REVIEW ARTICLE

The colors of adipose tissue

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Abstract

Adipose tissue is an endocrine organ with high metabolic activity. Countless adipose tissue-secreted adipokines and lipokines, as well as peptides and lipids with biological activity have thus far been discovered. Both white and brown and beige adipose tissue are known to contribute to energy homeostasis and metabolic regulation. The purpose of this review is to report on the most recent findings related to adipose tissue according to its color and its relationship with metabolic alterations associated with obesity. After a review of the specialized literature, white, brown and beige adipocyte populations were identified to be able to coexist within the same structure, and to modify global metabolic state in physiological or pathological situations.

KEY WORDS: *Adipose tissue. Adipocyte. Metabolism.*

Los colores del tejido adiposo

Resumen

El tejido adiposo es un órgano endocrino con gran actividad metabólica. A la fecha se han descubierto innumerables adipocinas y lipocinas, péptidos y lípidos con actividad biológica, secretadas por el tejido adiposo. Se sabe que tanto el tejido adiposo blanco como el pardo y el beige contribuyen a la homeostasis energética y a la regulación metabólica. Esta revisión tiene como finalidad comunicar los hallazgos más recientes relativos al tejido adiposo según su color y la relación de este con las alteraciones metabólicas asociadas con la obesidad. Después de la revisión de la literatura especializada, se identificó que en una misma estructura pueden coexistir poblaciones blancas, pardas y beige, que modifican el estado metabólico global en situaciones fisiológicas o patológicas.

PALABRAS CLAVE: *Tejido adiposo. Adipocito. Metabolismo.*

Adipose tissue basic concepts

Adipose tissue accounts for 20 to 28 % of the body mass of healthy individuals, a percentage that varies according to gender and energy status, so that fat mass can account for up to 80 % of body mass in individuals with obesity. The distribution and localization of said fat mass determine its function. Subcutaneous adipose tissue, localized under the skin, represents the highest proportion of adipose tissue.[1] Visceral adipose tissue surrounds the organs, especially the kidney (perirenal adipose tissue), the intestines (mesenteric and omental adipose tissue), the gonads (epididymal and parametrial adipose tissue), the vasculature (perivascular or periadventitial adipose tissue) and the heart (epicardial and pericardial adipose tissue)[2] (Fig. 1).

Adipose tissue belongs to the group of connective tissues that confer cohesion to organs or systems. A clear example of this function is that of mesenteric

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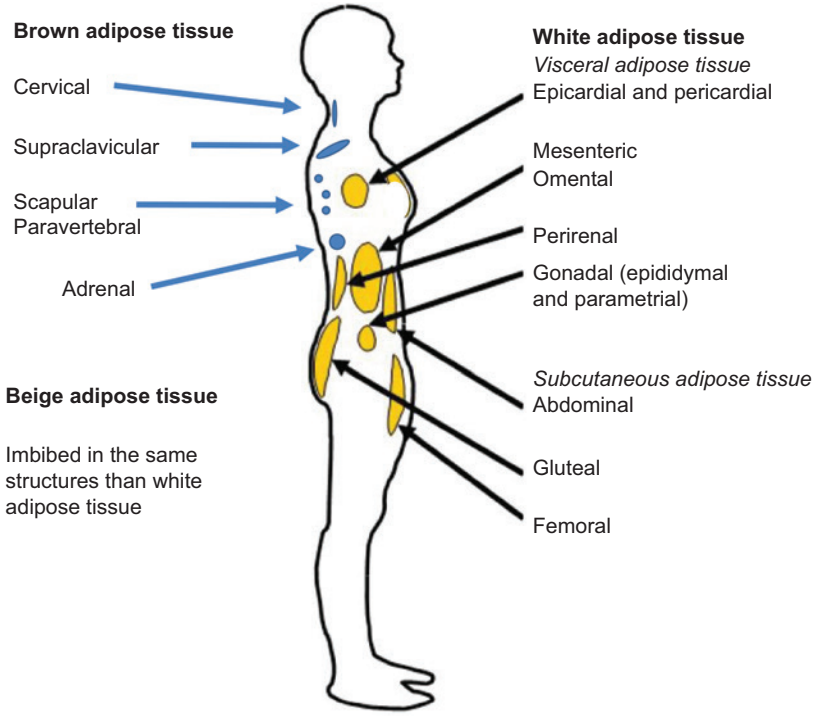

