Obesity, adipose tissue types and adipocytokines (Review of Articles)

Nuha Abdulkader Shareef* , Maryam Hani Abduljalal**
***Department of chemistry , colledge of science , university of Mosul**
****Department of Biochemistry , College of Medicine , University of Mosul , Mosul , Iraq**
Correspondence: ruqayafiras50@gmail.com

(Ann Coll Med Mosul 2020; 42 (2):177-183).
Received: 5th Sept. 2020; Accepted: 8th Nov. 2020.

ABSTRACT

The prevalence of obesity has increased worldwide in the last 50 years, reaching pandemic levels. The etiology of obesity is multifactorial, involving a complex of interaction among genetics, hormones and the environment. The adipose tissue plays a central role in regulating whole body energy. In one hand, the adipose tissue stores energy in the form of lipid and controls the lipid mobilization and distribution in the body, and on the other hand, adipose tissue acts as an endocrine organ and produces numerous bioactive factors such as adipocytokines. Moreover, brown and beige adipose tissue burn lipid by dissipating energy in the form of heat to maintain euthermia and have been considered as a new way to counteract obesity. In this review, we will summarize the recent findings of the types of adipose tissue and their role in controlling metabolism, focusing on its endocrine function. This review describes the molecular actions and clinical significance of the some important adipocytokines.

Keywords: obesity, adipose tissue, white adipose tissue, brown adipose tissue and adipocytokines.

السمنة، انواع النسيج الدهنى والاديبوسايتوكاينز
(مقالة استعراضية)

نهى عبد القادر شريف* ، مريم هاني عبد الجلال**
***قسم الكيمياء / كلية العلوم / جامعة الموصل ، **فرع الكيمياء الحياتية / كلية طب الموصل / جامعة الموصل ، الموصل ، العراق**

الخلاصة

معدل السمنة قد ازداد في جميع انحاء العالم في الخمسين سنة الماضية. أسباب السمنة تكون متعددة العوامل, تتضمن تداخلات معقدة بين الجينات و الهرمونات والعوامل الخارجية. النسيج الدهني يلعب دورا أساسيا في تنظيم طاقة الجسم الكلية. من ناحية النسيج الدهني يخزن الطاقة على شكل دهون وينظم عملية انتقال الدهون وتوزيعها داخل الجسم, ومن ناحية أخرى النسيج الدهني يعمل كجهاز من أجهزة الغدد الصماء - ويقوم بأنتاج العديد من العوامل الفعالة بايولوجيا مثل الاديبوسايتوكاينز. بالإضافة الى ذلك فان النسيج الدهني البني والنسيج الدهني البني الفاتح يحرقان الدهون وينتجان الطاقة على شكل حرارة للمحافظة على درجة حرارة الجسم الطبيعية وتم اعتبارهما كطريقة جديدة للتغلب على السمنة

في هذه المقالة قمنا بتلخيص احدث المستجدات عن أنواع النسيج الدهني ودورهم في تنظيم الايض، وقمنا بالتركيز حول عملهم كغدد صماء. هذا المقال سوف يوضح العمل الجزيئي والاهمية السريرية لبعض انواع السايتوكاينز المهمة.

الكلمات المفتاحية : السمنة, النسيج الدهني الأبيض, النسيج الدهني البني, الاديبوسايتوكاينز.

INTRODUCTION

The prevalence of obesity has increased worldwide in the last 50 years, reaching pandemic levels. Obesity represents a major health challenge because it substantially increases the risk of diseases such as type 2 diabetes mellitus, hypertension, fatty liver disease, myocardial infarction, stroke, dementia, obstructive sleep apnoea, osteoarthritis and several cancers, thereby contributing to a decline in both the quality of life and life expectancy. [1, 2]

Adipose Tissues

Adipose tissues is a loose connective tissue which is primarily composed of adipocytes as well as pre-adipocytes, macrophages, fibroblasts, endothelial cells and leucocytes, Adipose tissue is not only a passive fuel reservoir, but also an endocrine organ. Extensive effort has been made to understand adipose tissue derived hormones and their physiological functions in the past two decades.[3] These bioactive factors secreted from adipose tissue circulate and transport information to other metabolically active organs such as muscle, liver, brain, and pancreas via endocrine mechanisms, so modulating the systemic metabolism .[4]

Types Of Adipose Tissues

In mammals, there are two types of adipose tissues: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT and BAT have distinct morphologies and functions, but recent studies discover a third adipose tissue type named beige or brite adipose tissue.

