



# The Nutritional System

# 17

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## Abstract

The white and brown adipose tissues are organized to form a true organ. They have a different anatomy and perform different functions, but they collaborate thanks to their ability to convert mutually and reversibly following physiological stimuli. This implies a new fundamental property for mature cells, which would be able to reversibly reprogram their genome under physiological conditions. The subcutaneous mammary gland provides another example of their plasticity. Here fat cells are reversibly transformed into glands during pregnancy and breastfeeding. The obese adipose organ is inflamed because hypertrophic fat cells, typical of this condition, die and their cellular residues must be reabsorbed by macrophages. The molecules produced by these cells during their reabsorption work interfere with the insulin receptor, and this induces insulin resistance, which ultimately causes type 2 diabetes. The adipose organ collaborates with those of digestion. Both produce hormones that can influence the nutritional behavior of individuals. They produce molecules that mutually influence functional activities including thermogenesis, which contributes to the interruption of the meal. The nutrients are absorbed by the intestine, stored in the adipose organ, and distributed by them to the whole body between meals. Distribution includes offspring during breastfeeding. The system as a whole is therefore called the nutritional system.

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This chapter is a component of Part II: Specialist Versus Generalist Nutritional Care in Aging. For an explanation of the grouping of chapters in this book, please see Chap. 1: “Overview of Nutrition Care in Geriatrics and Orthogeriatrics.”

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**Keywords**

Adipocytes · White · Brown · Beige · Mammary gland · Obesity

**Learning Outcomes**

By the end of this chapter, you will be able to:

- Understand the main physiologic aspects of a new organ that plays a pivotal role in the complex physiology that regulates the most important behaviors for the survival of mammals.

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**17.1 Introduction**

It has been calculated that the human body is made up of approximately 37,000 billion cells. Each of them must be fed daily. The nourishment for each cell type comes from the food that needs to be researched and ingested. The search for food is a fundamental behavior for survival that arises from the balance between brain activities that receive instinctual impulses and those that elaborate rational responses. Food intake is a subsequent and consequent behavior, and it also needs the collaboration of the two components underlying the behavioral activity.

Today it is difficult to understand how an instinctual impulse is needed to activate the search for food, but until a few 100 years ago, obtaining food was not a trivial activity and often involved survival risks. Just think of the fact that by leaving the cave, primitive man could easily become from predator to prey. So, the impulse must have been enough to overcome even the strong instinct for survival.

It is even more difficult to think how stimuli may be needed to take food, which in itself determines a physical satisfaction or at least the interruption of an unpleasant condition such as that due to prolonged fasting.

For both of these two behavioral activities, complex-acting hormones are needed, mainly produced by white adipocytes.

These cells form a tissue, which therefore represents the central fulcrum for the nutrition of our organism. They are also able to store high-energy molecules in relatively small spaces that nourish the body between meals, allowing us to turn our attention and our activity to other functions that are not exclusively dedicated to nutrition. The ability to have a fasting period between meals allows time not only to search for other food but also to search for a partner, procreate, breed offspring, and carry out all those activities that can guarantee the offspring the best possible future.

## 17.2 Hormones Produced by White Adipocytes

The hormone for food research was discovered in 1994 by Jeffrey Friedman's team [1]. It has been attributed the name of leptin (from the Greek leptòs, thin), a hormone with endocrine and paracrine activity that acts on various organs but mainly on the brain and in particular on the limbic system [2], informing us about the nutritional status of the organism. In fact, it determines a leptinemia that is proportional to the amount of white adipose tissue, i.e., the body's energy supplies. When supplies are low, leptinemia is low, and the brain receives uncontrollable impulses to search for food. Mice and humans, who do not produce leptin, take triple the food taken by normal subjects becoming massively obese, and the administration of recombinant leptin allows the recovery of a phenotype and normal behavior [3].

