**PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPARS)**

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**Abstract**

Peroxisome proliferator-activated receptors are a group (PPARs) of transcription factors whose differential distribution in different tissues, including adipocytes, hepatocytes, muscles and endothelial cells lead to different clinical outcomes. They are called lipid and insulin sensors due to the important role in lipid and glucose homeostasis. They are mainly of three types; 1) PPARα which influences fatty acid metabolism and its activation lowers lipid levels, 2) PPARβ causes fatty acid oxidation in skeletal and cardiac muscles, as well as regulates blood glucose and cholesterol levels and 3) PPARγ which is mostly involved in the regulation of the adipogenesis, energy balance, and lipid biosynthesis. The expression of these receptors is influenced by many natural and synthetic ligands. Realistic data on the expression and function of natural PPAR agonists on glucose and lipid metabolism are still missing, mostly because the same ligand influences several receptors and a number of reports have provided conflicting results. The current minireview focuses on the structure, functions, types and ligands of the PPAR.

**Key words:** peroxisome proliferator-activated receptors, adipocytes, ligand, glucose homeostasis

**I. Introduction**

**PPARs**

Peroxisomes are the cellular organelles present in all eukaryotic cell (Neels and Grimaldi 2014). These are involved in several cellular functions including the beta oxidation of fatty acids (Baker et al., 2015). Lack of peroxisomes in cell causes many human disorders and this is proved by many scientific discoveries (Shiomi et al., 2015). Peroxisomes have ability to proliferate in response to the certain cellular as well as synthetic chemicals (Neels and Grimaldi 2014). Cellular disparate chemicals are designated as the Peroxisomes proliferators (Keller and Wahl 1995; Berg et al., 2015). There is structural diversity in peroxisomes proliferators but they induce peroxisomal gene transcription through same mechanism (Mast et al., 2015). The isolation and characterization of one of the peroxisomes proliferators was the breakthrough in scientific knowledge and that was the Peroxisomes proliferators activated receptors (PPAR) (Lalwani et al., 1987).
PPARs actually belong to the super-family of transcriptional regulators (Murthi et al., 2013). In 1990, Isseman and Green reported the new member of super-family of nuclear receptors (also regulators) and these were the followings:

- Peroxisomes proliferator activated receptors
- Receptors for Steroid
- Receptors for Thyroid hormone
- Receptors for Retinoic acid (Issemann and Green 1990)

**Evolution of the gene**

Pioneering work on the cloning of PPARs was start with the PPARs of mouse. At the same time independent cloning of three different PPARs also started including PPARs of *xenopus*, rat and of human (Dreyer et al., 1993). Dreyer et al. 1993 did the evolutionary analysis by comparison of the conserved portion of gene encoded for PPARs. They formed the phylogenetic tree of PPARs to observe its evolution throughout the past. According to the analysis there was correspondence of appearance of PPARs in early vertebrates. Moreover phylogenetic analysis strongly suggested the iso-forms of PPAR in mammalian species (Keller et al., 1993; Keshamouni et al., 2007).

**Modular structure of PPARs**

All the isoform of PPARs have same structural and functional features (Monsalve et al., 2013). There is contradiction between scientists regarding the domains of PPAR (Wurtz et al., 1996; Zhou et al., 2015; Diezko and Suske 2013). Some scientists agree on 4 domains while others believe on 6 domains. If we go with the four functional domains then these are:

- Domain A/B
- Domain C
- Domain D
- Domain E/F

The N-terminal A/B domain contains the ligand independent activation function and the domain plays very crucial role for functioning of PPAR and that is phosphorylation of PPAR (La Cour Poulsen et al., 2012). Domain C also known as DNA binding domain (DBD) and its function is to promote the attachment of PPAR at peroxisomes proliferator response element PPREs and this is present under the prompter region of target gene. Region C contains 66 amino acid that forms two zing fingers (Berger & Moller 2002).

These zing fingers functions as the core of this domain. These fingers have conserved amino acid sequences. The docking domain that is D domain is for the attachment of co-factor (La Cour Poulsen et al., 2012). Other name of Ligand binding domain is E domain that plays a very important role as it’s responsible for activation and specification of PPARs binding to the PPREs (Buzón et al., 2012). The attachment of co-factor on E domain increases the expression of target gene (Gearing et al., 1993). The other modular structure of PPARs contains the six functional domains; (Helsen et al., 2012).
• Domain A
• Domain B
• Domain C
• Domain D
• Domain E
• Domain F

Difference between these two modular structures is just of domains A, B, E and F (Lee et al., 1995). In first model domain A and B are the same while this is not case of second model, same is with the domains E and F (Fig 1) (Motojima 1993; Attianese and Desvergne 2015).

![Diagram](image.png)

Figure 1: Isoform of PPAR gene (PPARα, PPARβ and PPARγ) and basic overview of PPAR structure (Daynes and Jones 2002).