1. White adipose tissue (WAT) or white fat: In a normal non_over weight human beings, white adipose tissue composes about 20% of the body weight in males and 25% in females. WAT adipocytes store triglycerides as energy source and each has a single large lipid (fat) droplet which squeezes the nucleus to the periphery, adipocytes have receptors for insulin, sex hormones, norepinephrine, and glucocorticoids.[5]
2. Brown adipose tissue (BAT): Brown adipose tissue was first identified in 1951. It is present in newborn, but adults either lack or have only a small amount of it. BAT is primarily located around the neck and large blood vessels of the thorax. In contrast to white adipose tissue brown adipose tissue, adipocyte contains multiple small lipid droplets and many mitochondria.[6] Brown fat is a specialized form of adipose tissue important for adaptive thermogenesis in humans and other mammals. BAT can generate heat by uncoupling the respiratory chain of oxidative phosphorylation within mitochondria through tissue-specific expression of uncoupling protein 1 (UCP1). BAT is activated upon cold exposure by the release of catecholamines from sympathetic nerves that results in uncoupling protein 1 activation. BAT activation may also occur in response to overfeeding or spicy food.[7, 8]
   The physiological role of brown adipose tissue in humans is debated, but it is quite clear that brown adipose tissue in rodents has an important role in the prevention and therapy of obesity and diabetes and specific drugs can induce brown fat development in adult animals. This rised a hope in the development of brown adipose tissue in human adults as a new challenge for the treatment of obesity and related diseases.[9]
3. Beige or brite adipocyte: More recent studies discovered a third adipose tissue type. They demonstrate that many subcutaneous adipose depots traditionally classified as white adipose tissue also express brown adipose-specific markers and are thus referred to as “beige” or “brite” adipose.[10]
   A process called browning of white adipose tissue is discovered; by which multilocular brown adipocytes expressing an uncoupling protein 1 appear at anatomical sites characteristic of white adipose tissue only. This phenomenon occurs after prolonged exposure to high levels of catecholamine (epinephrine and nor-epinephrine) like in patients with a pheochromocytoma -or a thermogenic stimulus after prolonged cold exposure, which also causes the recruitment of brown adipose tissue at their classical anatomical sites (eg, interscapular depots). The browning process can be mimicked by chronic treatment with β3-adrenergic receptor activators , all β3-AR activators are in the developmental stage to treat obesity and DM, but mirabegron is the only drug proved by FDA and used for urinary incontinence .[11]

Adipocytokines

Until 1994, the only known role of adipose tissue was energy storage in the form of lipids; but in the recent years, it has been recognized as a major endocrine organ as it produces hormones such as leptin, estrogen, resistin, and the cytokine tumor necrosis factor-alpha (TNFα).[12] These cell signaling proteins that is secreted by adipose tissue is named the adipocytokines, the first adipokine to be discovered was leptin in 1994. Since that time, hundreds of adipokines have been discovered.[13-15].

Examples of these adipokines are apelin, leptin, retinol binding protein 4 (RBP4), adiponectin, plasminogen activator inhibitor-1 (PAI-1), chemerin, interleukin-6 (IL-6), (TNFα), progranulin, visfatin, resistin, omentin, vaspin.