Most of the essential obese subjects develop a leptin resistance [4]. A physiological justification for this may be considered, for example, where an organism has awareness of impending food shortage, and despite the presence of high energy supplies and therefore high leptinemia, a leptin resistance is established allowing for further food intake that guarantees the possibility of surviving long periods of fasting.

This resistance to hormone is the basis of essential obesity, as the individual who consumes overeating makes the energy balance positive and needs a particular development of the white adipose tissue. The latter responds appropriately with expansion capacity both in the volume of each individual cell (hypertrophy) and in the number of cells (hyperplasia). The extraordinary expansive capacity of the white adipose tissue means that its weight, which represents about 20% of the total weight of a lean adult individual, multiplies to the point that it represents about 70% of the total body weight [5].

These data allow us to easily understand how it must also produce a whole series of paracrine-acting molecules that facilitate interaction with the extracellular matrix to allow adequate expansion in the event of a chronically positive energy balance up to extraordinary levels such as those abovementioned. The details of these secretion factors have recently undergone extensive revision [6].

The instinctual stimulus for the behavior of food intake is given by a hormone produced by the white adipocyte discovered, more recently, in 2016 by Dr. Chopra's team, asprosin (from the Greek àspros, white) [7].

The most convincing fact that this hormone is essential for food intake is that subjects with lipodystrophy (therefore with low leptinemia) and who have a gene mutation that prevents them from producing asprosin eat very little food [8]. Another important function of asprosin is to induce hepatic glucose release. So, during fasting, the white adipocyte releases fatty acids that are essential and usable directly for cardiac activity and stimulates the hepatic release of glucose, which is essential for brain activity.

In summary, the white adipocyte produces two hormones that act on the brain to induce the individual to look for food (leptin) and ingest it (asprosin). It also guarantees survival by supplying energy to the body's cells and allowing long intervals between meals.

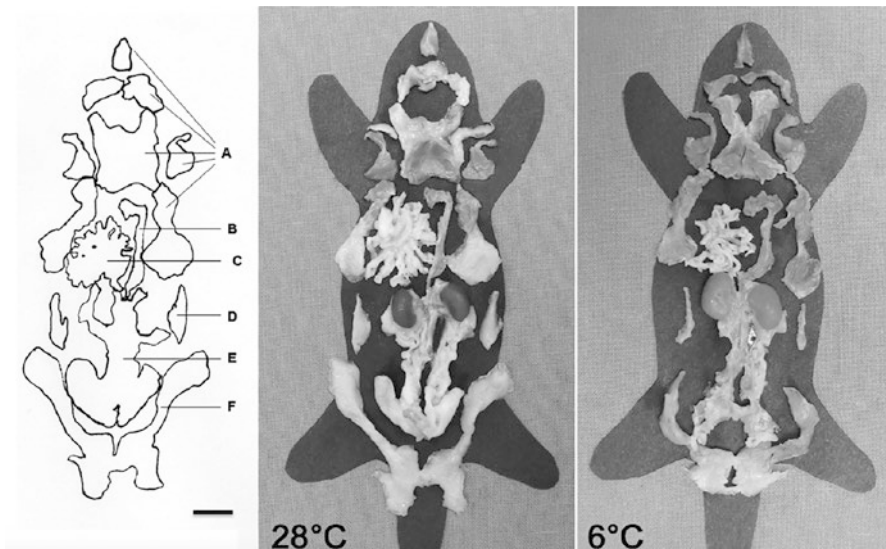
### 17.3 The Adipose Organ

From an anatomical point of view, the adipose tissue is contained in distinct depots which can be dissected from the rest of the body and occupy superficial (subcutaneous) and deep (visceral) compartments. The depots have their own morphology and are delimited by connective tissue capsules or serous membranes. The former is mainly located in the subcutaneous compartment, while the latter in the visceral one.

