

## **Obesity: Deciphering the biological, genetic and environmental issues**

**Karine Clément**

**Service de Nutrition, Hôpital Pitié-Salpêtrière Paris, INSERM / Sorbonne Université - unité Nutrition et Obésités : approches systémiques (Nutriomique), UMRS 1269 Paris, AFERO : Association d'Étude et de Recherche sur l'Obésité**

Understanding the mechanisms of obesity is essential for developing effective prevention and treatment strategies. The epidemic progression of obesity is undeniable and represents a major challenge for global public health, particularly due to numerous associated complications. Research highlights the complex interactions between biology, genetics/epigenetics, inter-organ dialogues and their biological alterations, as well as environmental aspects.

In certain situations, genetic factors are at the forefront. However, in most cases, environmental factors such as physical inactivity, dietary changes, psychosocial stress, and exposures like pollutants interact with individual predispositions to modulate the risk and severity of obesity.

The brain, particularly the hypothalamus, plays a central role in the homeostatic regulation of energy balance and metabolism by integrating numerous hormonal signals from peripheral organs (intestine, liver, muscle, adipose tissue, etc.). Adipose tissue is at the heart of certain metabolic disturbances, systemic inflammation, and fibrotic processes. The gut microbiota also influences these signals and participates in inter-organ dialogues, impacting inflammation and immune response.

This introductory conference will examine these complex interactions and discuss nutritional interventions, lifestyle modifications, and therapeutic approaches to combat obesity. New pharmacological developments are likely to revolutionize both management and research. By deepening our understanding of the underlying mechanisms, inter-organ dialogues, and the combined influence of genetic and environmental factors, more effective strategies for improving global public health are highly anticipated.

## **Adipose tissue progenitors, key players of cardiometabolic health**

**Nathalie Boulet**

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

White and brown adipose tissues (AT) play a key role in metabolic and energetic homeostasis. Obesity is an accumulation of white AT together with a decrease of brown AT, associated with an increased risk to develop cardiometabolic diseases. However, more importantly than total body fat, white AT distribution is a critical determinant of cardiometabolic health. It is now well established that gluteofemoral subcutaneous fat is protective whereas visceral fat is deleterious. The subcutaneous to visceral AT ratio is different according to sex and is modulated with ageing. AT homeostasis and expansion rely on their progenitor cells. Indeed, each adipose depot contains progenitor cells which are multipotent mesenchymal cells. Their adipogenic potential allows adipocyte renewal and hyperplasia, promoting AT homeostasis, while their myofibrogenic potential is involved in AT remodelling and fibrosis. Studies have shown that 1. the progenitor cell population is heterogeneous, composed of several progenitor subsets, and 2. the regulation of the progenitor cell fate involves intrinsic and extrinsic factors. Taken together, we will see how the progenitor cells contribute to the different adipose depot-associated benefit or risk, thus to cardiometabolic health.

## **Role of adipose tissues in the pathophysiology of insulin resistance and type 2 diabetes**

**Mireille Cormont**

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

The white adipocyte in adipose tissues is a cell type specialized in energy storage and mobilization. White adipocyte metabolism plays an essential role in systemic glucose and lipid homeostasis. Dysfunction of white adipocyte metabolism in obesity is a key event in the development of insulin resistance and related disorders. We will review the physiological role of adipocytes and adipose tissue in energy homeostasis (glucose transport, storage and release of fatty acids) and the importance of their endocrine function. Recent advances in the field will be presented, from the identification of novel regulators to the discovery of the cellular heterogeneity of adipocytes. At the molecular level, we will focus on the role of the endosomal system, which controls the trafficking of key proteins, in adipocyte functions. We will describe the alterations in adipocyte metabolism that are involved in the development of obesity-related metabolic disorders, in particular insulin resistance, and how defects in the endosomal system may contribute to the alterations of adipocyte metabolism and to adipose tissue dysfunction.