1. Apelin

Apelin is a peptide that was identified in 1998. It participates in the control of blood pressure and its activation promotes the formation of new blood vessels (angiogenesis).[16, 17]

Apelin hormone has hypotensive effect which partially results from the release of nitrogen oxide, a potent vasodilator, which induces relaxation of

the smooth muscle cells of the arterial wall. More-over, apelin receptors in the brain are involved in regulating water and food intake, It was found that apelin injection increases water intake and decreases the hypothalamic secretion of the antidiuretic hormone (vasopressin). This diuretic effect of apelin is also associated with its hypotensive effect. [18-20]

2. Leptin

It is one of the most important adipose derived hormones. It is a 16 kDa protein hormone that plays a key role in regulating energy intake and energy expenditure. In 1950, a severely obese mouse trait with an autosomal recessive inheritance was discovered. This was associated with a syndrome that includes hyperphagia, infertility, and a variety of hormonal and metabolic disturbances. The mutation, located at chromosome 6, was designated “obese” and the mouse trait as ob/ob.[21]

In 1966, a mouse trait with a very similar phenotype was found. This mutation “diabetes” was found on chromosome 4, and the trait was called db/db. In 1994, research showed that the ob gene encodes a peptide chain of 167 amino acids in length, soon designated as leptin. [21]

In addition to white adipose tissue, the major source of leptin, it can also be produced by brown adipose tissues, placenta, ovaries, skeletal muscle, stomach (lower part of fundic glands), mammery epithelial cells, bone marrow, pituitary and liver. [22]

Leptin acts on receptors in the hypothalamus of the brain where it inhibits appetite,In women, leptin concentrations are approximately three fold that in men, the secretion is highest in the middle of the night, the opposite of what is seen for cortisol. [23]

Obese individuals generally exhibit an unusually high circulating concentration of leptin. These people are said to be resistant to the effects of leptin, in much the same way that people with type 2 diabetes are resistant to the effects of insulin. [24, 25]

3. Retinol binding protein 4 (RBP4)

This protein belongs to the lipocalin family and is the specific carrier for retinol (vitamin A) in the blood. It delivers retinol from the liver stores to the peripheral tissues. RBP 4 has been a drug target for eye diseases which is an essential nutrient for the visual cycle. [26, 27]

4. Adiponectin

This is a 244-amino acid long polypeptide hormone. Adiponectin was first characterized in 1995 and was shown to be involved in regulating glucose levels as well as fatty acid breakdown. In humans it is encoded by the ADIPOQ gene and it is produced in adipose tissue. Adiponectin hormone decreases gluconeogenesis, increases glucose uptake and increases insulin sensitivity so it has a favorable effect on blood glucose level. More-over, it enhances triglyceride clearance and weight loss so it protects from atherosclerosis . [28, 29]

Contrary to expectations, despite being produced in adipose tissue, adiponectin was found to be low in obesity. This down regulation has not been fully explained. The gene was localized to chromosome 3q27, a region that increases genetic susceptibility to type 2 diabetes and obesity. Supplementation by adiponectin was able to improve blood glucose, insulin control and triglyceride levels in mouse models. [30-32]

5. Plasminogen activator inhibitor-1 (PAI-1)

In mammals, two plasminogen activators have been identified: tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA); both are activators of plasminogen and hence activation of fibrinolysis PAI-1 is a serine protease inhibitor (serpin) that functions as the principal inhibitor of tissue plasminogen activator and urokinase plasminogen activator, so elevated level of PAI-1 is a risk factor for thrombosis and atherosclerosis. [33]

(PAI-1) is present in increased levels in various disease states such as obesity, a number of forms of cancer as well as the metabolic syndrome. It has been linked to the increased occurrence of thrombosis in patients with these conditions. [34, 35]

6. Chemerin

Also known as retinoic acid receptor responder protein 2 (RARRES2), chemerin has been implicated in signaling for adipocyte differentiation and also stimulation of lipolysis. [36]

Studies in mice have shown that chemerin is not-highly expressed in brown adipose tissue, indicating that chemerin plays a role in energy storage rather than thermogenesis. In humans, chemerin levels are significantly different between individuals with normal glucose tolerance and individuals with typeII diabetes and first degree relatives. Moreover, chemerin levels show a significant correlation with blood pressure, plasma triglyceride levels and body mass index. [37, 38]

7. Interleukin-6 (IL-6)

Interleukin 6 (IL-6) is encoded by the *IL6* gene, it acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine, which means a cytokine produced from muscle and elevated in response to muscle contraction. It is significantly

elevated with exercise, and precedes the appearance of other cytokines in the circulation. [39]

