Role of PPARs in inflammatory processes associated with metabolic syndrome (Review)

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Abstract. Metabolic syndrome (MS) includes the presence of arterial hypertension, insulin resistance, dyslipidemia, cardiovascular disease (CVD) and abdominal obesity, which is associated with a chronic inflammatory response, characterized by abnormal adipokine production, and the activation of certain pro-inflammatory signaling pathways. Furthermore, the changes presented by the adipose tissue in MS favors the secretion of several molecular mediators capable of activating or suppressing a number of transcription factors, such as the peroxisome proliferator-activated receptors (PPARs), whose main functions include storage regulation and fatty acid catabolization. When they are activated by their ligands (synthetic or endogenous), they control several genes involved in intermediate metabolism, which make them, together with the PPAR gamma coactivator-1-α (PGC-1) and the silent information regulator T1 (SIRT1), good targets for treating metabolic diseases and their cardiovascular complications.

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1. Introduction

The regulation of lipid and carbohydrate metabolism is of vital importance for homeostasis, involving the organization and appropriate response to environmental variables, such as food intake, stress, physical activities and temperature (1,2). In addition, to achieve this goal, there are several levels of metabolic controls, all of which require the involvement of numerous metabolic mediators, hormones, growth factors and ultimately transcription factors (3). Moreover, metabolic syndrome is a condition that consists of a large number of symptoms that affect the metabolism (4,5).

Metabolic syndrome apperars to have three potential etiological categories: obesity and disorders of adipose tissue, insulin resistance and a constellation of independent factors (molecules of hepatic, vascular and immunologic origin) that mediate specific components of the metabolic syndrome (6).

With respect to disorders of adipose tissue, adipocytes are a critical component of metabolic control and endocrine organs that have both positive and negative effects (7).

Obesity is associated with a chronic inflammatory response, characterized by abnormal adipokine production, and the activation of certain pro-inflammatory signalling pathways, resulting in the induction of several biological inflammation markers (8). The main physical consequence of obesity is atherosclerosis and CVD (9). Furthermore, obesity is accompanied by other medical complications; these include fatty liver, cholesterol gallstones, sleep apnea, osteoarthritis, and polycystic ovary disease (10).

Inflammation is receiving an increasing amount of attention for its potential role in the pathogenesis of a variety of disorders, from insulin resistance and type 2 diabetes mellitus (DM2) to fatty liver and CVD (11). The changes presented by adipose tissue in MS favor the secretion of several molecular mediators capable of activating, or suppressing, numerous transcription factors, such as peroxisome proliferator-activated receptors (PPARs) (12,13).

Expressed in three isoforms (α, δ and γ), PPARs are nuclear hormone receptors, structurally similar to steroid hormone receptors (14,15). Upon activation by a ligand, including endogenous fatty acids and fatty acid derivatives, the receptor forms a heterodimer with members of the retinoid X receptor (RXR) family and may act as a transcription factor (16). The

activation of PPAR pathways has a favorable effect on lipid synthesis and oxidation, glucose uptake, inflammation and the expression of immunoregulatory genes (17,18).

This review presents the principal molecular aspects of the role of PPARs in adipose tissue inflammation in MS and future therapeutics based on novel molecular pathways.

2. Adipose tissue in metabolic syndrome

The MS is characterized by a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function (19). Patients with MS present with high blood pressure, a large waist circumference and high levels of plasma triglycerides with an increased risk of developing DM2 and CVD (20,21). Physiopathological changes encountered in MS are varied, including insulin resistance, dyslipemia and obesity (22,23). Any metabolic changes related to obesity may be attributed to the increased intra-abdominal fat mass, and are independent of the total mass of the body (24).

