Peroxisome Proliferator-activated Receptors

Subjects: Biochemistry & Molecular Biology

Contributor: Elisabetta Benedetti

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that exert important functions in mediating the pleiotropic effects of diverse exogenous factors such as physical exercise and food components. Particularly, PPARs act as transcription factors that control the expression of genes implicated in lipid and glucose metabolism, and cellular proliferation and differentiation. In this review, we aimed to summarize recent advancements reported on the effects of lifestyle and food habits on PPAR transcriptional activity.

PPAR, metabolism, lifestyle

1. Introduction

Modern lifestyle characterized by unbalanced composition of the diet and poor physical activity, accompanied by the presence of environmental pollutants, has resulted in dramatic increases in the rates of metabolic disease and age-related diseases. These chronic diseases, such as diabetes, cardiovascular disease (CVD), autoimmune diseases, cancers (breast, colorectal, pancreas), and neurodegenerative diseases are all characterized by a chronic sterile systemic low-grade inflammation [1,2,3]. Moreover, these chronic diseases correlate with the metabolic syndrome (MetS), defined by a cluster of interrelated factors: dyslipidemia, hypertension, dysregulated glucose homeostasis, abdominal obesity, and insulin resistance (IR) [4]. Particularly, the obesity and insulin resistance emerge to be the heart of the pathophysiology of the MetS [5]. Different environmental factors of Western lifestyle play a key role in inducing chronic sterile systemic low-grade inflammation and, eventually, the correlated chronic disease. These factors may be divided in the unbalanced composition of the diet [6,7,8] and non-food related factors [9]. Regarding the diet, in Western society there is a consumption of high glycemic index foods (cookies, chocolate, pastries), thus is associated with obesity and IR [10,11,12,13]. This kind of diet increases inflammatory biomarkers [14] and it is related to chronic disease, such as CVD, diabetes, cancer, Alzheimer's disease [10,15,16,17]. In Western diet there is also an elevated consumption of certain saturated fatty acids (SAFA) [18], and industrially produced trans fatty acids [19,20]. Moreover, in Western diet there is an high ω6/ω3 fatty acid ratio [21,22,23], mostly because of a low intake of long-chain polyunsaturated fatty acids of the ω3 series, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish, and alpha-linolenic acid (ALA) from vegetable sources [24]. Among the non-food related factors, it is possible to mention smoking habit, insufficient physical activity [25,26,27,28], and environmental pollution [9] such as exposition to endocrine disruptors [29]. Thus, these kinds of lifestyle and food habits promote a chronic inflammatory status that as mentioned above is characteristic of chronic diseases. Biochemical mediators of lipids are represented by PPARs [30]. This review provides an update of lifestyle and food habits on low grade inflammation in two main chronic diseases, polycystic ovary syndrome (PCOS) and non-alcoholic fatty liver disease (NAFLD), with particular

attention on the mechanism that involve the activation of the major metabolic and inflammatory players, the PPARs.

PPARs are ligand-activated transcription factors, belonging to the superfamily of nuclear receptors (NR). PPARs act as lipid sensors; therefore, they have attracted much attention for their ability to improve metabolic syndromes [31]. They take part in nutrient and energy metabolism regulating whole-body energy homeostasis [32],[33]. PPARs regulate nutrient metabolism such as lipid, glucose, and cholesterol and sustain the intraorgan metabolic flexibility (Box 1); indeed PPARs play also an important role in regulating the correct inflammation tone [30]. There are three PPARs subtypes: PPARα (NR1C1), PPARβ/δ (NR1C2), and PPARγ (NR1C3), that are highly homologous but differ for tissue distribution and biological functions (Table 1). Fatty acids and their derivatives are the main endogenous agonists of PPARs [34], while among the synthetic ligands there are the main drug utilized for counteracting MetS (Table 1). Their main activity in regulating lipid, glucose metabolism, and inflammation suggests that PPARs are the crossroad of several molecular signaling pathways, implicated in metaflammation onset [35].

Table 1. PPARs tissue distribution and biological functions.

Isoforms	Tissues Distribution	Target Genes	Functions	Synthetic Ligands	Natural Ligands
PPARγ	White and brown adipose tissue, the large intestine, skeletal muscle, spleen, pancreas, and brain.	aP2, FATP, FAT/CD36.	Regulation of adipogenesis, energy balance, lipogenesis, gluconeogenesis, lipid storage, glucose uptake, metabolism uptake and differentiation.	Rosiglitazone, Pioglitazone, Troglitazone, T3D-959, DBZ.	9-HODE, 13-HODE, 15d-PGJ2, EPA.
PPARα	Liver, heart, skeletal muscle, intestinal mucosa, white and brown adipose	Acyl-CoA oxidase, Thiolase, Apolipoprotein A-I, Apolipoprotein A-II, CYP8B1,	Fatty acid metabolism, inflammation, thermogenesis, ketogenesis, glucose uptake, fatty acid oxidation	Wy-14643, GW-2331, GW-9578, K-877 Fibrates.	Palmitic acid, Oleic acid, Linoleic acid, Arachidonic acid, DHA, oleoylethanolamide.

Isoforms	Tissues Distribution	Target Genes	Functions	Synthetic Ligands	Natural Ligands
	tissue, pancreas, and brain.	FATP, FAT/CD36, and Lipoprotein lipase.	and lipid storage.		
PPARβ/δ	Liver, intestine, kidney, abdominal white and brown adipose tissue, skeletal muscle, heart, pancreas, and brain.	Genes involved in lipid uptake, metabolism, and efflux, Lpin2, St3gal5.	Fatty acid oxidation, fatty acid metabolism, regulates blood cholesterol, glucose uptake, glucose utilization, insulin secretion, ketogenesis and inflammation.	L-796449, L-783483, GW-2433, MBX-8025, T3D-959, GW501516, GW610742.	Dihomo-γ-linolenic acid, Arachidonic acid, Methyl palmitate, 2-bromopalmitic acid, prostacyclin I2, 4-HNE.