There is some early evidence that IL-6 can be used as an inflammatory marker for severe COVID-19 infection with poor prognosis, in the context of the wider coronavirus pandemic.[40, 41]

Obesity is a known risk factor in the development of severe asthma. Recent data suggests that the inflammation associated with obesity, potentially mediated by the cytokine IL6, plays a role in causing poor lung function and increased risk for developing asthma exacerbations. [42]

IL-6 stimulates the inflammatory and autoimmune processes in many diseases like diabetes,[43] atherosclerosis[44], rheumatoid arthritis, depression, Alzheimer disease [45] and intracerebral hemorrhage. [46]

Hence, there is an interest in developing anti-IL-6 agents as therapy against many of these diseases. [47]

8. Progranulin

Progranulin is the precursor protein for granulin, while progranulin is associated with anti-inflammation, its cleaved granulin peptides have been implicated in pro-inflammatory behavior. Increased serum and plasma progranulin levels in patients with type 2 diabetes and visceral obesity implicate a role of progranulin in metabolic diseases. [48]

Progranulin is a pleiotropic protein and it plays diverse roles in the brain. Frontotemporal dementia (FTD) is caused by progranulin mutations. Many genetic variation in progranulin is linked to multiple neurodegenerative disorders. [49]

9. Visfatin

Visfatin is an adipokine that is localized to the blood stream, also known nicotinamide phosphoribosyl transferase (NAmPRTase or Nampt). It is an enzyme that in humans is encoded by the *NAMPT* gene. This protein is the rate-limiting enzyme in the nicotinamide adenine dinucleotide (NAD+) salvage pathway that coverts nicotinamide to nicotinamide mononucleotide in mammals to enable NAD+ biosynthesis and has various functions; including the promotion of vascular smooth muscle cell maturation and inhibition of neutrophil apoptosis. It also activates insulin receptor and has insulin-mimetic effects, lowering blood glucose and improving insulin sensitivity. The protein is highly expressed in visceral fat and serum levels of the protein correlate with obesity. [50, 51]

10. Resistin.

Resistin was discovered in 2001, it is a cysteine-rich peptide hormone, the length of the resistin pre-peptide in human is 108 amino acid residues and the molecular weight is 12.5 kDa. In humans, resistin is encoded by the RETN gene. In primates, pigs and dogs, resistin is secreted by immune and epithelial cells, while in rodents and human beings it is secreted by adipose tissue. [52-54]

It was called resistin because of the observed insulin resistance in mice injected with resistin. Resistin was found to be produced and released from adipose tissue to serve endocrine functions likely involved in insulin resistance so resistin physiologic role has been the subject of much controversy regarding its involvement with obesity and type II diabetes mellitus. Further research has linked resistin to other physiological systems such as inflammation and energy homeostasis. [55, 56]

Resistin increases the production of low-density lipoprotein (LDL) in human liver cells and also degrades LDL receptors in the liver. As a result, the liver is less able to clear bad cholesterol from the body so resistin has been shown to cause high levels of the bad cholesterol LDL. More-over, resistin accelerates the accumulation of LDL in arteries so increasing the risk of heart disease.[57]

CONCLUSIONS

Adipose tissue plays a major role in the regulation of systemic metabolic homeostasis via its profound effects on energy storage, endocrine function and adaptive thermogenesis. The dysfunction of adipose tissue as a causal factor is linked to obesity and its related disorders. Therefore, understanding adipose tissue biology and pathology is of great importance for the identification of novel and potential therapeutic targets for the prevention and treatment of obesity-related disorders.

It is now recognized that the adipose tissue produces a variety of bioactive peptides, collectively termed adipokines. Alteration of adipose mass in obesity affects the production of most adipose secreted factors. So obesity is associated with multiple metabolic disorders and increased risk of cardiovascular diseases, diabetes mellitus, cancers and many other diseases. The idea has emerged that adipose tissues could be instrumental in these complications by virtue of its secreted factors. Several adipokines are increased in the obese state and have been implicated in hypertension like angiotensinogen, impaired fibrinolysis like plasminogene activator inhibiter (PAI-1) and insulin resistance like TNFα, IL-6, resistin.