**Transcriptional machinery of PPARs**

PPARs can be activated by natural as well as synthetic ligands (Sakharkar et al., 2015). Natural ligand includes the retinoid X receptor (RXR), PPREs and certain co-factors that plays crucial role in achieving the desired transcriptional activity (Berger & Moller 2002). Transcriptional machinery of PPARs having;

• RXR and hetero-dimerization
• Peroxisomes proliferator response elements (PPREs)
• Cofactors (co-activator/ co-repressors) (Sauer 2015).

**RXR and heterodimerisation**

For the binding on PPREs, ligand binding domain (LBD) has to make dimer with the (RXR) retinoid X receptor (Osz et al., 2015). With the recruitment of co-factors on domain E, heterodimer of Ligand binding domain and retinoid X receptor (LBD and RXR) binds to the PPREs (Gearing et al., 1993; Osz et al., 2015).

**Peroxisomes proliferator response elements (PPREs)**

Structure of PPREs consist direct repeats (DR-1) elements and these contain two hexanucleotides sequences (AGGTCA) (Juge-Aubry et al., 1997). Spacer of Single nucleotide can separated both hexanucleotide. The direct
repeats pattern of DR-1 is specific for the homodimer of RXR and PPAR which makes it different from the other Directs repeats (DR3 and DR4) (Piskunov 2012).

**Co-factor (co-activator and co-repressor)**

To initiate or suppress the transcriptional process there are several proteins act as co-repressor or co-activator. These co-factors mediate the transcriptional process by the attachment on domain E of PPAR (Varga et al., 2011). They recruit on domain and interact in ligand dependent manner. The process of transcription basically controls by the ligand bound and unbound state of the PPAR (Chen and Evans 1995, Dharap et al., 2015).

In ligand unbound state heterodimer associates with the co-repressor, that contains the histone deacetylase activity such as thyroid hormone receptor and nuclear receptor co-repressor (Dharap et al., 2015). Transcription inhibited by the state of histone which is deacetylation (Murata et al., 2001). In alternative manner co-activator such as PPAR binding protein and steroid receptor co-activator contain histone acetylase activity that can initiate the series of events which induces the transcriptional process upon binding of ligand. So this is liganded state of PPAR (Qi et al., 2000; Tzeng et al., 2015).

**Isoforms of PPAR**

To date there are 3 different isoforms of PPARs, encoded by the separate gene.

- **PPARα**
- **PPARβ**
- **PPARY (Harris & Phipps 2012).**

**a). PPARY**

As described earlier PPAR has three iso-forms, the first one is PPARY (Schild et al., 2002). On the short arm of chromosome 3 (3p25) the gene which is encoding for PPARY (PPARG) is located. The entire gene is of 100 kilo bases approximately and nine exons encoded this specific gene (Ikezoe et al., 2001).

The PPARY contains three different promoters that on transcription yields further three iso-forms of PPARY, namely PPARY1, PPARY2 and PPARY3 (Fajas et al., 1999; Kalonia et al., 2010). Transcript of PPARY1 and PPARY3 translate into identical protein. Expression of PPAR is basically tissue dependent. PPARY1 is the iso-form (Banks et al., 2015). PPARY3 express abundantly in white adipose tissue, in macrophages, and in large intestine (Singh et al., 2013; Mair and McGarvey 2008).

**PPARYgene mediated transcription**

The transcription mechanism of all iso-forms of PPAR is identical (Banks et al., 2015). Transcriptional process begins when ligand bind to the PPARY receptor, ligand can be exogenous or endogenous (Penumetcha and Santanam 2012). Ligand bound the heterodimer of PPAR and RXR, this heterodimer binds to the promoter region which is PPREs after the recruitment of co-activators (Penumetcha and Santanam 2012; 46 Hörlein, et al., 1995). These all events lead to enhance the transcription of number of genes that are involved in the biological process of body. The biological process
includes adipogenesis, lipid metabolism, and homeostasis of glucose. The major mechanism in which PPARγ is involved is the improvement of insulin resistance (Fig 2) (Shi et al., 2006).

**Biological mechanism of PPARγ**

Biological mechanism of PPARγ includes;

- Insulin sensitization
- Adipocyte differentiation
- Cancer
- Inflammation and atherosclerosis
- Retinal disorders

**Insulin sensitization**

PPARγ is associated with a number of genes that are directly and indirectly effect insulin action (Banks et al., 2015). Tissue necrosis factor alpha which is cytokine in nature, has been linked to the resistance of insulin (Ferrante 2007). In-vivo experimentation proved that PPARγ agonists improve insulin resistance by inhibiting the TNF-α effect on adipocytes (Jin et al., 2014). For glucose transport there is a gene GLUT4 (Kitagawa et al., 2004). Expression of this gene by PPARγ agonists’ adipocytes is playing crucial role in the process of glucose uptake (Cohen et al., 2003).

Resistin is a hormone that is secreted by the adipocytes and its function is to elevate the glucose level in blood. Resistin can be inhibited by thiazolidinediones TZDs (Lee et al., 2003). TZDs are the exogenous ligands for PPARs. There are many studies depicts that TZDs also increases glucose disposal in skeletal muscles by the mechanism of increasing
membranous protein kinase activity and phosphatidylinositol 3-kinase activity (Savage et al., 2003; Cock et al., 2004). PPARγ expression is lesser in skeletal muscles as compare to adipocytes. There are certain adipocytes-derived factors such as adipocytes related complement protein and 11β-hydroxysteroid dehydrogenase 1, are influenced by the PPARγ activation in glucose homeostasis and in improving insulin resistance (Cock et al., 2004).

