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Adiponectin and PPAR: a setup for intricate crosstalk between obesity and non-alcoholic fatty liver disease

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Abstract
Adiponectin, a soluble adipocytokine, plays an important role in the functioning of adipose tissue and in the regulation of inflammation, particularly hepatic inflammation. The adiponectin subsequently imparts a crucial role in metabolic and hepato-inflammatory diseases. The most recent evidences indicate that lipotoxicity-induced inflammation in the liver is associated with obesity-derived alterations and remolding in adipose tissue that culminates in most prevalent liver pathology named as non-alcoholic fatty liver disease (NAFLD). A comprehensive crosstalk of adiponectin and its cognate receptors, specifically adiponectin receptor-2 in the liver mediates ameliorative effects in obesity-induced NAFLD by interaction with hepatic peroxisome proliferator-activated receptors (PPARs). Recent studies highlight the implication of molecular mediators mainly involved in the pathogenesis of obesity and obesity-driven NAFLD, however, the plausible mechanisms remain elusive. The present review aimed at collating the data regarding mechanistic approaches of adiponectin and adiponectin-activated PPARs as well as PPAR-induced adiponectin levels in attenuation of hepatic lipoinflammation. Understanding the rapidly occurring adiponectin-mediated pathophysiological outcomes might be of importance in the development of new therapies that can potentially resolve obesity and obesity-associated NAFLD.

Keywords Adiponectin · Obesity · NAFLD · PPAR

1 Introduction

Obesity develops from a prolonged imbalance of energy intake and energy expenditure [1, 2] that tends to alter adipose tissue metabolism as well as its functions [3]. It has been proven experimentally [4–6] and epidemiologically [3, 7, 8] that adipose tissue does not function solely as an energy store. Although it is now being recognized as a key endocrine organ that releases a number of adipokines with pro- or anti-inflammatory properties and stimulate the obesity complications [8–10], affecting the vital organs of the body, notably the liver [11, 12]. One of the most prominent liver pathology prevalent globally is nonalcoholic fatty liver disease (NAFLD) [13, 14]. The presence of fat (steatosis) in the liver exhibits a collection of adverse alterations in conjugation with adipose tissue-driven immune responses and hepatic inflammation [15]. These key factors are involved in the development of insulin resistance [16], dyslipidemia, and hepatocellular lipotoxicity in the pathogenesis of NAFLD [15, 17] (Fig. 1). In addition, these adipose tissue-driven factors are responsible for metabolic dysregulation and initiation of molecular signaling in the liver leading to inflammatory changes. The underlying mechanisms are mediated by generation of oxidative stress, inflammatory changes in the liver [18–20], infiltration of macrophages or infiltrate cells and storm of inflammatory cytokines [21, 22]. Blocking of inflammatory pathways and mediators of NAFLD in steatosis are promising therapeutic strategies to overcome obesity and obesity-prompted NAFLD.

Low-grade inflammation in hepatic-adipocytes stimulates liver macrophages, which perpetuate a vicious cycle of inflammatory cells recruitment, secretion of free fatty acids and deleterious adipokines (leptin, vesfatin and resistin) that predispose to high incidence of metabolic complications (Fig. 2). However, the abundance of adiponectin, an anti-inflammatory adipo-cytokine [10], efficiently ameliorates and dampens the obesity-induced hepatic inflammation. In