The color of the adipose tissue is yellowish in humans, but in some locations, the color is quite brown (Fig. 17.1). In humans, the most consistent brown area is placed in close relationship with the aorta and its main branches. Brown area quantity is highly variable and depends above all on age (higher in young people), nutritional status (higher in lean), and exposure to cold (higher in exposed).

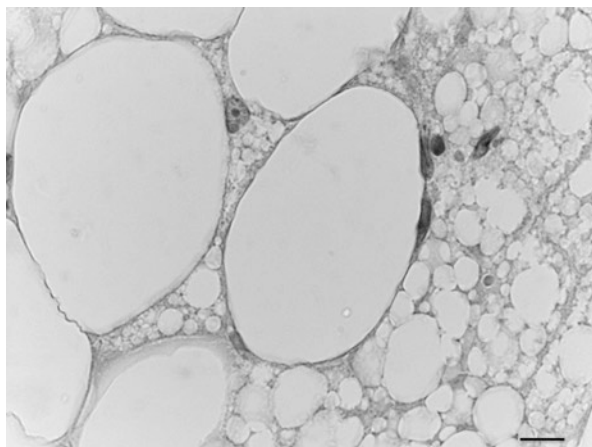
In these sites, the fat cells have different characteristics than those of the white adipocytes. Mitochondria are numerous, large, and rich in laminar cristae. The adipocytes of the brown areas, which are called brown adipocytes, are therefore very different from the white adipocytes (Fig. 17.2).

Brown adipocytes have opposite functions to those of white adipocytes: they disperse energy by burning fatty acids and produce heat [9]. Since the lipid vacuoles are in multilocular form, the quantity of fatty acids released by the adrenergic



**Fig. 17.1** Gross anatomy of adipose organ from mice maintained at 28 or 6 °C for 10 days. Subcutaneous (A and F) and visceral (B–E) depots are indicated. Kidneys are in site for orientation. The gray areas are brown in color, brown adipose tissue; white areas correspond to white adipose tissue. At 6 °C, the browning of the organ is visually evident. Bar, 15 mm. (From Murano, I. et al. The Adipose Organ of Sv129 mice contains a prevalence of brown adipocytes and shows plasticity after cold exposure. *Adipocytes* 2005; 1 (2), 121–130, with permission)

**Fig. 17.2** Light microscopy. Mixed adipose tissue. Unilocular white adipocytes (left) and multilocular brown adipocytes (right) are visible. Bar, 10  $\mu\text{m}$



stimulus is enormous, and since the mitochondria are numerous, large, and rich in cristae, the heat produced is physiologically relevant. If we consider that the human body must be constantly maintained at a temperature of about  $37^{\circ}\text{C}$ , while the environmental one varies from about  $-70$  to about  $+50$ , it is easy to understand how thermogenetic systems are more important than those of heat dispersion and the brown adipose tissue is the most important thermogenetic systems in the body.

In summary, the adipose organ is formed by dissectible structures with a specific anatomy and formed by two tissues with different morphology and function: the white and the brown adipose tissues. In fact, organs, by definition, are dissectible anatomical structures, formed by at least two tissues that cooperate with each other for a specific functional purpose. For example, the stomach is dissectible and composed of both glands that produce gastric juice and muscles that make peristalsis. Glands and muscles are different tissues that cooperate for the common purpose of digestion. The cooperation in the adipose organ would consist in the particular plasticity of fat cells which would be able, in particular physiological situations, to convert mutually to distribute the intrinsic energy of the lipids toward thermogenesis or toward the metabolic reserve [10–13].

These data imply two relevant aspects: (1) browning of the adipose organ could be used to increase energy expenditure and therefore as a treatment for obesity and its complications, and (2) mature cells can change their phenotype under physiologic stimuli.

