The Adipose Organ: Implications For Prevention And Treatment Of Obesity

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Saverio Cinti
Director Center of Obesity
University of Ancona (Politecnica delle Marche)
Ancona,
Italy

cinti@univpm.it

White adipocytes

Adipocytes are characterized by the abundance of cytoplasmic lipid droplets (1). White adipocytes show a unique large spherical lipid droplet (unilocular adipocytes) that predominate its general morphology FIG 1. In fact a thin rim of cytoplasm surrounding the lipid droplet and including a crescent shaped nucleus forms the rest of the cell. Thus, the size of the cell is tightly related to the size of the lipid droplet. The size of white adipocyte is around 60-70 μm in mice and about 30% larger in humans. The thin cytoplasmic rim contains sparse organelles mainly formed by elongated mitochondria. The lipid droplet is separated by the cytoplasm by a dense line without a specific structural aspect. During intense lipolysis smooth endoplasmic cisternae are visible often in thigh contact with the lipid droplets. Glycogen is usually absent in large mature adipocytes, but is often present in small developing adipocytes (2, 3) and some lipofuscin is usually present in aged animals and in humans (4). A distinct basal membrane, tightly apposed on the external surface of cytoplasmic membrane, surrounds every adipocyte. Several pinocytotic vesicles are visible at this level Fig 2.

The function of white adipocytes is complex because it includes the secretion of several important molecules. The main secreted molecules are fatty acids for the metabolic needs of the organism in the intervals between meals that can, therefore, be prolonged up to three-four weeks. This property is of paramount importance for mammal's survivals in conditions in which food is not easily available as it was until a century ago even in the so-called civilized parts of the world. Another important secreted molecule is a protein called leptin (5). Leptinemia is correlated with the total amount of fat in the body and represents an important signal for the limbic system that induces mammals to search for food. Genetic alterations in its synthesis or in its functional receptor have been found in mice and humans(6). These subjects have a strong signal of absence of energetic reserve and their behavior is that of hungry people that induce morbid obesity. Absence of functional leptin can be corrected by the administration of recombinant protein and patients recover completely from obesity in few years (7).

Adiponectin is another important protein secreted by adipocytes (8). It is very important for metabolic fitness. It is involved in regulating glucose levels as well as fatty acid oxidation (9).

Adipsin/complement factor D is the first described protein secreted by white adipocytes, which catalyzes the rate-limiting step of the alternative pathway of complement activation (10, 11), but its function in relation to energy homeostasis and systemic metabolism is unknown.

Interestingly leptin is positively correlated and adiponectin and adipsin are inversely correlated to body fat, thus in obese mammals high levels of leptin and low levels of adiponectin and adipsin are found. The leptin resistance of obese mammals prevents a positive control of food intake (12) and the low levels of adiponectin and adipsin could contribute to the metabolic disregulation of obese animals and humans (13).

Many other factors are secreted by white adipocytes (reviewed in (14)) that allow to consider white adipocytes as important endocrine cells mainly involved in the metabolic homeostasis .

Brown adipocytes

Brown adipocytes are smaller than white adipocytes and with a general shape that can be described as polygonal. Nucleus is central and roundish. Cytoplasm contains several small lipid droplets (multilocular adipocytes) Fig 1 and 2 and numerous typical mitochondria: spherical and packed with laminar cristae. A distinct basal lamina surround each brown adipocyte but it is interrupted at the level of gap junctions that couple electrically these cells (15). Other organelles are sparse (16, 17).