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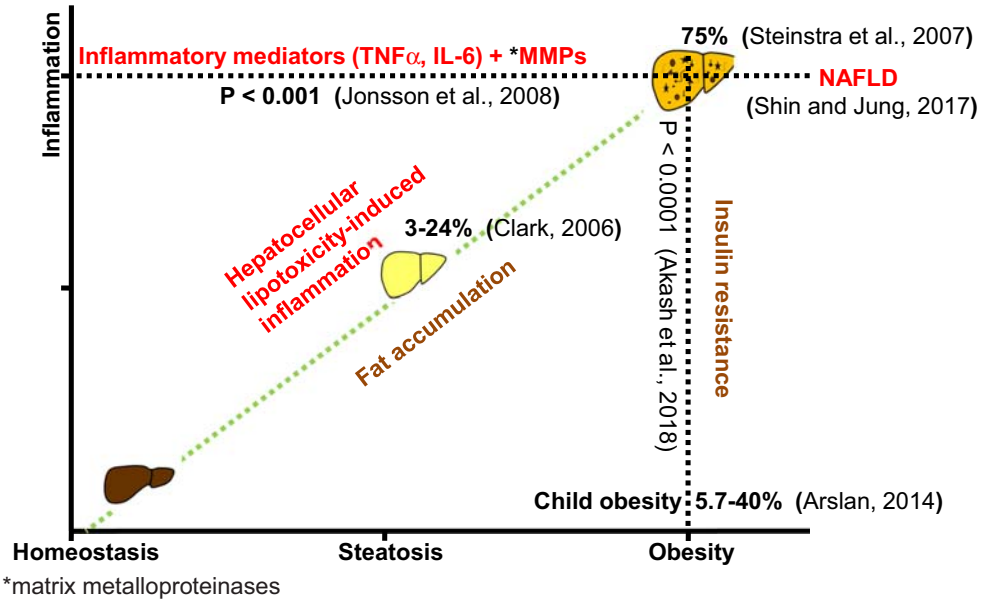

Fig. 1 Prevalence and pathogenesis of obesity-prompted NAFLD. Obesity is a chronic disease with equal prevalence of 5.7–40% in children, mediated by multiple factors, including dyslipidemia, insulin resistance and lipoinflammation are above all. Hepatocellular lipotoxicity-induced inflammation and steatosis-induced insulin resistance simultaneously (with prevalence of 3–24%) are major drivers towards 75% of the liver injuries; whereas, NAFLD has been reported as one of the most prevalent liver pathologies

the liver, an intricate crosstalk at cellular level assists the adiponectin to control lipid dysregulation as well as cellular inflammatory process. One of the substantial player for this cellular regulation is peroxisome proliferator-activated receptors (PPARs) [23, 24]. The PPARs belong to nuclear receptor (NR) subfamily1, group C, member 3 (NR1C3) and these are highly expressed in the liver and exerting anti-inflammatory effects on following receptor-ligand binding [25–29] (Table 1).

2 Adiponectin and adiponectin level in metabolic disorders as a potential therapeutic target

Post-translationally the adiponectin, an adipocyte-specific factor and a monomeric glycoprotein, modifies into different multimers, comprising of low molecular weight (LMW) or trimer, middle molecular weight (MMW) or hexamer, and high molecular weight (HMW) [12]. Since first described in

