



# ADIPOMYOBIOLOGY OF OBESITY AND RELATED DISEASES: THERAPY INSIGHTS

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## Abstract

Today, the most widespread disease around the world is not COVID-19 or any other communicable disease. Indeed, obesity and type 2 diabetes mellitus (T2DM) have been recognized as the main risks for cardiometabolic diseases (CMD) and their morbidity and mortality signature. Recent studies revealed that the adipose tissue and the skeletal muscles may function as endocrine and paracrine organs secreting multiple proteins termed adipokines and myokines respectively. Some of them being produced both by adipose and skeletal tissue, hence dubbed adipomyokines. The contents of this review highlights the following two topics: (i) the progress in knowledge of adipomyokines may lead to better understandings of the process of pathogenesis of obesity and related CMD, and (ii) in-depth studies on Palade-Blobel's general theory of cell protein secretion may allow to explore its pharmacological potentials for new therapies of these diseases. This may open up an intriguing line of scientific enquiry that will unite adipobiologists and myobiologists in the fight against obesity and related CMD.

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## Introduction

### Paradigm shifts in adipobiology

In 1962 Thomas S. Kuhn published his book *The Structure of Scientific Revolutions* (1st edition, University of Chicago Press, Chicago, USA). Epistemology (Greek *epistēmē* means „knowledge“) is the study of knowledge. Kuhn argued for a model in which periods of „development-by-accumulation“ of accepted facts and theories in *normal science* were interrupted by paradigm shifts in *revolutionary science*.

Such a paradigm shift has been Jeffrey Friedman's 1994 discovery of leptin (Greek *leptos* meaning “thin”), a white adipocyte-secreted *Ob* gene-encoded protein (1). It became a “big bang” for the current explosion of studies on adipose-derived secretory proteins designated adipokines (2, 3). Thus, paradigm shifts emerged (Table 1).

In brief, it is an adipose tissue's Renaissance marked by at least two par-

**Table 1.** The paradigm shifts in adipobiology

<b>From</b>
Adipose tissue is a lipid and energy storage involved in obesity
<b>To</b>
Adipose tissue is an endocrine and paracrine 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 produces Alzheimer's disease-related proteins
Adipose tissue is thus involved in numerous diseases beyond obesity

adigm shifts not listed in Table 1: (i) the internal (organ-associated, viewed by imaging technology) adipose depots are even more important than the external depots calculated usually as BMI, and (ii) the brown and beige adipocytes are as important as the white adipocytes in health and disease.

### Adipobiology and myobiology of cardiometabolic diseases

One of the recent achievements in studying the pathogenesis of cardiometabolic diseases (CMD) (Table 2), is its association with adipomyokines, the secretory proteins released from both adipose tissue and skeletal muscles. There is now solid evidence that type 2 diabetes mellitus (T2DM) is strongly associated with the obese man (*Homo obesus*) (4). Obesity predisposes to diabetes and is largely responsible for its current epidemic signature predicting to double the number of diabetic people worldwide within the period of 30 years, from 150 million in 1995 to over 300 million in 2025. Thus, diabetes (5, 6) has been moving to centre stage being one of the most challenging biomedical and social threats. Accordingly, the term *Homo diabetes* was recently introduced (7). Moreover, adipomyokines are also involved in the pathogenesis of cognitive disorders, including Alzheimer's disease (AD) (8-10).

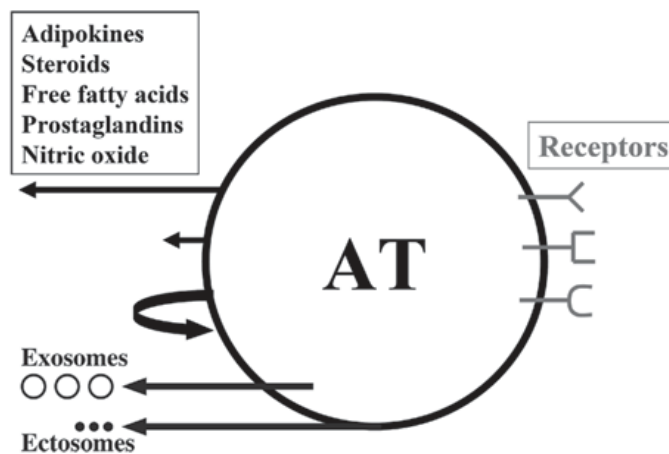
### Adipokines and myokines

There are two major subtypes of adipose tissue: (i) white adipose tissue (WAT), the body's largest endocrine and paracrine organ producing multiple adipokines (2, 3, 11, 12) (Fig. 1), and (ii) brown adipose tissue (BAT), the major thermogenic organ. Brite (brown in white) and beige adipose tissue were recognized recently (Fig. 2). Also found was that some adipomyokines (irisin, BDNF, FGF-21) act as browning hormones (13, 14).