Adipocyte differentiation

Adipogenesis is the process refers to the differentiation of pre-adipocyte precursor’s cell into mature adipocyte that can perform various functions such as capable of lipid filling, expression of cytokines and hormones (Cipolletta et al., 2012). PPARγ is the important transcription factor that is involve in the adipocyte cell growth and stop of cell growth, followed by the progress of cells into phenotype which is fully differentiated (Wang et al., 2007). PPARγ activation also promotes the process of apoptosis in mature adipocytes which are lipid filled (Moerman et al., 2004).

In addition to that process ligand induced apoptosis of mature cells stimulate the adipogenesis of others pre adipocyte precursors, leads in the increase of small number of adipocytes which are insulin sensitive (Morrison & Farmer 2000).

Cancer

Cell differentiation and apoptosis are the properties of PPARγ. It is found that these properties of PPARγ make it very important in treatment of different types of human cancer that includes pancreatic, breast, prostate, Colon, gastric and pituitary (Giovannucci et al., 2007; Heaney et al., 2003; Sarraf et al., 1999; Rovito et al., 2013).

Inflammation and atherosclerosis

Macrophages and Smooth muscle cells (VSMCs), have relation with PPARγ for its functions with metabolism of lipid (Handschin and Spiegelman 2013). This fact prompt research on PPARγ properties which are anti-inflammatory. Similarly, role of PPARγ in arthritis and inflammatory bowel syndrome are also under study (Schmuth et al., 2014). Different animal studies were shown that PPARγ agonists have anti-atherosclerotic effects (Chawla et al., 2001). However, these all agonists were also showed many deleterious effects by the over expressing the oxidized LDL scavenger and by induction in foam cell (Pasceri et al., 2000).

There are many mechanisms reported in which counteracted the PPARγ pro-atherogenic activity. In endothelial cells, TZDs inhibited the site of the intercellular adhesion molecule (ICAM-1) and cell adhesion molecule (VCAM-1) expression, which results in reduction of arterial accumulation of monocyte (Marx et al., 1998).

Retinal disorders

In retinal pigment epithelial (RPE) cells and vascular endothelial growth factor (VEGF)-induced choroidal angiogenesis can be inhibited by Troglitazone (Marx et al., 1998). In monkey and rats progression of choroidal neovascularization can also repressed by Troglitazone. These all effects suggested the application of PPARγ ligands in retinal disorders which are induced by diabetes and age-related retinal disorders (Aoun et al., 2003).
a). PPARα

PPARα is also a receptor like the PPARY for structurally different class of compounds that includes the hypolipidemic fibrates. In human and rodents, PPARα is expressed in many tissues including heart, liver, skeletal muscle, kidney and brown fat (Schmuth et al., 2014, Auboeuf et al., 1997). There is also expression of PPARα in a numerous vascular cells such as monocytes/macrophages and endothelial cells VSMCs (Fig 3) (Diep et al., 2000).

b). PPARβ

Despite extensive research on PPARα and PPARY, the functional characterization of PPARβ still unclear (Yao et al., 2013). Like other PPARS PPARβ is also expressed into variety of tissues and cells, but the expression level in the brain is high comparatively. Expression is also there in skin and adipose tissue (Fig 3) (Berger & Moller 2002).

Figure 3: PPARs gene transcription mechanisms and their biologic effects in different organs (Kota et al., 2005).
c). Role of PPARγ in diabetes

Obesity and dyslipidemias have strong correlation with diabetes (Bray and Popkin 2014). Elevated level of triglycerides and free fatty acids has been linked with the development of insulin resistant in muscle (Steneberg et al., 2015). Normalization of lipid storage by correcting the adipocyte function might be the cause to improve insulin sensitivity. A study on rats supported this hypothesis (Lefebvre et al., 1997). The inhibitory effect of TNF-α on insulin signaling was overcome by treated with TZD and other PPAR-RXR agonists, in 3T3-L1 adipocyte cell line. The effect of PPARγ stimulation is specific to the action of TNF-α on signaling (Murphy & Holder 2000). Another mechanism that could result to enhance insulin sensitivity is suggested by the study that showing the treatment to induce adipogenesis with PPARγ in rat model (Fasshauer & Paschke 2003). Insulin resistance in humans is also correlated with the abdominal obesity (Fig 3) (Ruderman et al., 2013).

Mutation resulting in loss of function of PPARγ caused the development of severe insulin resistance that leads to diabetes in two patients (Ruderman et al., 2013; Barroso et al., 1999; Purdel et al., 2014). Mis-sense mutation Pro115Gln and Ser114 constitute the negative effects on activity of protein and cause insulin resistance. This observation was supported by the experiment on transgenic mice (Kubota et al., 1999). Higher expression of PPARγ observed in the muscle derived from obese and diabetic patients (Mayoral et al., 2015). In this view up-regulation PPARγ mRNA and protein expression following treatment with the insulin sensitizers in in-vitro study (Fig 4) (Murphy & Holder 2000).