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## 17.4 Browning of the Adipose Organ as a Therapy for Obesity and Related Diseases

If we eliminate the brown adipose tissue with genetic manipulation, after a few weeks, the mice, while eating and moving like the controls, i.e., those with brown fat, become massively obese and develop type 2 (T2) diabetes [14]. On

the other hand, the administration of beta-3-adrenergic drugs or brown fat explants to obese mice reduces obesity and treats T2 diabetes [15]. It has also been shown that the activation of brown fat improves lipid metabolism and promotes the prevention of atherosclerosis [16]. Therefore, it is not surprising to find an extension of life in genetically manipulated mice that had an activation of brown fat.

In recent years, it has been confirmed not only that brown fat is also present in the human adipose organ but also that the phenomenon of white-brown conversion is also present in humans and that “browning” has health properties also in humans [17]. All this makes us hope that drugs capable of mimicking exposure to the cold can be identified without giving the unpleasant negative sensations that it induces and without promoting or facilitating the typical infectious cold diseases. In this regard, it is relevant that physical exercise induces activation of the sympathetic nervous system with browning in the adipose organ [18]. A hormone called irisin has also been identified that is produced by the muscle during shivering and exercise, which is able to promote browning of the fatty organ [19]. Recent data indicate that the hormone also has beneficial effects on the bone by promoting its reinforcement in physical exercise and by preventing and treating experimentally induced osteoporosis and muscle atrophy on mice [20].

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## 17.5 The Physiology of the Mammary Gland Confirms the Plasticity of the Adipose Organ

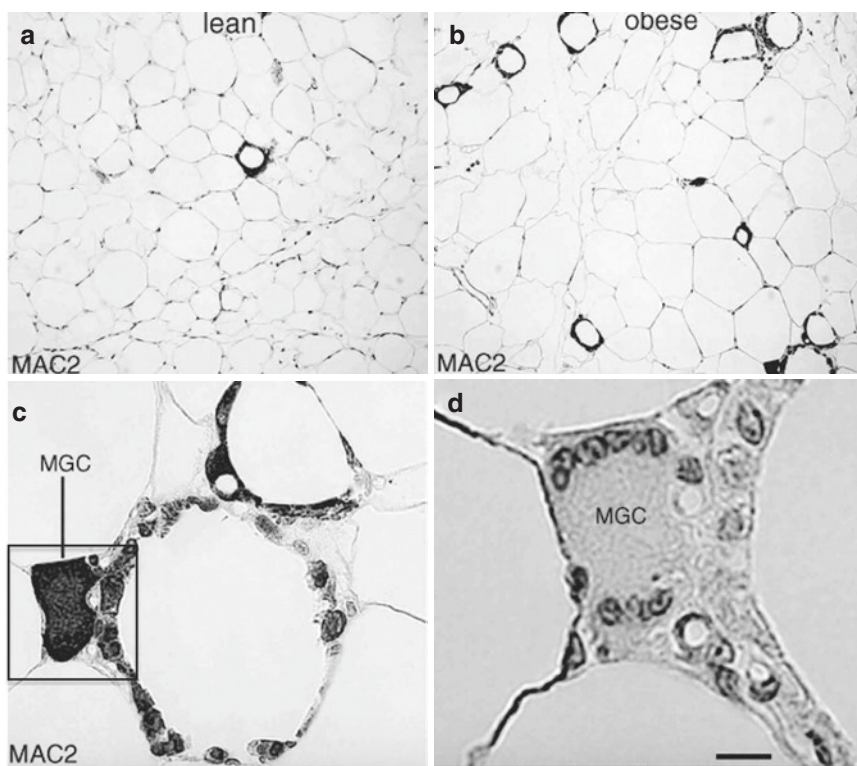
The second aspect that derives from our studies concerns a new fundamental property of cells hitherto unknown, the physiological and reversible conversion (or trans-differentiation) of the mature cell.

To confirm this new cellular property, we looked for other examples and found confirmation in another physiological condition that changes the morphology and function of the adipose organ in females, pregnancy. In this condition, the mammary gland develops forming the structures necessary for the production of milk (alveoli). At the end of pregnancy, the alveoli disappear, restoring the pre-gravid anatomy of the breast, subcutaneous fat infiltrated by branched ducts that collect in a single nipple. During the development of the alveoli, the fat cells disappear, as well as during the involution; when the alveoli disappear, the fat cells reappear.

