Project 1: Obesity under pressure

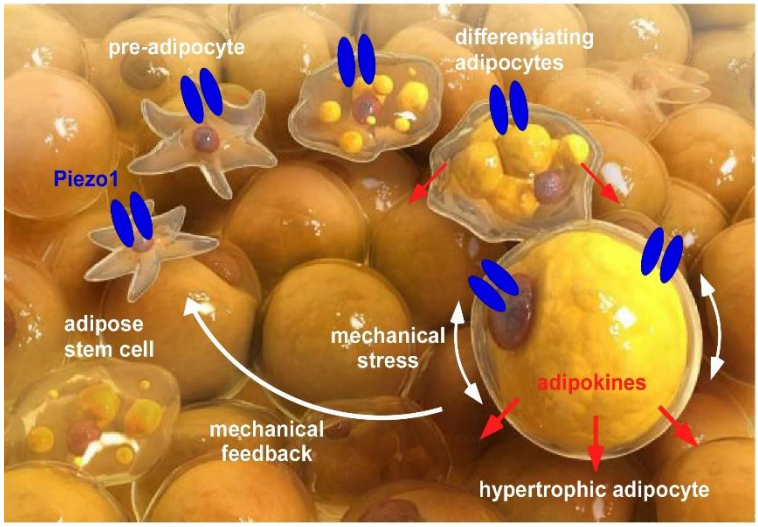
The increase in the prevalence of overweight/obese people worldwide has reached epidemic proportions, with at least 600 million clinically obese adults (WHO, 2014). Numbers are expected to further increase, particularly promoted by the demographical change towards the elderly. Obesity is multifactorial and constitutes a substantial risk factor for type 2 diabetes, cardiovascular diseases, cancer and a variety of additional disorders, thus presaging tremendous burdens for the public health care system. Efficient and safe pharmacological treatments against obesity with significant long-term success are still critically needed. Thus, there is an urgent need to better understand the basic mechanisms of adipose tissue expansion, in view of designing effective strategies against obesity.

Obesity is an energy imbalance between calories consumed and expended. Adipose tissue plays a key physiological role in storing and regulating whole-body energy (*63-69*). Two major types of adipose tissue can be distinguished: i) white adipose tissue (WAT) that stores energy in the form of lipid and controls lipid mobilization and distribution; ii) brown adipose tissue (BAT), which dissipates energy in the form of heat (*65, 70, 71*). WAT expansion is an important homeostatic mechanism to cope with excess energy (*63-69*). In obesity, hypertrophic adipocytes fail to further store triglycerides, resulting in lipid spillover and deposition in non-adipose tissues [including skeletal muscle and liver], causing major adverse effects (*63-69*). Moreover, a strong correlation was shown between the increase in adipocyte size, altered hormonal (adipokines) release, adipose tissue inflammation and the development of insulin resistance (*72-74*). **The mechanisms that govern the regulation of adipocyte size, WAT expandability and how they become altered in chronically obese patients are key processes that remain to be better understood.**

Adipocytes are characterized by a unique ability for size expansion upon triglyceride accumulation within an intracellular lipid droplet, increasing their volume by more than 30-fold (*75, 76*). The growing lipid droplet, which is liquid but effectively stiffer than the cytosol, ultimately occupies most of the cytoplasm of hypertrophic ADs and thereby generates a complex mechanical stress (*75*). We postulate that adipose mechanical stress may influence lipid storage, as well as adipokine release. **According to this hypothesis, the development and progression of obesity may result, at least in part, from an altered regulatory control of adipocytes by mechanical force.** *In vitro* evidence indicates that static stretching promotes adipogenesis, a phenomenon possibly relevant to a sedentary lifestyle (*77*). By contrast, dynamic stretching or whole body vibrations, as occurring during exercise, inhibit adipogenesis (*78*). **Thus, the mechanical environment is increasingly recognized as an important determinant of adipose biology (*77, 78*).**

Metabolic syndrome is a severe pathological condition consisting of a cluster of metabolic disorders including visceral obesity, insulin resistance, alterations in glucose and lipid metabolism and increased blood pressure (*66, 79, 80*). In visceral obesity, besides the growth of adipocytes (i.e. hypertrophy), the increase in fat mass is also due to the recruitment of additional adipocytes upon differentiation of adipose precursor cells, including adipose stem cells and pre-adipocytes (*81-83*). A positive mechanical feedback loop acting in the process of WAT expansion was postulated based on phenomenological finite element simulations (*84*). **It is hypothesized that force transmission from hypertrophic adipocytes to resident adipose precursor cells (i.e. resulting in cell deformation), might stimulate their proliferation and/or**

differentiation by activating specific mechanosensitive pathways, contributing to hyperplasia in visceral WAT, with enhanced lipid accumulation.



Thus, mechanical stress within WAT is expected to significantly influence adipose structure and function, representing a novel and important factor to be considered in the context of obesity. Physics of adipose tissue need to be clarified by reductionist approaches to understand the mechanics within this complex soft tissue (collaboration with Dennis Discher, University of Pennsylvania, Philadelphia, PA, USA). At the integrative level, *in vivo* mapping of force distribution within fat pads, using novel tension reporter transgenic mouse models, represents a real experimental challenge (collaboration with Carsten Grashoff, Max Planck Institute of biochemistry, Martinsried, Germany). Another important goal is to gain insights into the role of Piezo1 in the regulation of WAT growth, adipokines synthesis/secretion, as well as adipose inflammation (collaboration with Aimin Xu, The Hong Kong University, China and with Stefan Offermanns, Max Planck Institute, Bad Nauheim, Germany).

This rationalized and integrated collection of accessible experimental data, should allow us to gain important novel insights into the basic mechanisms of WAT expansion, with expected translational applications for the fight against obesity and associated metabolic syndrome or conversely to improve soft tissue bioengineering procedures for reconstructive medicine (Défi mécanobiologie CNRS, collaboration with Pierre Nassoy, LP2N, Bordeaux, France).

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