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PPAR Gamma at the Crossroads of Health and Disease: A Masterchef in Metabolic Homeostasis

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Abstract

The peroxisome proliferator-activated receptor gamma (PPARγ) is a ligand-activated transcription factor involved conferring the role of an active gland to the adipose tissue. This nuclear receptor is actively involved, mainly through its regulation to the physiology and the endocrine activity of the adipose tissue, in the regulation of a variety of processes governing the metabolic homeostasis. PPARγ, activated by a wide variety of fatty acids molecule or their metabolite, governs metabolic processes implicated in glucose and lipid metabolism and adipose mass control by modulating the expression of a large number of target genes. Furthermore, PPARγ is a molecular target for antidiabetic thiazolidinedione molecules that selectively bind this nuclear receptor to improve systemic insulin sensitivity and glucose tolerance. Accordingly, the specific position of PPARγ in systemic metabolic control is resumed in its pivotal role in the regulation of glucose and lipid homeostasis, lipid storage and adipogenesis. Here, we present an overview of the involvement of PPARγ in metabolic control leading to health improvement.

The emphasis is on adipose tissue mass regulation by PPARγ and its implication in glucose homeostasis and cardiovascular modulation.

Keywords: Metabolic homeostasis; Adipogenesis; Cardiovascular modulation

Review

Since their identification in 1990s [1], the peroxisome proliferator-activated receptors (PPARs) are soliciting considerable interest and our knowledge about their physiological roles is evolving. Involved in the regulation of the metabolism of lipids and lipoproteins, glucose homeostasis, cell proliferation and cell differentiation, PPARs are a pharmacological target for the treatment of metabolic disorders such as diabetes or dyslipidemia.

The discovery of PPARs started when our view towards adipose tissue changed [2]; long believed to be a simple energy storage tissue, adipose tissue is nowadays considered an endocrine gland itself. The development of fibrate family to treat hyperlipidemia in 1962 [3,4] leaded to the discovery in the 1990s of the first PPARs member the PPARα [5]. This finding thus stimulated worldwide research to elucidate PPARs family's role in the systemic metabolism control [6].

Peroxisome Proliferation Response Elements (PPRE) were then described in the promoter of microsomal and peroxisomal genes known to be upregulated during proliferation of peroxisome as CYP4A1, CYP4A6 and acyl CoA oxidase [7-9]. International interest in the study of PPARs took on even greater significance after the identification and cloning of three subtypes of PPAR [10,11], named α, β/δ and γ, each being encoded by a specific gene to play key roles in metabolic homeostasis [12-15].

PPARγ a ligand-activated nuclear receptor

PPARγ was first identified as a mediator of the activity of the oral antidiabetic thiazolidinedione (TZD) family and recognized as a major regulator of glucose homeostasis and adipogenesis [16,17]. PPARγ belongs to the nuclear receptors superfamily of ligand-inducible transcription factors [13,18]. Often of lipid nature, ligands activate PPARγ forcing it to bind to PPRE of the promoter region of specific target genes involved in adipogenesis, lipid metabolism, inflammation and metabolic homeostasis. Similarly to typical nuclear receptors domain structure, PPARγ primary structure is composed of approximately 500 amino acids, and their structure is represented by a sequence of six areas (Figure 1). The N-terminal domain (A/B domain) is of length and primary structure variable from one receptor to another. It contains the ligand-independent transactivation segment (AF-1, Activation Function-1) that binds co-activators.

The C domain contains the DNA Binding Domain (DBD) characterized by a double folding of the protein chain held by two zinc atoms interacting with four cystein residues. The DNA binding occurs on consensus sequences called hormone response element located before the target gene near the promoter. This domain is highly conserved between nuclear receptors sequences allowing the three members of PPARs family to bind to the same PPRE DNA sequence. The D domain is a hinge region involved in binding of the chaperone protein to the receptor and in the DNA binding. The E domain liaises mediators on the C-terminal portion of the receptor. This Ligand-Binding Domain (LBD) also provides receptor dimerization and comprises a second pattern of AF-2 transactivation. This later protein sequences differs between the three subtypes of PPARs members leading to three pharmacologically distinct forms of nuclear receptors

appointed α, β/δ and γ. The F domain, meanwhile, is a variable sequence that constitutes the C-terminal portion of the protein sequence of each receptor.

