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Anatomy and physiology of the nutritional system

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ABSTRACT

The organisms of mammals are composed of organs cooperating as systems that are organized to perform functions which allow the survival of the individual and maintenance of the species. Thus, to reach the main goals of these functions we need systems that ensure nutrient uptake and distribution, thermogenesis, oxygen uptake and distribution, the discharge of toxic internal by-products, the defense from internal and external pathogens, gamete fertilization, and the fine-tuning of the activity of all the tissues composing the organs. Most of these activities also require interactions with the internal and external environment. The latter function is served by the nervous system and the others by the cardiovascular, respiratory, excretory, immune, reproductive and endocrine systems. Nutrient intake and distribution and thermoregulation are realized by the collaborative work of the adipose and the digestive organs. In this review I will outline data on adipose tissue anatomy and function which have been collected during the past 40 years. They provide a convergent body of evidence toward a new concept regarding the collaborative work between the adipose organ and the organs of the gastrointestinal tract, which constitute a system ensuring nutrient search, intake and distribution to the organism. Furthermore, the same system also seems to enable nutrient distribution to the offspring to ensure not only short-term but also long-term homeostasis.

1. Anatomy and physiology of the adipose tissues

The term adipocyte describes the anatomical characteristics of cells that are capable of storing large amounts of lipids. It is widely recognized that this definition indicates two widely different cell types, white and brown adipocytes. Although both contain large amounts of lipids, white and brown adipocytes play different and almost opposite functions.

1.1. White adipose tissue

White adipocytes are large (70–140 μm in diameter), spherical cells whose cytoplasm contains a unilocular lipid droplet which accounts for about 90% of the cell volume (Figs. 1 and 2). The spherical shape – which is due to the fact that this is the geometrical figure that accommodates the largest volume in the smallest space – achieves the main goal of this cell: to provide a reservoir of energy capable of ensuring energy distribution to the rest of organism in the intervals between meals (Cinti, 2018a). The lipids contained in white adipocytes are triglycerides. These high-energy molecules are the ideal fuel for the heart, whose continuing function is essential for the survival of the organism. But, right after the heart, the brain also needs feeding. This is achieved through a mechanism whereby fasting induces the secretion of asprosin by white adipocytes; in turn, this protein induces hepatic glucogenesis, thus providing fuel for the brain (Romere et al., 2016; Duerrschmid et al., 2017; Rosen and Spiegelman, 2014; Cohen and Spiegelman, 2016; Tontonoz and Spiegelman, 2008). White adipose tissue (WAT) is also the main production site of the hormone leptin (Friedman, 2016) by mature adipocytes; leptinemia positively correlates with the total amount of fat contained in the body (Maffei et al., 1995). When the fat stores are low, and insufficient to ensure survival, low leptinemia triggers a strong stimulus which, combined with asprosin secretion, induces food search and feeding behaviors. The widespread distribution of leptin receptors in several key areas of the limbic system supports the idea that leptin plays a central role in the food search behavior (De Matteis and Cinti, 1998). The role of other hormones produced by WAT is less clear-cut and has recently been reviewed elsewhere (Cohen and Spiegelman, 2016; Cinti, 2018b).

1.2. Brown adipose tissue

Brown adipocytes are about one third smaller than white adipocytes and contain numerous, small lipid droplets (Figs. 1 and 2). The reason for the multilocular distribution of lipids in these cells is that brown

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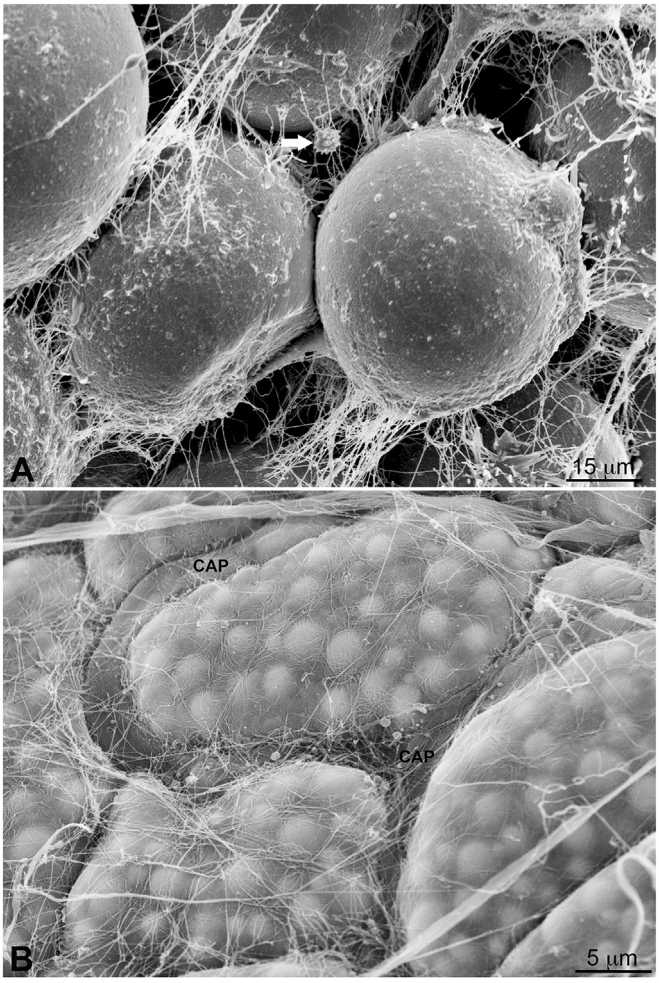

Fig. 1. Scanning electron microscopy image of white (WAT) and brown (BAT) adipose tissue of a CD1 mouse maintained at 6 °C for 24 h. A-WAT composed of spherical unilocular cells. Note a resident macrophage (arrow). B-BAT composed of polygonal multilocular cells surrounded by capillaries (CAP).