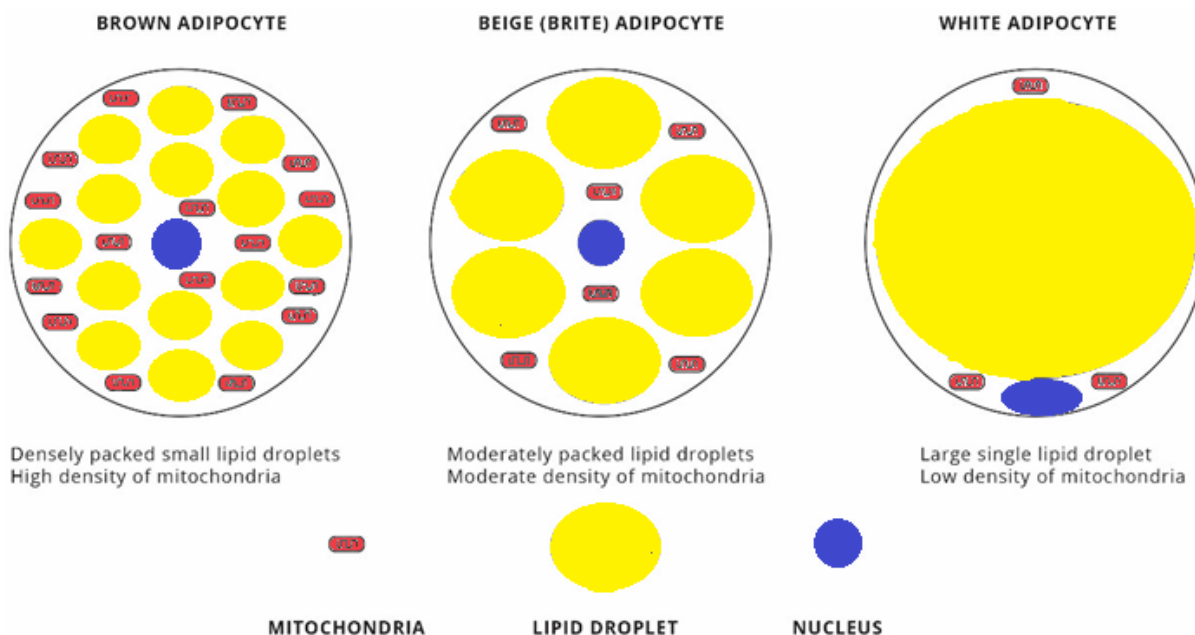
**Table 2.** Cardiometabolic diseases\*

Atherosclerosis, Hypertension, Acute coronary syndromes (coronary heart diseases)
Congestive heart failure, Atrial fibrillation
Stroke (ischemic and hemorrhagic), the major example of cerebrovascular diseases
Obesity
Type 2 diabetes mellitus
- Diabetic neuropathy
- Diabetic retinopathy
- Diabetic erectile dysfunction
- Diabetic nephropathy
Metabolic syndrome, Metabolic-cognitive syndrome
Type 3 diabetes mellitus (Alzheimer's disease)
Obstructive sleep apnea

\* The term cardiometabolic diseases (CMD) is conceptually more correct than cardiovascular diseases (CVD), the latter represent a number of heart and blood vessel diseases, and is a conceptually narrow than the list of CMD shown. In the USA, diabetes cost an estimated \$174 billion in 2007. In CVD, according the American Heart Association and the American Stroke Association the total medical cost moves from \$318 billion (2005) to \$749 billion (2035).



