Adipobiology
ISSN 1313-3705 (online)

REVIEW

ADIPOMYOBIOLOGY OF OBESITY AND RELATED DISEASES: THERAPY INSIGHTS

George N. Chaldakov[1*], Luigi Aloe[2], Manlio Vinciguerra[3], Anton B. Tonchev[1], Marco Fiore[4], and Levent Oztürk[5]

[1]Departments of Anatomy and Cell Biology and Translational Stem Cell Biology, Research Institute, Medical University, Varna, Bulgaria,
[2]Fondazione Iret Tecnopolo R. Levi-Montalcini Rome, Italy,
[3]Department of Translational Stem Cell Biology, Research Institute, Medical University, Varna, Bulgaria,
[4]Institute of Biochemistry and Cell Biology, Section of Neurobiology, National Research Council (CNR), Rome, Italy,
[5]Department of Physiology, Trakya University, Edirne, Turkey

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.

Adipobiology 2021; 11: 27-34

Keywords: adipomyokines, irisin, adiponectin, BDNF, obesity, cardiometabolic diseases, protein secretion, therapy

Received 8 December 2021, revised 19 December 2021, accepted 19 December 2021
*Correspondence to: Dr George N. Chaldakov, Department of Anatomy and Cell Biology, Medical University, BG-9002 Varna, Bulgaria.E-mail: chaldakov@yahoo.com

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

From
Adipose tissue is a lipid and energy storage involved in obesity
To
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, diabesity (5, 6) has been moving to centre stage being one of the most challenging biomedical and social threats. Accordingly, the term *Homo diabesus* 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).

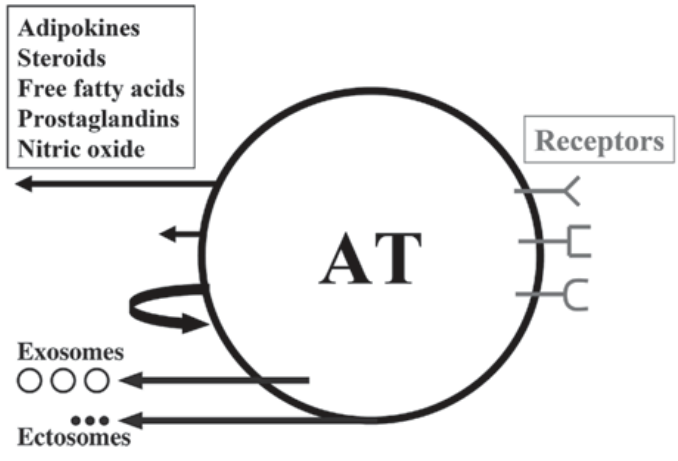

Figure 1. Schematic illustration of white adipose tissue (AT) as a multicrine organ. Note, the adipose tissue is consisted of (not shown) adipocytes, fibroblasts, mast cells, macrophages and other immune cells. All these are *bona fide* secretory cell types, that is, they synthesize, store, and release 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).

