The Adipose Organ

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Abstract Mammals are provided with the adipose organ, a multi-depot organ made up by adipocytes, i.e. cells whose distinctive structure allows storing large amount of lipids. White adipocytes store lipids for release as free fatty acids during fasting periods; brown adipocytes burn glucose and lipids to perform thermogenesis; pink adipocytes produce milk for pup nourishment. A range of metabolic and environmental challenges highlights the plasticity of the adipose organ. Cold induces an increase in the "brown" component of the organ to maintain the body temperature constant; during positive energy balance, the "white" component expands to store excess nutrients; finally, the "pink" component only develops in subcutaneous depots during pregnancy and lactation to ensure litter feeding. At cellular level, plasticity is due to a significant extent by direct and reversible transdifferentiation of mature adipocytes. The adipose organ secretes, and is targeted by, numerous hormones, peptides and nutrients through which interacts with the brain and other organs involved in energy balance regulation. This poses the adipose organ at a crucial point of a novel mammalian system, the nutritional system, devoted to the careful storage and use of energy to meet metabolic and behavioral challenges.

1 Adipose Tissues

All mammals are provided with adipose tissues: white (WAT) and brown (BAT). WAT is composed of white adipocytes, large and spherical cells with a very variable diameter ranging in lean adult mice from about 30 to 70 μm. In humans their dimensions are about 30–40% larger [1]. White adipocytes are characterized by the fact that contain a single large cytoplasmic lipid vacuole, which occupies about 90%

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of their volume. For this reason, the morphology of this cell is very characteristic (Fig. 1) and the residual cytoplasm forms a thin rim that also contains a squeezed crescent nucleus. In the thin rim, all the normal cytoplasmic organelles are present, generally poorly represented. The morphology of this cell is in full harmony with the functional need to supply the body with energetic molecules between meals. In fact, the spherical form of the lipid vacuole ensures maximum volume in the minimum space and the intrinsic energy of the molecules that form the lipid vacuole (mainly fatty acids) guarantees, in mammals, the possibility to survive to fasting for several weeks. Fatty acid supply to the body induces a progressive reduction of the lipid vacuole, which, in extreme cases, disappears from the cell, leaving the cell slimming down. The slimmed adipocytes look similar to fibroblasts at light microscopy, but displays a specific morphology when are observed under the electron microscope. Ultrastructurally, typical microvillous-like projections appear since the first stages of the slimming process when the cell still contain lipid droplets, and they persist even after the lipid content is disappeared.

White adipocytes produce and secrete a series of endocrine, paracrine and autocrine molecules. The most important hormones produced are leptin, asprosin

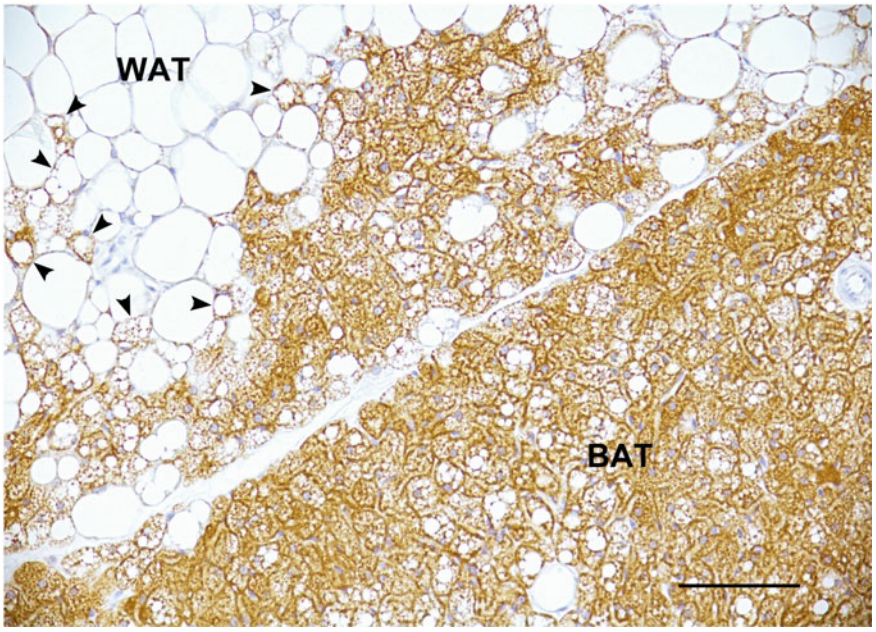


Fig. 1 UCP1 immunohistochemistry on the interscapular adipose depot from a C57BL/6 mouse exposed to cold (4 °C for 3 days). In the bottom right part of the figure, a fat lobule is made up by intensely UCP1-positive multilocular brown adipocytes, forming BAT; in the upper left corner of the figure, some UCP1-negative unilocular white adipocytes form WAT. Note the presence of white to brown transdifferentiating adipocytes (some indicated by arrowheads) in the mixed areas located between BAT and WAT. Bar: 100 μm

and adiponectin [2–4]. Leptin is a satiety hormone positively correlated to total fat mass, primarily acting on hypothalamic feeding centers. When circulating leptin levels fall down, leptin deficiency is a strong stimulus for the brain limbic system to force the individual to search for and intake food [5]. Rare individuals with genetic mutations that make leptin ineffective become massively obese for unbridled hyperphagia; recombinant leptin treatment in these patients induces a full normalization [6]. In essential obesity, there are high blood levels of leptin (correlated with the increased adipose mass), that however are not able to reduce food intake due to the establishment of brain leptin-resistance [7]. Many peripheral organs are also provided with the functional receptor for leptin [8, 9], and their location at the gonadal level could explain the reduced fertility of excessively lean subjects with low levels of leptinemia. More recently, it has been discovered that the fasted white adipose cell produces asprosin [4, 10]. This hormone stimulates hepatic gluconeogenesis and hypothalamic NPY/AgRP neurons located in the arcuate nucleus, that subsequently inhibit MC-4R (receptor of α-MSH secreted by POMC neurons) bearing neurons, mainly located in the hypothalamic PVN (paraventricular nucleus) and responsible for the satiety sensation. Subjects with a mutation of the gene that produces asprosin undergo severe partial lipodystrophy. The role of adiponectin is less clear, although numerous data indicate that its role is mainly to promote glucose metabolism and to increase insulin sensitivity in important peripheral organs such as adipose organ and the skeletal muscle [11, 12]. In contrast to leptin, this hormone is produced in inverse relation to adipocyte size and lipid content.