Figure 1. *Localization of white, brown and beige adipose tissue. In yellow, white adipose tissue structures, and in blue, brown adipose tissue deposits.*

adipose tissue, which keeps the convolutions of the small intestine in a more or less constant position.[3] In addition to the function of giving support to structures, adipose tissue very importantly regulates energy balance. Recently, adipose tissue was shown to be not only an energy store or a passive organ of metabolism, but to also influence and participate in energy status. In fact, it has been considered an endocrine organ capable of secreting hormones that travel through the bloodstream to reach their target tissues. Other adipose tissue functions refer to the regulation of physiological processes such as sexual dimorphism, immunity, reproduction, adipogenesis, angiogenesis, extracellular matrix restructuring, steroid metabolism, hemostasis and body temperature maintenance.[4,5]

The performance of these functions is conferred by the variety cell types that make up adipose tissue: adipocytes, preadipocytes, fibroblasts, macrophages, monocytes, vascular stromal cells and innervation cells. The highest proportion of cells in this tissue appears not to be represented by adipocytes, but by the other cells. In fact, up to 80 % of total DNA extracted from adipose tissue comes from vascular cells, fibroblasts, leukocytes and macrophages.[6]

There are three types of adipose tissue according to their functions, coloration, vascularization and structure (Fig. 2):

- White adipose tissue.
- Brown adipose tissue.
- Beige adipose tissue.

White adipose tissue

White adipose tissue is characterized for being a white or yellow tissue with less vascularization and innervation than brown tissue. White adipose tissue fat cells have a size that ranges from 20 to 200 µm and are unilocular, i.e. they contain a single lipid vacuole. In said vacuole, lipids are stored for use when there is energy demand. Of the totality of lipids encompassed by the white adipocyte lipid vacuole, 90 to 99% are triacylglycerols.[3] The triacylglycerols deposited in the lipid vacuole contain enough energy to meet the energy requirements of a healthy adult for at least two months.

White adipose tissue generates a large number of adipokines and lipokines. Adipokines are peptides that act as hormones or messengers that regulate metabolism. Around 40 % of the genes expressed by

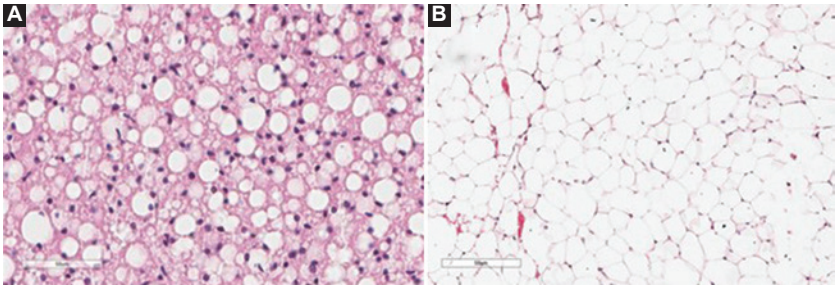

Figure 2. *Brown* **(A)** *and white* **(B)** *adipose tissue histology, staining with hematoxylin and eosin, 40x, 50 µm scale. Notice that brown adipocytes contain several lipid vacuoles, that the tissue is highly innervated and that nuclei are indeterminately located. White adipose tissue is less innervated and contains a large lipid vacuole per cell, which is why the nucleus is located towards the periphery and is observed to be flattened.*

adipose tissue are estimated to be novel in their function, and 20 or 30 % of them are estimated to correspond to secretion proteins.[7] We know that adipose tissue secretes proteins with high versatility of functions related to proinflammatory cytokines, immunity, the complement, the fibrinolytic system, the renin-angiotensin system, lipid metabolism and transport and steroid metabolism enzymes, among others. For these reasons, adipose tissue is considered to be an endocrine organ that produces adipokines such as adiponectin or prokineticin or meteorine-like hormone.[8,9] Lipokines, which are lipid in nature, exert the same function when secreted by the adipocyte and influence on metabolism.

