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VIEWPOINT

Reevaluating the roles of PPARs and nuclear receptors in human peroxisome biology

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Peroxisome biogenesis in humans is not governed by PPARα, overturning a paradigm established in rodents. PPARα agonists fail to induce canonical peroxisomal genes, and functional response elements are absent from key promoters. Human peroxisomes nonetheless expand through PPAR-independent pathways, positioning them as organelles tuned to immunometabolic and redox demands and redefining strategies for therapeutic intervention.

Introduction

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptor transcription factors that regulate lipid metabolism and energy homeostasis. Their discovery was linked to the ability of xenobiotic peroxisome proliferators to drive peroxisome biogenesis in rodents, establishing a paradigm in which PPAR activation was presumed to be the principal determinant of peroxisome abundance. However, while this model holds across many mammalian species, evidence has challenged its applicability to humans. Here, we revisit the historical basis of PPAR-mediated peroxisome regulation and propose that while human peroxisomes are inducible, the extent and nature of their induction have diverged significantly from this classical PPAR-driven paradigm established in rodents. Resolving these species-specific differences is critical for understanding peroxisomal contributions to human metabolism, disease pathology, and therapeutic intervention.

Peroxisome proliferation as a druggable target

The biochemical identity of peroxisomes became inseparable from their morphological plasticity when hypolipidemic agents—compounds that lower circulating lipid levels—induced a striking expansion of peroxisomes in rodent livers to the point that peroxisomes displaced other organelles (Fig. 1) (Svoboda and Azarnoff, 1966). This expansion suggested a functional link between peroxisomes and lipid metabolism, an idea substantiated by the discovery of peroxisomal β-oxidation (Lazarow and de Duve, 1976). The capacity to induce peroxisome proliferation pharmacologically implied a level of molecular regulation beyond passive metabolic demand, catalyzing efforts to exploit peroxisomal control as a therapeutic avenue for metabolic disease. Structurally diverse peroxisome proliferators, including fibrates, phthalate ester plasticizers, herbicides, and long-chain fatty acids, initiate both peroxisome expansion and the coordinated upregulation of peroxisomal enzymes. This response suggested that peroxisome abundance was transcriptionally controlled rather than dictated by metabolic flux alone. The search for mediators of this regulation converged on nuclear receptors, revealing a mechanism in which peroxisome biogenesis is transcriptionally programmed, rather than passively accumulated, in response to environmental and physiological cues.

The regulatory logic of peroxisome biogenesis

Nuclear receptors form a superfamily of ligand-activated transcription factors that coordinate gene expression in response to metabolic and hormonal cues. PPARs belong to a subclass of orphan nuclear receptors that are responsive to fatty acids and their derivatives, thereby coupling directly transcriptional control to lipid metabolism.

The identification of PPARs revealed a transcriptional framework in which peroxisome abundance adjusts dynamically to metabolic demand (Issemann and Green, 1990). In simpler eukaryotes, a single transcription factor pair suffices to activate β-oxidation genes in response to fatty acids (Fig. 1). In mammals, the expansion of lipid metabolic networks is coupled to a diversification of the nuclear receptor repertoire, yielding three PPAR isoforms that partition transcriptional control over distinct metabolic programs (Evans and Mangelsdorf, 2014).

As revealed primarily in rodent models, PPARα, enriched in oxidative tissues, such as liver, heart, and muscle, induces peroxisomal and mitochondrial β-oxidation, coupling lipid catabolism to energy demand. PPARγ regulates adipocyte differentiation and lipid uptake, promoting storage and insulin sensitivity (Fig. 1). PPARδ finely tunes systemic lipid utilization, governing β-oxidation and thermogenesis in muscle and brown adipose tissue. All three PPAR isoforms are contingent on obligate heterodimerization with retinoid X receptors (RXRs), imposing a transcriptional logic characteristic of asymmetric self-upregulation (Ratushny et al., 2012) (Fig. 1). Here, PPARs serve as metabolic sensors responding to lipid-derived ligands, while RXR provides a constitutive regulatory scaffold insulated