BAT is composed of polygonal cells of about 30–50 μm in diameter in mice (man about 30% larger) (Fig. 1). The nucleus is round and often central. Lipid vacuoles (triglycerides) are small and numerous (multilocular cell). Among the lipid vacuoles there are numerous and characteristic mitochondria (large and with laminar cristae) [13, 14]. These mitochondria are provided with a protein called UCP1 (Uncoupling Protein 1) which is uniquely expressed by these cells and plays a key role for their function [15]. UCP1 is indeed a protonophore that dissipates the electrochemical gradient created by the beta-oxidation of fatty acids into the mitochondria. The H^+ protons, derived from the oxidation of fatty acids, accumulate in the mitochondrial compartment between the two membranes. In normal cells the gradient determines a proton flow in the channel of the ATP-base enzymatic complex and the energy of the proton flow produces phosphorylation of ADP to ATP [16]. In brown adipocytes, the abundant presence of UCP1 nullifies the gradient, allowing protons to reach the matrix without forming ATP. The net consequence of this process is that the oxidation of fatty acids determines only the formation of heat (obligatory secondary effect of all oxidative processes). Since the molecules burned are many and the mitochondria are numerous, the production of heat has significant thermogenic value. During cold exposure (below the thermo-neutrality, i.e. below the temperature that requires thermogenesis and which is specific for each species, in the naked man about 28 °C) the hypothalamus activates the sympathetic system which, through nerve parenchymal fibers, reaches the brown adipocytes directly and stimulates their β3 noradrenergic receptors [17]. Downstream signaling determines the thermogenic process. Thermogenesis is particularly important for the survival of all terrestrial

mammals living in environments whose temperature is often below that required for normal cellular functioning (37 °C). The lipid multilocular arrangement of brown adipocytes ensures a high contact relationship between the lipid surface and the cellular hyaloplasm, allowing a rapid and massive mobilization of fatty acids to be burned in the numerous and large mitochondria [18]. The need for thermogenesis depends on both the environmental temperature and the volumetric conformation of the animal. The latter is related to the fact that heat dispersion depends on the volume/surface ratio for which in small mammals (rodents) is higher than in man and in newborns is higher than in adults [19]. It follows that rodents and newborns need more BAT. However, numerous data have shown that BAT is also present and functionally active in adult humans, and its amount depends on exposure to cold, age (higher in young people) and body mass index (BMI; higher in lean subjects) [20–24].

2 Anatomy of the Adipose Organ

In anatomy, organs are defined as macroscopically dissectible structures that are microscopically composed of at least two different tissues that cooperate for common functional purposes [25]. The adipose organ fulfils this definition because it is anatomically dissectible and composed by two tissues: WAT and BAT [25–29]. Its shape is very characteristic (Fig. 2) and occupies a noticeable space mainly in two anatomical compartments of the body: the subcutaneous and the intra-truncal, this latter among several thoracic and abdominal viscera. Both compartments contain the two tissues, with a great prevalence of WAT in adult humans.

In adult mice the subcutaneous component is prevalent (about 60–70%) and arranged to form two depots (anterior and posterior) located at the root of the limbs [30–32]. The anterior depot (in relation with the forelimbs) is very complex and occupies predominantly the dorsal region of the animal. In the interscapular zone, bilateral symmetrical processes extend to the subscapular, superficial cervical, deep cervical and axillary-thoracic areas from a central body. This central body is formed by WAT in the most superficial layer and by BAT in the more conspicuous deep part. The extensions are mainly formed by BAT. The posterior depot (in relation with the hindlegs) is simpler and consists of a continuous elongated depot that starts from the dorsal-lumbar region, extends in the inguinal fold to continue at the pubic level with the contralateral one. The pubic portion widens toward the back to form the gluteal component. In humans, the subcutaneous fat forms an almost continuous layer that wraps the whole body between the skin and the muscles. In the areas where the vascular-nerve bundles are pushed into the intermuscular portions of the limbs, fat also accompanies them in this compartment [33].

Inside the trunk, fat is arranged around the aorta and its main branches both in the thoracic mediastinum and the abdominal retroperitoneal space. In addition, in the abdomen and pelvis fat occupies the space within peritoneal ligaments, including mesentery, omentum, mesocolon, mesosigmoid and the parametrium.

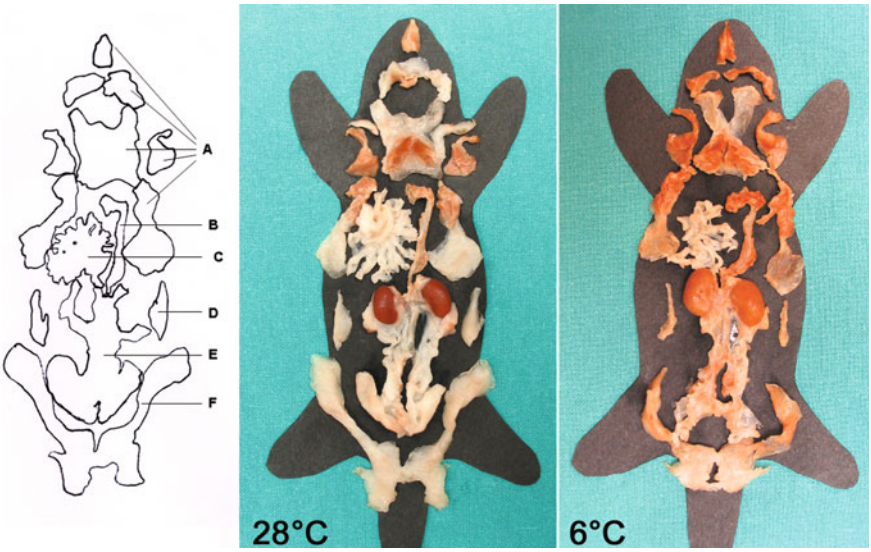


Fig. 2 The adipose organ of adult Sv129 female mice kept at 28 °C (controls) or 6 °C for 10 days. The organ was dissected with the aid of a surgical microscope and each depot was placed on a mouse template indicating its original anatomical position. Kidneys and ovaries were dissected together with the depots. The organ is made up of two subcutaneous depots: A = anterior (deep cervical, superficial cervical, interscapular, subscapular, axillo-thoracic) and F = posterior (dorso-lumbar, inguinal, gluteal) and of several visceral depots: B = mediastinal, C = mesenteric, D = retroperitoneal and E = abdomino-pelvic (perirenal, periovarian, parametrial, perivesical). Reproduced from [30] with permission

The relative amount of WAT and BAT in the adipose organ is genetically affected, but also depends on the above-mentioned conditions, i.e. environmental temperature, age and BMI. In Sv129 mice kept at 28 °C (near the thermoneutrality) about 60% of the adipose organ is formed by BAT while in C57/BL6 J mice this percentage is reduced to about 20% [32]. In adult humans there are only small amounts of BAT localized mainly in the supraclavicular region (in relation to the subclavian arteries) and in the perirenal region (in relation to the renal arteries). Importantly, exposure to cold increases the amount of active BAT even in humans [34].