REFERENCES

1. Wirth, A., Wabitsch, M., Hauner, H. The Prevention and Treatment of Obesity. Deutsches Ärzteblatt International. 2014; 111 (42): 705–713. doi:10.3238/arztebl.2014.0705. ISSN 1866-0452. PMC 4233761. PMID 25385482.
2. Blüher M. Obesity: global epidemiology and pathogenesis. Nature Reviews Endocrinology. 2019; 15: 288–298.
3. Giralt M., Cereijo R., Villarroya F. Adipokines and the endocrine role of adipose tissues. Handbook of Experimental Pharmacology 2016;233265–282. (doi:10.1007/164_2015_6).
4. Parimisetty A., Dorsemans AC., Awada R., Ravanan P., Diotel N., Lefebvred'Hellencourt C. Secret talk between adipose tissue and central nervous system via secreted factors-an emerging frontier in the neurodegenerative research. Journal of Neuroinflammation. 2016 ; 1367. (doi:10.1186/s12974-016-0530-x).
5. Zhou Y. and Rui L. Leptin signaling and leptin resistance. Frontiers of Medicine. 2013. 7 (2): 207–22. doi:10.1007/s11684-013-0263-5. PMC 4069066. PMID 23580174).
6. Russell, A. P., Crisan, M., Leger, B., Corselli, M., McAinch, A. J., O'Brien, P. E., Cameron-Smith, D., Peault, B., Casteilla, L., and Giacobino, J. P. Brown adipocyte progenitor population is modified in obese and diabetic skeletal muscle. Int. J. Obes. 2012; 36: 155–158.
7. Cannon B. and Nedergaard J. Brown adipose tissue: function and physiological significance. Physiological Reviews. 2004. 84 (1): 277–359.
8. Seale, P., Conroe, H. M., Estall, J., Kajimura, S., Frontini, A., Ishibashi, J., Cohen, P., Cinti, S., and Spiegelman, B. M. Prdm16 determines the thermogenic program of subcutaneous white adipose tissue in mice. J. Clin. Invest. 2011; 121, 96–105.
9. Cinti S, The role of brown adipose tissue in human obesity. Nutrition, Metabolism and Cardiovascular Diseases.2006;16 (8): 569-574 https://doi.org/10.1016/j.numecd.2006.07.009)
10. Yamamoto, Y., Gesta S., Lee, K. Y., Tran, T. T., Saadatirad, P. and Kahn, C. R. Adipose depots possess unique developmental gene signatures. Obesity. 2010; 18: 872–878.
11. Walden, T. B., Hansen, I. R., Timmons, J. A., Cannon, B., and Nedergaard, J. Recruited vs. nonrecruited molecular signatures of brown, "brite," and white adipose tissues. Am. J. Physiol. Endocrinol. Metab. 2012; 302, E19–E31
12. Buck C.O., Eliot M.N., Kelsey K.T., Chen A., Kalkwarf H., Lanphear B.P., Braun J.M. *Neonatal adipocytokines and longitudinal patterns of childhood growth.* Obesity.2019; 27(8). http://doi.org/10.1002/oby.22519
