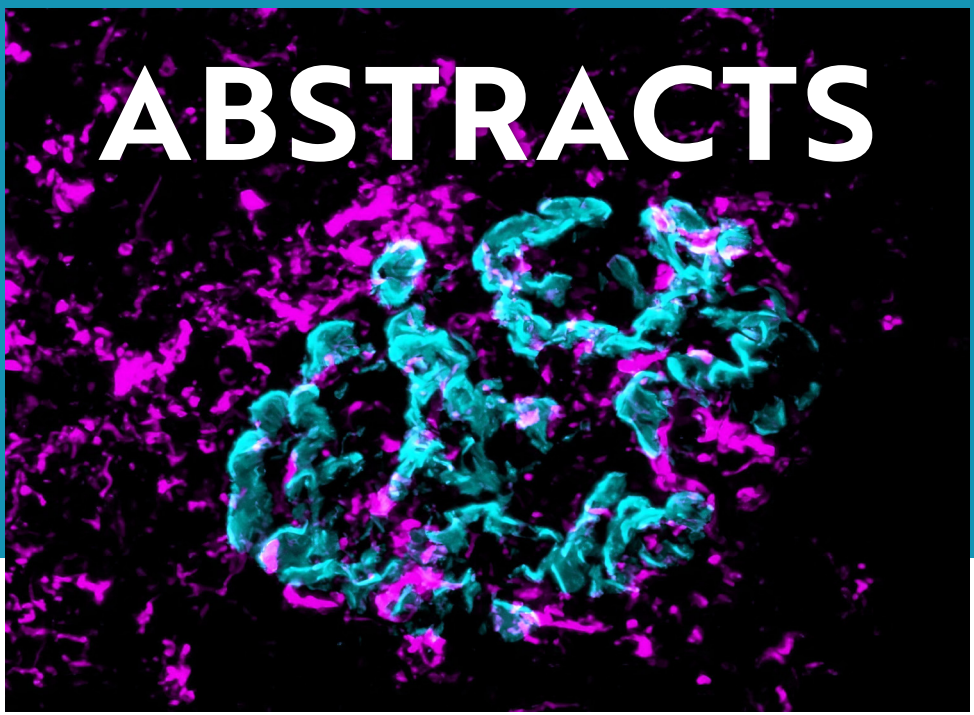
WINTER SCHOOL

Mitochondria in Health, Disease and Aging

DEC 16 - DEC 20, 2024

GRAND CHATEAU, UNIVERSITÉ CÔTE D'AZUR,
AV. VALROSE, NICE, FRANCE




Welcome to the
Mitochondria in
Health, Disease,
and Aging
2024
Winter School

This Winter School, as part of the Life and Health Sciences Graduate School at Université Côte d'Azur, combines research and training, with contributions by experts in the field of mitochondrial diseases.

The goal is to faster reflexion and exchange with national and international researchers, who will present their work focused on mitochondrial functions and dysfunctions.

Monday Dec 16th

Moderators
Sandrine Marchetti (C3M), Jean-Ehrland Ricci (C3M)

9:30
10:30 **Mitochondrial-driven inflammation in cancer and aging** p01
Stephen Tait, University of Glasgow, UK

10:30
11:30 **Novel causes of type I interferonopathies linked to mitochondrial integrity** p02
Alice Lepelley, Imagine Institute, France

Tuesday Dec 17th

Moderators
Olfa Khalfallah (IPMC), Emmanuelle Genin (IRCAN)

9:30
10:30 **Pluripotent stem cells and brain organoids in mitochondrial research** p03
Alessandro Prigione, Düsseldorf University, Germany

10:30
11:30 **Elucidating the mechanisms underlying mitochondrial dysfunctions in Alzheimer's disease: diagnostic and therapeutic perspectives** p04
Mounia Chami, IPMC, France

Wednesday Dec 18th

Moderators
Cécile Rouzier (IRCAN), Stéphane Rocchi (C3M)

9:30
10:30 **Nifuroxazide rescues the deleterious effects associated with MICOS instability in disease models** p05
Baptiste Ropert, IRCAN Institute, France