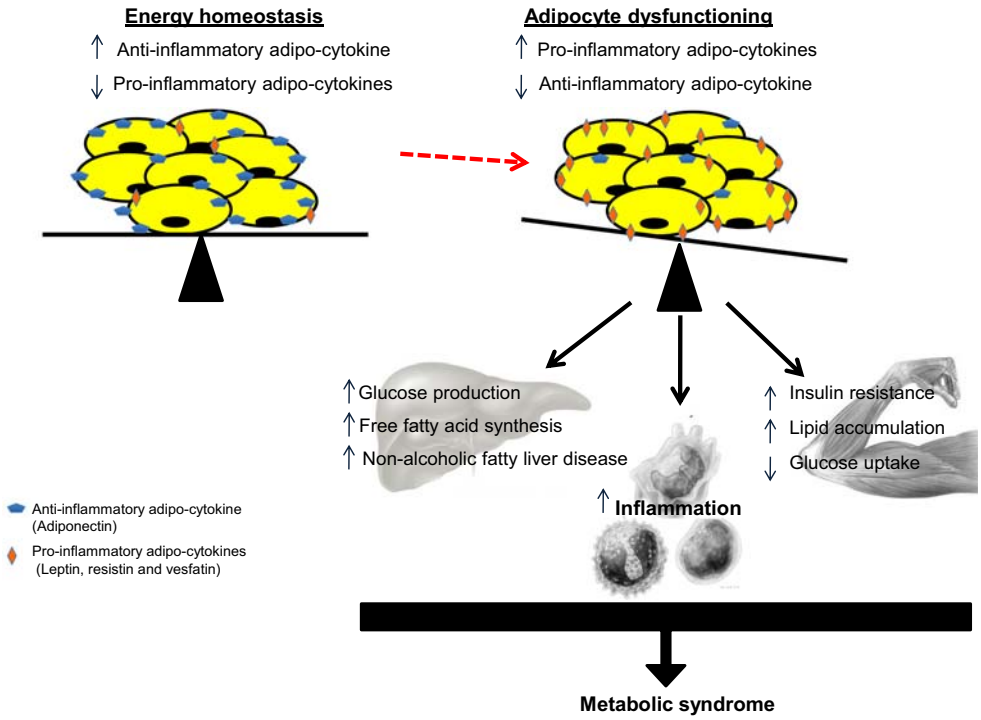

Fig. 2 Energy homeostasis vs adipocyte dysfunctioning: role of adipo-cytokines in development of metabolic syndrome. The effects of adiponectin balance on a variety of organs and its immunological implications have proposed the adiponectin as a key player in diverse metabolic processes. Such implications would have important applications in drug development, diagnosis and research for metabolic syndrome

Table 1 Exogenous anti-obesity and anti-inflammatory PPAR ligands

Ligand	PPAR isotype	Model	Mechanism and outcome	Ref.
Gemfibrozil	PPARα	Acetaminophen (APAP)-induced hepatotoxic model of mice	Decreased oxidative status, decreased degeneration, vacuolation and necrosis of hepatocytes and infiltration of inflammatory cells	[30]
Pioglitazone	PPARγ	*Schistosoma japonicum*-infected mice	Increased percentages of $CD4^+CD25^+Foxp3^+$ Treg cells and decreased percentages of $CD3^+CD4^+IFN\text{-}\gamma^+$ and $CD3^+CD4^+IL\text{-}4^+$ cells in the liver and spleen immune-pathologies	[31]
Fenofibrate	PPARα	Diabetes model	Increased interleukin-1 receptor-associated kinase-3 (Irak3) and decreased monocyte chemoattractant protein-1 (Mcp1) expressions	[32]
GW0742	PPARβ	HFD-induced obesity model	Reduced ER stress by improving the insulin sensitivity and maximizing the hepatic energy metabolism with a shift towards beta-oxidation	[33]
Chalcone derivatives (13e, 13 g and 19f)		Streptozotocin (STZ)-induced T2DM animal model	Upregulated AdipoR1 and AdipoR2, in addition, increased expression of PPARα and activation of AMPK pathway.	[34]
Bromocriptine	A sympatholytic dopaminergic D2 receptor agonist triggers PPARγ/adiponectin signaling	Diabetic rats	Normalized glucose/lipid profile, as well as leptin and GLP-1 levels. In muscles, curtailed the inflammatory signal IL-6/JAK2/*p*-STAT3/SOCS3, while enhanced the PPAR-γ/adiponectin signaling, resulting in activation of the insulin signaling pathway (*p*-IR/*p*-AKT/GLUT4). Moreover, confirmed its antioxidant capabilities by altering Nrf2 and PARP-1	[35]
MEKT1	PPARγ	Murine corticotroph-derived AtT20 cells	Inhibited proopiomelanocortin gene (Pomc)/adrenocorticotropic hormone (ACTH) expression	[36]
Indomethacin	A non-steroidal anti-inflammatory drug triggers PPARγ	Interscapular brown adipose tissue (iBAT) of obese mice	Upregulated both mRNA and protein levels of uncoupling protein 1 (UCP1) and PPARγ coactivator 1-alpha	[37]
PPAR ligands with dual activities				
RB392	PPARγ, soluble epoxide hydrolase (sEH) inhibitor	Obese spontaneously hypertensive (SHROB) rat and the obese diabetic Zucker fatty/spontaneously hypertensive heart failure F1 hybrid (ZSF1) rat	RB394 blunted the development of hypertension, insulin resistance, hyperlipidemia and kidney injury in SHROB rats and reduced fasting blood glucose and HbA1c, improved glucose tolerance, reduced blood pressure and improved lipid profiles, reduced liver fibrosis and hepatosteatosis in obese ZSF1 rats	[38]
Rosiglitazone+AG490	PPARγ agonist+JAK2 inhibitor	LPS-induced hepatic steatosis model, BRL-3A cells	Alleviated steatosis through reducing suppressor of cytokine signaling3 (SOCS3) expression by inhibiting JAK2/STAT3 in hepatocytes and BRL-3A cells	[39]
Sodium butyrate, N-(1-carbamoyl-2-phenyl-ethyl) butyramide (FBA)	PPARγ, PPARγ-coactivator PGC1α	Rat model of insulin resistance and steatosis induced by HFD	Significantly reduced hepatic TNF-α expression and restored GLUTs, reduced pro-inflammatory parameters in the liver, via suppression of Toll like receptors and NFκB activation	[40]