2. PPARs and Metabolism

All three PPARs are involved in adipose tissue homeostasis. Tissues with high rates of fatty acids catabolism, such as brown adipose tissue (BAT), liver, and skeletal muscles, present high level of PPARα activity. Most PPARα studies have been conducted on the liver [36], in which this nuclear receptor is able to increase the transcription of gene related to the fatty acid transport and catabolism [36,37,38], ketogenesis [37], and gluconeogenesis [39,40]. PPARα in liver is a key factor for the adaptation of fasting and, consequently, energy switch from carbohydrate to fatty acid produced by WAT lipolysis. In the fed state, insulin-dependent PI3K pathway activates rapamycin complex 1 (mTORC1) that in turn suppresses, through nuclear receptor corepressor 1, PPARα activity [41]. PPARα agonist reduces obesity-related metabolic disorders. Experiments conducted on obese mice showed that PPARα agonist treatments improved the obesity condition and glucose homeostasis in terms of glucose intolerance, insulin resistance, and hyperglycemia [42,43]. Goto proposes three options to explain the ability in improving glucose metabolism via adipose tissue [44]. The first option proposes that one of the PPARα capabilities is to increase the expression of a particular hepatokine, the fibroblast growth factor 21 (FGF21) [42], a cytokine able to increase the energy consumptions in white adipose tissue (WAT) via the enhancement of the brown adipose tissue (BAT)

activity (generally called “browning”) [45],[46]. In fact, the authors showed that fibrate treatment increases the energy consumptions and adipocyte dysfunction and improve glucose homeostasis in WAT of high-fat diet (HFD) wild-type mice, but not in fibroblast growth factor (FGF21)-deficient mice [42]. The second option is the PPARα-mediated enhancing of the production and the release of a particular lipokine, 1-palmitoyl lysophosphatidylcholine, by the liver [47]. This lipokine is able to recover the glucose uptake in insulin-resistant adipocytes, and is an endogenous ligand of PPARα, suggesting a positive feedback loop between PPARα activation and 1-palmitoyl lysophosphatidylcholine production in the liver [47]. Finally, the last option is the improvement of glucose metabolism, via direct action of PPARα on adipose tissue. In fact, transgenic mice that express in adipose tissues constitutive active human PPARα, presented under HFD, recovered insulin sensitivity [48], suggesting an important role of this NR in attenuating obesity-induced insulin resistance in WAT. Two isomeric forms of PPARγ exist, PPARγ1 and PPARγ2; PPARγ1 is most copious in WAT, but it presents also in other tissue (Table 1), while the expression of PPARγ2 is restricted in BAT and WAT [49],[50]. Both isoforms are able to induce adipocytes differentiation although PPARγ2 appears more potent in this function [51]. In adipose tissue PPARγ plays key roles in adipocytes differentiation and survival, in the same time, this NR regulates insulin sensitivity and lipogenesis [37], [52]. In BAT, the activation of PPARγ triggers the expression of genes linked to thermogenic program, comprising PPARγ coactivator protein 1α (PGC1A) and uncoupling protein 1 (UCP1) [53]. Regarding MetS, PPARγ is the most studied NR since 1995; it was recognized as a molecular target of thiazolidinediones, a class of antidiabetic and insulin-sensitizing drugs [54]. The activation of PPARγ, inducing adipocytes differentiation and strengthening the capacity of lipid accumulation in WAT [50] protects the body from IR and free FA release leading to the attenuation of lipotoxicity. In fact, negative regulation of adipogenic transcription factors, such as PPARγ in adipose tissue, has been demonstrated to cause visceral obesity [55]. Under over-nutrition, the increase of adipose tissue has a protective role in preventing the release of free fatty acids in the systemic circulation. This is possible because in WAT there are stem cells that can differentiate in adipocytes, thus increasing its ability in lipids storage; in this mechanism PPARγ plays an essential role. The fact that fat is not always bad is derived from the evidence that a significant part of obese individuals (healthy obese) do not show dysmetabolism while a significant percentage of lean individuals do [56],[57]. Healthy WAT is composed by different adipocytes, showing an increase of hyperplasia and a decrease of hypertrophy; the latter is a definite feature of pathologic obesity [58],[59],[60],[61],[62],[63]. Recently, it has been demonstrated that the recruit of new adipocytes from PDGFRβ+ pre-adipocytes determines the visceral WAT health in obesity [64]. Notably, in the hypothalamus of HFD rodents, by inhibiting PPARγ in the central nervous system (CNS), the sensitivity of the leptin pathway was improved. Another study demonstrated that transgenic mice knockout for PPARγ in hypothalamic neurons had enhanced energy consumption; on the contrary, food intake and body weight were decreased. In addition, these mice had improved glucose metabolism upon High Fat Diet (HFD) [65]. Thus, PPARγ signaling in the brain influence the energy balance and stimulate the obesity phenotype [66]. Although the same obesogenic effects have been reported for activation of PPARα in the brain, the PPAR β/δ isotype appears to exert opposite role. Mice with PPPAR β/δ deleted showed a strong expression of PPARγ and PPARα in the hypothalamus [67]. Regarding PPAR β/δ, in genetic models, it has been demonstrated that the activation of this NF protects against obesity [68]. Transgenic mice encoding an active form of PPAR β/δ specifically in adipose tissue, fed with a standard chow diet, showed decrease of body weights (20%), of inguinal fat pad masses (40%), and less circulating free FAs and triglycerides compared to control animals [68]. The same

mice upon HFD or genetically predisposed to the obesity are protected against weight gain, adipocyte hypertrophy, hypertriglyceridemia, and steatosis [68]. Moreover, an increase of browning was observed in these mice [68]. In opposite, the loss of PPARβ/δ function rendered mice more prone to weight gain and had reduced expression of brown fat UCP1 upon HFD [68]. While PPARα is the most present isoform in the liver, PPARβ/δ isoform is the most expressed in muscle and it is preferentially found in oxidative rather than glycolytic myofibers [69],[70],[71]. In muscle cells, the activation of PPARβ/δ switches energy production from glycolysis to fatty acid oxidation enhancing muscle endurance [72]. Moreover, the activation of this NF increases the fatty acid uptake and catabolism via oxidation in skeletal muscle cells [73]. PPARβ/δ expression in muscle has several physiological implications such as decreased skeletal muscle fatigability and increased resistance to HFD-induced obesity [71]. Insulin-resistant obese monkeys treated with GW501516; a ligand PPARβ/δ showed an increased serum high-density lipoprotein cholesterol and a decrease of low density lipoprotein, fasting triglycerides, and insulin [74]. The activation of PPARβ/δ, during HFD, increases consumption of lipid in skeletal muscles, avoiding hypertrophy of adipocytes and IR [68],[69],[75]. Finally, physical exercise and fasting increase the expression of PPARβ/δ in muscles [75],[76],[77], demonstrating that PPARs act as an interface between lifestyle and health.