10:30
11:30 **TK2 deficiency: from diagnosis to treatment** p06
Cristina Dominguez Gonzalez, Neurology Department, Neuromuscular Unit, Hospital '12 de Octubre', i+12 Research Institute, CIBERER, ERN-NMD, Spain

Thursday Dec 19th

Moderators
Sylvie Bannwarth (IRCAN) et Hervé Techer (IRCAN)

9:30
10:30 **mtDNA, disease and aging** p08
Maria Falkenberg, University of Göteborg, Sweden

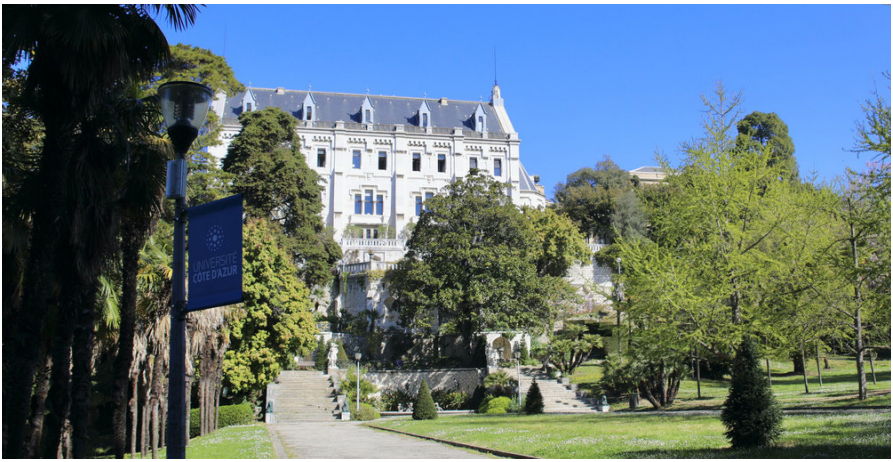
10:30
11:30 **Topoisomerase 3 alpha: from molecular mechanisms to disease** p09
Thomas Nicholls, Newcastle University, UK

Friday Dec 20th

Moderators
Michèle Studer (IBV), Véronique Paquis-Flucklinger (IRCAN)

9:30
10:30 **In vitro iPSC-derived models of mtDNA-related disorders** p10
Valéria Tiranti, Fondazione IRCCS Instituto Neurologico Carlo Besta, Italy

10:30
11:30 **Developing neuronal models to study mitochondrial diseases,** p11
Denisa Hathazi, University of Cambridge, UK



Mitochondrial-driven inflammation in cancer and aging

Stephen Tait

University of Glasgow, UK

The major form of regulated cell death in our bodies is mitochondrial apoptosis. During apoptosis, mitochondrial outer membrane permeabilisation (MOMP) occurs committing a cell to death – or at least this is what we thought for many years. Rethinking this dogma, I'll discuss how MOMP can occur under sub-lethal conditions, contributing to wide-ranging activities in cancer, aging and innate immunity.

Underpinning these functions, permeabilized mitochondria drive inflammation through various pathways. These include through mitochondrial DNA (mtDNA) dependent activation of cGAS-STING activity as well as direct activation of pro-inflammatory NF-kB signaling. I'll discuss how we think mitochondria provoke inflammation, suggesting this may stem from their bacterial ancestry.

Finally, I'll highlight how understanding these pathways provides new opportunities to target mitochondrial function in various pathologies – for instance, by making cancer therapy more effective and promoting healthy aging..

Novel causes of type I interferonopathies linked to mitochondrial integrity

Alice Lepelley
Imagine Institute, France

The immune response to viral infection involves the recognition of pathogen-derived nucleic acids by intracellular sensors, leading to type I interferon (IFN), and downstream IFN- stimulated gene, induction. Ineffective discrimination of self from non-self nucleic acid can lead to autoinflammation, a phenomenon implicated in an increasing number of disease states, and well highlighted by the group of rare genetic disorders referred to as the type I interferonopathies.

To understand the pathogenesis of these monogenic disorders, and polyfactorial diseases associated with pathogenic IFN upregulation, such as systemic lupus erythematosus and dermatomyositis, it is important to define the self-derived nucleic acid species responsible for such abnormal IFN induction. Recently, attention has focused on mitochondria as a novel source of immunogenic self nucleic acid.