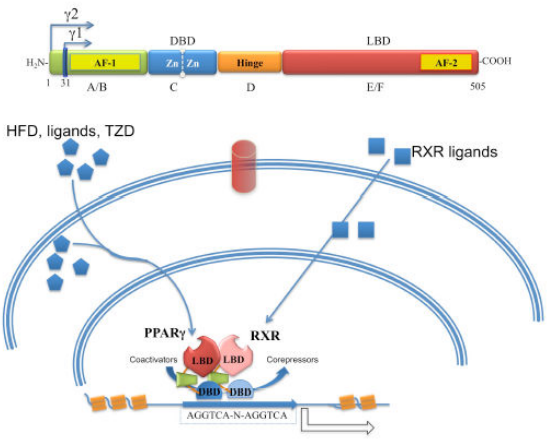

Figure 1: PPARγ domain structure. PPARγ is a ligand-activated transcription factors belonging to the nuclear receptors family. Upon their activation by their ligands, PPARγ form heterodimers with the nuclear receptor RXR. The heterodimer binds to specific DNA-response elements in target genes known as PPRE. The PPARγ2 (γ2) protein contains an additional 30 amino acids at the N terminus compared to PPARγ1 (γ1). DNA-binding domain (DBD), ligand-binding domain (LBD), and activation function 1 & 2 (AF-1/2) are shown.

Although these domains are all potential targets mediating its signaling cascade, PPARγ transcriptional activity is initiated by endogenous and exogenous ligands. These later induce chaperone proteins dissociation from the nuclear receptor that represses its activity and conformational changes allowing PPARγ heterodimerisation with the retinoid X receptors (RXR, vitamin A and 9-cis-retinoic acid receptor) [5] (Figure 1). The complex, thus enabled, will bind to the typical PPRE sequences located in the promoter regions of many genes involved in adipogenesis, adipokines secretion and glucose and lipid homeostasis (Table 1) whose expression is thus stimulated [19].

Adipogenesis	
FABP4	Fatty Acid Binding Protein 4, also known as adipocyte fatty acid binding protein P2 (aP2)
Pref-1	Preadipocyte factor 1
UCP1	UnCoupling Protein 1 (key determinant of brown adipocytes)
PLIN1/2/4	Perilipin-1, 2 & 4, also known as lipid droplet-associated protein
C/EBPα	CCAAT/enhancer binding protein (C/EBP), alpha
STAT 1	Signal Transducers and Activators of Transcription-1
STAT5A/B	
CDKN1A	Cyclin-Dependent Kinase inhibitor 1A
Cidec	Cell death-inducing DFFA-like effector c
Nr1d1	Nuclear receptor subfamily 1, group D, member 1
Adipokine secretion	
ADPN	Adiponectin, also known as adipoQ
FGF1/21	Fibroblast Growth Factor 1 & 21
Ob (Lep)	Leptin
RETN	Resistin also known as adipose tissue-specific secretory factor (ADSF)
APLN	Apelin
ACS	Acylation Stimulating Protein
FIAF	Fasting Induced Adipose Factor
OMN	Omentin
Rbp-4	Retinol Binding Protein-4
Serpina12	Vaspin
PBEF1	Visfatin also called pre-B cell enhancing factor (PBEF) or nicotinamide phosphoribosyltransferase (Nampt)
RARRES2	Chemerin, also known as retinoic acid receptor responder protein 2 (RARRES2)
SERPINE1	Plasminogen activator inhibitor-1 (PAI-1)
ANGPTL2	Angiopoietin-like Protein 2
Lipid homeostasis	
Lpl	Lipoprotein lipase
Gyk	Glycerol kinase, key player of glycolysis/glycogenesis process
ACS	Acetyl-CoA synthetase
Pnpla2	Patatin-like phospholipase domain containing 2, involved in the triglyceride hydrolysis
Dbi	Diazepam binding inhibitor, involved in lipid metabolism and dislocation of β-carbolines and benzodiazepines
ACACA	Acetyl-CoA carboxylase-α
ELOVL4	Elongation of very long-chain fatty acids-like 4
LXRA	Liver X receptor α
ME1	Malic enzyme 1; involved in acetyl-CoA is transport
SCD1	Stearoyl-CoA desaturase 1, (delta) Δ9-desaturase
APOA2	Apolipoprotein A-II
APOE	Apolipoprotein E
CD36	Leukocyte differentiation antigen 36, also known as fatty acid translocase,