![Figure 4: Role of Peroxisome-Proliferator–Activated Receptor (Ristow et al., 1998).](image)

PPARγ and its mutations

Up to date, there are 1 non coding sequence mutation and 17 coding sequences mutation of PPARγ gene have been reported (Agostini et al., 2006). Majority of these mutations are associated with FPLD3 (Monajemi et al., 2007;
Lüdtke et al., 2007). Out of these ten are mis-sense mutation, which is either located on LBD or DBD (Savage et al., 2003; Lüdtke et al., 2007; van Beekum et al., 2008). In addition two non-sense mutations (Monajemi et al., 2007), two frame-shift mutations and one mutation of promoter are also reported (Savage et al., 2002). Except for the mutation of promoter all other mutations can affect the protein function and cause the reduction of transcriptional activity of protein (Fig 5) (Francis et al., 2006).

**Figure 5:** Overview of PPARγ mutations. Distinct domains of the PPARγ2 protein (with PPARγ1 missing the first 30 amino acids) and the location of the different mutations. In addition, 1 non-coding sequence mutation in the PPARγ4 promoter has been reported and is depicted separately (Jeninga et al., 2009)

II. Conclusion

Peroxisome proliferator-activated receptors are a group (PPARs) of transcription factors also known as lipid and insulin sensors. PPARs actually belong to the super-family of transcriptional regulators. They are mainly of three types; PPARα, PPARβ and PPARγ. All the isoform of PPARs have same structural and functional features. PPARγ has more importance due to its important functions. Up to date there are 1 non-coding sequence mutation and 17 coding sequences mutation of PPARγ gene have been reported. Mutation of gene all can affect the protein function and cause the reduction of transcriptional activity of protein.

References

Neels, J. G. & Grimaldi, P. A. 2014. Physiological functions of peroxisome proliferator-activated receptor β. *Physiological Reviews, 94*(3): 795-858.

Baker, A.; Carrier, D. J.; Schaedler, T.; Waterham, H. R.; van Roermund, C. W. & Theodoulou, F. L. 2015. Peroxisomal ABC transporters: functions and mechanism. *Biochemical Society Transactions, 43*(5): 959-965.

Shiomi, Y.; Yamauchi, T.; Iwabu, M.; Okada-Iwabu, M.; Nakayama, R. & Orikawa, Y. 2015. A novel peroxisome proliferator-activated receptor (ppar) α agonist and pparγ antagonist, z-551, ameliorates high-fat diet-induced obesity and metabolic disorders in mice. *Journal of Biological Chemistry, M114. 622191.*

Keller, H. & Wahli, W. 1993. Peroxisome proliferator-activated receptors A link between endocrinology and nutrition? *Trends in Endocrinology and Metabolism, 4*(9): 291-296.
Berg, E. L.; Polokoff, M. A.; O'Mahony, A.; Nguyen, D. & Li, X. 2015. Elucidating mechanisms of toxicity using phenotypic data from primary human cell systems - A chemical biology approach for thrombosis-related side effects. *International Journal of Molecular Sciences*, **16**(1): 1008-1029.

Mast, F. D.; Rachubinski, R. A. & Aitchison, J. D. 2015. Signaling dynamics and peroxisomes. *Current Opinions in Cell Biology*, **35**: 131-136.

Lalwani, N. D.; Alvares, K.; Reddy, M. K.; Reddy, M. N.; Parikh, I. & Reddy, J. K. 1987. Peroxisome proliferator-binding protein: identification and partial characterization of nafenopin-, clofibric acid-, and ciprofibrate-binding proteins from rat liver. *Proceedings of the National Academy of Sciences*, **84**(15): 5242-5246.

Murthi, P.; Kalionis, B.; Cocquebert, M.; Rajaraman, G.; Chui, A. & Keogh, R. 2013. Homeobox genes and downstream transcription factor PPARγ in normal and pathological human placental development. *Placenta*, **34**(4): 299-309.

Issemann, I. & Green, S. 1990. Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature*, **347**(6294): 645-650.

Dreyer, C.; Keller, H.; Mahfoudi, A.; Laudet, V.; Krey, G. & Wahli, W. 1993. Positive regulation of the peroxisomal β-oxidation pathway by fatty acids through activation of peroxisome proliferator-activated receptors (PPAR). *Biology of the Cell*, **77**(1): 67-74.

Keller, H. R.; Dreyer, C.; Medin, J.; Mahfoudi, A.; Ozato, K. & Wahli, W. 1993. Fatty acids and retinoids control lipid metabolism through activation of peroxisome proliferator-activated receptor-retinoid X receptor heterodimers. *Proceedings of the National Academy of Sciences*, **90**(6): 2160-2164.

Keshamouni, V. G.; Han, S. & Roman J. 2007. Peroxisome proliferator-activated receptors in lung cancer. *PPAR Research*, 2007.

