Gene expression of adipose tissue, endothelial cells and platelets in subjects with metabolic syndrome (Review)

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Abstract. Metabolic syndrome is a combination of medical disorders including hypertension, dyslipidemia, hyperglycemia, insulin resistance and increased waist circumference, and is associated with a higher risk of cardiovascular disease. An increase in adipose tissue mass is associated with the augmented secretion of certain adipokines, such as interleukin-6, tumor necrosis factor-α and resistin, which cause endothelial dysfunction (an increase in vasoconstrictor molecules and in the expression of adhesion molecules as well as a decrease of vasodilator molecules, amongst other features) and hemostasis alterations that also favor a prothrombotic state (increased fibrinogen and plasminogen activator inhibitor-1 concentrations and platelet activation/aggregation). This interaction between adipose tissue, endothelial cells and platelets is associated with an increase or decrease in the expression of several transcription factors (peroxisome proliferator-activated receptors, CCAAT-enhancer-binding proteins, carbohydrate responsive element-binding proteins and sterol regulatory element-binding proteins) that play a crucial role in the regulation of distinct metabolic pathways related to the metabolic syndrome. In the present review, we present the primary changes in adipose tissue, endothelial cells and platelets in subjects with metabolic syndrome and their possible target sites at the gene expression level.

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Contents

1. Introduction

Metabolic syndrome (MS) is a combination of pathophysiological changes that include arterial hypertension, insulin resistance, dyslipidemia and abdominal obesity (1). Previous studies have revealed that subjects with MS present a high risk of developing type-2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) (2). MS presents a prothrombotic state, a result of endothelial dysfunction and hypercoagulability produced by an imbalance between coagulation factors and the proteins that regulate fibrinolysis (3). The principal characteristic of endothelial dysfunction is a decrease in the bioavailability of nitric oxide (NO) at the vascular level, accompanied by other changes in the endothelial phenotype along with an increase in vasoconstriction and inflammation (4). As regards hypercoagulability, MS has also been found to present elevated levels of fibrinogen, vitamin K-dependent coagulation factors (FII, FVII, FIX and FX), factor XIII and von Willebrand factor (5). This increase in fibrinogen levels is proportional to the overexpression of GPIIb/IIIa and the size of the platelet aggregates (6).

This series of changes presented in MS (in which adipose tissue, endothelial cells and platelets are involved) favors the secretion of several molecular mediators (adipokines, cytokines and chemokines, amongst others) capable of activating or suppressing a number of transcription factors [peroxisome proliferator-activated receptors (PPARs), sterol regulatory element-binding proteins (SREBPs), carbohydrate responsive element-binding proteins (ChREBPs) and CCAAT-enhancer-binding proteins (C/EBPs)]; these transcription factors (depending on DNA-binding affinity, the recruitment of

co-activators and proteasomal degradation) regulate different MS-related metabolic pathways (7). To a certain extent, the action of agonists on these transcription factors varies the metabolic changes associated with MS (8).

This review presents the principal molecular aspects of MS and how these can become modifiable target sites through the action of the mediators produced by adipose tissue, endothelial cells and platelets.

2. Gene expression and the metabolic syndrome

The pathophysiological changes presented in MS are diverse and include endothelial dysfunction and hypercoagulability (9). Changes specifically associated with endothelial dysfunction include decreased synthesis of NO and prostacyclin, increased vascular cell adhesion molecule-1 (VCAM-1), soluble CD40 ligand (sCD40L), endoperoxide, reactive oxygen species (ROS) and endothelin-1 levels and asymmetric dimethylarginine (10). Changes in hemostasis and the fibrinolytic system, elevated plasma levels of plasminogen activator inhibitor-1 (PAI-1) (significantly associated with diastolic arterial pressure, triglycerides and waist-line circumference) and of fibrinogen (negatively associated with HDL-C) contribute to the expansion of CVD (11).

Dietary habits and physical activity are important factors of the first-line intervention for MS (12). However, there are key factors in MS regulation that depend on those transcription factors that, by responding and adapting to signals from the environment, are able to change the levels of relevant gene expression and thereby regulate energy expenditure, substrate metabolism and food consumption in MS (13,14). The genes expressed during the development of MS include various groups of genes: genes specific to adipose tissue, genes involved in the proliferation and differentiation of adipocytes and genes that code for insulin-receptor substrate proteins, amongst others (15).

To date, four families of nuclear receptors involved in MS have been described (16). These families correspond to those transcription factors that, when activated by ligands, bind to target gene regulatory regions and thus modulate the expression of MS (17). PPARs, C/EBPs, ChREBPs and SREBPs have been identified as regulators of distinct metabolic pathways during the transcription of genes expressed in MS (18). The following descriptions provide more background on each.