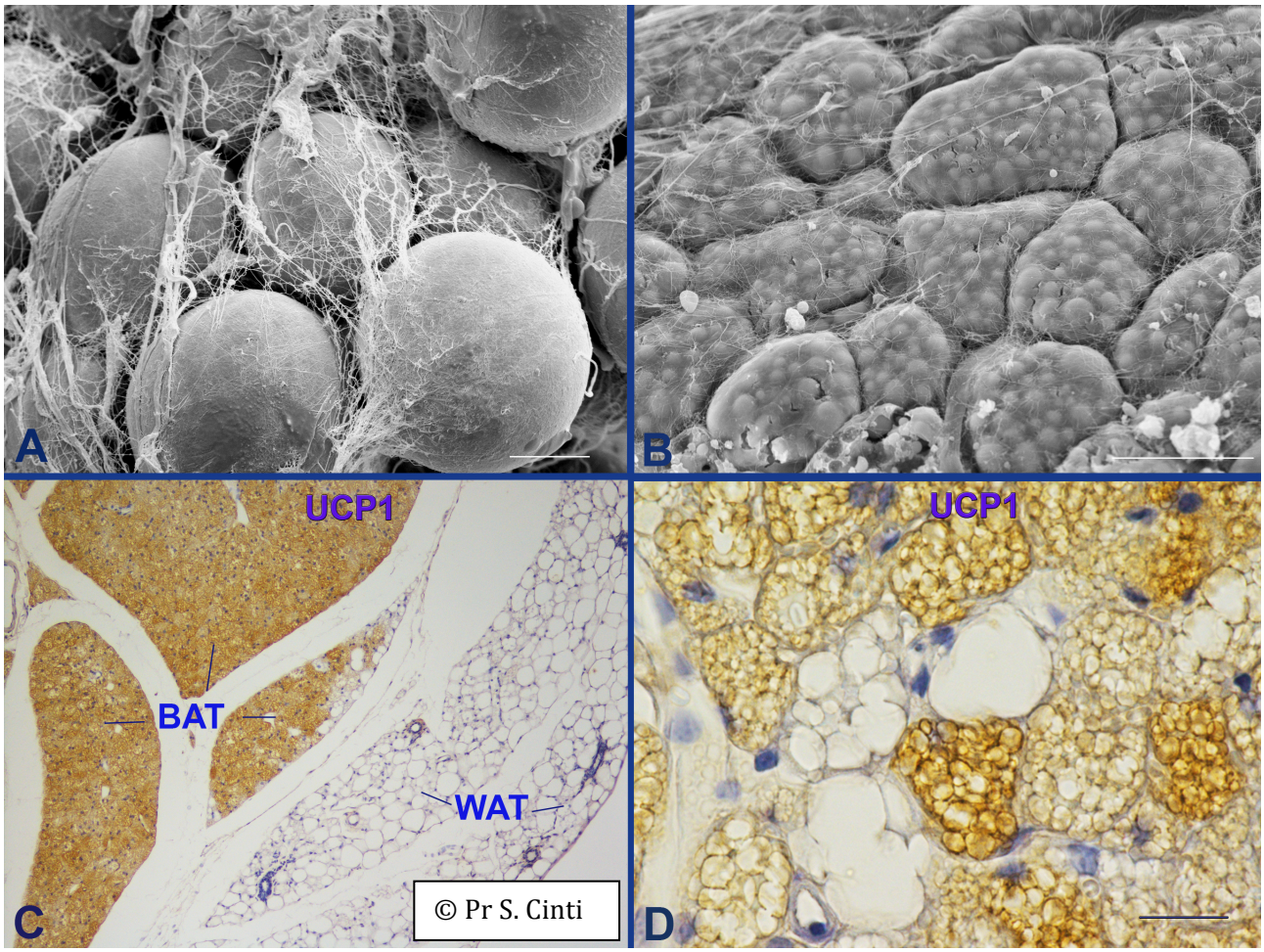

Figure 1. *Scanning Electron Microscopy of white adipose tissue (A) and brown adipose tissue (B). Bar: 20 µm. C: Histology and immunohistochemistry showing the specific UCP1 immunostaing of interscapular brown adipose tissue. D: Detail of interscapular brown adipose tissue showing white-brown transitional forms. Only multilocular adipocytes are UCP1 immunostained. Note that immunostaining is not at the same intensity in all multilocular adipocytes (Harlequin phenomenon (34)). WAT: white adipose tissue. BAT: brown adipose tissue. C and D bar: 50 µm.*

