

Review Article

Molecular Targets Related to Inflammation and Insulin Resistance and Potential Interventions

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Received 6 July 2012; Revised 13 September 2012; Accepted 13 September 2012

Academic Editor: Hartmut Jaeschke

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Inflammation and insulin resistance are common in several chronic diseases, such as obesity, type 2 *diabetes mellitus*, metabolic syndrome, cancer, and cardiovascular diseases. Various studies show a relationship between these two factors, although the mechanisms involved are not completely understood yet. Here, we discuss the molecular basis of insulin resistance and inflammation and the molecular aspects on inflammatory pathways interfering in insulin action. Moreover, we explore interventions based on molecular targets for preventing or treating correlated disorders, advances for a better characterization, and understanding of the mechanisms and mediators involved in the different inflammatory and insulin resistance conditions. Finally, we address biotechnological studies for the development of new potential therapies and interventions.

1. Crosstalk between Inflammatory Pathways and Insulin Signaling

1.1. Mechanism of Insulin Action. Insulin receptor is a tetramer protein composed by two extracellular α subunits and two transmembrane β subunits. The α subunits have a binding site to insulin while the β subunits contain an intrinsic tyrosine kinase activity towards intracellular side. Insulin binding to the α subunit leads to a conformational change and activation of the β subunit, resulting in tyrosyl autophosphorylation of the insulin receptor. After being activated and phosphorylated, several intracellular docking proteins bind to the insulin receptor and are also tyrosyl phosphorylated, including insulin receptor substrates 1 and 2 (IRS-1 and IRS-2) [1, 2], Src homology collagen (SHC), and associated protein substrate (APS) [3]. IRS proteins are the major and better characterized proteins involved in insulin signaling. These proteins activate several signaling pathways involved in the regulation of important cellular events such as glucose uptake and metabolism, protein synthesis, gene expression, cell survival, growth, development, and differentiation [4–6]. IRS proteins are phosphorylated on

various tyrosine residues of the C-terminal region, generating specific sites for binding of proteins containing Src homology-2 (SH2) domains, including phosphatidylinositol-3 kinase (PI-3K), Nck, and Grb-2. PI-3K is composed by a catalytic subunit (p110) and a regulatory subunit (p85). This kinase is an important signaling molecule, mediating metabolic effects of the insulin. Binding of p85 subunit to phosphorylated tyrosine residues of IRS proteins leads to activation of the catalytic activity of p110 subunit and subsequent increase in the generation of phosphatidylinositol 3,4-bisphosphate (PIP2) and phosphatidylinositol 3,4,5-trisphosphate (PIP3) content. Downstream proteins from PI3 K pathway comprehend several serine/threonine kinases, for example, phosphoinositide-dependent protein kinase-1 (PDK-1), protein kinase B (PKB, also known as Akt), protein kinase C (PKC), p70 S6 kinase (p70S6K), and glycogen synthase kinase-3 (GSK-3). These kinases are involved in the most important biological effects induced by insulin, such as translocation of glucose transporter-4 (GLUT-4) from intracellular vesicles to plasma membrane, glycogen and protein synthesis, antiapoptotic effects, and gene expression (Figure 1) [7–11].

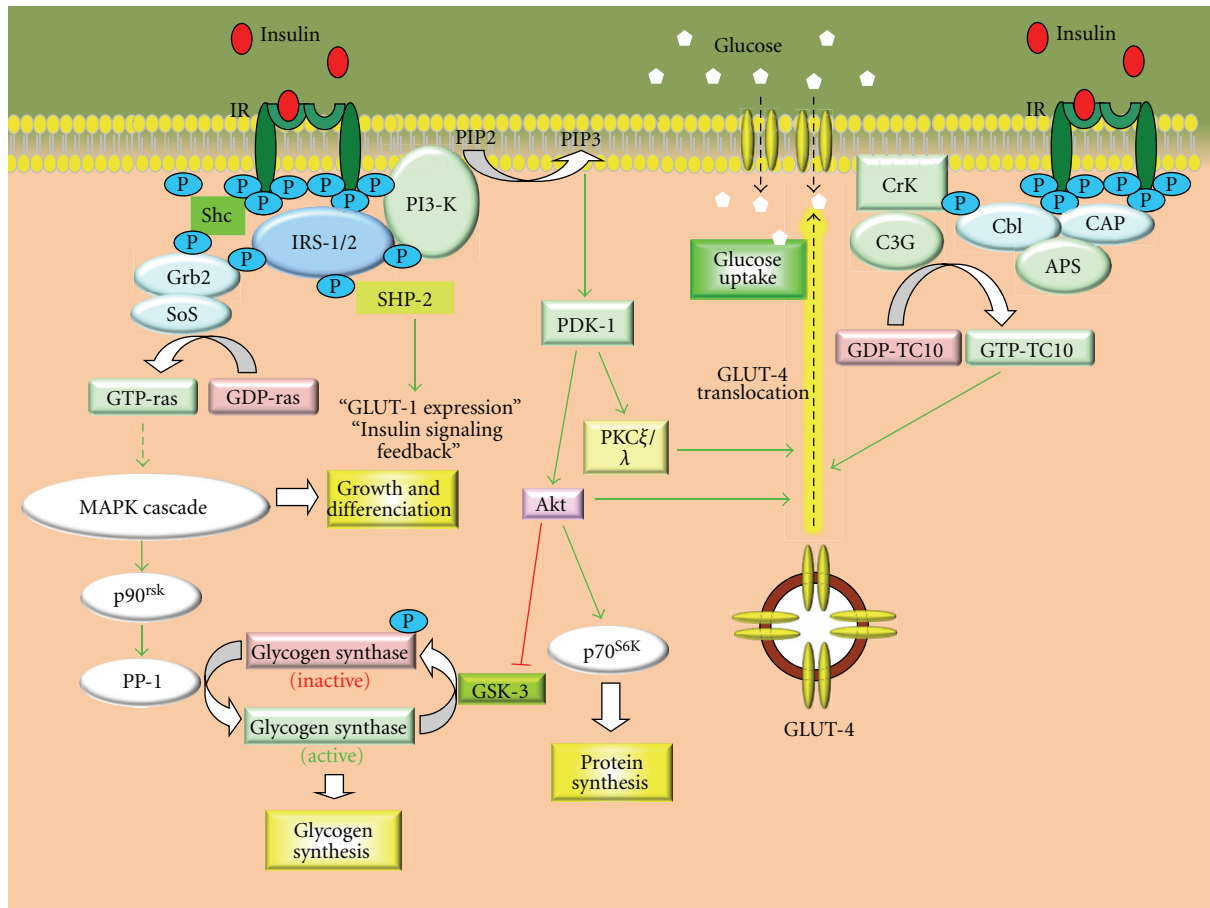


FIGURE 1: Summary of the main insulin signaling pathways. GLUT-1 and -4: glucose transporter-1 and -4; Grb-2: growth receptor binding-2; GSK-3: glycogen synthase kinase-3; IR: insulin receptor; IRS-1 and -2: insulin receptor substrate-1 and -2; MAPK: mitogen-activated protein kinase; PDK-1: phosphoinositide-dependent kinase-1; PIP2: phosphatidyl-inositol diphosphate; PI3: phosphatidyl-inositol triphosphate; P: phosphate; PKC: protein kinase C; PP-1: phosphoprotein phosphatase-1; p70S6K: protein 70 S6 kinase; p90rsk: protein 90 ribosomal S6 kinase; Shc: Src homology collagen; SHP-2: phosphatase with Src homology 2 domain; SoS: Son of Sevenless.