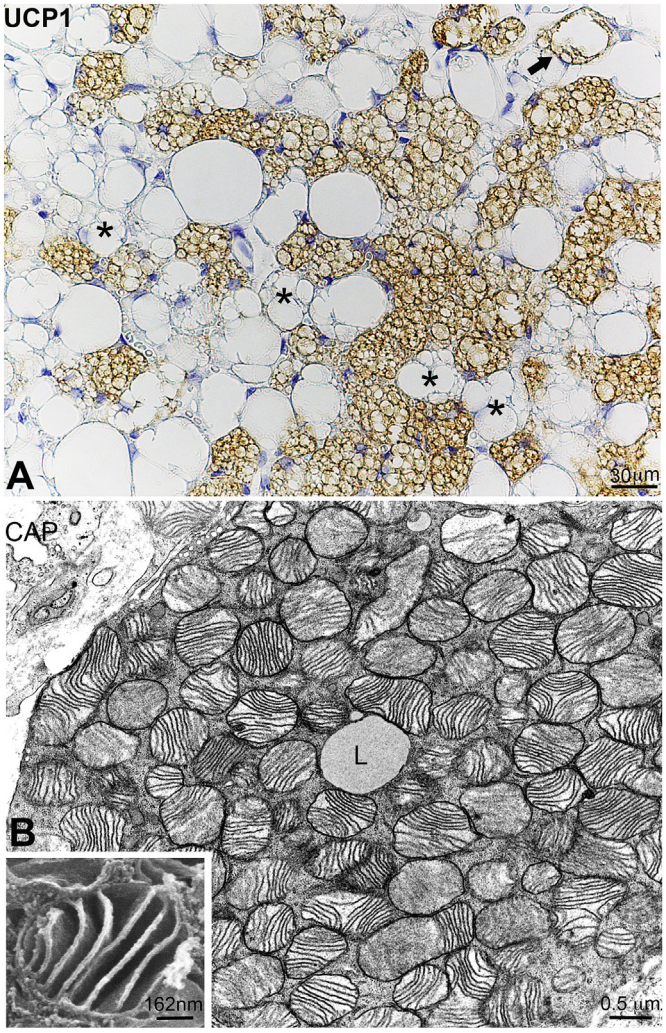

Fig. 2. Immunohistochemistry and transmission electron microscopy images of adipocytes. A-Mixed area in the anterior subcutaneous depot of an Sv129 mouse maintained at 6 °C for 5 days. Immunohistochemistry with anti-UCP1 antibodies. Only multilocular brown adipocytes show staining. Several cells in a transitional stage between the white and brown phenotype (some indicated by an asterisk) are all UCP1-negative. A single cell with an intermediate (paucilocular) phenotype is UCP1-positive (arrow, upper right corner). B-Transmission electron microscopy image of the interscapular BAT of a 4-day-old rat. Cytoplasm of a brown adipocyte filled with typical mitochondria packed with laminar cristae. The 3D image of a mitochondrion in a high-resolution scanning microscopy micrograph (inset) allows appreciating the laminar extension of the cristae. L: lipid droplet, CAP: capillary. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

adipocytes contain special mitochondria, which burn fatty acids to produce heat (Cannon and Nedergaard, 2004; Seale et al., 2009; Kajimura et al., 2010; Kozak, 2014). The wide lipid-cytoplasm contact surface, due to the multilocular distribution of lipids, and the presence of uncoupling protein 1 (UCP1) on the inner membrane of their large mitochondria, which are packed with laminar cristae, are the key factors underpinning the thermogenic activity of brown adipocytes (Cinti et al., 1989). Cold exposure activates neurons in the dorsomedial hypothalamic nucleus, triggering sympathetic nervous system (SNS) activity – i.e. a noradrenergic stimulus for brown adipocyte beta3 adrenergic receptors – through synaptoid contacts among parenchymal nerve endings and brown adipocytes (Trayhurn and Nicholls, 1986; Stock, 2003). The temperature at which the SNS is activated to produce heat (thermoneutrality) varies among species: for example, it is about 34 °C in mice, about 28 °C in rats and naked humans, and about 22 °C in clothed humans (Cannon and Nedergaard, 1986). The adrenergic signaling has two major effects: the synthesis and activation of UCP1 (Himms-Hagen et al., 1986); the latter function may be due to the fatty acids produced by the intense lipolysis taking place on the extensive multilocular lipid surface (Cannon and Nedergaard, 2004; Nedergaard et al., 1983; Sadurskis et al., 1995). Fatty acid oxidation by mitochondria induces a proton gradient between the external and the internal mitochondrial compartment (Ricquier, 1989). UCP1 is found in the membrane forming the laminar cristae and separating the two compartments. In coupled cells (lacking UCP1) the proton gradient results in ATP formation via exploitation of the energy of the proton flux through the enzyme channel formed by ATPase, which is also found on mitochondrial cristae (Ricquier, 2017). In brown adipocytes UCP1 acts as a protonophore, providing an alternative way for protons to reach the internal mitochondrial compartment and to uncouple fatty acid oxidation from ADP phosphorylation (Klaus et al., 1991; Collins and Surwit, 2001). The result of the uncoupling process is heat production, due to the inevitable side effect of fatty acid oxidation (Cannon and Nedergaard, 1978, 1985, 2004). Given the large amount of fatty acids that are oxidized in the large, numerous brown adipocyte mitochondria, heat production plays a physiological role, enabling survival in cold climates. For example, since in Greenland musk-ox cows usually calve in April, newborns face an extreme change in environmental temperature, from about 39 °C to about −30 °C, and need to be

capable of efficient heat production (Trayhurn and Nicholls, 1986).

WAT and brown adipose tissue (BAT) have quite a different vascular and nerve supply. It has been calculated that the density of capillaries in BAT is about six-fold greater than in WAT (Nechad et al., 1986). The difference is easily explained by the large amount of oxygen required by the high oxidative rate of BAT and by the need for swift transfer of the heat to the rest of the organism. Furthermore, fast heat distribution can also prevent thermal damage to tissues. As a matter of fact, acutely activated BAT shows a characteristic patchy UCP1 immunostaining pattern (Harlequin phenomenon) (Cinti et al., 2002). The phenomenon seems to be due to the expression of heat shock proteins by the cells endowed with high UCP1 expression, and suggests that heat production should be blocked to avoid cell damage. In line with this hypothesis, during chronic BAT activation UCP1 immunoreactivity is more homogeneous and less intense.