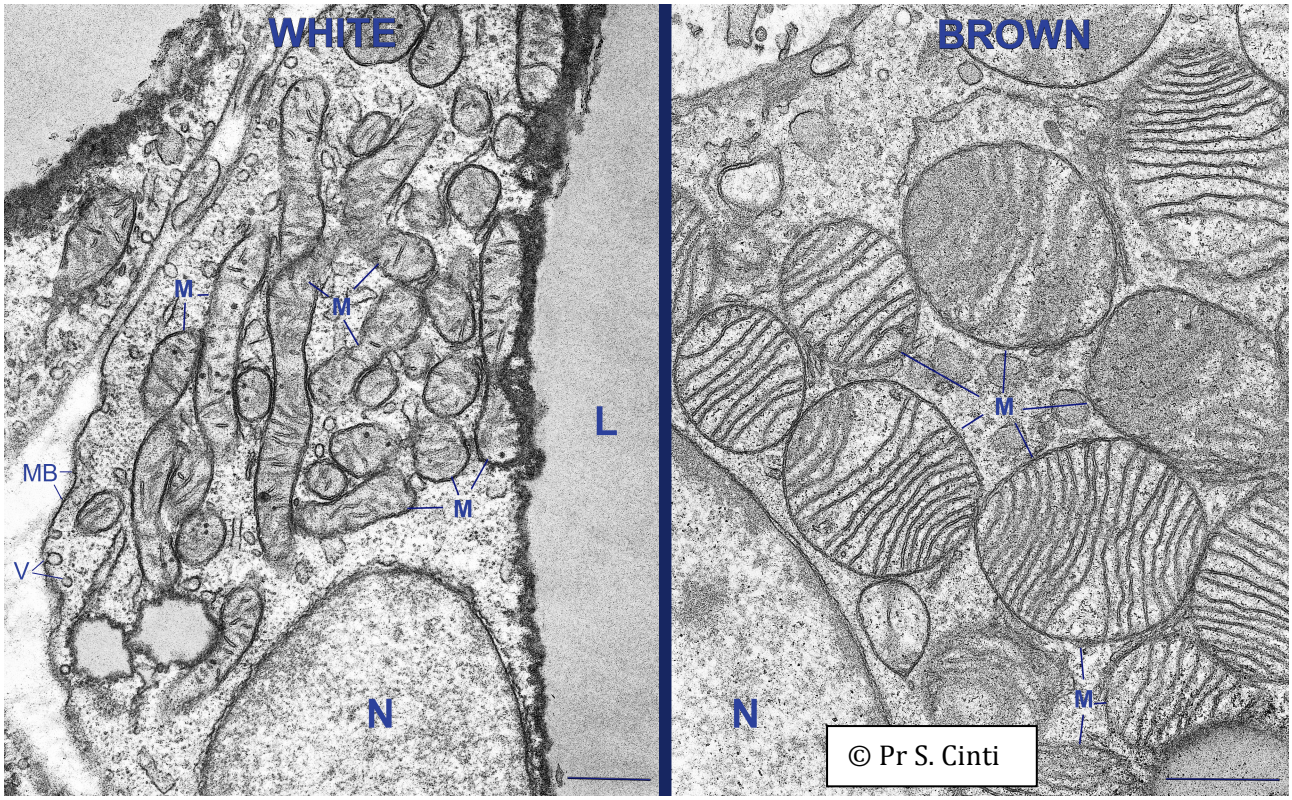

Figure 2. *Transmission Electron Microscopy of white and brown adipocytes. Note the morphologic differences between mitochondria (M) of these two cell types. In white adipocyte nucleus (N), lipid droplet (L), pinocytotic vesicles (V) and external basal membrane (BM) are also indicated. Bar: 0.7μm. In brown adipocyte nucleus (N) and some mitochondria (M) are indicated. Bar: μm 0.6 From: Cinti S. "The Adipose Organ" Kurtis, Milan 1999.*

This morphology therefore is quite different from that of white adipocytes and this account for their very different function that is thermogenesis. The multilocular arrangement of lipids allows an extended surface from which a considerable amount of fatty acids can pass in the cytoplasm when the cell is functionally activated. Fatty acids are transported into mitochondria for their beta-oxidation, thus a proton gradient is created between the external and internal mitochondria membrane. The presence of a protonophore called UCP1 (uncoupling protein 1) nullifies the proton gradient, thus obtaining that the only result from the massive fatty acids oxidization is heat production (18, 19). Because of the massive substrate and the large number of uncoupled mitochondria the heat production is about 300 times that produced from the normal metabolism of an average cell in the organism and this is physiologically relevant (20).

Thus the only similitude between white and brown adipocytes consists in the presence of abundant cytoplasmic lipids that account for their denomination as adipocytes. Nevertheless both cell types share unusual properties such as the ability of accumulate and release lipids. Furthermore both are provided with a special adrenergic receptor called beta3 (21), that is expressed quite exclusively on adipose tissues (22).

Recently it has been observed that brown adipocytes have endocrine properties, they in fact are able to produce and secrete hormones (betatrophin) and growth factors (FGF21). Betatrophin acts on pancreatic islets and promotes beta cells proliferation (23). FGF21 is an important regulator of glucose metabolism and in the plastic properties of adipose tissues (24, 25) (see below).

White Adipose Tissue (WAT)

White adipocytes are organized to form WAT (FIG 1). Although about 90% of the tissue volume is due to adipocytes they represent only about 30-40% of the cells present in this tissue (26). The rest is due to vascular and nerve structures, interstitial cell among which fibroblasts, macrophages, mast cells, lymphocytes, and preadipocytes are the most frequently found. Preadipocytes are found in white adipose tissue even in old humans and are characterized by their tight connection with the wall of capillaries, their small size, high nucleo-cytoplasm ratio and the presence of a basal membrane (1, 3). Cytoplasmic organelles are represented by few organelles among which glycogen and few very small mitochondria are often present. During development, several intermediate steps are visible and white preadipocytes assume a unilocular aspect even in very small cells, thus the main developmental aspect remain the progressive increase in size until the characteristic average size for that specific fat depot (3, 27). Nerves are mainly formed by bundles in tight connection with vasculature, but parenchymal nerves are seldom observed. These last nerves are often mielinated (therefore probably sensitive) and immunohistochemistry also showed the presence of CGRP, SP(28). Innervation expands under the condition of fasting (29). In this condition parenchymal noradrenergic fibers in tight contact with adipocytes are found.

Brown Adipose Tissue (BAT)

Brown adipocytes are organized to form BAT (FIG 1). Parenchymal composition of BAT is similar to that of WAT and, again, about 30-40% of the parenchyma is composed by other cell types (30). The main aspect of typical BAT are the presence of a very dense capillary network (about six times that of WAT(16)) and dense parenchymal innervation(28, 31). Each brown adipocyte is in thigh contact with capillaries and, often, parenchymal noradrenergic fibers reach the plasma membrane of brown adipocytes (1, 16). This innervation and the gap junctions connecting brown adipocytes, are very important for the tight neural regulation of BAT thermogenesis (19).