Other signaling pathways involved in the glucose uptake induced by insulin start with the recruitment of APS to the activated insulin receptor and subsequent association and tyrosine phosphorylation of Cbl, which interacts with Cbl associated protein (CAP) through an SH3 domain and with flotillin, a constituent of lipid raft, through a sorbin domain. The complex CrkII/C3G then binds to the phosphorylated tyrosine residues of Cbl, activating the C3G activity that exchanges GDP for GTP of TC10, a small G-protein that belongs to the Rho family. After being activated, TC10 participates in the GLUT-4 translocation (Figure 1) [12–16].

Mitogen-activated protein kinase (MAPK) cascade starts with the association of Shc to insulin receptor, binding of Grb-2 to Shc or to IRS-1, and formation of the Grb-2/SoS (Son of Sevenless) in the plasma membrane [17–19]. This complex leads to the activation of c-Ras and raf, starting the MAPK cascade [20]. MAPK pathway is involved in the differentiation, cell growth, and development induced by insulin [21], as well as some metabolic effects, as glycogen synthesis and GLUT-4 translocation to plasma membrane (Figure 1) [22–24]. However, this cascade is not enough or even required to this later effect [25].

Disturbances in several proteins involved in the insulin signaling pathways have been found in different conditions of insulin resistance, including obesity, type 2 *diabetes mellitus*, metabolic syndrome, cardiovascular diseases, inflammatory disorders, and cancer [26–28]. Here, we will discuss possible mechanisms involved in the development of insulin resistance related to inflammatory processes.

1.2. Molecular Basis of Insulin Resistance. Insulin resistance occurs when the insulin-sensitive tissues, mainly skeletal muscle, adipose tissue, and liver, lose the ability to respond properly to the hormone [29, 30]. It is associated with several chronic diseases, especially those linked to obesity, such as type 2 *diabetes mellitus*, metabolic syndrome, dyslipidemias, cardiovascular diseases, cancer, and neurodegenerative diseases [31–33]. However, the precise mechanisms involved in insulin resistance are not fully understood yet [34–37]. Several factors have been proposed to participate in the development of insulin resistance, including increased plasma-free fatty acid level, subclinical chronic inflammation, oxidative and nitrative stress, altered gene expression, and mitochondrial dysfunction [29, 37].

Since free fatty acids are elevated in obesity and related diseases, these metabolites have been proposed to be responsible for the impairment in the insulin action, but the mechanisms are not completely known yet [38, 39]. High availability of fatty acids, specially long-chain saturated fatty acids, results in the establishment of insulin resistance in liver, skeletal muscle, and adipose tissue [40, 41]. Various hypothesis have been proposed to explain the insulin resistance induced by saturated fatty acids, including Randle cycle, oxidative stress, modulation of gene transcription, inflammation, accumulation of intracellular lipid derivatives (diacylglycerol and ceramides), and mitochondrial dysfunction [42–47] (for review, see Martins et al. [37]).

A chronic state of inflammation in the insulin responsive tissues is a major contributor to insulin resistance in obesity and related diseases. Thus, a crosstalking between inflammation and insulin resistance has been suggested by several authors. However, the precise mechanism as well as the mediators involved in this interaction is not completely defined yet. In this paper, we discuss how inflammatory signaling pathways impair insulin signaling (see below).

Intracellular redox balance is a finely regulated process that involves several generating pathways and degrading systems. Physiologically, ROS participate in important biological responses, but accumulation of these molecules leads to oxidative stress condition [48]. ROS are highly oxidant molecules that can oxidize various intracellular components, including membrane phospholipids, proteins, and DNA [49, 50]. Usually, these reactions cause cellular damage, reducing the function of oxidized biomolecules. In insulin resistance, increased ROS production and/or decreased ROS degradation is observed, leading to an oxidative stress condition [51] and activation of signaling pathways related to stress. There is evidence that oxidative stress is also involved in muscle disorders, contributing to the insulin resistance process. Transgenic mice expressing human ubiquitin protein E3 ligase, a protein that binds and promotes degradation of superoxide dismutase-1, resulting in reduced superoxide degradation and consequently oxidative stress, present muscle dysfunction (atrophy and sclerosis) [52].

Activation of signaling pathways to stress has been suggested to participate in the development of insulin resistance by impairing the signaling by this hormone. Several serine/threonine kinases activated by oxidative stress pathways, including JNK, PKC, GSK-3, NF- κ B, and p38 MAPK, have been suggested to impair insulin signaling pathways [53, 54], as described below.

Expression of several genes is also altered in insulin resistance conditions. For example, expression of genes involved in lipid and glucose metabolism, insulin signaling, inflammation, redox balance, and mitochondrial function is modified, suggesting that these processes participate in the pathophysiology of insulin resistance [55–57]. Disturbed mitochondrial function has been suggested to have a central role in these alterations, since this organelle participates in all these processes (for review, see Martins et al. [37]).

1.3. Molecular Basis of Inflammation. Inflammation is a coordinated process evoked by the tissues in response to

noxious stimuli or conditions including the presence of infection, tissue injury, or malfunction. The inflammatory response is activated by molecules released by microorganisms including microbial associated molecular patterns (MAMPs) such as lipopolysaccharide, flagellin, and peptidoglycans or produced/released by host cells including intracellular components, the so-called damage-associated molecular patterns (DAMPs), of which, HMGB1, DNA, and nucleotides are part. These inducers of inflammation bind to their respective receptors and activate biological responses by the resident cells, mainly, macrophages and mast cells. These cells act directly or indirectly on the vasculature and on leukocytes to induce, among other effects, the migration of leukocytes and extravasations of plasma proteins to the tissues [58].

Several receptors have been demonstrated to act as cell sensors of damage or infection. Examples of proteins with this function include the receptors of the toll-like (TLRs) family, the C-type lectin receptors, the purinergic and advanced glycation endproducts receptors (RAGE), and the intracellular nucleotide oligomerization domain (NOD), and retinoic acid-inducible gene (RIG)-I-like receptors (RLRs). After recognizing their ligands, several downstream pathways including c-Jun NH(2)-terminal kinase (JNK) and I κ B kinase complex (IKK) are activated, resulting in changes on transcription factors activity and expression of proteins such as cytokines, enzymes, chemokines, adhesion molecules, and amplification of the inflammatory response.