In conclusion, both in mice and humans the adipose organ is a multi-depot dissectible structure formed by two anatomically and physiologically different tissues.

2.1 BAT Thermogenic Activity is Metabolically Relevant

Experiments on mice have clearly shown that BAT activation prominently counteracts obesity and related diseases [35]. In fact, a total functional inhibition of BAT

determines massive obesity in a few weeks in beta-less mice (i.e., mice genetically devoid of all beta-adrenergic receptors) even if their diet and exercise did not differ from controls. In addition, BAT activation or explants cure obesity and related diseases, prevent atherosclerosis and prolong life [36–40]. BAT activation improves the parameters of glucose metabolism even in adult men [41].

3 Cooperation Between WAT and BAT

The concept of organ implies that the different tissues it contains carry out cooperative functions for functional purposes. Thus, for example, in the stomach (dissectible organ) the muscular tissue performs peristalsis while the mucosa produces the gastric juice. Both functions cooperate for the digestive purpose.

Several experimental studies have shown that the beta-adrenergic stimulus, physiologically due to exposure to cold, causes an increase in BAT (browning) of the adipose organ (Fig. 2). Morphological, ultrastructural, morphometric, mitotic index (by BrdU) and lineage tracing studies have shown that organ browning is mainly due to direct conversion of white to brown adipocytes in a reversible fashion (Fig. 3) [42, 43]. Recent data also support an identical stem source for the two cytotypes

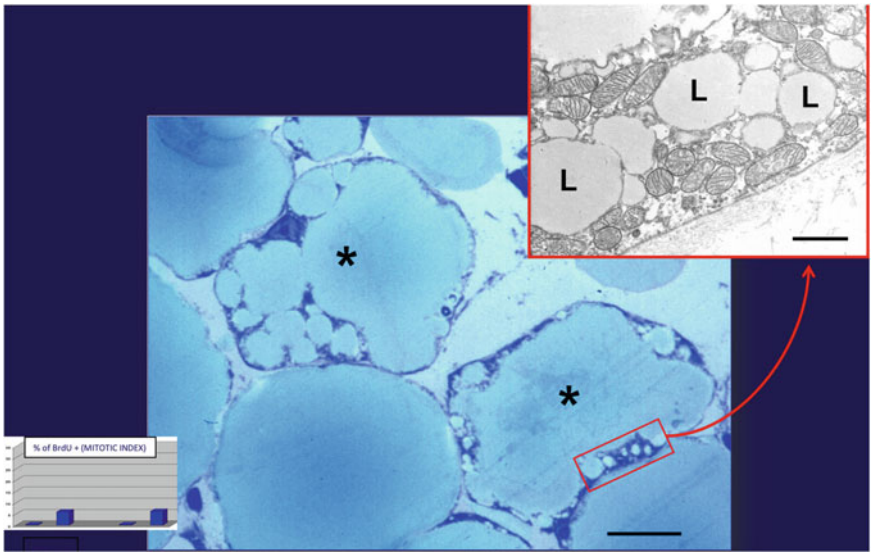


Fig. 3 Light microscopy of a resin embedded section showing two white to brown transdifferentiating adipocytes (asterisks) in the retroperitoneal depot of an old rat treated with a beta3 adrenergic agonist. In the upper right corner, the framed area is observed at transmission electron microscopy: the cytoplasmic rim of a transdifferentiating adipocyte is thick and contains numerous brown-like mitochondria and small lipid droplets (L). Bars: 10 μm, inset 2 μm. Reproduced from [42] with permission and with some modification

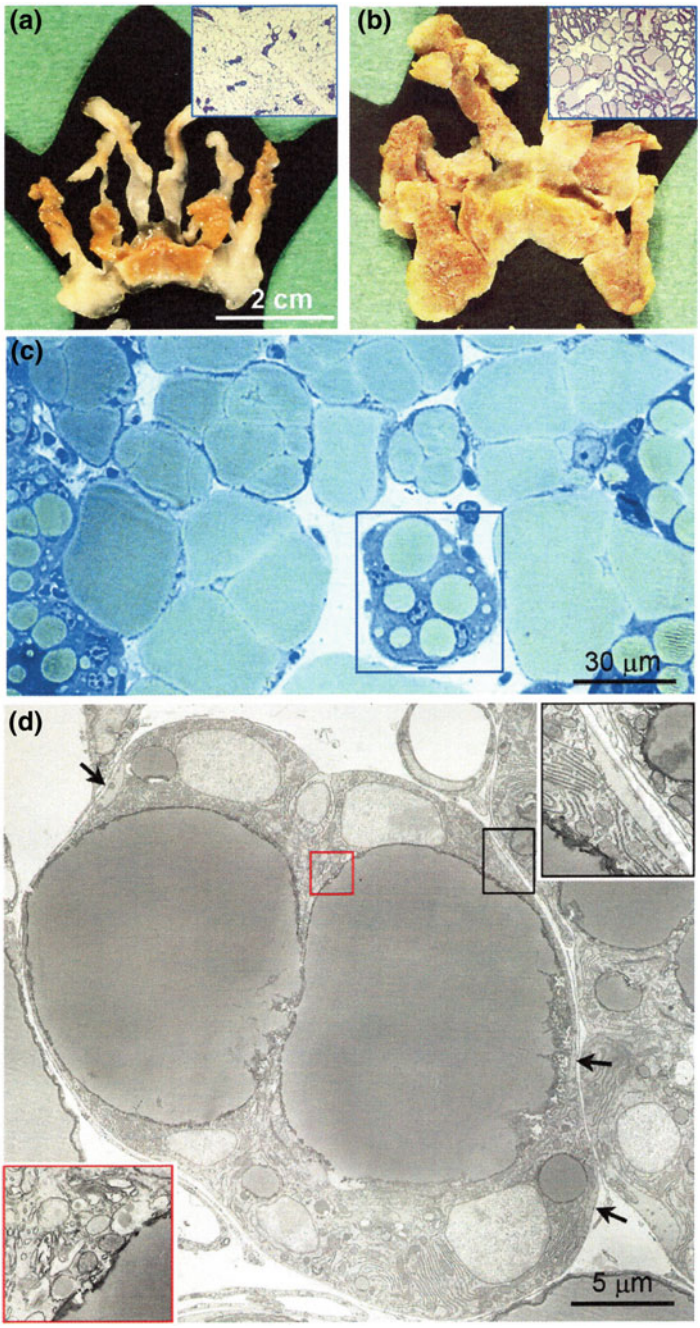
that reinforces the concept of phenotypic interchangeability [44, 45]. Importantly, this phenomenon of physiological and reversible transdifferentiation seems also to occur in adult humans [46]. It could explain the cooperation between the two tissues. When the animal is subjected to enduring sympathetic adrenergic stimulation (due, for example, to chronic cold exposure) WAT convert to BAT to increase thermogenesis; on the other hand, when the animal is subjected to chronic caloric over intake BAT turns into WAT to increase lipid storing abilities of the adipose organ, to eventually face periods of fasting.