Mast cells are also very frequently found in BAT (32), but their function is still unknown even if the presence of H3 receptors on endothelial cells of BAT is abundant and suggest a role in the thermogenesis for these cells (33). The high vascular density account for two main functional reasons: need of oxygen for intense beta-oxidation and quick heat removal from the tissue. Excess of heat in acutely activated brown adipocytes could be responsible for the Harlequin phenomenon(34). It consists in the fact that UCP1 immunostaining in this condition assume a patchy picture in some way recalling the classic Harlequin mask (1). We showed the presence in the same strongly UCP1 stained brown adipocytes of heat shock protein that could down regulate the gene in order to avoid heat due self damages to cell (34). In line, chronically activated BAT, shows lower levels of staining intensity homogeneously diffuse in the tissue. Mechanisms responsible for the transition from Harlequin to diffuse UCP1 activation are still unknown.

The concept of Adipose Organ

Anatomy defines as an organ any dissectible structure composed by two or more tissues devoted to a collaborative finalistic purpose.

WAT and BAT are contained in dissectible structures, called fat depots, with a well defined shape and widely distributed into the organism of mammals (35-37). Two main anatomic sites contain fat depots: subcutaneous and trunk compartments Fig 3. The subcutaneous compartment is located beneath the skin. In small mammals subcutaneous fat is limited to two depots located at the root of front and rear legs (anterior and posterior subcutaneous fat depots). In humans this depot occupies most of the subcutaneous space, but in females it is abundant at the level of breasts and gluteal-femoral area.

Trunk contains thoracic and abdominal depots (visceral fat). Thoracic depot surrounds heart, aorta and its main branches.

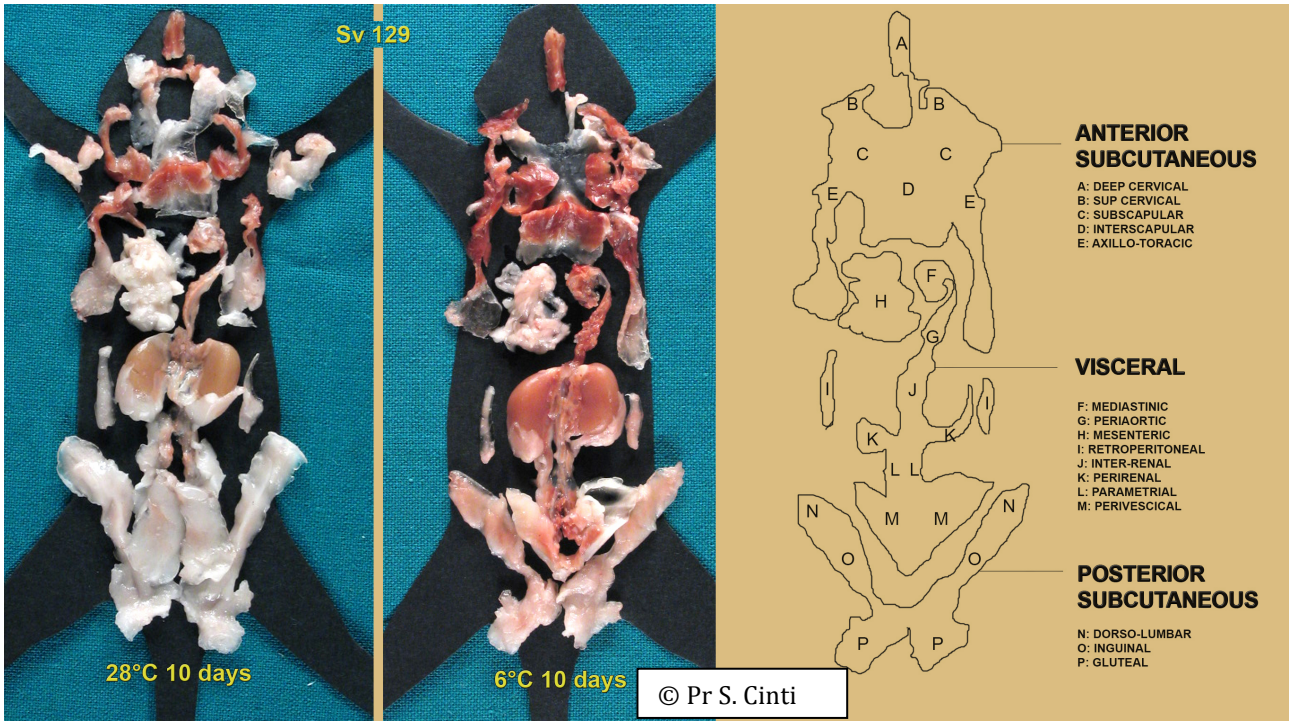

Figure 3. *Adipose Organ of adult female mice. Note that white and brown areas are visible in both subcutaneous and visceral depots in the adipose of organ of warm acclimated mouse (28°C 10 days). In the cold acclimated mouse (6°C 10 days) the brown areas are extended to almost all areas of the organ (browning). Bar: 1cm. Small depots such as omental (39) , thigh and popliteal (62) depots are not shown here.*