Between the decades of 1950 and 1970, parabiosis studies showed the existence of circulating factors that regulated body weight: when blood from thin rodents was introduced in obese rodents, the weight of the latter was observed to become normalized.[10-12] In 1994, Dr. Friedman and his group first described one of these factors. It was leptin, a protein fundamentally secreted by adipocytes and, therefore, an adipokine. Leptin is made up of 167 aa, it weighs 16 kDa, belongs to the cytokine family and is considered an anorexigenic hormone because it causes satiety. In animals, local infusion of leptin into the hypothalamus reduces energy consumption and body weight.[13] Initially, it was thought that this would be the expected antidote to obesity, but clinical trials showed that the biological effect of the hormone was not significant. In an interview for *The Journal of Clinical Investigation*, Dr. Friedman stated that most patients produce enough leptin; however, its action is decreased in obese individuals, which is regarded as leptin resistance.[14]

Now we know that hyperleptinemia in obesity is associated with leptin resistance, hyperphagia and increased lipid storage capacity and oxidation in adipose tissue and peripheral organs.[15-18]

Subsequently, adiponectin was discovered, which is a 30 kDa adipokine that forms hexamers and dodecamers,[19] and that has high molecular weight associations that promote insulin sensitivity, increase lipid oxidation in muscles and the liver and decrease the expression of adhesion molecules and proinflammatory cytokines. In humans, hypoadiponectinemia is related to obesity, diabetes and metabolic syndrome.[20]

Omentin is also an adipokine with favorable effects on metabolism; it is found at lower concentration in the circulation of individuals with obesity, type 2 diabetes or cardiovascular disease. Omentin exerts its functions by activating insulin signaling pathways and by inhibiting inflammatory pathways and atherogenic processes.[21]

Other adipokines such as resistin, a retinol-binding protein or RBP-4, chemerin and visfatin are increased in the serum of individuals with obesity and promote insulin resistance and cardiovascular risk,[22] thus contributing to metabolic syndrome.

As previously mentioned, there is a group of molecules known as lipokines. De novo lipogenesis in adipose tissue gives rise to fatty acids such as palmitoleate (16:1n7) and fatty acid esters of hydroxy fatty acids (FAHFA), which are attributed favorable metabolic effects.[23] Palmitoleate has been shown to regulate the expression of lipogenic genes in the liver, to promote insulin sensitivity in the liver and muscle tissue,[24] and to antagonize the inflammatory effects produced by palmitic fatty acid in diet-induced obesity animal models.[25-27] Also as a product of de novo lipogenesis in adipose tissue, PAHSA, a FAHFA isomer consisting of a palmitic acid (16:0) and a stearic acid (18:0), is regulated by fasting-postprandial cycles, and

Table 1. Description of some adipokines/lipokines, secreting organ, influence on energy consumption and metabolism

