Pharmacological Research 103 (2016) 144–148

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Invited perspective

PPARα in lysosomal biogenesis: A perspective

ARTICLE INFO

Keywords:
Lysosomal biogenesis
TFEB
Lipid metabolism
Fibrate drugs
PPARα

ABSTRACT

Lysosomes are membrane-bound vesicles containing hydrolytic enzymes, ubiquitously present in all eukaryotic cells. Classically considered to be central to the cellular waste management machinery, recent studies revealed the role of lysosomes in a wide array of cellular processes like, degradation, cellular development, programmed cell death, secretion, plasma membrane repair, nutritional responses, and lipid metabolism. We recently studied the regulation of TFEB, considered to be the master regulator of lysosomal biogenesis, by activation of peroxisomal proliferator activated receptor α (PPARα), one of the key regulators of lipid metabolism. In this article, we discuss how the recent finding could be put in to perspective with the previous findings that relate lysosomal biogenesis to lipid metabolism, and comment on the possibility of a bi-directional interplay between these two distinct cellular processes upon activation of PPARα.

Lysosome (derived from the Greek word *lysis,* meaning 'to loosen', and *soma,* meaning 'body') is a membrane bound vesicle containing hydrolytic enzymes, present ubiquitously in almost all eukaryotic cells, both in plants and animals [1,2]. Lysosomes are classically considered to be cellular waste management machinery, programmed for recycling and degradation of metabolic wastes by endocytosis, phagocytosis, autophagy, and exocytosis [1,3–6]. However, recent developments in this field suggest a much wider array of functions for lysosomes involving major cellular processes, including antigen presentation, regulation of certain hormones, bone remodeling, necrotic cell death, cell surface repair, degradation, cellular development, programmed cell death, secretion, plasma membrane repair, and nutritional responses [7–15]. The diverse roles and responses of the lysosome to different stimuli suggest a coordinated regulation of expression of lysosomal genes [16–19]. According to recent findings, TFEB is a master regulator of lysosomal biogenesis [16,18,19]. Subsequently, we and others have demonstrated how TFEB regulates/can be regulated by factors not directly involved in lysosomal activity, viz. PPARα, PGC1α (PPARγ co-activator1α)—two of the major players in lipid metabolism and mitochondrial biogenesis [18,20–22]. In this article, we describe the interplay among three factors—TFEB, PPARα and PGC1α, and how this might contribute to our understanding of the cell signaling processes.

In our recent study, we have observed that the activation of the PPARα:RXRα:PGC1α complex by gemfibrozil and retinoic acid (RA) leads to the transcriptional activation of TFEB [20]. Although gemfibrozil, marketed as 'Lopid', is an agonist of PPARα and a FDA-approved drug for hyperlipidemia [23,24], it has been shown to have multiple beneficial effects [25–30]. The ability of gemfibrozil to cross blood–brain–barrier (BBB) has already been documented [31]. In another study, we have delineated the induction of *Cln2* gene in brain cells in response to gemfibrozil and RA [32]. Our recent findings indicate that either gemfibrozil or RA alone could increase TFEB levels, which was expected, as activation of either PPARα or RXRα could initiate the formation of PPARα:RXRα heterodimeric complex (Fig. 1). Further investigation suggests the possible role of PPARα in the process. PPARα has been shown to play significant role in different regulatory and modulatory pathways [33–37]. Certain polyunsaturated fatty acids and oxidized derivatives and lipid-modifying drugs of the fibrate family, including fenofibrate and gemfibrozil have been known to activate PPARα. Fibrate drugs replace the HSP90 repressor complex which sequesters PPARα in the cytosol and help to rescue the transcriptional activity of PPARα [29]. While assessing the role of the PPAR group of receptors in this phenomenon, we have seen the involvement of PPARα, but not PPARβ and PPARγ, in the upregulation of TFEB by gemfibrozil [20]. Furthermore, silencing of RXRα by siRNA also abrogates the effect of gemfibrozil and RA on TFEB induction, possibly due to reduced formation of PPARα:RXRα, resulting from the lower levels of RXRα. Presence of peroxisome proliferator responsive element (PPRE) in the *Tfeb* gene promoter and upregulation of reporter activity driven by *WT-Tfeb*, but not *mutated PPRE Tfeb*, promoter in response to gemfibrozil shows the direct involvement of PPARα in gemfibrozil-mediated transcription of *Tfeb* . Chromatin immunoprecipitation data also demonstrates the recruitment of the PPARα and RXRα along with PGC1α and RNA Pol on the PPRE site of the *TFEB* promoter, outlining a unique mechanism where gemfibrozil, a known activator of PPARα, and RA, an agonist of RXRα, together can upregulate *Tfeb* gene in brain cells via the formation of the PPARα:RXRα:PGC1α transcriptional complex. Furthermore, assessment of lysosomal content, as measured from Lysotracker Red positive signals, also indicates increased lysosomal biogenesis in WT and PPARβ (−/−), but not PPARα (−/−), cells when