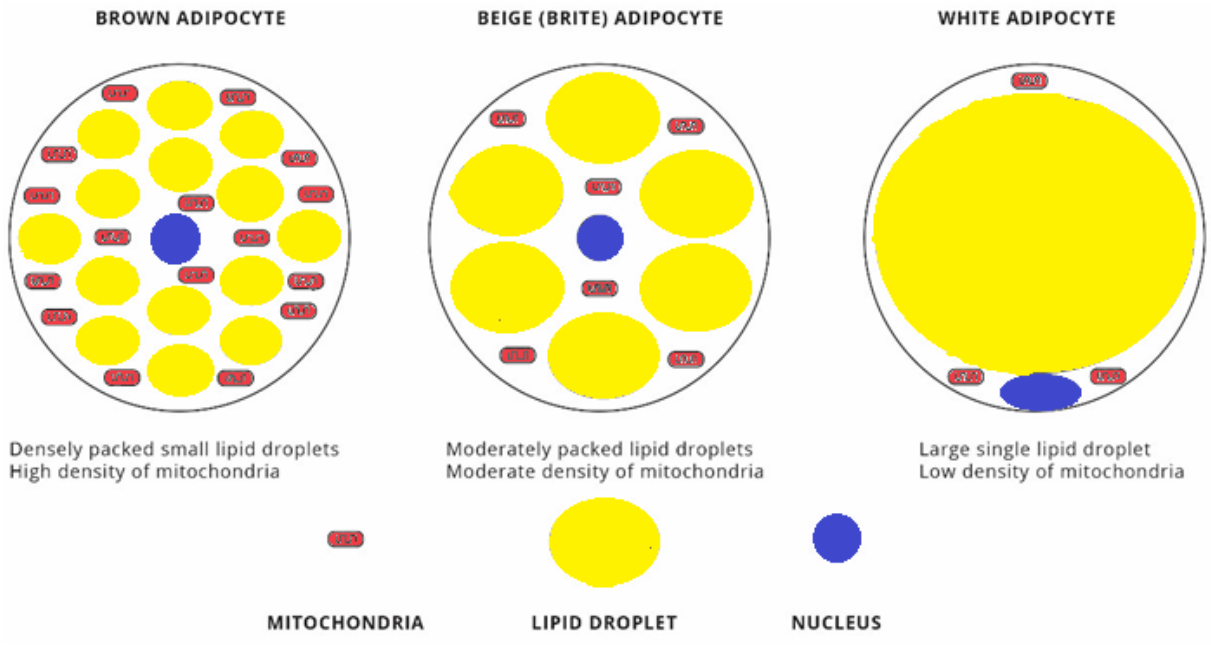

Figure 2. Schematic presentation of the different types of adipocytes. From: Jacob VD, Manoj KM. *Adipobiology* 2018;10:1-10.

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*

Irisin - a cleavage protein of fibronectin type III domain 5 (FNDC5)
Brain-derived neutrophic 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)**

* 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 insuline 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 $p75^{NTR}$ 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 $TrkB^{BDNF}$ 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 $TrkB^{BDNF}$ 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
PALADE's RER-Golgi pathway
Rough endoplasmic reticulum-Golgi complex-Microtubules-Exocytosis/Porosomes
GÜNTER BLOBEL
Signal hypothesis of sorting and targeting of proteins
Non RER-Golgi pathway
- Exosomes (MVB-derived microvesicles)
- Ectosomes (plasmalemma-derived microparticles)