Adipokine/lipokine	Secreting organ or tissue	Orexigenic/ anorexigenic	Metabolic effect
Leptin	Adipocytes, stomach and intestinal epithelium, placenta, muscle, mammary gland and brain	Anorexigenic	Satiety, lipid oxidation, thermogenesis, insulin sensitivity
Adiponectin	Adipocytes	Anorexigenic	Lipid oxidation, hepatic gluconeogenesis suppression, monocyte adhesion inhibition (anti-inflammatory and anti-atherogenic)
Omentin	Visceral adipose tissue vascular stromal cells and intestinal cells	Orexigenic	Increased capture of insulin-stimulated glucose and release of orexigenic peptides in the hypothalamus
Resistin	Adipocytes	Anorexigenic	Resistance to the action of insulin and fatty acid synthesis in liver
Reintol-binding protein-4	Adipocytes	---	Retinol transport and resistance to insulin action due to lower GLUT4 expression
Chemerin	Adipocytes, hepatocytes and lung cells	Orexigenic if chronically infused	Adipogenesis, angiogenesis, pro-inflammatory
Visfatin	Adipocytes in visceral adipose tissue	—	Possible influence on the development of obesity, pro-inflammatory and pro-atherogenic
Palmitoleic acid	Adipocytes	—	Insulin sensitivity, decreased lipogenesis
PAHSA (palmitic acid-hidroxy-stearic acid)	Fasting subcutaneous and perigonadal adipose tissue	—	Insulin sensitivity due to increased glucose capture, increased insulin and glucagon-like peptide-1 secretion, anti-inflammatory

its elevated concentrations have been associated with increased insulin sensitivity.[28] In clinical trials, insulin-resistant patients were shown to have lower PAHSA concentration[29] (Table 1).

The proportion of released adipokines or lipokines with anti-inflammatory action in relation to those of pro-inflammatory and pro-atherogenic action influences on the establishment of the metabolic alterations that accompany obesity. Finally, adipokine production imbalance is a reflection of adipocyte functionality loss under conditions of energy excess. The ability to buffer energy abundance by storing lipids in adipose tissue is due to an adequate expansion of this tissue, which is a characteristic of adequate functionality of this tissue.

In fact, healthy white adipose tissue can dramatically expand, more than any other tissue, which occurs in response to changes in energy status and as a result of higher lipid deposit and a lower utilization rate. Adipose tissue can grow due to hyperplasia and hypertrophy.[30] Hyperplasia is an increase in the number of adipocytes and hypertrophy is an increase in the size of adipocytes. In physiological growth states such as adolescence and pregnancy, adipose tissue grows, mainly through hyperplasia. In adulthood, preadipocyte maturation capacity declines.[31] The expression of peroxisome proliferator-activated receptor gamma 2 (PPAR-γ), one of adipogenesis key regulators, has been shown to be higher in young individuals than in older adults.[32] Adipose tissue grows by hypertrophy as a result of the inability for maturating preadipocytes. Hypertrophic adipocytes are those that can release a higher concentration of free fatty acids and a larger proportion of pro-inflammatory adipokines.[33] This is accompanied by tissue blood flow changes and increased fibrotic process, which causes cell death.[34]

Finally, the dysfunctional adipose tissue hypothesis associates energy excess with cardiometabolic risk. For this reason, the scientific community has delved into the metabolism of adipose tissue in order to prevent such risks.

Brown adipose tissue

Adipose tissue brown coloration is due to the fact that it is more vascularized and has a high content of

mitochondria, which, in turn, have cytochromes, which are responsible for giving color. The fat cells that make up the brown adipose tissue are multilocular or have several lipid vacuoles. These cells have a polygonal shape and measure 15 to 50 µm.[31] Brown adipose tissue has a progenitor cell (positive for Myf5 expression) in common with skeletal muscle;[35] i.e., brown adipocytes do not stem from white adipocytes, but from muscle tissue precursor cells.

Unlike white adipose tissue, brown tissue does not have the function of storing energy, but it dissipates energy through thermogenesis. To achieve body temperature regulation, brown adipose tissue is localized in superficial and deep sites. In superficial sites, the interscapular, cervical and axillary regions are found, while in deep sites contain the perirenal, periaortic, inguinal and pericardial brown adipose tissues.[30] In humans, the interscapular, axillary and cervical regions acquire special importance (Fig. 1).

