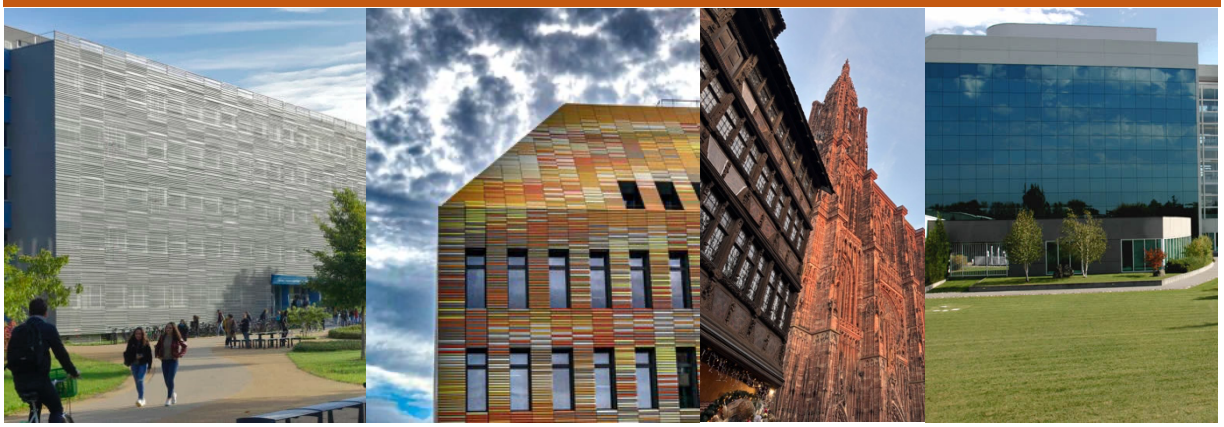
TOR Signaling Metabolism & Cancer



30th June 2026

Centre de Recherche en Biomédecine de Strasbourg

Organized by :

H. BECKER & P. ANTONY

Claudio DE VIRGILIO	Fribourg University, Switzerland
Ludovic ENKLER	CRBS – UR3072– MitoCross,, Strasbourg
Robbie LOEWITH	University of Geneva, Switzerland
Sunghoon KIM	Yonsei University, South Korea
Farida TRIPODI	University of Milano-Bicocca, Italy
Nathaniel YAKOBOV	University of Geneva

Registration: email to **h.becker@unistra.fr**

Participation to the symposium is free of charge

Conference organization

Organizers & Conference Chairs

Mrs. Solène ZUTTION (University of Strasbourg – UMR 7156 GMGM – IPCB, **IMCBio – MitoCross**)

Dr. Ludovic ENKLER (University of Strasbourg – UR3072 – CRBS, **MitoCross**)

Dr. Sylvie FRIANT (University of Strasbourg – U1112 – CRBS)

Dr. Bruno SENGER (University of Strasbourg – UMR 7156 GMGM – IPCB)

Pr. Hubert D. BECKER (University of Strasbourg – UMR 7156 GMGM – IPCB, **MitoCross – IMCBio**)

Dr. Pierre ANTONY (University of Strasbourg – CNRS UMR 7104 - Inserm U 1258 – IGBMC, **INRT**)

Session Chairs

Dr. Ali HAMICHE (University of Strasbourg – CNRS UMR 7104 - Inserm U 1258 – IGBMC, **INRT**)

Dr. Jacky GOETZ (University of Strasbourg – UMR1109 – CRBS)

Conference sponsors

Scientific Program – June 30th

9:00 Hubert BECKER – University of Strasbourg

Welcome Talk

Morning Session

Session Chair – Jacky Goetz

9:10 Sunghoon KIM – Yonsei University
Aminoacyl-tRNA synthetase as an integrator of amino acid and energy metabolism

9:40 Ludovic ENKLER – UR3072 – MitoCross
TORC1 spatial segregation & hysteresis in yeast

10:10 Coffe Break

10:40 Farida TRIPODI – University of Milano-Bicocca
SNF1/AMPK in budding yeast: a kinase with several functions

11:10 Patricio AGUIRE PINEDA – University of Strasbourg-U1112
Role of the PI3K complex subunit Vps15 in LD metabolism

11:40 Robbie LOEWITH – University of Geneva
Target Of Rapamycin Complex 2 and the maintenance of plasma membrane homeostasis

12:10 Lunch

Afternoon Session

Session Chair – Ali HAMICHE

14:10 Nathaniel YAKOBOV – University of Geneva
TORC1 integrates multiple environmental cues to regulate appressoria formation in the rice blast fungus

