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# PPARα in lysosomal biogenesis: A perspective

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## 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.

### Keywords

Lysosomal biogenesis; TFEB; Lipid metabolism; Fibrate drugs; 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

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[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. 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 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 towards 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 over-expression 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 upregulated by TFEB over-expression or starvation. Interestingly, among those genes that are significantly enhanced by increased TFEB activity are PPARα and PGC1α. According to the data [22], PGC1α is transcriptionally activated by TFEB upon starvation and deletion of TFEB reduces the expression of PGC1α. Furthermore, the authors [22] also suggest that PGC1α may control the lipid catabolism function of TFEB by controlling PPARα. However, compared to PGC1α, PPARα shows relatively lesser fold increase upon TFEB over-expression. Nevertheless, this study provides a detailed analysis of interaction between the lipid metabolism and TFEB expression and activity. It is quite possible that TFEB regulates lipid metabolism via PPARα and PGC1α, both of which have very significant role in regulating lipid metabolism. On the other hand, our data indicates that a direct stimulation of PPARα can induce the recruitment of PPARα:RXRα:PGC1α complex on the *Tfeb* promoter, thereby influencing lysosomal biogenesis [20].

Starvation deprives the cells of essential nutrients and the cell switches to its glycogen stores to be utilized as alternative fuel source for survival [53]. Therefore, upregulation of genes responsible for lipid catabolism is a logical event in case of starvation. The recent finding delineates a novel role of TFEB in controlling starvation-induced lipid metabolism, by directly inducing PGC1α, one of the primary regulators of lipid metabolism [22]. This is interesting because, PGC1α is also known to regulate mitochondrial function, and it is well

known that mitochondria play an important role in cellular energy production and lipid metabolism [54,55]. Moreover, the increase in the levels of PPARα, involved in peroxisomal proliferation and subsequent peroxisomal β-oxidation of fatty acids, provides a link between peroxisome, lipid metabolism, mitochondrial function, and lysosomal biogenesis. However, from a therapeutic perspective, in disease scenarios where induction of lysosomal biogenesis could be beneficial for degradation of pathological waste materials, starvation may not prove to be a feasible mode of treatment. In our study, we demonstrate that FDA approved drugs like gemfibrozil and RA potentially upregulate TFEB in brain cells [20]. However, our findings suggest that TFEB can be transcriptionally regulated by activation of PPARα and RXRα through external stimuli, and PGC1α is also involved in the process [20]. Another clinically relevant study shows that 5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one (Genistein), a natural isoflavone, increases both mRNA and protein levels of TFEB in a dose and time-dependent manner [56]. The study also shows detailed analysis of changes in TFEB expression, nuclear translocation and changes in expression profiles of TFEB target genes, and indicates that inhibition of mTORC1 by genistein to be the possible cause of TFEB activation and induction through its autoregulatory loop. However, it is interesting to note that genistein has also been shown to induce both mRNA and protein levels of PPARα, thereby enhancing genes involved in fatty acid catabolism [57]. In another study, the data suggest that 2-hydroxypropyl-β-cyclodextrin (HPβCD), an FDA approved excipient, activates TFEB nuclear translocation, resulting in enhanced autophagy and clearance of ceroid lipopigments in fibroblasts of patients with late infantile neuronal ceroid lipofuscinosis (LINCL) [58]. Interestingly, HPβCD has also been reported to induce PGC1α, when used as a complex with naringenin, a flavanoid aglycone [59]. Collectively, these findings indicate a nice crosstalk between the factors involved lipid metabolism and lysosomal biogenesis. However, there is an apparent contradiction in the sequence of events leading to TFEB regulation - whether TFEB is regulated by or TFEB itself regulates the genes responsible for lipid metabolism. In our opinion, the regulation of/by TFEB is more complex than it appears and based on the previous findings, there are certain possibilities which need to be investigated in detail to get a better picture of this complex cross-talk.

1) Presence of a bi-directional interplay between TFEB and lipid metabolism: It is well established that TFEB can regulate genes responsible for lipid metabolism and we have demonstrated that factors like PPARα and PGC1α can participate in transcriptional activation of TFEB [18,20-22]. Therefore, there is a possibility that activation of PPARα by its ligands results in TFEB upregulation which in turn further activates the lipid metabolism genes and may control its own subsequent activation by the autoregulatory loop. On the other hand, stress-mediated TFEB activation may induce the same signaling pathway, where PPARα and PGC1α would act as secondary activators of TFEB.

2) Stimuli- or tissue-specific activation of signaling pathway: A major concern for comparing the findings from different studies is the type of cell/tissue or animal models used in the studies. In this case, the regulation of lipid metabolism by TFEB was tested in mouse liver, whereas, experiments for PPARα or PGC1α mediated transcriptional activation of TFEB was performed in mouse brain tissue/cells [20-22]. The expression and activity levels of nuclear hormone receptors and associated co-activators and the response to stimuli (starvation, drug treatment, etc.) vary between cell types and tissues. It would be interesting

to investigate, how the TFEB and lipid metabolism signaling axis is activated in different tissue/cells in response to different stimuli.

However, more detailed studies are necessary to decipher the presence of any such feed forward regulatory mechanism and the apparent bi-directional interplay between lipid metabolism and lysosomal biogenesis as well as any possible variations based on the stimuli and tissue.

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