We hypothesized that the disappearance during glandular development is due to the conversion of adipocytes into glandular cells of the alveoli, just as during the involution the glandular cells are transformed back to fat cells. If this were true, we would have found a new example of physiological and reversible trans-differentiation in the adipose organ. To confirm the hypothesis, we used the lineage tracing technique that allows to follow destiny of developing cells [21]. Our experimental data confirm the large plastic capacity of fat cells that are able to undergo phenotypic and functional transformations following physiological stimuli and in a reversible way to respond to different functional needs of the body.

## 17.6 The Obese Adipose Organ

Although detailed explanation is beyond the remit of this introductory chapter, the obese adipose organ has distinct properties. For example, the adipose organ of obese mice and humans is infiltrated by inflammatory cells mainly consisting of macrophages [22, 23]. The degree of infiltration correlates with the size of the adipocytes, but the visceral adipocytes die at a size smaller than that of the subcutaneous adipocytes. This offers an explanation for the greater morbidity of visceral fat, probably because it derives largely from brown-white conversion [24]. Macrophages reabsorb dead hypertrophic cells forming multinucleated giant cell structures that we have called crown-like structures (CLS) (Fig. 17.3). During reabsorption activities,



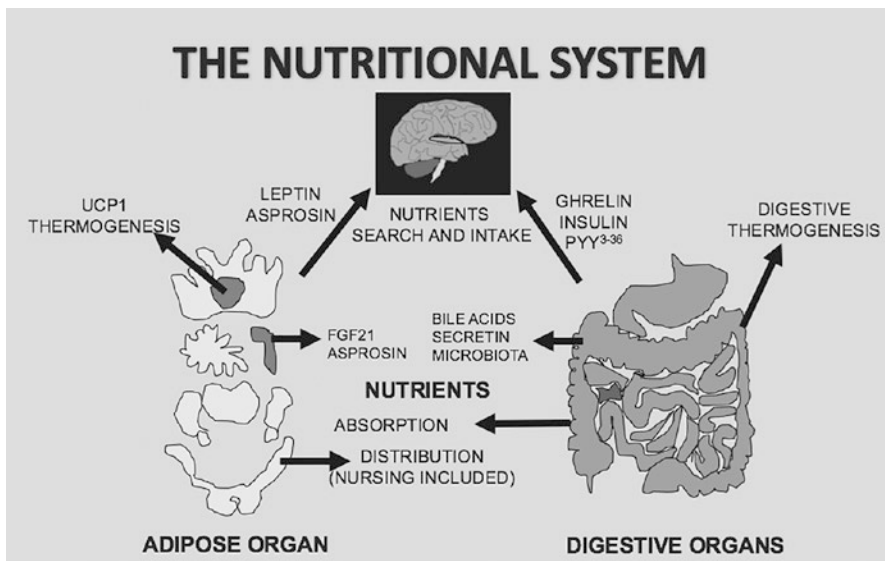
**Fig. 17.3** Immunohistochemistry with antibodies as indicated. MAC2 stains active macrophages. Perilipin1 (d) stains vital adipocytes. Several crown-like structures are visible in the adipose tissue from obese mouse (b), but few are also present in adipose tissue from lean mouse (a). (c) Enlargement of CLS at the bottom right corner of (b). A giant macrophage and several MAC2 immunoreactive macrophages surround debris of a dead adipocyte. (d) Enlargement of serial section corresponding to squared area in C showing that the giant macrophage is multinuclear. A perlipin immunoreactive adipocyte is visible on the left, and the absence of immunoreactivity is visible in the CLS. Bar, 100  $\mu\text{m}$  (a and b), 28  $\mu\text{m}$  for (c), and 10  $\mu\text{m}$  for (d). (From Cinti, S. et al. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *J Lip Res* 2005; 46: 2347–2355, with permission)