Best appreciated for their function in oxidative phosphorylation, metabolism and apoptosis, mitochondria are double membrane-bound organelles that represent vestigial bacteria in the cytosol of eukaryotic cells, containing their own DNA and RNA enclosed within the inner mitochondrial membrane.

There is increasing recognition that a loss of mitochondrial integrity and compartmentalization can allow the release of mitochondrial nucleic acid into the cytosol, leading to IFN induction. We will provide recent insights into the potential of mitochondrial- derived DNA and RNA to drive IFN production in Mendelian disease.

Specifically, we will summarize current understanding of how nucleic acids are detected as foreign when released into the cytosol, and then consider the findings implicating mitochondrial nucleic acid in type I interferonopathy disease states. Finally, we will discuss the potential for IFN-driven pathology in primary mitochondrial disorders.

Pluripotent stem cells and brain organoids in mitochondrial research

Alessandro Prigione
Düsseldorf University, Germany

Energy metabolism is essential for providing the energy necessary to ensure proper cellular function. Mutations in genes regulating this process lead to inherited mitochondrial disorders that can particularly affect tissues with high energy demands like the brain.
The limited access to patient neural tissue and the difficulty to manipulate mitochondrial genome complicates the development of transgenic animal models and cellular models, which are needed for treatment discovery.
In this talk, I will summarize our efforts in using patient-derived and engineered induced pluripotent stem cells (iPSCs) to study mitochondrial neurological diseases using 3D brain organoid models.
I will show examples of this approach in the context Leigh syndrome, which is the most frequent and most severe mitochondrial disease affecting 1/40,000 newborns. Our findings can help gaining new knowledge in the mechanisms underlying the neural pathology of mitochondrial diseases and could pave the way to identify innovative disease-modifying therapies.

Elucidating the mechanisms underlying mitochondrial dysfunctions in Alzheimer's disease: diagnostic and therapeutic perspectives

Mounia Chami
IPMC, France

Mitochondria structure and function alterations are major features of Alzheimer's disease (AD). In addition, impairments in mitophagy, the process of selective mitochondrial degradation by autophagy leading to a gradual accumulation of defective mitochondria, have also been reported in neurodegenerative diseases including AD. Specifically, mitochondria dysfunctions and mitophagy failure have been mostly linked to toxic Amyloid beta (Aβ) peptides.

Several lines of recent evidence also indicate that the amyloid precursor protein-derived C-terminal fragments (APP-CTFs) are etiological triggers of AD pathology. However, their genuine contribution to mitochondrial dysfunction and mitophagy process were unknown.

In my presentation, I will provide an overview of recent data showing the specific contribution of the APP-CTFs to mitochondrial structure, function, and mitophagy defects.

These results have been reported in cellular and mice models mimicking familial forms of AD. We also reported that mitophagy failure molecular signature correlates with APP-CTFs accumulation in post-mortem human sporadic AD (SAD) brains, and demonstrated altered mitochondrial structure and function and mitophagy failure in a cohort of fibroblasts isolated from SAD patients. I will then focus on our latest data demonstrating the impact of the bioenergetic sensor, AMP-activated protein kinase (AMPK) on mitochondrial dysfunctions, mitophagy and neuroinflammation in cellular, ex vivo and mice AD study models.

Together, these studies unraveled new molecular mechanisms underlying AD development and provide future directions for AD diagnosis and therapeutics.

Nifuroxazide rescues the deleterious effects associated with MICOS instability in disease models

Baptiste Ropert
IRCAN Institute, France

The identification of a point mutation (p.Ser59Leu) in the CHCHD10 gene was the first genetic evidence that mitochondrial dysfunction can trigger motor neuron disease.
Since then, we have shown that this mutation leads to the disorganization of the MItochondrial contact site and Cristae Organizing System (MICOS) complex that maintains the mitochondrial cristae structure. Here, we generated yeast mutant strains mimicking MICOS instability and used them to test the ability of more than 1600 compounds from 2 repurposed libraries to rescue the growth defect of those cells.
Among the hits identified, we selected nifuroxazide, a broad-spectrum antibacterial molecule. We show that nifuroxazide rescues mitochondrial network fragmentation and cristae abnormalities in CHCHD10S59L/+ patient fibroblasts. This molecule also decreases caspase-dependent death of human CHCHD10S59L/+ iPSC-derived motor neurons.
Its benefits involve KIF5B-mediated mitochondrial transport enhancement, evidenced by increased axonal movement and syntaphilin degradation in patient-derived motor neurons.
Our findings strengthen the MICOS-mitochondrial transport connection. Nifuroxazide and analogues emerge as potential therapeutics for MICOS-related disorders like motor neuron disease. Its impact on syntaphilin hints at broader neurological disorder applicability for nifuroxazide.

