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DANCE ROUND

We dance round in a ring and suppose,
But the Secret sits in the middle and knows.
Robert Frost

ADIPOSE TISSUE: THE RENAISSANCE MARKED BY FOUR PARADIGM SHIFTS

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One of the biggest recent achievements in the study of cardiometabolic diseases (atherosclerosis, hypertension, obesity, type 2 diabetes mellitus, metabolic syndrome, and Alzheimer's disease, which is recently viewed as type 3 diabetes, see below) is associated with the "rediscovery" of a neglected tissue, the adipose tissue.

Here we will *Dance Round* four paradigm shifts in the study of adipose tissue.

In 1962, Thomas S. Kuhn published his book *The Structure of Scientific Revolutions* (1st edition, University of Chicago Press, Chicago, USA). Its publication was a landmark event in the history and philosophy of scientific knowledge (epistemology). Kuhn challenged the prevailing view of "normal science" which was viewed as "development-by-accumulation" of accepted facts and concepts leading - most often - to *epistemological paralysis*, we dubbed it neophobia (the term also used for children above the age of 1 year). Kuhn argued for a model in which a period of such conceptual continuity in normal science were interrupted by a period of revolutionary science leading to a new paradigm, an event he designated *paradigm shift*.

At epistemological level, the adipose tissue has undergone four major paradigm shifts in last 20 years, which "upregulated" it above the horizon. Consequently, adipose tissue takes center stage in so many diseases that it leaves most scientists and medical doctors astonished.

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The first paradigm shift: never before has adipose tissue been so active

While considered a passive lipid storage-release tissue by most cell biologists and pathologists for a long period of time, adipose tissue is now appreciated as the biggest endocrine and paracrine organ of the human body (1-7) (Table 1). The discovery of leptin, an *ob/ob* gene encoded adipocyte-secreted cytokine, by Jeffrey Friedman and colleagues in 1994 (1) marked this revolutionary event, which opened the first adipose-brain talk (Table 2). Here the pioneering contribution of Douglas Coleman (1931-2014) has to be acknowledged. His work established the first clues to a genetic component in obesity. In the 1970s, Coleman conducted a series of experiments that led him to propose the existence of a *satiety factor* that would account for obesity and type 2 diabetes among certain laboratory mice.

Onward, it is demonstrated that adipose tissue is able to send and receive different types of protein and non-protein signals, thus communicating with many organs in the body. And, in effect, contributing to the control of lipid and glucose metabolism, inflammation, immunity, reproduction, hemostasis, vascular smooth muscle contraction-relaxation, learning, memory and emotions among many other biological functions. Altogether, this matter was conceptualized in two novel research fields, adipobiology and adipopharmacology (2, 4).

The second paradigm shift: external *versus* internal adipose depot

This paradigm shift derived from the study of Jeffrey Bell and colleagues (8) who have scanned nearly 800 people with magnetic resonance imaging (MRI) technique, aimed at obtaining

Table 1. An example of paradigm shifts in studying adipose tissue*

FROM The adipose tissue is a lipid storage-release organ involved in obesity
TO Adipose tissue is an endocrine, paracrine and autocrine organ Adipose tissue is a neuroendocrine organ Adipose tissue is a steroidogenic organ Adipose tissue is an immune organ Adipose tissue is a source of and target for inflammatory mediators Adipose tissue produces all components of rennin-angiotensin system Adipose tissue is a storage-release organ of xenobiotics, xenobiotic-metabolizing cytochromes P450 being expressed in adipose tissue** Adipose tissue is thus involved in numerous diseases beyond obesity - Atherosclerosis, Hypertension, Type 2 diabetes, Nonalcoholic fatty liver disease, Polycystic ovarian syndrome, Obstructive sleep apnea syndrome***, Cancer, Osteoarthritis, Alzheimer's disease, Depression

*Modified from (6).
**See (7), also Carmen Purdel and colleagues' review in this volume of *Adipobiology*.
*** See Gülnur Ozturk and colleagues' review in this volume of *Adipobiology*.

