Review

Peroxisome biogenesis in mammalian cells: The impact of genes and environment☆

Rebecca L. Farr [a,b], Celien Lismont [a], Stanley R. Terlecky [b], Marc Fransen [a,*]

[a] Laboratory of Lipid Biochemistry and Protein Interactions, Department of Cellular and Molecular Medicine, KU Leuven—University of Leuven, Herestraat 49 box 601, B-3000 Leuven, Belgium
[b] Department of Pharmacology, Wayne State University School of Medicine, 540 E. Canfield Ave., Detroit, MI 48201, USA

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ABSTRACT

The initiation and progression of many human diseases are mediated by a complex interplay of genetic, epigenetic, and environmental factors. As all diseases begin with an imbalance at the cellular level, it is essential to understand how various types of molecular aberrations, metabolic changes, and environmental stressors function as switching points in essential communication networks. In recent years, peroxisomes have emerged as important intracellular hubs for redox-, lipid-, inflammatory-, and nucleic acid-mediated signaling pathways. In this review, we focus on how nature and nurture modulate peroxisome biogenesis and function in mammalian cells. First, we review emerging evidence that changes in peroxisome activity can be linked to the epigenetic regulation of cell function. Next, we outline how defects in peroxisome biogenesis may directly impact cellular pathways involved in the development of disease. In addition, we discuss how changes in the cellular microenvironment can modulate peroxisome biogenesis and function. Finally, given the importance of peroxisome function in multiple aspects of health, disease, and aging, we highlight the need for more research in this still understudied field. This article is part of a Special Issue entitled: Peroxisomes.

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1. Introduction

Throughout their lifetime, organisms are continually exposed to a multitude of genetic, biological, environmental, and behavioral risk factors governing disease susceptibility. To survive and flourish against such a backdrop, they have to react appropriately to new circumstances as they arise. Most, if not all, organisms have the ability to respond to internal and external stimuli with altered programs of gene expression. This temporally and spatially regulated process, often referred to as 'epigenetic reprogramming', is driven in large part by changes in chromatin structure (e.g., DNA methylation and histone modifications) and gene transcription levels (e.g., transcription factor regulation and RNA processing) [1]. In general, these changes are coordinated by a diverse array of

signals related to cellular metabolic state (e.g., $NAD^+/NADH$ ratios, tricarboxylic acid (TCA)[1] cycle intermediates, total and reduced glutathione concentrations, and acetyl-coenzyme A (acetyl-CoA) levels) [2]. Over recent decades, peroxisomes have emerged as key regulators in overall cellular lipid metabolism [3]. In addition, these organelles have been recognized as important intracellular hubs for redox-, lipid-, and inflammatory-mediated signaling pathways, and – very

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[1] Abbreviations: 4-PBA, 4-phenylbutyrate; 5mC, 5-methylcytosine; α-KG, α-ketoglutarate; ABCD, ATP-binding cassette, subfamily D; ART, ADP-ribosyltransferase; CoA, coenzyme A; DDM, DNA demethylase; DHA, docosahexaenoic acid; DNMT, DNA methyltransferase; ERT, enzyme replacement therapy; FAD, flavin adenine dinucleotide; FDA, United States Food and Drug Administration; GSH (reduced) glutathione; GSSG, oxidized glutathione; HAT, histone acetylase; HDAC, histone deacetylase; HDM, histone demethylase; HIF, hypoxia inducible factor; HMT, histone methyltransferase; JmjC, Jumonji C; IDH, isocitrate dehydrogenase; IRD, infantile Refsum disease; miR, microRNA; NAD(P)(H), (reduced) nicotinamide adenine dinucleotide (phosphate); NALD, neonatal adrenoleukodystrophy; ncRNA, non-coding RNA; PARP, poly(ADP-ribose) polymerase; PBD, peroxisome biogenesis disorder; PED, peroxisomal enzyme/transporter deficiency; PPAR, peroxisome proliferator-activated receptor; PPARGC1A, PPAR γ coactivator 1α; PTS1, C-terminal peroxisomal targeting signal; RCDP, rhizomelic chondrodysplasia punctata; ROS, reactive oxygen species; SAH, S-adenosylhomocysteine; SAHA, suberoylanilide hydroxamic acid; SAM, S-adenosylmethionine; RXR, retinoid X receptor; TCA, tricarboxylic acid; VLCFA, very-long-chain fatty acid; X-ALD, X-linked adrenoleukodystrophy; ZS, Zellweger syndrome; ZSD, Zellweger spectrum disorder.

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* Corresponding author at: University of Leuven, Department of Cellular and Molecular Medicine, Laboratory of Lipid Biochemistry and Protein Interactions, Herestraat 49 box 601, 3000 Leuven, Belgium.
E-mail address: marc.fransen@med.kuleuven.be (M. Fransen).

recently – as the primary sites that initiate type III interferon expression in response to viral and bacterial infections (see [4–6], and references therein). Despite these developments, the cause and effect relationships that exist between peroxisomal (dys)functions and epigenetic alterations are just starting to be explored.

In the following sections, we first provide background information on the mechanisms by which cells integrate genetic and environmental stimuli and translate them into phenotypic outcomes. Next, we explore the link between genetic/environmental interactions and peroxisome biogenesis/function in mammalian cells. Finally, we highlight research directions designed to extend our knowledge in these areas. This is of paramount importance, given that peroxisomes play a pivotal role in human physiology and that effective therapeutic strategies for treatment of patients with peroxisomal deficiencies are still very much limited [7].

2. Molecular mechanisms of epigenetics

Epigenetic changes are a critically important mechanism by which the environment directly impacts gene expression without changing the underlying genomic sequence. As currently understood, these changes are brought about by DNA methylations, histone modifications, and non-coding RNA regulations [1]. In the following sections, we briefly outline epigenetic alterations that can be directly, or indirectly, linked to changes in peroxisomal function.