14:40 Claudio DE VIRGILIO – Fribourg University
Metabolic Control of TORC1

15:10 Solène ZUTTION – University of Strasbourg – IMCBio – MitoCross
Control of the Tor pathway by vacuolar echoforms of yeast cytosolic aminoacyl-tRNA synthetases

15:40 Sylvie FRIANT
Closing Remarks

15:50 Pierre ANTONY – INRT
Passing the Torch

16:00 Musical Interlude

Abstracts

Role of the PI3K complex subunit Vps15 in LD metabolism

Patricio AGUIRRE-PINEDA
University of Strasbourg – UMRS 1112
Email: patricio.aguirre-pineda@etu.unistra.fr

Abstract

Patricio Aguirre-Pineda[1], Irene Álvarez-Guerra[4], Solène Zuttion[1], Bianca M. Esch[2], Stefan Walter[3], Severine Bär[1], Sabrina Büttner[4], Florian Fröhlich[2] and Sylvie Friant[1]

[1]UMRS 1112 INSERM – CRBS, Université de Strasbourg, Strasbourg, France.
[2]Osnabrück University, Department of Biology-Chemistry, Bioanalytical Chemistry Section, Osnabrück, Germany.
[3]Osnabrück University, Center for Cellular Nanoanalytic Osnabrück (CellNanOs), Osnabrück, Germany
[4]Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, Stockholm, Sweden

The Vps15 (Vacuolar Protein Sorting 15) protein is conserved among eukaryotes and was first characterized in the yeast *Saccharomyces cerevisiae*. Vps15 is the membrane adaptor of the lipid kinase Vps34 forming two distinct phosphatidylinositol-3-kinase complexes (PI3KC I and II), responsible for synthesis of phosphatidylinositol-3-phosphate (PI3P). This lipid signaling molecule, PI3P is a key component of autophagosome and endosomal membranes, recruiting specific downstream effectors essential for autophagy and endosomal protein sorting to the vacuole (lysosome in mammals).
Our full proteome analysis of *vps15Δ* cells revealed that different effectors of fatty acid metabolism and ergosterol synthesis are downregulated. To this date no reports of a link between Vps15 and LD dynamics exist. Thus, we aim at exploring this link by assessing whether this new Vps15 function is independent of PI3K complexes and how. LD phenotype studies indicate that, nitrogen starved *vps15Δ* cells accumulate LDs contrary to *vps34Δ*, *vps30Δ*, *vps38Δ* and *atg14Δ* cells. Moreover, both *vps15Δ* and *vps34Δ* cells are sensitive to cerulenin (inhibitor of FAS complex) and terbinafine (Erg1 inhibitor). Finally, *vps15Δ* but not *vps34Δ* cells present defects in glucose exhaustion induced lipophagy. We hypothesize that in different metabolic conditions i) a pool of Vps15 is responsible for regulating transcription of genes implicated in synthesis of neutral lipids and ii) affects LD turnover independently of the PI3KC complexes.

Metabolic Control of TORC1

Claudio DE VIRGILIO
University of Fribourg
Email: Claudio.devirgilio@unifr.ch

Abstract

Claudio de Virgilio[1]
[1]Department of Biology, University of Fribourg, Fribourg, Switzerland

The eukaryotic target of rapamycin complex 1 (TORC1) couples nutrient, energy, and hormonal signals with cell growth, division, and metabolism, and aberrant TORC1 signaling contributes to the progression of human diseases such as cancer and diabetes. Amino acids are important and primeval cues that stimulate TORC1 to promote anabolic processes and inhibit catabolic processes via the conserved heterodimeric Rag family GTPases. In yeast, the pentameric EGOC complex, composed of Ego1, Ego2, Ego3, and the Rag GTPases Gtr1 and Gtr2, mediates these amino acid signals to TORC1. Here, we explore the mechanistic basis by which these Rag GTPases control TORC1 localization and activity. We reveal that the protein Tco89 acts as a molecular tether that binds the active Rag GTPase module to TORC1, keeping the complex anchored to vacuolar membranes when amino acids are plentiful. Upon amino acid starvation, Tco89 is hypophosphorylated and degraded, causing TORC1 to be released from the vacuole and relocate to signaling endosomes. Furthermore, we identify Pib2 as a glutamine and cysteine sensor that not only controls TORC1 cooperatively with the Rag GTPases, but also contributes to tethering TORC1 to these endosomal membranes. Ultimately, these findings demonstrate that TORC1 activity is not a monolithic entity within cells; rather, it predominantly functions at distinct cellular membranes where it is locally and temporally harnessed to target specific effectors in response to fluctuating nutrient levels.