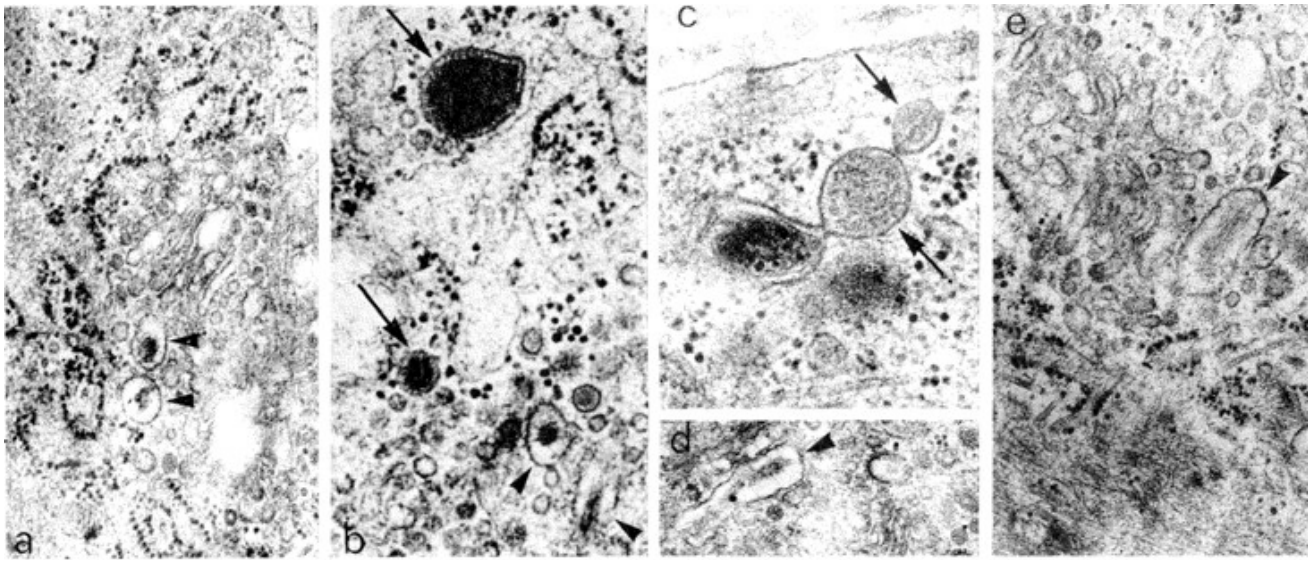

Figure 3. Electron micrographs of secretory-state (secretory phenotype) aortic smooth muscle cells of the rabbit. **a-e.** Spherical-shaped (arrows) and elongated-shaped (arrowheads) secretion granules**. a-e**, x20 000. From (60).

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 β 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 rafficking (61).

Of note, adiponectin inhibits the secretion of the metabolically dangerous tumor necrosis factor-alpha (TNF-α) (see 12). Since treatment with the microtubule-disassembling agent colchicine (62) also inhibits TNF-α secretion and exerts anti-inflammatory effects, one may wonder as to whether adiponectin may also be an microtubule-disassembling (antitubilin) 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 flatten nucleus (black), unilocular lipid droplet (white), and basal (pericellular) lamina (red).

Acknowledgements

The authors express their Tribute to Albert Claude, Christian De Duve and George E. Palade, the Nobel Prize winners in Physiology or Medicine 1974 „for their discoveries concerning the structural and functional organization of the cell". We apologize to the authors of many relevant articles that were not quoted here for reasons of brevity.

Conflict of interest statement

The authors declare that no conflicts of interest exists.

