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Oxygen regulated transcription of cytochrome *c* and cytochrome *c* oxidase genes in yeast

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Introduction

Oxygen has profound effects on the energy metabolism of most organisms. Oxygen tension per se determines whether ATP will be produced primarily by respiration-linked oxidative phosphorylation or glycolysis-linked substrate level phosphorylation [1,2]. Because oxidative phosphorylation is far more efficient than glycolysis in capturing the redox energy of reduced substrates [3] the ratio of ATP produced by these two processes effects the amount of biomass produced, the amount of heat released, and the types and amounts of metabolic end products that accumulate. Consequently, oxygen tension may be an important environmental and developmental signal for the regulation of cell growth and differentiation. An understanding of the molecular processes through which cells adapt to growth in different oxygen tensions should help in understanding how they adjust the ratio of ATP produced by glycolysis and oxidative phosphorylation and, in addition, may allow for the metabolic engineering [4] of energy metabolism.

Several recent studies with the yeast *Saccharomyces cerevisiae* have revealed that the intracellular levels and activities of a large number of protein are affected by oxygen tension [5]. Many of these proteins are involved in pathways or processes that use oxygen. They include cytochromes of the respiratory chain as well as enzymes involved in the synthesis of heme, sterols, and unsaturated fatty acids. In addition, they include both cytosolic and peroxisomal catalases, manganese superoxide dismutase, and a translational initiation factor, eIF5A. Some of these proteins are expressed optimally in the presence of oxygen while others are repressed by it. Although the effects of oxygen on the intracellular concentrations of many of these proteins has been shown to be exerted through the transcription of their genes, oxygen may also effect expression via translational control, especially for proteins encoded by mitochondrial DNA [5,6]. In addition, oxygen tension may have indirect effects on the expression of some proteins. For example, because O_2 is required for heme biosynthesis [7] oxygen tension may effect the folding or assembly of hemoproteins by affecting the availability or redox state of their prosthetic groups.

In this paper we focus on the role of oxygen in the expression of cytochrome *c* and the subunits of cytochrome *c* oxidase in yeast. Yeast cytochrome *c* is a monomer encoded by a multigene family composed of two genes *CYC1* and *CYC7* [8]. The *CYC1* and *CYC7* genes encode iso-1- and iso-2-cytochrome *c*, respectively. Although either isoform can transfer electrons from cytochrome *c* reductase to cytochrome *c* oxidase [9] it is not clear if they are functionally identical. Yeast cytochrome *c* oxidase is a complex multimer composed of nine subunits [10]. The three largest subunit (I, II and III) are encoded by the *COX1*, *COX2* and *COX3* genes on the mitochondrial genome while the six smallest subunits (IV, Va or Vb, VI, VII, VIIa and VIII) are encoded by the nuclear genes *COX4*, *COX5a* or *COX5b*, *COX6*, *COX7*, *COX9* and *COX8*, respectively [11–13]. *COX5a* and *COX5b* encode interchangeable isoforms of subunit V, designated Va and Vb [14,15]. These alter the turnover number of holocytochrome *c* oxidase by altering the rate of at least one of the intramolecular electron transfer reactions of the holoenzyme [16]. The other subunits are encoded by single copy genes [11,13]. Currently, it is thought that two of the subunits (I and II) encoded by mitochondrial genes contain the catalytic redox centers of the enzyme [17] and that those subunits encoded by nuclear genes modulate intracellular levels of cytochrome

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