Hypotheses have altered from the theory that adipose tissue is used solely as a storage site for energy, to the theory that adipose tissue has an active role in energy homeostasis and various other processes (25,26). The functional failure of adipose tissue occurs due to alterations in the delivery of systemic energy, the impaired consumption of glucose and the activation of self-regulatory mechanisms which extend their influence to the body's entire homeostasis system, with elevated levels of adipokine secretion and vascular effects (27,28). The progression of obesity is accompanied by chronic inflammation which involves innate and acquired immunity (29). Inflammation is a key process which underlies a variety of metabolic diseases and is often found in obese patients (30). Studies have shown that when mice are provided with a high-fat diet, their weight gain correlates with the induction of adipose tissue inflammatory pathways (31).

The production of proinflammatory molecules [interleukin (IL)-6, tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor (PAI)-1, angiotensinogen, complement factor 3 (C3), tissue factor and other inflammatory cytokines] in the adipose tissue during obesity contributes to a low degree of systemic inflammation, which is observed in a variety of chronic diseases associated with MS (Fig. 1) (31-33). Resistin and TNF-α, are adipokines associated with insulin resistance in the skeletal muscle (34,35). Furthermore, increasing adiposity and insulin resistance may interact, thus raising the levels of C-reactive protein (36).

The association between insulin resistance, chronic inflammation, hypertension, endothelial dysfunction and dyslipidemia may be due to the activation of NF-κB (37). TNF-α is elevated in the adipose tissues of obese rodents and humans and is implicated in the induction of atherogenic adipokines, such as PAI-1 and IL-6, as well as the inhibition of the anti-atherogenic adipokine, adiponectin (38). Even, obese individuals (with hyperinsulinemia) expresses 2.5-fold more TNF-α mRNA in fat tissue compared with normal controls (39). The transcription factor NF-κB and the TNF-α gene promoter have been activated by hypoxia in adipocytes and fibroblasts. In turn, NF-κB signaling represses E2F transcription factors, therefore inhibiting adipogenesis and maintaining a chronic inflammatory condition (40).

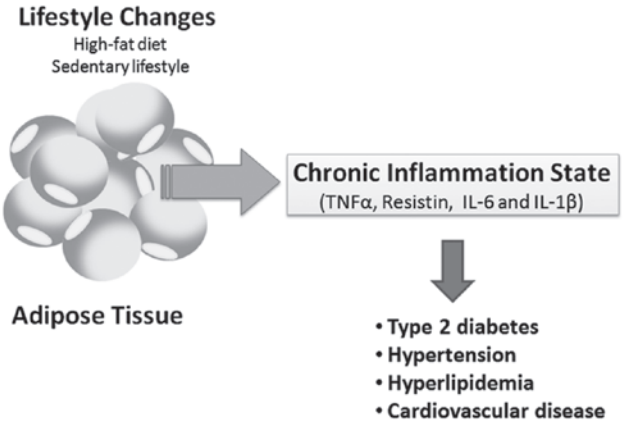

Figure 1. Inflammation as a link between adipose tissue and metabolic syndrome. TNF-α, tumor necrosis factor-α; IL, interleukin.

3. Molecular interaction and gene expression in adipose tissue

In order to reduce the risk factors of obesity, patients are required to alter their lifestyle and food habits (41). Factors dependant upon transcription factors, which are able to change the levels of relevant gene expression by adapting to signals from the surrounding environment are used to regulate MS (42,43). Observations regarding alterations in gene expression found in adipose tissue have led to the theory that the modification of carbohydrates may affect the risk to the patient of CVD and DM2 (44).

A series of transcription factors, the majority of which are PPARs, regulate the maturation of adipocytes and hundreds of other proteins that participate in the metabolism and storage of lipids (45). In adipose tissues, chronic inflammation is evident from the differential expression of genes involved in inflammatory responses and natural immunity (46).

PPARs are connected to the nuclear membrane, and their main function is storage regulation and the catabolization of fatty acids (47), when activated by their ligands (synthetic or endogenous), PPARs control several genes which are involved in intermediate metabolism (48). To date, three isoforms have been identified: PPAR-α, PPAR-β/δ and PPAR-γ (49). Each PPAR forms a heterodimer with RXR. This heterodimer joins the PPAR response elements (PPREs), which regulate target gene domains. The activation of PPARs by an appropriate ligand results in the recruitment of co-activators and the loss of co-repressors that remodel chromatin and activate transcription (50).