Abdomen contains intra-peritoneal and retroperitoneal depots (38). Intra-peritoneal depots are mainly contained into omentum (present, but small in mice (39)) and mesentery. Some Authors refer to these two depots as visceral depots because they drain their blood into the portal vein and this can be important for some clinical aspect linked to visceral fat accumulation(40). We prefer to use the term visceral for all fat in the trunk, regardless of their blood drainage, to outline the anatomical position and in view of the most recent discoveries regarding the pathogenesis of clinical problems related to visceral fat accumulation(39, 41). In small male mice another consistent and widely studied depot is contained into a peritoneal sac linked to epididymis (epididymal depot). Retroperitoneal depots are mainly located between parietal peritoneum and anterior (small) or posterior wall of the abdomen and in the pelvis. Those in contact with the posterior wall of abdomen are tightly connected with aorta and its main branches, thus forming perirenal-retroperitoneal depot. Pelvic fat in female mice forms a unique structure we denominated abdomino-pelvic depot (17, 36, 37). It consists of perirenal, periovaric, parametrial and perivescical parts and it is in continuity with periaortic thoracic depot at the level of aortic hiatus of diaphragm. An important feature of the adipose organ concept is histology: WAT and BAT are the two main parenchymal tissue contained together in the organ. Even if we consider the multi-depots organization of murine adipose organ the mixed composition can be found in most of the subcutaneous and visceral depots. Of course WAT is found in the white parts and BAT in the brown parts of the organ. As a matter of fact white and brown adipocytes derive their names from these colors due to the intrinsic composition of the cells and tissues: mainly lipids for white and mitochondria and vessels for brown. The relative amount of BAT and WAT in adipose organ is variable and depends mainly on genetic background, age and environmental conditions. Many other anatomic sites contain small amount of white adipocytes, such as bone marrow, skin (dermal fat), parotid glands, parathyroid, lymphnodes, skeletal muscles, orbital cavity and synovial sheaths. The fine properties of adipocytes in these organs are largely unknown.

Plasticity of Adipose Organ

Cold exposed animals and humans increase the relative amount of BAT in adipose organ and white areas turn into brownish areas (42-45) Fig 3. This phenomenon is called browning, in small animals it can be obtained also by administration of beta3 agonists (43) and our as well as other's studies suggest that it is due to direct conversion (transdifferentiation) of white adipocytes into brown adipocytes (43, 46, 47). This phenomenon is highly regulated by sympathetic nervous system with branching of parenchymal noradrenergic fibers with a positive correlation between density of these fibers and number of brown adipocytes in most subcutaneous and visceral depots (36, 37). Lack of the beta3 adrenoceptors strongly reduce the phenomenon(48). Recent lineage tracing studies confirmed this phenomenon (49-51), but also outline that it is accompanied by the appearance of a new population of brown adipocytes (50). Some Authors consider these newly appeared brown adipocytes different from those present in classic BAT depots (interscapular area) and different names have been proposed: beige or brite (52, 53). The arguments used to justify these different names are mainly ontogenetic and of genetic signature. Our and other's recent work on the origin of brown and white adipocytes suggest that endothelial cells of adipose tissues are the source for both white and brown preadipocytes (54, 55), although other Authors were not able to confirm that lineage, at least for the white adipocytes (56). What is the origin of endothelial cells able to develop into preadipocyes is unknown.

A very recent paper suggests a mesothelial origin for visceral adipocytes (57) It remains to be established if the brown-like adipocytes appearing in WAT during browning are truly brown or not. To date there is no data showing that the UCP1 immunoneactive multilocular adipocytes found in browned parts of the adipose organ that, in warm conditions, are predominantly composed by WAT have a different function from those present in the interscapular area when studied in vivo at single cell level. On the other end we should outline that browning is accompanied to increased thermogenesis with all the healthy effects that can be obtained by the activation of classic interscapular BAT (58, 59).

As a matter of fact browning is of healthy relevance because BAT prevents obesity and related disorders (23, 60-65). Thus browning of adipose organ could be an important strategy to prevent or treat obesity and its related disorders whatever we like to call the newly appeared UCP1 immunoreactive multilocular adipocytes: brown (our preference), beige or brite.

This plasticity could explain the normal coexistence of white and brown adipocytes in most depots of adipose organ: during chronic cold exposure white adipocytes convert into brown adipocytes to contribute to thermogenesis and vice versa in case of chronic positive energy balance brown adipocytes convert into white adipocytes to offer larger energy store capacity(66-68). In line with this theory obese animals have a whitening of brown parts of adipose organ. Thus, these cells are able to reprogram their DNA in order to distribute energy toward essential functions for survival: thermogenesis or general metabolism.

Pink adipocytes

In order to find further evidence of physiologic reversible transdifferentiation we explored the adipose organ in other physiologic conditions and found that striking reversible adipo-epithelial transdifferentiation phenomenon occurs in adipose organ of female mice during pregnancy-lactation and post-lactation stages.