**Figure 1.** Schematic illustration of white adipose tissue (AT) as a multicrine organ. Note, the adipose tissue is consisted of (not shown) adipocytes, fibroblasts, mast cells, macrophages and other immune cells. All these are *bona fide* secretory cell types, that is, they synthesize, store, and release more than 500 different adipokines (15, 16). The arrows, left from up-to-down, indicate endocrine, paracrine and autocrine pathway; other two arrows show the extracellular vesicles exosomes and ectosomes. At the right, depicted are adipose cells' receptors for various ligands. From: (11).



**Figure 2.** Schematic presentation of the different types of adipocytes. From: Jacob VD, Manoj KM. *Adipobiology* 2018;10:1-10.

Accordingly, browning of WAT is considered as a sanogenic phenomenon, whereas whitening of BAT – as pathogenic one.

Recently, skeletal muscles also “became” an endocrine gland in response to contraction. Their secretory products were collectively dubbed myokines (Table 3). Accumulating findings suggest that myokines may exert anti-inflammatory, anti-obesogenic and insulin-sensitizing effects (17-20).

**Table 3.** A selected list of myokines\*

<p>Irisin - a cleavage protein of fibronectin type III domain 5 (FNDC5)          Brain-derived neurotrophic factor (BDNF)          Interleukines (IL-6, IL-15), Angiopoietin-like 4 (ANGPTL4)          Fibroblast growth factor 21 (FGF21)          Monocyte chemoattractant protein-1 (MCP-1/CCL2)          Adiponectin, Leukemia inhibitory factor (LIF)          Myonectin, Myostatin (GDF-8 - growth differentiation factor 8)          Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP)**</p>
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\* In mice were identified 119 myokines, 79 adipokines and 22 adipomyokines (21).

\*\* We also include these natriuretic peptides in the list of myokines, because the heart muscles cardiomyocytes secrete both ANP and BNP, from the cardiac atria and from the ventricles respectively. ANP decreases blood pressure and cardiac hypertrophy, whereas BNP acts locally to reduce ventricular fibrosis (22).

## Adipomyokines

The adipomyokines are secretory proteins released from both adipose tissue and skeletal muscles for endocrine, paracrine and autocrine signaling (13, 17, 21, 23-29). Herein, we focus on the adipomyokines irisin, adiponectin and brain-derived neurotrophic factor (BDNF) and their relevance to obesity and associated CMD (also see Lakshmi and Sridhar in this volume of *Adipobiology*).

## Irisin

Irisin (named after the Greek mythology goddess Iris, a messenger of the gods) is a newly identified adipomyokine. It is a cleavage protein of fibronectin type III domain 5 (FNDC5), the latter converted to irisin after exercise. Several recent studies demonstrated an association between irisin and endothelial function. Lower levels of irisin was found to be independently associated with endothelial dysfunction in nonhypertensive, nondiabetic obese subjects (30). Circulating irisin levels are positively associated with endothelium-dependent arterial dilation in diabetic patients (31). Whereas elevated circulating irisin level was suggested to have role in the development of insulin resistance and atherosclerosis in patients with obstructive sleep apnea (32). Altogether, these data collectively suggest that diabetes and related CMD might, at least in part, be viewed as irisin-mediated disorders (30-42).

## Adiponectin, a “therapeutical anti-kine”

As recently reviewed (12, 43), adiponectin is an adipocyte-secreted protein sharing significant similarity with collagens type VIII and type X and complement protein C1q. Today, adiponectin is one of the best-characterized adipomyokine (44) with a great potential for developing novel therapeutics for various diseases. Adiponectin is the major endogenous insulin-sensitizing factor, which exerts anti-inflammatory, anti-atherogenic, anti-diabetic, anti-obesity, anti-fibrotic, and anti-cancer effects. Hence, we name it “therapeutical anti-kine”.

There is a strong link between lower adiponectin levels and higher incidence of obesity, T2DM, and metabolic syndrome (45). Experimental evidence showed that both aerobic (46) and anaerobic exercise (47) led to significant increase in circulating adiponectin levels.