This different UCP1 immunostaining pattern seen in BAT may also be a consequence of the diverse parenchymal nerve density described in animals exposed to different temperatures. In fact, parenchymal nerve density as measured by PGP 9.5, a general marker of peripheral fibers, has been reported to undergo a 50% reduction in BAT of adult rats maintained at 28 °C for two weeks and a reduction of about 30% in those kept at 20 °C compared to rats maintained at 4 °C for two weeks. The density of noradrenergic parenchymal fibers – which are immunoreactive for tyrosine hydroxylase (TH) – decreased even more, respectively by 95% and 90% at 28 °C and 20 °C (Murano et al., 2009; Vitali et al., 2012).

WAT also shows parenchymal innervation, but it is much less dense (Trayhurn and Ashwell, 1987). Fasting induces an increased density of parenchymal fibers, which are mainly TH-immunoreactive (Giordano et al., 2005).

Human WAT and BAT share the morphological and functional characteristics described above (Lean and James, 1986; Heaton, 1972; Huttunen et al., 1981; Zingaretti et al., 2009), and human adipocytes are larger (about 30%) than those of small mammals (Cinti, 2018a).

2. The adipose organ

The adipose tissues are contained in a dissectible organ, the adipose organ (Fig. 3), which is subdivided into two compartments, the subcutaneous and the intratruncal (or visceral) (Cinti, 1999; Cinti et al., 2018).

In humans, the subcutaneous portion appears as a continuous layer extending between the cutis and the muscles, whereas in mice it forms two large depots found at the root of the hind legs. The intratruncal portion consists of mediastinal, abdominal, and pelvic depots. Most of the mediastinal depot is found around the aorta and its main branches. The abdominal portion forms a large, complex depot including perirenal, mesenteric, periovarian, parametrial, retroperitoneal, and perivesical portions. Clearly, the periovarian and parametrial depots are found only in females, whereas in males the continuity between the perirenal and the pelvic depot is ensured by periureteral fat. Males also have a large epididymal depot. A small depot at the level of the large curvature of the stomach is found in both males and females.

In small mammals several depots are mixed BAT and WAT areas. Accurate quantitative studies have demonstrated that in animals kept in a warm environment (28 °C) BAT is the predominant tissue (about 60%) in obesity-resistant Sv129 mice, whereas WAT is the predominant tissue (about 80%) in obesity-prone C57/BL6 (B6) mice (Vitali et al., 2012; Murano et al., 2005).

The main BAT depot is the one contained in the deep interscapular area, which also shows extensions into the subscapular, cervical, and axillary areas of the anterior subcutaneous depot.

In the visceral compartment, BAT is mostly found at the thoracic and abdominal level around the aorta and its main branches, which enable heat to be rapidly distributed to the rest of the body.

In adult humans the adipose organ is mainly white, although remnants of metabolically active BAT have been identified, mainly in the supraclavicular area close to the aortic arch branches (Cypess et al., 2009; Saito et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009; Enerback, 2010; Cypess et al., 2015; Cypess and Kahn, 2010).

2.1. The plasticity of the adipose organ

The literature does not provide a univocal definition of an organ. However, I think that it may be defined by combining several aspects of widely accepted definitions, as “an anatomically dissectible structure endowed with specific functions and composed of at least two different tissues that cooperate reciprocally to achieve a unitary functional purpose” (Cinti, 2018b). A structure that is widely considered as an organ is the stomach, which in fact meets the above definition: it is dissectible and it consists of multiple tissues (muscle and mucosa) that clearly cooperate in the digestion process. The stomach also has other functions, such as control of food intake through hormone (ghrelin, leptin) secretion and meal size control through activation of neural afferents.

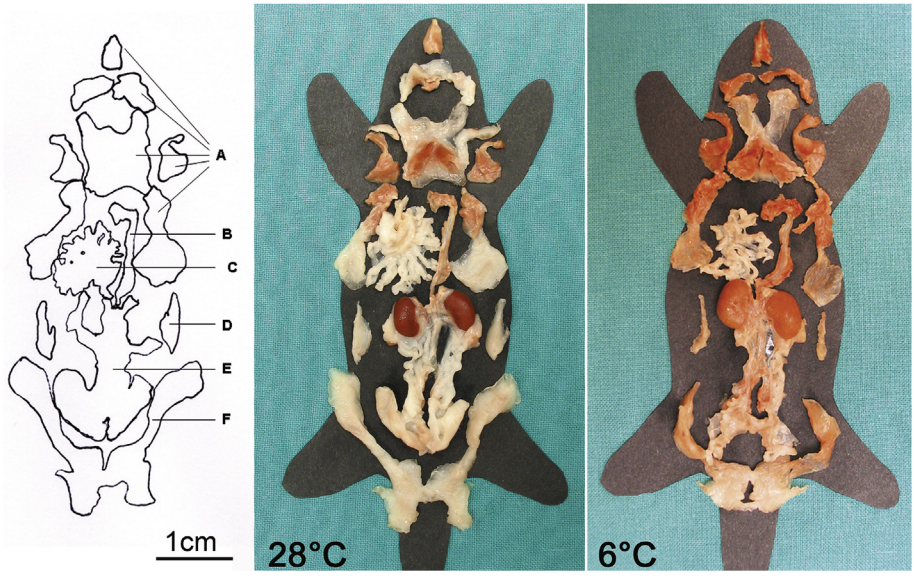

Fig. 3. Gross anatomy of the adipose organ of an adult female Sv129 mouse. The kidneys and ovaries are left in situ for orientation. 28°C-Mouse maintained at 28 °C for 10 days. A: anterior subcutaneous depot; white areas are found only around interscapular fat, in the superficial cervical projections, and in the thoracic extension of the axillary-thoracic projections. The deep cervical and subscapular projections are all brown. B: mediastinal periaortic fat (brown). C: mesenteric fat (white). D: retroperitoneal depot (white). E: abdominopelvic depot – composed of inter-renal (pale brown), periovarian (white), parametrial (white), and perivesical (white) portions. F: posterior subcutaneous depot – composed of symmetric dorsolumbar, inguinal, and gluteal portions (all white). 6°C-Mouse maintained at 6 °C for 10 days. Most areas of the adipose organ are brown (browning phenomenon). (From Murano et al. Adipocytes 2005, with permission). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

As regards the adipose organ, it is dissectible and is composed of WAT and BAT, which have several distinct functions including the distribution of energy molecules to the organism (to ensure survival during fasting), thermogenesis, and the behavioral control of food search and feeding through the secretion of hormones (leptin, asprosin).