Striated muscle plays central roles in MetS, since it is a regulator of total body mass and energy consumption. A surplus of glucose, free fatty acid, and triglycerides concomitant with physical inactivity altered muscular metabolism, that in turn contributes to the onset of obesity and IR [78]. In a healthy-weight individual, skeletal muscles represent ~40% of the total human body mass, and with the cardiac tissue, use almost 30% of the resting energy and nearly 100% of energy utilization during physical exercise [78]. Skeletal muscle is composed of heterogeneous myofibers, slow-, mixed- and fast-twitch, that differ in the composition of contractile protein apparatus and metabolism. In particular, slow-twitch (TypeI) has high oxidative aptitude using fatty acids as substrate for ATP production; mixed oxidative/glycolytic fast-twitch (type IIA) with both phenotype, and type IIB display high strength of contraction but lower oxidative ability doing anaerobic glycolysis [79]. Thus, systemic energy is impacted mostly by fiber type composition [80],[81]. Physical activities, especially aerobic exercises, increase the amount of slow fiber type, while the opposite is observed in obesity and diabetes in which there is an enhance of caloric intake without an increase of metabolic demand [82]. Instead, in both diabetic and obese patients, physical activity improve IR and lean mass [83],[84]. Similar to adipose tissue, the muscle secretes factors, named myokines, that act in an autocrine and/or paracrine manner [85],[86]. Myokines panel production depends on exercise and may modulate, as adipokines, glucose and lipids metabolism [87],[88],[89]. Among these myokines, myostatin regulate glucose and lipid metabolism, and myostatin-deficient animal are not susceptible to diet-induced obesity [89]. Other myokines involved in systemic metabolism are angiopoietin-like protein 4 (ANGPTL4) [90], irisin, FGF-21, Interleukin-15 (IL-15), [85], meteorin-like protein [91] and Growth differentiation factor 11 (GDF11) [92]. Finally, β-aminoisobutyric acid (BAIBA), belongs to a recent class of factors called “myometabokines,” is able to regulate systemic metabolism crosstalk [86], and to induce browning phenotype in white adipose tissue [93]. These last discoveries highlight the importance of muscle on energy homeostasis and thus the influence of moderate physical activity on human health.

3. Conclusions

It is becoming noticeable that the primary cause of most Western chronic diseases, with systemic low-grade inflammation as the common denominator, is not following a correct lifestyle and improper food habits. Ruiz-Núñez and Colleagues 2013 [94] deduce as human predisposition to develop IR depends on the rapid brain growth in the past millennium. During this period, the interaction between our immune system and metabolism was strongly conserved, indeed, with the advent of the agricultural and industrial revolutions, leads to chronic inflammation. Lifestyle modifications in Western countries are necessary especially in the first years of life. However, during pathology onset, since improving lifestyle is not that easy, pharmacotherapy is required. PPARs represent the interface between environment metabolism and immune system; moreover, their presence in all metabolic tissues suggests that they play an important role in regulating the fine crosstalk between them. Thus, these receptors are targets for the therapy of metabolic syndrome and the low-grade inflammatory state. Because of the collateral effects induced by fenofibrates and TZDs, new therapeutic approaches are necessary in order to obtain new PPARs ligands characterized by minor negative effects and increased positive effects. Recently, more attention is pointed toward the possible use of natural compounds, such as PUFAn3, oleoylethanolamide and β-aminoisobutyric acid, natural and endogenous ligands of PPARs. Finally, the development of PPARα/γ/δ pan-agonists or PPARα/γ dual agonist [95] could be a potential therapy for a concomitant pharmacological activity on carbohydrate and lipid metabolism.

References

1. Gerald M. Reaven; THE INSULIN RESISTANCE SYNDROME: Definition and Dietary Approaches to Treatment. *Annual Review of Nutrition* **2005**, *25*, 391-406, 10.1146/annurev.nutr.24.012003.132155.
2. Dandona, P.; Aljada, A.; Chaudhuri, A.; Mohanty, P.; Garg, R.; Metabolic Syndrome: A Comprehensive Perspective Based on Interactions between Obesity, Diabetes, and Inflammation. *Circulation* **2005**, *111*, 1448–1454, 10.1161/01.CIR.0000158483.13093.9D.
3. Peter Libby; Inflammation in atherosclerosis. *Nature* **2002**, *420*, 868-874, 10.1038/nature01323.
4. Eva Kassi; Panagiota Pervanidou; Gregory Kaltsas; George Chrousos; Metabolic syndrome: definitions and controversies. *BMC Medicine* **2011**, *9*, 48-48, 10.1186/1741-7015-9-48.
5. Marc-Andre Cornier; Dana Dabelea; Teri L. Hernandez; Rachel C. Lindstrom; Amy J. Steig; Nicole R. Stob; Rachael E. Van Pelt; Hong Wang; Robert H. Eckel; The Metabolic Syndrome. *Endocrine Reviews* **2008**, *29*, 777-822, 10.1210/er.2008-0024.
6. Leo Galland; Diet and Inflammation. *Nutrition in Clinical Practice* **2010**, *25*, 634-640, 10.1177/0884533610385703.
7. Preetha Anand; Ajaikumar B. Kunnumakara; Chitra Sundaram; Kuzhuvelil B. Harikumar; Sheeja T. Tharakan; Oiki S. Lai; Bokyung Sung; Bharat B. Aggarwal; Cancer is a Preventable Disease

that Requires Major Lifestyle Changes. *Pharmaceutical Research* **2008**, *25*, 2097-2116, 10.1007/s11095-008-9661-9.