The presence of brown adipose tissue is especially clear in the neonatal stage. In fact, brown adipose tissue was long thought to be highly restricted in mass after birth. However, several recent studies have shown that brown adipose tissue in humans is represented by several metabolically active tissue structures.[36-38] Exposure to cold and overeating increases the activity and size of these structures, whereas age decreases them.[39] On the other hand, in rodents, brown adipose tissue is maintained throughout life and highly significantly contributes to energy expenditure by thermogenesis.[40]

β-adrenergic receptor activation in brown adipose tissue promotes the stimulation of uncoupling proteins (UCP), which use oxidative phosphorylation proton flow and thus produce heat instead of ATP. So far, three UCP isoforms have been identified and cloned: UCP1 and UCP2, which are expressed in white adipose tissue, while UCP3 is mainly expressed in brown adipose tissue and skeletal muscle.[41] It is in brown adipose tissue mitochondria where heat is produced by UCPs function and, as a consequence, energy expenditure is increased. When food is unavailable, hunger signals from the hypothalamus activate gabaminergic neurons, which block sympathetic system activation in order to decrease thermogenesis in brown adipose tissue and reduce energy expenditure.[42]

There is evidence that brown adipose tissue, like white adipose tissue, regulates energy homeostasis in response to overall metabolic status. In this regard, the description of the transdifferentiation or interconversion process has given clues about the possibility of white adipose tissue being transformed into brown. In adult animal models, fat mass in anatomical regions such as the epididymal and interscapular areas is known to be essentially composed of white and brown adipose tissue, respectively. However, in epididymal adipose tissue, the presence of brown adipocytes has been verified, whereas in interscapular adipose tissue, white adipocytes have been found.

There are conditions, such as a higher concentration of thyroid hormones, bile acids, natriuretic peptides and retinoids, that increase the number of brown adipocytes in white adipose tissue.[43] The development of brown adipocytes in white deposits has been associated with a lower risk for developing obesity and diabetes[44-47] and this is achieved with exposure to cold and with treatment with β-adrenergic receptor agonists.[48] In contrast, the conversion of brown into white adipocytes has been demonstrated in diet-induced obesity animal models.[49]

Probably by delving into the understanding of transdifferentiation, in the future there will be tools available that offer a preventive or therapeutic strategy for obesity.

Beige adipose tissue

Recently, adipose cells similar to brown adipocytes, with beige coloration and positive for UCP1 expression, were shown to be likely to appear in response to certain stimuli such as exercise, exposure to cold or some hormones.[50] They can accumulate in white adipose tissue typical deposits and have been called beige or “brite” adipocytes (a combination of the terms brown and white).

Although beige adipocytes have similar characteristics to the brown ones, such as their morphology (they contain several lipid vacuoles), they have different anatomical localizations. While beige adipocytes are immersed in the subcutaneous regions of white adipose tissue, brown adipocytes are essentially found in the aforementioned superficial regions (Fig. 1).

Brown and beige adipocytes appear to develop from different embryonic precursors.[51] As previously mentioned, brown adipocytes originate from Myf5-positive cells. In turn, beige adipose cells appear to descend from a Myf5-negative lineage,[52] although their exact origin is still under debate and two possibilities have been proposed: the first one suggests that they are derived from white adipocyte precursors and become beige adipocytes in response to environmental stimuli, such as exposure to cold; the second one proposes that mature white adipocytes can be transdifferentiated by having contact with the appropriate stimuli to become beige.[53] Finally, it is possible that both proposals are correct and that, depending on the environment,

genetic background and beige cell-containing adipose tissue localization, one or the other occurs.[54]

Under basal conditions, beige adipocytes express a signature of molecular markers that is similar to that of white adipocytes, but after transdifferentiation, they acquire an expression pattern similar to that of brown adipocytes. That is, a thermogenic expression pattern that reflects higher energy expenditure and oxygen consumption.[55]

Exercise is a stimulus that favors white adipose tissue transdifferentiation to beige adipose tissue. In 2012, a peptide released by skeletal muscle subjected to exercise in rodents was found to be able to influence on white adipose tissue "browning". In mouse white adipocyte cultures, this peptide turned the cells into UCP1-positive, with a beige phenotype; that peptide was named irisin;[56] it was observed to be present in the serum, and its concentration increases after short-term training. Circulating irisin increase resulted in a higher expression of mitochondrial genes and oxygen consumption in white adipose tissue. Since then, research on irisin has gained interest for the possible influence of this peptide on the metabolism of white adipose tissue and, therefore, on obesity.[57]

Adipose tissue color hues, what is the clinical reality?