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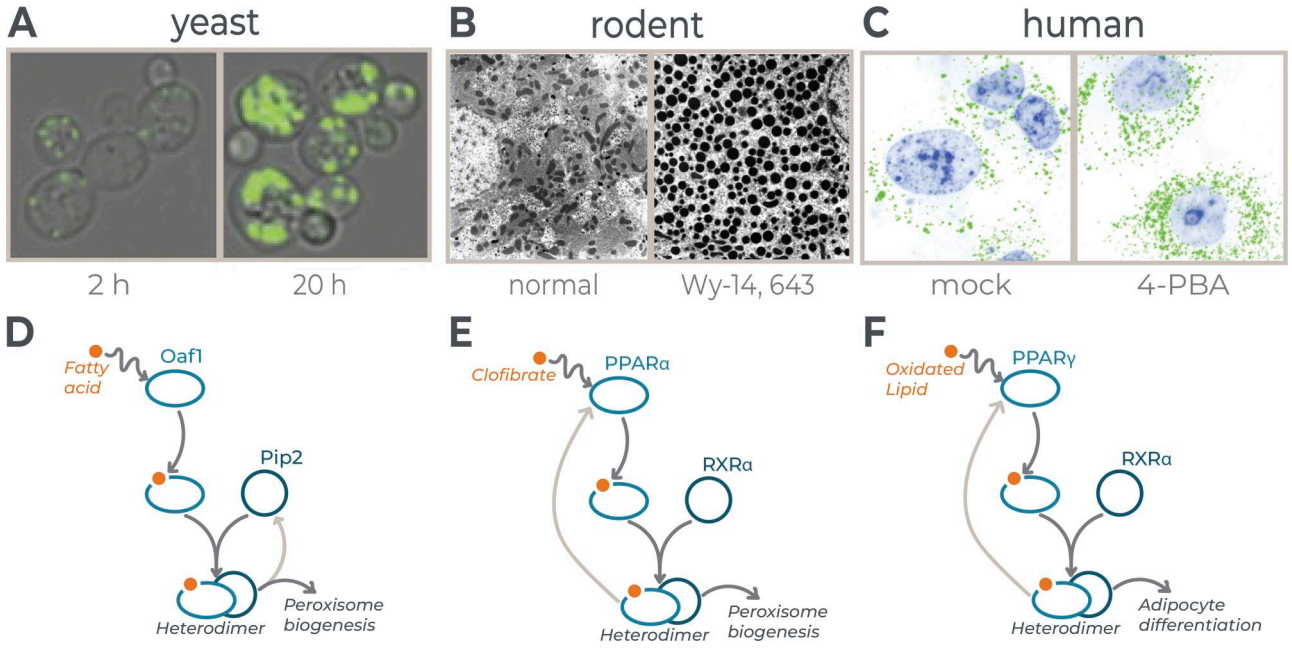

Figure 1. **The dynamics of peroxisome proliferation and species-specific transcriptional control of peroxisome biogenesis. (A)** *Saccharomyces cerevisiae* cells expressing Pot1-GFP, a peroxisomal protein, were imaged after 2 and 20 h of oleic acid induction. Peroxisome number and size increase markedly over time, reflecting transcriptional activation of the biogenic program. Image area: 30 × 30 µm. Reproduced from Saleem et al. (2008). **(B)** Transmission electron micrographs of rodent hepatocytes under basal conditions (left) and after treatment with the peroxisomal proliferator Wy-14,643 (right), showing robust induction of peroxisome proliferation. Modified from (Reddy, 2004), with permi. **(C)** Immunofluorescence microscopy of huh7 cells treated with 4-phenylbutyrate (4-PBA) or mock (DMSO) control. Peroxisomes (green) are markedly increased in number following 4-PBA treatment. Image area: 16 × 16 µm. **(D–F)** Transcriptional circuits regulating peroxisome abundance in yeast and rodents and adipocyte differentiation in humans. Altered from Ratushny et al. (2012). **(D)** In yeast, fatty acids activate Oaf1, which heterodimerizes with Pip2 to induce expression of peroxisomal genes. **(E)** In rodents, the hypolipidemic drug clofibrate activates PPARα, which forms a heterodimer with RXRα to stimulate transcription of peroxisomal genes. **(F)** In humans, oxidized lipids activate PPARγ, which dimerizes with RXRα to primarily regulate the expression of genes involved in adipogenesis; PPARγ activation does not robustly drive peroxisome biogenesis.

from feedback. This architecture confers a robust and tunable response, buffering transcriptional output against variations in heterodimer affinity while preserving sensitivity to ligand availability.

Still, PPARs do not function in isolation. Their transcriptional programs intersect with broader nuclear receptor networks that shape peroxisome function (Evans and Mangelsdorf, 2014). These interactions establish peroxisomes as metabolic-responsive organelles, attuned to nuclear receptor transcriptional logic and to shifting physiological and environmental demands.