### **Human brown adipose tissue in obesity**

**Kirsi A. Virtanen**

**Turku PET Centre, University of Turku, Finland**

Oxidative capacity of human brown adipose tissue (hBAT) is blunted in obesity, along with blunted glucose and fatty acid uptake. Cold-induced oxygen uptake in hBAT is inversely related to body mass index and waist circumference of the subject while abdominal obesity is a major risk factor for cardiometabolic dysfunction. Triglyceride content of hBAT also affects its oxidative capacity: the higher the triglyceride content, the lower is metabolic rate of oxygen. Becher et al. showed that people with active BAT have less cardiometabolic diseases, and surprisingly, people with obesity benefited even more from active BAT: prevalence of type 2 diabetes was 7.5 % with active hBAT while with nonactive hBAT the prevalence of type 2 diabetes was 20 %. On the other hand, repeated cold acclimation stimulates hBAT metabolic activity introducing an attractive option for prevention of prediabetes and type 2 diabetes in abdominally obese subjects.

Cold stimulation increases fatty acid oxidation in the whole body and generally in obesity, whole body fat oxidation is decreased. However, high hopes on hBAT activation for obesity treatment (=weight loss) have turned out to be too optimistic. hBAT seems to have more potential for body weight maintenance rather than for body weight loss, partly due to its relative small tissue mass in the human body. On the other way around, weight loss increases hBAT activity.

Recent studies have revealed information on the role of hBAT in obesity in cross-sectional studies. Longer term follow-up studies are needed in order to understand the role of hBAT activation in obesity.

### **Adipose Tissue Macrophages**

**Adeline Bertola**

**Myeloid Cells and Metabolism team, Laboratory of Molecular Physiomedicine (LP2M), CNRS, Université Côte d'Azur, Nice, France**

Macrophages are innate immune cells present in virtually all tissues where they have core functions as phagocytes but also tissue-specific activities in response to environmental cues. They represent the most abundant immune cell type found in the stromal vascular fraction of adipose tissue. Adipose tissue macrophages (ATMs) were initially classified according to the oversimplified M1/M2 model of

macrophage polarization. The prevailing view was that lean adipose tissue is enriched in anti-inflammatory, alternatively activated (M2) macrophages whereas pro-inflammatory, classically activated (M1) macrophages accumulate in obese adipose tissue and promote metabolic dysfunction. It was later shown that, during obesity, pro-inflammatory ATMs adopt a metabolically activated phenotype distinct from classical activation. More recently, technical advances providing phenotypic resolution at the single-cell level have revealed that ATMs are heterogeneous and comprise several distinct subpopulations with specific subtissular localization and functions. Emerging evidence supports that ATMs play a dual role in both maintaining adipose tissue homeostasis and contributing to metabolic inflammation.

## **Epicardial Adipose Tissue and Heart Diseases in Obesity**

**Benedict Gaborit**

**C2VN (AMU - INSERM 1263 - INRAE 1260), Aix-Marseille Université - Faculté des Sciences Médicales et Paramédicales, Marseille, France**

**Objective:** Epicardial adipose tissue (EAT) is a visceral fat, located between visceral pericardium and myocardium, that allows unique paracrine cross-talk between adipocytes and cardiomyocytes or cells of the arterial wall. EAT inflammatory phenotype has been associated with coronary artery disease (CAD). EAT is also a beige adipose tissue with thermogenic properties, the latter being progressively lost with aging, CAD, and type 2 diabetes. Immune cells that infiltrate ATs could participate in inflammation and/or beiging. The objective of our work was to characterize the immune cells in EAT compared to other adipose tissues and decipher their role in its inflammatory/beige phenotype.

**Methods:** First, a new pan-genomic microarray analysis was performed on previously collected paired human EAT and thoracic subcutaneous AT (thSAT) from the EPICAR study (n = 31) to decipher a specific immune signature and its link with browning genes. Then, adaptive (T and B cells) and innate lymphoid cell (ILC1, ILC2, and ILC3) immunophenotyping assay panels, including CD127, CD117, and prostaglandin D2 receptor 2, were performed on prospectively collected paired human multiorgan donors (n = 18; INTERFACE study).