PPARs are transcriptions factors of a superfamily of nuclear receptors. Three isoforms exist: PPAR-α, PPAR-β (before PPAR-δ) and PPAR-γ (19). PPARs form heterodimers with the retinoid X receptor and, after ligand binding, modulate the downstream gene expression of target genes, which are translated into specific complexes that regulate proliferation, differentiation and cell survival (20). PPARs play a crucial role in the regulation of intermediary metabolism and inflammation, where their activity is not affected by phosphorylation resulting from p38-MAPK, PKA, PKC, AMPK and GSK3 (21,22).

The main components are PPAR-α and PPAR-γ, which also have a direct relation to hypertriglyceridemia and insulin resistance, respectively (23). PPAR-α participates in the initiation and development of atherosclerosis, promoting an increase in angiotensin II levels, oxidative stress and arterial pressure (24). PPAR-γ plays a fundamental role in adipogenesis (25), as a key regulator in the differentiation and function of adipocytes and the absorption of stored fatty acids (26). Additionally, it has been recently suggested that PPAR-γ is a key regulator of inflammatory and immune response (27). Mutations and single nucleotide polymorphism in PPAR-γ are associated with metabolic disease and inflammation (28). PPAR-β participates in the regulation of several metabolic pathways: metabolism of fatty acids, cellular respiration and the programming of muscle fiber types (29). It is particularly active in the regulation of the various genes involved in the inflammatory process (30).

C/EMPs are a family of transcription factors that feature a basic region leucine zipper domain (31). They participate in the differentiation of a wide range of cell types, with a key role in the regulation of cell proliferation via interaction with cell cycle proteins (32). Furthermore, they are important regulators of hepatic metabolism, affecting the expression of genes implicated in gluconeogenesis, glycogen storage and lipid metabolism (33). At least six members of this family have been isolated and characterized (34). Of these, C/EBP-α, β and δ are tissue-specific and highly expressed in adipose tissue. Additionally, C/EBP-α and β are expressed in the liver. Based on this, C/EBP-α, β and δ may represent potential targets for obesity and the metabolic changes that contribute to the development of MS (35).

ChREBP is a transcription factor that plays a critical role in the glucose-mediated induction of genes involved in glycolysis, lipogenesis and gluconeogenesis (36). Blood glucose levels affect the activity of ChREBP in hepatocytes largely via dephosphorylation (37), which increases its translocation to the nucleus, in order to stimulate lipogenic genes (38). During fasting, PKA and AMPK phosphorylate ChREBP, which inhibits its activity. During feeding, protein phosphatase 2 activates ChREBP during its dephosphorylation (39).

SREBPs constitute the major family of transcription factors regulating the expression of genes that encode the necessary enzymes for the biosynthesis of fatty acids and cholesterol (40,41). The activation of Akt induces the synthesis and accumulation of SREBP-1, necessary for the expression of fatty acid synthase, a key regulatory enzyme in the biosynthesis of lipids (42). The activation/degradation of SREBPs and the stability of this rate-limiting enzyme during the synthesis of lipids are both regulated by the ubiquitin-proteasome system in a sterol-dependent process (43). Insulin, by means of post-translational modification, activates the transcription and proteolytic maturation of the SREBP-1c present in the membranes of endoplasmic reticulum (44).

3. Gene expression of adipose tissue, endothelial cells and platelets during metabolic syndrome

An increase in the amount of free fatty acids participates in platelet activation and leads to an increase in the production of low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL). This, in turn, is associated with an increase in ROS yielding oxidized LDL (ox-LDL) and its subsequent accumulation in damaged subendothelium (45). Lipoproteins affect the platelet function through binding to specific receptors (CD36, SR-B1 and LOX-1) (46,47).

It is precisely the erosion or rupture of these lesions that provokes the platelet/endothelium interaction, whose communication at various levels is a key in the response to vascular