The activation of the inflammatory pathways described above is a hallmark of obesity, and it has been associated with the development of insulin resistance, atherosclerosis, and other tissue dysfunctions that are secondary to fat accumulation. An increased production of inflammatory mediators and activation of inflammatory pathways in several tissues including adipose tissue (AT), liver, pancreas, skeletal muscle, and hypothalamus are present in obese individuals [59] and define a subclinical inflammatory process also known as “meta-inflammation” (metabolically induced inflammation) [60].

In opposition to other inflammatory conditions, little information is available regarding the inducers and sensors involved in obesity-associated inflammation. In this respect, some hypotheses to explain the initial activation/recruitment of leukocyte to the tissues (mainly, AT) have been proposed. The release of DAMPs by necrotic adipose cells, the increase in the flux of nonesterified fatty acids (increased rates of lipolysis), the reduction in the oxygen tension (hypoxia) leading to activation of hypoxia-induced factor (HIF)-1, which controls the expression of proinflammatory proteins, and the production of chemokines by adipose cells have been suggested to play a role in the initiation of inflammatory process [61]. Despite several advances in the field, the initial events involved in the beginning of inflammation in the AT and the complex interactions between them are not clearly understood, and new components are continuously described and added to the puzzle such as leukotrienes and the apoptosis inhibitor of macrophage (AIM) [62, 63]. This latter protein has been shown to stimulate lipolysis in adipocytes. The release of fatty acids, through interaction

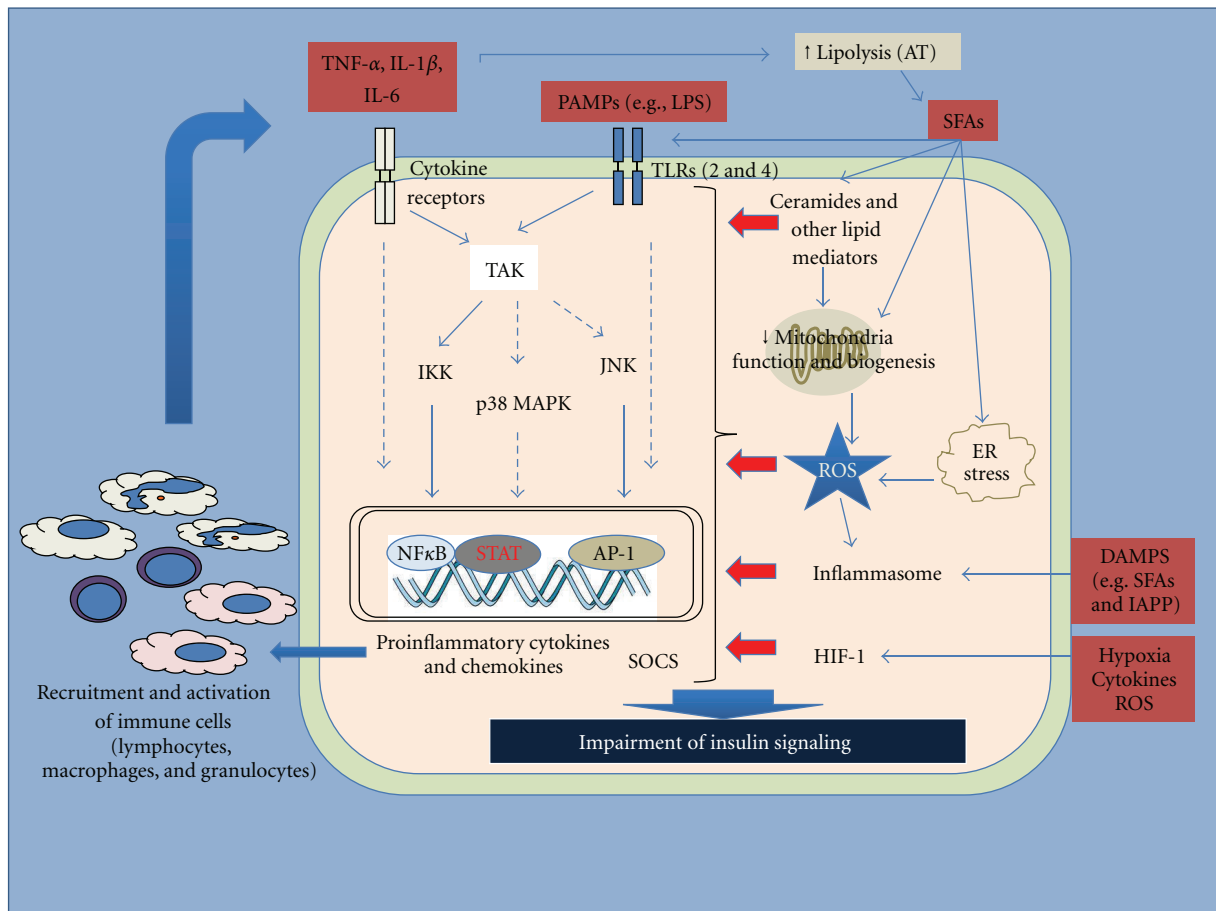


FIGURE 2: Inflammatory pathways activated during obesity and their cross talk with insulin signaling. Different signals act directly through membrane (e.g., toll-like receptors [TLRs] and cytokine receptors) and intracellular proteins (inflammasomes) or indirectly by their effect on cell organelles such as mitochondria and endosomal reticulum and generation of metabolites (e.g., ceramides and other lipid mediators) to activate inflammatory pathways. Transcription factor such as nuclear factor κ B (NF κ B), activator protein-1 (AP-1), and signal transducers and activators of transcription (STAT) are activated downstream to these pathways and lead to the expression of proteins that inhibit insulin signaling and induce a pro-inflammatory state by recruiting and activating immune cells. AT, adipose tissue; DAMPS, damage associated molecular patterns; ER, endoplasmic reticulum; HIF-1, hypoxia factor-1; IAPP, islet amyloid polypeptide; PAMPs, pathogen associated molecular patterns; ROS, reactive oxygen species; SFAs, saturated fatty acids; SOCS, suppressor of cytokine signaling; TAK, transforming growth factor β -activated kinase.

with TLR4, induces the expression of chemokines that lead to macrophage recruitment [63].

The obesity-induced inflammation is associated with activation of resident cells such as Kupffer cells in the liver [64] and leukocyte infiltration and shift in the polarized state of tissue/recruited leukocytes. These changes are better characterized in the adipose tissue, in which an increased infiltration by proinflammatory M1-type macrophages (classical macrophages), Th1, Th17 and CD8⁺T cells and a reduction in the content of less inflammatory cells such as M2-macrophage, T reg, and Th2 cells were demonstrated [65–68]. The overproduction of inflammatory mediators by the infiltrating cells together with changes in adipokines production and NEFA release by AT contribute to the tissue dysfunctions observed in obesity, as discussed below.

1.4. Relationship between Inflammation and Insulin Resistance. Several chronic diseases are characterized by increased inflammatory process and insulin resistance, such as obesity, type 2 diabetes mellitus, metabolic syndrome, cardiovascular diseases, and cancer [50]. The relationship between these two factors has been proposed by several authors. For example, various studies suggest the involvement of some inflammatory factors in the development of insulin resistance, including cytokines (TNF- α , IL-1, IL-6), ROS, and RNS (Figure 2). These factors lead to the activation of signaling pathways that ultimately impair insulin signaling (see below). In addition, other factors involved in inflammatory processes also can impair insulin sensitivity, particularly lipopolysaccharides (LPSs) and environmental stress (hypoxia, nutrients, and pH) (Figure 2).