**Results:** In the EPICAR study, a positive correlation between the T helper cell subtype Th2 immune pathway and browning genes was found in EAT versus thSAT ( $r = 0.82$ ;  $p < 0.0001$ ). In the INTERFACE study, this correlation was also observed ( $r = 0.31$ ;  $p = 0.017$ ), and a preponderance of CD4+T cells, CD8+T cells, and a few B cells was observed in all ATs ( $p < 0.0001$ ). An increase in ILCs was observed in visceral AT (VAT) (i.e., EAT + VAT;  $30 \pm 5$  ILCs per gram of AT) compared with subcutaneous counterparts (i.e., thSAT + abdominal SAT;  $8 \pm 2$  ILCs per gram of AT;  $p = 0.001$ ), with ILC1 being the most frequent (ILC1 > ILC3 > ILC2). Numbers of ILCs per gram of AT correlated with several Th2 or browning genes (IL-13, TNF receptor superfamily member 9 [TNFRSF9], and alkaline phosphatase, biomineralization associated [ALPL]). Interestingly, a specific increase in EAT-ILC2 compared with other ATs was observed, including a significant proportion expressing CD69 and/or CD25 activation markers ( $97.9\% \pm 1.2\%$ ;  $p < 0.0001$ ). Finally, more natural killer cells were observed in EAT + VAT than in thSAT + abdominal SAT ( $p = 0.01$ ). Exclusion of patients with coronary artery disease in the EPICAR and INTERFACE studies did not modify the main findings. Gene expression phenotyping confirmed specific upregulation of Th2 pathway and browning genes (IL-33 and uncoupling protein 1 [UCP-1]) in EAT.

**Conclusions:** This is the first study, to our knowledge, to provide a comparison between innate and adaptive lymphoid cells in human EAT. Further studies are ongoing to decipher whether these cells, via extracellular vesicles could play a role in the phenotype of EAT and its inflammatory or beige profile.

## **Obesity, Adipose tissue and Cancer: an infernal trio**

**Camille Attane**

**Microenvironment, Cancer and Adipocytes team, Institute of Pharmacology and Structural Biology, CNRS, Université de Toulouse, Toulouse, France**

In addition to its metabolic complications, it is now widely recognized that obesity increases the onset and negatively affects the prognosis of many cancers. Adipose tissue (AT) is found in close proximity to invasive cancers such as breast with mammary adipose tissue and prostate with periprostatic adipose tissue.

We will show that mature adipocytes are modified by cancer cells and through their secretory and metabolic activities are able to promote tumor progression. We will then discuss how obesity affects AT and how it could contribute to amplify the endocrine and paracrine effect of ATs on tumor progression in breast and prostate cancer. Such studies provide unique opportunities to set up specific strategies for the treatment of obese patients exhibiting aggressive diseases.

## **Obesity as an Unexpected Protector in Lung Cancer**

**Marco Alifano**

**Hôpital Cochin, AP-HP Centre Université de Paris, Université de Paris, Paris, France**

Adapting therapies and providing personalised care for patients with resectable non-small cell lung cancer (NSCLC) is a major challenge but requires a deeper knowledge of the pathophysiology of the disease. Integrating multiple parameters into patient assessment, beyond the raw tumour data (histology, staging, molecular biology, expression of markers of susceptibility to immunotherapies that all remain the cornerstone of management), will improve understanding of the mechanisms involved in tumour progression. Many studies have investigated the impact of host and tumour characteristics and their interactions through inflammatory processes or the tumour immune environment, which represents the tumour-host interface. Beyond tumour stage, malnutrition, sarcopenia and inflammatory state have been identified as independent factors that can directly influence postoperative outcome. The interplay between inflammation, obesity and malnutrition in lung cancer patients is currently poorly understood. Although obesity has been shown to be protective in patients undergoing surgery for lung cancer, not only in terms of postoperative complications and mortality, but also in terms of long-term survival (the so-called lung cancer paradox), the mechanisms are poorly understood. Furthermore, direct correlations have been shown between body mass index and total psoas areas, suggesting that sarcopenia would not be a feature of obese patients with lung cancer: whether this is another element of the lung cancer paradox deserves further study. More generally, a broader and more complete view, including morphometric assessment of the patient, physical performance, inflammatory state and nutritional status, would provide additional information that needs to be integrated into the patient work-up and could help in predicting postoperative outcome and, more importantly, in understanding patient-disease interactions.

