic.platteeuw@inserm.fr
POILLET	Laura	laura.poillet@inserm.fr
PRADEL	Baptiste	baptiste.pradel@irim.cnrs.fr
PROCHIANTZ	Alain	alain.prochiantz@college-de-france.fr
REMY	Solène	solene.remy@univ-lyon1.fr
RODRIGUEZ	Aida	arl@cancer.dk

LIST OF PARTICIPANTS

LAST NAME	FIRST NAME	PROFESSIONAL E-MAIL
ROGER	Benoît	benoit.roger@u-bordeaux.fr
ROJAS	Maria-Laura	maria-laura.rojas@inserm.fr
ROLLAND	Léo	leo.rolland@univ-tlse3.fr
ROMAGNOLO	Béatrice	beatrice.romagnolo@inserm.fr
ROTARD	Ludivine	ludivine.rotard@etu.univ-lyon1.fr
ROUSSEL	Benoît	broussel@cyceron.fr
ROZIÈRES	Aurore	aurore.rozieres@inserm.fr
RUBIOLA	Alessia	alessia.rubiola@inserm.fr
RUGGIERO	Sonia	sonia.ruggiero@curie.fr
SCHLÄFLI	Anna	anna.schlaefli@unibe.ch
SEILIEZ	Iban	iban.seiliez@inrae.fr
SETTEMBRE	Carmine	settembre@tigem.it
SINGH	Rajat	rajatsingh@mednet.ucla.edu
SMEELE	Paulien	paulien.smeele@unimi.it
STAGNI	Venturina	venturina.stagni@cnr.it
STRAPPAZZON	Flavie	flavie.strappazzon@univ-lyon1.fr
TRISCIUOGLIO	Daniela	daniela.trisciuoglio@uniroma1.it
TROJANI	Marie-Charlotte	mctroj@hotmail.fr
TSCHAN	Mario	mario.tschan@unibe.ch
VAUCOURT	Mathilde	mathilde.vaucourt@inserm.fr
VELEZ	Emilio-José	emilio-jose.velez-velazquez@inrae.fr
VERGNE	Isabelle	isabelle.vergne@ipbs.fr
VILLARES	Marie	marie.villares@irim.cnrs.fr
VIRARD	François	francois.virard@lyon.unicancer.fr
VIRET	Christophe	christophe.viret@inserm.fr
WALTER	Ludivine	ludivine.walter@univ-lyon1.fr
WODRICH	Harald	harald.wodrich@u-bordeaux.fr

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