TORC1 spatial segregation & hysteresis in yeast

Ludovic ENKLER
UR3072 – University of Strasbourg
Email: enkler@unistra.fr

Abstract

Ludovic Enkler[1]

[1]UR3072 – CRBS, Université de Strasbourg, Strasbourg, France.

TORC1 is a central regulator of growth, integrating inputs from kinases and signaling proteins. How TORC1 activity is regulated, is still not completely understood. The small GTPase Arf1 has been implicated in TORC1 regulation, but the underlying mechanism remains elusive. Here, we show that Arf1 controls TORC1 in an allele-specific manner under nutrient and heat stress in yeast. Unexpectedly, both the hyperactive mutant arf1-11 and the loss-of-function mutant arf1-18 reduce TORC1 activity, while other loss-of-function alleles did not. We reveal two distinct functions of Arf1: first, it ensures Golgi-to-vacuole/lysosome transport for the functional maintenance of these organelles; second, it regulates TORC1 activity at the ER-Golgi-vacuole interface. Hyperactive Arf1-11 drives sequestration of Kog1 and Tor1 into cytoplasmic foci, to which Arf1-11 can be equally recruited. Importantly, Arf1 also promotes TORC1 re-activation during stress recovery - so-called hysteresis. Our data reveal an unexpected dual function for Arf1 as a negative and a positive regulator of TORC1 activity in a context-dependent manner.

Aminoayl-tRNA synthetases as integrator of amino acid and energy metabolism

Sunghoon KIM
Yonsei University
Email: sunghoonkim@yonsei.ac.kr

Abstract

Sunghoon KIM[1]

[1] Medicinal Bioconvergence Research Center – Institute for Artificial Intelligence and Biomedical Research – College of Pharmacy & College of Medicine, Yonsei University, Republic of Korea.

Aminoacyl-tRNA synthetases (ARSs) have evolved to play diverse regulatory roles beyond their canonical activities in protein synthesis. Since they use amino acids and ATP as their catalytic substrates, some of these enzymes can sense the intracellular levels of these metabolites and coordinate protein synthesis with the connected metabolism and signal pathways. For instance, LARS1 (leucyl-tRNA synthease 1) can activate mTORC1 pathway[1] via conformational change upon binding to leucine[2]. However, at lower glucose or ATP level, LARS1 undergoes post-translational modifications to block its catalytic activity and guide leucine for TCA cycle for energy production[3, 4]. LARS1 is normally anchored to the multi-tRNA synthetase complex (MSC) via its interaction with isoleucyl-tRNA synthetase 1 (IARS1) and the CryoEM structure of the LARS1:IARS1 complex revealed how LARS1 can respond to external stimuli[5].

1. Leucyl-tRNA synthetase is an intracellular leucine sensor for the mTORC1-signaling pathway. Han JM, et al. *Cell,* 149: 410, 2012
2. Leucine-sensing mechanism of leucyl-tRNA synthetase 1 for mTORC1 activation. Kim S, Yoon I, et al. *Cell Rep.,* 35: 109031, 2021
3. Glucose-dependent control of leucine metabolism by leucyl-tRNA synthetase 1. Yoon I, et al. *Science.,* 367: 205, 2020
4. O-GlcNAc modification of leucyl-tRNA synthetase 1 integrates leucine and glucose availability to regulate mTORC1 and the metabolic fate of leucine. Kim KB, et al. *Nat Commun.*, 13: 2904, 2022
5. Cryo-EM Structure of the LARS1-IARS1 Complex Reveals A Nutrient-Responsive Switch Controlling mTORC1 Signaling" to Nature Communications. Park HS et al, *Nature comm*., in press, 2026

Target Of Rapamycin Complex 2 and the maintenance of plasma membrane homeostasis

Robbie LOEWITH

University of Geneva

Email: Robbie.Loewith@unige.ch

Abstract

Robbie Loewith[1]

[1]Department of Molecular and Cellular Biology, University of Geneva, Geneva, Switzerland

Despite it too being broadly conserved, rapamycin-insensitive TORC2 remains underappreciated relative to rapamycin-sensitive TORC1. Studying TORC2 in budding yeast, we discovered that it operates as part of a feedback loop to maintain the biophysical properties of the cell envelop. I will present our on-going efforts to understand how physical properties of the plasma membrane and metabolic precursors important for secreted and membrane proteins are sensed and how this information is signaled to TORC2 to regulate its kinase activity.