In virgin adult mice the five bilateral mammary glands correspond to all subcutaneous depots (FIG 4).


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Figure 4. *Adipose organ of adult female mouse at day 14th of lactation. Note the anatomical transformation of both subcutaneous depots (compare with Fig 3). Bar:*
From: Cinti S. "The Adipose Organ" Kurtis, Milan 1999.

A network of branched epithelial ducts ending in three bilateral nipples infiltrates the anterior depot. The posterior depot is also infiltrated by a similar network but ending in two bilateral nipples. Thus, in general, ten mammary glands are considered: six in the anterior subcutaneous depot and four in the posterior subcutaneous depot. The lobulo-alveolar (or alveoli) component of the gland is absent outside pregnancy and lactation periods. During pregnancy a progressive alveologenesis develop with two main steps: early and late. Early alveologenesis (10^{th}-15^{th} day) is characterized by the formation of alveoli in tight connection with ducts. Epithelial cells forming these alveoli do not contain lipid droplets at light microscopy. Late alveologenesis (14^{th}-20^{ty}) is characterized by alveoli formed by epithelial cells containing big cytoplasmic lipid vacuoles . We called these cells pink adipocytes (FIG 5) because they are parenchymal cells of adipose organ containing large cytoplasmic lipid droplets, with a specific function: milk production (69). Pink is the color of mammary glands during pregnancy and symbol for female gender. Of note, in parallel with the progressive alveologenesis the mammary glands loose progressively most adipocytes. We showed with different techniques, including lineage tracing and explants experiments, white-pink-white transdifferentiation, thus offering a new example of physiologic reversible transdifferentiation phenomenon in adipose organ (70-72)

Also this type of transdifferentiation is linked with the general role of the organ of energy repartition: in this case to the pups for survival. Thus, adipose organ seems to play a pivotal role in maintenance of homeostasis at both short and middle term.

