Seminars in Cell & Developmental Biology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

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

Review

Oxygen-responsive transcriptional regulation of lipid homeostasis in fungi: Implications for anti-fungal drug development

Risa Burr, Peter J. Espenshade*

Department of Cell Biology, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA

ARTICLE INFO

Article history:
Received 13 April 2017
Received in revised form 8 August 2017
Accepted 22 August 2017
Available online xxx

Keywords:
Hypoxia
Lipid metabolism
Transcription
Fungi
Anti-fungal drug

ABSTRACT

Low oxygen adaptation is essential for aerobic fungi that must survive in varied oxygen environments. Pathogenic fungi in particular must adapt to the low oxygen host tissue environment in order to cause infection. Maintenance of lipid homeostasis is especially important for cell growth and proliferation, and is a highly oxygen-dependent process. In this review, we focus on recent advances in our understanding of the transcriptional regulation and coordination of the low oxygen response across fungal species, paying particular attention to pathogenic fungi. Comparison of lipid homeostasis pathways in these organisms suggests common mechanisms of transcriptional regulation and points toward untapped potential to target low oxygen adaptation in antifungal development.

Contents

Abbreviations: HIF, hypoxia inducible factor; GO, gene ontology; SREBP, sterol regulatory element-binding protein; ER, endoplasmic reticulum; SCAP, SREBP cleavage activating protein; TAG, triacylglycerol; GPL, glycerophospholipid; Sre1N, Sre1 N-terminal transcription factor fragment; SFA, saturated fatty acid; UFA, unsaturated fatty acid; RUP, regulated ubiquitin/proteasome-dependent processing.

* Corresponding author at: Department of Cell Biology, The Johns Hopkins University School of Medicine, 725 N. Wolfe St., Physiology 107B, Baltimore, MD 21205, USA.
E-mail address: peter.espenshade@jhmi.edu (P.J. Espenshade).

http://dx.doi.org/10.1016/j.semcdb.2017.08.043
1084-9521/

1. Introduction

The estimated 3.5–5 million species comprising the fungal kingdom populate a wide variety of environments including soil, tropical forests, city indoor air, dust, deserts, human tissue, and animal feces [1–3]. Many of these environments differ greatly in oxygen availability and fungi that travel between environments of varying oxygen saturation must adapt in order to survive. This is particularly relevant for pathogenic fungi, which live in both the 21% oxygen terrestrial environment and the 1–5% oxygen host environment [2,4,5]. In metazoans, the oxygen response is largely regulated by the hypoxia inducible factor (HIF) pathway [6]. In response to low oxygen, the HIF transcription factor upregulates glycolysis, autophagy, and angiogenesis, and downregulates ATP consumption and oxidative phosphorylation [6]. The mechanism and regulation of this HIF oxygen response has been extensively reviewed [6]. In contrast, fungi do not have HIF homologs, and instead have developed different mechanisms for regulating the response to low oxygen. Particularly well studied are the transcription factors regulating the lipid response, including sterol and glycerophospholipid metabolism. Here we review the recent advances in our understanding of transcriptional responses to low oxygen across a number of fungal species. We also review the mechanism of oxygen sensing by specific transcription factors, focusing on lipid regulation, including recent observations of coordination between oxygen-responsive transcriptional programs. We conclude with a review of the current worldwide burden of fungal disease and perspectives on the future of antifungal treatment.

2. Low oxygen transcriptional response

Numerous studies have identified hypoxic responsive transcriptional programs in different fungal species [7–13]. To focus this review, we analyzed the significantly up and down-regulated genes from those studies for gene ontology (GO) term enrichment and assembled broad categories of regulation from those GO terms. It is important to note that experimental protocols varied greatly among these reports, with oxygen concentrations ranging from 0 to 1% (or not defined when flasks were flushed with nitrogen) and low oxygen incubation times from 1.5–12 h. Despite these experimental differences and millions of years of divergence, we observed a shared program of transcriptional regulation among species. A large proportion of genes regulated in response to low oxygen fall into four significantly enriched categories: upregulation of lipid anabolism including sterols and glycerophospholipids, upregulation of carbohydrate catabolism, downregulation of gene expression including transcription and translation, and downregulation of aerobic respiration (Fig. 1).

Lipid biosynthesis is a highly oxygen consumptive process and is crucial for maintenance of membrane integrity, cell growth, and proliferation. In order to adapt to low oxygen environments and maintain lipid homeostasis, fungi upregulate lipid biosynthetic enzymes to more efficiently utilize available oxygen. Lipid synthesis is also dependent on acetyl-CoA produced by pyruvate dehydrogenase during carbohydrate catabolism. Therefore upregulating carbohydrate catabolism and acetyl-CoA production and downregulating aerobic respiration may serve to increase acetyl-CoA pools and free up molecular oxygen for lipid biosynthesis under hypoxic conditions. In contrast, non-specific downregulation of gene expression serves to reduce energy expenditure for protein synthesis, suggesting that general transcription is sacrificed during low oxygen stress. Thus, lipid biosynthesis seems to be the uniformly conserved anabolic pathway upregulated under low oxygen, while regulation of other pathways occurs with the purpose of generating energy and components for lipid biosynthesis.