Monsalve, F. A.; Pyarasani, R. D.; Delgado-Lopez, F. & Moore-Carrasco, R. 2013. Peroxisome proliferator-activated receptor targets for the treatment of metabolic diseases. *Mediators of Inflammation*, 2013.

Wurtz, J-M.; Bourguet, W.; Renaud, J-P.; Vivat, V.; Chambon, P. & Moras, D., 1996. A canonical structure for the ligand-binding domain of nuclear receptors. *Nature Structural and Molecular Biology*, **3**(1): 87-94.

Zhou, T.; Yan, X.; Wang, G.; Liu, H.; Gan, X. & Zhang, T. 2015. Evolutionary pattern and regulation analysis to support why diversity functions existed within ppar gene family members. *BioMed Research International*, 2015.

Diezko, R. & Suske, G. 2013. Ligand binding reduces SUMOylation of the peroxisome proliferator-activated receptor γ (PPARγ) activation function 1 (AF1) domain. *PloS One*, **8**(6): e66947.

La Cour Poulsen, L.; Siersbæk, M.; Mandrup, S. 2012. editors. PPARs: fatty acid sensors controlling metabolism. Seminars in Cell and Development Biology, Elsevier.

Berger, J. & Moller, D. E. 2002. The mechanisms of action of PPARs. *Annual Review of Medicine*, **53**(1): 409-435.

Buzón, V.; Carbó, L. R.; Estruch, S. B.; Fletterick, R. J. & Estébanez-Perpiñá, E. 2012. A conserved surface on the ligand binding domain of nuclear receptors for allosteric control. *Molecular and Cellular Endocrinology*, **348**(2): 394-402.
Gearing, K.; Göttlicher, M.; Teboul, M.; Widmark, E. & Gustafsson, J-Å. 1993. Interaction of the peroxisome-proliferator-activated receptor and retinoid X receptor. Proceedings of the National Academy of Sciences, 90(4): 1440-1444.

Helsen, C.; Kerkhofs, S.; Clinckemalie, L.; Sparks, L.; Laurent, M. & Boonen, S. 2012. Structural basis for nuclear hormone receptor DNA binding. Molecular and Cellular Endocrinology, 348(2): 411-417.

Lee, S.; Pineau, T.; Drago, J.; Lee, E. J.; Owens, J. W. & Kroetz, D. L. 1995. Targeted disruption of the alpha isoform of the peroxisome proliferator-activated receptor gene in mice results in abolishment of the pleiotropic effects of peroxisome proliferators. Molecular and Cellular Biology, 15(6): 3012-3022.

Motojima, K. 1993. Peroxisome proliferator-activated receptor (PPAR): structure, mechanisms of activation and diverse functions. Cell Structure and Function, 18(5): 267-277.

Attianese, G. M. G. & Desvergne, B. 2015. Integrative and systemic approaches for evaluating PPARβ/δ (PPARD) function. Nuclear Receptor Signaling, nrs-13001.

Daynes, R. A. & Jones, D. C. 2002. Emerging roles of PPARs in inflammation and immunity. Nature Reviews Immunology, 2(10): 748-759.

Sakharkar, M. K.; Shashni, B.; Sharma, K.; Chandra, R. & Sakharkar, K. R. 2015. PPAR responsive regulatory modules in breast cancer. Post-genomic Approaches in Cancer and Nano Medicine, 4:61.

Sauer, S. 2015. Ligands for the nuclear peroxisome proliferator-activated receptor gamma. Trends in Pharmacological Sciences, 36(10): 688-704.

Osz, J.; McEwen, A. G.; Poussin-Courmontagne, P.; Moutier, E.; Birck, C. & Davidson, I. 2015. Structural Basis of Natural Promoter Recognition by the Retinoid X Nuclear Receptor. Scientific reports. 5.

Juge-Aubry, C.; Pernin, A.; Favez, T.; Burger, A. G.; Wahli, W. & Meier, C. A. 1997. DNA binding properties of peroxisome proliferator-activated receptor subtypes on various natural peroxisome proliferator response elements importance of the 5'-flanking region. Journal of Biological Chemistry, 272(40): 25252-25259.

Piskunov, A. 2012. Nuclear retinoic acid receptor alpha (RARα): Novel unconventional non-genomic effects and novel partners: Université de Strasbourg; 2012.

Varga, T.; Czimmerer, Z. & Nagy, L. 2011. PPARs are a unique set of fatty acid regulated transcription factors controlling both lipid metabolism and inflammation. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1812(8): 1007-1022.

Chen, J. D. & Evans, R. M. 1995. A transcriptional co-repressor that interacts with nuclear hormone receptors. Nature, 454-457.

Dharap, A.; Pokrzywa, C.; Murali, S.; Kaimal, B. & Vemuganti, R. 2015. Mutual induction of transcription factor PPARγ and microRNAs miR-145 and miR-329. Journal of Neurochemistry, 135(1): 139-146.

Murata, T.; Kurokawa, R.; Krones, A.; Tatsumi, K.; Ishii, M. & Taki, T. 2001. Defect of histone acetyltransferase activity of the nuclear transcriptional coactivator CBP in Rubinstein–Taybi syndrome. Human Molecular Genetics, 10(10): 1071-1076.

