Iron in yeast: Mechanisms involved in homeostasis

Ernest Kwok and Daniel Kosman

Abstract

Iron homeostasis results from matching iron uptake to cell growth and division in the context of the overall cell requirement for iron. Fungi achieve this balance by transcriptional regulation of the genes that encode iron uptake activities; post-transcriptional regulation of the synthesis of proteins that use iron; and storage and recycling of iron to meet short-term needs in times of iron deprivation. In the Fungal Kingdom, both repression and activation mechanisms of transcriptional regulation have been elucidated; both mechanisms rely on transcription factors that directly or indirectly are regulated by cell iron status. Among fungi, however, one or the other transcriptional regulatory mechanism is used by a given organism but not both. In contrast, of those fungi examined in detail, all employ at least two of the four iron uptake mechanisms characterized in fungi in general: siderophore iron uptake; direct ferrous iron permeation; coupled ferroxidase/permease uptake; and heme/hemin uptake. All of these pathways rely on the activity of a metalloreductase enzyme at some point. The yeast vacuole serves as iron store while the mitochondrion, as the site of heme and Fe-S cluster biosynthesis, is the primary end-user of cell iron. The recycling of iron from both organelles plays a role in the maintenance of homeostasis both in terms of iron utilization and regulation of iron uptake.

1 Introduction

There are six cellular compartments that are known to be involved in iron homeostasis in yeast: plasma membrane, cytoplasm, vacuole, mitochondria, nucleus, and lastly, the exocytoplasmic milieu. Indeed, in free-living organisms like yeasts and other fungi, the iron status of the exocytoplasmic milieu *determines* the mechanisms adopted to maintain cellular iron homeostasis. This review describes the protein components and iron metabolic events that occur in each of these compartments and then summarizes current knowledge as to how these events are integrated so as to maintain the cell's iron balance. Several other excellent reviews that cover somewhat earlier literature and/or various aspects of fungal iron metabolism in more depth are recommended complements to this one (Winkelmann 2002; Van Ho et al. 2002; Schroder et al. 2003; Nelson 1999; Kosman 2003; Kap-

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lan 2002; Howard 2004; De Luca and Wood 2000; Boukhalfa and Crumbliss 2002).

2 The plasma membrane and exocytoplasmic milieu

The iron metabolic process that dominates these two compartments is iron uptake. Yeasts and fungi exhibit three primary mechanisms of iron accumulation: 1) siderophore-mediated; 2) ferrous iron transporter-mediated; and 3) ferroxidase, permease complex-mediated (Van Ho et al. 2002; Kosman 2003; Howard 2004). All three mechanisms are metalloreductase-dependent with the Fe^{3+}/Fe^{2+} redox reaction catalyzed by this enzyme activity required either at the end of the accumulation process (siderophore-mediated uptake) or at the beginning (the transporter and permease pathways). De Luca and Wood have nicely contrasted the mechanisms of iron accumulation *via* these two reductive pathways (De Luca and Wood 2000). Hemin/heme also is a source of iron for some pathogenic fungi including *Candida albicans* (Santos et al. 2003; Weissman and Kornitzer 2004) and *Histoplasma capsulatum* (Foster 2002). The iron could be released from the organic matrix in either case by ferrireduction in the exocytoplasmic space with the Fe^{2+} produced as substrate for subsequent uptake *via* any one of the three mechanisms above (with an autooxidation to Fe^{3+} preceding siderophore binding). Timmerman and Woods have characterized a glutathione-dependent extracellular reductase activity produced by *H. capsulatum* that they suggest supports this particular mechanism (Timmerman and Woods 1999, 2001). On the other hand, cell-surface heme-binding proteins have been identified in *C. albicans* indicating that like siderophore iron, Fe^{3+} in heme/hemin also can be mobilized intracellularly by metalloreduction following endocytic internalization (Santos et al. 2003). Following, we briefly review the three most broadly used uptake mechanisms; these are illustrated in Fig. 1 using as paradigm the yeast, *S. cerevisiae*.

2.1 Siderophore-mediated iron uptake

Although few yeasts (as distinct from fungi; see below) produce their own siderophore(s), all are likely to express siderophore receptors and the means to release the iron exocytoplasmically and to process the siderophore-iron complex once internalized. The *S. cerevisiae* genome encodes receptors that recognize members of several classes of siderophores, *e.g.,* FOB (*SIT1*) (Lesuisse et al. 1998); TAF (*TAF1*) (Heymann et al. 1999; Lesuisse et al. 2001); ferricrocin (*ARN1*) (Heymann et al. 2000b); and FC (*ARN1*, *TAF1*). A fourth locus – *ENB1* – encodes a facilitator that exhibits relative specificity for enterobactin (Heymann et al. 2000a), but, as this brief summary indicates, one is better served to consider all of these receptors to have, at best, limited specificity. Orthologs to some of these four *S. cerevisiae* genes (also known generically as *ARN* loci since all are upregulated by the iron-responsive transcription factor, Aft1p) (Yun et al. 2000) have