A major target for PPAR-γ agonists are adipocytes (51). PPAR-γ is crucial in adipogenesis, as it acts as a regulator of the differentiation and function of adipocytes and the absorption of stored fatty acids (52-54). However, PPAR-γ is also a key regulator of inflammatory and immune responses (55).

The activation of PPAR-γ does not affect the expression of M1 or M2 markers in resting macrophages, which indicates that only native monocytes may be stimulated by PPAR-γ activators to a M2 phenotype (56). Furthermore, PPAR-γ transcriptional signaling is required for the maturation of the anti-inflammatory M2 phenotype, whereas PPAR-β/δ controls the expression of alternative phenotypes in the Kupffer cells of obese mice (57).

Dominant mutations may cause a loss of function of PPAR-γ, which in turn leads to an increase in insulin resistance and the early onset of severe hypertension (58,59). The loss of PPAR-γ function in immune cells reduces the ability of abscisic acid to increase insulin sensitivity by suppressing the expression of MCP-1 and the infiltration of macrophages into white adipose tissue (60).

Furthermore, PPAR-α belongs to a subfamily of nuclear receptors which control the expression of proteins and enzymes that participate in inflammation and metabolism (48). Therefore, the activation of PPAR-α prevents inflammation in adipose tissue and the dual activation of PPAR-α and PPAR-γ enhances the action of adiponectin by increasing the adiponectin and adiponectin receptors, which may result in the amelioration of obesity-induced insulin resistance (61).

Contrary to PPAR-α and PPAR-γ, PPAR-β/δ is expressed ubiquitously, yet its pharmacology is understood less compared with other subtypes. PPAR-β/δ knockout mice demonstrate an obese phenotype when administered with a high-fat diet (62).

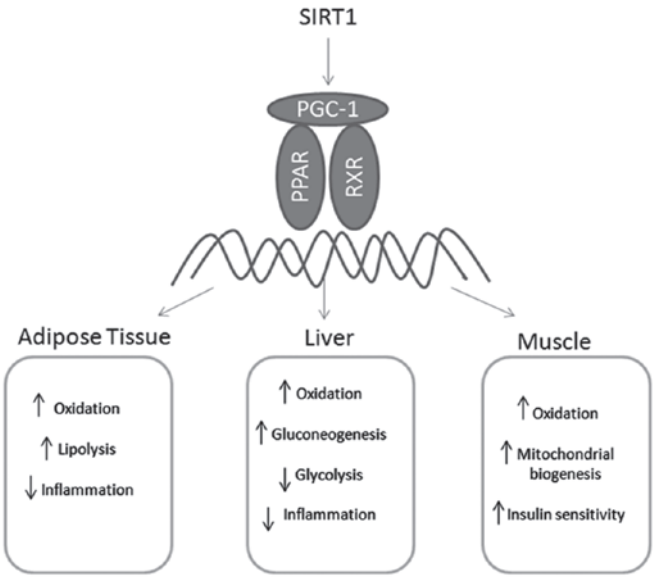

Figure 2. Participation of transcription factors in metabolic syndrome. PPARs, peroxisome proliferator-activated receptors; SIRT1, silent information regulator T1; PGC-1, peroxisome proliferator-activated receptor-γ coactivator-1-α; RXR, retinoic X receptor.

4. Future therapeutics based on novel molecular pathways

PPARs are potential targets for the treatment of metabolic diseases and their cardiovascular complications. PPARs regulate gene expression by binding with RXR as a heterodimeric partner to specific DNA sequences and modulating other transcription factor pathways in an independent manner (Fig. 2) (63,64).