The PPAR-peroxisome paradigm is mechanistically coherent, its phenotypic effects in rodents unmistakable, and its logic pervasive enough to feel universal. And yet, in humans, it fails.

Beyond universality: The reconfiguration of human peroxisomes and PPAR function

The assumption that nuclear receptors universally govern peroxisome biogenesis does not hold in hominids. In rodents, PPARα couples fasting to lipid oxidation, transcriptionally coordinating peroxisomal β-oxidation with systemic metabolic demand. In contrast, human hepatocytes fail to mount this response, peroxisome proliferators do not induce peroxisomal expansion, and canonical peroxisomal genes remain unresponsive to PPARα activation. Yet peroxisomes in humans remain inducible (Fig. 1). Their abundance and protein composition vary by tissue and developmental context (Mast et al., 2020), supporting roles in liver regeneration, cardiomyogenesis, auditory protection, skeletal muscle lipid metabolism, and macrophage-related myelin clearance. Peroxisomes adapt to immunologic context as well, remodeling in response to viral infection and contributing to the architecture of signaling platforms such as MAVS and mTOR. The regulatory disconnect is not due to receptor loss but to a fundamental reconfiguration of peroxisomal gene regulation.

Peroxins (PEX proteins) constitute the core machinery for peroxisome biogenesis. In humans, the expression of PEX genes is driven by promoters that lack functional peroxisome proliferator response elements (PPREs), thereby severing peroxisomal gene expression from direct transcriptional activation by PPARs, particularly PPARα. In rodents, PPARα agonists drive robust induction of genes for acyl-CoA oxidase (ACOX1), the peroxisomal ATP-binding cassette transporter ABCD3, and other peroxisomal proteins; yet in cynomolgus monkeys and humans, the ACOX1 promoter retains a putative PPRE that remains unresponsive to PPARα agonists active in other organisms (Kane et al., 2006). Even when PPARα is overexpressed to supraphysiological levels in human HepG2 cells, peroxisomal gene expression remains unaltered (Lawrence et al., 2001). The failure of rat PPARα to restore peroxisomal gene activation in human hepatocytes also underscores that the regulatory autonomy of human peroxisomes arises not from insufficient receptor availability but from a broader transcriptional reorganization (Ammerschlaeger et al., 2004).

Genome-wide analysis of PPARα binding in human hepatocytes reveals extensive chromatin occupancy by PPARα upon agonist stimulation, yet peroxisomal genes are conspicuously absent from its target repertoire (van der Meer et al., 2010). Instead, PPARα is repurposed toward mitochondrial lipid metabolism, governing ketogenesis, cholesterol homeostasis, and fatty acid oxidation. The mechanistic basis of this realignment remains unresolved, but interactions of PPARα with SREBP, STAT, and C/EBPα suggest that peroxisomal control has been redistributed across alternative transcriptional programs (van der Meer et al., 2010). Through this rewiring, PPARα retains its metabolic role in lipid metabolism but relinquishes direct peroxisomal control, thereby transitioning from a peroxisome-proliferating agent to a regulator of mitochondrial oxidative capacity.

PPARγ may retain a limited regulatory foothold over select peroxisomal genes, though its role appears highly context-dependent. PPARγ agonist treatment results in mild induction of the peroxisome biogenic genes PEX3 and PEX16 in keratinocytes, suggesting that peroxisome formation is influenced directly or indirectly by nuclear receptor activation in select epithelial and mesenchymal lineages (Karnik et al., 2009). A similar effect is observed in fibrotic lung fibroblasts, where PPARγ activation partially rescues peroxisomal biogenesis following TGF-β1 suppression, restoring PEX13 and catalase levels. These findings suggest that while PPARγ has not supplanted PPARα as a primary regulator of peroxisomes in humans, PPARγ retains a residual influence on peroxisomal maintenance in certain cellular contexts. Whether this reflects immune-metabolic specialization or vestigial regulatory function of PPARγ remains unresolved, but the attenuation of PPARα control over peroxisomal genes marks a fundamental divergence in peroxisome regulation between rodents and humans.