## **Loss of pancreatic $\beta$ -cell mass, identity and function during obesity-associated type 2 diabetes: molecular and cellular insights**

**Jean-Sébastien Annicotte**

**INSERM UMR 1167, Institut Pasteur de Lille, Lille, France**

Type 2 Diabetes (T2D) is characterized by high blood glucose levels and develops due to inadequate pancreatic  $\beta$ -cell mass and function (i.e. insulin secretion) in the face of peripheral insulin resistance.  $\beta$ -

cell dysfunction is thought to have a major role in the pathogenesis of T2D. The restoration of  $\beta$ -cell mass, identity and function has therefore become a field of intensive research seeking for the next generation of anti-diabetic drugs. Although it is well supported that obesity contributes to  $\beta$ -cell dysfunctions through gluco-lipotoxicity and inflammatory signals, the precise molecular mechanisms remain less understood. Loss of  $\beta$ -cell identity, due to dedifferentiation, may be at the origin of the loss of  $\beta$ -cell function and mass and could represent a molecular triggering factor involved in T2D pathogenesis. In the last decades, tremendous efforts and illuminating investigations have focused on deciphering epigenetic regulations –the subtle and reversible chemical modifications on DNA or proteins– that control  $\beta$ -cell function and identity. More recently, the emerging concept that posttranscriptional modifications of RNAs, named epitranscriptome, may contribute to pancreatic  $\beta$ -cell dysfunctions and defective insulin secretion during metabolic stress, thus favoring the susceptibility to T2D, has been proposed. In this Adipocible winter school, we will summarize the pathophysiology of T2D at the molecular (epigenome, transcription) and cellular ( $\beta$ -cell) levels, discuss the latest data and concepts related to differentiation, proliferation and dedifferentiation of  $\beta$ -cells to better appreciate its contribution to the pathology. Finally, we will present pluridisciplinary approaches that could help to better study and model inter-organ crosstalk during obesity-associated T2D.

## **Understanding how gut hormone multiagonists are changing the treatment of type 2 diabetes and obesity**

**Fabrizio ANDREELLI**

**Pole Coeur et Metabolisme, Service de Diabétologie-Métabolismes, Ap-HP, Paris, France**

Considerable efforts have been made to better understand the pathophysiology of obesity and its associated comorbidities, such as type 2 diabetes (T2D). These chronic diseases are interrelated and most of the metabolic and molecular changes observed in T2D are the result of excess body weight. Their therapeutic management is complex and requires the combination of lifestyle changes with drugs. The development of hypoglycaemic drugs has led to a significant reduction in the risk of developing complications of diabetes, but has not been sufficient to manage body weight. Since 1906 and the first observation that intestinal extracts could reduce glucose levels in humans, the identification of gut-derived hormones that act on the endocrine pancreas has been a major goal that has been achieved step by step. The demonstration that ingested glucose stimulates insulin secretion more than its parenteral administration (the so-called "incretin effect") proved that entero-endocrine cells are present in the gut and control insulin secretion during meals. The identification of the incretin effect was followed by the isolation of gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), the two gut hormones that act as physiological incretin hormones. The discovery that the acute insulinotropic effects of GLP-1, but not GIP, are relatively preserved in people with T2D focused attention on the therapeutic potential of GLP-1 and ultimately supported several clinical development programmes for GLP-1 receptor agonists (GLP-1RA). Preclinical studies with peripherally administered GLP-1RAs were associated with reduced food intake and weight loss, both of which were later confirmed in healthy humans. Clinical trials with GLP-1RAs subsequently confirmed weight loss in people with T2D and later obesity. In addition, observations of significant improvement in chronic hyperglycaemia, mainly through correction of insulin secretion defects rather than weight loss confirmed specific effects of GLP-1RA on beta cells viability. Importantly, The GLP-1RA family has now been completed by the bi-agonists GIP/GLP-1 and the tri-agonists glucagon/GIP/GLP-1 based medicines. Clinical studies have shown that these new compounds are more potent than GLP-1 RAs and are promising therapies for improving the health of populations living with chronic cardiometabolic disorders.