	FAT
LDLR	LDL receptor
LIPC	Hepatic triglyceride lipase (HTGL)
LRP1	LDL receptor-related protein 1
LPL	Lipoprotein lipase
OLR1	Oxidized LDL (oxLDL) receptor, also known as the endothelial oxLDL receptor: LOX-1
FATP1/2	Fatty acid transport protein 1 & 2
Glucose homeostasis	
Glut-4	Glucose transporter type 4
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
CAP	Catabolite Activator Protein
IRS-1/2	Insulin receptor substrate 1 & 2
Sorbs1	Sorbin and SH3 domain containing 1
Aqp7	Aquaporin 7
G6PC	Glucose-6-phosphatase
GPD1	Glycerol-3-phosphate dehydrogenase 1
GCK	Glucokinase
PEPCK 1	Phosphoenolpyruvate carboxykinase 1
PDK4	Pyruvate dehydrogenase kinase 4
ACAT1	Acetyl-CoA acetyltransferase
Other factor type	
EBF1	Early B cell factor 1, Transcription factor essential for the maintenance of B cell identity
GSTA2	Glutathione S-transferase alpha 2
BR1	Bradykin receptor type1
NFκb	Nuclear factor-kappa B

Table 1: PPARγ target genes

A wide range of compounds could be identified as PPARγ ligands [20]. Several studies have focused their research on the elucidation of the link between the lipid nature and their capacity to activate PPARγ [20,21]. Dietary fats and oils are major source of PPARγ activators especially polyunsaturated fatty acids (PUFA) that activate it in micromolar concentration [3,22]. Other natural ligands derived from arachidonic degradation such as 15-deoxy-Δ12,14-prostaglandin J2 acid show high affinity to PPARγ [23]. Finally, the FFA oxidized phospholipids derived from oxidized LDL (9- and 13-HODE) can also activate PPARγ. Depending on its ligand nature, PPARγ activation can be differently modulated [24-30]. All these potential natural ligands are summarized in the Table 2.

Unsaturated Fatty Acids	
ω3-PUFA	
α-Linolenic acid	[175]
γ-Linolenic acid	[176]
Eicosapentaenoic acid (EPA)	[177]
Docohexaenoic acid (DHA)	[178]
4-Hydroxy docosahexaenoic acid (4-HDHA)	[178]
4-Oxodocosahexaenoic acid (4-oxo-DHA)	[178]
ω6-PUFA	
Linoleic acid	[179]
Nitrolinoleic acid	[179]
Conjugated linoleic acid isomers (CLA)	[180]
9/10-NO2-linoleic acid	[181]
12-NO2-linoleic acid	[181]
13-NO2-linoleic acid	[181]
Arachidonic acid	[182]
ω9-MUFA	
Palmitoleic acid	[183]
Oleic acid	[184]
Eicosanoids	
9-Hydroxyoctadecadienoic acid (9-HODE)	[179]
13-Hydroxyoctadecadienoic acid (13-HODE)	[179]
15-Deoxy-Δ12, 14-PGJ2	[185]
Other	
Azelaoyl phosphatidylcholine (component of the lipid pool within oxLDL)	[186]
Isoflavones:	
Genistein	[187]
Daidzein	[188,189]
Equol	[188,189]
Biochanin A	[189]
Flavonoids:	
Psi-baptigenin	[190]
Hesperidin	
Quercetin (from dill, bay leaves, and oregano)	[191]
2′-Hydroxy chalcone (cinnamon in polymeric form)	[191]
Rosmarinic acid (marjoram)	[191]

Table 2: PPARγ natural ligands

There is also well-known synthetic ligand of PPARγ thiazolidinedione family (TZD) for treatment of type 2 diabetes and insulin resistance [16,17,31]. Other active ingredients such as non-steroidal anti-inflammatory drugs may also be PPAR agonists.

