CTM U1231 SCIENTIFIC SEMINAR

December 12, 2022
1 to 2 pm, Amphitheatre Martin, UFR des Sciences de Santé
Chairman: Dr Tony Jourdan

Invited speaker: Dr Xavier Prieur
Thorax Institute
Nantes, France

Seipin deficiency as a model of severe adipocyte dysfunction

Obesity is tightly associated with cardiometabolic multimorbidity. Growing evidence supports that adipocyte dysfunction is central to the development of these obesity-related metabolic complications. Although several factors have been highlighted, how do adipocytes become dysfunctional remains a key issue. In addition, the mechanisms linking adipose tissue failure and the cardiometabolic complications associated with obesity, such as insulin resistance, diabetes and its long-term complications, hepatic diseases and heart failure, remain not completely understood. A better comprehension of the pathways controlling adipocyte homoeostasis is crucial to decipher the multiple mechanisms by which adipocytes become dysfunctional.

To this purpose, as a model of adipocyte dysfunction, our group has been studying the pathophysiology of the most severe form of lipodystrophy (nearly complete lack of adipose tissue), the Berardinelli-Seip lipodystrophy (BSCL). In 50% of the cases, BSCL is caused by loss of function mutations in the gene *BSCL2*, which encodes Seipin, an endoplasmic reticulum transmembrane protein highly expressed in adipose tissue. Our research aims to unravel the role of Seipin in mature adipocyte and to highlight the molecular mechanism involved in the associated cardiometabolic complication with a specific focus on cardiomyopathy.

Recently, we highlighted that seipin is enriched at ER-mitochondria contact sites (MAMs) in human and mouse cells and localizes in the vicinity of calcium regulators SERCA2, IP3R and VDAC. Seipin association with MAM calcium regulators is stimulated by fasting-like stimuli, while seipin association with lipid droplets is promoted by lipid loading. Acute seipin removal led to defective mitochondrial calcium import accompanied by a widespread reduction in Krebs cycle metabolites and ATP levels. In mice, inducible seipin deletion leads to mitochondrial dysfunctions preceding the development of metabolic complications.

Together, these data suggest that seipin controls mitochondrial energy metabolism by regulating mitochondrial calcium influx at MAMs. In seipin deficient adipose tissue, reduced ATP production compromises adipocyte properties, contributing to lipodystrophy pathogenesis.

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2. Joubert M, Jagu B, Montaigne D, Marechal X, Tesse A, Ayer A, Dollet L, Le May C, Toumaniantz G, Manrique A, Charpentier F, Staels B, Magré J, Cariou B, **Prieur X**. The SGLT2 Inhibitor Dapagliflozin Prevents Cardiomyopathy in a Diabetic Lipodystrophic Mouse Model. Diabetes (2017) PMID: 28052965
3.Dollet L, Levrel C, Coskun T, Le Lay S, Le May C, Ayer A, Venara Q, Adams AC, Gimeno RE, Magré J, Cariou B, **Prieur X**. FGF21 Improves the Adipocyte Dysfunction Related to Seipin-Deficiency. Diabetes (2016) PMID: 27554469
4. **Prieur X**, Dollet L, Takhashi M, Nemani M, Pillot B, Le May C, Mounier C, Takigawa, Zelinka K, Matsuda F, Féve B, Capeau J, Lathrop M, Costet P, Cariou B, Magré J. Thiazolidinediones partially reverse the metabolic disturbances observed in Bscl2/seipin-deficient mice. Diabetologia (2013) PMID: 23680914