TLRs comprehend a family of receptors involved in the recognition of microbes. It has been demonstrated that fatty acids, specially saturated fatty acids, are able to activate TLR-4 in skeletal muscle cells, resulting in increased activity of IKK and JNK. The first kinase degrades the inhibitor of κ B ($I\kappa$ B α), resulting in the nuclear factor- κ B (NF κ B) release and migration to the cell nucleus, where it induces the transcription of proinflammatory genes. The second kinase activates members of the signal transducers and activators of transcription (STAT) family, which are involved in several biological effects, such as expression of genes related to inflammation, apoptosis, differentiation, growth, morphogenesis, migration, and proliferation [69]. Both JNK and IKK β have been proposed to be the mediators of insulin resistance induced by saturated fatty acids (Figure 2). It has been shown that these kinases phosphorylate serine residues on IRS proteins, blocking IRS phosphorylation on tyrosine residues by the activated insulin receptor [70] and consequently inhibiting insulin effects [71]. Moreover, phosphorylation on serine/threonine residues also increases IRS protein degradation, contributing to the establishment of insulin resistance [71–73].

These effects are confirmed by several studies involving gene manipulation. Nonfunctional TLR-4 expression protects mice from insulin resistance and inflammation induced by high-fat diet [74], and TLR-4 gene silencing by small interference of RNA reduces inflammation in acute lung injury induced by lipopolysaccharide [75]. Obese and type 2 diabetic animals are prevented from insulin resistance and inflammation by specific inhibitors or gene mutation (knockout or nonfunctional gene) of IKK or JNK [76–78].

Possible mediators of inflammation and insulin resistance are the fatty acids. These metabolites have been linked to the establishment of inflammatory process, by modulating several signaling pathways related to inflammation. For example, fatty acids can directly activate toll-like receptors (TLRs), G-protein coupled receptors (GPCRs), and tumor necrosis factor- α (TNF- α) receptor as well as modulate inflammatory signaling pathways involved in the increase in cytokine secretion (TNF- α , IL-1 β , and IL-6) [60, 79, 80], oxidative and nitrative stress, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and proinflammatory gene expression. Alterations in the expression of genes and proteins involved in the inflammatory process are clearly associated with insulin resistance and several metabolic abnormalities, including mitochondrial dysfunction, decreased fat oxidation, increased ectopic lipid storage, and impaired insulin signaling pathways (Figure 2) [81].

Proinflammatory cytokines were also involved in the reduction of mitochondrial function [79, 82]. Palmitate-stimulated IL-1 β production in macrophages occurs via NLRP3-ASC inflammasome and participates in the mitochondrial dysfunction induced by this fatty acid. This dysfunction is also observed when the cells are exposed to other cytokines, such as TNF- α or IL-6 [83, 84].

Therapies aimed at neutralizing proinflammatory cytokines such as TNF- α and IL-1 β , such as the monoclonal antibody infliximab and canakinumab, respectively, have been under investigation in the treatment of type 2 diabetic

patients. Considering anti-TNF antibodies, the results are disappointing as many clinical trials in type 2 diabetic patients have failed to demonstrate an effect of TNF neutralization on insulin sensitivity [85–89]. On the other hand, in patients with high grade inflammatory diseases such as rheumatoid arthritis and ankylosing spondylitis, anti-TNF therapy has been successfully associated with reduction in insulin resistance and metabolic syndrome components [90–95]. The molecular mechanisms of TNF- α blockade on insulin signaling were related to reduction in IRS-1 serine phosphorylation and increase in AKT phosphorylation in peripheral mononuclear cells from rheumatoid arthritis patients [95].

Potential effects of IL-1 β blockade on insulin sensitivity are current under investigation in humans. The long-term effects of anti-IL-1 β therapy are now examined in the large phase III clinical trial CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) [96]. The study included and treated 17,200 patients with various doses of anti-IL-1 β antibody every 3 months and followed up over 4 years. The primary endpoint of the CANTOS study will be cardiovascular events, and secondary endpoints include new onset type 2 diabetes and diabetes-specific markers. Such large and long-term trials could provide a novel cytokine-based therapy for the secondary prevention of new-onset diabetes as well as confirm the autoinflammatory nature of metabolic disorders.

Another potential molecular target for treatment of inflammatory diseases is JNK. This kinase regulates both the development of insulin resistance and inflammation. However, identification of pharmacologically potent and selective small molecule JNK inhibitors has been limited. Compound A, a reversible ATP-competitive aminopyridine inhibitor of JNK, was developed by Pfizer. Testing this compound in obese mice decreased their body weight as well as blood glucose and triglyceride concentrations and increased insulin sensitivity to levels comparable to those in lean control mice [97]. A substrate competitive inhibitor of JNK, BI-78D3, has also been shown to restore insulin sensitivity in a murine model of type 2 diabetes after a single dose [98]. A more recent drug discovery is the compound 19, a potent and selective dual substrate and ATP-competitive JNK bidentate inhibitor [99]. Glucose intolerant NONcNZO10/LtJ mice were injected intraperitoneally daily for four days with 25 mg/kg 19, and this compound was remarkably effective in restoring normoglycemia without inducing hypoglycemia compared to the vehicle control. These studies demonstrate that inhibition of JNK is an effective strategy to ameliorate insulin resistance. However clinical trials are needed to test these compounds in humans and show their efficacy and long-term toxicity.