1995, the adiponectin was studied by many researchers demonstrating its exclusive physiological effects while the mystery of adiponectin as a hormone was resolved later. Pharmaco-dynamically active adiponectin following release interacts with its specific surface receptors designated as "AdipoR1" and "AdipoR2" [41, 42]. These receptors are ubiquitously expressed throughout the body organs particularly in skeletal muscle and liver, respectively, where a remarkable contribution of adiponectin in energy homeostasis and role of its ligands has been reported by various experimental studies [11, 12, 43]. Recent data [12, 44–46] of over expression and/or suppression of receptor activity have shown that both isoforms of adiponectin receptor allow binding of the multimerized fragments of adiponectin with varying affinities for globular (LMW) and full-length (MMW, HMW) multimers. The AdipoR1 preferably binds to globular adiponectin than a full-length adiponectin that has a weak affinity. In contrary, the AdipoR2 has moderate affinity for both globular as well as full-length adiponectin [42, 45, 47].

Adiponectin is a crucial adipokine that is associated with obesity, although the physiological role of adiponectin in the pathology of many organs remains obscure. The plasma concentration of adiponectin ranges from 0.01–0.05% of total plasma proteins (5-10 μg/ml) with a half-life of approximately 75 min [45, 48]. The soluble level of adiponectin are higher in women than men revealing a sexual predisposition [45]. Contrary to other adipokines, the adiponectin level surprisingly declines in obese patients that is a hallmark of obesity [46]. Recent studies [41, 49–52] reflect inverse association of impaired level of adiponectin in pathogenesis of obesity and obesity-prompted metabolic syndrome and hepatocellular carcinoma [53]. Moreover, diversity in cellular localization of AdipoR1 and AdipoR2 affects the resident tissue crucially (Fig. 2). Kubota et al., [54] in 2002 was first to elucidate the direct relation of adiponectin signaling with diabetes and atherosclerosis in vivo. They reported the mild insulin resistance-to-moderate along with mild glucose tolerance in adipo$^{\pm}$ and adipo$^{-/-}$ mice, respectively. Whereas, adipo$^{-/-}$ mice showed a two-fold neo-intimal formation in response to external vascular injury. Further experimental evidence [55] revealed that globular adiponectin in transgenic ob/ob mice showed partial amelioration of insulin resistance and diabetes, but not of obesity. Moreover, a recent study shows that the expression of AdipoR1 in duodenum-jejunum can improve type 2 diabetes mellitus (T2DM). According to this research, a microRNA (miRNA)-320 is a potential candidate for expressing AdipoR1 in the duodenum and subsequently mediate amelioration of T2DM in the duodenum-jejunum bypass (DJB) surgery [56]. In the liver, the AdipoR2 existence dominantly triggers cellular mechanisms (adenosine monophosphate-activated protein kinase-(AMPK)-pathway) to regulate adiponectin-prompted lipid regulation, gluconeogenesis as well as hepatic stellate cells (HSCs) mediated liver fibrosis in contrast to KO mice [57]. Moreover, the adiponectin-activated AMPK pathway protects against liver cancer development [53].

2.1 Adiponectin-activated AdipoR2 dependent hepatic-communication: A mechanistic approach to immune transrepression and/or transactivation