## **Cardiovascular disease, cardiac regeneration and the link to lipid metabolism and adipose tissue**

**Kay Wagner**

**Vessel formation in development and disease team, Institute of Biology of Valrose, CNRS, INSERM, Université Côte d'Azur, Nice, France**

Cardiovascular diseases account for approximately 40% of all deaths in the European Union. Furthermore, the prevalence of overweight and obesity is on the rise globally, reaching epidemic proportions. Obesity increases the risk for type 2 diabetes. Obesity and diabetes in turn augment the risk of cardiovascular disease (CVD), increasing morbidity and mortality by greater than 2-fold. Obesity and type 2 diabetes result in a multitude of structural and functional modifications within the cardiovascular system. These include reduced left ventricular function, coronary artery stenoses and peripheral artery disease. This may lead to myocardial infarctions, amputations and premature death. The present discussion will focus on the pathophysiological mechanisms linking obesity, diabetes and alterations in lipid and glucose metabolism to cardiovascular and peripheral artery disease. Based on this knowledge, the current therapeutic concepts will be introduced. In light of recent molecular insights and approaches, we will present an outlook on potential novel strategies to induce regeneration in the cardiovascular system and to overcome the detrimental effects of obesity and diabetes on the cardiovascular system.

**Metabolic dysfunction-associated steatotic liver disease (MASLD): from pathogenesis to treatment**

**Philippe Gual**

**Head of the Team "Chronic liver diseases associated with obesity and alcohol"(LIVDISEASES)**

**INSERM U1065, Centre Méditerranéen de Médecine Moléculaire (C3M), Université Côte d'Azur, Nice, France**

Metabolic dysfunction-associated steatotic liver diseases (MASLDs) are the most common chronic liver diseases, with a worldwide prevalence of 32%. MASLDs covers the full spectrum of steatotic liver diseases from hepatic steatosis to metabolic dysfunction-associated steahepatitis (MASH), fibrosis/cirrhosis and hepatocellular cancer. The overall prevalence of MASLD is growing in parallel with the global epidemic of obesity. Weight gain, insulin resistance, type 2 diabetes mellitus and hypertension are risk factors for MASLD progression. Reciprocally, MASLD is a risk factor for many metabolic diseases, including cardiovascular disease and type 2 diabetes. The development of MASH, the progressive form of MASLD, is the consequence of aberrant activation of hepatic conventional immune, parenchymal and endothelial cells in response to inflammatory mediators from the liver, adipose tissue and gut. In this review, we will highlight the processes triggering MASLD development and progression, with a focus on the interactions of the gut and adipose tissue with the liver enhancing liver metabolic disorder (steatosis and insulin resistance), chronic inflammation and injury-mediated fibrosis. On-going studies and preliminary results from global and specific therapeutic strategies to manage MASLD will also be discussed.

**Impact of Obesity on Osteoarthritis and Other Joint Diseases**

**Christian Roux**

**Rheumatology, Centre Hospitalier Universitaire de Nice, Université Côte d'Azur, Nice, France**

Obesity and osteoarthritis (OA) are closely linked conditions that have garnered significant attention in the scientific community. Osteoarthritis, a degenerative joint disease characterized by the breakdown of cartilage, predominantly affects weight-bearing joints such as the knees and hips. The association between obesity and OA is multifaceted, involving both mechanical and metabolic factors.