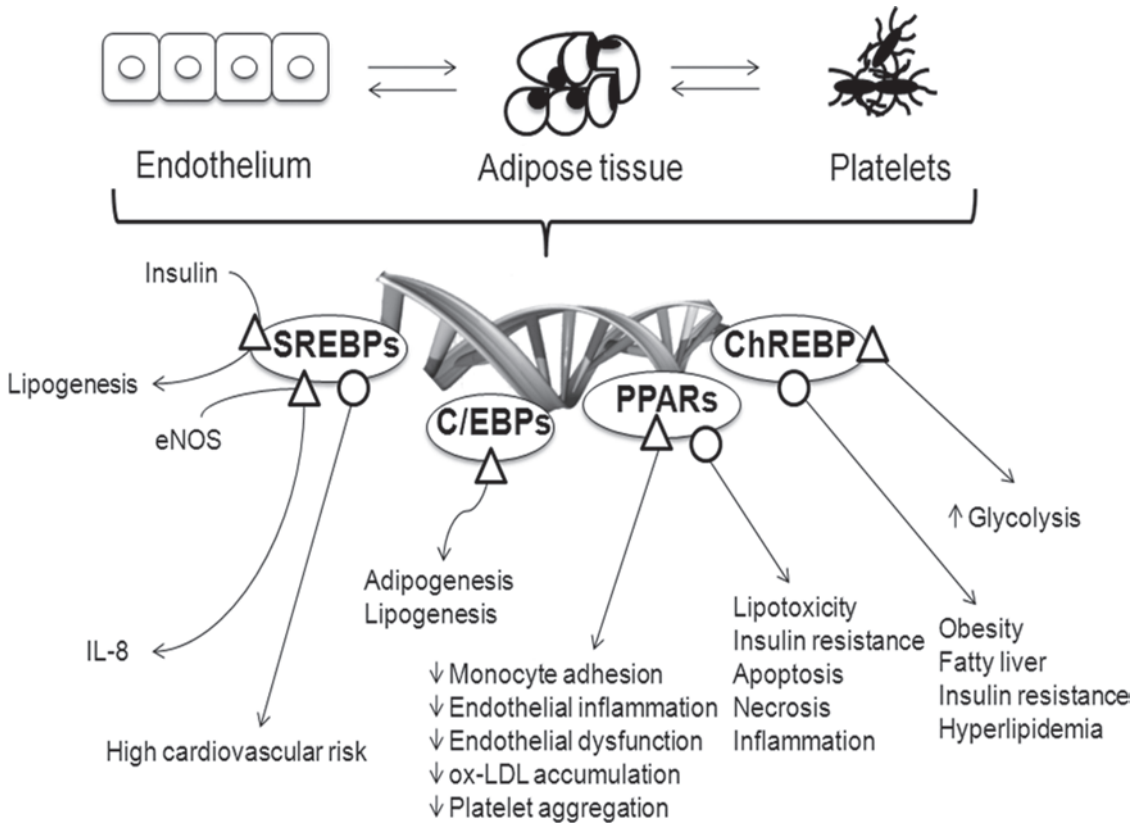

Figure 1. Molecular interactions and gene expression of adipose tissue, endothelial cells and platelets during metabolic syndrome. The triangle symbol indicates transcription factor activation and the circular symbol indicates suppression of the transcription factor. eNOS, endothelial nitric oxide synthase; IL-8, interleukin-8. SREBPs, sterol regulatory element-binding proteins; C/EBPs, CCAAT-enhancer-binding proteins; PPARs, peroxisome proliferator-activated receptors; ChREBP, carbohydrate responsive element-binding protein; ox-LDL, oxidized low-density lipoprotein.

damage (48). These interactions between adipose tissue, endothelial cells and platelets secrete a series of atherogenic and pro-inflammatory factors that have implications in the genetic expression of MS (Fig. 1) (49). The principle genetic expression present in adipose tissue, endothelial cells and platelets during MS is described below.

Adipose tissue and its gene expression in MS. In MS, adipose tissue secretes elevated quantities of adipokines, in particular tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and resistin (50), which contributes to insulin resistance during diabetes and obesity by inhibiting glucose uptake, glycogen synthesis and glucose oxidation (51).

The global burden of metabolic disease necessitates the development of new therapeutic strategies, in which the available alternative is to alter the main transcription pathways that regulate the absorption of glucose, lipid manipulation or adipokine secretion (52). Changes in the gene expression of adipose tissue suggest that carbohydrate modification affects the risk of CVD and T2DM (53). The gene expression in the adipose tissue of individuals with MS seems to be affected by changes in tissue morphology or insulin sensitivity, where a diet high in saturated fatty acids produces a pro-inflammatory state via the repression of PPARs (54). The exceptions to ligands for PPAR are short-chain fatty acids and long-chain monounsaturated fatty acids (55).

The maturation of adipocytes is regulated by a series of transcription factors, mainly PPAR-γ and C/EBP, which in conjunction regulate the expression of hundreds of proteins that participate in the metabolism and storage of lipids and, as such, the secretion of adipocytes (56). Adiponectin is a protein specific to adipose tissue with anti-inflammatory and anti-atherogenic properties (57,58). The double action of PPAR-α and PPAR-γ increases the action of adiponectin and the expression of its receptors, which results in an improvement in obesity and a reduction of the inflammatory process (59). On the contrary, the loss of function of PPAR-γ due to dominant mutations brings about a resistance to insulin and the early onset of severe hypertension (60).