This theory implies a new mechanism of cell physiology: the possibility that a mature cell could reprogram its genetic expression to change its structure and function [47, 48].

4 A New Example of Physiological and Reversible Transdifferentiation in the Adipose Organ

The mammary gland of non-pregnant mammals is composed of WAT (about 90% of the parenchyma) infiltrated by branched epithelial ducts that collect in a nipple. Alveoli responsible for milk production develop only during pregnancy. As the alveolar component develops, the adipose component is reduced in parallel. During lactation, about 90% of the volume of each mammary gland is composed of alveoli and ducts with almost complete disappearance of fat cells (Fig. 4). In mice, within a few hours after the end of lactation the initial anatomy is reconstituted with disappearance of the alveoli and formation of fat cells. This phenomenon of high plasticity of tissues in adult mammals has been explained by the complete delipidation and apparent disappearance of fat cells during pregnancy and lactation due to the need of high energy by the alveoli. Slimmed adipose cells would remain hidden between the glands and then re-filled with lipids at the end of lactation. Our experimental data have proposed the possibility that it is a new phenomenon of physiological and reverse transdifferentiation: adipose-epithelial during pregnancy and epithelium-adipose in post-lactation [49]. Several morphological aspects of the developing gland support this hypothesis and in particular, the fact that newly formed alveoli have a very distinctive epithelial composition. In fact, these cells, already able to produce milk proteins and with intense nuclear immunoreactivity for ELF5, the key transcription factor of alveologenesi, have their cytoplasm filled by a single large lipid vacuole that makes their morphology very similar to that of adipocytes (Fig. 4). Since the term adipocyte refer just to parenchymal cell of the adipose organ rich in lipids with no reference to their function, we have defined the epithelial cells of the newly-formed alveoli as pink adipocytes [50]. This name derives from the fact that white adipocytes occupy the white regions of the organ, brown adipocytes the brown ones and the color of the organ during pregnancy is pink.

It should be noted that in the first phase of pregnancy alveoli devoid of cytoplasmic lipids are present suggesting a double derivation: from ductal stem cells in the first


(a)
2 cm
(b)
(c)
30 µm
(d)
5 µm

◀**Fig. 4** The mammary gland is a subcutaneous fat depot with extremely plastic morphology. **a** Macroscopic appearance of the anterior mammary glands of a virgin female mouse (histological appearance shown in the inset in the upper right corner). The scale bar in panel (**a**) applies also to panel (**b**). **b** Macroscopic appearance of the same depot during lactation (histological appearance shown in the inset in the upper right corner of the panel). **c** Histological appearance of mammary gland in late pregnancy showing developing alveoli with unusual features (in the blue square) intermediate between adipocytes and glands. **d** Electron microscopy of the adipoepithelial structure highlighted in (**c**). To note, the big lipid droplets (droplets of this size are typical only of white adipocytes) are surrounded by several nuclei owning to cells with cytoplasmic evidence of milk protein containing granules (inset at the lower left corner) that are typical of milk-secreting mammary alveoli. Further evidence for the nature of this milk-secreting alveolar structure is the presence of myoepithelial cells (arrows and inset in the upper right corner) at the periphery underneath the basal membrane. Reproduced from [59] with permission

part of pregnancy and from white to pink transdifferentiation in the late pregnancy. This double alveolar population could explain the phenomenon of complete alveologenesis in the explants of ductal stem cells and that in animals without adipose tissue. Lineage tracing experiments that allow to follow the evolutionary development of genetically labelled cells and explant experiments of single mature labelled cells confirmed not only the reversible white-pink transdifferentiation, but also the pink-brown, i.e. the transformation of epithelial cells that produced milk in UCP1 immunoreactive brown adipose cells [51–53].

5 Exercise and Adipose Organ

Several experimental data have shown that physical exercise induces important changes in the anatomy of the adipose organ. The first obvious change consists in reducing the size of white adipocytes [54]. This change is in line with the need to provide the heart and muscle apparatus with energy-rich molecules. The lipolytic stimulus is driven not only by increased norepinephrine release from sympathetic nerves but is also supported by sympathetic nerve branching [55]. It is indeed possible to demonstrate in these sites an increase in the density of adrenergic fibres.

In mice and rats subjected to chronic physical exercise there is also a white-brown transdifferentiation (browning) [54]. Browning is greater with the same physical exercise if this latter is performed in a particular environment (enriched environment) that determines an increase in hypothalamic BDNF. In other words, physical exercise must be determined in a pleasant way [56]. The increase in BDNF would result in a stimulus for hypothalamic neurons responsible for the increase in activity of the sympathetic system.