Tissue distribution of PPARγ

The tissue distribution and the expression level of PPARs differ for each isoform [32,33]. PPARγ is mainly found in adipose tissue and the gastrointestinal tract. The PPAR γ gene encodes two protein sub-types, γ1 and γ2, arising from differential splicing of exon B [34-36]. PPARγ2 possess 28 amino acids more than its counterpart γ1 at its N-terminus protein sequence in mice and 30 in humans. This additional peptide sequence confers transcriptional activity 10 times higher for PPARγ2 compared to PPARγ1 subtype [34]. Whereas PPARγ1 is expressed in muscle cells, hepatocytes, monocytes and others, PPARγ2 is, for its part, the specific form of PPAR γ in the adipose tissue [37,38]. Recently, two new subtypes of PPARγ were identified in human: PPARγ3 and PPARγ4 from two different promoters. PPARγ4 expression seems to be restricted to adipose tissue [39] while mRNA PPARγ3 was detected in white adipose tissue, large intestine and macrophages [37,40].

PPARγ is also expressed in cells of the vascular wall, monocytes and macrophages [38,41-43]. Further, PPARγ is present in the atherosclerotic plaque at the sub-endothelial area in the lipid core and of atherosclerotic lesions where they co-localize with specific markers of macrophages, smooth muscle cells and foam cells [44-46].

Adipose tissue and PPARγ

PPARα and PPARδ/β appear to have limited adipogenic effect on the adipose tissue. The PPARα is mainly expressed in the brown adipose tissue controlling β-oxidation for heat production [47-50], while the PPARδ/β is found in preadipocytes controlling the expression of genes involved in their proliferation but seems to be slightly implicated in the adipogenesis process [51].

In adipose tissue, the predominant PPAR isoform controlling its differentiation is PPARγ particularly PPARγ2 subtype [35,52-54] (Figure 1). PPARγ is involved in both processes of adipogenesis, lipid metabolism and the secretion of several hormones called adipokine in adipose tissue. Thus, PPARγ confers the endocrine functions of the mature adipocyte.

PPARγ and adipose mass control

PPARγ is the main nuclear receptor implicated in the adipose mass control triggering the recruitment of new preadipocytes and steer their differentiation into mature adipocytes controlling thus the adipose tissue homeostasis [17,55]. The expression of this nuclear receptor is highly important for the embryogenic development and a decrease in its activity lead to a lipodystrophy in human [39,56-59].

Adipogenesis refers to the process of differentiation of progenitor cells, called preadipocytes, into mature adipocytes in which the gene expression, the cell morphology and the sensitivity to exogenous hormones and factors change. During differentiation, the expression of various genes encoding proteins involved in lipid uptake and metabolism, such as aP2, Pref-1, phosphoenolpyruvate carboxykinase (PEPCK) and lipoprotein lipase (LPL) (Table 1), are induced through the activation of PPARγ [54,60,61]. PPARγ is the most important factor implicated in the formation of mature adipocytes and its overexpression in non-adipocytes cells is sufficient to induce their transformation to adipocytes [52,53]. Furthermore, an increased level of circulating fatty acids in the body is believed to raise PPARγ activity that will lead to increased adipose tissue mass and obesity development. If so, it explains the fact that TZD treatment, through its activation of PPARγ, increase body weight gain. However, it has been shown that selective activation of PPARγ in the adipose tissue is sufficient to prevent diabetes in HFD-fed mice without any change in their body mass [62]. These data demonstrate that PPARγ adipose tissue activation is essential to improve insulin sensitization but not responsible of the nuclear receptor activation side effect such as weight gain. Moreover, recent studies showed that PPARγ activation in the brain, rather than in the adipose tissue, is directly linked to weight gain [63,64]. Thus, the development of a treatment that could selectively activate adipose tissue PPARγ seems to be a highly interesting alternative of a TZD treatment.