## Brain-derived neurotrophic factor

Brain-derived neurotrophic factor belongs to the family of proteins named neurotrophins. As discussed by Aloe *et al* in this volume of *Adipobiology*, this family consists of nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3), NT-4/5 and NT-6 (48, 49). Neurotrophins mediate their effects *via* ligation of receptor tyrosine kinase (tropomyosin-related kinase) (Trk), namely, TrkA (for NGF), Trk B (for BDNF and NT-4), TrkC (for NT-3) and panneurotrophin receptor p75<sup>NTR</sup> and its coreceptor sortilin. Reduced circulating and/or local NGF and BDNF levels are implicated in the pathogenesis of both neurodegenerative and CMD (50-52). The investigations on TrkB<sup>BDNF</sup> agonists, therefore, are critically needed for the therapy of these diseases (53). For example, (i) polyphenols (in fruit and vegetables, red wine, olives, extra virgin olive oil, green and black tea, coffee, chocolate) express both cardioprotection and neuroprotection by stimulating the TrkB<sup>BDNF</sup> signaling pathway (54) and (ii) Metformin, a commonly used antidiabetic drug, significantly increased BDNF level (55; also see Aloe *et al* in this volume of *Adipobiology*). However, after a brief treatment with Metformin of women with polycystic ovary syndrome, blood plasma irisin levels and BAT activity were not change (56).

The secretory proforms of NGF and BDNF, pro-NGF and pro-BDNF respectively, are as active as their respective mature forms. Pro-NGF and pro-BDNF are released extracellularly through the tissue type plasminogen activator (tPA), a serine protease-plasmin pathway. Today's the widely administrated cholesterol-lowering drugs statins can induce tPA, hence releasing pro-BDNF (57). These “nonaged” NGF and BDNF required further studies in the adipomyobiology of CMD.

## The cell protein secretion

### -kines sweet -kines

The Human Genome Project was finalized estimating over 20 000 genes encoding more than 100 000 functionally distinct proteins. “Diabetes has been one of the first major disorders that was studied for its genetic basis, soon after results of the Human Genome Project were published” (58).

In the postgenome time, many other “-ome” projects have emerged including proteome, transcriptome, interactome, metabolome, adipokinome, exposome, connectome so much numerous to be listed. Perhaps, this prompted Jeff Lichtman and Joshua Sanes to entitle one of their connectome articles *Ome sweet ome* (*Curr Opin Neurobiol* 2008; 18:346–53) – reminding of the Italian *Casa dolce casa* (Home sweet home).

Discovery of novel secretory proteins, like cytokines, chemokines, osteokines, hepatokines, adipokines and myokines, may provide new opportunities for better understanding the pathogenesis of many diseases. Also for the development of new drug therapies. Exported and transmembrane proteins being relevant pharmacological targets. They are accessible to various drug delivery initiatives, because they are presented within the extracellular space and the cell surface respectively (59).

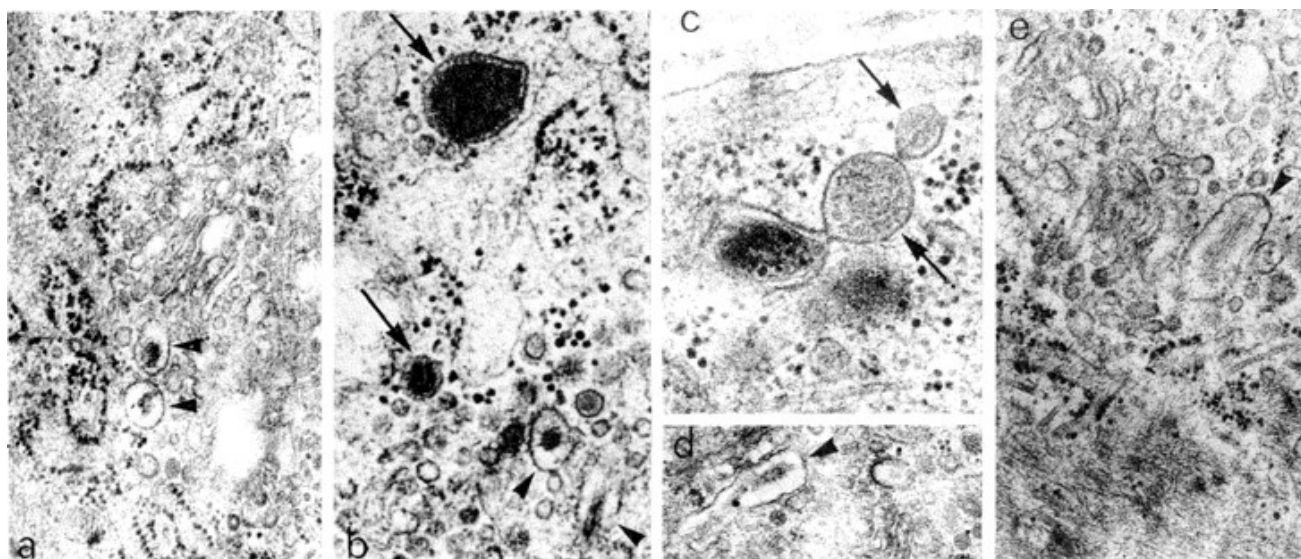
In the present context, adipomyokines (i) could be administered directly and/or targeted by specific antibodies, and (ii) small molecules could boost or inhibit their intracellular secretory pathways. Noteworthy, a large-scale effort, termed the Secreted Protein Discovery Initiative (SPDI), was undertaken to identify novel exported and transmembrane proteins (59).