8. G. Egger; J. Dixon; Inflammatory effects of nutritional stimuli: further support for the need for a big picture approach to tackling obesity and chronic disease. *Obesity Reviews* **2010**, *11*, 137-149, 10.1111/j.1467-789x.2009.00644.x.
9. G. Egger; J. Dixon; Non-nutrient causes of low-grade, systemic inflammation: support for a ‘canary in the mineshaft’ view of obesity in chronic disease. *Obesity Reviews* **2010**, *12*, 339-345, 10.1111/j.1467-789x.2010.00795.x.
10. Ellen E. Blaak; Carbohydrate quantity and quality and cardio-metabolic risk. *Current Opinion in Clinical Nutrition and Metabolic Care* **2016**, *19*, 1-293, 10.1097/mco.0000000000000290.
11. Niina E. Kaartinen; Paul Knekt; Noora Kanerva; Liisa M. Valsta; Johan G. Eriksson; Harri Rissanen; Tuija Jääskeläinen; Satu Männistö; Dietary carbohydrate quantity and quality in relation to obesity: A pooled analysis of three Finnish population-based studies. *Scandinavian Journal of Public Health* **2016**, *44*, 385-393, 10.1177/1403494815622860.
12. Angela Cornejo-Monthedoro; Isel Negreiros-Sánchez; Carlos Del Águila; Marlit Ysla-Marquillo; Percy Mayta-Tristán; Association between dietary glycemic load and metabolic syndrome in obese children and adolescents. *Archivos Argentinos de Pediatria* **2017**, *115*, 323-330, 10.5546/aap.2017.eng.323.
13. Kellen Cristine Silva; Luciana Neri Nobre; Sofia Emanuelle De Castro Ferreira Vicente; Lidiane Lopes Moreira; Angelina Do Carmo Lessa; Joel Alves Lamounier; Influence of glycemic index and glycemic load of the diet on the risk of overweight and adiposity in childhood. *Revista Paulista de Pediatria (English Edition)* **2016**, *34*, 293-300, 10.1016/j.rppede.2015.12.009.
14. Alireza Milajerdi; Parvane Saneei; Bagher Larijani; Ahmad Esmaillzadeh; The effect of dietary glycemic index and glycemic load on inflammatory biomarkers: a systematic review and meta-analysis of randomized clinical trials. *The American Journal of Clinical Nutrition* **2018**, *107*, 593-606, 10.1093/ajcn/nqx042.
15. Stacey J. Bell; Barry Sears; Low-Glycemic-Load Diets: Impact on Obesity and Chronic Diseases. *Critical Reviews in Food Science and Nutrition* **2003**, *43*, 357-377, 10.1080/10408690390826554.
16. Matthew K Taylor; Debra K Sullivan; Russell H Swerdlow; Eric D Vidoni; Jill K Morris; Jonathan D Mahnken; Jeffrey M Burns; A high-glycemic diet is associated with cerebral amyloid burden in cognitively normal older adults.. *The American Journal of Clinical Nutrition* **2017**, *106*, 1463-1470, 10.3945/ajcn.117.162263.
17. Hu, J.; La Vecchia, C.; Augustin, L.S.; Negri, E.; de Groh, M.; Morrison, H.; Mery, L.; Canadian Cancer Registries Epidemiology Research Group Glycemic index, glycemic load and cancer risk. *Ann. Oncol.* **2013**, *24*, 245–251, 10.1093/annonc/mds235.

18. Yolanda Jiménez-Gómez; José López-Miranda; Luis M. Blanco-Colio; Carmen Marín; Pablo Perez-Martinez; Juan Ruano; Juan A. Paniagua; Fernando Rodríguez; Jesús Egido; Francisco Pérez-Jiménez; et al. Olive oil and walnut breakfasts reduce the postprandial inflammatory response in mononuclear cells compared with a butter breakfast in healthy men. *Atherosclerosis* **2009**, *204*, e70-e76, 10.1016/j.atherosclerosis.2008.09.011.
19. Dariush Mozaffarian; Trans fatty acids – Effects on systemic inflammation and endothelial function. *Atherosclerosis Supplements* **2006**, *7*, 29-32, 10.1016/j.atherosclerosissup.2006.04.007.
20. D Mozaffarian; A Aro; W C Willett; Health effects of trans-fatty acids: experimental and observational evidence. *European Journal of Clinical Nutrition* **2009**, *63*, S5-S21, 10.1038/sj.ejcn.1602973.
21. C N Serhan; N Chiang; Endogenous pro-resolving and anti-inflammatory lipid mediators: a new pharmacologic genus. *British Journal of Pharmacology* **2007**, *153*, S200-S215, 10.1038/sj.bjp.0707489.
22. Artemis P. Simopoulos; The Importance of the Omega-6/Omega-3 Fatty Acid Ratio in Cardiovascular Disease and Other Chronic Diseases. *Experimental Biology and Medicine* **2008**, *233*, 674-688, 10.3181/0711-mr-311.
23. Philip C Calder; n−3 Polyunsaturated fatty acids, inflammation, and inflammatory diseases. *The American Journal of Clinical Nutrition* **2006**, *83*, 1505S-1519S, 10.1093/ajcn/83.6.1505s.
24. Ka He; Kiang Liu; Martha L. Daviglus; Nancy Swords Jenny; Elizabeth Mayer-Davis; Rui Jiang; Lyn Steffen; David Siscovick; Michael Tsai; David Herrington; et al. Associations of dietary long-chain n-3 polyunsaturated fatty acids and fish with biomarkers of inflammation and endothelial activation (from the Multi-Ethnic Study of Atherosclerosis [MESA]).. *The American Journal of Cardiology* **2009**, *103*, 1238-43, 10.1016/j.amjcard.2009.01.016.
25. Kim M. Huffman; Gregory P. Samsa; Cris A. Slentz; Brian D. Duscha; Johanna L. Johnson; Connie W. Bales; Charles J. Tanner; Joseph A. Houmard; William E. Kraus; Response of high-sensitivity C-reactive protein to exercise training in an at-risk population. *American Heart Journal* **2006**, *152*, 793-800, 10.1016/j.ahj.2006.04.019.
26. Anne Marie W. Petersen; Bente Klarlund Pedersen; A. M. W. Petersen; The anti-inflammatory effect of exercise. *Journal of Applied Physiology* **2005**, *98*, 1154-1162, 10.1152/japplphysiol.00164.2004.
27. Ronenn Roubenoff; Molecular Basis of Inflammation: Relationships Between Catabolic Cytokines, Hormones, Energy Balance, and Muscle. *Journal of Parenteral and Enteral Nutrition* **2008**, *32*, 630-632, 10.1177/0148607108324875.
28. Handschin, C.; Spiegelman, B.M.; The role of exercise and PGC1α in inflammation and chronic disease. *Nature* **2008,**, *454*, 463–469, https://www.nature.com/articles/nature07206.