SNF1/AMPK in budding yeast: a kinase with several functions

Farida TRIPODI
University of Milano-Bicocca
Email: farida.tripodi1@unimib.it

Abstract

Farida Tripodi[1], Hind Moukham[1], Marco Caligaris[2,3], Raffaele Nicastro[2,4], Claudio De Virgilio[2], Paola Coccetti[1]
[1]Department of Biotechnology and Biosciences, University of Milano-Bicocca, Milano, Italy.
[2]Department of Biology, University of Fribourg, Fribourg, Switzerland.
[3]Present address: Molecular and Cell Biology Laboratory, The Salk Institute for Biological Studies, La Jolla, CA, USA.
[4]Present address: Department of Biological Sciences, University of Limerick, Limerick, Ireland.

To sustain growth microbial organisms must cope with environmental stresses and adapt to efficiently exploit available nutrients. In Saccharomyces cerevisiae, the TORC1 pathway primarily mediates the cellular response to amino acid and nitrogen availability, whereas the Ras/PKA and the SNF1/AMPK pathways regulate cellular metabolism according to the supply of glucose, thereby promoting either fermentative growth or mitochondrial respiration.
In our laboratory, we have been studying the regulatory mechanisms of SNF1/AMPK for many years, especially considering its role in cell-cycle regulation and in the rewiring of carbon metabolism. In recent years, we have explored the crosstalk between SNF1/AMPK and TORC1 pathways, as well as the upstream regulation of SNF1/AMPK itself. In this presentation, I will discuss new regulatory mechanisms, focusing on an intricate negative-feedback control network that fine-tunes SNF1/AMPK activity during glucose depletion. Our findings reveal that SNF1 directly phosphorylates its upstream kinase Sak1, as well as the regulatory subunit Sip2, thereby establishing a dynamic negative feedback mechanism, required for proper adaptation to glucose scarcity.

TORC1 integrates multiple environmental cues to regulate appressoria formation in the rice blast fungus

Nathaniel YAKOBOV
University of Geneva
Email:nathaniel.yakobov@unige.ch - +33646062874

Abstract
Nathaniel Yakobov[1], Yvonne Scamarcia[1], Lenny Bonadei[1] & Robbie J. Loewith[1]

[1]Department of Molecular and Cellular Biology, University of Geneva, Geneva, Switzerland

The rice blast fungus, *Magnaporthe oryzae*, is the causative agent of one of the most widespread and serious disease of cultivated crops, severely impacting cultivars in the *Poaceae* family. To gain entry to plant hosts, airborne conidia attach to the **hydrophobic** and **nutrient-free** leaf surface where they develop a specialized infection structure, the appressorium. During differentiation the 3-celled conidium undergoes autophagy mediated cell death while the remaining cell becomes an appressorium – a highly pressurized structure designed to provide the mechanical force needed to breach the leaf cuticle. Better understanding of the molecular mechanisms underlying appressoria formation could identify vulnerable signalling nodes and thus generate novel strategies to tackle blast disease. In this vein, we investigate the role that Target Of Rapamycin (TOR) signalling plays in appressorium formation as components of this otherwise well conserved signalling network are present in fungi, but absent in plants, and could thus represent suitable targets for effective control of blast disease.
Using an optimized CrispR protocol, we can now manipulate the *M. oryzae* genome with relative ease. This facilitated affinity purification of *Mo*TOR Complex1 (*Mo*TORC1) and *Mo*TORC2. Subsequent proteomics analyses in combination with cryo-electron-microscopy (cryo-EM) allowed us to identify the composition and to obtain high-resolution structures of both native complexes. Deletion *MoTCO89*, encoding a non-essential *Mo*TORC1 subunit, yielded "blind" conidia, no longer able to transduce environmental cues, including nutrients and hydrophilic surfaces, which in *WT* conidia would prevent appressoria development. Moreover, inhibition of *Mo*TORC1 with caffeine, but not rapamycin, restores appressoria formation in these non-inductive conditions. These observations suggest upstream factors that inhibit *Mo*TORC1 signalling could serve as drug targets to block plant infection.

Control of the Tor pathway by vacuolar echoforms of yest cytosolic aminoacyl-tRNA synthestases

Solène ZUTTION
University of Strasbourg – UMR 7156
Email: solene.zuttion@etu.unistra.fr

Abstract

Solène Zuttion[1,2], Raffaele Nicastro[3,4], Bruno Senger[1], Patricio Enrique Aguirre-Pineda[2], Ludovic Enkler[1,5], Johan-Owen De Craene[1,6], Claudio De Virgilio[3], Sylvie Friant[2] and Hubert Dominique Becker[1]

[1]UMR 7156, CNRS, Université de Strasbourg, Strasbourg, France.
[2]UMRS 1112 INSERM – CRBS, Université de Strasbourg, Strasbourg, France.
[3]University of Fribourg, Department of Biology, Fribourg, Switzerland.
[4]University of Limerick, Department of Biological Sciences, Limerick, Ireland.
[5]UR3072 – CRBS, Université de Strasbourg, Strasbourg, France.
[6]EA 2106, Université de Tours, Tours, France.