Mechanically, excess body weight increases the load on joints, accelerating the wear and tear of cartilage. Studies indicate that for each kilogram of body weight, an additional four kilograms of pressure is exerted on the knee joint during activities like walking. This increased load contributes to the faster degradation of joint tissues and can exacerbate the symptoms of OA, such as pain and reduced mobility. Metabolically, obesity induces systemic inflammation that further aggravates osteoarthritis. Adipose tissue, particularly visceral fat, secretes pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ). These cytokines promote chronic low-grade inflammation, which not only affects joint health but also contributes to the progression of OA by promoting cartilage degradation and inhibiting its repair mechanisms. Furthermore, obesity is associated with metabolic syndrome, a cluster of conditions including insulin resistance and dyslipidemia, which may also play a role in OA development. Insulin resistance can lead to increased levels of circulating insulin, which has been implicated in cartilage degradation. Addressing obesity through weight management strategies, including diet and exercise, has been shown to alleviate OA symptoms and improve joint function. Studies suggest that even modest weight loss can significantly reduce joint pain and enhance quality of life for individuals with osteoarthritis. Therefore, understanding and addressing the obesity-OA connection is crucial for developing effective prevention and treatment strategies.

### **Nutrition is integral to both preventing and managing obesity**

**Stephane Schneider**

**Gastroenterology and Nutrition, Centre Hospitalier Universitaire de Nice, Université Côte d'Azur, Nice, France**

Prevention involves fostering healthy eating habits and choices early on. It includes nutritional education, a balanced diet, portion control, healthy food choices and hydration. Protective nutritional factors against obesity, besides regular physical activity include a high intake of dietary non-starch polysaccharides and fibers, supportive home and school environments for children and breastfeeding. Risk factors for obesity, besides a sedentary lifestyle, include a high intake of energy-dense, micronutrient-poor foods, heavy marketing of energy-dense foods and fast-food outlets, as well as sugar-sweetened soft drinks and fruit juices.

The epidemic has spurred significant advances in the understanding of nutritional approaches to treating obesity. Although the primary challenge is to introduce a dietary intake that creates an energy deficit, clinicians should also consider targeted risk factor modifications with manipulation of the nutrient profile of the weight-reducing diet. Treatment therefore requires personalized dietary interventions with controlled caloric restriction, continuous support and guidance, and a holistic approach that includes physical activity. By addressing both the quantity and quality of food intake, nutrition can effectively contribute to the reduction and management of obesity. Offering short-term interventions may reach people otherwise unwilling or unable to enroll in or complete longer programs. However, the more restrictive the dietary counsel, the higher the risk of relapse in the mid- to long-term.

Future research is needed to better understand how to personalize nutrient prescriptions further to promote optimal risk modification and maintenance of long-term energy balance in the weight-reduced state.

### **Exercise and obesity treatments: immunometabolism as the core of vitality capacity**

**Anne-Sophie ROUSSEAU**

**Université Côte d'Azur, CNRS, Inserm, Adipocible Research Study Group, iBV, Nice, France**

As new methods emerge to assist individuals in managing obesity, it is crucial to ensure that physical activity remains a cornerstone of the strategy to achieve several key goals: (1) prevent adverse effects associated with weight reduction (e.g., loss of skeletal muscle mass), (2) improve insulin sensitivity, (3) prevent weight regain and related cardiometabolic complications, and (4) preserve or enhance overall health. Vitality capacity, a health criterion, represents the physiological determinant of intrinsic capacities, defined by the interaction of metabolic, neuromuscular, immune, and stress response components. In the context of obesity reduction, vitality capacity should be a targeted measure to assess intervention effectiveness. We will explore this interaction, particularly through the muscle-adipose tissue-T cell relationship. Immunometabolism, a research field investigating the interaction between the immune system and metabolism, examines how metabolic processes influence immune function and reciprocally how immune activation affects metabolism. Immunometabolism is central to understanding the impact of vitality capacity on health. We will discuss the effects of strategies aimed at reducing/regulating fat mass, which induce metabolic changes in these components, and the necessary training load and planning—considering circadian effects and age—to optimize the long-term outcomes of obesity treatments. Additionally, we will examine the complementarity, redundancy, and interaction of exercise-mimicking approaches in this context, along with the potential benefits and risks associated with translating these findings into clinical practice.