Although human peroxisomes are uncoupled from canonical PPARα-mediated control, they remain metabolically responsive via alternative pathways. For example, 4-phenylbutyrate stimulates peroxisome proliferation independently of PPAR activation, underscoring the existence of compensatory pathways. Likewise, overexpression of PPARγ coactivator 1-alpha, a transcriptional coactivator best known for regulating mitochondrial biogenesis, elevates PEX11A, PEX13, and PEX16 expression in human U2OS cells (Bagattin et al., 2010). Whether this reflects direct transcriptional engagement of peroxisome genes or arises secondarily from elevated mitochondrial oxidative demand remains unresolved. Importantly, these findings, together with the putative context-dependent role of PPARγ, illustrate that peroxisome regulation in hominids is not organized as a linear transcriptional hierarchy but rather as an integrated signal-responsive system. This distinction has been obscured by the assumption of conserved PPAR-centric control.

Decoupling peroxisomes and PPARs: Evolutionary constraints and specialization

What evolutionary pressures drove dismantling of nuclear receptor control over peroxisomes in hominids?

One possibility is that loss of PPAR-mediated peroxisomal expansion in humans parallels another metabolic shift, i.e., the inactivation of urate oxidase, the peroxisomal enzyme required for purine catabolism. Unlike other lost enzymes that were reassigned to other pathways, urate oxidase was lost without replacement, leaving xanthine oxidase as the terminal peroxisomal enzyme in purine degradation and elevating systemic uric acid (Friedman et al., 1985). Despite being linked to diseases like gout, hypertension, and metabolic syndrome, the relative abundance of uric acid may have benefits to humans that include enhanced redox buffering, metabolic adaptations to fructose-rich diets, and immunomodulatory effects. Thus, its evolutionary persistence suggests that uric acid may serve a meaningful adaptive function that extends beyond passive metabolic redundancy (Álvarez-Lario and Macarrón-Vicente, 2010). Like PPAR regulation, the loss of urate oxidase is not an isolated event but part of a broader evolutionary shift that repositions peroxisomes within a distinct human regulatory landscape, uncoupling their function from ancestral metabolic constraints and integrating them into emerging immunometabolic and redox networks.

This shift extends beyond peroxisomes, reflecting a broader evolutionary reorganization of metabolic control in hominids. Just as peroxisomes have shed their dependence on nuclear receptor control, PPARs themselves have undergone evolutionary specialization (Xie et al., 2025). In rodents, PPARα couples fasting with peroxisomal β-oxidation, whereas in humans, PPARα is repurposed for mitochondrial metabolism, ketogenesis, and cholesterol homeostasis. The key distinction is not whether rodent peroxisomes have immunometabolic roles, because they do, but rather what is gained by decoupling peroxisomal expansion from systemic transcriptional control in hominids.

We propose that this decoupling, coincident with urate oxidase loss, enabled peroxisome specialization within hominid immunometabolic niches (Di Cara et al., 2023; Ye et al., 2025). In this context, peroxisomes act more as locally tuned redox–lipid regulators than as uniformly proliferating metabolic organelles. In tissue macrophages and neutrophils, peroxisomes buffer urate-driven danger signaling by detoxifying H_2O_2 and modulating NLRP3 inflammasome thresholds, thereby calibrating sterile inflammation—the inflammatory response triggered by endogenous danger signals rather than microbes. Within the inflammatory milieu, peroxisomal β-oxidation of ω-oxidized eicosanoids promotes resolution by generating specialized pro-resolving mediators, a class of lipid-derived signals that actively turn off inflammation and drive tissue repair, thereby restraining collateral damage. Peroxisome–phagosome contacts further optimize lipid composition and ROS balance during pathogen killing, while in T cells and memory lymphocytes, peroxisomal fatty acid oxidation and acetyl-unit export reinforce persistence (sustained survival and function) and trained immunity (epigenetically programmed innate immune memory). In the central nervous system, microglial and astrocytic peroxisomes integrate uric acid's priming effects with local redox buffering, protecting synapses, and long axons from runaway inflammation. In each case, the selective advantage derives not from bulk proliferative capacity but from context-specific control, embedding peroxisomes within immune circuits that support barrier defense, adaptive memory, and neuroimmune resilience, at the cost of heightened susceptibility to gout, sterile inflammation, and neurodegeneration.

Whether this transition conferred a net advantage or constraint to humans remains unresolved. The evolutionary specialization and differential control of peroxisomes in

humans may have led to a greater precision in what peroxisomes do by localizing peroxisomal function within specialized niches and enabling selective regulation under defined conditions. The challenge is to decode the molecular architecture that governs human peroxisomes so as to determine whether their adaptability can be therapeutically harnessed to combat peroxisomal, infectious, and metabolic diseases.

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