PPARα-Lysosomal Crosstalk in NAFLD

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Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors which belong to the nuclear hormone receptor superfamily. They regulate key aspects of energy metabolism within cells. Recently, PPARα has been implicated in the regulation of autophagy-lysosomal function, which plays a key role in cellular energy metabolism. PPARα transcriptionally upregulates several genes involved in the autophagy-lysosomal degradative pathway that participates in lipolysis of triglycerides within the hepatocytes. Interestingly, a reciprocal regulation of PPARα nuclear action by autophagy-lysosomal activity also exists with implications in lipid metabolism. This review succinctly discusses the unique relationship between PPARα nuclear action and lysosomal activity and explores its impact on hepatic lipid homeostasis under pathological conditions such as non-alcoholic fatty liver disease (NAFLD).

Keywords: PPARs ; lysosomes ; NCoR1 ; PGC1α ; lipophagy ; peroxisomes ; autophagy ; NAFLD

1. Introduction

NAFLD is a disease spectrum which is one of the most prevalent constituents of the metabolic syndrome in the world [1]. Its more concerning subtype, known as NASH, is accompanied by hepatic inflammation and eventually fibrosis. NASH can further progress to life-threatening cirrhosis and hepatocellular carcinoma, and as such, represents an emerging cause for liver transplantation [2]. It is projected that NAFLD could affect 33.5% of the adult population by 2030, out of which, 27% patients could develop NASH [1]. However, currently, no effective approved therapy other that lifestyle intervention exists for NASH, thereby demanding urgent development and newer treatment modalities for its treatment [3] [4]. PPARs have gained attention for their possible anti-NASH action owing to their known anti-steatotic and anti-inflammatory activity in liver [3]. In mice, hepatic PPARα levels increase acutely upon challenge with a high-fat diet (HFD) as an adaptive response [5]; however, in chronic high fat diet (HFD) model, their levels decreased [6]. In humans, hepatic PPARα levels negatively correlated with NASH, and an increase in PPARα expression levels was associated with histological improvement after lifestyle intervention or bariatric surgery [7]. Similarly, PPARα−/− mice exhibited more hepatic triglycerides, oxidative stress, inflammation, and cell death with a significantly higher NAFLD activity score (NAS) when fed HFD as compared with the WT controls fed HFD [8][9]. These findings suggest that PPARα could be a potential therapeutic target for NASH. In this connection, the PPARα agonist, Wy-14643, prevented NASH-induced intrahepatic triglyceride accumulation and liver injury in wild type mice fed a methionine- and choline-deficient diet, but had no effect on PPARα−/− mice fed with the same diet [70]. This study showed that PPARα activation prevents triglyceride accumulation in NASH by increasing fatty acid turnover and catabolism via induction of acyl-CoA oxidase, liver fatty acid binding protein, L-bifunctional enzyme, and peroxisomal ketothiolase gene expression [10]. Similarly, in a rodent G6Pase model of the glycogen storage disease, GSD1a, in which patients developed NASH and cirrhosis, the PPARα mixed agonist, bezafibrate, or selective PPARα agonist, fenefibrate, decreased hepatic triglycerides and increased β-oxidation of fatty acids with a concomitant increase in autophagy [11][12].

2. Implication of PPARα-Lysosomal Crosstalk in NAFLD

Unfortunately, the efficacy of PPARα agonist for the prevention or treatment of NASH found in rodents has not been observed in human trials. Small pilot studies of fibrates in patients with NAFLD did not show any histological improvements in steatosis, inflammation, or fibrosis, nor a reduction in ALT, AST, GGT, bilirubin, or cholesterol, which has led to the discontinuation of its evaluation [13][14]. Yet another study involving 46 patients with NASH demonstrated that four weeks of gemfibrozil treatment resulted in an improvement in serum ALT levels as compared with the non-placebo controls [15]. However, pemafibrate, a novel selective PPAR-α agonist, was shown to ameliorate liver dysfunction in type 2 diabetes patients [16]. Encouragingly, elafibranor a dual PPAR-α/δ agonist, has been shown to resolve NASH after a 52-week treatment indicated by reduced liver enzymes, steatosis, and markers of systemic inflammation and fibrosis [17]. Therefore, general trials with PPARα agonist alone have failed to produce optimal histological improvement of NASH in

patients. This apparent discrepancy between the efficacies of PPARα agonist in rodent versus human NAFLD could be due to either a difference in PPARα tissue expression patterns or species-specific differences in PPARα biology [8]. Furthermore, resistance to PPARα activation in human NAFLD could be another possibility.

Both autophagy and lysosomal activity are impaired in human NAFLD and NASH [18][19]. The impairment of autophagy by saturated fatty acids is considered to be due to impaired fusion of autophagosomes with lysosomes [20][21]. Extended exposure to high lipid concentrations alters the lipid composition of membranes or vesicular compartment impairing their fusion [20][21]. Furthermore, high-fat diet also upregulates the expression of vesicular fusion proteins leading to a block in autophagic flux and can explain the altered autophagy after prolonged fatty diets [19]. Attenuation of chaperone-mediated autophagy (CMA) was also observed after lipid challenge [22]. Other reports have demonstrated a decrease in the clearance of autophagosomes attributed to a disturbed acidification of lysosomal compartments or downregulated cathepsin expression as a contributor of autophagy-lysosomal impairment in NAFLD and NASH [23][24][25].

Intriguingly, autophagy induction in NAFLD and NASH has been seriously considered as a key treatment regimen [26]. Already, caloric restriction, time-restricted feeding [27], and exercise which are known autophagic stimuli, at least in part, underlie some of their beneficial consequences in liver dysfunction and steatosis [28][29]. Similarly, enhancing autophagy through drugs metformin or the disaccharide trehalose, thyromimetics, green tea and caffeine to enhance lipophagy and beta-oxidation have also shown promising anti-steatogenic effects [30][28][31][32]. In addition, the use of TFEB agonists has recently been the focus of a study based on the demonstration that TFEB overexpression in hepatocytes protects against steatosis and insulin resistance via autophagy in mice fed on a high-fat diet [33]. Consistent with these reports, the activation of TFEB by ezetimibe, an inhibitor of NPC1L1-dependent cholesterol transport, also protects against steatosis and hepatocyte injury [34]. Interestingly, some of these autophagy inducing drugs are already FDA-approved, and ezetimibe has been evaluated in clinical trials for patients with NASH [35], although conclusive results require larger studies.

Intriguingly, the increased incidence of NAFLD in aged population [36] could also be related to observed reduction in both PPARα [37] and autophagy with aging [38]. Consistent with this, lifestyle modifications such as calorie restriction and exercise which increase autophagy during aging are also known inducers of PPARα and hepatic lipid catabolism [37][38].

Given the role of the autophagy-lysosomal pathway in regulating PPARα levels and transcriptional activity, it is possible that the PPARα activity induced by fibrates could be suboptimal in NAFLD patients due to this accompanying autophagy/lysosomal defect. It is, therefore, intriguing to speculate that induction of autophagy/lysosomal activity in combination with PPARα agonist therapy could yield better results in patients with NAFLD/NASH. In agreement with this notion, autophagy inducers in rodents have been effective in resolving NAFLD and are associated with a corresponding induction of PPARα signaling [30][39].

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