In parallel with its adipogenic activity, PPARγ seems to induce apoptosis in adipocytes in a process of regeneration and cells turnover of the adipose tissue [55,65]. Thus, PPARγ regulates the adipose tissue mass by enabling and recruiting new adipocytes more sensitive to insulin and lipid storage and disabling and clearing mature adipocytes with saturated lipid vacuoles and less sensitive to insulin.

PPARγ and endocrine function of the adipose tissue

PPARγ is not only a key factor controlling adipogenesis and adipose tissue mass control but also serves as the master regulator of metabolic genes in this tissue (Figure 2). This activity conferred the definition of an active endocrine gland to the adipose tissue allowing it to secrete a wide range of bioactive substances called adipokines [2,66,67] actively implicated in the regulation of glucose and lipid homeostasis [17,31,53]. By governing adipokines production through ligand systemic availability in the body (natural ligand, TZD, etc.), PPARγ improves insulin sensitivity both at adipocyte, muscular and hepatic levels by stimulation of adipogenesis, increasing muscle glucose and FFA consumption, inhibiting the hepatic glycolysis and decreasing the release of FFA in the blood [31,68,69]. The most important determinant of amount and nature of adipokine secreted by the adipose tissue is the nature of the ligand that stimulates PPARγ activity, the number of adipocytes contained in the adipose tissue and their size [24,70,71].

The first hormone to be identified as adipokine was leptin discovered in 1994 [10]. Leptin is an adipokine secreted exclusively by mature adipocytes and its plasma level is positively correlated with body fat mass [70,72]. During a meal, increased systemic FFA level are positively correlated with PPARγ activity that leads to increased leptin secretion [73]. Leptin seems to be secreted by mature adipocytes as a negative retrocontrol on PPARγ activity [74-76] to limit the adipose tissue over-expansion. However, this adipokine has a central role in glucose homeostasis acting on several organs. Leptin act on the sympathetic nervous system to regulate satiety [77,78], inhibit insulin secretion from pancreatic β-cells [79,80] and decrease insulin receptor sensitivity in the peripheral cells to limit glucose uptake and lipid overload [81,82]. Leptin limits also adipose tissue expansion by increasing TNFα production [83], also known to decrease insulin systemic sensitivity [84-86], to inhibit adipogenesis and to decrease the fat storage [86-89]. On the other hand, leptin activates the 5'-AMP-activated protein kinase (AMPK) in target tissues [90,91]. This kinase stimulates the oxidation of FFA by inhibiting the activity of acetylcoenzyme A carboxylase governing the production of the

enzyme malonyl-CoA responsible for lipogenesis [92]. As a result, leptin prevents fat accumulation in peripheral tissues and prevent lipotoxicity. Thus, increased caloric intake will cause PPARγ activity to be higher and leptin secretion to elevate, leading to a leptin systemic resistance [93,94] that will be developed into systemic insulin resistance and diabetes.

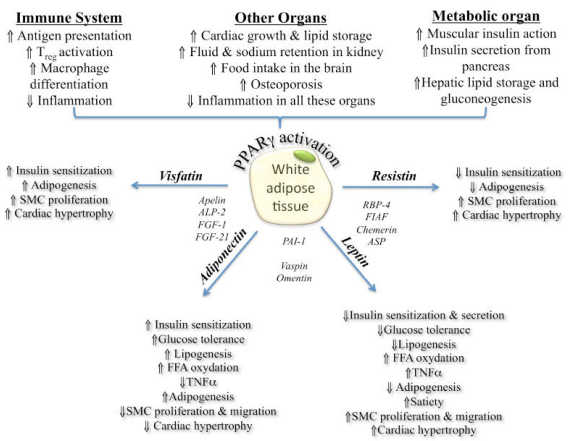

Figure 2: PPARγ has multiple direct and indirect, through adipokine secretion, effects on glucose and lipid homeostasis as well as on several physiologic organ function.