13. Conde J, Scotece M, Gómez R, López V, Gómez-Reino JJ, Lago F, Gualillo O. Adipokines: BioFactors from white adipose tissue. A complex hub among inflammation, metabolism, and immunity. BioFactors. 2011;37 (6):413–420. doi:10.1002/biof.185. PMID 22038756.
14. Lehr S, Hartwig S, Sell H. Adipokines: a treasure trove for the discovery of biomarkers for metabolic disorders. Proteomics Clinical Applications. 2012 Jan; 6 (1–2): 91–101. doi:10.1002/prca.201100052. PMID 22213627.
15. Jaganathan R. Ravindran R. and MPhil S D k. Emerging Role of Adipocytokines in Type 2 Diabetes as Mediators of Insulin Resistance and Cardiovascular Disease. Canadian Journal of Diabetes; 2018; 42(4) :446-456.
16. Hashimoto H, Matsuda T, Hinuma S, Baba A. Apelin is a novel angiogenic factor in retinal endothelial cells. Biochem. Biophys. Res. Commun. 2004;325 (2): 395–400. doi:10.1016/j.bbrc.2004.10.042.PMID 15530405.
17. Cox CM, D'Agostino SL, Miller MK, Heimark RL, Krieg PA. "Apelin, the ligand for the endothelial G-protein-coupled receptor, APJ, is a potent angiogenic factor required for normal vascular development of the frog embryo". Dev. Biol.2006Aug;296:177–89.doi:10.1016/j.ydbio. 2006.04.452. PMID 16750822.
18. Tatemoto K, Takayama K, Zou MX, Kumaki I, Zhang W, Kumano K, Fujimiya M. The novel peptide apelin lowers blood pressure via a nitric oxide-dependent mechanism. Regul. Pept. 2001 June; 99 (2–3): 87–92. doi:10.1016/S0167-0115(01)00236-1. PMID 11384769.
19. Mesmin C, Dubois M, Becher F, Fenaille F, Ezan E . Liquid chromatography/tandem mass spectrometry assay for the absolute quantification of the expected circulating apelin peptides in human plasma. Rapid Commun Mass Spectrom. 2010; 24 (19): 2875– 84. doi:10.1002/rcm.4718. PMID 20857448.
20. Kechyn S. Barnes G. Thongmee A. Howard L. Effect of apelin on cardiopulmonary performance during endurance exercise. European Respiratory Journal. 2015 (46 suppl 59): 2241. doi:10.1183/13993003.congress-2015.PA2241
21. Flier JS, Maratos-Flier E. Lasker lauds leptin. Cell. 2010; 143: 9-12.
22. Gautron L, Elmquist JK. Sixteen years and counting: an update on leptin in energy balance. J. Clin. Invest. 2011;121: 2087-293.
23. Yonis R.A. and Al-Doski F.S. serum leptin, estradiol and testosterone concentration in normal healthy fertile women with different weights. Tikret Journal of Pharmaceutical Sciences. 2013; 9(2): 231-244.

