INTRODUCTION

*Histoplasma capsulatum* (*Hc*; teleomorph, *Ajellomyces capsulatus*) is the etiologic agent of histoplasmosis, one of the most common systemic fungal infections of humans. Estimates of the incidence of histoplasmosis in the United States alone are approx 500,000 per year (1). The worldwide incidence is unknown but is almost certainly in the millions. The mold form grows in the soil and converts to the pathogenic yeast form in the lungs of the host after inhalation of mold fragments or spores. Typically, in individuals with healthy immune systems, the disease is a self-limiting respiratory infection with influenza-like symptoms. However, in some otherwise healthy people and especially in individuals with weakened immune systems, histoplasmosis is a systemic and life-threatening disease. In particular, *Histoplasma* is a common and serious opportunistic pathogen in cancer patients, organ transplant patients, and AIDS patients (2,3).

Significant advances have been made in elucidating the molecular basis of dimorphism and virulence in *Hc*. Theoretically, any gene product that is critical for yeast formation/maintenance or necessary for survival within the host could serve as a therapeutic target. Several laboratories, including ours, are working to identify genes that are critical for mold-yeast dimorphism in *Hc*. Although no genes critical for the morphotype switch have been reported, several gene products required for survival within the host phagocyte have been identified (4,5). Much has been learned by using existing low-throughput methods such as subtractive screening and differential display, and we are now poised to utilize new genomic tools which will allow *Hc* researchers to make more rapid progress in our efforts to understand dimorphism and virulence in this important human pathogen.

PHYSIOLOGY OF DIMORPHISM

The *Hc* organism exhibits the intriguing biological phenomenon of dimorphism, which is integral to its pathogenesis (reviewed in ref. 6). In the soil, *Hc* grows as a saprophytic differentiated multicellular mold, but in the infected host *Histoplasma* grows in an undifferentiated form as a unicellular budding yeast. When spores or...
mycelial fragments are inhaled, the organism converts to the yeast form. This mold-to-yeast (M–Y) conversion is critical for the disease process because cells treated to block this dimorphic shift cannot cause disease (7). The M–Y or Y–M shift is easily seen in vitro by simply changing the incubation temperature to favor Y (e.g., 37°C) or M (e.g., 25°C). Because of interest in the biology of the multicellular/unicellular shift as well as its role in pathogenesis, several laboratories have done extensive studies on the cell biology, physiology, biochemistry, and more recently, the molecular biology, of dimorphism in Hc.

Maresca et al. (8) described three stages in the mold-to-yeast conversion in vitro as summarized in Fig. 1. In stage 1, the cells appear to undergo a shock response followed by a sharp drop in metabolic rate uncoupling of oxidative phosphorylation and loss of cytochromes. Early in stage 1, the cells begin expressing a yeast-specific enzyme, cystine reductase. In stage 2, which lasts about 2–4 days depending on the Hc strain, the metabolic rate as measured by oxygen consumption remains very low. At this stage, sulfhydryl-containing compounds (preferably cysteine) are required to progress to stage 3. Stage 3 is characterized by a rapid increase in metabolic rate, expression of a second yeast-specific enzyme (cysteine oxidase), and formation of yeast.

Clearly, -SH compounds, particularly cyst(e)ine, are important in the M–Y shift. Most strains of Hc are cysteine prototrophs in the mold form but cysteine auxotrophs in the yeast form because of the absence of sulfate reductase in the Y form (9). The yeast form expresses cystine reductase and cysteine oxidase, and the mold form does not. Also, the sulfhydryl blocker PCMS (p-chloromercury-phenylsulfonic acid) inhibits the M–Y shift. A likely possibility is that cyst(e)ine and/or other -SH compounds are needed to modulate intracellular redox for the formation and/or maintenance of the yeast form. Further support is given to this idea by the results of Rippon, who showed that Y would grow at the nonpermissive temperature of 25°C if the redox potential was lowered (i.e., made more reducing) by passing a weak direct electrical current through the growth medium (10).