29. Demetrios Petrakis; Loukia Vassilopoulou; Charalampos Mamoulakis; Christos Psycharakis; Aliki Anifantaki; Stavros Sifakis; Anca Oana Docea; John Tsiaoussis; Antonios Makrigiannakis; Aristides M. Tsatsakis; et al. Endocrine Disruptors Leading to Obesity and Related Diseases. *International Journal of Environmental Research and Public Health* **2017**, *14*, 1282, 10.3390/ijerph14101282.

30. Walter Wahli; Liliane Michalik; PPARs at the crossroads of lipid signaling and inflammation. *Trends in Endocrinology & Metabolism* **2012**, *23*, 351-363, 10.1016/j.tem.2012.05.001.

31. Fan Hong; Shijia Pan; Yuan Guo; Pengfei Xu; Yonggong Zhai; PPARs as Nuclear Receptors for Nutrient and Energy Metabolism.. *Molecules* **2019**, *24*, 2545, 10.3390/molecules24142545.

32. Michael Schupp; Mitchell A. Lazar; Endogenous Ligands for Nuclear Receptors: Digging Deeper*. *Journal of Biological Chemistry* **2010**, *285*, 40409-40415, 10.1074/jbc.R110.182451.

33. Steven J. Bensinger; Peter Tontonoz; Integration of metabolism and inflammation by lipid-activated nuclear receptors. *Nature* **2008**, *454*, 470-477, 10.1038/nature07202.

34. Aurore Woller; Hélène Duez; Bart Staels; Marc Lefranc; A Mathematical Model of the Liver Circadian Clock Linking Feeding and Fasting Cycles to Clock Function. *Cell Reports* **2016**, *17*, 1087-1097, 10.1016/j.celrep.2016.09.060.

35. Tiziana Caputo; Federica Gilardi; Béatrice Desvergne; From chronic overnutrition to metaflammation and insulin resistance: adipose tissue and liver contributions. *FEBS Letters* **2017**, *591*, 3061-3088, 10.1002/1873-3468.12742.

36. Alexandra Montagner; Arnaud Polizzi; Edwin Fouché; Simon Ducheix; Yannick Lippi; Frédéric Lasserre; Valentin Barquissau; Marion Régnier; Céline Lukowicz; Fadila Benhamed; et al.Alison IrozJustine Bertrand-MichelTalal Al SaatiPatricia CanoLaila Mselli-LakhalGilles MithieuxFabienne RajasSandrine LagarrigueThierry PineauNicolas LoiseauCatherine PosticDominique LanginWalter WahliHervé Guillou Liver PPARα is crucial for whole-body fatty acid homeostasis and is protective against NAFLD. *Gut* **2016**, *65*, 1202-1214, 10.1136/gutjnl-2015-310798.

37. Vanessa Dubois; Jérôme Eeckhoute; Philippe Lefebvre; Bart Staels; Distinct but complementary contributions of PPAR isotypes to energy homeostasis.. *Journal of Clinical Investigation* **2017**, *127*, 1202-1214, 10.1172/JCI88894.

38. Philippe Lefebvre; Giulia Chinetti; Jean-Charles Fruchart; Bart Staels; Sorting out the roles of PPARα in energy metabolism and vascular homeostasis. *Journal of Clinical Investigation* **2006**, *116*, 571-580, 10.1172/JCI27989.

39. Sarawut Jitrapakdee; Marc Slawik; Gema Medina-Gomez; Mark Campbell; John C. Wallace; Jaswinder K. Sethi; Stephen O'rahilly; Antonio J. Vidal-Puig; The peroxisome proliferator-activated receptor-gamma regulates murine pyruvate carboxylase gene expression in vivo and in vitro.. *Journal of Biological Chemistry* **2005**, *280*, 27466-76, 10.1074/jbc.M503836200.

40. Sherrie Tafuri; Michael Muller; David Patsouris; Stéphane Mandard; Peter J. Voshol; Pascal Escher; Nguan Soon Tan; Louis M. Havekes; Wolfgang Koenig; Winfried März; et al.Walter WahliSander Kersten PPARα governs glycerol metabolism. *Journal of Clinical Investigation* **2004**, *114*, 94-103, 10.1172/JCI20468.

41. Shomit Sengupta; Timothy R. Peterson; Mathieu Laplante; Stephanie Oh; David M. Sabatini; mTORC1 controls fasting-induced ketogenesis and its modulation by ageing. *Nature* **2010**, *468*, 1100-1104, 10.1038/nature09584.

42. Tsuyoshi Goto; Mariko Hirata; Yumeko Aoki; Mari Iwase; Haruya Takahashi; Minji Kim; Yongjia Li; Huei-Fen Jheng; Wataru Nomura; Nobuyuki Takahashi; et al.Chu-Sook KimRina YuShigeto SenoHideo MatsudaMegumi Aizawa-AbeKen EbiharaNobuyuki ItohTeruo Kawada The hepatokine FGF21 is crucial for peroxisome proliferator-activated receptor-α agonist-induced amelioration of metabolic disorders in obese mice. *Journal of Biological Chemistry* **2017**, *292*, 9175-9190, 10.1074/jbc.M116.767590.

43. Tsuyoshi Goto; Joo-Young Lee; Aki Teraminami; Yong-Il Kim; Shizuka Hirai; Taku Uemura; Hiroyasu Inoue; Nobuyuki Takahashi; Teruo Kawada; Activation of peroxisome proliferator-activated receptor-alpha stimulates both differentiation and fatty acid oxidation in adipocytes.. *Journal of Lipid Research* **2011**, *52*, 873-84, 10.1194/jlr.M011320.

44. Tsuyoshi Goto; A review of the studies on food-derived factors which regulate energy metabolism via the modulation of lipid-sensing nuclear receptors. *Bioscience, Biotechnology, and Biochemistry* **2018**, *83*, 579-588, 10.1080/09168451.2018.1559025.

45. Tamer Coskun; Holly A. Bina; Michael A. Schneider; James D. Dunbar; Charlie C. Hu; Yanyun Chen; David E. Moller; Alexei Kharitonenkov; Fibroblast Growth Factor 21 Corrects Obesity in Mice. *Endocrinology* **2008**, *149*, 6018-6027, 10.1210/en.2008-0816.