References

1. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994; 372(6505): 425-432. [DOI: 10.1038/372425a0]
2. Chaldakov G, Fiore M, Ghenev P, Stankulov IS, Aloe L. Atherosclerotic lesions: Possible interactive involvement of intima, adventitia and associated adipose tissue. *In Med J* 2000; 7:43-49.
3. Chaldakov G, Stankulov I, Hristova M, Ghenev P. Adipobiology of disease: Adipokines and adipokine-targeted pharmacology. *Curr Pharm Des* 2003; 9:1023-1031. [DOI: 10.2174/1381612033455152]
4. Chaldakov G, Fiore M, Tonchev A, Dimitrov D, Pancheva R, Rancic G, *et al.* Homo obesus: A metabotrophin-deficient species. Pharmacology and nutrition insight. *Curr Pharm Des* 2007; 13:2176-2179. [DOI: 10.2174/138161207781039616]
5. Astrup A, Finer N. Redefining Type 2 diabetes: 'Diabesity' or 'Obesity Dependent Diabetes Mellitus'? *Obesity Rev* 2000; 1(2): 57-59. [DOI: 10.1046/j.1467-789x.2000.00013.x]
6. Farag YM, Gaballa MR. Diabesity: an overview of a rising epidemic. *Nephrol Dial Transplant* 2011; 26(1): 28-35. [DOI: 10.1093/ndt/gfq576]
7. Aloe L, Tonchev AB, Fiore M, Chaldakov GN. Homo diabesus: involvement of metabotrophic factors. *Adipobiology* 2013; 5(45-49. [DOI: 10.14748/adipo.v5.297]
8. Naderali EK, Ratcliffe SH, Dale MC. Review: Obesity and Alzheimer's disease: A link between body weight and cognitive function in old age. *Am J Alzheimer's Dis Other Demen* 2009; 24(6): 445-449. [DOI: 10.1177/1533317509348208]
9. Frisardi V, Solfrizzi V, Seripa D, Capurso C, Santamato A, Sancarlo D, *et al.* Metabolic-cognitive syndrome: A cross-talk between metabolic syndrome and Alzheimer's disease. *Ageing Res Rev* 2010; 9(4): 399-417. [DOI: 10.1016/j.arr.2010.04.007]
10. Forny-Germano L, De Felice FG, Vieira MNdN. The Role of Leptin and Adiponectin in Obesity-Associated Cognitive Decline and Alzheimer's Disease. *Front Neurosci* 2019; 12(1027). [DOI: 10.3389/fnins.2018.01027]
11. Chaldakov G. Human body as a multicrine system, with special reference to cell protein secretion: from vascular smooth muscles to adipose tissue. *Adipobiology* 2017; 8: 6-17. [DOI: 10.14748/adipo.v8.2089]
12. Töre F, Tonchev A, Fiore M, Tunçel N, Atanassova P, Aloe L, *et al.* From Adipose Tissue Protein Secretion to Adipopharmacology of Disease. *Immunol Endocr Metab Agents Med Chem* 2007; 7:149-155. [DOI: 10.2174/187152207780363712]
13. Rodríguez A, Becerril S, Ezquerro S, Méndez-Giménez L, Frühbeck G. Crosstalk between adipokines and myokines in fat browning. *Acta Physiol* 2017; 219(2): 362-381. [DOI: 10.1111/apha.12686]
14. Calton EK, Soares MJ, James AP, Woodman RJ. The potential role of irisin in the thermoregulatory responses to mild cold exposure in adults. *Am J Hum Biol* 2016; 28(5): 699-704. [DOI: 10.1002/ajhb.22853]
15. Renes J, Rosenow A, Mariman E. Novel adipocyte features discovered by adipoproteomics. *Adipobiology* 2009; 1: 7-18. [DOI: 10.14748/adipo.v1.245]
16. Renes J, Mariman E. Application of proteomics technology in adipocyte biology. *Mol Biosyst* 2013; 9(6): 1076-1091. [DOI: 10.1039/c3mb25596d]
17. Broholm C, Pedersen BK. Leukaemia inhibitory factor--an exercise-induced myokine. *Exerc Immunol Rev* 2010; 16: 77-85.
18. Matthews VB, Aström MB, Chan MH, Bruce CR, Krabbe KS, Prelovsek O, *et al.* Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. *Diabetologia* 2009; 52(7): 1409-1418. [DOI: 10.1007/s00125-009-1364-1]
19. Pedersen BK, Pedersen M, Krabbe KS, Bruunsgaard H, Matthews VB, Febbraio MA. Role of exercise-induced brain-derived neurotrophic factor production in the regulation of energy homeostasis in mammals. *Exp Physiol* 2009; 94(12): 1153-1160. [DOI: 10.1113/expphysiol.2009.048561]
20. Matsakas A, Foster K, Otto A, Macharia R, Elashry MI, Feist S, *et al.* Molecular, cellular and physiological investigation of myostatin propeptide-mediated muscle growth in adult mice. *Neuromuscul Disord* 2009; 19(7): 489-499. [DOI: 10.1016/j.nmd.2009.06.367]
21. Schering L, Hoene M, Kanzleiter T, Jähnert M, Wimmers K, Klaus S, *et al.* Identification of novel putative adipomyokines by a cross-species annotation of secretomes and expression profiles. *Arch Physiol Biochem* 2015; 121(5): 194-205. [DOI: 10.3109/13813455.2015.1092044]