2.1. DNA methylations

DNA methylation is a process in which methyl groups are added to cytosine or adenine nucleotides in genomic DNA. In mammals, methylation typically takes place on cytosine residues immediately preceding guanine bases. As cytosine methylation both physically impedes transcription factor binding and attracts specific methyl-DNA binding proteins that subsequently recruit other chromatin remodeling proteins that can modify histones (e.g., histone deacetylases; see Section 2.2.2), this process is, in general, associated with transcriptional repression [8]. DNA methylation is catalyzed by a family of S-adenosylmethionine (SAM)-dependent enzymes, called DNA methyltransferases (DNMTs), that transfer a methyl group from SAM to the 5-position of cytosine to form 5-methylcytosine (5mC), yielding S-adenosylhomocysteine (SAH) as a byproduct [9]. DNA demethylation can be achieved in both passive and active fashion. For example, as DNMT1 maintains methylation during DNA replication, its inhibition allows newly incorporated cytosine to remain unmethylated [9]. Active DNA demethylation in mammals is a complex multistep process that is controlled by DNA demethylases (DDMs) that belong to different protein families (e.g., TET, BER, and AID/APOBEC). For additional details regarding these enzymes and the chemical intermediates that are formed during the demethylation process, we refer the reader to Kohli and Zhang [10].

2.2. Histone modifications

Histones are a family of basic proteins that package nuclear DNA into structural units, called nucleosomes. These proteins can undergo a wide variety of posttranslational modifications, including methylation, acetylation, ADP-ribosylation, phosphorylation, ubiquitination, and sumoylation. These and other modifications contribute to a precise regulation of gene expression by controlling chromatin conformation (e.g., through electrostatic and structural changes) and providing binding sites for non-histone DNA-binding proteins such as transcription factors, transcriptional coactivators, and chromatin remodeling complexes [11]. As there is little evidence that links peroxisomes to histone phosphorylation, ubiquitination, and sumoylation, these modifications will not be considered further here.

2.2.1. Histone methylations

In mammals, there are different classes of histone methyltransferases (HMTs) and histone demethylases (HDMs) that control the methylation status of particular lysine and arginine residues in histones. The functional outcome of histone methylation strongly depends on the number of methyl groups that are added and the location/context of where they occur [8]. Like DNMTs, all HMTs use SAM as a cofactor and methyl donor and produce SAH as a byproduct. HDMs are classified into two distinct groups depending on their catalytic mechanism: lysine-specific demethylases, which are FAD-dependent amine oxidases; and demethylases containing a Jumonji C domain (JmjC) that catalyze a dioxygenase reaction dependent on Fe^{2+} and α-ketoglutarate (α-KG) [12].

2.2.2. Histone acetylations

Histones can be acetylated on specific lysine residues. This process neutralizes the basic charge of these residues, thereby promoting a general relaxation of chromatin structure and an induction of gene expression [8]. The acetylation status of histones is controlled by a dynamic interplay of histone acetylases (HATs) and histone deacetylases (HDACs). HATs require cytoplasmic acetyl-CoA as donor of the acetyl moiety and release free coenzyme A (CoA) [13]. HDACs yield free acetate that subsequently can be incorporated into acetyl-CoA by acetyl-CoA synthetases. HATs and HDACs are classified into multiple protein families, each having distinct opportunities for mechanistic regulation [8]. In the context of this review, it is important to mention that class I and class II HDACs (the non-sirtuin HDACs) share a catalytic mechanism that involves the coordination of a divalent metal ion, and class III HDACs (the sirtuins) are NAD^+-dependent histone deacetylases whose activity is controlled by the cellular $[NAD^+]/[NADH]$ ratio. Note also that the activity of the non-sirtuin HDACs is influenced by the availability of metabolic intermediates such as free CoA, CoA-derivatives, butyrate, and NADPH [14].

2.2.3. Histone ADP-ribosylation

ADP-ribosylation is an important posttranslational modification in which one or more ADP-ribose moieties are added to a protein. The addition of ADP-ribosome units to histones is catalyzed by members of the poly(ADP-ribose) polymerase (PARP) protein family and occurs preferentially on glutamate or lysine residues [8]. This modification can affect gene expression at various levels (e.g., relaxation of chromatin structure, transcription factor binding, and mRNA processing). Importantly, all ADP-ribosyltransferase (ART) family members consume NAD^+ and release nicotinamide as a byproduct [8]; and excessive PARP activity may cause cell dysfunction (or even cell death) due to a depletion of NAD^+ and the subsequent drop in ATP levels [8]. Mono- and poly(ADP-ribose) moieties can also be enzymatically removed from histones — for more details, see [15].

2.2.4. Regulatory non-coding RNAs

The discovery that some classes of non-coding RNAs (ncRNAs) can also silence transcriptional activity has added an additional layer of complexity to how genes are expressed. The modes of action of these regulatory ncRNAs can vary depending on their size, structure and function. For example, long (>200 nucleotides) regulatory ncRNAs, which are often tissue-specifically expressed and involved in the long-term silencing of particular developmental control genes [8], can function as decoys, scaffolds, or guides for regulatory proteins and protein complexes [16]. Other regulatory ncRNAs such as microRNAs (miRs; ~21–22 nucleotides), and piwi-interacting RNAs (~24–30 nucleotides), can negatively impact gene expression by binding to the 3′-untranslated region of target mRNAs [1]. Importantly, regulatory ncRNAs have emerged as critical factors in cellular metabolism and development; altered expression of these molecules has been implicated in a number of diseases [1].