Qi, C.; Zhu, Y. & Reddy, J. K. 2000. Peroxisome proliferator-activated receptors, coactivators, and downstream targets. Cell Biochemistry and Biophysics, 32(1-3): 187-204.
Tzeng, J.; Byun, J.; Park, J. Y.; Yamamoto, T.; Schesing, K. & Tian, B. 2015. An ideal PPAR response element bound to and activated by PPARα. PloS One, 10(8): e0134996.

Harris, S. G. & Phipps, R. P. 2012. Receptor gamma (ppar-γ) binding. Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation, and Radiation Injury, 5: 507:421.

Schild, R. L.; Schaiff, W. T.; Carlson, M. G.; Cronbach, E. J.; Nelson, D. M. & Sadovsky, Y. 2002. The activity of PPARγ in primary human trophoblasts is enhanced by oxidized lipids. The Journal of Clinical Endocrinology and Metabolism, 87(3): 1105-1110.

Ikezoe, T.; Miller, C. W.; Kawano, S.; Heaney, A.; Williamson, E. A. & Hisatake, J. 2001. Mutational analysis of the peroxisome proliferator-activated receptor γ gene in human malignancies. Cancer Research, 61(13): 5307-5310.

Fajas, L.; Schoonjans, K.; Gelman, L.; Kim, J. B.; Najib, J. & Martin, G. 1999. Regulation of peroxisome proliferator-activated receptor γ expression by adipocyte differentiation and determination factor 1/sterol regulatory element binding protein 1: implications for adipocyte differentiation and metabolism. Molecular and Cell Biology, 19(8): 5495-5503.

Kalonia, H.; Kumar, P. & Kumar, A. 2010. Pioglitazone ameliorates behavioral, biochemical and cellular alterations in quinolinic acid induced neurotoxicity: Possible role of peroxisome proliferator activated receptor-γ (PPARY) in Huntington's disease. Pharmacology Biochemistry and Behavior, 96(2): 115-124.

Banks, A. S.; McAllister, F. E.; Camporez, J. P. G.; Zushin, P-JH.; Jürczak, M. J. & Laznik-Bogoslavski, D. 2015. An ERK/Cdk5 axis controls the diabetogenic actions of PPAR [ggr]. Nature, 517(7534): 391-395.

Singh, J.; Mansoori, A.; Yadav, S.; Verma, S.; Sitapura, J. S. & Naramau, K. N. 2013. A review on 2, 4-thiazolidinedione in type-2 diabetes. International Journal of Advance Pharmacetical and Biological Sciences, 3: 395-399.

Mair, R. & McGarvey, S. T. 2008. Application of genetic epidemiology to understanding pediatric obesity. Handbook of Childhood and Adolescent Obesity: Springer, pp. 163-179.

Penumetcha, M. & Santanam, N. 2012. Nutraceuticals as Ligands of PPAR. PPAR Research, 2012.

Hörlein, A. J.; Niiär, A. M.; Heinzel, T.; Torchia, J.; Gloss, B. & Kurokawa, R. 1995. Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor.

Shi, H.; Kokoeva, M. V.; Inouye, K.; Tzameli, I.; Yin, H. & Flier, J. S. 2006. TLR4 links innate immunity and fatty acid–induced insulin resistance. Journal of Clinical Investigation, 116(11): 3015.

Kota, B. P.; Huang, TH-W. & Roufogalis, B. D. 2005. An overview on biological mechanisms of PPARs. Pharmacological Research, 51(2): 85-94.

Ferrante, A. 2007. Obesity-induced inflammation: a metabolic dialogue in the language of inflammation. Journal of Internal Medicine, 262(4): 408-414.

Jin, D.; Sun, J.; Huang, J.; He, Y.; Yu, A. & Yu, X. 2014. TNF-α reduces g0s2 expression and stimulates lipolysis through PPAR-γ inhibition in 3T3-L1 adipocytes. Cytokine, 69(2): 196-205.
Kitagawa, Y.; Bujo, H.; Takahashi, K.; Shibasaki, M.; Ishikawa, K. & Yagui, K. 2004. Impaired glucose tolerance is accompanied by decreased insulin sensitivity in tissues of mice implanted with cells that overexpress resistin. *Diabetologia, 47*(10): 1847-1853.

Cohen, A. W.; Razani, B.; Wang, X. B.; Combs, T. P.; Williams, T. M. & Scherer, P. E. 2003. Caveolin-1-deficient mice show insulin resistance and defective insulin receptor protein expression in adipose tissue. *American Journal of Physiology-Cell Physiology, 285*(1): C222-C235.

Lee, J. H.; Chan, J. L.; Yiannakouris, N.; Kontogianni, M.; Estrada, E. & Seip, R. 2003. Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. *The Journal of Clinical Endocrinology and Metabolism, 88*(10): 4848-4856.