2. Identification of New Molecular Targets for Reducing Inflammation in Insulin Resistance Models

2.1. GPCRs. G-protein coupled receptors (GPCRs) constitute a family of membrane proteins characterized by

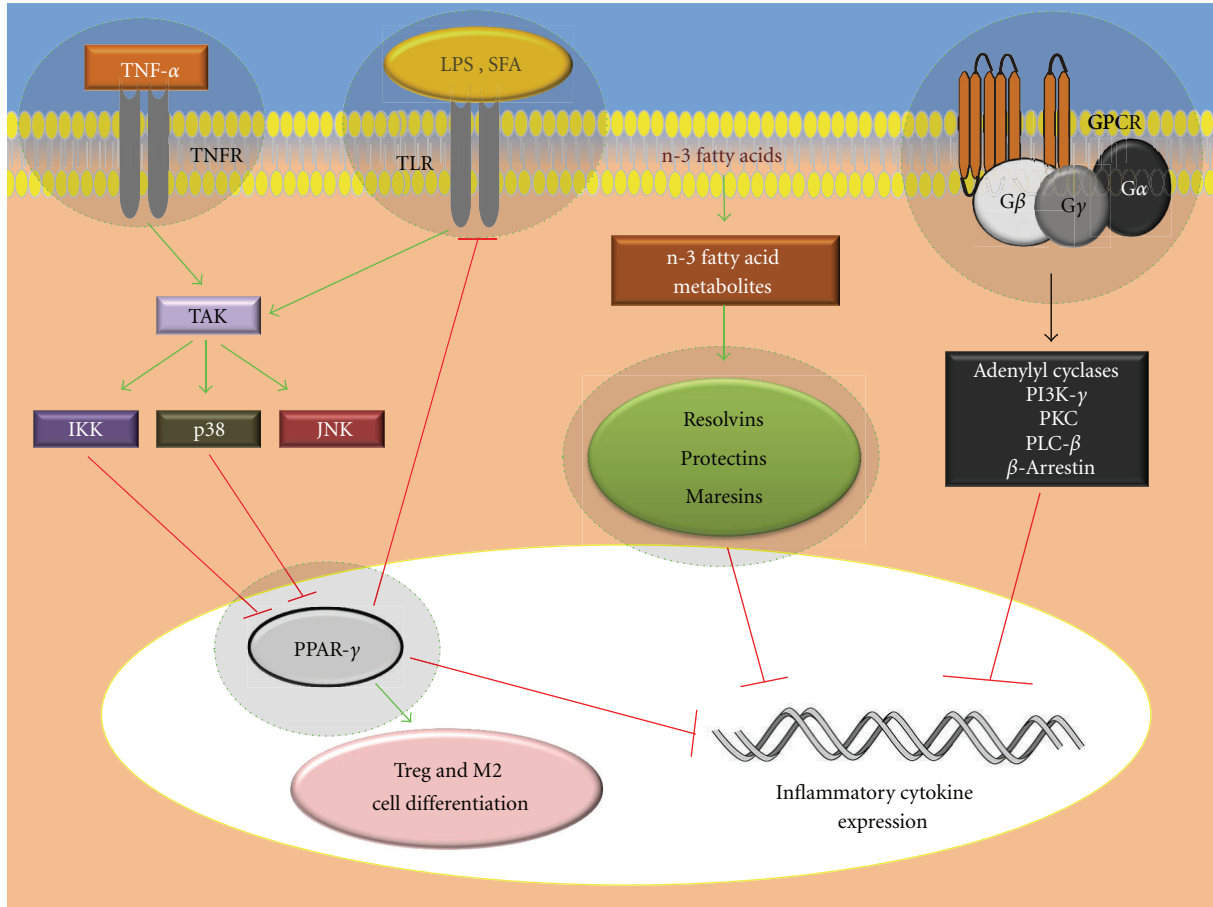


FIGURE 3: Potential molecular targets for reducing inflammation in insulin resistance conditions. Circulated proteins and lipid mediators are included as potential targets. Resolvins, protectins, and maresins are lipid mediators generated from n-3 fatty acid metabolism that have potent anti-inflammatory and immunoregulatory actions, promoting decreased inflammatory cytokine expression. Toll-like receptors (TLRs) are transmembrane receptors that are activated by saturated fatty acids (SFAs) and lipopolysaccharides (LPSs) inducing inflammatory responses. TLRs activate intracellular pathways that inhibit the peroxisome proliferator-activated receptor- γ (PPAR- γ) activity). This transcriptional factor is involved with decreased inflammatory cytokine expression and increased Treg cell differentiation. Other cytokines, including tumor necrosis factor- α (TNF- α), also promote PPAR- γ inhibition. G-protein coupled receptor (GPCR) activation may attenuate the production of TNF- α , interleucin-6 (IL-6) and macrophage chemoattractant protein-1. GPR120 is a GPCR activated by n-3 fatty acids in insulin resistance models. COX: cyclooxygenase; IKK: I κ B kinase; JNK: c-Jun NH(2)-terminal kinase; PI3K- γ : phosphatidylinositol 3-kinase- γ ; PKC: protein kinase C; PLC- β : phospholipase C- β .

a common motif, the seven transmembrane domains. Ligand binding to these receptors leads to conformational changes in the receptor and activation of intracellular guanine nucleotide-binding proteins (G-proteins). Several enzymes including adenylyl and guanylyl cyclases, phospholipases A2 and C, phosphodiesterases and phosphatidylinositol 3-kinases (PI3Ks) and other intracellular transduction cascades are triggered downstream to these receptors. These pathways affect both the insulin signaling and the inflammatory proteins expression (Figure 3).

In the recent years, new GPCRs were described and deorphanized. Several of these receptors have been shown to regulate insulin secretion and tissue sensibility to this hormone, becoming potential targets for intervention in conditions of insulin resistance/deficiency. In this paper, we will briefly discuss a class of GPCRs that share in common the fact of being activated by fatty acids (FAs-GPCRs). Other

GPCRs implicated in the glucose metabolism and regulation of inflammation such as GLP-1, glucose-dependent insulinotropic polypeptide (GIP), the bile acid (TGR5), cholecystokinin, the cannabinoid receptors (CBs), and muscarinic receptors are beyond the focus of the present paper and are discussed elsewhere. Proteins that regulate GPCRs signaling such as GPCR kinases and arrestins, which are implicated in the control of food intake, regulation of insulin action, inflammation, adipogenesis, and other processes that are associated with weight gain and development of insulin resistance, are the focus of recent reviews [100, 101], so they are not discussed here.

The FAs-GPCRs receptors, which include the GPRs 40, 41, 43, 84, 119, and 120, present distinct ligand specificity and tissue distribution [102]. These receptors play a relevant role in physio- and pathological conditions [102]. Regarding their participation in the glucose metabolism, it has been

demonstrated that their activation (at least, GPR40 and GPR119) directly stimulates insulin secretion by β -cells and protects these cells from gluco- and lipotoxicity (GPR40) [103, 104]. Activation of FAs-GPCRs induces also the release of gut-derived hormones including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [105–109]. These latter two-gut-derived hormones not only modulate the gastrointestinal functions such as motility, but also the insulin secretion and food intake. In addition to these effects, FAs-GPCRs, mainly, GPR43, 84, and 120, present relevant effects in the inflammatory cell activation [102]. In this sense, activation of GPR120 and β -arrestin 2 by n-3 fatty acids (docosahexaenoic and α -linolenic acids) attenuates the production of TNF- α , IL-6, and macrophage chemoattractant protein-1 (MCP-1, also known as CCL2). This anti-inflammatory effect seems to be important for the beneficial action of these fatty acids in the model of obesity induced by high-fat diet, preventing development of glucose intolerance, insulin resistance, and obesity [110].

Altogether the findings herein discussed highlight the importance of these receptors for glucose homeostasis, control of inflammatory cells activation, and food intake, processes that are linked through complexes interaction, which are not completely understood.

2.2. Histone Deacetylases. Histone deacetylase (HDAC) is a family of enzymes that together with the histone acetyltransferases (HATs) controls the degree of protein acetylation. Inhibition of HDAC activity by different compounds (e.g., short chain fatty acids such as butyrate, valproic acid, trichostatin A, and other compounds) increases the acetylation of histone and nonhistone proteins including NF κ B, MyoD, p53, and N-FAT [111] and, consequently, affects gene expression and proteins activities leading to changes in different aspects of cell biology including cell motility, proliferation, differentiation, and apoptosis.