As previously mentioned, brown and beige adipocytes share the ability to transform chemical energy into heat, thus contributing to adaptive thermogenesis. We know that the presence and activation of these cell types are not limited to the neonatal stage, but that can be induced in human adults.

In human adults, the most common areas of brown adipose tissue are supraclavicular and cervical.[58] The supraclavicular region appears to be abundant in brown and beige adipocytes, and its metabolic function has been established to be correlated with individual overall metabolic profile.[59]

Clinical trials have demonstrated that females have a larger mass of brown and beige adipose tissue in comparison with males, and that it is more active. It has also been established that the higher the adiposity, the lower the content and activity of brown and beige adipose tissue. Consistently, weight loss by bariatric surgery promotes an increase in the mass and function of brown adipose tissue.[60]

Actually, brown adipose tissue in humans is composed of a combination of multilocular brown or beige adipocytes and unilocular white adipocytes.[61] There is evidence that these adipose tissue deposits are waiting for environmental signals to "turn brown" and activate, as it was explained in animal models. Thus, hormones such as leptin, fibroblast growth factor 21, adrenergic hormones and some cytokines promote adaptive thermogenesis, by transdifferentiating white adipocytes in areas of brown adipose tissue and increasing their activation. As a result, the expression of UCP1 and other brown and beige adipose tissue markers is increased and energy expenditure is higher, which is accompanied by improved glucose tolerance.

Adaptive thermogenesis generated by cold or "shivering" is clearly accompanied by structural changes in the brown adipose tissue of humans, which affects energy homeostasis. For example, a change in room temperature from 24 to 19 and 17 °C increases brown adipose tissue mass, as well as energy expenditure, through an increase in the use of lipids and glucose.[62] Since physical activity and "shivering" simultaneously induce heat and irisin production in muscle tissue, the influence of this hormone on human white adipose tissue "browning" or transdifferentiation has been studied. Investigations are controversial. The conclusions of some studies show that physical training in human adults does not significantly increase irisin concentration, and neither does it promote an increased expression of genes related to adipose tissue "browning", such as UCP1, PGC-1b and PRDM16.[57] However, other investigations indicate that during exposure to cold, the secretion of irisin is proportional to the intensity of the "shivering" and similar to that induced by resistance exercise. The same group points out that irisin induces the conversion of human preadipocytes into beige adipocytes, while generating more heat by thermogenesis.[62]

Irisin and other signals appear to be responsible for causing adaptive thermogenesis and changing adipose tissue "color shades" in humans; however, this will have to be confirmed in the future. Nevertheless, it is clear that adipose tissue plasticity, its capacity for interconversion, transdifferentiation and "browning" offer an opportunity to modulate energy metabolism. Finally, the knowledge that is to be generated from the pathways that activate brown or beige adipose tissue might be used to establish therapeutic interventions to counteract insulin resistance and obesity.

Conclusions

The study of adipose tissue and its functions has provided valuable information for the understanding and possible treatment of the metabolic disorders that accompany obesity. White adipose tissue maintains metabolic homeostasis through adipokines or lipokines

regulated release. In turn, they respond to signals of the environment by promoting hunger or satiety, sensitivity or resistance to the action of insulin, lipid use or storage, inflammation or coagulation, among other processes. In white adipose tissue, areas with brown or beige cells that respond to physical activity or thermogenesis needs, which contribute to energy expenditure, both in animal and human models, can be generated. For this, the remodeling of adipose tissue is required, which results in a change in vascularization, inflammation, hypoxia, gene expression pattern and protein and lipid factors content. Finally, current knowledge on the colors of adipose tissue and its hues sheds light on the influence of global metabolism; in the future, we might have tools available for its modulation.

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