Savage, D. B.; Tan, G. D.; Acerini, C. L.; Jebb, S. A.; Agostini, M. & Gurnell, M. 2003. Human metabolic syndrome resulting from dominant-negative mutations in the nuclear receptor peroxisome proliferator-activated receptor-γ. *Diabetes, 52*(4): 910-917.

Cock TA, Houten SM, Auwerx J. Peroxisome proliferator-activated receptor-γ: too much of a good thing causes harm. *EMBO reports* reports. 2004;5(2):142-7.

Cipolletta, D.; Feurer, M.; Li, A.; Kamei, N.; Lee, J. & Shoelson, S. E. 2012. PPAR-[ggr] is a major driver of the accumulation and phenotype of adipose tissue Treg cells. *Nature, 486*(7404): 549-53.

Wang, P.; Renes, J.; Bouwman, F.; Bunschoten, A.; Mariman, E. & Keijer, J. 2007. Absence of an adipogenic effect of rosiglitazone on mature 3T3-L1 adipocytes: increase of lipid catabolism and reduction of adipokine expression. *Diabetologia, 50*(3): 654-665.

Moerman, E. J.; Teng, K.; Lipschitz, D. A. & Lecka-Czernik, B. 2004. Aging activates adipogenic and suppresses osteogenic programs in mesenchymal marrow stroma/stem cells: the role of PPAR-γ2 transcription factor and TGF-β/BMP signaling pathways. *Aging Cell, 3*(6): 379-389.

Morrison, R. F. & Farmer, S. R. 2000. Hormonal signaling and transcriptional control of adipocyte differentiation. *The Journal of Nutrition, 130*(12): 3116S-3121S.

Giovannucci, E.; Liu, Y; Platz EA; Stampfer MJ; Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. *International Journal of Cancer*. 2007;121(7):1571-8.

Heaney, A. P.; Fernando, M. & Melmed, S. 2003. PPAR-γ receptor ligands: novel therapy for pituitary adenomas. *Journal of Clinical Investigation*. 2003;111(9):1381.

Sarraf, P.; Mueller, E.; Smith, W. M.; Wright, H. M.; Kum, J. B. & Aaltoinen, L. A. 1999. Loss-of-function mutations in PPARγ associated with human colon cancer. *Molecular Cell, 3*(6): 799-804.

Rovito, D.; Giordano, C.; Vizza, D.; Plastina, P.; Barone, I. & Casaburi, I. 2013. Omega-3 PUFA ethanolamides DHEA and EPEA induce autophagy through PPARγ activation in MCF-7 breast cancer cells. *Journal of Cellular Physiology, 228*(6): 1314-1322.

Handschin, C. & Spiegelman, B. M. 2013. Editors. Peroxisome proliferator-activated receptor γ coactivator 1 coactivators, energy homeostasis, and metabolism, *Endocrine Society*. 52
Schmutz, M.; Moosbrugger-Martinz, V.; Blunder, S.; Dubrac, S. 2014. Role of PPAR, LXR, and PXR in epidermal homeostasis and inflammation. *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids*, **1841**(3): 463-473.

Chawla, A.; Barak, Y.; Nagy, L.; Liao, D.; Tontonoz, P. & Evans, R. M. 2001. PPAR-γ dependent and independent effects on macrophage-gene expression in lipid metabolism and inflammation. *Nature Medicine*, **7**(1): 48-52.

Pasceri, V.; Wu, H. D.; Willerson, J. T. & Yeh, E. T. 2000. Modulation of vascular inflammation in vitro and in vivo by peroxisome proliferator–activated receptor-γ activators. *Circulation*, **101**(3): 235-238.

Marx, N.; Schönbeck, U.; Lazar, M. A.; Libby, P. & Plutzky, J. 1998. Peroxisome proliferator-activated receptor gamma activators inhibit gene expression and migration in human vascular smooth muscle cells. *Circulation Research*, **83**(11): 1097-1103.

Aoun, P.; Simpkins, J. W. & Agarwal, N. 2003. Role of PPAR- ligands in neuroprotection against glutamate-induced cytotoxicity in retinal ganglion cells. *Investigative Ophthalmology & Visual Science*, **44**(7): 2999-3004.

Auboeuf, D.; Rieusset, J.; Fajas, L.; Vallier, P.; Frering, V. & Riou, J. P. 1997. Tissue distribution and quantification of the expression of mRNAs of peroxisome proliferator-activated receptors and liver X receptor-α in humans: no alteration in adipose tissue of obese and NIDDM patients. *Diabetes*, **46**(8): 1319-1327.

Diep, Q. N.; Touyz, R. M. & Schiffrin, E. L. 2000. Docosahexaenoic acid, a peroxisome proliferator–activated receptor-α ligand, induces apoptosis in vascular smooth muscle cells by stimulation of p38 mitogen-activated protein kinase. *Hypertension*, **36**(5): 851-855.

Yao, P.-L.; Borland, M. G.; Krishnan, P.; Zhu, B.; Gonzalez, F. J. & Peters, J. M. 2013. Inhibition of clonogenicity and xenograft tumor growth by activation and/or over-expression of peroxisome proliferator-activated receptor-{(beta)/(delta)}(PPAR {(beta)/(delta)}). *Cancer Research*, **73**:1295.