A hyperglycemic state is the result of a minor expression of glucose transporter-2 (GLUT-2), which is related to a low expression of SREBP-1c (61). Glucose also stimulates ChREBP by dephosphorylation of specific amino acids (62), driving the activation of target genes that code for acetyl-CoA carboxylase, fatty acid synthase and liver-specifc pyruvate kinase (63). It has also been shown that ChREBP increases the expression of enzymes that participate in the fatty acid synthesis, such as stearoyl-CoA desaturase, which facilitates the conversion of glucose into fatty acids (64).

Endothelial cells and gene expression in MS. Endothelial dysfunction in MS appears to be the consequence of an increase in oxidative stress with a decrease in the bioavailability of NO (65). In addition to catalyzing NO production (66), endothelial NO synthase (eNOS) participates in the activation and increase in the transcription of

SREBP, which finally induces the expression of IL-8 (67). In combination, vascular endothelial growth factor (VEGF) mediates the activation of SREBP through its receptor in endothelial cells (VEGFR2), which is translated into the overexpression of IL-8 and the LDL receptor, accelerating the inflammatory process via the recruitment and adhesion of leukocytes and the accumulation of LDL in the subendothelial space, respectively (68,69).

On the contrary, PPAR-δ inhibits the production of ROS induced by TNF-α, while also stimulating the expression of important antioxidant enzymes (superoxide dismutase, catalase and thioredoxins), thereby acquiring a potential role in endothelial survival and proliferation (70). Within this same family of transcription factors, PPAR-α inhibits the overexpression of VCAM-1 and the hyperactivity of endothelial cells prior to stimulation with TNF-α (71). In addition, PPAR-γ (by inhibiting the activity of NF-κB and AP-1) suppresses the expression of chemokine genes (IFN-γ) and inhibits the expression of pro-inflammatory adhesion molecules (VCAM-1, ICAM-1 and E-selectin) with a decrease in the adhesion of monocytes to active endothelial cells (72). Consistent with this, heterozygous mice with a minor expression of PPAR-γ present with endothelial dysfunction and systolic hypertension (73). Additionally, transgenic mice with a recessive expression of PPAR-γ develop endothelial dysfunction in response to a high-fat diet (74).

Platelets and gene expression in MS. Platelets are small fragments of circulating cells that perform a critical role in the progress of CVD, T2DM, inflammation and metastasis of cancerous cells (75). Numerous biochemical abnormalities have been found that correlate with the platelet hyperactivity in MS (76), apparently where hyperglycemia seems to promote platelet hyperactivity and increases the overexpression of glycoproteins (77). This, in turn, brings about the production of thromboxane A2 with increased platelet sensitivity (76).

Despite their absence of nucleus, selective agonists for their nuclear receptors (principally PPARs) regulate platelet activation and aggregation (78). PPAR-β is present in platelets, by action of the synergistic effect between prostacyclin and NO, decreases the inflammatory process and delays the formation of atheromatous plaque, thus attenuating the progression of atherosclerosis (79). Another transcription factor present in platelets is PPAR-γ, which, in response to two natural ligands [lysophosphatidic acid and 15-deoxy-δ 12 14-prostaglandin J2 (metabolite of prostaglandin-d)], attenuates the release of pro-inflammatory mediators, such as sCD40L and thromboxane A2 (80). Furthermore, PPAR-γ agonists inhibit the platelet aggregation induced by collagen by modulating the signal pathways of GPVI (81). On the contrary, the transitory activation of the genes that express PAI-1 via the activation of PPAR-γ in fatty liver disease could be implicated in the increased risk of CVD due to a decrease in fibrinolytic activity (82). PPAR-α performs biological functions not only in the liver, but also in the skeletal muscle, heart, endothelial cells, platelets, macrophages and lymphocytes (83). Activators of PPAR-α provide vascular protection by suppressing the production of platelet-derived growth factor as much as in megakaryocytes as platelets (83).

4. Conclusion

MS is a pathophysiological state characterized by insulin resistance, dyslipidemia and arterial hypertension, with a major predisposition for T2DM and CVD. The main molecular alterations present in MS create a pro-inflammatory state which, along with increased free fatty acids in adipose tissue, favors the oxidation of LDL and its accumulation in the subendothelium. This vascular environment produces a state of platelet hyperreactivity, favoring the formation of arterial thrombosis. Indeed, the molecular interactions of adipose tissue, endothelial cells and platelets and their participation in gene expression represent important pathophysiological aspects of MS. The expression of PPARs, C/EBPs, ChREBP and SREBPs depends on their DNA-binding affinity, proteasomal degradation and on activators or repressors developed by adipose tissue, endothelium and platelets during MS. Ultimately, these findings indicate that the transcription factors may represent valid, modifiable binding sites where their controlled regulation can be translated into the gradual improvement of MS.

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