In addition to their well-known anti-inflammatory effects [112], other recent evidence has been obtained, which together strongly indicates HDAC as a target for novel therapies in insulin resistance and diabetes.

- (i) Histone hyperacetylation has been associated with an increase in insulin expression and protection of β -cells against cytokine-induced apoptosis, as reviewed by Christensen et al. [113].
- (ii) The isoforms 4, 5, and 9 of HDAC are associated with the development of β and δ cells of the pancreas [48].
- (iii) Oral administration of HDACi (ITF2357) reduced β -cells toxicity associated with streptozotocin administration. Additionally, the authors also showed that this HDACi protected islets from cytokine-induced toxicity and reduced production of NO and chemokines in islets [114];
- (iv) Administration of sodium butyrate (diet supplementation or oral tributyrin (a prodrug of butyrate)) to high-fat fed mice attenuated body weight gain, improved lipid and glucose metabolism parameters, and inhibited the development of obesity-associated

changes including activation of inflammatory pathways and hepatic steatosis [115, 116]. Recently, it has been suggested that this effect of butyrate involves inhibition of HDAC 3 activity, an effect that leads to activation of PPAR- α and expression of FGF21, which stimulates lipid oxidation, triglyceride clearance, and energy expenditure [117];

- (v) HDAC 6 knockout mice are protected from hyperglycemia, glucose intolerance, and insulin resistance secondary to chronic corticoid administration [118];
- (vi) HDACi increases the number of T regulatory cells and their suppressive function, an effect that may be important in the context of adipose tissue inflammation [119, 120].

2.3. Peroxisome Proliferator-Activated Receptor- γ (PPAR- γ).

PPAR- γ receptor activation has been shown to have significant effects on increasing insulin sensitivity in fat and muscle cells. It improves glucose metabolism and reduces inflammation (Figure 3) [121] and has a crucial role in adipocyte differentiation. PPAR- γ is a nuclear receptor that acts as a transcription factor upon activation, by regulating the transcription and expression of specific genes such as adipokines. There are two isoforms of PPAR- γ : PPAR- γ 1 and PPAR- γ 2. PPAR- γ 1 is expressed ubiquitously and PPAR- γ 2 is mainly expressed in adipocytes.

Several studies have demonstrated the anti-inflammatory activities of PPAR- γ . Inhibition of PPAR- γ function by inflammatory cytokines may contribute to pathogenesis of many diseases such as insulin resistance, atherosclerosis, inflammation, and cancer cachexia [122–124]. Its inhibition by TNF- α is involved in inflammation pathogenesis characteristic of insulin resistance. Activation of serine kinases including IKK, ERK, JNK, and p38 may be involved in the TNF regulation of PPAR- γ (Figure 3) (reviewed in [125]). IKK acts through at least two mechanisms: inhibition of PPAR- γ expression [126] and activation of PPAR- γ corepressor [127].

In macrophages, where PPAR gamma is also expressed, it inhibits TLR and IFN- γ mediated inflammatory responses. In obesity, macrophages invade adipose tissue promoting the inflammation characteristic of insulin resistance [128]. Therefore, macrophage PPAR- γ function gained considerable pharmacological interest [129]. Diet-induced obesity influences the state of adipose tissue macrophages from an M2-polarized state (that protects adipocytes from inflammation) to an M1 proinflammatory state. Studies have demonstrated that this obesity-induced phenotypic alteration of macrophage polarization is orchestrated by PPAR- γ [130]. These researchers demonstrated that PPAR- γ is required for the maturation of alternatively activated macrophages (M2 macrophages) by using mice with specific macrophage deletion of PPAR- γ .

Prolonged nutrient excess promotes the accumulation and activation of leukocytes in visceral adipose tissue and other tissues, leading to metabolic abnormalities such as insulin resistance. Cipolletta et al. [131] showed that PPAR- γ is involved with adipose tissue-specific lymphocyte

accumulation and activation, leading to cell differentiation. T regulatory cells (Tregs) are a small subset of T lymphocytes, normally constituting only 5–20% of the CD4⁺ compartment. These cells are thought to be one of the most critical defenses against excessive immune responses, avoiding autoimmunity, allergy, inflammation, infection, and tumorigenesis [132, 133]. Typically, Tregs control other T cell populations, but can also influence the activities of innate immune system cells. Treg cells are characterized by high-level expression of the forkhead/winged-helix transcription factor, Foxp3. Cipolletta et al. [131] have demonstrated that PPAR- γ collaborates with Foxp3 to impose on naive CD4⁺ T cells the characteristic of visceral adipose tissue Treg cells. In fact, Feuerer et al. [134] demonstrated that Treg cells with a unique phenotype were highly enriched in the abdominal fat of normal mice, but were specifically reduced at this tissue in an insulin-resistant model of obesity. Studies have suggested that adipokines may control T cell responses leading to Treg differentiation [135]. A recent study highlighted the negative effect of leptin on the proliferative capacity of Treg [136]. In fact, it is well demonstrated that obese subjects present low Treg cell number and adiponectin production and high leptin secretion [134]. Probably, PPAR- γ is involved with adipokines regulation of lymphocyte differentiation in adipose tissue.

2.4. Toll-Like Receptors (TLRs). TLRs are transmembrane receptors that play a critical role in the detection of microbial infection and in the induction of inflammatory and immune responses against conserved microbial structures, called pathogen-associated molecular patterns [137]. Each member of TLR family recognizes a specific pathogen component which, upon activation, triggers a signaling cascade leading to cytokine production and adaptive immune response. Among the TLRs, TLR2 and TLR4 play a critical role in the pathogenesis of insulin resistance, diabetes, and atherosclerosis in both clinical and experimental conditions [138, 139].

C3H/HeJ mice with a mutation in TLR4 are protected against the development of high fat diet-induced obesity. In addition, these mice demonstrate decreased adiposity, increased oxygen consumption, a decreased respiratory exchange ratio, improved insulin sensitivity, and enhanced insulin-signaling capacity in adipose tissue, muscle, and liver. Moreover, in all these tissues, control mice fed a high-fat diet showed an increase in IkappaB kinase complex and c-Jun NH(2)-terminal kinase activity, which is prevented in C3H/HeJ mice.

Studies in mice demonstrate that TLR-2 and TLR-4 activation and cytokine production stimulated by these receptors lead to the development of diabetes (Figure 3) [140, 141]. More recently, TLR4 has been indicated as a molecular link between free fatty acids, inflammation, and the innate immune system. Dasu et al. [139] studied TLR2 and TLR4 mRNA and protein expression, their ligands, and intracellular signaling in monocytes of recently diagnosed type 2 diabetic patients and observed that there is significant elevation of TLR2 and TLR4 protein, mRNA, endogenous

ligands, and cofactors which, together with hyperglycemia, contribute to the proinflammatory state of type 2 diabetes.