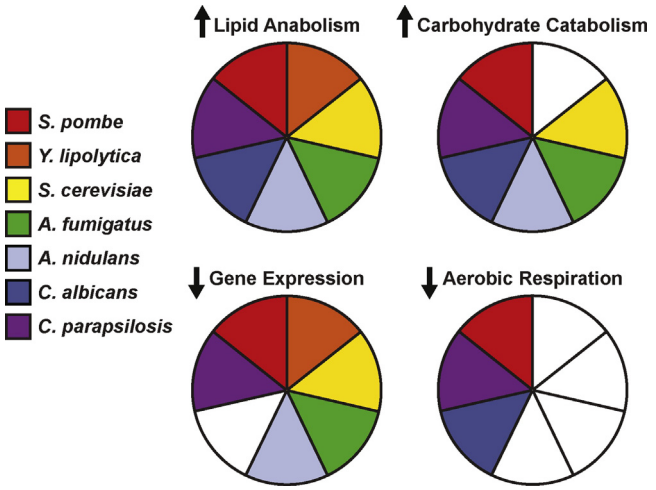

Fig. 1. Pathways transcriptionally regulated in response to oxygen. Genes significantly up and down regulated under low oxygen conditions in *S. pombe* (1.5 h, 0% O_2) [7], *S. cerevisiae* (12 h, 0% O_2) [8], *C. albicans* (3.5 h, 1% O_2) [9], *C. parapsilosis* (3 h, 1% O_2) [10], *A. fumigatus* (2 h, 0.2% O_2) [13], *A. nidulans* (6 h, low O_2) [11], and *Y. lipolytica* (~6 h, 1% O_2) [12] were analyzed for GO term enrichment using AmiGO for *S. cerevisiae*, and FungiFun2 for the remaining species [123]. Biological process annotations were identified using directly and indirectly annotated associations. Resulting enriched GO terms were grouped using REVIGO with an allowed similarity of 0.5 [124] and additional hand categorization. Broad categories were then analyzed for enrichment in each fungal species, represented as colored (enriched) or blank (not enriched) wedges.

3. Ergosterol

3.1. S. pombe *and* A. fumigatus

Gene ontology (GO) biological process terms significantly upregulated in multiple fungal species under low oxygen include lipid metabolic process (GO:0006629), sterol biosynthetic process (GO:0016126), and ergosterol metabolic process (GO:0008204), implicating sterol anabolism in low oxygen adaptation (Fig. 1). The major fungal sterol, ergosterol, is essential for membrane organization and function. Synthesis of one molecule of ergosterol requires 12 molecules of oxygen [14] (for a review of lipid synthesis pathways in fungi, see [15]). Accordingly, the ergosterol synthesis pathway is regulated by transcription factors that sense and respond to cellular oxygen availability in order to maintain lipid homeostasis. In *Schizosaccharomyces pombe*, the transcription factor that regulates sterol biosynthesis is Sre1, a member of the sterol regulatory element-binding protein (SREBP) family that in mammals regulates cholesterol synthesis [16]. *sre1* is required for fission yeast survival under low oxygen conditions and regulates 20% of all oxygen responsive genes [7]. Sre1 is a basic-helix-loop-helix (bHLH) leucine zipper transcription factor that is initially synthesized as an inactive precursor form integral to the endoplasmic reticulum (ER) membrane (Fig. 2) [16]. In the ER, Sre1 is bound by the multi-pass transmembrane protein and mammalian SREBP cleavage activating protein (SCAP) homolog, Scp1, which senses sterols. Whereas Insig proteins inhibit SREBP-Scap binding under cholesterol-replete conditions in mammals, Sre1-Scp1 binding in fission yeast is not regulated by Insig [16]. Instead, *S. pombe* Insig directly binds and inhibits the major ergosterol biosynthesis enzyme HMG-CoA reductase [17]. Sre1 that is not bound by Scp1 in the ER is degraded by ER associated degradation (ERAD); therefore it is probable that all Sre1 in the ER is bound by Scp1 [18]. There is a basal level of Sre1-Scp1 traffic to the Golgi under normoxia, but when oxygen (and subsequently ER ergosterol) is low, the rate of trafficking is greatly increased [19]. These steps of Sre1 processing closely mirror the mammalian system for SREBP processing.

Please cite this article in press as: R. Burr, P.J. Espenshade, Oxygen-responsive transcriptional regulation of lipid homeostasis in fungi: Implications for anti-fungal drug development, Semin Cell Dev Biol (2017), http://dx.doi.org/10.1016/j.semcdb.2017.08.043