In my view, the reciprocal cooperation of WAT and BAT consists in their ability to convert reversibly into one other in physiological conditions, a process that is called transdifferentiation. According to a large number of studies, several stimuli can modify the composition of the adipose organ, which may become more brown (browning) (Fig. 3) or more white (whitening). Detailed investigation of browning in Sv129 and B6 mice showed that after ten days of cold exposure the BAT component had increased and the WAT component had decreased in both strains, although the total number of adipocytes in the organ had remained unchanged (Vitali et al., 2012; Murano et al., 2005). Interestingly, in either strain the WAT decrease matched the BAT increase, suggesting that WAT had converted directly to BAT and confirming earlier findings, which have recently been reviewed (Cinti, 2018b; Himms-Hagen et al., 2000; Granneman et al., 2005; Barbatelli et al., 2010; Cousin et al., 1992; Collins et al., 2014; Mao et al., 2017; Rosenwald et al., 2013; Mercader et al., 2006; Fuster et al., 2008).

The clearest data documenting the reverse phenomenon, BAT whitening, in physiological conditions have been provided by aging and obesity research (Cinti et al., 1997; Sbarbati et al., 1991; Morroni et al., 1995; Lecoultre and Ravussin, 2011). BAT whitening due to aging probably depends on reduced SNS activity, as demonstrated by prompt browning of whitened BAT in cold-exposed old rats (Morroni et al., 1995) and by clear BAT whitening in beta-less mice (Bachman et al., 2002). The accumulation of energy molecules in BAT, due to a chronic intake of excess calories, can be considered as an example of physiological whitening (Cinti et al., 1997; Cancello et al., 1998), because even excess energy is too valuable to be destroyed and is thus stored against a possible future fasting period.

Thus, a converging body of evidence seems to suggest that a physiological stimulus can induce a reversible change in the phenotype and function of a mature cell. To find support for this novel basic cell property, we looked for other instances of plasticity and found another striking example, again in the adipose organ: the mammary gland.

2.2. The pink adipocyte

The mammary gland functions as a true gland only during pregnancy and lactation, because its glandular portion, the milk-producing alveoli, develop only at this time and then disappear after the end of lactation (Robinson et al., 1995; Masso-Welch et al., 2000; Richert et al., 2000). In all the other periods of life, it consists of fat infiltrated by branched ducts that converge into a nipple. The alveolar cells derive from luminal progenitors contained in the ducts; however, their morphology points at another possible origin: direct adipocyte conversion (Fig. 4). Comparison of newly-formed alveoli found in early and late pregnancy has shown that the main morphological difference lies in the amount of lipids that are stored in their cytoplasm. All the alveolar epithelial cells found in late pregnancy are immunoreactive for late differentiation markers – such as whey acidic protein (WAP) and the nuclear transcription factor E74-like factor5 (ELF5, a key regulator of alveologenesis) – and contain an exceptional (for epithelial cells) amount of lipids in a single cytoplasmic vacuole, a morphology that is reminiscent of unilocular adipocytes (Morroni et al., 2004; De Matteis et al., 2009; Prokesch et al., 2014).

Since during pregnancy the mammary gland has a pink color, and since the term adipocyte merely describes a lipid-rich parenchymal cell of the adipose organ, irrespective of its function, we decided to call these epithelial cells pink adipocytes (Giordano et al., 2014; Cinti, 2018c). The reversible conversion of white to pink adipocytes and of pink to brown adipocytes is supported by electron microscopy studies,

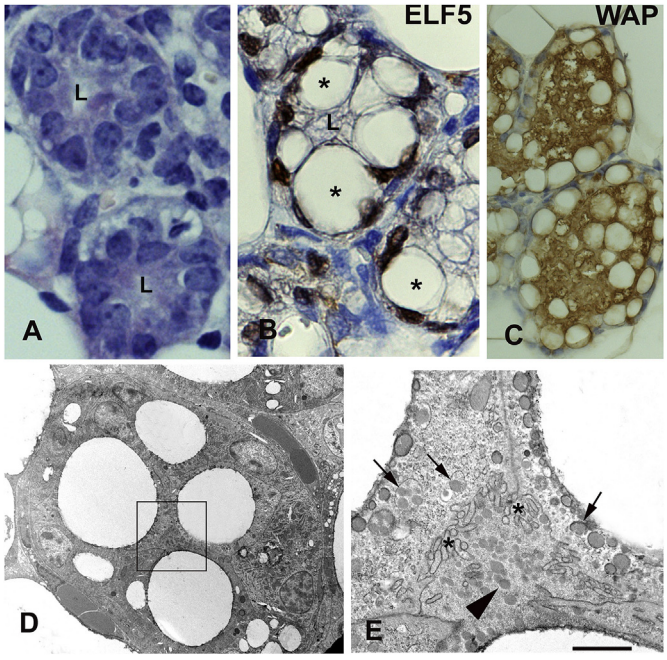

Fig. 4. Histological, immunohistochemical, and electron microscopic details of mammary gland alveologenesis in pregnant mice. A: newly-formed alveoli in the early stage of gland development (days 10–15); note the absence of lipid droplets in the epithelial cell cytoplasm (compare to B and C). L: alveolar lumen. B: newly-formed alveoli in the late stage of gland development (days 15–20); note the large lipid droplets (some indicated by an asterisk) in the alveolar cell cytoplasm. L: alveolar lumen. Epithelial alveolar cells show intense nuclear immunoreactivity for ELF5, the master transcription factor of alveologenesis. C: newly-formed alveoli in the late stage of gland development (days 15–20); lipid-rich epithelial alveolar cells are intensely immunoreactive for WAP. D: electron microscopy image of lipid-rich alveolar epithelial cells, corresponding to those depicted in B and C. Note the large lipid droplets (white holes), corresponding to those depicted in epithelial cells in B and C. E: enlargement of the area framed in D. The early stage of alveolar gland development depicted in D is demonstrated by the very early stage of lumen formation, corresponding to the area showing interdigitating microvilli (*) surrounded by unequivocal polarized milk protein granules (some indicated by an arrow). (From Prokesch et al. Stem Cells 2014 with permission).