Koopet et al. [142] observed that TLR activation promotes upregulation of IL-6 and MCP-1 release in isolated human adipocytes via specific activation of Erk. TLR-4 deficient mice had also markedly lower circulating concentrations of MCP-1 and much less NF-kB protein in nuclear extracts prepared from adipose tissue. In contrast, TLR-4 deficiency did not attenuate the induction of tumor necrosis factor-alpha (TNF- α) or interleukin-6 (IL-6) expression in adipose tissue promoted by diet with high saturated fatty acids [143]. Nowadays, based on several studies it is clear that TLR4 inhibition is a pharmacologic tool to avoid inflammation in insulin resistance patients.

2.5. N-3 Fatty Acids-Derived Lipid Mediators. Arachidonic acid (n-6 fatty acid) serves as precursor of immune-active lipid mediators known as eicosanoids. Classes of eicosanoids include lipoxins, leukotrienes, and PGs, and their effects on the immune system have been extensively explored and reviewed [144].

First identified by Serhan et al. [145], resolvins are new mediators generated from n-3 fatty acids docosahexaenoic acid (DHA, C22:6n-3) and eicosapentaenoic (EPA, C20:5n-3) identified first in resolving inflammatory exudates and in tissues enriched with DHA. The names resolvin (resolution phase interaction products) and docosatrienes were given because these bioactive compounds demonstrate potent anti-inflammatory and immunoregulatory actions (Figure 3). These mediators prevented neutrophil entry to inflammation sites and cytokine production and reduced exudates in rats with experimental peritonitis [146]. The compounds derived from EPA carrying potent biological actions are named the E series and are denoted as resolvins of the E series. Those synthesized from DHA are resolvins of the 17S-D series that have immunoregulatory [145] and neuroprotective actions [147]. Protectin D1 (formerly known as neuroprotectin D1) is also generated from DHA [148]. These compounds are produced after acetylation of COX-2 by aspirin. In addition, aspirin treatment triggers the formation of 15-epimeric lipoxins, termed aspirin-triggered lipoxins, that also play a role in resolution of inflammation through inhibition of neutrophil tissue infiltration [146] and stimulation of macrophage phagocytosis of apoptotic neutrophils [149].

Studies demonstrate that n-3 fatty acid feeding promotes endogenous production of resolving D1 and 17-hydroxy-DHA, a marker of resolvin biosynthesis, in adipose tissue of obese-diabetic mice [150]. Transgenic overexpression of fat-1, which encodes a desaturase enzyme that is able to convert ω -6 to ω -3 fatty acids, partially protects against obesity-induced insulin resistance in mice and is associated with an increase in the resolvin biosynthetic pathway marker 17-hydroxy-DHA [151]. These studies demonstrated that high-fat feeding results in a deficient endogenous resolvin and protectin biosynthesis and that these compounds are restored in fat-1 transgenic mice.

Horrillo et al. [152] provided evidence that adipose tissue expresses all the enzymes necessary for the formation of

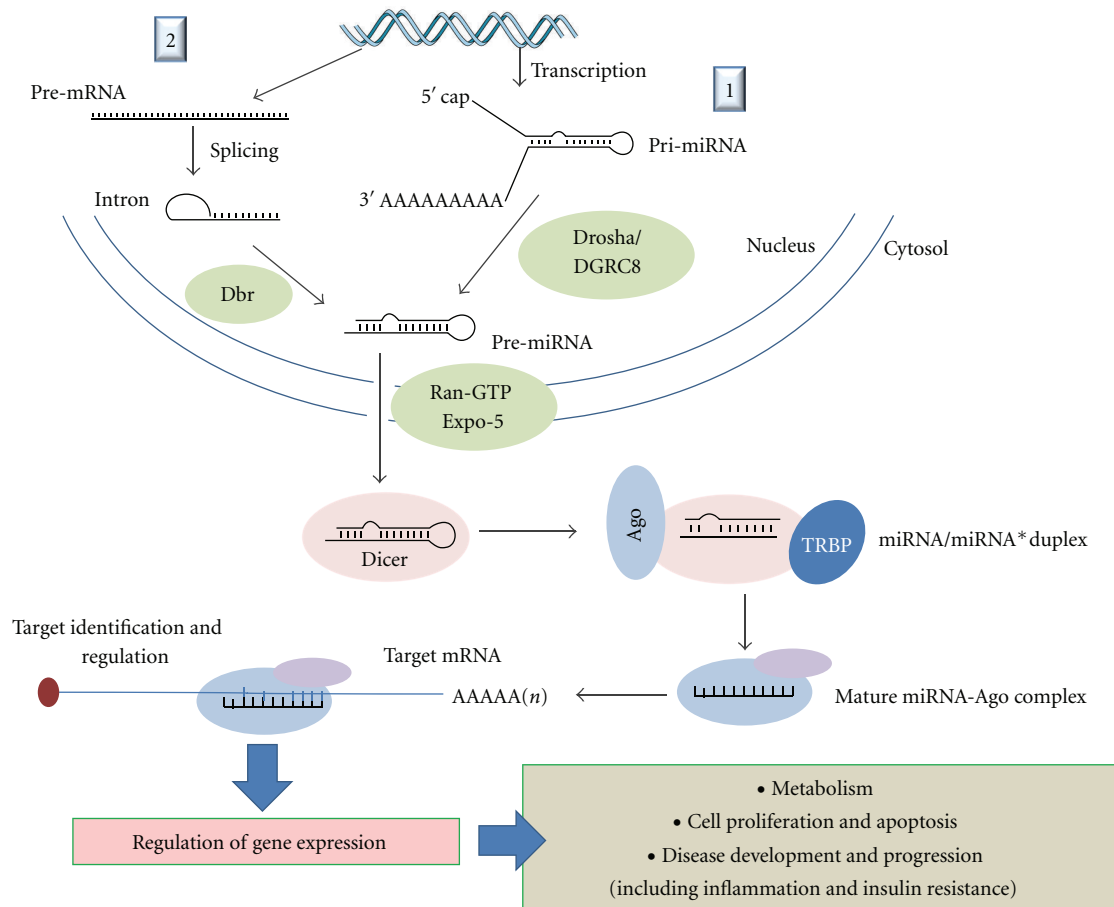


FIGURE 4: MicroRNA (miRNA) biogenesis and gene expression control in human cells. (1) Canonical pathway produces pre-miRNA by Drosha/DGCR8 cleavage of pri-miRNA. (2) Noncanonical pathway mirtrons are produced by spliced introns debranched by debranching enzyme (Dbr), after which they fold into pre-miRNA hairpins. Pre-miRNA hairpins are exported from the nucleus to cytosol by exportin-5 (Expo-5) and cleaved by Dicer to produce 22 nucleotides RNA duplexes. One strand of the duplex is transferred to Argonaute complex (Ago) and guided to base-pair with its target mRNA throughout its seed sequence. TRBP: tar-RNA binding protein.

bioactive lipid mediators derived from both omega-6 and omega-3-PUFAs. In ob/ob mice DHA significantly increased adipose tissue levels of adiponectin, which alleviated hepatic steatosis and insulin resistance [150]. Recent findings indicate also that DHA (at micromolar concentrations) and resolvin D1 (at nanomolar concentrations) consistently decrease M1 macrophage activation in adipose tissue and increase M2 cells. These effects are related to stimulation of arginase 1 expression and attenuation of IFN γ /LPS-induced Th1 cytokine secretion [153].