Although, PPAR-γ is widely expressed in tissues, it is highly concentrated in adipose tissue. PPAR-γ is essential for the differentiation of adipocytes and promotes the accumulation of lipids in adipocytes (65). Furthermore, adipocyte-specific knockout mice for PPAR-γ demonstrated adipocytic hypocellularity, developing only hepatic insulin resistance. Anti-diabetic thiazolidinediones (TZDs) suppress insulin resistance in adipose tissue, but also affect the liver and muscles, despite exhibiting low concentrations of PPAR-γ in these tissues. There are two well-identified PPAR-γ isoforms which are derived from the same gene due to the use of alternative promoters. PPAR-γ2 is expressed specifically in adipose tissue, and differs from PPAR-γ1 by the presence of 30 additional amino acids in the N-terminal region. PPAR-γ is not only involved in the metabolism of lipids and carbohydrates, but also in inflammation (66,67) and is key in neoplasic growth (68,69).

Studies regarding genetic expression have revealed that insulin sensibilizing TZDs alter the expression of genes involved in recapturing lipids, lipid metabolism and in the action of insulin in adipocytes (70). This leads to an increased accumulation of lipids in the adipose tissue and a decrease in the release of free fatty acids. The effect on lipid metabolism by TZDs is greater than that of adipokine secretion, thus, they reduce the secretion of inflammatory cytokines (71) and chemokines which promote insulin resistance, such as TNF-α (72). This action occurs in adipocytes and associated macrophages. Other adipokines are over-regulated, particularly adiponectin (73), which is known to be a potential sensitizer of insulin for the liver and skeletal muscle. These insulin sensibilizing effects on the skeletal muscle and liver are controlled by alterations in the gene expression of adipokines due to the activation of the PPAR-γ receptor. Furthermore, the activation of PPAR-γ increases the expression and translocation towards the cell surface of glucose transporters GLUT 1 and 4 (74). This also increases the capture of hepatic and muscular glucose, thereby lowering glucose plasma levels. PPAR-γ agonists restore sensibility to insulin, lowering the expression of TNF-α and increasing the expression of adiponectin (52).

An ideal dual PPAR-α/γ agonist would provide glycemic control and enhance the lipid profile with well-tolerated therapeutic doses (75).

PPAR-α agonists have been proven to lower the production of certain inflammatory cytokines (76), such as TNF-α, in a dependent mechanism, involving NF-κB and AP-1 (77). Furthermore, the PPAR-α WY14643 agonist may directly increase the expression of adiponectin expression and it may also exert anti-diabetic, anti-atherosclerotic and anti-inflammatory effects. PPAR-α is the molecular target for fibrate-type hypolipemiant agents, such as fenofibrate and gemfibrozil. PPAR-α is highly expressed in the liver and the activation results in an increase of hepatic recapture and oxidation (12). During fasting, PPAR-α knockout mice present with hypoglycemia, hypoketonemia, hypertriglyceridemia and hepatic steatosis (12,78,79).

The treatment of DM2 patients with metformin reduces the production of hepatic glucose, by lowering gluconeogenesis. It has been suggested that metformin exerts its action by using incretins, which raises the levels of glucagon-like peptide-1 (GLP-1) (80) and those receptors for incretins in pancreatic β-cells by mechanisms that are both independent and dependent upon PPAR-α (81).

PPAR-α activators are used for the treatment of dyslipidemia. They lower the plasma levels of triglycerides and increase the plasma levels of HDL-c. These effects take place due to an increase in the production of the major component of HDL-c, apolipoprotein AI (82) and AII (83).

Lipid peroxidation and its subsequent production of 4-hydroxynonenal (4-HNE) in β-cells have been described as triggers of insulin secretion by a mechanism dependent on PPAR-β/δ as an antagonist of this nuclear factor, thereby blocking its effect (84). Research has demonstrated that PPAR-β/δ has a protective function in metabolic diseases that presents with chronic inflammatory conditions (85).