### **Physical activity, persistent organic pollutants and obesity. Links and possible interactions.**

**Quentin A. Serrano<sup>1</sup>, Sébastien Le Garf<sup>2</sup>, Vincent Martin<sup>3,4</sup>, Serge S. Colson<sup>1</sup>, Nicolas Chevalier<sup>2</sup>**

<sup>1</sup> **Université Côte d'Azur, LAMHESS, Nice, France**

<sup>2</sup> **Université Côte d'Azur, CHU, INSERM, C3M, Nice, France**

<sup>3</sup> **Université Clermont Auvergne, AME2P, Clermont-Ferrand, France**

<sup>4</sup> **Institut Universitaire de France (IUF), Paris, France**

Although many environmental and behavioural factors can explain the development of obesity, some of them, persistent organic pollutants (POPs), are poorly known by the general population. POPs originate, among other things, from pesticide use and industry. Every human being is regularly exposed to POPs through food intake, inhalation and skin contact. In contrast to POPs, physical activity (PA) is a therapeutic approach known to limit the development of obesity. Our aim is to compare the effects of POPs and PA on certain mechanisms of obesity. Based on our literature review prepared using the PubMed search engine, we will discuss various in vivo and in vitro models. While POPs promote adipogenesis and lipid accumulation through specific physiological mechanisms, PA has opposite effects on these mechanisms and/or helps to rebalance them. The protective effect of PA also seems to affect other mechanisms associated with the development of obesity and influenced by POPs (e.g., inflammation, loss of insulin sensitivity, dysbiosis of the intestinal microbiota). Finally, it should be noted that several studies suggest that, through mechanisms including sweating, PA may help to excrete a proportion of plasma POPs. PA appears to be an effective intervention method for reducing the harmful influence of POPs in the context of obesity.

### **Metabolic and Bariatric Surgery**

**Antonio Iannelli**

**Department of digestive surgery, Centre Hospitalier Universitaire de Nice, Université Côte d'Azur, Nice, France**



This presentation on Metabolic and Bariatric Surgery (MBS) aims to provide comprehensive knowledge to deepen course participants' understanding of surgical interventions for obesity and metabolic disorders currently used in clinical practice.

## **Aims**

### **1. Understanding the Scope of MBS**

- Provide a detailed overview of the various types of metabolic and bariatric surgeries, including gastric bypass, sleeve gastrectomy, adjustable gastric banding, and biliopancreatic diversion with duodenal switch.
- Explore the indications, contraindications, and patient selection criteria for each surgical procedure.

### **2. Preoperative and Postoperative Care**

- Outline the essential components of preoperative evaluation and patient preparation, including psychological assessment and nutritional counseling.
- Emphasize the importance of postoperative care, including dietary modifications, supplementation, and long-term follow-up to monitor and manage potential complications.

### **3. Physiological and Metabolic Impacts**

- Explain the physiological changes and metabolic improvements resulting from MBS.
- Discuss the mechanisms through which these surgeries affect weight loss, hunger regulation, and the resolution of obesity-related comorbidities.

### **4. Risk Management and Complications**

- Identify potential risks and complications associated with MBS.

### **5. Research and Evidence-Based Practice**

- Encourage engagement with current basic and fundamental research and evidence-based practices in MBS.

## **Data Science for Health**

**Lionel Fillatre**

**Université Côte d'Azur, CNRS, I3S Laboratory, Sophia-Antipolis, France**

This talk is an introduction to Data Science applied to real-life data. Data science is the study of data to extract meaningful insights for decision support. We will present several aspects of Data Science. First, we will describe a few tools useful for analyzing data and sharing algorithms. Second, we will discuss the importance of visualizing data with or without machine learning techniques such as principal component analysis. Third, we will emphasize the importance of cleaning and encoding features before any advanced processing. Fourth, in the case where the data are labeled, we will study supervised learning for label prediction. We will present some methods such as decision trees, random forests, boosting and neural networks. Finally, we will see unsupervised learning when the goal is to cluster the data into homogeneous groups without any labels. Unsupervised learning will be illustrated with K-means, DBSCAN and autoencoder.