Hellmann et al. [154] suggested that stimulation of the inflammation resolution with the endogenous proresolving mediator resolving D1 provides a novel therapeutic strategy for treating obesity-induced diabetes. The authors observed that in leptin-receptor deficient mouse resolvin D1 prevents the accumulation of macrophages in adipose tissue and restores systemic insulin sensitivity. Notably, these inflammation-resolving factors are important tools to decrease adipose tissue inflammation that is common in insulin resistance.

2.6. MicroRNAs. MicroRNAs (miRNAs or miRs) are short noncoding RNAs that have been demonstrated to be master regulators of the cellular transcriptome and proteome [155–157]. Regulatory miRNAs bind to the complementary segments within 3'-untranslated region (3'UTR) of target transcripts through Watson-Crick base pairing, causing translational inhibition or mRNA cleavage and suppression of gene expression. Over 1000 miRNAs have been identified in the human genome, which are estimated to regulate thousands of protein-coding genes [158, 159]. There is also increasing experimental evidence that miRNAs are involved in the control of several critical biological processes such as metabolism, cell proliferation, apoptosis, and disease development and progression [160–163].

Single-stranded mature miRNAs with 20–24 nucleotides in length are derived from genomically encoded sequences through transcription and complex mRNA processing. Change in gene expression or processing in dysfunctional or abnormal cells or tissues leads to an altered miRNA expression level. Figure 4 summarizes biogenesis and gene

expression control by miRNAs. Profile of these molecules may be used as biomarkers for classifying human diseases and disease status [162, 164, 165].

Recent studies have observed an association between specific miRNAs and insulin resistance [166, 167], supporting the fact that miRNAs may play a role in the pathological development of type 2 *diabetes mellitus* and leading also to the hypothesis that miRNAs may represent a new class of glucose metabolism regulators with therapeutic potential for improving insulin sensitivity in peripheral tissues. Supporting this idea, Frost and Olson [168] have demonstrated that global and pancreas-specific overexpression of the miRNA *Let-7* in mice results in impaired glucose tolerance and reduced glucose-induced pancreatic insulin secretion. Pharmacological inhibition of the miRNA *Let-7* family with specific anti-miR was sufficient to prevent and treat impaired glucose tolerance in diet-induced obesity mice, at least in part, by improving insulin sensitivity in liver and muscle. In addition, miRNA *Let-7* was able to block glucose-induced insulin secretion from the pancreas, suggesting that knockdown of this miRNA also might improve pancreatic β -cell function.

A role of the heart in systemic metabolic control and the involvement of the heart-specific microRNA, miR-208a, as potential therapeutic target for metabolic disorder have been proposed. Impaired metabolism of energy-providing substrates and myocardial lipid accumulation are early abnormalities in obese and insulin-resistant individuals [169]. Grueter et al. [170] have shown that MED13, a subunit of the Mediator complex, controls transcription by thyroid hormone and other functions of nuclear hormone receptors in heart, controlling metabolic homeostasis and energy expenditure in mice. They have also shown that miR-208a, a heart-specific miRNA encoded by an intron of the cardiac-specific α -myosin heavy-chain (MHC) gene, negatively regulates MED13 expression. Elevated cardiac expression of MED13 or pharmacologic inhibition of miR-208a in mice led to resistance to high-fat diet-induced obesity and improved systemic insulin sensitivity and glucose tolerance in mice. Conversely, genetic deletion of MED13 specifically in cardiomyocytes enhanced obesity in response to high-fat diet and exacerbated metabolic syndrome [170].

As discussed previously, inflammation and oxidative stress participate in the propagation and development of obesity and associated metabolic disorders associated to insulin resistance. Maladaptive production of various adipokines (e.g., adiponectin, resistin, visfatin, and leptin), migration of monocytes, and subsequent transformation into macrophages within affected tissues are key factors in the self-perpetuating inflammation associated with metabolic disorders [171, 172]. In particular, plasma levels of adiponectin are significantly lower in obese individuals and have been associated with inflammation, insulin resistance, and cardiovascular disease. The involvement of miRs in the protective effects of adiponectin has been recently evaluated. Hulsmans et al. [173] identified miR-146b-5p as a downregulated miR in monocytes of obese subjects with targets in the IRAK/NF κ B-related gene cluster. They identified obesity-associated low levels of globular adiponectin as cause of the

decrease in miR-146b-5p. The role of miR-146b-5p in the protection against inflammation was further supported by the finding that, after sequestration of miR-146b-5p, the cells lost their potency to raise their anti-inflammatory action in response to high levels of adiponectin.

A possible role of miR-107 in regulating the inflammatory process that might lead to type 2 *diabetes mellitus* has been proposed by Foley and O'Neill [174]. Because the TLR4 (LPS receptor) has been shown to downregulate miR-107 in activated macrophages located in adipose tissue [175], and miR-107 has been demonstrated to be dysregulated in murine and rodent models of obesity and insulin resistance, respectively [176–178], it has been suggested that miR-107 may be the link between obesity, inflammation, and insulin resistance. The authors hypothesize that decreased miR-107 by TLR4 is required to limit proinflammatory signaling pathways, since this effect will stabilize Caveolin-1, blocking the TLR4 pathway by displacement of MYD88. Decreased miR-107 is an attempt to increase insulin sensitivity in the resolution phase of inflammation. A defect in this process, particularly in the ability of TLR4 to decrease miR-107, could therefore promote inflammation and type 2 *diabetes mellitus*. Further investigations are warranted to assess this hypothesis. An interesting model would be transgenic mice, in which we could manipulate miR-107 *in vivo* and pharmacologically inhibit miR-107.

3. Concluding Remarks

The discovery and identification of new biomarkers involved in the pathogenesis of chronic inflammation and insulin resistance have been fundamental to understanding how these processes work and to direct further studies for the prevention or treatment of related disorders. Particularly, these discoveries have aided to identify new target genes, lipids, proteins, and other metabolites involved in the development or severity of chronic diseases, for example, obesity, type 2 *diabetes mellitus*, metabolic syndrome, cardiovascular diseases, cancer, dyslipidemia, and cancer. Probably, with the help of new tools and advanced methodologies, we will have a better characterization and understanding of the mechanisms and mediators involved in the different inflammatory and insulin resistance conditions, addressing further biotechnological studies for the development of new potential clinical therapies and interventions.

Acknowledgments

This study was supported by grants from São Paulo Research Foundation (FAPESP), Coordination for the Improvement of Higher Level Personnel (CAPES), National Council for Scientific and Technological Development (CNPq)/National Institute of Science and Technology in Obesity and Diabetes (INOD), Center of Lipid Research and Education (CLEaR), and Dean's Office for Research/University of São Paulo. A. Rodrigues is a recipient of fellowship from FAPESP (2011/05876-6).

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