22. Potter LR, Yoder AR, Flora DR, Antos LK, Dickey DM. Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. *Handbook Exp Pharmacol* 2009;191:341-366. [DOI: 10.1007/978-3-540-68964-5_15]
23. Görgens SW, Eckardt K, Jensen J, Drevon CA, Eckel J. Exercise and Regulation of Adipokine and Myokine Production. *Prog Mol Biol Transl Sci* 2015; 135: 313-336. [DOI: 10.1016/bs.pmbts.2015.07.002]
24. Li F, Li Y, Duan Y, Hu CA, Tang Y, Yin Y. Myokines and adipokines: Involvement in the crosstalk between skeletal muscle and adipose tissue. *Cytokine Growth Factor Rev* 2017; 33: 73-82. [DOI: 10.1016/j.cytogfr.2016.10.003]
25. Raschke S, Eckel J. Adipo-myokines: two sides of the same coin--mediators of inflammation and mediators of exercise. *Mediators Inflamm* 2013; 2013(320724. [DOI: 10.1155/2013/320724]
26. Trayhurn P, Drevon CA, Eckel J. Secreted proteins from adipose tissue and skeletal muscle - adipokines, myokines and adipose/muscle cross-talk. *Arch Physiol Biochem* 2011; 117(2): 47-56. [DOI: 10.3109/13813455.2010.535835]
27. Oh KJ, Lee DS, Kim WK, Han BS, Lee SC, Bae KH. Metabolic adaptation in obesity and type II diabetes: Myokines, adipokines and hepatokines. *Int J Mol Sci* 2016; 18(1). [DOI: 10.3390/ijms18010008]
28. Chung HS, Choi KM. Adipokines and myokines: A pivotal role in metabolic and cardiovascular disorders. *Curr Med Chem* 2018; 25(20): 2401-2415. [DOI: 10.2174/0929867325666171205144627]
29. Kirk B, Feehan J, Lombardi G, Duque G. Muscle, bone, and fat crosstalk: the biological role of myokines, osteokines, and adipokines. *Curr Osteopor Rep* 2020; 18(4): 388-400. [DOI: 10.1007/s11914-020-00599-y]
30. Xiang L, Xiang G, Yue L, Zhang J, Zhao L. Circulating irisin levels are positively associated with endothelium-dependent vasodilation in newly diagnosed type 2 diabetic patients without clinical angiopathy. *Atherosclerosis* 2014; 235(2): 328-333. [DOI: 10.1016/j.atherosclerosis.2014.04.036]
31. Sesti G, Andreozzi F, Fiorentino TV, Mannino GC, Sciacqua A, Marini MA*, et al.* High circulating irisin levels are associated with insulin resistance and vascular atherosclerosis in a cohort of nondiabetic adult subjects. *Acta Diabetol* 2014; 51(5): 705-713. [DOI: 10.1007/s00592-014-0576-0]
32. Ozturk G, Demirel O, Tekatas A, Celebi C, Avci B, Gurel EE*, et al.* Circulating irisin levels in newly diagnosed obstructive sleep apnea patients. *Scr Sci Med* 2019; 51(1): 16-20. [DOI: 10.14748/ssm.v51i1.5908]