Table 2. Adipose-brain talk: examples of neuromediators in leptin signaling

Anorexigenic pathway ↑	**Orexigenic pathway ↓**
Proopiomelanocortins	Neuropeptide tyrosine (NPY)
Melanocortin 4	*Agouti*-related protein
α-melanocyte stimulating hormone	Endocannabinoids
Brain-derived neurotrophic factor	

map of WAT. The authors demonstrated that as many as 45% of women and nearly 60 percent of men scanned have normal scores of the body mass index (BMI, 20-25 kg/m^2). These people are thin outside (TO), while actually have excessive levels of internal adipose tissue - they are fat inside (FI), hence TOFI phenotype of body fatness (Table 3). Noteworthy, TOFI phenotype was also found among people who are professional models. TOFI may thus be considered a specific, "invisible" expression of both *Homo obesus* and *Homo diabesus* (6, 9).

Table 3. Adipotopography (fat map): variations+

TOFI**	thin outside, fat inside
TOTI*****	thin outside, thin inside
FOFI*	fat outside, fat inside
FOTI**	fat outside, thin inside

+ The number of asterisks indicates the quality of cardiometabolic health, as related to adipose tissue. From (9).

The third paradigm shift: white *versus* brown adipocytes

This paradigm shift features the increasing significance of brown adipose tissue in health and disease.

Adipose tissue is a very plastic tissue, being constantly remodeled along with weight gain and weight loss. It is a dynamic cellular and extracellular matrix assembly composed of adipocytes, stromal vascular cells (fibroblasts, endothelial cells, macrophage, mast cells and other immune cells) and matrix components, also rich in sympathetic nerve fibers, blood vessels, and stem cells, the latter being with great regenerative power. In human body, there are two major subtypes of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT). While WAT stores energy, BAT has the ability to dissipate energy by producing heat. BAT-mediated increase in energy expenditure is realized by uncoupling respiration from ATP synthesis *via* uncoupling protein 1 (UCP1), which is the signature protein of brown adipocytes.

Until 10-15 years ago BAT was considered to be biologically active in neonates and young children generating heat during cold exposure by adaptive thermogenesis to maintain normal body temperature. And then regressed with aging by transforming into WAT. At that time, it was demonstrated with ^{18}F-fluorodeoxyglucose (FDG), an intravenously administered radioactive glucose analog, in positron emission tomography (PET) and computed tomography (CT) (PET-CT fusion) scans that the main BAT depots were disseminated throughout the human body (around the aorta, common carotid artery, brachiocephalic artery, kidney, adrenal glands, liver, pancreas; in anterior mediastinum, supraclavicular fossa, axilla and thoracic paravertebral loci, also between neck muscles). The magnitude of ^{18}FDG uptake by BAT was reported to increase with exposure to low temperature, to be higher in women than men, and to decrease with age and body fat mass (reviewed in 10, 11).

Animal studies have shown that activation of BAT counteracts diet-induced weight gain and related disorders such as type 2 diabetes and metabolic syndrome; it may also be the case for humans (10-12). The knowledge about WAT and BAT were enriched with their relatives, namely *brite* (brown in white) and *bruscle* (brown in skeletal muscle) adipocytes (13).

Taken together, brown adipobiology as well as stem cell adipobiology became new, optimistic challenges in biomedical research.

The emerging fourth shift: adipose-Alzheimer?

Recent results have revealed that adipose cells secrete various neurotrophic factors, including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (14-16; 17 for the role of NGF in amyloid precursor protein/APP processing) (Table 4). Likewise, a growing body of evidence demonstrated a link between obesity, adipokines and the pathogenesis of Alzheimer's disease (18-22). Noteworthy, it was found an extraneuronal production of APP including in the adipose tissue (23-25). Further, streptozotocin model of inducing experimental diabetes (26) is now also applying in the induction of Alzheimer's disease (27, 28). Thus, the hypothesis of adipose tissue as a third brain (29) and consequently of *adipose-Alzheimer* may sounds more plausible at present.

Table 4. Selected list of adipose-secreted neurotrophic factors: neuroadipokines

Nerve growth factor
Brain-derived neurotrophic factor
Ciliary neurotrophic factor
Glial cell line-derived neurotrophic factor
Leptin
Adiponectin
Angiopoietin-1
Vascular endothelial growth factor
Steroids (estrogens)
Metallothioneins

Conflict of interest

The authors declare no conflict of interest.

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