TK2 deficiency: from diagnosis to treatment

Cristina Dominguez Gonzalez
Neurology Department, Neuromuscular Unit, Hospital '12 de Octubre', i+12 Research Institute, CIBERER, ERN-NMD, Spain

Thymidine kinase 2 deficiency (TK2d) is an extremely rare autosomal recessive mitochondrial disorder classified as a mitochondrial DNA (mtDNA) depletion/multiple deletion syndrome (MIM #609560). The TK2 enzyme plays a critical role in the pyrimidine deoxynucleotide salvage pathway by phosphorylating deoxythymidine (dThd) and deoxycytidine (dCtd). When TK2 is deficient, the balance of mitochondrial deoxynucleoside triphosphates is disrupted, impairing mtDNA replication.
TK2d can manifest in three main forms, a quantitative defect (mtDNA depletion), a qualitative defect (multiple mtDNA deletions caused by replication errors), or a combination of both defects.
The severity of the disease is directly related to the number of mtDNA copies in muscle tissue, resulting in a continuous spectrum of clinical presentations. This spectrum ranges from infantile-onset forms with rapid progression and fatal outcomes within months to late-onset cases with milder phenotypes and variable rates of progression

There are no approved treatments for TK2 deficiency. Therefore, management is limited to supportive and invasive therapies. However, recent preclinical studies have shown promising results:

- In a TK2-deficient mouse model (H126N knock-in), oral administration of TK2 products (dCMP and dTMP) as a molecular bypass therapy extended the median lifespan by 2- to 3-fold.
- Subsequent studies revealed that these nucleotides are rapidly catabolized to deoxyribonucleosides (dC and dT), suggesting that nucleosides are the primary active therapeutic agents.
- Treatment with dC and dT in TK2-deficient mice delayed disease onset, extended lifespan, and restored mtDNA copy number. In this context, deoxynucleosides function as a substrate enhancement therapy.

Based on these promising preclinical findings, compassionate use of oral dC + dT was approved for patients with TK2 deficiency. An open-label study evaluated the outcomes of 16 patients receiving these pharmacological therapies, demonstrating a favorable side-effect profile and a significant clinical efficacy, including functional improvement and disease stabilization.

Currently, a clinical program sponsored by UCB Pharma is underway to formally evaluate the safety and efficacy of this approach, with the goal of obtaining regulatory approval for patients with genetically confirmed TK2 deficiency.

This presentation will review the main characteristics of TK2 deficiency, strategies to recognize and diagnose its various clinical forms, and the development of what may be the first treatment capable of modifying the natural history of a mitochondrial disease. We will explore the journey from laboratory discoveries to bedside application.

mtDNA, disease and aging

Maria Falkenberg
University of Göteborg, Sweden

[Abstract Non Available]

Topoisomerase 3 alpha: from molecular mechanisms to disease

Thomas Nicholls
Newcastle University, UK

Human cells each contain thousands of copies of mitochondrial DNA (mtDNA), and this number of mtDNA copies per cell is maintained by mtDNA replication. At the end of mtDNA replication, the daughter molecules remain interlinked and require a protein called TOP3A to separate them. In addition to its mitochondrial role, TOP3A is also found in the nucleus, where it takes part in homologous recombination together with a helicase called BLM.

Mutations in TOP3A have been found to cause two very different disease phenotypes. Certain variants cause Bloom syndrome (characterised by short stature, predisposition to tumours, and a photosensitive rash), similar to the pathology associated with the loss of BLM, an interaction partner of TOP3A in the nucleus. However, other variants cause an adult-onset mitochondrial disease (characterised by PEO, myopathy, axonal sensory-motor neuropathy, and cardiac conduction defects) without the main features of Bloom syndrome.