BrdU experiments, immunohistochemical investigations of serial sections, and lineage tracing and explant experiments (Morroni et al., 2004; De Matteis et al., 2009; Prokesch et al., 2014). A particularly significant finding is that during pregnancy adipocytes undergo several morphological changes, including intermediate forms between adipocytes and milk-secreting alveolar cells, which are easily documented by electron microscopy. Equally impressive are the electron microscopic and immunohistochemical data supporting the epithelial-adipocytic conversion after lactation and the experiments documenting that explanted tagged mature adipocytes give rise to tagged mammary epithelial glandular cells in the host (De Matteis et al., 2009). Furthermore, lineage tracing experiments using WAP-Cre mice, which express Cre (hence the reporter gene) only in milk-secreting cells, have provided evidence for epithelial-adipocytic conversion at different time points (a few hours, ten days, and six months) with clear evidence of reporter gene expression (beta-gal by x-gal staining). Importantly, x-gal crystals were also demonstrated by electron microscopy, which is highly specific (Morroni et al., 2004). We have also obtained electron microscopic and lineage tracing evidence for pink to brown adipocyte conversion (Giordano et al., 2017). Although a recent lineage tracing study using different transgenic mice has been unable to find data for this conversion (Zwick et al., 2018), I feel that epigenetic mechanisms acting during phenotypic changes can explain this negative result.

Brown to pink adipocyte conversion has not yet been demonstrated;

however, the conversion of a brown adipocyte to a myoepithelial cell has recently been documented (Li et al., 2017). Although the molecular mechanisms underpinning this process are still being investigated, preliminary data suggest that the pregnancy hormones need a contribution from paracrine factors secreted by ductal cells, and that osteopontin may be involved (data recently reviewed in (Cinti, 2018c)).

Thus, transdifferentiation seems to be a basic physiological property of the adipose organ, ensuring optimal energy distribution to meet a wide range of needs that include thermogenesis (brown adipocytes), body nutrition (white adipocytes), and pup feeding (pink adipocytes).

3. The concept of nutritional system

The human adipose organ collaborates with the digestive organs in ensuring the function of a critical homeostatic mechanism. In fact, these organs secrete hormones that influence behaviors related to survival, i.e. nutrient search, intake, and distribution to the rest of the organism (see graphical abstract). Leptin is mainly produced by white adipocytes in proportion to their size and to the amount of WAT found in the body (Friedman, 2016). Low leptinemia due to energy store depletion alerts the brain and induces a strong stimulus that triggers food search and feeding behaviors (Zhang et al., 1994; Friedman, 2000, 2009). Mice and humans bearing gene mutations that suppress functional blood leptin eat about three times more than their healthy counterparts and develop a massive early-onset obesity (Friedman, 2000; Montague et al., 1997; Farooqi, 2005). Administration of recombinant leptin restores normal conditions (Farooqi et al., 1999); interestingly, the first effect in humans is the recovery of taste, suggesting that leptin deficiency alerts the brain to a dangerous situation, where distinguishing among different foods is unimportant and any source and amount of energy is well accepted. The brain's response to these endogenous stimuli is to activate the limbic system, which induces behaviors that ensure first of all the individual's survival. Leptin receptors are found in the limbic system (De Matteis and Cinti, 1998). Eating entails a search for food which until about 100 years ago was a high-risk endeavor, since for primitive humans it involved leaving the safety of their cave. Only a very strong stimulus could achieve this goal. The action of leptin on the limbic system therefore plays a key role in driving the primeval survival behavior. However, the search for food must then be followed by its intake. The recent discovery of asprosin has shed new light on this behavior (Romere et al., 2016; Duerrschmid et al., 2017).

Asprosin derives from the cleavage of profibrillin (FBN1), an extracellular matrix protein produced by adipocytes. It has been discovered while studying a human gene that is responsible for a rare and severe condition, neonatal progeroid lipodystrophy. These patients have little appetite and are extremely thin, because circulating asprosin crosses the blood-brain barrier and activates orexigenic AgRP hypothalamic neurons; this results in inhibition of anorexigenic POMC (proopiomelanocortin) neurons and appetite stimulation. These findings suggest that after the hormonal stimulus for food search we need another that induces eating.

The digestive organs cooperate in this complex behavior by producing the orexigenic gastric hormone ghrelin, the anorexigenic intestinal hormone PYY^{3-36}, and pancreatic insulin (Morton et al., 2006; Batterham et al., 2002; Muller et al., 2015; Howard et al., 1996). These hormones act on the same neurons of the hypothalamic arcuate nucleus, which bear the receptors for all such appetite-modulating hormones (Giordano et al., 2018).

Food intake is also controlled by afferent neural inputs to the nucleus of the solitary tract (stomach wall distension) and by intestinal and BAT-derived thermogenesis, especially in neonates (Himms-Hagen, 2006; Read, 1992). Post-prandial BAT thermogenesis is stimulated by intestinal products such as bile acids and secretin (Li et al., 2018), while BAT-produced factors such as FGF21 promote glucose oxidation in the liver and pancreas (Villarroya et al., 2017; Giralt et al., 2015; Fisher et al., 2012).

Finally, the intestinal microbiota provides another functional link between the gut and the adipose organ.