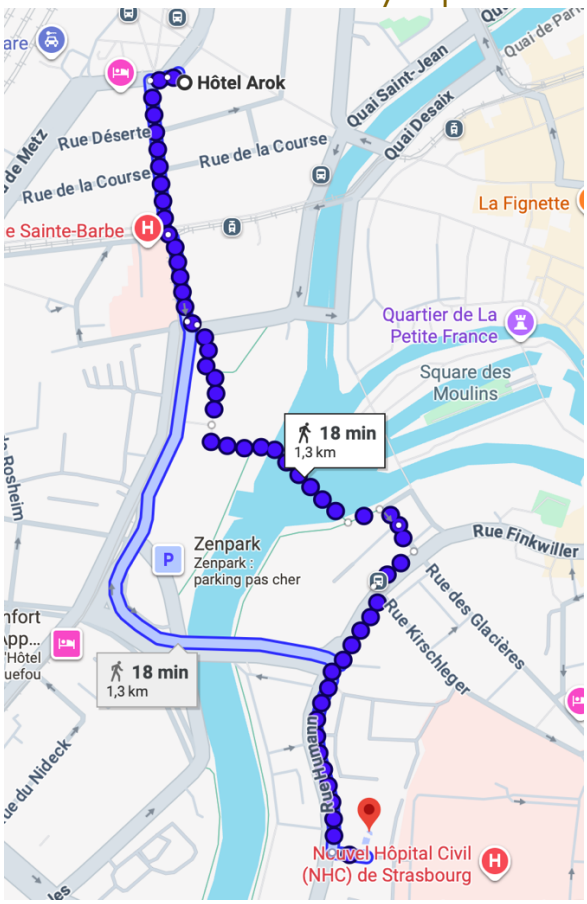
The target of rapamycin (Tor) pathway is a major cell signaling cascade that is highly conserved from yeast to Human. Critical regulator of cell growth and metabolism, it regulates thanks to the Tor Complex 1 (TORC1 in yeast and mTORC1 in mammals) a wide range of processes going from ribosome biogenesis to autophagy by phosphorylating numerous target proteins *via* its kinase Tor1. (A. González and M. N. Hall, *EMBO J*. (2017) **36 (4)**: 397-408).
Localized at the surface of the vacuole (yeast lysosome), its regulation mainly relies on the nutrient availability including amino acids (aa). Although their sensing by TORC1 is poorly characterized, several mechanisms and key regulators have been identified such as leucyl-tRNA synthetase (LRS), that relocates to the vacuole and sense leucine availability to TORC1 (G. Bonfils *et al*., *Mol. Cell* (2012) **46 (1)**: 105-10).
Having demonstrated in the lab that 18 cytosolic aminoacyl-tRNA synthetases (aaRSs) localize to the vacuolar surface using the Vacuolar Split-CFP tool we developed, we sought to determine whether additional aaRSs could contribute to TORC1 sensing of amino acid availability in the cell. We focused in particular on the multi-aminoacyl-tRNA synthetase complex (AME), which is composed of the glutamyl-tRNA synthetase (ERS), the methionyl-tRNA synthetase (MRS), and their cofactor Arc1.
Using a wide range of experimental approaches, we found that ERS, MRS, and Arc1 interact with several TORC1 components with high affinity. We also examined their interactions with the GTPases Gtr1 and Gtr2, which are known to be involved in the LRS-mediated leucine detection mechanism, and demonstrated an interaction between each of our proteins of interest and Gtr1.
Finally, to assess whether the AME complex influences TORC1 activity, we measured TORC1 activity under conditions of amino acid sufficiency and specific starvation, using strains expressing different forms of Arc1 and MRS. Our results indicate that each protein can independently regulate TORC1, with Arc1 promoting activation and MRS exerting an inhibitory effect.

Accomodations

Hotel Arok

7- 8 Place De La Gare, Strasbourg, 67000, France
Tel : +33 3 88 11 45 00

Itinerary from your Hotel to the auditorium where the PhD defense and the symposium will take place – 18 min walk.



You can download the itinerary on you cell phone with the following web link:
https://maps.app.goo.gl/RUN2DZ2C4fFbunWT7