Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Cell Biology

Signaling dynamics and peroxisomes

Fred D Mast[1,2], Richard A Rachubinski[3] and John D Aitchison[1,2]

Peroxisomes are remarkably responsive organelles. Their composition, abundance and even their mechanism of biogenesis are influenced strongly by cell type and the environment. This plasticity underlies peroxisomal functions in metabolism and the detoxification of dangerous reactive oxygen species. However, peroxisomes are integrated into the cellular system as a whole such that they communicate intimately with other organelles, control signaling dynamics as in the case of innate immune responses to infectious disease, and contribute to processes as fundamental as longevity. The increasing evidence for peroxisomes having roles in various cellular and organismal functions, combined with their malleability, suggests complex mechanisms operate to control cellular dynamics and the specificity of cellular responses and functions extending well beyond the peroxisome itself. A deeper understanding of the functions of peroxisomes and the mechanisms that control their plasticity could offer opportunities for exploiting changes in peroxisome abundance to control cellular function.

Addresses
[1] Center for Infectious Disease Research, formerly Seattle Biomedical Research Institute, Seattle, USA
[2] Institute for Systems Biology, Seattle, USA
[3] Department of Cell Biology, University of Alberta, Edmonton, Canada

Corresponding author: Aitchison, John D (John.Aitchison@CIDResearch.org)

Current Opinion in Cell Biology 2015, **35**:131–136

This review comes from a themed issue on **Cell organelles**

Edited by **Maya Schuldiner** and **Wei Guo**

For a complete overview see the Issue and the Editorial

Available online 29th May 2015

http://dx.doi.org/10.1016/j.ceb.2015.05.002

Introduction

Peroxisomes are spherical compartments delimited by a single phospholipid bilayer and are found distributed throughout the cytoplasm of most eukaryotic cells. In most cell types investigated to date, peroxisomes exhibit remarkable plasticity, responding to various environmental stimuli to alter their size and number per cell and their metabolic functions [1]. Peroxisomes are formed by two separate, and possibly complementary, biogenesis pathways: *de novo* budding from the endoplasmic reticulum (ER), and growth and division of existing peroxisomes [1,2]. They possess a posttranslational protein translocation system, termed the peroxisomal importomer [3], which imports exclusively fully folded, and sometimes oligomeric, protein complexes composed of enzymes destined for the peroxisomal matrix together with their peroxisome-targeting chaperone [4–6]. Peroxisomes are metabolically plastic, which is due in part to the enzyme-mediated production of, and protection from, reactive oxygen species (ROS) and the broad specificity in substrates these oxidative reactions confer [7]. Beyond their metabolic functions, and in alignment with an increasing recognition of the complexity and interconnectedness of various components of the cell, peroxisomes are increasingly being revealed as hubs or platforms for signaling in their own right, with roles critical for innate immunity, development and differentiation [8]. Therefore, the mechanisms controlling the plasticity of peroxisomes and the formation of signaling complexes on peroxisomes offer exciting avenues for research. In this review, we highlight recent findings from yeast and mammalian cells that reveal the coordinated control that gives rise to both the dynamic formation of peroxisomes and the signaling events carried out at the organelle.

Peroxisomes — control at the level of transcription

Factors involved in the biogenesis and proliferation of peroxisomes have been well conserved during evolution [9], and particularly since the divergence of metazoan and fungal lineages some 1.5–1.2 billion years ago. *PEX* genes encode proteins called peroxins that facilitate the varied aspects of the peroxisome life cycle, including membrane protein targeting, matrix protein targeting and translocation, peroxisome division, peroxisome movement, and selected peroxisome turnover, or pexophagy. This conservation in cellular pathways regulating peroxisomal biogenesis extends to the underlying transcriptional response to environmental and metabolic signals that initiate peroxisome proliferation. Ligand-mediated regulation of genes coding for peroxisomal proteins in the budding yeast *Saccharomyces cerevisiae* starts with the fatty-acid-mediated activation of the oleate-activated transcription factor 1 and peroxisome induction pathway 2 (Oaf1/Pip2) heterodimer [10,11]. Upon its binding to a fatty acid, Oaf1 complexes with Pip2 to form a heterodimer, which binds to DNA sequences known as oleate response elements located in the upstream promoter regions of many peroxisomal genes, including *PIP2* itself. Similarly, transcriptional regulation of peroxisomal genes in mammals was first discovered in rodent models where peroxisome proliferators such as fatty acids, but also hypolipidemic drugs, activate the peroxisome proliferator-activated receptor

(PPAR) and retinoic acid receptor (RAR) family of nuclear receptors, leading to the upregulation of expression of genes encoding peroxisomal proteins and the proliferation of peroxisomes [12,13].