different substances produced by macrophages (TNF $\alpha$ , resistin, specific miRNA, etc.) interfere with the activity of the insulin receptor offering an explanation to the fact that the appearance of inflammation of the adipose tissue coincides with the appearance of insulin resistance, which eventually leads to T2 diabetes. Additionally, experimental data on obese mice and humans indicate a progressive increase in noradrenergic fibers in the islands of Langerhans [25]. This may, for example, be responsible for the reduction of insulin secretion with the appearance of T2 diabetes and offer an explanation for the rapid post-bariatric recovery from diabetes.

### 17.6.1 Summary

The organs of our organism work together for complex functions and organize themselves into systems. The adipose organ mainly collaborates with those of digestion. Both produce hormones that influence the brain with regard to nutrition, and both produce different molecules that mutually influence alternative organ activities. The organs of digestion also produce postprandial thermogenesis, and thermogenesis is one of the mechanisms involved in the regulation of food intake [26–29]. The intestine absorbs nutrients, which are then distributed to the adipose organ, which stores them in the form of triglycerides, to be made available to the body between meals.

In conclusion, it can be stated that in addition to the various systems that allow complex functional activities such as the nervous, endocrine, immune, urogenital, cardiovascular, and respiratory systems, we can now also speak of a true nutritional system [30] (Fig. 17.4).



**Fig. 17.4** Scheme of the nutritional system concept



## Take-Home Points

- The white and brown adipose tissues are organized to form a true organ.
- This organ plays a pivotal role in the complex physiology that regulates the most important behaviors for the survival of mammals.

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## References

1. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM (1994) Positional cloning of the mouse obese gene and its human homologue. *Nature* 372(6505):425–432
2. De Matteis R, Cinti S (1998) Ultrastructural immunolocalization of leptin receptor in mouse brain. *Neuroendocrinology* 68(6):412–419
3. Farooqi IS, O’Rahilly S (2014) 20 years of leptin: human disorders of leptin action. *J Endocrinol* 223(1):T63–T70
4. Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, Fei H, Kim S, Lallone R, Ranganathan S 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
5. Prins JB, O’Rahilly S (1997) Regulation of adipose cell number in man. *Clin Sci (Lond)* 92(1):3–11
6. Cinti S (2018) Adipose organ development and remodeling. *Compr Physiol* 8(4):1357–1431
7. Romere C, Duerrschmid C, Bournat J, Constable P, Jain M, Xia F et al (2016) Asprosin, a fasting-induced glucogenic protein hormone. *Cell* 165(3):566–579
8. Duerrschmid C, He Y, Wang C, Li C, Bournat JC, Romere C et al (2017) Asprosin is a centrally acting orexigenic hormone. *Nat Med* 23(12):1444–1453
9. Cannon B, Nedergaard J (2004) Brown adipose tissue: function and physiological significance. *Physiol Rev* 84(1):277–359
10. Murano I, Barbatelli G, Giordano A, Cinti S (2009) Noradrenergic parenchymal nerve fiber branching after cold acclimatisation correlates with brown adipocyte density in mouse adipose organ. *J Anat* 214(1):171–178
11. Himms-Hagen J, Melnyk A, Zingaretti MC, Ceresi E, Barbatelli G, Cinti S (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
12. Granneman JG, Li P, Zhu Z, Lu Y (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
13. Rosenwald M, Perdikari A, Rüllicke T, Wolfrum C (2013) Bi-directional interconversion of brite and white adipocytes. *Nat Cell Biol* 15(6):659–667
14. Bachman ES, Dhillon H, Zhang CY et al (2002) betaAR signaling required for diet-induced thermogenesis and obesity resistance. *Science* 297(5582):843–845
15. Nedergaard J, Bengtsson T, Cannon B (2011) New powers of brown fat: fighting the metabolic syndrome. *Cell Metab* 13:238–240
16. Berbée JF, Boon MR, Khedoe PP, Bartelt A, Schlein C, Worthmann A et al (2015) Brown fat activation reduces hypercholesterolaemia and protects from atherosclerosis development. *Nat Commun* 6:6356
17. Betz MJ, Enerbäck S (2015) Human Brown adipose tissue: what we have learned so far. *Diabetes* 64(7):2352–2360
18. De Matteis R, Lucertini F, Guescini M, Polidori E, Zeppa S, Stocchi V et al (2013) Exercise as a new physiological stimulus for brown adipose tissue activity. *Nutr Metab Cardiovasc Dis* 23(6):582–590
19. Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC et al (2012) A PGC1- $\alpha$ -dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* 481(7382):463–468