Interestingly, it has been demonstrated that the microbiota of obese animals has special characteristics, and that lean germ-free animals colonized with this microbiota gain fat mass, whereas animals transfected with microbiota from a “lean” phenotype do not (Ley et al., 2006; Turnbaugh et al., 2006). Further insights into the link between the adipose organ and the intestinal microbiota have been provided by work demonstrating that exposure to cold as well as food changes alter the intestinal flora (Chevalier et al., 2015; Suarez-Zamorano et al., 2015). In fact, germ-free animals implanted with bacterial flora from cold-acclimatized mice lost weight and experienced an improved metabolic condition and insulin sensitivity; their inguinal and perigonadal deposits were characterized by smaller adipocytes and upregulation of the typical BAT marker UCP1, which reflect a browning process; and their intestinal absorption surface increased significantly, enhancing their metabolic fitness. Moreover, cold exposure induced a change in the bacterial community, increasing the *Firmicutes* to *Bacteroidetes* ratio and severely depleting *Verrucomicrobia*. The new “pro-browning" flora would be able to improve host homeostasis and metabolic rate (Chevalier et al., 2015).

The same team reported that in germ-free as well as antibiotic-treated mice microbiota depletion induced an improved metabolic rate and weight loss; moreover adipocytes, especially those found in subcutaneous depots, transdifferentiated to a brown phenotype (Suarez-Zamorano et al., 2015). These findings further emphasize the link between the gut microbiota and the adipose organ.

The molecular mechanisms underpinning this phenomenon are still unclear, although some mechanistic hypotheses have been advanced. The three main hypotheses are based on:

1-the ability of intestinal bacteria to modify the bile salt pool (Ridlon et al., 2006, 2014; Broeders et al., 2015),
2-the indirect activation of intestinal GLP-1 (Thomas et al., 2009),
3-an increased production of short-chain fatty acids by intestinal fermentation with possible effects on browning (Kasubuchi et al., 2015; Gao et al., 2009; Lin et al., 2012).

4. Conclusions

Cooperation between the adipose organ and the digestive organs seems to be a key process supporting the complex system that coordinates the two main survival behaviors and functions of mammals: food search and feeding. After food intake, nutrients must be absorbed (intestine) and transformed into useful energy that then needs to be provided to the rest of the organism to enable the survival of the individual between meals (adipose organ). Energy must also be supplied to newborns, to ensure species survival: pink adipocytes (mammary alveolar cells) derived from WAT conversion during pregnancy and lactation seem to serve this key function (see graphical abstract).

Altogether, I feel that this system can be defined as a nutritional system, which together with the other body systems serves key functions for individual and species survival.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mam.2019.04.001.

References

Bachman, E.S., et al., 2002. betaAR signaling required for diet-induced thermogenesis and obesity resistance. Science 297 (5582), 843–845.
Barbatelli, G., et al., 2010. The emergence of cold-induced brown adipocytes in mouse