The size reduction of white adipocytes is similar to that observed under fasting conditions whereas browning appears similar to the typical cold response. In both situations, the sympathetic system appears to be activated and branching of parenchymal noradrenergic nerves also occurs [54]. Notably, the similar adrenergic stimuli

determine completely different effects on white adipocytes in these two physiological conditions, likely due to different environmental hormonal changes that occur in the two conditions. Thus, physical exercise stimulus is a third physiological condition that determines a still different type of peripheral response: simultaneous lipolysis and transdifferentiation. Recent data indicate that exercise induces the production of myokines that could be involved in this particular reaction of the adipose organ. In particular, the hormone irisin determines in vitro and in vivo browning of the adipose organ [57] even if its main target seems to be the skeletal apparatus [58].

It should be noted that the simple volumetric reduction of white adipocytes has a certain beneficial effect on the organism. In fact, numerous studies suggest that adipocyte hypertrophy determines a whole series of negative consequences for health [59].

6 Obese Adipose Organ

Hypertrophic adipocytes from obese animals have visible and quantifiable organelle alterations by the electron microscope [60]. In particular, they have cholesterol crystals that are never observed in normal adipocytes. Hypertrophic adipocytes activate the NLRP3 system of inflammasome with production of caspase 1 responsible for the activation of IL-18 and IL-1β and adipocyte death by pyroptosis [60]. The hypertrophic and stressed adipocyte produces chemoattractants (predominantly MCP1) that recruit macrophages from the blood. In the obese fat, macrophages are arranged around dying adipocytes to clear their post-mortem cellular residues. Approximately 90% of the macrophages infiltrating the obese adipose tissue forms crown-like-structures (CLS) around the dead adipocyte residue that is essentially formed by the lipid vacuole (Fig. 5) [61]. The volumetric relationship between the lipid residue and the macrophages is particularly unfavorable for these latter, which also form syncytia (multinucleated giant cells) to better perform their function. This creates a situation similar to that of the foreign body reaction and causes chronic low-grade inflammation with high levels of toxic cytokine production by the macrophages themselves. In particular, TNFα, IL-6 and miRNA secreted by macrophages have a negative effect on the function of the insulin receptor, leading to insulin resistance in the liver, muscle and fat. This resistance requires an increase in the production of the hormone at the pancreatic level, which, with the passing of time, causes a functional breakdown with a consequent drastic fall of insulinemia, increase of glycemia, and consequently type 2 diabetes mellitus.

Particularly important is the fact that the critical dimension of adipocytic hypertrophy (critical death size) is different in the different compartments of the adipose organ with a particular propensity to death for low critical death size of the adipose cells of the visceral compartment [62, 63]. This data provides an explanation to the well-known clinical observation that has shown that the accumulation of visceral fat (visceral obesity) involves clinical complications far more serious than subcutaneous obesity (typical of pre-menopausal women) [64]. The simple volumetric reduction

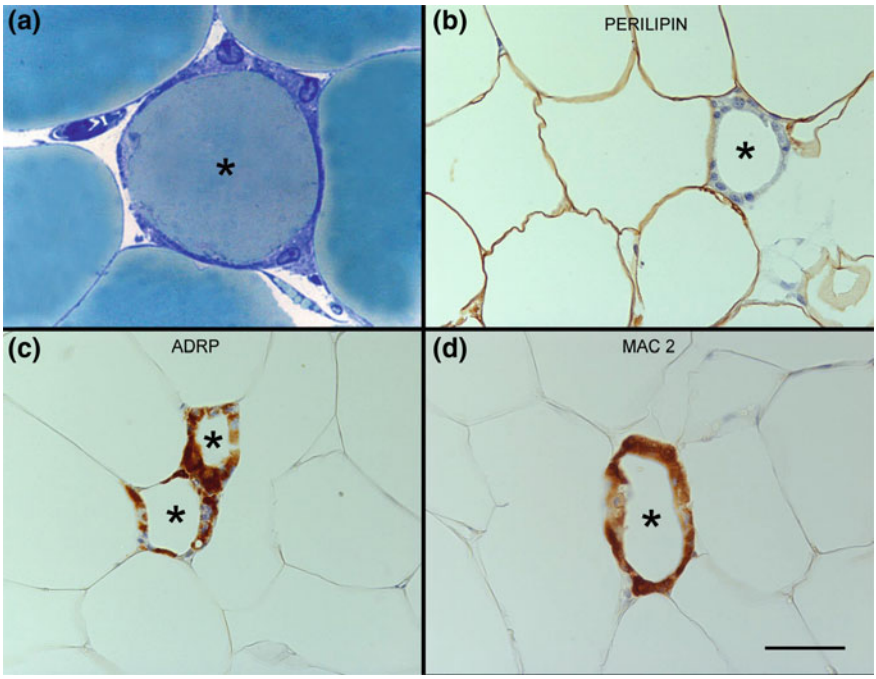


Fig. 5 WAT from obese db/db mouse showing the typical arrangement of macrophages into CLS (asterisks). Light microscopy of resin (**a**) and paraffin (**b–d**) embedded tissue. Immunohistochemistry (**b–d**) experiments demonstrate that perilipin surround all the lipid droplets within adipocytes, but not the lipid droplet in CLS (**b**), suggesting the absence here of a viable adipocyte. The cells forming the "crown" of the lipid droplets in the CLS are immunoreactive for antigens typical for lipid containing (ADRP) and active (MAC 2) macrophages. Bar = 15 μm (**a**) and 25 μm (**b–d**). Reproduced from [81] with permission

of the adipocytes obtained with physical activity therefore represents a beneficial improvement of the functional conditions of the adipose organ.

Recently it has also been discovered that physical exercise in the mouse determines a non-thermogenic activity of BAT that would produce a lipokine with healthy properties. In particular, 12.13-diHOME would favor the use of circulating fatty acids in the muscular system facilitating lipid metabolism [65]. These last data are in line with our observations that after exercise the BAT clearly shows morphological aspects suggestive of an increase in its functional activity, in the absence of increased production of UCP1 (typical thermogenic functional marker) [54]. At the time we had attributed the increase in activity to a clear increased production of MCT-1 (Mono Carboxylate Transporter: lactate transporter) demonstrated by immunohistochemistry. Therefore, the adipose organ during exercise, stimulated by the sympathetic adrenergic system, is not only devoted to partitioning fundamental energy molecules for the heart and

skeletal muscles through its "white" component, but also contributes to achieving an ideal motor performance by promoting lactate metabolism and facilitating peripheral intake of fatty acids through the action of BAT [63].