PPARγ management of metabolic homeostasis passes also through the regulation of the adiponectin secretion, an insulin-sensitizing adipokine [95,96] (Figure 2). In contrast to leptin, plasma concentrations decrease with weight gain and obesity and hypo-adiponectinemia is correlated with insulin-resistant diabetes [70,97]. This counterbalance between leptin and adiponectin is not fully elucidated, but a possible action of leptin on the adiponectin expression level in order to limit adipose tissue expansion could be the answer as seen with PPARγ activity leptin-control. This mechanism could be plausible in the perspective of the main leptin action working on reduction of systemic lipid overload. In fact, adiponectin work on improving insulin sensitivity and controls FFA oxidation through the activation of AMPK [98,99] leading to a decrease in muscles and liver lipid accumulation and an improvement of the signal transduction of insulin. Adiponectin also increases the translocation of GLUT4 transporters from the cytoplasm to the plasma membrane to facilitate the glucose uptake [100]. Adiponectin also improves blood glucose by inhibiting the expression of mRNA coding for hepatic G6Pase and PEPCK, which has the effect of reducing the production of glucose [98,101]. Finally, adiponectin abolish or reprehend the leptin-induced TNFα secretion improving thus the insulin sensitivity [102]. Thus, by increasing adiponectin level [103,104], PPARγ work in concert with insulin receptors to improve systemic glycemia by improving insulin sensitivity and glucose tolerance. However, a possible role of increased leptin level in the blood, correlated with obesity, could be the main cause of decreased glycemic parameters correlated with decreased adiponectin levels and insulin resistance. Furthermore, resistin, a relatively new adipokine that is gaining in importance in research for its implication in glucose homeostasis [105], directly impact adiponectin action. Its secretion profile is also governed by PPARγ activity [106,107] and its circulating levels are increased with obesity inducing insulin resistance and an impaired glucose tolerance [108-110]. The implication of resistin in diabetogenesis remains very controversial and several studies showed that resistin couldn't be implicated in metabolic diseases [111,112]. These contradictory data could be due to the fact that resistin is very weakly expressed in adipose tissue in humans and the small amounts found in adipose tissue are originate from macrophages [113,114]. More investigations should be pursued on this adipokine.

The list of the PPARγ regulated adipokine is expanding day after day and regrouping more family subtype [71]. Among them the exclusive adipose tissue adipokine vaspin [115,116], the insulin-like adipokine visfatin [117,118] and the insulin and TNFα-stimulated adipokine apelin [119,120] are recent adipokine secreted during PPARγ activation. These adipokines, like adiponectin, are increased in weight gain to counteract the development of insulin resistance and improve glucose intolerance, but decreases with the progression of diabetes and obesity. Further, the lipogenic adipokine ASP (Acylation Stimulating Protein) [121], the Fasting Induced Adipose Factor (FIAF) [122] are all adipokines that their genes contain a PPRE sequence and their expression is therefore controlled by PPARγ activity. These adipokines play key role in glucose homeostasis by improving systemic insulin sensitivity and lipid metabolism by stimulating hepatic FFA uptake and inhibiting LPL.

PPARγ-mediating adipokine secretion activity depends on different factors including ligand nature, adipocyte status and systemic metabolic changes. The whole system is settled to control metabolic homeostasis by stimulation of insulin sensitizer adipokines secretion and suppression of other diabetogenic factors. However, the maintaining of harmful exogenous factors supply will unbalance the system towards a decrease of PPARγ activity that becomes dangerous for systemic homeostasis, to limit unlimited adipose tissue expansion and glucose storage; all together will lead to metabolic disease development.