Closer examination of the kinetics of regulation of the Oaf1/Pip2 and PPAR/RAR heterodimers revealed that they function as asymmetric positive feedback loops, so named because ligand-mediated heterodimerization upregulates the expression of only one member of the heterodimer pair [14•]. Asymmetric positive feedback is a core network motif and a prominent feature of many biomolecular regulatory systems, including systems involved in adipocyte differentiation, cholesterol homeostasis, myogenesis and cellular antiviral response [14•]. Mathematical and experimental tests comparing asymmetric positive feedback, termed ASSURE for ASymmetric Self-UpREgulation, to a symmetric positive feedback (SPF) system where both regulators are upregulated upon activation revealed the ASSURE motif to be more robust. For example, the response time of ASSURE was robust to changes in ligand K_d and provided the cell with the ability to adapt to rapid changes in environmental conditions [14•].

The Oaf1/Pip2 heterodimer does not regulate peroxisomal genes exclusively. Instead, this core regulatory motif functions within a larger regulatory network that coordinates peroxisome induction with many other activities (Figure 1a). For example, the network includes alcohol dehydrogenase regulator 1 (Adr1) [15,16], a global regulator of glucose-repressed genes [17,18], and Oaf3, a negative regulator of Oaf1/Pip2 that serves to dampen the cellular response to their autoactivation [19]. Yet, even these four regulators are insufficient to explain all of the transcriptional control of peroxisome biogenesis; whereas most of the metabolic machinery and fatty acid transporters required for the β-oxidation of oleate respond dramatically to oleate and are controlled by Oaf1/Pip2, of the 34 *PEX* genes in yeast, only *PEX5*, *PEX6*, *PEX11* and *PEX18* are similarly responsive [20].

A network model has been developed that predicts the transcriptional response of yeast to oleate exposure on a genome-wide level [20]. This network was generated by integrating data from a compendium of 1516 publicly available mRNA expression datasets, known network interactions, and common promoter regions for known transcription factor binding motifs. The topology of the network was then explored with a linear regression algorithm that made predictions for the ability of any given transcription factor to control the expression of a given bicluster, that is, a collection of genes with coherent expression profiles, for a given environmental condition. Focusing on the transcriptional control of peroxisome biogenesis, predicted regulators were validated in more focused studies that included time course analysis of transcriptional responses, analysis of regulator deletion data, ChIP-chip data and transcription factor binding motif data. This analysis revealed complex transcriptional networks that coordinate transcriptional activities across the genome.

Given the complexity of transcriptional control of peroxisome proliferation in yeast, it is perhaps not surprising that mechanisms to control peroxisome numbers in mammalian cells are not well understood. For example, evidence for a role of the eponymously labeled PPARs in regulating the transcription of peroxisomal genes in humans is lacking [13]. The upstream promoter elements of human peroxisomal genes lack canonical PPAR-binding elements, and the evidence for the transcriptional regulation of peroxisomal genes by PPARs is indirect. For example, ChIP-chip analysis of PPARα chromatin binding in response to treatment with agonist found enrichment for the promoter region of the gene for the peroxisomal matrix enzyme acyl-CoA oxidase but not for *PEX* genes [21]. In a study of the molecular underpinnings of scarring alopecia, it was shown that loss of peroxisomes correlated with decreased expression of PPARγ and that treatment with PPARγ agonists induced the expression of genes for metabolic enzymes known to localize to peroxisomes [22].

The signaling networks controlling both biogenesis (perhaps directly) and transcription are also a means for cells to coordinate peroxisomes with various other cellular activities [23–25]. Components of these networks have been revealed in yeast, and similarly to transcriptional networks, they have proven highly complex, suggesting that cells invest considerable resources to control peroxisome number, while retaining the capacity to rapidly change peroxisome abundance. For example, a study that modeled organelle biogenesis mechanisms on organelle variance — the fluctuation in organelle number from cell to cell — concluded that peroxisomes in yeast switch from a *de novo* biogenesis mechanism to one primarily reliant on fission when yeast were transferred from a glucose-rich to a fatty-acid-rich environment [26•]. This observation raises the intriguing possibility that cells respond appropriately to environmental signals through direct signaling and transcriptional mechanisms that act to control peroxisome production [1]. The temporal differences in responsiveness or molecular composition of differently produced peroxisomes could contribute to peroxisome heterogeneity and influence peroxisome controlled signaling dynamics.

Peroxisomes are not autonomous

Mitochondria and peroxisomes share proteins, some metabolic functions, and communicate through vesicular transport [27,28]. Indeed, it has been known for quite some time that cross-talk between mitochondria and