7 The Ciliary Neurotrophic Factor and the Adipose Organ

The adipose organ is not only a source of secretory products, but is also targeted by several hormones and circulating peptides that act on its "white" and/or "brown" component. Ciliary neurotrophic factor (CNTF) administration to humans and experimental animals results in decreased food intake, weight loss, and an improvement of obesity-associated hyperglycaemia, hyperinsulinaemia and dyslipidaemia (reviewed in [66]). In the hypothalamus, CNTF is distinctively produced by the tanycytes [67], ependymal cells bordering the bottom half of the third ventricle (Fig. 6a–c). Here, its expression is upregulated in high-fat diet obese mice and down regulated in mice kept in calorie restriction [68], suggesting a role for this peptide in energy balance regulation. In the brain, CNTF mainly acts on the median eminence [68] and the area postrema [69] (Fig. 6d, e), two circumventricular organs through which circulating molecules gain access to the two main nodal centers of energy balance neurocircuits, the hypothalamic arcuate nucleus and, respectively, the brainstem solitary tract nucleus. Collectively, CNTF appears to be a novel circulating factor able to affect food intake and energy balance homeostasis at both central and peripheral levels. On the adipose organ, it plays remarkable metabolic effects by inducing lipolysis in white adipocytes [70] and thermogenesis in brown adipocytes [71]. Future research will be mainly focused on further morphologic and molecular mechanisms regulating this complex organ.

8 The New Concept of a Nutritional System in Mammals

Over the past decades, the spiraling epidemic of obesity and related diseases has spurred a lot of basic research in the mechanisms controlling hunger and satiety, fat accumulation and energy expenditure, and ultimately body weight regulation. After leptin, a number of circulating hormones, nutrients and peptides that regulate energy balance through a short- and/or long-term activity have been discovered in the adipose organ, the gastrointestinal tract, and the endocrine pancreas (reviewed in [72]). Collectively, these circulating factors act on both peripheral organs and hypothalamic and brainstem energy balance neuronal centers, giving rise to an extremely complex, overlapping and redundant hormonal crosstalk.

In particular, the adipose organ cooperates with digestive organs for nutritional purposes. In fact, they both produces hormones that play a key role for inducing food search and intake: leptin and asprosin by the adipose organ [4, 10, 73] and PYY3-36

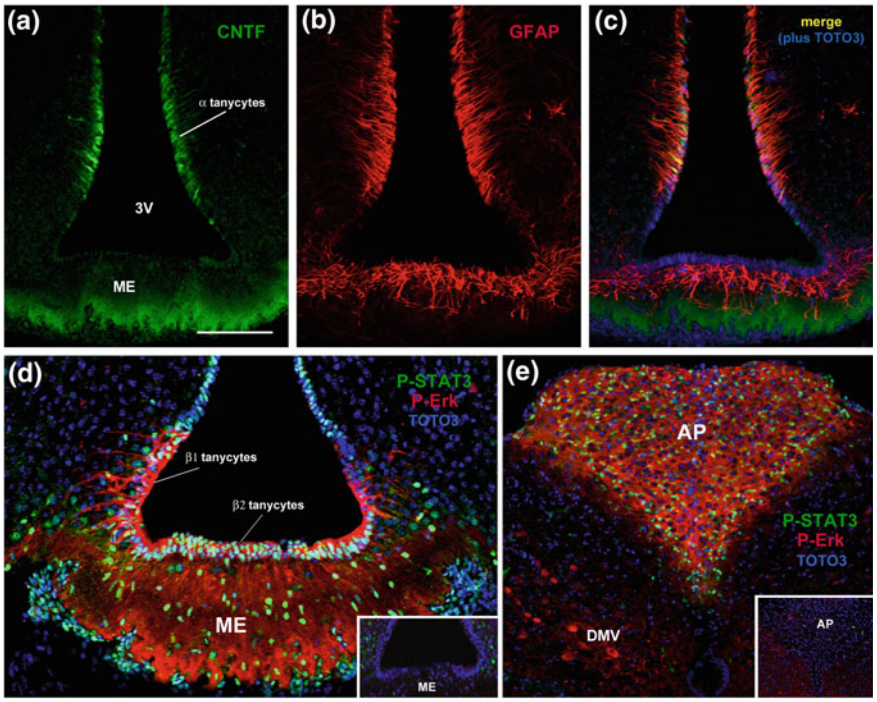


Fig. 6 Double immunofluorescent staining on mouse brain coronal sections observed under the confocal microscope. In the hypothalamus, the CNTF (**a**, green) is expressed in glial fibrillary acidic protein-positive (GFAP; **b**, red) α tanycytes, located in the ependymal layer of the bottom half of the lateral walls of the third ventricle. Treating a mouse with recombinant CNTF for 45 min leads to STAT3 (green) and Erk (red) phosphorylation/activation in numerous cells of hypothalamic median eminence (ME; **d**) and brainstem area postrema (AP; **e**). DMV, dorsal motor nucleus of the vagus nerve. Insets of **d** and **e**: corresponding sections from vehicle-injected mice. TOTO3 is a blue nuclear counterstaining. Bar: **a**–**c** 50 μm, **b** 35 μm, **d** 80 μm

[74], ghrelin [75, 76] and insulin by the digestive organs. They both are responsible for post-prandial thermogenesis that may play a role in meal interruption, especially in the neonatal period [77]. The digestive organs also produce secretin and bile acids that have been shown to exert stimulatory effects on BAT [78]. Liver and BAT are a source of FGF21 that influences the plastic properties of the adipose organ and plays a role in glucose metabolism [3]. Furthermore, their cooperation is quite evident in the uptake of energy (intestinal food uptake) and storage and distribution (adipose organ), including distribution to pups (pink adipocytes) [50].

In conclusion, the Adipose Organ, with its storage and endocrine abilities, continuously interacts with the central nervous system and energy balance regulating peripheral organs and tissues for nutritional purposes. It is a true important organ, playing a key role in a supra-organ novel system that can be denominated the mammalian nutritional system [79–81].

