Recent data indicate that cell size fluctuation, a key property in adipocyte pathophysiology primarily dependent on lipid storage, is linked to a novel function of lipid droplet organelles acting as mechano-active organelles to regulate cell membrane remodeling and caveolae dynamics.

Adipose tissue is the primary energy storage organ in mammals, and as such, has evolved as a highly efficient and flexible metabolic tissue. Because nutrient availability largely fluctuates, adipose tissue fat stores appropriately provide a continuous energy supply. In this context, the molecular form in which energy is stored within adipose tissue (i.e. esterified fatty acids) ensures optimal packing in neutral lipids within lipid droplet organelles. This lipid storage form provides a highly efficient volume sparing process, over water-dependent storage of carbohydrates as glycogen. During evolution, periods of famine and nutrient scarcity favored adaptive pathways toward optimal filling of adipose stores in prosperous conditions. These include insulin-driven channeling of nutrients to adipose tissue lipids by means of integrated multi-level regulations involving gene transcription, protein synthesis, as well as post transcriptional modifications toward regulated protein abundance, activities and interactions with functional partners. Another important aspect in adipose tissue function is limited basal release of lipids by appropriate coating of lipid droplets to avoid uneven lipolytic mobilization.

Beyond metabolic responses, highly efficient adipocyte lipid storage processes also involve adaptations in cell architecture, since lipid stores in fat cells dominate over other intracellular compartments. Indeed, rapid lipid accretion results in large-scale intracellular volume changes, and requires concomitant adaptive responses by the cell membrane. Conversely, extensive mobilization of stored lipids from adipocytes requires bilayer remodeling to prevent an excess of membrane surface area. These cellular aspects are poorly documented, as the adipocyte is a difficult cell type to apply common cellular biology tools. Physiologists have long observed huge variations in adipose cell size upon fasting-refeeding in rodent models or in humans with extreme lean- or obesity. For example, a 48h-fast in mice can induce an almost complete disappearance of lipids from adipocytes. Depending upon whether an individual is lean or obese, the diameter of a single human adipocyte varies from 70 to 120 μm, which affects cell surface area by nearly 4-fold. Therefore, a major component of metabolic flexibility in adipose tissue is the ability of the adipocyte to respond to volume changes linked to the fluctuations of lipid stores. In the long term, formation of additional lipid reservoirs by means of differentiation of new adipocytes will be required to cope with sustained energy excess.

The exploration of cell responses to size changes and the subsequent physiological consequences primarily rely on manipulation of osmolarity in the cell environment to alter volume. When faced with a hypotonic extracellular medium, cells first respond by swelling followed by the so-called “Regulatory Volume Decrease (RVD)” process to recover their original cellular size. Cell swelling has been reported to occur during different clinical situations such as hypoxia, ischemia, hyponatremia, hypothermia, and during over other intracellular compartments.
intracellular acidosis and diabetic ketoacidosis. Therefore osmosensing or osmo-signaling is the subject of extensive research. In particular, some TRP (Transient Receptor Potential) channels have been identified as osmosensors involved in controlling the RVD process.2,3

The regulation of cell volume after osmotic changes is similar to that of the response of the adipocyte to changes in lipid store: the mechanical stretching of the lipid bilayer is transiently applied in both situations, potentially threatening cell integrity. Very little is known about the role of TPR channels and associated-omoslyte changes in maintaining energy homeostasis.4 Of interest, one particular TPR, TPRV4, shown to be activated by cellular swelling5,6 and by cellular stretch,7,8 was identified as a negative regulator of adipocyte oxidative metabolism and inflammation.9 Therefore, it is possible that TPRV4 might be a link between adipocyte distension in obesity and cellular dysfunction. In the same line, cell swelling has been reported to directly activate NLRP3 inflammasome in macrophages.10