Treatment with PPAR-β/δ agonist, L-165041, decreases IL-1, IL-6 and TNF-α levels in mice with streptozotocin-induced diabetes (86). It was also demonstrated that PPAR-β/δ agonists may prevent renal alterations for the same type of diabetes. As far as the latter aspect, the PPAR-β/δ agonist GW0742, reduces the excretion of albumin, the infiltration of macrophages and the accumulation of type VI collagen amongst other effects that help to heal renal alterations related to diabetes (87).

Animals that are administered a high-fat diet develop metabolic alterations, such as glycemia, muscle glucose storage, alterations in the enzymes involved in carbohydrate metabolism and fat accumulation in the liver. All these alterations are reversible by treatment with NNC61-5920, a PPAR-β/δ agonist (88). The same agonist, causes a differential response in the treatment of metabolic alterations related to MS and diabetes. This evidence demonstrates that PPAR agonists may have outstanding metabolic effects, yet this is not always optimal, as the response to treatment may be too dependent on the etiology of the base. In this sense, an association has been made amongst brain-vascular accidents, weight gain and carcinogenesis along with other unwanted effects of the treatment with PPAR agonists (89).

5. Other targets

Peroxisome proliferator-activated receptor γ coactivator-1-α PGC-1. PPARs are important in regulating metabolism, there are molecules which may exert a co-stimulatory or co-repressor effect on the activity of these nuclear receptors, such as PGC-1α. This metabolic regulatory molecule was first described in 1998, as a key molecule in the regulation of the thermogenesis of brown adipose tissue (90,91). Various regulatory mechanisms have been described, which not only involves PPAR receptors, but also estrogen-related receptors (ERRs), thyroid hormone receptors, glucocorticoid receptors and non-nuclear receptors, such as myocyte enhancer factor-2 (MEF-2), among others. By modulating all these nuclear and non-nuclear receptors, PGC-1 is capable of regulating energy metabolism (92). A number of mechanisms have been described in which PGC-1 participates and regulates, and acts as a therapeutic target for cancer (93), DM2 (94) and heart failure (95). It has been hypothesized that PGC-1 is capable of inhibiting proinflammatory cytokine production through the inhibition of NF-κB, by inhibiting the phosphorylation of the p65 subunit (96).

Silent information regulator T1 (SIRT1). SIRT1 was the first gene of the sirtuin genes to be located, which is also capable of metabolism regulation and has been proposed as a new therapeutic target in metabolic diseases (97) and aging (98). Sirtuins are a class of enzymes, NAD-dependent histone deacetylases, found in prokaryotic and eukaryotic cells, which affect the regulation of cellular metabolism and the expression of certain genes. It is a cellular regulator of the balance between NADH and NAD^+. SIRT1 has been postulated as a sensor which is connected to metabolic homeostasis (99), and directly regulates the activity of the acetyl-CoA synthetases through deacetylation (100). Furthermore, SIRT1 may directly interact with PGC-1 (101), suggesting that SIRT1 is capable of regulating the transcriptional activity of PGC-1 and thereby regulating the energy balance and metabolism (92).

6. Conclusion

MS represents a clustering of cardiometabolic risk factors that are considered to be a direct consequence of overnutrition, sedentary lifestyles and the resultant obesity. Inflammation is receiving increased attention for its potential role in the pathogenesis of a range of disorders from insulin resistance and DM2 to fatty liver and CVD, the unexpected overlap between inflammatory and metabolic sensors and their downstream tissue responses indicates that inflammation plays a crucial role in the numerous complications of obesity.

The ability of PPARs to serve as master regulators of various metabolic processes, including lipid, glucose and energy homeostasis, inflammation and cardiovascular events, has made them the ideal target for the development of new pharmacological tools by which to treat individual risk factors. However, as TZDs and fibrates only have an impact on individual components of MS, they exhibit undesirable side effects, particularly with the use of TZDs, and are ineffective against CVD.

Further studies are required in order to approach the role of the innate immune system in maintaining obesity, and the teleological reasons for obesity-dependent inflammation.

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