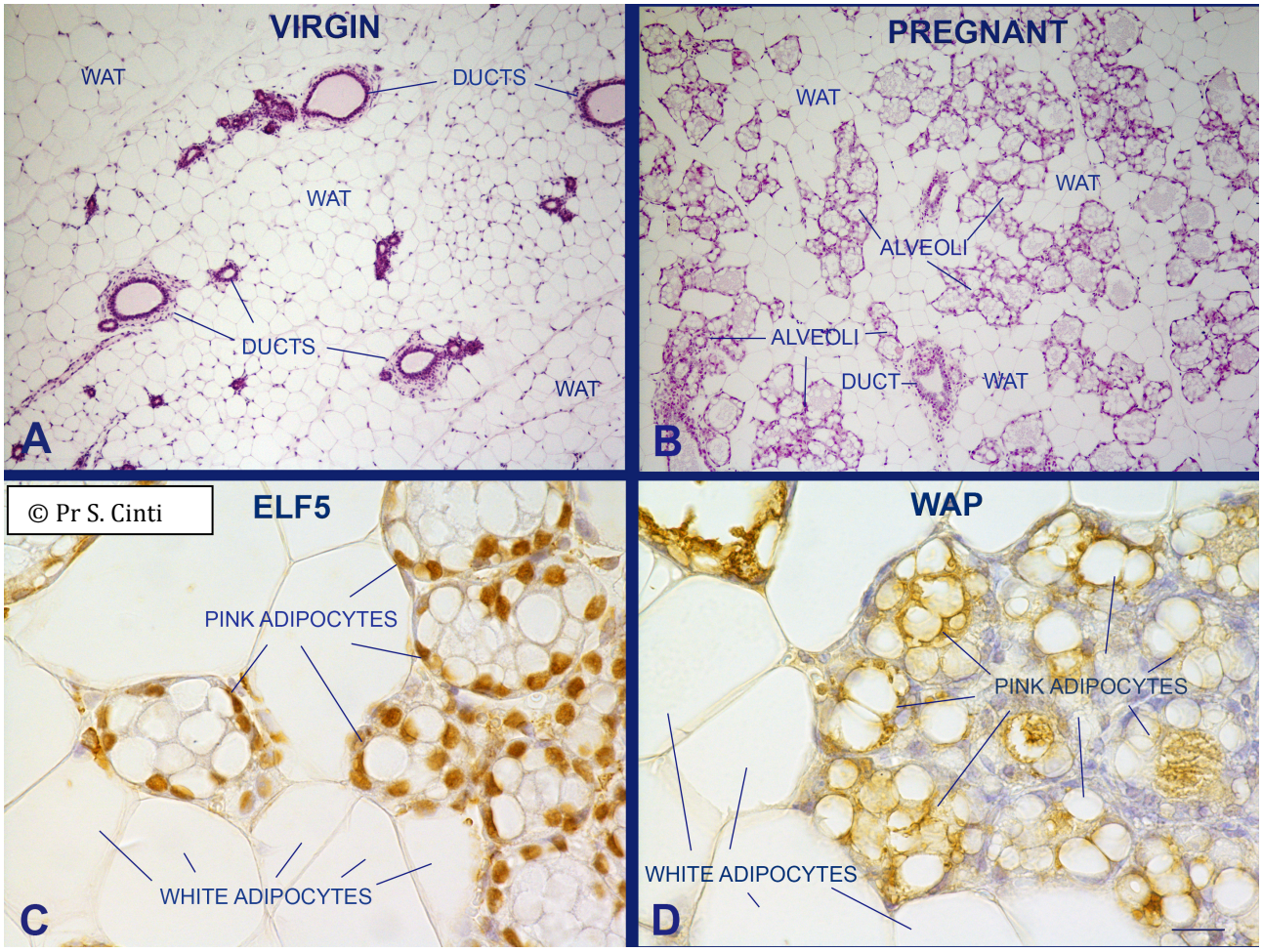

Figure 5. *Histology and immunohistochemistry of mammary gland of adult female mice. Alveoli composed by pink adipocytes are absent in virgin mice (A) and appear in the second half of pregnancy (B). Pink adipocytes (C and D) are immunoreactive for the master transcription factor of alveologenesis ELF5 in nuclei (C) and for the milk protein WAP (whey acidic protein) in cytoplasm (D). Bar: 50 μm in A and B, 12 μm in C and D.*

The obese adipose organ

In 2004 two US groups simultaneously discovered that obese adipose tissue of mice and humans is infiltrated by macrophages. They noted that this infiltration is coincident with the appearance of insulin resistance and that most of TNFα, IL6 and NO is present in the stroma-vascular fraction (containing small lipid-poor cells including macrophages) and not in the floating fraction (containing mature adipocytes) of the obese tissue (73, 74). Thus all together these findings pointed to the importance of this macrophages infiltration in the relationship between obesity and insulin-resistance that is a prelude to T2 diabetes.
We discovered that macrophages infiltrate obese fat to remove debris of death adipocytes (75).

The vast majority of active macrophages form crown-like structures (CLS) formed by macrophages surrounding the remnant lipid droplet of death adipocyte (Fig 6).