In this talk we will discuss the molecular and cellular role of TOP3A in mitochondria, the pathologies associated with mutations within the TOP3A gene, and why different mutations in TOP3A cause different disease phenotypes. This will illustrate some of the complexities of studying mtDNA disease, as well as studying proteins that localise to more than one cellular compartment.

In vitro iPSC-derived models of mtDNA-related disorders

Valéria Tiranti,
Unit of Medical Genetics and Neurogenetics, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

Mitochondrial diseases are caused by mutations in nuclear or mitochondrial genes, affecting OXPHOS and mitochondrial function. They impact tissues with high energy needs, such as the nervous system, heart, and skeletal muscles. iPSCs technology allows the development of models that carry specific pathogenic mtDNA mutations and mimic the functional properties of affected cells. We focus on iPSC-derived models of mitochondrial diseases caused by mtDNA mutations, such as Leber Hereditary Optic Neuropathy (LHON) and Kearns-Sayre syndrome (KSS).

LHON involves loss of retinal ganglion cells (RGCs), leading to blindness, and is primarily due to three homoplasmic missense mtDNA mutations in genes coding for complex I subunits. KSS is a neurodegenerative disease with cardiac manifestations associated to mtDNA heteroplasmic macro-deletion. iPSCs from LHON and KSS patients, unaffected carriers, and controls were used to generate neural progenitor cells (NPCs) and neurons. LHON and KSS NPCs showed impaired mitochondrial respiration. LHON neurons exhibited increased mitophagy, especially in the soma, without compensatory mitochondrial biogenesis, potentially mimicking RGC loss in vivo. We are currently testing iPSC derived RGCs from LHON patients to see if they show similar bioenergetic and mitophagic profiles.

For KSS, cardiomyocytes (CMs) were derived from patients and controls. CMs with mtDNA deletion showed reduced oxygen consumption, higher spontaneous beating rates, and a higher propensity for arrhythmias. Calcium transient studies linked these deletions to abnormal calcium signaling. RNAseq confirmed calcium homeostasis as a dysregulated pathway and identified additional processes, including OXPHOS and mitophagy. These models provide unique opportunities to investigate pathogenic mechanisms of disease and test genetic and pharmacological therapies.

Development of neuronal models to study mitochondrial disorders

Denisa Hathazi
University of Cambridge, Department of Clinical Neurosciences, John Van Geest Cambridge Centre for Brain Repair, Cambridge United Kingdom

Mitochondrial diseases encompass a heterogeneous group of disorders that frequently affect the brain, often resulting in progressive, disabling, or fatal outcomes, with limited effective therapeutic options. Among these, MELAS syndrome—also caused by the m.3243A>G mtDNA mutation—is a severe form of mitochondrial disease characterized by epilepsy, stroke-like episodes, and cognitive impairment. In vitro modeling of such complex disorders remains challenging due to factors like fluctuating heteroplasmy (the ratio of wild-type to mutant mitochondria), variations in mitochondrial copy number, and nuclear-genomic interactions.

To address these challenges, we developed cortical organoids from patient-derived induced pluripotent stem cells (iPSCs) harboring the m.3243A>G mutation. These organoids were generated from iPSCs with varying heteroplasmy levels from the same patient and were cultured up to 200 days. The models demonstrated stable heteroplasmy, mitochondrial dysfunction, and the presence of diverse cellular populations, including mature neurons, glia, astroglia, and various progenitor cells. We observed that impaired bioenergetics disrupted neuronal structure and function, leading to a significant loss of deep-layer neurons. Functional analyses using multielectrode array (MEA) on day-200 organoids revealed pronounced hypersynchrony in the neuronal network, especially under mitochondrial stress conditions.

These models represent a valuable tool for developing and testing novel therapies aimed at ameliorating the neurological phenotypes associated with mitochondrial diseases like MELAS.

Théâtre du Grand Château - Campus Valrose

Notes

Notes

MAP

DEC 16th - SALLE DES ACTES (GRAND CHÂTEAU)
DEC 17th TO 20th - THÉÂTRE (GRAND CHÂTEAU)

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