Apart from ion channels, caveolae are other cell membrane components shown to respond to stretch or swelling-related mechanical stress.11 Caveolae are organized on the cell surface as small flask-shaped invaginations and were shown to disassemble upon membrane stretching, providing a lipid reservoir for membrane extension. Indeed, a specific lipid composition enriched in tightly packed phospholipid/cholesterol molecules resembling lipid rafts is a hallmark of caveolar membranes.12

Because caveolae are particularly abundant structures in adipocytes estimated to cover nearly 30% of the cell surface, and caveolins, which form the caveolar protein coats, are highly induced during adipocyte differentiation, caveolae represent good candidate mediators in lipid-driven fat cell size adaptation. In a recently published paper,18 we provide experimental evidence for this hypothesis. By using retroviral-based stable transfection of caveolin-1 in the well-characterized adipose 3T3-L1 and 3T3F442A cell lines, we produced adipocytes that had higher than normal cell surface caveolae density, which enabled the accommodation of larger intracellular lipid droplets. Furthermore, taking advantage of the ability of 3T3 preadipocytes to drive exogenous formation of adipose tissue in mice, it was confirmed that subcutaneous injection of caveolin-overexpressing preadipocytes could generate fat pads containing larger adipocytes, indicating that caveolin/caveolae are rate limiting for adipocyte enlargement. These findings can also be translated in human physiology. It is well known that adipose tissue expansion can proceed from hyperplastic formation of new adipocytes or hypertrophic growth of existing adipose cells. By examining the response of healthy subjects to a controlled overfeeding trial, it was found that among individuals who responded to overfeeding by adipocyte hypertrophy, caveolin-1 expression at baseline significantly correlated with the degree of adipocyte enlargement. In addition, adipocyte shrinkage due to extensive lipid mobilization was also examined. In particular, prolonged treatment of cell lines in vitro with a lipolytic agent (8Br-cAMP) was found to induce lipid emptying of adipocytes and caveolae disassembly from the cell surface. Similarly, long-term fasting in mice was found to associate with massive lipid mobilization and a reduction in adipocyte caveolae number. Caveolar membrane remodeling was shown to rely on selective destabilization and targeted protein degradation of cavin proteins, which are caveola adaptors previously identified to critically regulate caveola formation.14-16

Altogether, these data argue for a role of adipocyte caveola dynamics in metabolic flexibility and adaptation to lipid store fluctuations (Fig. 1). By identifying the importance of caveolae structures, which are known to respond to mechanical stress in other cell types, this study suggests that adipocyte lipid droplets act as mechano-active intracellular organelles, adding a novel item in the fast-growing list of lipid droplet organelle functions.18 Also, the presence of caveolin proteins onto adipocyte lipid droplets, which are in close vicinity with plasma membrane, has previously been reported.17 Caveolin-deficient mouse models have been shown to display marked insulin-resistance, which has led to the hypothesis that caveolae might serve in the transmission of the insulin signal, as well as vascular dysfunction (reviewed in19). Caveolae-deficient mice also exhibit other adipocyte abnormalities, including impaired lipid storage, augmented adipocyte autophagy,21 and metabolic inflexibility.22 Moreover, tissue-specific caveolin reintroduction demonstrated a central contribution of adipocyte caveolae in metabolic dysfunction.23 Accordingly, loss of function mutations in genes coding for caveolar

Figure 1. Caveolae dynamics links to lipid store fluctuations in adipocytes. Fully mature adipocytes engineered for a high caveolae density favor lipid droplet expandability and lipid storage (left). Conversely, forced lipid droplet shrinkage and extensive mobilization induces caveolae disassembly (right). Caveolae are represented as membrane invaginations in cell membrane, cell nucleus is shown in gray, lipid droplets are yellow.
associated-proteins in patients primarily cause lipoatrophic syndromes.\textsuperscript{24-26} These new data therefore highlight the interweaving of adipocyte metabolic flexibility, insulin response, and caveolae dynamics in adipose tissue physiology.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Acknowledgments
We thank Brandon D Kayser for reading the manuscript.

Funding
Funding by EU-FP7 (LipidomicNet-202272) is acknowledged.

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