## **The role of the sperm epigenome in obesity**

**Marie-Charlotte Dumargne**

**Institut de Pharmacologie Moléculaire et Cellulaire (IPMC), CNRS UMR7275, INSERM U1323, Université Côte d'Azur, CNRS, Valbonne, France**

Despite trendy dieting and desperate attempts to get in shape, Humanity is heavier than ever. In 2023, nearly half of French adults were overweight or obese. And while public authorities continue to tell us to eat less and move more, agrifood multinationals make sure that food is available everywhere at any time. European surveys recently reported that despite being on a diet, 70% of the people attempting to lose weight in the past 12 months did not achieve clinically meaningful weight loss. In this presentation I will show you that parents do not only transmit half their chromosomes to their children, but they also bequeathed ancestral experiences of the family encoded in their gametes in the form of epigenetic information. Given the acceleration of obesity over generations, we think that the contribution of epigenetics to the etiopathogenesis of this pandemic may be underestimated. We will see that obesity leaves an epigenetic imprint that may predispose the offspring genomic make-up. I will present previous and current work from the lab which showed that 1) spermatozoa from obese men carry a distinct epigenetic signature at genes controlling brain development and function compared to lean men, and that 2) the sperm DNA methylome is dynamically remodeled after surgery-induced weight loss at gene regions involved in the central control of appetite. These regions represent a potential heritable information that can be passed to future generations and may predispose their (epi)genetic make-up to easier weight gain or fat storage.

**Anatomy of the chemical senses**

**Jeremie Topin**

**Institut de Chimie de Nice, Université Côte d'Azur, UMR 7272 CNRS, Nice, France**

The perception of smells and flavours enables us to interpret our chemical environment. The influence of these senses on our behaviour is often underestimated, even though it has a direct impact on our survival. These chemical senses help us to identify and appreciate our food, detect dangers such as fire or spoiled food, and even influence social interactions. In this talk, we will look at the anatomy of these chemical senses, focusing on the molecular mechanisms involved in the recognition of odorous and gustatory molecules. Understanding the molecular basis of these senses involves examining the role of specific proteins and genes. The olfactory system relies on a vast array of receptor proteins to identify a wide range of odours, each receptor being encoded by a different gene. Similarly, taste perception is induced by specific taste receptors that bind to various chemical compounds.

We will also see how this sensory information is processed by the brain and how it influences our behaviour. For example, the perception of taste and smell can give rise to food likes and dislikes which, in turn, affect our food choices and our general health. In addition, these senses can trigger emotional reactions and memories, demonstrating their profound impact on our daily lives.

**Hypothalamic inflammation and energy balance deregulations: focus on chemokines.**

**Carole Rovère**

**Institut de Pharmacologie Moléculaire et Cellulaire (IPMC), CNRS UMR7275, INSERM U1323, Université Côte d'Azur, CNRS, Valbonne, France**

The hypothalamus is a key brain region in the regulation of energy balance. Especially, it controls food intake and both energy storage and expenditure through integration of humoral, neural and nutrient-

related signals and cues. Hypothalamic neurons and glial cells act jointly to orchestrate, both spatially and temporally, regulated metabolic functions of the hypothalamus. Thus, the existence of a causal link between hypothalamic inflammation and the deregulations of feeding behaviour, such as involuntary weight-loss or obesity, was suggested. Among the inflammatory mediators that could induce deregulations of hypothalamic control of the energy balance, chemokines represent interesting candidates. Indeed, chemokines, primarily known for their chemoattractant role of immune cells to the inflamed site, have also been proposed to be capable of neuromodulation. Therefore, chemokines could disrupt cellular activity together with synthesis and/or secretion of multiple neurotransmitters/mediators that are involved in the maintenance of energy balance. Here, we will relate on recent results showing the primary role of the central chemokinergic signalling CCL2/CCR2 for metabolic and behavioural adaptation to high-grade inflammation, especially loss of appetite and weight, through action on hypothalamic neurons producing the orexigenic peptide Melanin-Concentrating Hormone (MCH). We will also discuss results suggesting that other chemokines such as CCL5 could deregulate these hypothalamic circuits and have the opposite effect, possibly contributing to the onset/development of obesity.