46. Ffolliott M. Fisher; Sandra Kleiner; Nicholas Douris; Elliott C. Fox; Rina J. Mepani; Francisco Verdeguer; Jun Wu; Alexei Kharitonenkov; Jeffrey S. Flier; Eleftheria Maratos-Flier; et al.Bruce M. Spiegelman FGF21 regulates PGC-1α and browning of white adipose tissues in adaptive thermogenesis. *Genes & Development* **2012**, *26*, 271-281, 10.1101/gad.177857.111.

47. Haruya Takahashi; Tsuyoshi Goto; Yota Yamazaki; Kosuke Kamakari; Mariko Hirata; Hideyuki Suzuki; Daisuke Shibata; Rieko Nakata; Hiroyasu Inoue; Nobuyuki Takahashi; et al.Teruo Kawada Metabolomics reveal 1-palmitoyl lysophosphatidylcholine production by peroxisome proliferator-activated receptor α. *Journal of Lipid Research* **2014**, *56*, 254-265, 10.1194/jlr.m052464.

48. Haruya Takahashi; Kohei Sanada; Hiroyuki Nagai; Yongjia Li; Yumeko Aoki; Takeshi Ara; Shigeto Seno; Hideo Matsuda; Rina Yu; Teruo Kawada; et al.Tsuyoshi Goto Over-expression of PPARα in obese mice adipose tissue improves insulin sensitivity. *Biochemical and Biophysical Research Communications* **2017**, *493*, 108-114, 10.1016/j.bbrc.2017.09.067.

49. Peter Tontonoz; Bruce M. Spiegelman; Fat and Beyond: The Diverse Biology of PPARγ. *Annual Review of Biochemistry* **2008**, *77*, 289-312, 10.1146/annurev.biochem.77.061307.091829.
50. Michael Lehrke; Mitchell A. Lazar; The Many Faces of PPARγ. *Cell* **2005**, *123*, 993-999, 10.1016/j.cell.2005.11.026.
51. Evan D. Rosen; Chung-Hsin Hsu; Xinzhong Wang; Shuichi Sakai; Mason W. Freeman; Frank J. Gonzalez; Bruce M. Spiegelman; C/EBPα induces adipogenesis through PPARγ: a unified pathway. *Genome Research* **2002**, *16*, 22-26, 10.1101/gad.948702.
52. Martina I. Lefterova; Anders Kristian Haakonsson; Mitchell A. Lazar; Susanne Mandrup; PPARγ and the global map of adipogenesis and beyond.. *Trends in Endocrinology & Metabolism* **2014**, *25*, 293-302, 10.1016/j.tem.2014.04.001.
53. Takeshi Inagaki; Juro Sakai; Shingo Kajimura; Transcriptional and epigenetic control of brown and beige adipose cell fate and function. *Nature Reviews Molecular Cell Biology* **2016**, *17*, 480-495, 10.1038/nrm.2016.62.
54. J. M. Lehmann; L. B. Moore; T. A. Smith-Oliver; W. O. Wilkison; T. M. Willson; S. A. Kliewer; An Antidiabetic Thiazolidinedione Is a High Affinity Ligand for Peroxisome Proliferator-activated Receptor (PPAR). *Journal of Biological Chemistry* **1995**, *270*, 12953-12956, 10.1074/jbc.270.22.12953.
55. Arya M. Sharma; Bart Staels; Peroxisome Proliferator-Activated Receptor γ and Adipose Tissue—Understanding Obesity-Related Changes in Regulation of Lipid and Glucose Metabolism. *The Journal of Clinical Endocrinology & Metabolism* **2007**, *92*, 386-395, 10.1210/jc.2006-1268.
56. Garry Egger; John Dixon; Obesity and chronic disease: always offender or often just accomplice?. *British Journal of Nutrition* **2009**, *102*, 1238-1242, 10.1017/s0007114509371676.
57. Rachel P. Wildman; Paul Muntner; Kristi Reynolds; Aileen P. McGinn; Swapnil Rajpathak; Judith Wylie-Rosett; MaryFran R. Sowers; The Obese Without Cardiometabolic Risk Factor Clustering and the Normal Weight With Cardiometabolic Risk Factor Clustering. *Archives of Internal Medicine* **2008**, *168*, 1617, 10.1001/archinte.168.15.1617.
58. J. Hoffstedt; E. Arnér; H. Wahrenberg; Daniel Peter Andersson; V. Qvisth; P. Löfgren; M. Rydén; A. Thorne; M. Wirén; M. Palmer; et al.A. ThorellE. ToftP. Arner Regional impact of adipose tissue morphology on the metabolic profile in morbid obesity. *Diabetologia* **2010**, *53*, 2496-2503, 10.1007/s00125-010-1889-3.
59. Birgit Gustafson; Silvia Gogg; Shahram Hedjazifar; Lachmi Jenndahl; Ann Hammarstedt; Ulf Smith; Inflammation and impaired adipogenesis in hypertrophic obesity in man. *American Journal of Physiology-Endocrinology and Metabolism* **2009**, *297*, E999-E1003, 10.1152/ajpendo.00377.2009.

60. Mi-Jeong Lee; Yuanyuan Wu; Susan K. Fried; Adipose tissue remodeling in pathophysiology of obesity.. *Current Opinion in Clinical Nutrition and Metabolic Care* **2010**, *13*, 371-6, 10.1097/MCO.0b013e32833aabef.

61. Kai Sun; Christine M. Kusminski; Philipp E. Scherer; Adipose tissue remodeling and obesity.. *Journal of Clinical Investigation* **2011**, *121*, 2094-101, 10.1172/JCI45887.

62. Birgit Gustafson; Ann Hammarstedt; Shahram Hedjazifar; Ulf Smith; Restricted Adipogenesis in Hypertrophic Obesity. *Diabetes* **2013**, *62*, 2997-3004, 10.2337/db13-0473.

63. Nora Klöting; Matthias Blüher; Adipocyte dysfunction, inflammation and metabolic syndrome. *Reviews in Endocrine and Metabolic Disorders* **2014**, *15*, 277-287, 10.1007/s11154-014-9301-0.

64. Mengle Shao; Lavanya Vishvanath; Napoleon C. Busbuso; Chelsea Hepler; Bo Shan; Ankit X. Sharma; Shiuhwei Chen; Xinxin Yu; Yu A. An; Yi Zhu; et al.William L. HollandRana K. Gupta De novo adipocyte differentiation from Pdgfrβ+ preadipocytes protects against pathologic visceral adipose expansion in obesity.. *Nature Communications* **2018**, *9*, 890, 10.1038/s41467-018-03196-x.

