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Opinion

Visceral Adipose Tissue Mesothelial Cells: Living on the Edge or Just Taking Up Space?

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Visceral adiposity and pathological adipose tissue remodeling, a result of overnutrition, are strong predictors of metabolic health in obesity. Factors intrinsic to visceral adipose depots are likely to play a causal role in eliciting the detrimental effects of this tissue on systemic nutrient homeostasis. The visceral adipose-associated mesothelium, a monolayer of epithelial cells of mesodermal origin that line the visceral serosa, has recently attracted attention for its role in metabolic dysfunction. Here we highlight and consolidate literature from various fields of study that points to the visceral adipose-associated mesothelium as a potential contributor to adipose development and remodeling. We propose a hypothesis in which adipose mesothelial cells represent a visceral depot-specific determinant of adipose tissue health in obesity.

Trends

Mesothelial cells form a cobblestone monolayer over the visceral and parietal surfaces of the peritoneal, pleural, and pericardial cavities.

Visceral adipose tissues contain a defined mesothelium; mesothelial cells in this layer may contribute to inflammation, fibrosis, and adipocyte development.

Mesothelial dysfunction in obesity may play a role in the detrimental effects of visceral adiposity on energy metabolism.

Adipose Tissue Distribution and Remodeling: Critical Determinants of Metabolic Health in Obesity

Contribution of Adipose Tissue Distribution to Metabolic Health in Obesity

The growing epidemic of obesity in adults and children worldwide is alarming as increased adiposity confers significant risk for developing chronic metabolic diseases. However, nearly one-third of obese individuals appear to be protected from acquiring the metabolic syndrome, at least for a period of time [1–3]. This suggests that additional factors, beyond increased adiposity *per se*, determine metabolic health in obesity. Clinical efforts have focused on elucidating better predictors of metabolic syndrome than mere body mass index (BMI). Body fat distribution has emerged as one of the best predictors of metabolic health. Those individuals who preferentially store excess adiposity in the visceral compartment [i.e., expansion of **omental adipose tissue** (see Glossary)] are at a greater risk than those who accumulate adipose tissue in the subcutaneous regions [4]. There is a tremendous sexual dimorphism in the anatomical distribution of fat tissue and the role of sex hormones such as estrogen in this patterning are well established [5,6].

The location of visceral adipose tissue is likely to mediate some of its detrimental effects on energy metabolism. Lipids, metabolites, and cytokines can drain directly into the portal circulation and affect liver function [7]. However, whole adipose depot transplantation experiments in mice indicate that factors intrinsic to these depots determine their effect on glucose homeostasis, and recent reports have shown that intra-abdominal transplantation of subcutaneous fat protects against glucose intolerance, insulin resistance, and inflammation in mice [8,9]. This has sparked an emerging hypothesis that anatomically distinct adipocytes are functionally unique, differing in their ability to undergo lipolysis and lipogenesis and activate thermogenic programs [10–12]. Along these lines, recent lineage analyses reveal that anatomically distinct white

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adipocytes can originate from developmentally different precursor cells and emerge at different times during development [13–15]. A better understanding of how anatomically distinct adipocytes are formed will be essential for developing therapeutic strategies to alter body fat distribution and improve metabolic health.

Modes of Adipose Tissue Expansion in Obesity: Hypertrophy versus Hyperplasia

Another clear predictor of metabolic disease is the cellularity of visceral and subcutaneous adipose depots [16,17]. Adipose tissue expansion, in principle, can occur through increased lipid loading into existing adipocytes leading to cellular hypertrophy. **Adipocyte hypertrophy** is characteristic of adipose tissue of obese individuals with metabolic syndrome. The prevailing theory is that engorged fat cells outstrip their vascular supply, leading to local hypoxia, **fibrosis**, adipocyte dysfunction, and cell death. Consequently, circulating lipid is deposited in peripheral non-adipose tissues that are incapable of safely storing excessive amounts of triglyceride [18–23]. Accumulated lipids, including diacylglycerols and ceramides, can ultimately impair the insulin signaling pathway and trigger insulin resistance [24,25].