In context to evidences of a latest study [57], suggests that the presence of both AdipoR1 and AdipoR2 to restrain liver fibrosis is not essential in vivo. Moreover, absence of AdipoR2 correlates with enhanced liver fibrosis. In activated HSCs [58] the AdipoR2 is necessary for mediating adiponectin-prompted anti-fibrotic responses and cell migration as absence of AdipoR2 is unable to activate AMPK in vitro [57]. The adiponectin is critical to modulate AMPK pathway [59] for insulin sensitivity and glucose metabolism and to acetyl CoA carboxylase (ACC) [6], as an adjunct to AMPK for lipid metabolism [57, 60]. Additionally, the indirect protective effect of adiponectin is by enhancing the levels of key players in lipid lowering mechanisms, namely- ceramidase [61, 62] which inhibits hepatic lipid accumulation and improves insulin sensitivity, and carnitine palmitoyltransferase (CPT)-1 [48] . The over expression of acid ceramidase induced by adiponectin is key to its potential therapeutic effect in lipid and glucose homeostasis [61, 62]. Whereas, a latest research revealed that CPT-1 is a latent regulator of fatty acid β-oxidation (FAO) in fatty acid degradation that facilitates amelioration diet-induced obesity and hepatic steatosis [63]. Moreover, FAO is a bioenergetic pathway for self-differentiation and self-renewal of many immune cells by yielding adenosine tri-phosphate (ATP) [64]. Moreover, the adiponectin interacts with adaptor protein containing a pleckstrin homology domain (APPL1) and provokes the activation of AMPK and PPAR- alpha (PPARα). Thereby, decreasing hepatic glucose production (gluconeogenesis) and increasing fatty acid oxidation that leads to lower insulin resistance (IR) as a result of decreased triglycerides [60].

The adiponectin-activated AdipoR2 appears to have a direct effect on progression of inflammation in antagonizing outcomes of 1) other deleterious adipokines and 2) pro-inflammatory cytokines released by activated resident immune cells, mainly Kupffer cells (KCs), dendritic cells (DCs), liver sinusoidal endothelial cells (LSEC), vascular endothelial cells (VECs), HSCs [1, 65]. Consequential synergistic inflammatory responses by these collective pro-inflamamtory cytokines challenge adiponectin. Therefore, the adiponectin-activated AdipoR2 activates both AMPK downstream signaling and PPARα. As a result, restorative effects of adiponectin against lipoinflammation have been reported by inhibiting the release of plethora of pro-inflammatory cytokines notably tumor necrosis factor (TNF)-α, interleukin (IL)-6, interferon (IFN)-γ [60] and

nuclear factor kappa B (NFκB), induction of IL-10 expression, IL-1 receptor antagonist (IL-1RA) [66] and suppression of reactive oxygen species (ROS) [59, 67]. This extensive crosstalk of adiponectin, immune cells and inflammatory mediators at hepatocellular level enable adiponectin to control steatosis in obesity as well as obesity-prompted NAFLD (Fig. 3).

3 A crosstalk of PPAR signaling and adiponectin activity in the liver

It has been proposed by recent findings [14, 68] that NAFLD occurrence is a "dual-hit" process. According to this hypothesis, the first hit results from triglyceride accumulation in the hepato-adipocytes due to prolonged imbalance of glucose [21] and lipid input and output. Therefore, the adipocyte dysregulation proves a driving force for insulin resistance (IR) and subsequently to the pathogenesis of NAFLD. The second hit in this NAFLD progression model is an imbalance of pro- and anti-inflammatory factors accompanying with the generation of reactive oxygen species (ROS) resulting in exacerbating inflammation [18]. Recent data [40, 66] highlighted high levels of TNFα [69] and IL-6 for IR and NFκB as a remarkable proinflammatory mediator that are crucially involved in the pathogenesis of NAFLD [70, 71]. A direct relationship between obesity and inflammation was first proposed by Hotamisligil et al., [72] that indicated the positive association between adipose mass and expression of proinflammatory cytokine namely- TNFα [21, 73]. Thus, over production of TNFα by adipocytes [23], activation of PPARα by adiponectin and PPAR-gamma(γ)-induced adiponectin expression [23, 47, 67] and immune-related proteins are key mediators of obesity-induced NAFLD (Fig. 3).

Chronic inflammation and dyslipidemia concomitantly suggest targeting the hepatic PPARs for pleiotropic pharmacological actions. The isoforms of PPARα/β/γ work communally to confer amelioration in obesity and obesity-induced NAFLD. The PPARα and PPARγ prominently operate for attenuation of inflammatory mechanisms, while other isoform, PPAR-beta(β) has been reported as a potential target for treatment of IR [74]. The PPARα activation recovers steatosis and inflammation in pre-clinical models of NAFLD [75]. Interestingly, PPARα is also a transcriptional regulator of genes involved in peroxisomal and mitochondrial β-oxidation, fatty acid (FA) transport and hepatic glucose production. The anti-inflammatory effects of PPARα regulate transactivation of anti-inflammatory genes including IL-10 and IL1RA along with transrepression of pro-inflammatory response genes essentially of ACC, NFκB, sterol-regulatory-element-binding protein $_1$C (SREBP$_1$C), a main transcriptional factor regulating expression of genes encoding mediators of lipid synthesis [75]. A recent research confirms the PPARγ induced transrepression of inflammatory cytokines. Evidently, the PPARγ agonism significantly inhibits lipopolysacchride (LPS)- induced secretion of TNFα, IL-1β and nitric oxide (NO) and attenuates inflammation in BV-2 microglial cells during neuroinflammation [24].