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References

1. Cinti S (2018) Adipose Organ development and remodeling. Compr Physiol 8:1357–1431
2. Giralt M, Cereijo R, Villarroya F (2015) Adipokines and the endocrine role of adipose tissues. In: Herzig S (ed) Metabolic control. Handbook of experimental pharmacology. Springer, pp 265–282
3. Villarroya F, Cereijo R, Villarroya J et al (2017) Brown adipose tissue as a secretory organ. Nat Rev Endocrinol 13:26–35
4. Duerrschmid C, He Y, Wang C et al (2017) Asprosin is a centrally acting orexigenic hormone. Nat Med 23:1444–1453
5. Friedman J (2016) The long road to leptin. J Clin Invest 126:4727–4734
6. Farooqi IS, Jebb SA, Langmack G et al (1999) Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med 341:879–884
7. Maffei M, Halaas J, Ravussin E et al (1995) Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med 1:1155–1161
8. De Matteis R, Cinti S (1998) Ultrastructural immunolocalization of leptin receptor in mouse brain. Neuroendocrinology 68:412–419
9. De Matteis R, Dashtipour K, Ognibene A et al (1998) Localization of leptin receptor splice variants in mouse peripheral tissues by immunohistochemistry. Proc Nutr Soc 57:441–448
10. Romere C, Duerrschmid C, Bournat J et al (2016) Asprosin, a fasting-induced glucogenic protein hormone. Cell 165:566–579
11. Scherer PE (2014) Adiponectin: basic and clinical aspects. Preface. Best Pract Res Clin Endocrinol Metab 28:1–2
12. Matsuzawa Y (2010) Adiponectin: a key player in obesity related disorders. Curr Pharm Des 16:1896–1901
13. Cinti S (2006) The role of brown adipose tissue in human obesity. Nutr Metab Cardiovasc Dis 16:569–574
14. Cinti S (2011) Between brown and white: novel aspects of adipocyte differentiation. Ann Med 43:104–115
15. Ricquier D (2017) UCP1, the mitochondrial uncoupling protein of brown adipocyte: a personal contribution and a historical perspective. Biochimie 134:3–8
16. Trayhurn P, Nicholls D (1986) Brown Adipose Tissue, Edward Arnold
17. Cannon B, Nedergaard J (2017) What ignites UCP1? Cell Metab 26:697–698
18. Nedergaard J, Lindberg O (1982) The brown fat cell. Int Rev Cytol 74:187–286
19. Himms-Hagen J (1986) Brown adipose tissue and cold-acclimation. In: Trayhurn P, Nicholls D (eds) Brown adipose tissue. Edward Arnold, p 214

20. Zingaretti MC, Crosta F, Vitali A et al (2009) The presence of UCP1 demonstrates that metabolically active adipose tissue in the neck of adult humans truly represents brown adipose tissue. FASEB J 23:3113–3120
21. Virtanen KA, Lidell ME, Orava J et al (2009) Functional brown adipose tissue in healthy adults. N Engl J Med 360:1518–1525
22. Cypess AM, Lehman S, Williams G et al (2009) Identification and importance of brown adipose tissue in adult humans. N Engl J Med 360:1509–1517
23. Saito M, Okamatsu-Ogura Y, Matsushita M et al (2009) High incidence of metabolically active brown adipose tissue in healthy adult humans: effects of cold exposure and adiposity. Diabetes 58:1526–1531
24. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM et al (2009) Cold-activated brown adipose tissue in healthy men. N Engl J Med 360:1500–1508
25. Cinti S (2018) Obesity, type 2 diabetes and the adipose organ. Springer
26. Cinti S (1999) The adipose organ. Kurtis
27. Cinti S (2001) The adipose organ: endocrine aspects and insights from transgenic models. Eat Weight Disord 6(3 Suppl):4–8
28. Cinti S (2001) The adipose organ: morphological perspectives of adipose tissues. Proc Nutr Soc 60:319–328
29. Cinti S (2005) The adipose organ. Prostaglandins Leukot Essent Fatty Acids 73:9–15
30. Murano I, Zingaretti MC, Cinti S (2005) The adipose organ of Sv129 mice contains a prevalence of brown adipocytes and shows plasticity after cold exposure. Adipocytes 1:121–130
31. Cinti S (2012) The adipose organ at a glance. Dis Model Mech 5:588–594
32. Vitali A, Murano I, Zingaretti MC et al (2012) The adipose organ of obesity-prone C57BL/6 J mice is composed of mixed white and brown adipocytes. J Lipid Res 53:619–629
33. Cinti S, Vettor R (2010) The adipose organ. In: Awad AB, Bradford PG (eds) Adipose tissue and inflammation. Taylor & Francis, pp 1–22
34. Kajimura S, Saito M (2014) A new era in brown adipose tissue biology: molecular control of brown fat development and energy homeostasis. Annu Rev Physiol 76:225–249
35. Bachman ES, Dhillon H, Zhang CY et al (2002) betaAR signaling required for diet-induced thermogenesis and obesity resistance. Science 297:843–845
36. Ghorbani M, Claus TH, Himms-Hagen J (1997) Hypertrophy of brown adipocytes in brown and white adipose tissues and reversal of diet-induced obesity in rats treated with a beta3-adrenoceptor agonist. Biochem Pharmacol 54:121–131
37. Seale P, Conroe HM, Estall J et al (2011) PRDM16 determines the thermogenic program of subcutaneous white adipose tissue in mice. J Clin Invest 121:96–105
38. Bartelt A, Bruns OT, Reimer RA et al (2011) Brown adipose tissue activity controls triglyceride clearance. Nat Med 17:200–205
39. Berbée JF, Boon MR, Khedoe PP et al (2015) Brown fat activation reduces hypercholesterolaemia and protects from atherosclerosis development. Nat Commun 6:6356
40. Ortega-Molina A, Efeyan A, Lopez-Guadamillas E et al (2012) PTEN positively regulates brown adipose function, energy expenditure, and longevity. Cell Metab 15:382–394
41. Chondronikola M, Volpi E, Børsheim E et al (2014) Brown adipose tissue improves whole-body glucose homeostasis and insulin sensitivity in humans. Diabetes 63:4089–4099
42. Himms-Hagen J, Melnyk A, Zingaretti MC et al (2000) Multilocular fat cells in WAT of CL-316243-treated rats derive directly from white adipocytes. Am J Physiol Cell Physiol 279:C670–C681
43. Rosenwald M, Perdikari A, Rülicke TM et al (2013) Bi-directional interconversion of brite and white adipocytes. Nat Cell Biol 15:659–667
44. Gupta RK, Kleiner S et al (2012) Isolation and localization of committed primary preadipocytes through Zfp423. Cell Metab 15:230–239
45. Tran KV, Gealekman O, Frontini A et al (2012) The vascular endothelium of the adipose tissue gives rise to both white and brown fat cells. Cell Metab 15:222–229