20. Colaiani G, Mongelli T, Cuscito C, Pignataro P, Lippo L, Spiro G et al (2017) Irisin prevents and restores bone loss and muscle atrophy in hind-limb suspended mice. *Sci Rep* 7(1):2811
21. Cinti S (2018) Pink adipocytes. *Trends Endocrinol Metab* 9(9):651–666
22. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr (2003) Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 112(12):1796–1808
23. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H (2003) Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 112(12):1821–1830
24. Kotzbeck P, Giordano A, Mondini E, Murano I, Severi I, Venema W et al (2018) Brown adipose tissue whitening leads to brown adipocyte death and adipose tissue inflammation. *J Lipid Res* 59(5):784–794
25. Giannulis I, Mondini E, Cinti F, Frontini A, Murano I, Barazzoni R et al (2014) Increased density of inhibitory noradrenergic parenchymal nerve fibers in hypertrophic islets of Langerhans of obese mice. *Nutr Metab Cardiovasc Dis* 24(4):384–392
26. Villarroya F, Cereijo R, Villarroya J, Giral M (2017) Brown adipose tissue as a secretory organ. *Nat Rev Endocrinol* 13(1):26–35
27. Li Y, Schnabl K, Gabler SM, Willershäuser M, Reber J, Karlas A et al (2018) Secretin-activated brown fat mediates prandial thermogenesis to induce satiation. *Cell* 175(6):1561–1574.e12
28. Chevalier C, Stojanović O, Colin DJ, Suarez-Zamorano N, Tarallo V, Veyrat-Durebex C et al (2015) Gut microbiota orchestrates energy homeostasis during cold. *Cell* 163(6):1360–1374
29. Himms-Hagen J (2006) Thermoregulatory feeding in newborn infants: an update. *Obesity (Silver Spring)* 14(9):1479–1480
30. Cinti S (2019) Anatomy and physiology of the nutritional system. *Mol Asp Med* 68:101–107

## Further Reading

- Cinti S (2009) Transdifferentiation properties of adipocytes in the adipose organ. *Am J Physiol Endocrinol Metab* 297(5):E977–E986. <https://doi.org/10.1152/ajpendo.00183.2009>. Epub 2009 May 19. PMID: 19458063
- Cinti S (2012) The adipose organ at a glance. *Dis Model Mech* 5(6):588–594. <https://doi.org/10.1242/dmm.009662>. PMID: 22915020; PMCID: PMC3424455
- Cinti S (2018a) Adipose organ development and remodeling. *Compr Physiol* 8(4):1357–1431
- Cinti S (2018b) Pink adipocytes. *Trends Endocrinol Metab* 29(9):651–666. <https://doi.org/10.1016/j.tem.2018.05.007>. Epub 2018 Jul 17. PMID: 30017740
- Giordano A, Frontini A, Cinti S (2016) Convertible visceral fat as a therapeutic target to curb obesity. *Nat Rev Drug Discov* 15(6):405–424. <https://doi.org/10.1038/nrd.2016.31>. Epub 2016 Mar 11. PMID: 26965204

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