PPARγ and cardiovascular alterations

Besides regulating numerous metabolic pathways, PPARγ also governs cardiovascular processes linked to their homeostasis (Figures 2 and 3). The expression of PPARγ has been shown in many cardiovascular cell types including monocytes and macrophages [38], smooth muscle cells [123] and endothelial cells [124]. The first clue towards cardio-protective effects of PPARγ came from observation of the cardiomyocyte-specific PPARγ knock out mice that exhibit a cardiac hypertrophy [125]. The cardioprotective effects of PPARγ in these mice are likely explained by the decrease of the glucose tolerance in the cardiomyocyte leading them to consume FFA as a source of energy but more susceptible to induce ROS secretion. These later are known to affect endothelial function and increase cardiac inflammation [126,127]. Various evidences have shown that PPARγ exerts an inhibitory effect on NF-κB [128,129], a nuclear factor involved in the transcription of many genes encoding inflammatory proteins. As a result, NF-κB is retained in a nonactive form leading to suppression of its transcriptional activity for inflammatory factors such as type 1 receptor of bradykinin [130] whose expression is increased in inflammation and in diabetes. The anti-inflammatory effects of PPARγ could also be explained by the inhibitory effect of this nuclear receptor on signal transducer and activator of transcription (Stat) and Activator protein-1 (AP-1) [129,131]. Here also, PPARγ act to inhibit the transcriptional activity of these inflammatory factors leading to a decreased impact of these molecules on systemic hypertension induction [129]. Furthermore, PPARγ action on

proliferation potential of vascular smooth muscle cells prevents hypertension events through adipokine secretions [24,123,132,133].

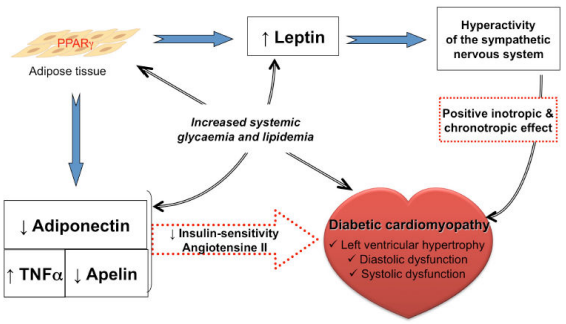

Figure 3: In obesity-linked type 2 diabetes, characterized by increased lipid and glucose circulating levels in the body, adipose tissue secretions profile actively contribute to the development of diabetic cardiomyopathy. In addition to the negative influence of glucose and lipid disturbed homeostasis on cardiac function, modulation of the adipose tissue activity, illustrated by an increase PPARγ activity, by the hyperlipidemia and hyperglycaemia directly influence the cardiac physiology through its adipokine secretion profile modulation.

It has been well established that TZD-PPARγ activation decreases the production of cytokines (TNFα, IL-1, IL-6, IL-18, CRP, etc.) by the macrophages [134], a potential anti- inflammatory effect. The glitazones could induce the transformation of macrophages into foam cells in the atherosclerotic lesions, but the results are somewhat contradictory depending on the chosen experimental system [135,136]. They inhibit the proliferation and migration of vascular smooth cells [123,137]. Finally, in endothelial cells in culture, TZD induce the expression of Plasminogen Activator Inhibitor -1 (PAI-1, an inhibitor of fibrinolysis) [138], whereas in diabetic patients treated with troglitazone reduces the concentration of PAI-1 circulating [139]. Such contradictory experimental observations led to several questions to determine if glitazones treatment is benefic or not for cardiovascular system.

Even if it has shown overt improvement in fasting glucose and insulin sensitivity, TZD treatment has worsened cardiac parameters in the normal, diabetic and transgenic rodent models [125,127,140,141]. PPARγ pharmacological activation also increased incidence of congestive heart failure and induce fluid retention as reported in the RECORD European clinical trial [142,143]. These data led to the withdrawal from the US and European markets of Rosiglitazone in 2010 and to the emission of black box warning on the other member of the TZD family.

Known as an agonist of PPARγ, TZD could induce FFA scavenger receptors expression in vascular cells wall leading to the development of foam cells and trigger thus atherosclerotic formation [24,135]. PPARγ activation also increases TNFα secretion that plays an autocrine role on the adipose tissue to inhibit adipogenesis and decrease fat storage [65]. However, TNFα exert its effects on other organs like heart and vascular cells leading to insulin resistance [144], which also leads to an increased oxidative stress and cell dysfunctions. Furthermore, TNFα down regulates the PPARα activity in cardiomyocytes [145] leading to a worsen status for these cells.