33. Hofmann T, Elbelt U, Stengel A. Irisin as a muscle-derived hormone stimulating thermogenesis – A critical update. *Peptides* 2014; 54: 89-100. [DOI: 10.1016/j.peptides.2014.01.016]
34. Gamas L, Matafome P, Seiça R. Irisin and Myonectin Regulation in the Insulin Resistant Muscle: Implications to Adipose Tissue: Muscle Crosstalk. *J Diab Res* 2015; 2015(359159-359159. [DOI: 10.1155/2015/359159]
35. Kurdiova T, Balaz M, Vician M, Maderova D, Vlcek M, Valkovic L*, et al.* Effects of obesity, diabetes and exercise on Fndc5 gene expression and irisin release in human skeletal muscle and adipose tissue: in vivo and in vitro studies. *J Physiol* 2014; 592(5): 1091-1107. [DOI: 10.1113/jphysiol.2013.264655]
36. Perakakis N, Triantafyllou GA, Fernández-Real JM, Huh JY, Park KH, Seufert J*, et al.* Physiology and role of irisin in glucose homeostasis. *Nat Rev Endocrinol* 2017; 13(6): 324-337. [DOI: 10.1038/nrendo.2016.221]
37. Moreno-Navarrete JM, Ortega F, Serrano M, Guerra E, Pardo G, Tinahones F*, et al.* Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. *J Clin Endocrinol Metab* 2013; 98(4): E769-778. [DOI: 10.1210/jc.2012-2749]
38. Aydin S, Aydin S, Kobat MA, Kalayci M, Eren MN, Yilmaz M*, et al.* Decreased saliva/serum irisin concentrations in the acute myocardial infarction promising for being a new candidate biomarker for diagnosis of this pathology. *Peptides* 2014; 56: 141-145. [DOI: 10.1016/j.peptides.2014.04.002]
39. Zhu D, Wang H, Zhang J, Zhang X, Xin C, Zhang F*, et al.* Irisin improves endothelial function in type 2 diabetes through reducing oxidative/nitrative stresses. *J Mol Cell Cardiol* 2015; 87: 138-147. [DOI: 10.1016/j.yjmcc.2015.07.015]
40. Hou N, Han F, Sun X. The relationship between circulating irisin levels and endothelial function in lean and obese subjects. *Clin Endocrinol* 2014; 83: 339-343. [DOI: 10.1111/cen.12658]
41. Park KH, Zaichenko L, Brinkoetter M, Thakkar B, Sahin-Efe A, Joung KE*, et al.* Circulating irisin in relation to insulin resistance and the metabolic syndrome. *J Clin Endocrinol Metab* 2013; 98(12): 4899-4907. [DOI: 10.1210/jc.2013-2373]
42. More CE, Papp C, Harsanyi S, Gesztelyi R, Mikaczo A, Tajti G*, et al.* Altered irisin/BDNF axis parallels excessive daytime sleepiness in obstructive sleep apnea patients. *Respir Res* 2019; 20(1): 67-67. [DOI: 10.1186/s12931-019-1033-y]
43. Yang D, Yang Y, Li Y, Han R. Physical Exercise as Therapy for Type 2 Diabetes Mellitus: From Mechanism to Orientation. *Ann Nutr Metab* 2019; 74(4): 313-321. [DOI: 10.1159/000500110]