white fat depots is determined predominantly by white to brown adipocyte transdifferentiation. Am. J. Physiol. Endocrinol. Metab. 298 (6), E1244–E1253.
Batterham, R.L., et al., 2002. Gut hormone PYY(3-36) physiologically inhibits food intake. Nature 418 (6898), 650–654.
Broeders, E.P., et al., 2015. The bile acid chenodeoxycholic acid increases human Brown adipose tissue activity. Cell Metabol. 22 (3), 418–426.
Cancello, R., et al., 1998. Leptin and UCP1 genes are reciprocally regulated in brown adipose tissue. Endocrinology 139 (11), 4747–4750.
Cannon, B., Nedergaard, J., 1978. Energy dissipation in brown fat. Exper. Suppl. (Basel) 32, 107–111.
Cannon, B., Nedergaard, J., 1985. The biochemistry of an inefficient tissue: brown adipose tissue. Essays Biochem. 20, 110–164.
Cannon, B., Nedergaard, J., 1986. Brown adipose tissue thermogenesis in neonatal and cold-adapted animals. Biochem. Soc. Trans. 14 (2), 233–236.
Cannon, B., Nedergaard, J., 2004. Brown adipose tissue: function and physiological significance. Physiol. Rev. 84 (1), 277–359.
Chevalier, C., et al., 2015. Gut microbiota orchestrates energy homeostasis during cold. Cell 163 (6), 1360–1374.
Cinti, S., 1999. The Adipose Organ, Kurtis.
Cinti, S., 2018a. Obesity, Type2 Diabetes and the Adipose Organ. Springer.
Cinti, S., 2018b. Adipose organ development and remodeling. Comp. Physiol. 8 (4), 1357–1431.
Cinti, S., 2018c. Pink adipocytes. Trends Endocrinol. Metabol. 29 (9), 651–666.
Cinti, S., et al., 1989. Immunoelectron microscopical identification of the uncoupling protein in brown adipose tissue mitochondria. Biol. Cell 67 (3), 359–362.
Cinti, S., et al., 1997. Immunohistochemical localization of leptin and uncoupling protein in white and brown adipose tissue. Endocrinology 138 (2), 797–804.
Cinti, S., et al., 2002. CL316,243 and cold stress induce heterogeneous expression of UCP1 mRNA and protein in rodent brown adipocytes. J. Histochem. Cytochem. 50 (1), 21–31.
Cinti, S., 2018. The adipose organ. In: Sbraccia, P., e, N.F. (Eds.), Obesity. Springer.
Cohen, P., Spiegelman, B.M., 2016. Cell biology of fat storage. Mol. Biol. Cell 27 (16), 2523–2527.
Collins, S., Surwit, R.S., 2001. The beta-adrenergic receptors and the control of adipose tissue metabolism and thermogenesis. Recent Prog. Horm. Res. 56, 309–328.
Collins, S., et al., 2014. Coordinate control of adipose 'browning' and energy expenditure by beta-adrenergic and natriuretic peptide signalling. Int. J. Obes. Suppl. 4 (Suppl. 1), S17–S20.
Cousin, B., et al., 1992. Occurrence of brown adipocytes in rat white adipose tissue: molecular and morphological characterization. J. Cell Sci. 103 (Pt 4), 931–942.
Cypess, A.M., Kahn, C.R., 2010. Brown fat as a therapy for obesity and diabetes. Curr. Opin. Endocrinol. Diabetes Obes. 17 (2), 143–149.
Cypess, A.M., et al., 2009. Identification and importance of brown adipose tissue in adult humans. N. Engl. J. Med. 360 (15), 1509–1517.
Cypess, A.M., et al., 2015. Activation of human brown adipose tissue by a beta3-adrenergic receptor agonist. Cell Metabol. 21 (1), 33–38.
Duerrschmid, C., et al., 2017. Asprosin is a centrally acting orexigenic hormone. Nat. Med. 23 (12), 1444–1453.
Enerback, S., 2010. Human brown adipose tissue. Cell Metabol. 11 (4), 248–252.
Farooqi, I.S., 2005. Genetic and hereditary aspects of childhood obesity. Best Pract. Res. Clin. Endocrinol. Metabol. 19 (3), 359–374.
Farooqi, I.S., et al., 1999. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N. Engl. J. Med. 341 (12), 879–884.
Fisher, F.M., et al., 2012. FGF21 regulates PGC-1alpha and browning of white adipose tissues in adaptive thermogenesis. Genes Dev. 26 (3), 271–281.
Friedman, J.M., 2000. Obesity in the new millennium. Nature 404 (6778), 632–634.
Friedman, J.M., 2009. Leptin at 14 y of age: an ongoing story. Am. J. Clin. Nutr. 89 (3), 973S–979S.
Friedman, J., 2016. The long road to leptin. J. Clin. Investig. 126 (12), 4727–4734.
Fuster, A., et al., 2008. Effects of 6-month daily supplementation with oral beta-carotene in combination or not with benzo[a]pyrene on cell-cycle markers in the lung of ferrets. J. Nutr. Biochem. 19 (5), 295–304.
Gao, Z., et al., 2009. Butyrate improves insulin sensitivity and increases energy expenditure in mice. Diabetes 58 (7), 1509–1517.
Giordano, A., et al., 2005. Regional-dependent increase of sympathetic innervation in rat white adipose tissue during prolonged fasting. J. Histochem. Cytochem. 53 (6), 679–687.
Giordano, A., et al., 2014. White, brown and pink adipocytes: the extraordinary plasticity of the adipose organ. Eur. J. Endocrinol. 170 (5), R159–R171.
Giordano, A., et al., 2017. Mammary alveolar epithelial cells convert to brown adipocytes in post-lactating mice. J. Cell. Physiol. 232 (11), 2923–2928.
Giordano, A., Nisoli, E., 2018. Neuroendocrinology of energy balance. In: Sbraccia, P., Finer, N. (Eds.), Obesity. Springer.
Giralt, M., et al., 2015. Fibroblast growth factor-21, energy balance and obesity. Mol. Cell. Endocrinol. 418 (Pt 1), 66–73.
Granneman, J.G., et al., 2005. Metabolic and cellular plasticity in white adipose tissue I: effects of beta3-adrenergic receptor activation. Am. J. Physiol. Endocrinol. Metab. 289 (4), E608–E616.
Heaton, J.M., 1972. The distribution of brown adipose tissue in the human. J. Anat. 112 (Pt 1), 35–39.
Himms-Hagen, J., 2006. Thermoregulatory feeding in newborn infants: an update. Obesity 14 (9), 1479–1480.
Himms-Hagen, J., 1986. Brown adipose tissue and cold-acclimation. In: Trayhurn, P., Nicholls, a.D. (Eds.), Brown Adipose Tissue. Edward Arnold, pp. 214.
Himms-Hagen, J., et al., 2000. Multilocular fat cells in WAT of CL-316243-treated rats derive directly from white adipocytes. Am. J. Physiol. Cell Physiol. 279 (3), C670–C681.
Howard, A.D., et al., 1996. A receptor in pituitary and hypothalamus that functions in growth hormone release. Science 273 (5277), 974–977.
Huttunen, P., et al., 1981. The occurrence of brown adipose tissue in outdoor workers. Eur. J. Appl. Physiol. Occup. Physiol. 46 (4), 339–345.
Kajimura, S., et al., 2010. Transcriptional control of brown fat development. Cell Metabol. 11 (4), 257–262.
Kasubuchi, M., et al., 2015. Dietary gut microbial metabolites, short-chain fatty acids, and host metabolic regulation. Nutrients 7 (4), 2839–2849.
Klaus, S., et al., 1991. The uncoupling protein UCP: a membraneous mitochondrial ion carrier exclusively expressed in brown adipose tissue. Int. J. Biochem. 23 (9), 791–801.
Kozak, L.P., 2014. Genetic variation in brown fat activity and body weight regulation in mice: lessons for human studies. Biochim. Biophys. Acta 1842 (3), 370–376.
Lean, J., James, P., 1986. In: Arnold, Edward (Ed.), Brown Adipose Tissue in Man in Brown Adipose Tissue.
Lecoultre, V., Ravussin, E., 2011. Brown adipose tissue and aging. Curr. Opin. Clin. Nutr. Metab. Care 14 (1), 1–6.
Ley, R.E., et al., 2006. Microbial ecology: human gut microbes associated with obesity. Nature 444 (7122), 1022–1023.
Li, Li, L, B., Niu, C., Wang, G., Li, T., Krol, E., Jin, W., Speakman, J.R., 2017. Brown Adipocytes can display a mammary basal myoepithelia cell phenotype in vivo. Molecular Metabolism 6 (10), 1198–1211.
Li, Y., et al., 2018. Secretin-activated Brown fat mediates prandial thermogenesis to induce satiation. Cell 175 (6), 1561–1574.
Lin, H.V., et al., 2012. Butyrate and propionate protect against diet-induced obesity and regulate gut hormones via free fatty acid receptor 3-independent mechanisms. PLoS One 7 (4), e35240.
Maffei, M., 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 (11), 1155–1161.
Mao, L., et al., 2017. Visualization and quantification of browning using a ucp1-2a-luciferase knock-in mouse model. Diabetes 66 (2), 407–417.
van Marken Lichtenbelt, W.D., et al., 2009. Cold-activated brown adipose tissue in healthy men. N. Engl. J. Med. 360 (15), 1500–1508.
Masso-Welch, P.A., et al., 2000. A developmental atlas of rat mammary gland histology. J. Mammary Gland Biol. Neoplasia 5 (2), 165–185.
De Matteis, R., Cinti, S., 1998. Ultrastructural immunolocalization of leptin receptor in mouse brain. Neuroendocrinology 68 (6), 412–419.
De Matteis, R., et al., 2009. In vivo physiological transdifferentiation of adult adipose cells. Stem Cell. 27 (11), 2761–2768.
Mercader, J., et al., 2006. Remodeling of white adipose tissue after retinoic acid administration in mice. Endocrinology 147 (11), 5325–5332.
Montague, C.T., et al., 1997. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 387 (6636), 903–908.
Morroni, M., et al., 1995. Immunohistochemical, ultrastructural and morphometric evidence for brown adipose tissue recruitment due to cold acclimation in old rats. Int. J. Obes. Relat. Metab. Disord. 19 (2), 126–131.
Morroni, M., et al., 2004. Reversible transdifferentiation of secretory epithelial cells into adipocytes in the mammary gland. Proc. Natl. Acad. Sci. U. S. A. 101 (48), 16801–16806.
Morton, G.J., et al., 2006. Central nervous system control of food intake and body weight. Nature 443 (7109), 289–295.
Muller, T.D., et al., 2015. Ghrelin. Mol Metab 4 (6), 437–460.
Murano, I., et al., 2005. The Adipose Organ of Sv129 mice contains a prevalence of brown adipocytes and shows plasticity after cold exposure. Adipocytes 1 (2), 121–130.
Murano, I., et al., 2009. Noradrenergic parenchymal nerve fiber branching after cold acclimatisation correlates with brown adipocyte density in mouse adipose organ. J. Anat. 214 (1), 171–178.
Nechad, M., 1986. In: Trayhurn, Paul, Nicholls, David, Arnold, Edward (Eds.), Structure and Development of Brown Adipose Tissue in: Brown Adipose Tissue, (London).
Nedergaard, J., et al., 1983. Effects of dietary essential fatty acids on active thermogenin content in rat brown adipose tissue. J. Nutr. 113 (9), 1717–1724.
Prokesch, A., et al., 2014. Molecular aspects of adipoepithelial transdifferentiation in mouse mammary gland. Stem Cell. 32 (10), 2756–2766.
Read, N.W., 1992. Role of gastrointestinal factors in hunger and satiety in man. Proc. Nutr. Soc. 51 (1), 7–11.
Richert, M.M., et al., 2000. An atlas of mouse mammary gland development. J. Mammary Gland Biol. Neoplasia 5 (2), 227–241.
Ricquier, D., 1989. Molecular biology of brown adipose tissue. Proc. Nutr. Soc. 48 (2), 183–187.
Ricquier, D., 2017. UCP1, the mitochondrial uncoupling protein of brown adipocyte: a personal contribution and a historical perspective. Biochimie 134, 3–8.
Ridlon, J.M., et al., 2006. Bile salt biotransformations by human intestinal bacteria. J. Lipid Res. 47 (2), 241–259.
Ridlon, J.M., et al., 2014. Bile acids and the gut microbiome. Curr. Opin. Gastroenterol. 30 (3), 332–338.
Robinson, G.W., et al., 1995. Mammary epithelial cells undergo secretory differentiation in cycling virgins but require pregnancy for the establishment of terminal differentiation. Development 121 (7), 2079–2090.
Romere, C., et al., 2016. Asprosin, a fasting-induced glucogenic protein hormone. Cell 165 (3), 566–579.
Rosen, E.D., Spiegelman, B.M., 2014. What we talk about when we talk about fat. Cell 156 (1–2), 20–44.
Rosenwald, M., et al., 2013. Bi-directional interconversion of brite and white adipocytes. Nat. Cell Biol. 15 (6), 659–667.
Sadurskis, A., et al., 1995. Polyunsaturated fatty acids recruit brown adipose tissue:

increased UCP content and NST capacity. Am. J. Physiol. 269 (2 Pt 1), E351–E360.
Saito, M., et al., 2009. High incidence of metabolically active brown adipose tissue in healthy adult humans: effects of cold exposure and adiposity. Diabetes 58 (7), 1526–1531.
Sbarbati, A., et al., 1991. Rat interscapular brown adipose tissue at different ages: a morphometric study. Int. J. Obes. 15 (9), 581–587.
Seale, P., et al., 2009. Transcriptional control of brown adipocyte development and physiological function–of mice and men. Genes Dev. 23 (7), 788–797.
Stock, M.a.C., S, 2003. Adipose tissue: structure and function of Brown adipose tissue. In: Encyclopedia of Food Sciences and Nutrition, second ed. Elsevier, pp. 29–34.
Suarez-Zamorano, N., et al., 2015. Microbiota depletion promotes browning of white adipose tissue and reduces obesity. Nat. Med. 21 (12), 1497–1501.
Thomas, C., et al., 2009. TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metabol. 10 (3), 167–177.
Tontonoz, P., Spiegelman, B.M., 2008. Fat and beyond: the diverse biology of PPARgamma. Annu. Rev. Biochem. 77, 289–312.
Trayhurn, P., Ashwell, M., 1987. Control of white and brown adipose tissues by the autonomic nervous system. Proc. Nutr. Soc. 46 (1), 135–142.
Trayhurn, P., Nicholls, D., 1986. Brown Adipose Tissue. Edward Arnold.
Turnbaugh, P.J., et al., 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 444 (7122), 1027–1031.
Villarroya, F., et al., 2017. Brown adipose tissue as a secretory organ. Nat. Rev. Endocrinol. 13 (1), 26–35.
Virtanen, K.A., et al., 2009. Functional brown adipose tissue in healthy adults. N. Engl. J. Med. 360 (15), 1518–1525.
Vitali, A., et al., 2012. The adipose organ of obesity-prone C57BL/6J mice is composed of mixed white and brown adipocytes. J. Lipid Res.
Zhang, Y., et al., 1994. Positional cloning of the mouse obese gene and its human homologue. Nature 372 (6505), 425–432.
Zingaretti, M.C., 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 (9), 3113–3120.
Zwick, R.K., et al., 2018. Adipocyte hypertrophy and lipid dynamics underlie mammary gland remodeling after lactation. Nat. Commun. 9 (1), 3592.