TNFα upregulate apelin expression levels [119], an adipokine known for its cardiotonic effects [146] that could lead to a heart failure. The apelin also controls blood pressure and heart activity due to its direct action on the cardiovascular system and its action on the autonomic nervous system [147-149] and an overexpression of this hormone could lead to several heart complications.

Other adipokines catalyze the effect of PPARγ activity on the cardiovascular system. Among them leptin and adiponectin are the most studied adipokines for this issue. Leptin is known to regulate the hypothalamic-pituitary-adrenal axis responsible for blood pressure regulation [77]. In subjects suffering of metabolic diseases this control is disturbed if not missing. Thus, high leptin concentration leads to diastolic dysfunction associated with higher cardiac sympathetic nervous system activity and increased left ventricle mass [150]. This dysfunction with a reduction in cardiac compliance is thus associated with left ventricle dilatation and an increased left ventricle mass in obesity-linked diabetic mice [70,151]. The leptin receptor Ob-R belongs to the cytokine receptor family class I [152,153] that include interleukins and growth hormone receptors. This suggests other possible biological effects of leptin such as inflammation associated with its related cytokine nature [154-156]. In addition, leptin stimulates the synthesis of ET-1 [157,158], NOS [159], ROS production [158] and expression of MCP-1 [160] that have a direct impact on the increasing of the oxidative stress in endothelial cells. All these factors could lead to the atherogenesis process.

Further, leptin has angiogenic activity and promotes migration and proliferation of vascular smooth muscle cells [24,161]. This effect is important in the physiological process of the expansion of adipose tissue that requires a good blood and oxygen supply. Leptin also promotes FFA oxidation, glucose uptake, platelet aggregation and accumulation of cholesterol in macrophages involved in atherogenesis effect [90,156,162,163].

In parallel, decreased level of adiponetin in obesity and diabetes is correlated with hypertension, presence of coronary heart disease and diabetic cardiomyopathy [70,151,164,165]. Its protective properties against atherosclerosis pass through its inhibitory effects on the expression of adhesion molecules on endothelial cells limiting the recruitment of monocytes to the vascular wall, and by its anti-inflammatory properties which inhibit the production of TNFα and macrophages activity [102,166-169]. This adipokine also inhibits smooth muscle cells proliferation by inhibiting the proliferative effects of PDGF [24,132].

Finally, cathepsins are adipokines with protease activity of the papain family actively involved in protein metabolism [170-173]. This family includes several members, including cathepsins S, K and L. They are secreted by adipose tissue in parallel with food intake and leptin secretion. They directly affect adipocyte differentiation and remodeling of the endothelial cells. This action of matrix remodeling (Degradation of collagen, elastin, fibronectin, etc.) is essential for adipogenesis and adipose tissue expansion; their secretion are thus increased in obese person and possibly implicated in several cardiovascular alterations [174].

All together, these data suggest that the modulation of the expression of PPARγ receptors in the diabetic or TZD treated mice might be a pharmacological model of two situations: a permanent blocking of these receptors as a response of the organism for obesity to

prevent diabetes or desensitization of this nuclear receptor due to continuous stimulation with its ligand during treatment.

Conclusion

This year, we are celebrating the 20th anniversary of the discovery of the first adipokine that gave us a novel definition for adipose tissue: leptin. Since then it has become clear that adipose tissue is a source of a wide range of bioactive molecules called adipokine leading the regulation of systemic metabolism. The secretion of these hormones is henceforth controlled by what we can call nowadays the masterchef of metabolic homeostasis: PPARγ.

Being modulated by a considerable variety of endogenous and synthetic ligand, PPARγ is at the present time considered as a crucial metabolic sensor modulating numerous gene expression implicated in body homeostasis. Although PPARγ has mostly been connected with glycemic modulation, it is now evident that its effects are much more extensive and cover adipogenesis, cardiometabolic control and lipid catabolism. One of the major challenges lying ahead remains to better understand the molecular mechanism underlying its modulated activity related to the ligand nature, to improve our knowledge of its specificity to the chosen ligand in each therapeutic treatment.

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