Bray, G. A. & Popkin, B. M. 2014. Dietary sugar and body weight: have we reached a crisis in the epidemic of obesity and diabetes? Health be damned! Pour on the sugar. *Diabetes Care*, **37**(4): 950-956.

Steneberg, P.; Sykaras, A. G.; Backlund, F.; Straseviciene, J.; Söderström, I. & Edlund, H. 2015. Hyperinsulinemia enhances hepatic expression of the fatty acid transporter Cd36 and provokes hepatosteatosis and hepatic insulin resistance. *Journal of Biological Chemistry*, **290**(31): 19034-19043.

Lefebvre, A.-M.; Peinado-Onsurbe, J.; Leitersdorf, I.; Briggs, M. R.; Paterniti, J. R. & Fruchart, J-C. 1997. Regulation of lipoprotein metabolism by thiazolidinediones occurs through a distinct but complementary mechanism relative to fibrates. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **17**(9): 1756-1764.

Murphy, G. J. & Holder, J. C. 2000. PPAR-γ agonists: therapeutic role in diabetes, inflammation and cancer. *Trends in Pharmacological Sciences*, **21**(12): 469-474.

Fasshauer, M. & Paschke, R. 2003. Regulation of adipocytokines and insulin resistance. *Diabetologia*, **46**(12): 1594-1603.

Ruderman, N. B.; Carling, D.; Prentki, M. & Cacicedo, J. M. 2013. AMPK, insulin resistance, and the metabolic syndrome. *The Journal of Clinical Investigation*, **123**(7): 2764.
Barroso, I.; Gurnell, M.; Crowley, V.; Agostini, M.; Schwabe, J. & Soos, M. 1999. Dominant negative mutations in human PPARγ associated with severe insulin resistance, diabetes mellitus and hypertension. *Nature*, 402(6764): 880-883.

Purdel, C.; Margină, D.; Ilie, M.; Miulescu, R. & Tirgoviste, C. 2014. Adipose tissue accumulation of endocrine disrupting compounds: Variant of a common theme in exposome research. *Adipobiology*, 6: 15-22.

Kubota, N.; Terauchi, Y.; Miki, H.; Tamemoto, H.; Yamauchi, T. & Komeda, K. 1999. PPARγ mediates high-fat diet–induced adipocyte hypertrophy and insulin resistance. *Molecular Cell*, 4(4): 597-609.

Mayoral, R.; Osborn, O.; McNelis, J.; Johnson, A. M.; Izquierdo, C. L. & Chung, H. 2015. Adipocyte SIRT1 knockout promotes PPARγ activity, adipogenesis and insulin sensitivity in chronic-HFD and obesity. *Molecular Metabolism*, 4(5): 378-391.

Ristow, M.; Müller-Wieland, D.; Pfeiffer, A.; Krone, W.; Kahn, C. R. 1998. Obesity associated with a mutation in a genetic regulator of adipocyte differentiation. *The New England Journal of Medicine*, 339(14): 953-959.

Agostini, M.; Schoenmakers, E.; Mitchell, C.; Szatmari, I.; Savage, D. & Smith, A. 2006. Non-DNA binding, dominant-negative, human PPARγ mutations cause lipodystrophic insulin resistance. *Cell Metabolism*, 4(4): 303-311.

Monajemi, H.; Zhang, L.; Li, G.; Jeninga, E. H.; Cao, H. & Maas, M. 2007. Familial partial lipodystrophy phenotype resulting from a single-base mutation in deoxyribonucleic acid-binding domain of peroxisome proliferator-activated receptor-γ. *The Journal of Clinical Endocrinology & Metabolism*, 92(5): 1606-1612.

Lüdtke, A.; Buettner, J.; Schmidt, H. H. & Worman, H. J. 2007. New PPARG mutation leads to lipodystrophy and loss of protein function that is partially restored by a synthetic ligand. *Journal of Medical Genetics*, 44(9): e88-e.

van Beekum, O.; Brenkman, A. B.; Grøntved, L.; Hamers, N.; van den Broek, N. J. & Berger, R. 2008. The adipogenic acetyltransferase Tip60 targets activation function 1 of peroxisome proliferator-activated receptor γ. *Endocrinology*, 149(4): 1840-1849.

Savage, D. B.; Agostini, M.; Barroso, I.; Gurnell, M.; Luan, J. & Meirhaeghe, A. 2002. Digenic inheritance of severe insulin resistance in a human pedigree. *Nature Genetics*, 31(4): 379-384.

Francis, G. A.; Li, G.; Casey, R.; Wang, J.; Cao, H. & Leff, T. 2006. Peroxisomal proliferator activated receptor-γ deficiency in a Canadian kindred with familial partial lipodystrophy type 3 (FPLD3). *BMC Medical Genetics*, 7(1): 3.

Jeninga, E. H.; Gurnell, M. & Kalkhoven, E. 2009. Functional implications of genetic variation in human PPARγ. *Trends in Endocrinology & Metabolism*, 20(8): 380-387.