Increases in fat cell number can also occur in obese individuals, resulting in the accumulation of more numerous and small adipocytes (**adipocyte hyperplasia**). 'Healthy-obese' individuals often exhibit a visceral adipose phenotype characterized by smaller and more numerous adipocytes correlated with low inflammation and fibrosis and preservation of levels of adiponectin, an anti-inflammatory adipokine that regulates lipid and glucose metabolism [26–28]. The storage of triglyceride over numerous adipocytes is believed to help limit cellular hypertrophy and the ensuing loss of adipocyte function. To date, the precise cellular origins of *de novo* differentiated adipocytes accumulating in obesity remain unclear. Furthermore, factors that control the balance between adipocyte hyperplasia and hypertrophy in an expanding fat pad remain largely unknown.

Adipose Tissue Inflammation

The discovery in the 1990s that adipose tissue produces the proinflammatory cytokine tumor necrosis factor alpha (TNF-α) sparked the concept of white adipose tissue (WAT) as an immunological organ [29]. Since then, several immune cell types have been found in the adipose tissue, including macrophages, B cells, T cells, neutrophils, eosinophils, and mast cells [30]. Immune cell populations can be found in lean animals, including T regulatory cells (Tregs) and M2 macrophages, both of which exert metabolically protective functions through the production of anti-inflammatory cytokines [31]. In obesity the abundance of immune cells increases dramatically; it is estimated that immune cells represent upwards of two-thirds of the stromal compartment of adipose tissue [32]. In histological sections of adipose tissue, clusters of immune cells can appear as crown-like structures surrounding dead or dying adipocytes [33]. In the omentum, leukocytes can be found in clusters often referred to as 'milky spots' or in other mesenteric depots as fat-associated lymphoid clusters (FALCs) [34]. The precise function of these clusters is uncertain; however, depot differences in immunological structures and composition may relate to the differential effects of anatomically distinct depots on metabolism.

Recent studies from Scherer and colleagues indicate that the acute inflammatory response in adipose tissue is essential for adipose remodeling in obesity; inhibition of adipocyte inflammatory pathways in high-fat diet-fed mice leads to a failure to adequately expand adipose tissue and impacts adipogenesis *in vivo* [35]. Thus, adipose inflammation is likely to be an adaptive response that enables safe storage of excess nutrients in adipocytes. However, chronic low-grade inflammation is now recognized as a key feature of pathological adipose expansion in obese individuals with metabolic syndrome; lower levels of adipose inflammation are observed in the metabolically healthy obese population [20,26,28,36]. As described further below, circulating proinflammatory cytokines can directly contribute to insulin resistance by interfering

Glossary

Adipocyte hyperplasia: increase in adipocyte cell number. Adipocytes are post-mitotic in adults; therefore, increases in adipocyte number are primarily a consequence of adipocyte differentiation from precursor cells.
Adipocyte hypertrophy: enlargement of adipocyte size due to increased triglyceride storage or decreased lipolysis.
Epicardial adipose tissue: adipose tissue located around the heart.
Fibrosis: formation of excessive fibrous connective tissue due to collagen deposition.
Gonadal adipose tissue: intra-abdominal WAT attached to the uterus and ovaries in females and epididymis and testis in males.
Inguinal adipose tissue: major white subcutaneous adipose tissue in rodents, located anterior to the upper region of the hindlimbs.
Mesenteric adipose tissue: visceral adipose tissue located along the intestine.
Mesothelium: monolayer of epithelial cells of mesodermal origin that lines the visceral serosa.
Omental adipose tissue: predominant visceral adipose tissue in humans, attached to the stomach and spleen. Not apparent or very small in young and older rodents, respectively.
Perirenal adipose tissue: adipose tissue located around the kidneys, containing a mixture of brown and white adipocytes.
Retroperitoneal adipose tissue: intra-abdominal WAT located on the dorsal side of the abdominal cavity.
Subcutaneous adipose tissue: WAT located just underneath the skin.
Visceral fat: the adipose tissue stored within the abdominal cavity. It is also known as intra-abdominal fat and is located inside the peritoneal cavity and between and/or around internal organs. Intra-abdominal fat comprises several different fat depots such as the omental, mesenteric, gonadal, perirenal, epicardial, and retroperitoneal adipose tissues.