24. Morton GJ, Schwartz MW. Leptin and the central nervous system control of glucose metabolism. Physiol. Rev. 2011; 91: 389-411.
25. Ghanem H.B., Elsheikh M., El-Benhawy S.A., Shahba A. Adipoytokines, inflammatory, epigenetic instability and angiogenesis biomarkers in type 2 diabetic Egyptian women with breast cancer. Diabetes and metabolic syndrome: Clinical Research and Reviews. 2019 ;13(1): 24-29.
26. Moraes-Vieira PM, Yore MM, Dwyer PM, Syed I, Aryal P, Kahn BB. RBP4 activates antigen-presenting cells, leading to adipose tissue inflammation and systemic insulin resistance. Cell Metabolism. March 2014; 19 (3): 512–26. doi:10.1016/j.cmet.2014.01.018. PMC 4078000. PMID 24606904.
27. Chou CM, Nelson C, Tarlé SA, Pribila JT, Bardakjian T, Woods S, Schneider A, Glaser T. *Biochemical Basis for Dominant Inheritance, Variable Penetrance, and Maternal Effects in RBP4 Congenital Eye Disease. Cell*. 2015 161 (3):634646. doi:10.1016/j.cell.2015.03.006. PMC 4409664. PMID 25910211.
28. Fang X, Sweeney G. Mechanisms regulating energy metabolism by adiponectin in obesity and diabetes. Biochemical Society Transactions. 2006; 34 (Pt 5): 798–801. doi:10.1042/BST0340798. PMID 17052201. S2CID 1473301.
29. Hafiane A, Gasbarrino K, Daskalopoulou SS . The role of adiponectin in cholesterol efflux and HDL biogenesis and metabolism". Metabolism: Clinical and Experimental.2019; 100: 153953. doi:10.1016/j.metabol.2019.153953.PMID 31377319.
30. Oh DK, Ciaraldi T, Henry RR . Adiponectin in health and disease. Diabetes, Obesity & Metabolism.2007;9(3):282–9.doi:10.1111/j.1463-1326 .2006.00610.x. PMID 17391153.
31. Nigro E, Scudiero O, Monaco ML, Palmieri A, Mazzarella G, Costagliola C, Bianco A, Daniele A . "New insight into adiponectin role in obesity and obesity-related diseases". BioMed Research International.2014;2014:1–14.doi:10.1155/2014 /658913. PMC 4109424. PMID 25110685.
32. Martinez-Huenchullan SF, Tam CS, Ban LA, Ehrenfeld-Slater P, Mclennan SV, Twigg SM. Skeletal muscle adiponectin induction in obesity and exercise. Metabolism: Clinical and Experimental.2020;102:154008.doi:10.1016/j.me tabol. 2019.154008. PMID 31706980.
33. Pautus S, Alami M, Adam F, Bernadat G, Lawrence DA, De Carvalho A, Ferry G, Rupin A, Hamze A, Champy P, Bonneau N, Gloanec P, Peglion JL, Brion JD, Bianchini EP, Borgel D. Characterization of the Annonaceous acetogenin, annonacinone, a natural product inhibitor of plasminogen activator inhibitor-1. Scientific Reports. 2016; 6: 36462. doi:10.1038/srep36462. PMC 5120274. PMID 27876785).
34. Vaughan DE . PAI-1 and atherothrombosis. Journal of Thrombosis and Haemostasis. 2005; 3 (8): 1879–83. doi:10.1111/j.1538-7836.2005.01420.x. PMID 16102055.
35. Carter JC, Church FC. "Obesity and breast cancer: the roles of peroxisome proliferator-activated receptor-γ and plasminogen activator inhibitor-1". PPAR Research. 2009; 345320. doi:10.1155/2009/345320. PMC 2723729. PMID 19672469.)
36. Roh SG, Song SH, Choi KC, Katoh K, Wittamer V, Parmentier M, Sasaki S. Chemerin--a new adipokine that modulates adipogenesis via its own receptor. Biochem. Biophys. Res. Commun. 2007; 362 (4): 1013–8. doi:10.1016/j.bbrc.2007.08.104.PMID 17767914.
37. Coimbra S, Brandão Proença J, Santos-Silva A, Neuparth MJ. *Adiponectin, leptin, and chemerin in elderly patients with type 2 diabetes mellitus: a close linkage with obesity and length of the disease*. Biomed Res Int. 2014; 1–8. doi:10.1155/2014/701915. PMC 4101968. PMID 25105135.
38. Takahashi M, Takahashi Y, Takahashi K, Zolotaryov FN, Hong KS, Kitazawa R, Iida K, Okimura Y, Kaji H, Kitazawa S, Kasuga M, Chihara K. Chemerin enhances insulin signaling and potentiates insulin-stimulated glucose uptake in 3T3-L1 adipocytes. FEBS Lett. 2008; 582(5):573–8. doi:10.1016/j.febslet.2008.01.023. PMID 18242188
39. Pedersen BK. Muscle as a secretory organ. Comprehensive Physiology. 2013; 3 (3): 1337–62.doi:10.1002/cphy.c120033.ISBN9780470650 714. PMID 23897689.
40. Mehta P, Mc Auley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al,. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395:1033–4.
41. Ulhaq ZS and Soraya.GV. Interleukin-6 as a potential biomarker of COVID-19 progression. Med Mal Infect; 2020 50(4): 382–383.
42. Peters MC, McGrath KW, Hawkins GA, Hastie AT, Levy BD, Israel E, et al,. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. The Lancet. Respiratory Medicine. 2016; 4 (7): 574–584. doi:10.1016/S2213-2600(16)30048-0. PMC 5007068. PMID 27283230 .
43. Kristiansen OP, Mandrup-Poulsen T (). *Interleukin-6 and diabetes: the good, the bad, or the indifferent?* . Diabetes. 2005; 54 Suppl 2: S114-