According to George Palade's classical concept and Gunter Blobel's signal hypothesis (11), the protein secretory pathway constitutes of several intracellular steps including synthesis, post-translational modifications, sorting, targeting, storage (in case of regulated *versus* constitutive secretion) and, finally, exocytosis (Table 4, Fig. 3). Each of these steps might be a pharmacotherapeutic target.

**Table 4.** The two major protein secretory pathways RER, rough endoplasmic reticulum; MVB, multivesicular body

CELL PROTEIN SECRETION
<b>PALADE's RER-Golgi pathway</b> Rough endoplasmic reticulum-Golgi complex- Microtubules-Exocytosis/Porosomes
<b>GÜNTER BLOBEL</b> Signal hypothesis of sorting and targeting of proteins
<b>Non RER-Golgi pathway</b> - Exosomes (MVB-derived microvesicles) - Ectosomes (plasmalemma-derived microparticles)





**Figure 3.** Electron micrographs of secretory-state (secretory phenotype) aortic smooth muscle cells of the rabbit. **a-e.** Spherical-shaped (arrows) and elongated-shaped (arrowheads) secretion granules. **a-e,** x20 000. From (60).

Generally, the secretory proteins are four major types: lysosomal, plasmalemmal, recycled, and exported. Adipomyokines are exported proteins, whilst glucose transporters (GLUT) are recycled membrane proteins. Accordingly, we should be focused in-depth on Palade-Blobel's general theory of the cell protein secretion to explore its pharmacological potentials for new therapies for obesity and its related CMD. The non RER-Golgi pathway using exosomes and ectosomes may also be a target for the discovery of new therapeutics. In the same stream, one of the pathways known to be crucial for the function of pancreatic  $\beta$  cells is the endoplasmic reticulum stress response. Recent study revealed that a group of babies developing diabetes soon after birth had mutations in the *YIPF5* gene involved in the RER-to-Golgi complex trafficking (61).

Of note, adiponectin inhibits the secretion of the metabolically dangerous tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (see 12). Since treatment with the microtubule-disassembling agent colchicine (62) also inhibits TNF- $\alpha$  secretion and exerts anti-inflammatory effects, one may wonder as to whether adiponectin may also be an microtubule-disassembling (antitubulin) agent. Other targets such as the microtubule-based motor proteins kinesin and dynein may also be considered. Therefore, studies on adiponectin secretory pathways are pressingly required. As we have previously proposed (12) dissecting the adiposecretion by microtubule-disassembling agents such as colchicine and nocodazole, microtubule-stabilizers such as taxol (the drug paclitaxel), or by brefeldin A, an inhibitor of RER-Golgi complex trafficking, may provide important pharmacological information.

## Conclusion

Future studies on adipobiology and myobiology of obesity and associated CMD might cultivate a more relevant thinking about how we can make adipomyokine secretion works for the improvement of physical and mental quality of life of our patients. In effect, a hope in understanding and managing obesity and related CMD might be materialized (63-65). Yet, many *food for thoughts* remain to be eaten (Fig. 4).



**Figure 4.** The dish shown may be viewed as a white adipocyte covered with plasmalemma (black circle), having marginally located flattened nucleus (black), unilocular lipid droplet (white), and basal (pericellular) lamina (red).

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## Conflict of interest statement

The authors declare that no conflicts of interest exists.

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