65. Madeliene Stump; Deng-Fu Guo; Ko-Ting Lu; Masashi Mukohda; Xuebo Liu; Kamal Rahmouni; Curt D. Sigmund; Effect of selective expression of dominant-negative PPARγ in pro-opiomelanocortin neurons on the control of energy balance. *Physiological Genomics* **2016**, *48*, 491-501, 10.1152/physiolgenomics.00032.2016.

66. Lihong Long; Chitoku Toda; Jing Kwon Jeong; Tamas L. Horvath; Sabrina Diano; PPARγ ablation sensitizes proopiomelanocortin neurons to leptin during high-fat feeding.. *Journal of Clinical Investigation* **2014**, *124*, 4017-27, 10.1172/JCI76220.

67. Heidi E. Kocalis; Maxine K. Turney; Richard L. Printz; Gloria N. Laryea; Louis J. Muglia; Sean S. Davies; Gregg D. Stanwood; Owen P. McGuinness; Kevin D. Niswender; Neuron-Specific Deletion of Peroxisome Proliferator-Activated Receptor Delta (PPARδ) in Mice Leads to Increased Susceptibility to Diet-Induced Obesity. *PLOS ONE* **2012**, *7*, e42981, 10.1371/journal.pone.0042981.

68. Hong Wang; Honglei Liu; Gender difference in glutathione metabolism during aging in mice. *Experimental Gerontology* **2003**, *38*, 507-517, 10.1016/s0531-5565(03)00036-6.

69. Toshiya Tanaka; Joji Yamamoto; Satoshi Iwasaki; Hiroshi Asaba; Hiroki Hamura; Yukio Ikeda; Mitsuhiro Watanabe; Kenta Magoori; Ryoichi X. Ioka; Keisuke Tachibana; et al.Yuichiro WatanabeYasutoshi UchiyamaKoichi SumiHaruhisa IguchiSadayoshi ItoTakefumi DoiTakao HamakuboMakoto NaitoJohan AuwerxMasashi YanagisawaTatsuhiko KodamaJuro Sakai Activation of peroxisome proliferator-activated receptor δ induces fatty acid β-oxidation in skeletal muscle and attenuates metabolic syndrome. *Proceedings of the National Academy of Sciences* **2003**, *100*, 15924-15929, 10.1073/pnas.0306981100.

70. O Braissant; F Foufelle; C Scotto; M Dauça; W Wahli; Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-alpha, -beta, and -gamma in the adult rat.. *Endocrinology* **1996**, *137*, 354-366, 10.1210/endo.137.1.8536636.

71. Yong-Xu Wang; Chun-Li Zhang; Ruth T Yu; Helen K Cho; Michael C Nelson; Corinne R Bayuga-Ocampo; Jungyeob Ham; Heonjoong Kang; Ronald M Evans; Regulation of muscle fiber type and running endurance by PPARdelta.. *PLOS Biology* **2004**, *2*, e294, 10.1371/journal.pbio.0020294.

72. Weiwei Fan; Wanda Waizenegger; Chun Shi Lin; Vincenzo Sorrentino; Ming-Xiao He; Christopher E. Wall; Hao Li; Christopher Liddle; Ruth T. Yu; Annette R. Atkins; et al.Johan AuwerxMichael DownesRonald M. Evans PPARδ Promotes Running Endurance by Preserving Glucose.. *Cell Metabolism* **2017**, *25*, 1186-1193.e4, 10.1016/j.cmet.2017.04.006.

73. Dorte Holst; Serge Luquet; Veronique Nogueira; Karsten Kristiansen; Xavier Leverve; Paul A. Grimaldi; Nutritional regulation and role of peroxisome proliferator-activated receptor δ in fatty acid catabolism in skeletal muscle. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* **2003**, *1633*, 43-50, 10.1016/s1388-1981(03)00071-4.

74. William R. Oliver; Jennifer L. Shenk; Mike R. Snaith; Caroline S. Russell; Kelli D. Plunket; Noni L. Bodkin; Michael C. Lewis; Deborah A. Winegar; Marcos L. Sznaidman; Millard H. Lambert; et al.H. Eric XuDaniel D. SternbachSteven A. KliewerBarbara C. HansenTimothy M. Willson A selective peroxisome proliferator-activated receptor δ agonist promotes reverse cholesterol transport. *Proceedings of the National Academy of Sciences* **2001**, *98*, 5306-5311, 10.1073/pnas.091021198.

75. S. Luquet; Joaquin Lopez-Soriano; Dorte Holst; Alexandre Fredenrich; Judith Melki; Minoo Rassoulzadegan; Paul A. Grimaldi; Peroxisome proliferator-activated receptor δ controls muscle development and oxidative capability. *The FASEB Journal* **2003**, *17*, 2299-2301, 10.1096/fj.03-0269fje.

76. M J Watt; R J Southgate; A G Holmes; M A Febbraio; Suppression of plasma free fatty acids upregulates peroxisome proliferator-activated receptor (PPAR) α and δ and PPAR coactivator 1α in human skeletal muscle, but not lipid regulatory genes. *Journal of Molecular Endocrinology* **2004**, *33*, 533-544, 10.1677/jme.1.01499.

77. D. J. Mahoney; S. Melov; Adeel Safdar; M. A. Tarnopolsky; G. Parise; Analysis of global mRNA expression in human skeletal muscle during recovery from endurance exercise. *The FASEB Journal* **2005**, *19*, 1498-1500, 10.1096/fj.04-3149fje.

78. Kedryn K. Baskin; Benjamin R. Winders; Eric N. Olson; Muscle as a "mediator" of systemic metabolism. *Cell Metabolism* **2015**, *21*, 237-248, 10.1016/j.cmet.2014.12.021.

79. Dirk Pette; Robert S. Staron; Myosin isoforms, muscle fiber types, and transitions. *Microscopy Research and Technique* **2000**, *50*, 500-509, 10.1002/1097-0029(20000915)50:63.3.co;2-z.