24. doi:10.2337/diabetes.54.suppl_2.S114. PMI D 16306329.
44. Dubiński A, Zdrojewicz Z. The role of interleukin-6 in development and progression of atherosclerosis. Polski Merkuriusz Lekarski 2007 ; 22 (130): 291–4. PMID 17684929.
45. Nishimoto N. Interleukin-6 in rheumatoid arthritis. Current Opinion in Rheumatology. 2006; 18(3):277–81. doi:10.1097/01.bor.0000218949. 19860.d1. PMID 16582692.
46. Zhu H, Wang Z, Yu J, Yang X, He F, Liu Z, Che F, Chen X, Ren H, Hong M, Wang J. Role and mechanisms of cytokines in the secondary brain injury after intracerebral hemorrhage. Prog. Neurobiol.2019;178:101610.doi:10.1016/j.pneuro bio. 2019.03.003. PMID 30923023. S2CID 85495400.
47. Smolen JS, Maini RN. Interleukin-6: a new therapeutic target. Arthritis Research and Therapy.2006;8(Suppl2):S5. doi:10.1186/ar1969. PMC 3226077. PMID 16899109
48. Nguyen AD, Nguyen TA, Martens LH, Mitic LL, Farese RV . *Progranulin: at the interface of neurodegenerative and metabolic diseases.* Trends in Endocrinology and Metabolism. 2013; 24(12): 597–606. doi:10.1016/j.tem.2013.08.003. PMC 3842380. PMID 24035620.
49. Zhou X, Sun L, Bracko O, Choi JW, Jia Y, Nana AL, et al,. Impaired prosaposin lysosomal trafficking in frontotemporal lobar degeneration due to progranulin mutations. Nature Communications.2017.8:15277.Bibcode:2017 NatCo...815277Z. doi:10.1038/ncomms15277. PMC 5477518. PMID 28541286
50. Revollo JR, Grimm AA, Imai S . The regulation of nicotinamide adenine dinucleotide biosynthesis by Nampt/PBEF/visfatin in mammals. Current Opinion in Gastroenterology. 2007;23(2):164–70. doi:10.1097/MOG.0b013e 32801b3c8f. PMID 17268245
51. Pramono AA, Rather GM, Herman H. *NAD- and NADPH-Contributing Enzymes as Therapeutic Targets in Cancer: An Overview.* Biomolecules.2020*; 10 (3):358.* doi*:*10 .3390/biom10030358*.* PMC 7175141*.* PMID 321 11066.
52. Stumvoll M, Häring H. Resistin and adiponectin of mice and men. Obes. Res. 2002; 10 (11): 1197–9. doi:10.1038/oby.2002.162. PMID 12429885.
53. Adeghate E An update on the biology and physiology of resistin. Cell. Mol. Life Sci. 2004; 61 (19–20): 2485–96. doi:10.1007/s00018-004-4083-2. PMID 15526156.
54. Vendrell J, Broch M, Vilarrasa N, Molina A, Gómez JM, Gutiérrez C, Simón I, Soler J, Richart C Resistin, adiponectin, ghrelin, leptin, and proinflammatory cytokines: relationships in obesity. Obes. Res. 2004; 12 (6): 962–71. doi:10.1038/oby.2004.118. PMID 15229336
55. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. *The hormone resistin links obesity to diabetes.* Nature. 2001; 409 (6818): 307–12. doi:10.1038/35053000. PMID 11201732.
56. Gabriely I, Ma XH, Yang XM, Atzmon G, Rajala MW, Berg AH, Scherer P, Rossetti L, Barzilai N. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process? . Diabetes. 2002; 51 (10): 2951–8. doi:10.2337/diabetes.51.10.2951.PMID1235143 2.
57. Degawa-Yamauchi M, Bovenkerk JE, Juliar BE, Watson W, Kerr K, Jones R, Zhu Q, Considine RV . Serum resistin (FIZZ3) protein is increased in obese humans. J. Clin. Endocrinol. Metab.2003;88(11):5452–5. doi:10.1210/jc.2002 -021808. PMID 14602788.