46. Frontini A, Vitali A, Perugini J et al (2013) White-to-brown transdifferentiation of omental adipocytes in patients affected by pheochromocytoma. Biochim Biophys Acta 1831:950–959
47. Cinti S (2009) Reversible physiological transdifferentiation in the adipose organ. Proc Nutr Soc 68:340–349
48. Cinti S (2009) Transdifferentiation properties of adipocytes in the adipose organ. Am J Physiol Endocrinol Metab 297:E977–E986
49. Morroni M, Giordano A, Zingaretti MC et al (2004) Reversible transdifferentiation of secretory epithelial cells into adipocytes in the mammary gland. Proc Natl Acad Sci USA 101:16801–16806
50. Cinti S (2018) Pink Adipocytes. Trends Endocrinol Metab 29:651–666
51. De Matteis R, Zingaretti MC, Murano I et al (2009) In vivo physiological transdifferentiation of adult adipose cells. Stem Cells 27:2761–2768
52. Prokesch A, Smorlesi A, Perugini J et al (2014) Molecular aspects of adipoepithelial transdifferentiation in mouse mammary gland. Stem Cells 32:2756–2766
53. Giordano A, Perugini J, Kristensen DM et al (2017) Mammary alveolar epithelial cells convert to brown adipocytes in post-lactating mice. J Cell Physiol 232:2923–2928
54. De Matteis R, Lucertini F, Guescini M et al (2013) Exercise as a new physiological stimulus for brown adipose tissue activity. Nutr Metab Cardiovasc Dis 23:582–590
55. Murano I, Barbatelli G, Giordano A et al (2009) Noradrenergic parenchymal nerve fiber branching after cold acclimatisation correlates with brown adipocyte density in mouse adipose organ. J Anat 214:171–178
56. Cao L, Choi EY, Liu X et al (2011) White to brown fat phenotypic switch induced by genetic and environmental activation of a hypothalamic-adipocyte axis. Cell Metab 14:324–338
57. Boström P, Wu J, Jedrychowski MP et al (2012) A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 481:463–468
58. Colaianni G, Mongelli T, Cuscito C et al (2017) Irisin prevents and restores bone loss and muscle atrophy in hind-limb suspended mice. Sci Rep 7:2811
59. Smorlesi A, Frontini A, Giordano A et al (2012) The adipose organ: white-brown adipocyte plasticity and metabolic inflammation. Obes Rev 13(Suppl 2):83–96
60. Giordano A, Murano I, Mondini E et al (2013) Obese adipocytes show ultrastructural features of stressed cells and die of pyroptosis. J Lipid Res 54:2423–2436
61. Cinti S, Mitchell G, Barbatelli G et al (2005) Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. J Lipid Res 46:2347–2355
62. Murano I, Barbatelli G, Parisani V et al (2008) Dead adipocytes, detected as crown-like structures, are prevalent in visceral fat depots of genetically obese mice. J Lipid Res 49:1562–1568
63. Kotzbeck P, Giordano A, Mondini E et al (2018) Brown adipose tissue whitening leads to brown adipocyte death and adipose tissue inflammation. J Lipid Res 59:784–794
64. Bjorntorp P (1993) Visceral obesity: a “civilization syndrome”. Obes Res 1:206–222
65. Stanford KI, Lynes MD, Takahashi H et al (2018) 12, 13-diHOME: An exercise-induced lipokine that increases skeletal muscle fatty acid uptake. Cell Metab 27:1111–1120
66. Pasquin S, Sharma M, Gauchat JF (2016) Cytokines of the LIF/CNTF family and metabolism. Cytokine 82:122–124
67. Severi I, Carradori MR, Lorenzi T et al (2012) Constitutive expression of ciliary neurotrophic factor in mouse hypothalamus. J Anat 220:622–631
68. Severi I, Perugini J, Mondini E et al (2013) Opposite effects of a high-fat diet and calorie restriction on ciliary neurotrophic factor signaling in the mouse hypothalamus. Front Neurosci 7:263
69. Senzacqua M, Severi I, Perugini J et al (2016) Action of administered ciliary neurotrophic factor on the mouse dorsal vagal complex. Front Neurosci 10:289
70. Zvonic S, Cornelius P, Stewart WC et al (2003) The regulation and activation of ciliary neurotrophic factor signaling proteins in adipocytes. J Biol Chem 278:2228–2235
71. Ott V, Fasshauer M, Dalski A et al (2002) Direct effects of ciliary neurotrophic factor on brown adipocytes: evidence for a role in peripheral regulation of energy homeostasis. J Endocrinol 173:R1–R8

72. Giordano A, Nisoli E (2018) Neuroendocrinology of energy balance. In: Sbraccia P, Finer N (eds) Obesity. Springer, Cham
73. Zhang Y, Proenca R, Maffei M et al (1994) Positional cloning of the mouse obese gene and its human homologue. Nature 372:425–432
74. Batterham RL, Bloom SR (2002) Gut hormone PYY(3-36) physiologically inhibits food intake. Nature 418:650–654
75. Howard AD, Feighner SD, Cully DF et al (1996) A receptor in pituitary and hypothalamus that functions in growth hormone release. Science 273:974–977
76. Müller TD, Nogueiras R, Andermann ML et al (2015) Ghrelin. Mol Metab 4:437–460
77. Himms-Hagen J (2006) Thermoregulatory feeding in newborn infants: an update. Obesity 14:1479–1480
78. Li Y, Schnabl K, Gabler SM et al (2018) Secretin-activated brown fat mediates prandial thermogenesis to induce satiation. Cell 175:1561–1574
79. Cinti S (2019) Anatomy and physiology of the nutritional system. Mol Asp Med 68:101–107
80. Cinti S (2018) The adipose organ. In: Sbraccia P, Nisoli E (eds) Obesity. Springer, Cham
81. Cinti S (2006) Morphology of the inflammatory state of the adipose organ in obese mice and humans. Obes Metab 2:95–103