Accordingly, the adiponectin-induced activation of hepatic PPARs as well as increased expression of adiponectin by PPARγ implicates signal transduction in the liver. Activation of a cascade of signaling events mediates adiponectin-induced

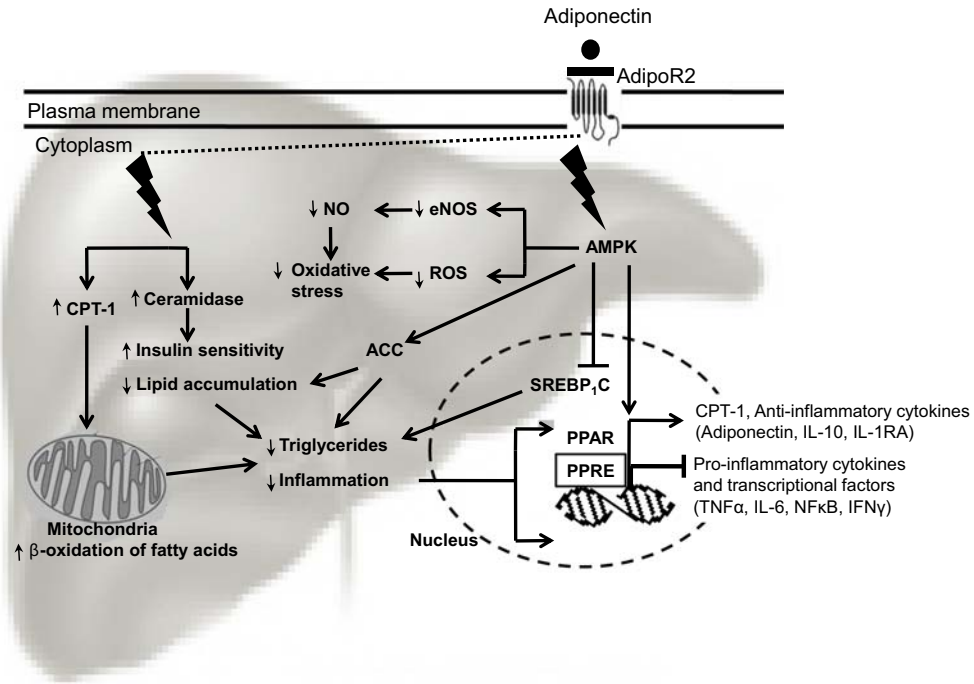

Fig. 3 Adiponectin-induced intricate crosstalk between AdipoR2 and PPAR in hepatocytes. A hypothetical model showing mechanistic approach of adiponectin and adiponectin-activated PPARs as well as PPAR-induced adiponectin levels in attenuation of deleterious inflammatory mechanisms, oxidative status and imbalance of triglycerides levels, simultaneously. Specifically, adiponectin provokes hepatic AdipoR2-induced AMPK downstream signaling and triggers PPAR-induced transcriptional factors to ameliorate oxidative status, inflammation and high levels of triglycerides resulted from adipocytes remodeling and obesity-driven alterations

biological responses that include increased enzyme synthesis, glucose uptake and utilization, glycogen synthesis, reduced inflammation, lipolysis, and gluconeogenesis.

3.1 PPAR ligand-mediated ameliorative effects in obesity and NAFLD: A therapeutic perspective

All three hepatic PPAR isotypes are potential targets for ligands and show pluripotent effects against lipoinflammation [76]. Each isotype has equal affinity for endogenous and/or exogenous ligands. Endogenous ligands such as polyunsaturated fatty acids and eicosanoid metabolites (e.g., prostacyclin and 15 hydroxyeicosatetraenoic acid (15-HETE) as well as exogenously administered artificial agonists, including GW501516, GW0742, L-165041, and carbacyclin are capable to initiate PPAR activity. In addition, the pharmacological activity of PPARs can be inhibited by several inverse agonists and antagonists [77]. The PPARs can be therapeutically exploited for dyslipidemia, IR, inflammation, and coagulation disorders that promote type 2 diabetes (T2DM) in obese patients. All three PPAR isotypes have demonstrated anti-inflammatory and anti-obesity effects in these conditions.