44. Martinez-Huenchullan SF, Tam CS, Ban LA, Ehrenfeld-Slater P, McLennan SV, Twigg SM. Skeletal muscle adiponectin induction in obesity and exercise. *Metabolism* 2020; 102(154008. [DOI: 10.1016/j.metabol.2019.154008]
45. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Inves* 2006; 116(7): 1784-1792. [DOI: 10.1172/JCI29126]
46. Yu N, Ruan Y, Gao X, Sun J. Systematic Review and Meta-Analysis of Randomized, Controlled Trials on the Effect of Exercise on Serum Leptin and Adiponectin in Overweight and Obese Individuals. *Horm Metab Res* 2017; 49(3): 164-173. [DOI: 10.1055/s-0042-121605]
47. Öztürk G, Kaya O, Gürel EE, Palabiyik O, Kunduracilar H, Süt N, *et al.* Acute supramaximal exercise-induced adiponectin increase in healthy volunteers: Involvement of natriuretic peptides. *Adipobiology* 2017; 8: 9-45. [DOI: 10.14748/adipo.v8.2092]
48. Levi-Montalcini R. The nerve growth factor 35 years later. *Science* 1987; 237(4819): 1154-1162. [DOI: 10.1126/science.3306916]
49. Rocco ML, Soligo M, Manni L, Aloe L. Nerve growth factor: Early studies and recent clinical trials. *Curr Neuropharmacol* 2018; 16(10): 1455-1465. [DOI: 10.2174/1570159x16666180412092859]
50. Chaldakov GN, Fiore M, Stankulov IS, Manni L, Hristova MG, Antonelli A, *et al.* Neurotrophin presence in human coronary atherosclerosis and metabolic syndrome: a role for NGF and BDNF in cardiovascular disease? *Prog Brain Res* 2004; 146: 279-289.
51. Sornelli F, Fiore M, Chaldakov GN, Aloe L. Adipose tissue-derived nerve growth factor and brain-derived neurotrophic factor: results from experimental stress and diabetes. *Gen Physiol Biophys* 2009; 28:179-183.
52. Yanev S, Aloe L, Fiore M, Chaldakov GN. Neurotrophic and metabotrophic potential of nerve growth factor and brain-derived neurotrophic factor: Linking cardiometabolic and neuropsychiatric diseases. *World J Pharmacol* 2013; 2(4): 92-99. [DOI:10.5497/wjp.v2.i4.92]
53. Yanev S, Fiore M, Hinev A, Ghenev P, Hristova M, Panayotov P, *et al.* From antitubulins to trackins. *Biomed Rev* 2016; 27: 59-67. [DOI: 10.14748/bmr.v27.2112]
54. Carito V, Venditti A, Bianco A, Ceccanti M, Serrilli A, Chaldakov G, *et al.* Effects of olive leaf polyphenols on male mouse brain NGF, BDNF and their receptors TrkA, TrkB and p75. *Natural Product Res* 2014; 28: 1970-1984 [DOI: 10.1080/14786419.2014.918977]
55. Fang W, Zhang J, Hong L, Huang W, Dai X, Ye Q, *et al.* Metformin ameliorates stress-induced depression-like behaviors via enhancing the expression of BDNF by activating AMPK/CREB-mediated histone acetylation. *J Affective Disord* 2020; 260: 302-313. [DOI: 10.1016/j.jad.2019.09.013]
56. Oliveira F, Mamede M, Bizzi M, Rocha AL, Ferreira C, Gomes K, *et al.* Effects of Short Term Metformin Treatment on Brown Adipose Tissue Activity and Plasma Irisin Levels in Women with Polycystic Ovary Syndrome: A Randomized Controlled Trial. *Horm Metab Res* 2020; 52: 718-723. [DOI: 10.1055/a-1157-0615]
57. Tsai S-J. Statins May Act Through Increasing Tissue Plasminogen Activator/Plasmin Activity to Lower Risk of Alzheimer's Disease. *CNS Spectrums* 2009; 14: 234-235. [DOI: 10.1017/S1092852900025360]
58. Sridhar GR: Encode, decode and diabetes. In: *Cognitive Science and Health Bioinformatics: Advances and Applications*. Singapore: Springer Singapore, 2018; 47-55.
59. Clark HF, Gurney AL, Abaya E, Baker K, Baldwin D, Brush J, *et al.* The secreted protein discovery initiative (SPDI), a large-scale effort to identify novel human secreted and transmembrane proteins: a bioinformatics assessment. *Genome Res* 2003; 13(10): 2265-2270. [DOI: 10.1101/gr.1293003]
60. Chaldakov GN, Vankov VN. Morphological aspects of secretion in the arterial smooth muscle cell, with special reference to the Golgi complex and microtubular cytoskeleton. *Atherosclerosis* 1986; 61(3): 175-192. [DOI: 10.1016/0021-9150(86)90137-1]
61. De Franco E, Lytrivi M, Ibrahim H, Montaser H, Wakeling MN, Fantuzzi F, *et al.* YIPF5 mutations cause neonatal diabetes and microcephaly through endoplasmic reticulum stress. *J Clin Invest* 2020. [DOI: 10.1172/jci141455]
62. Chaldakov GN. Colchicine, a microtubule-disassembling drug, in the therapy of cardiovascular diseases. *Cell Biol Int* 2018; 42(8): 1079-1084. [DOI: 10.1002/cbin.10988]
63. Arhire LI, Mihalache L, Covasa M. Irisin: A hope in understanding and managing obesity and metabolic syndrome. *Front Endocrinol (Lausanne)* 2019; 10: 524. [DOI: 10.3389/fendo.2019.00524]
64. Frohlich J, Chaldakov GN, Vinciguerra M. Cardio- and neurometabolic adipobiology: Consequences and implications for therapy. *Int J Mol Sci* 2021; *22(8):* 4137. [DOI:10.3390/ijms22084137]
65. Chaldakov GN, Aloe A, Rancic G, Pancheva RZ, Hiriart M, Fiore M, Yanev S. Chapter 16. The Relevance of Metabotrophic Factors in Pathobiology and Therapy of Obesity and Related Diseases. In: P.S. Tappia *et al.* (eds.), *Cellular and Biochemical Mechanisms of Obesity*, *Advances in Biochemistry in Health and Disease 23*. Springer Nature Switzerland AG 2021. [DOI:10.1007/978-3-030-84763-0_16]