80. Rhonda Bassel-Duby; Eric N. Olson; Signaling Pathways in Skeletal Muscle Remodeling. *Annual Review of Biochemistry* **2006**, *75*, 19-37, 10.1146/annurev.biochem.75.103004.142622.
81. Stefano Schiaffino; Carlo Reggiani; Fiber Types in Mammalian Skeletal Muscles. *Physiological Reviews* **2011**, *91*, 1447-1531, 10.1152/physrev.00031.2010.
82. Vamsi K Mootha; Cecilia M Lindgren; Karl-Fredrik Eriksson; Aravind Subramanian; Smita Sihag; Joseph Lehár; Pere Puigserver; Emma Carlsson; Martin Ridderstråle; Esa Laurila; et al.Nicholas HoustisMark J DalyNick PattersonJill P MesirovTodd R GolubPablo TamayoBruce SpiegelmanEric S LanderJoel N HirschhornDavid AltshulerLeif C Groop PGC-1α-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. *Nature Genetics* **2003**, *34*, 267-273, 10.1038/ng1180.
83. Silvano Zanuso; Alfonso Jimenez; Giuseppe Pugliese; G. Corigliano; S. Balducci; Exercise for the management of type 2 diabetes: a review of the evidence. *Acta Diabetologica* **2009**, *47*, 15-22, 10.1007/s00592-009-0126-3.
84. Leslie H. Willis; Cris A. Slentz; Lori A. Bateman; A. Tamlyn Shields; Lucy W. Piner; Connie W. Bales; Joseph A. Houmard; William E. Kraus; Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults.. *Journal of Applied Physiology* **2012**, *113*, 1831-7, 10.1152/japplphysiol.01370.2011.
85. Bente Klarlund Pedersen; Mark A. Febbraio; Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nature Reviews Endocrinology* **2012**, *8*, 457-465, 10.1038/nrendo.2012.49.
86. Cora Weigert; Rainer Lehmann; Sonja Hartwig; Stefan Lehr; The secretome of the working human skeletal muscle-A promising opportunity to combat the metabolic disaster?. *PROTEOMICS – Clinical Applications* **2014**, *8*, 5-18, 10.1002/prca.201300094.
87. Bente Klarlund Pedersen; A. Steensberg; Christian Fischer; C. Keller; P. Keller; Peter Plomgaard; E. Wolsk-Petersen; M. Febbraio; The metabolic role of IL-6 produced during exercise: is IL-6 an exercise factor?. *Proceedings of the Nutrition Society* **2004**, *63*, 263-267, 10.1079/pns2004338.
88. Muñoz-Cánoves, P.; Scheele, C.; Pedersen, B.K.; Serrano, A.L.; Interleukin-6 myokine signaling in skeletal muscle: A double-edged sword?. *FEBS J.* **2013**, *280*, 4131–4148, http://public-files.prbb.org/publicacions/efbd19c0-9f72-0130-2772-263316c03650.pdf.
89. Zhiqing Huang; Xiaoling Chen; Daiwen Chen; Myostatin: A novel insight into its role in metabolism, signal pathways, and expression regulation. *Cellular Signalling* **2011**, *23*, 1441-1446, 10.1016/j.cellsig.2011.05.003.
90. Frits Mattijssen; Sander Kersten; Regulation of triglyceride metabolism by Angiopoietin-like proteins. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* **2012**, *1821*, 782-789, 10.1016/j.bbalip.2011.10.010.

91. Rajesh R. Rao; Jonathan Z. Long; James P. White; Katrin J. Svensson; Jesse Lou; Isha Lokurkar; Mark P. Jedrychowski; Jorge L. Ruas; Christiane D. Wrann; James C. Lo; et al.Donny M. CameraJenn LacheySteven GygiJasbir SeehraJohn A. HawleyBruce M. Spiegelman Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis.. *Cell* **2014**, *157*, 1279-91, 10.1016/j.cell.2014.03.065.
92. Manisha Sinha; Young C. Jang; Juhyun Oh; Danika Khong; Elizabeth Y. Wu; Rohan Manohar; Christine Miller; Samuel G. Regalado; Francesco S. Loffredo; James R. Pancoast; et al.Michael F. HirshmanJessica LebowitzJennifer L. ShadrachMassimiliano CerlettiMi-Jeong KimThomas SerwoldLaurie J. GoodyearBernard RosnerRichard T. LeeAmy J. Wagers Restoring systemic GDF11 levels reverses age-related dysfunction in mouse skeletal muscle.. *Science* **2014**, *344*, 649-52, 10.1126/science.1251152.
93. Lee D. Roberts; Pontus Boström; John F. O'Sullivan; Robert T. Schinzel; Gregory D. Lewis; Andre Dejam; Youn-Kyoung Lee; Melinda J. Palma; Sondra Calhoun; Anastasia Georgiadi; et al.Ming-Huei ChenVasan S. RamachandranMartin G. LarsonClaude BouchardTuomo RankinenAmanda L. SouzaClary B. ClishThomas J. WangJennifer L. EstallAlexander A. SoukasChad A. CowanBruce M. SpiegelmanRobert E. Gerszten β-Aminoisobutyric acid induces browning of white fat and hepatic β-oxidation and is inversely correlated with cardiometabolic risk factors.. *Cell Metabolism* **2014**, *19*, 96-108, 10.1016/j.cmet.2013.12.003.
94. Begoña Ruiz-Núñez; Leo Pruimboom; D.A. Janneke Dijck-Brouwer; Frits A.J. Muskiet; Lifestyle and nutritional imbalances associated with Western diseases: causes and consequences of chronic systemic low-grade inflammation in an evolutionary context. *The Journal of Nutritional Biochemistry* **2013**, *24*, 1183-1201, 10.1016/j.jnutbio.2013.02.009.
95. Letizia Giampietro; Antonio Laghezza; Carmen Cerchia; Rosalba Florio; Lucia Recinella; Fabio Capone; Alessandra Ammazzalorso; Isabella Bruno; Barbara De Filippis; Marialuigia Fantacuzzi; et al.Claudio FerranteCristina MaccalliniPaolo TortorellaFabio VerginelliLuigi BrunettiAlessandro CamaRosa AmorosoFulvio LoiodiceAntonio Lavecchia Novel Phenyldiazenyl Fibrate Analogues as PPAR α/γ/δ Pan-Agonists for the Amelioration of Metabolic Syndrome. *ACS Medicinal Chemistry Letters* **2019**, *10*, 545-551, 10.1021/acsmedchemlett.8b00574.

Retrieved from https://encyclopedia.pub/entry/history/show/459