http://dx.doi.org/10.1016/j.phrs.2015.11.011
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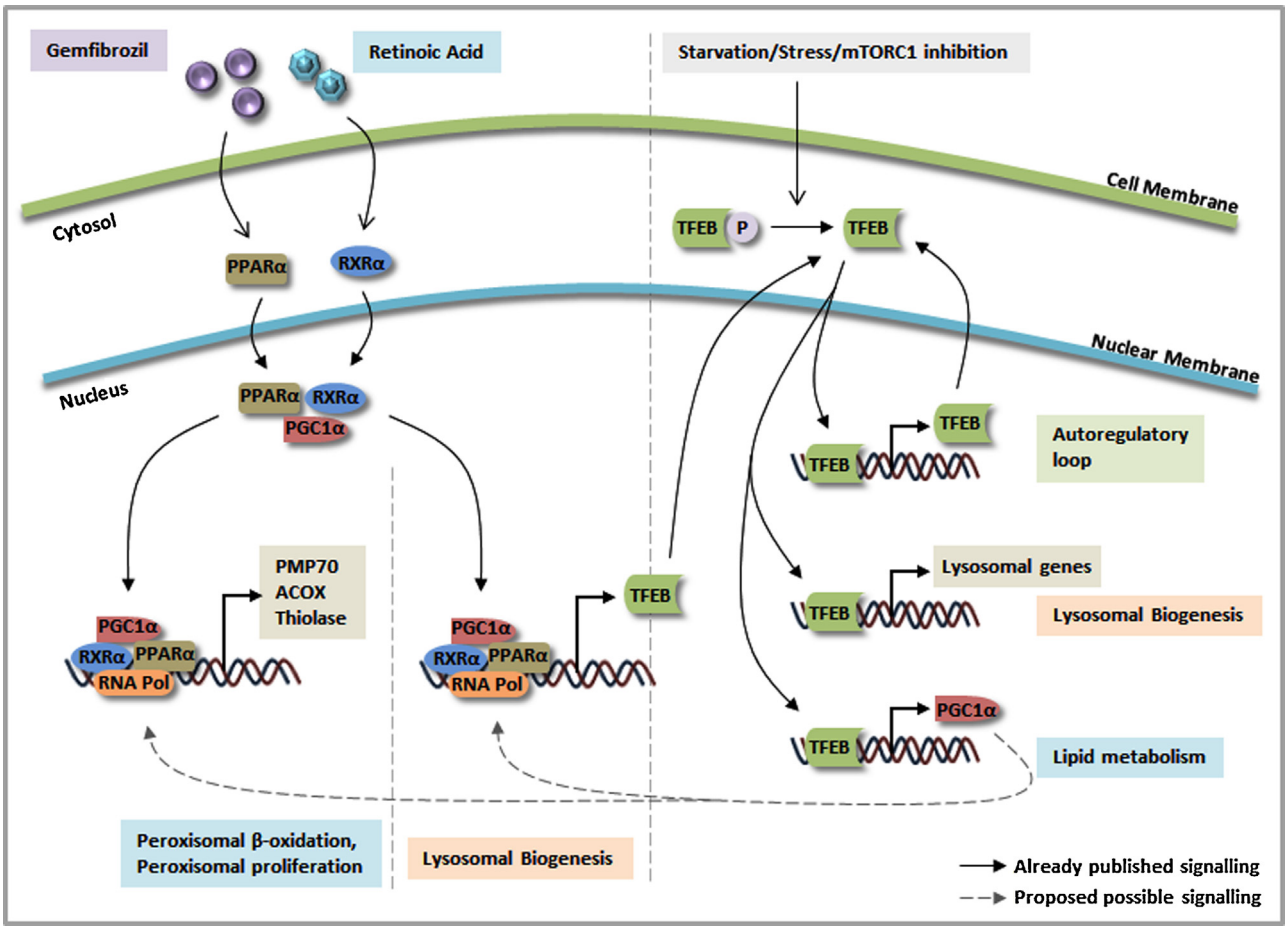