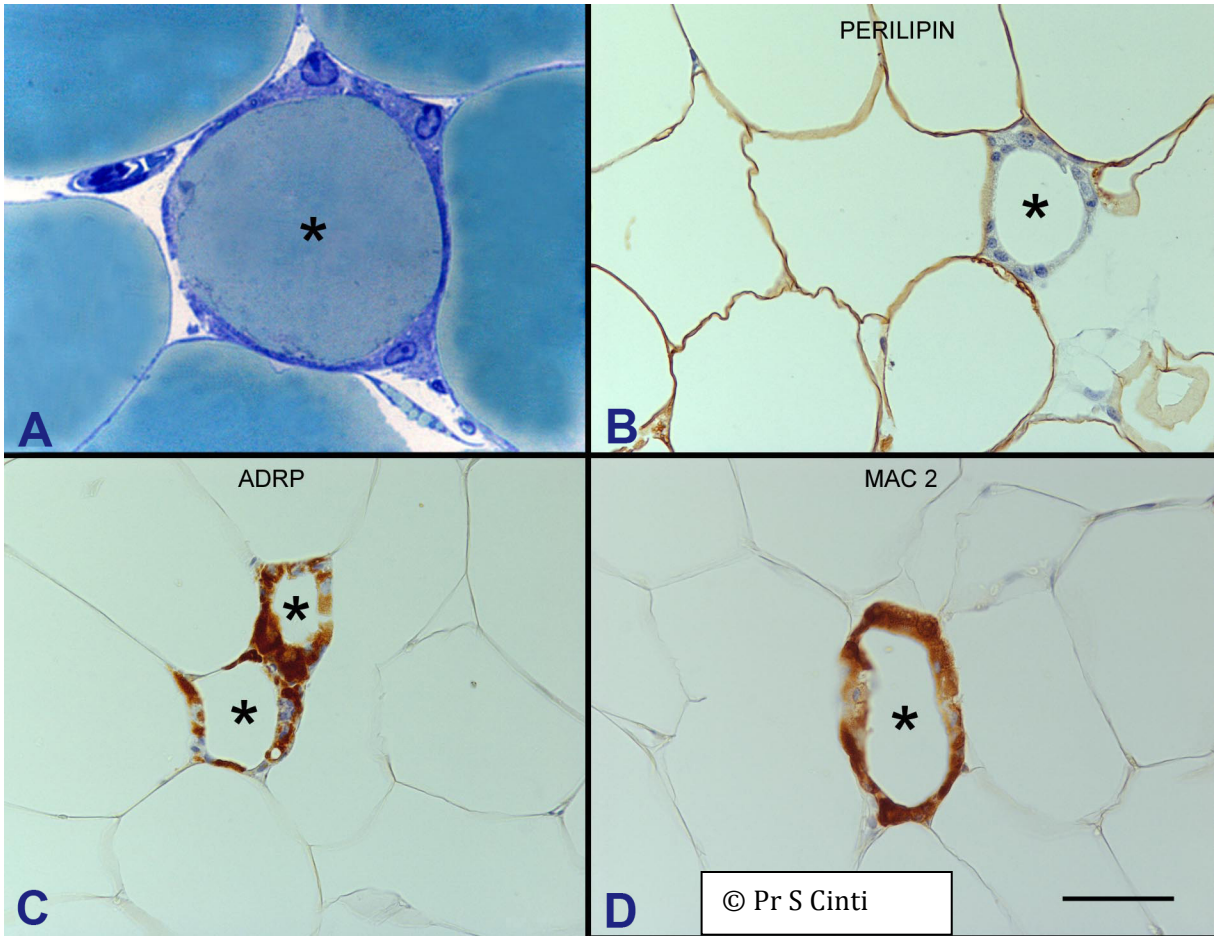

Figure 6. *Histology and immunohistochemistry of Crown-Like Structures (CLS) (asterisks) in white fat of obese mice. A: resin embedded tissue, toluidine blue staining showing macrophages surrounding a lipid droplet. B: perlipin immunostaining . This marker of alive adipocytes is absent in CLS. ADRP (C) and MAC2 (D) are markers of active macrophages. Bar: 15 µm in A and 25 µm in B-D. From: Cinti S, Obesity and Metabolism 2: 95-103, 2006.*

Macrophages are often fused in syncytia (like those fond in foreign body reactions) and show electron microscopic features suggesting that they are actively reabsorbing the remnant lipid droplet (39, 76). A transgenic model in which specific adipocyte death is inducible confirmed that CLS are formed at the level of all death adipocytes (77). Death of adipocytes seems to be the cause of their death because mice lacking lipolysis (HSL-KO) are lean but their adipocytes are very hypertrophic and shows the same CLS density than that of obese fat (75). Obese adipocytes have a series of organelles alterations visible at electron microscopy including mitochondrial dismorphisms, rough endoplasmic reticulum dilatation, calcium deposits, Golgi hypertrophy, glycogen accumulation, and rare cholesterol crystals. Most of these

alterations can cause DAMPS (damage associated molecular patterns) that can activate NLRP3 inflammosome inducing activation of a specific caspase1 responsible for IL-18 and IL 1β that induce cell death for pyroptosis (78), thus we checked for the specific caspase1 and found intense immunoreactivity in cytoplasm of obese adipocytes and not in control lean adipocytes. Furthermore, caspase1 was absent in adipocytes dying for induced apoptosis in transgenic mice, thus confirming that hypertrophic obese adipocytes die for pyroptosis (79). The visceral obesity is more morbigen than subcutaneous obesity and CLS density in mice under high fat diet is higher in visceral than in subcutaneous fat . We found that CLS density, in genetic obese mice, correlate positivity with adipocyte size in both visceral and subcutaneous fat, but visceral fat have higher density in spite of their smaller size (39). Thus the CLS index (CLS density/mean adipocyte area) is four times higher in visceral fat than in subcutaneous fat in db/db (diabetic obese) mice. These data offer an explanation to the well known morbigen property of visceral fat accumulation (40). In this contest it is interesting that forced expression of PRDM16, a key transcription factor for browning, in fat induce browning and all healthy consequences mainly in subcutaneous fat (58) and deletion of this gene specifically in fat induce a transformation of subcutaneous fat into a visceral like fat with all its unhealthy consequences (80). Thus a pharmacologic induction of browning factors could be used for future strategies not necessarily for real browning induction but just for transformation of adipocytes of adipose organ into more brown-prone healthy cells.

Conclusive remarks

In conclusion the lesson from the adipose organ anatomy suggests a new perspective angle for the future of cell biology with new preventive and therapeutic perspectives for important and epidemic diseases such as metabolic syndrome and breast cancer.
Understanding the molecular mechanisms underling the physiologic reversible transdifferentiation phenomena of this organ could help in the discoveries of new targets for drugs able to modulate the phenotype and physiology of mature cell.

Acknowledgments

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~ About the Authors ~

Saverio Cinti

Saverio Cinti is medical doctor and full professor of anatomy in School of Medicine at University of Ancona since 1986.

Actually he is Director of the Obesity Center at the same University. The main research interest is focused since 35 years on adipose tissues in relation to the medical problems of obesity and T2 diabetes. He published more than 250 papers (pub med) and his H index is 49 (Scopus Jan 2015). In 1999 published the book: The Adipose Organ. He published 14 chapters on obesity-related books.

The most important observations were on the physiologic reversible reprogramming of white and brown adipocytes. White-brown reprogramming opened new perspectives for future treatment of obesity and related disorders.

Most recently he discovered the white-pink reprogramming (mammary adipocytes can reversibly convert into glandular cells producing milk during pregnancy and lactation) with new perspectives in the field of breast cancer.

He also discovered the cause of chronic low-grade inflammation of obese adipose tissue describing the death of adipocytes (by pyroptosis) and consequent crown-like formations (CLS) providing one pathogenetic link between obesity and T2 diabetes.

In 2008 was awarded of Blaise Pascal Medal by the European Academy of Sciences and in 2013 was awarded of Wasserman Prize by the European Association for The Study of Obesity.

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