The expression of adiponectin induced by PPARγ agonists, rosiglitazone and pioglitazone are reported to improve IR in diabetic patients [45] and trigger downstream AMPK signaling. Rosiglitazone treatment reversed induction and progression of hepatic fibrosis and HSCs activation by sGC/cGMP/PKG and PI3K/AKT signals [78]. The activation of AMPK pathway reported by latest studies [79, 80] demonstrated improved IR and hepatic ischemia perfusion injury. Fibrate attenuates steatohepatitis by suppressing the expression of several cytokines [72] through PPARα agonism [68]. Moreover, fibrate induced expression of AdipoR2 modulates the adiponectin signaling and action [67]. A recent study investigated that 2-(4-(5-chlorobenzo[*d*]thiazol-2-yl)phenoxy)-2,2-difluoroacetic acid (MHY3200) is a more potent PPARα agonist than WY14643 in high fat diet (HFD)-induced hepatic lipoinflammation [81]. The HFD is the root cause for initiation of obesity and obesity-derived complications. Whereas, a recent study showed that HFD induces PPARγ expression by surplus free fatty acids (FA) in hyperlipidemic condition indicatinga positive feedback regulation over FAO and ketogenic enzymes by controlling lipotoxicity in 8 weeks old C57BL/6 wild type (WT) mice. While upregulation of mitochondrial metabolic enzymes 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS2), mitochondrial β-hydroxy butyrate dehydrogenase (BDH1) and pyruvate dehydrogenase kinase isoform 4 (PDK4) by PPARγ activation are responsible for cardiac dysfunction [82]. A study highlighted that expression of PPARγ and PPARβ by activated neutrophils. These cells activated by G protein coupled receptors (GPCRs) agonist N-formyl-l-methionyl-l-leucyl-l-phenylalanine (fMLP) that binds to membrane-formylated peptide and activates intracellular inflammation pathways. Later LYSO-7, an insulin sensitizing agent, inhibited resultant gene and protein expression of adhesion molecules, CD62 L and CD18, abolished adhesion of neutrophils to endothelial cells, impaired its chemotaxis, blocked the enhancement of intracellular calcium levels, induced the expression of PPARγ as well as PPARβ/δ and reduced NF-κB [83]. Accumulating evidences have indicated protective role of PPARs in fibrogenesis. In this context, a recent study reported a mechanistic approach of PPARγ in amelioration of hypoxia-induced hepatic fibrogenesis in a rat model.

Several pharmacotherapies modulate more than one PPAR form for treating metabolic challenges simultaneously by targeting transrepression and/or transactivation of genes. Thus, synthetic/artificial/exogenous PPARs ligands could be an essential tool to avoid NAFLD progression and other obesity related metabolic health issues (Table 1).

3.1.1 Future perspective

The worldwide increasing prevalence of obesity and related complications, a public health menace and create alarming conditions in the healthcare system. The major determinant of health problems seen in overweight and obesity is inflammation, which emphasizes the link between nutrition, metabolic organs, and the immune system. Nevertheless, interdependent pathophysiological linkage of these disorders may overcome resultant abnormalities aforetime. Indeed, intricate crosstalk between adiponectin and hepatic PPARs mediated by AdipoR2, AMPK pathway, transactivation of many anti-inflammatory genes of CPT-1, adiponectin, IL-10 and IL1RA along with suppression of transcriptional activation of pro-inflammatory response genes essentially of ACC, NFκB, $SREBP_1C$, activation of ceramidase and ACC, can be promising therapeutic targets in combating this multifactorial syndrome at cellular level.

Currently, adiponectin and PPAR serve as emerging modulators of cellular metabolic functions within the liver. Now, certain links between lipid signaling and inflammation underscores the need of finely tuned crosstalk at cellular and molecular level. Developing pharmacotherapeutic ligands that target integrated network of adiponectin and hepatic PPARs may provide potential therapeutic perspectives for synthesizing anti-obesity as well as anti-inflammatory ligands for treatment of obesity and obesity-induced NAFLD.

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