Fig. 1. Schematic representation of cross-talk between lysosomal biogenesis and lipid metabolism. While gemfibrozil activates PPARα, retinoic acid triggers RXRα. Then PPARα and RXRα form complex with PGC1α. In one hand, this complex binds to promoters of peroxisomal membrane protein 70 (PMP70), acyl-CoA oxidase (ACOX), thiolase, etc., ultimately leading to increased peroxisomal β-oxidation and peroxisomal proliferation. On the other, this complex is recruited to the TFEB gene promoter, leading to the transcription of TFEB and lysosomal biogenesis. In another pathway, starvation, stress and inhibition of mTORC1 (mammalian target of rapamycin complex 1) induce the dephosphorylation of TFEB, resulting in the activation of TFEB. Then activated TFEB binds to TFEB gene promoter to synthesize more TFEB (autoregulation) and more importantly leads to the transcription of genes specific for lysosomal function and biogenesis. Activated TFEB can also bind to the PGC1α gene promoter and PGC1α in turn may also stimulate lysosomal biogenesis and peroxisomal fatty acid β-oxidation.

stimulated with gemfibrozil and RA. Although one study reports lower levels of TFEB on day 4 of differentiation in PPARγ-null trophoblast stem (TS) cells, by using GW9662, a potent and known PPARγ antagonist, we do not find any substantial involvement of PPARγ in gemfibrozil-mediated upregulation of TFEB in brain cells [20,38]. This could possibly be due to variation in cell types, i.e., differentiating TS cells vs matured primary brain astrocytes/neurons or differential level of activation of PPARα.

Usually, the PPAR/RXR heterodimer regulates the transcription of genes for which products are involved in lipid homeostasis, cell growth and differentiation [35,39]. Gemfibrozil stimulates peroxisomal β-oxidation of very long chain fatty acids (VLCFA) by inducing the expression of peroxisomal β-oxidation enzymes (acyl-CoA oxidase, 2-*trans*-enoyl-CoA hydratase and thiolase) via PPARα-dependent pathways [40,41]. At the same time, gemfibrozil also upregulates the expression of catalase, carnitine acyltransferase and peroxisomal membrane protein-70 (PMP-70) via PPARα, which are involved in the clearance of H_2O_2 in peroxisome and the transport of VLCF-Acyl-CoA across peroxisomal membrane [42–46]. Additionally, gemfibrozil also mediates cholesterol efflux by upregulating ATP-binding cassette transporter (ABCA-1) by the action of PPARα responsive transcription factor liver X receptor α (LXRα) [47]. ABCA-1 facilitates the transfer of intracellular cholesterol molecule to extracellular HDL particle [48,49]. PPARα activation also leads to increased expression of NPC-1 and NPC-2 whose concerted action stimulates endosomal mobilization of cholesterol toward the plasma membrane [50]. Therefore, in certain storage diseases like neuronal ceroid lipofuscinosis (NCL) where the storage pigment are composed of lipid and protein, activation of PPARα may not only induce lysosomal biogenesis and subsequent clearance of storage materials, but may also play an important role in lowering the lipid content that contributes to the formation of toxic lipoprotein pigments.

A detailed study by Tsunemi et al. demonstrates a clinically relevant effect of PGC1α on TFEB regulation [21,51,52]. In Huntington disease (HD) transgenic mice, restoration of PGC1α reduces mutant htt protein aggregation and consequently ameliorates HD neurodegeneration. It is also observed that TFEB levels are lower in HD mice and that it could be rescued in HD transgenic mice by overexpression of PGC1α. Further investigation reveals that PGC1α can also transcriptionally activate TFEB expression and thereby controlling the autophagy-lysosomal pathway required for htt protein turnover. It is also noteworthy, that PGC1α not only plays an important role in lipid metabolism, but also a key factor for mitochondrial function. Another comprehensive study by Settembre et al., demonstrates that upregulation of TFEB could result in enhancement of its target genes involved in both autophagy and lipid metabolism [22]. The data suggest that 90% of genes involved in lipid catabolism are