

## *I. How Model and Pathogenic Fungi Sense the Environment and the Host*

As eukaryotic microorganisms, fungi serve as valuable models to understand how organisms sense and respond to their environment. Recent studies have revealed in elegant molecular detail how fungi sense nutrients, including nitrogen and carbon sources such as ammonia, glucose, amino acids, and inositol, and fungi also sense pheromones during mating, and even photons/light and gases such as carbon dioxide. Studies on these conserved signaling cascades are providing insights into how more complex multicellular organisms achieve similar discriminatory potential.

Morphogenesis and mating in fungi are often intimately linked, and reflect the roles that hyphal development and sexual reproduction play in both acquisition of nutrients, and responses to limiting nutrition in the environment. As a consequence, key pathways governing morphogenesis sense diverse carbon and nitrogen sources. In the model yeast *Saccharomyces cerevisiae*, filamentous pseudohyphal differentiation is elicited by the presence of abundant fermentable carbon sources and limiting nitrogen source. A novel G protein coupled receptor, Gpr1, senses glucose and activates the cAMP-protein kinase A pathway, whereas limiting ammonium is sensed via Mep2, a specialized ammonia permease that also functions as a receptor. Homologs of Gpr1 in the pathogenic fungi *Candida albicans* and *Cryptococcus neoformans* play similar roles in filamentous differentiation, mating and virulence, but have been rewired to sense the amino acid methionine rather than fermentable sugars. Central questions being addressed are: why sense methionine, and what is the source of the ligand (fungus, environment, host)? The Mep2 family of ammonia permeases are broadly conserved, and related to the Amt permease/sensors of bacteria and the Rh blood group antigens of mammals. Their roles in signal transduction are being explored in model and pathogenic yeasts and filamentous fungi. Recently we discovered that *Cryptococcus neoformans* and *C. gattii*, commonly found in association with trees in the environment, can be stimulated to complete their sexual cycle during a pathogenic association with plants. As part of this intimate association, plants secrete factors, including inositol and indole acetic acid (IAA/auxin), that activate fungal mating. How these small molecules are sensed is not known, but may involve specialized cell surface sensors elaborated by the fungus, intracellular pathways, or both.

In parallel with these studies on nutrient sensing by model and pathogenic fungi, we are addressing how fungi sense light and gases. Some years ago we discovered that mating of *Cryptococcus* is inhibited by light. Elucidation of the molecular basis revealed an ancestral blue light sensor, related to the white collar-one (WC-1) and -two (WC-2) proteins first discovered in *Neurospora crassa*, is broadly conserved in the fungal kingdom. This system functions to limit *Cryptococcus* mating in light, and also influences

virulence in the mammalian host. The mechanisms of light sensing were extended to the model zygomycete, *Phycomyces blakesleeanus*, revealing the white collar light sensor is even more ancient, and predates the divergence of fungi into the ascomycete, basidiomycete, and zygomycete phyla. Moreover, gene duplication events have generated a diverse array of candidate light receptors, including three WC-1 and four WC-2 flavin-dependent light sensor homologs. This diverse repertoire may be responsible for the dramatic range of light sensing abilities, which approximates that of the human eye and exhibits similar adaptive properties.

Carbon dioxide stimulates production of the capsule virulence factor in both *Cryptococcus* and also *Bacillus anthracis*, the cause of anthrax. Our studies reveal that a carbonic anhydrase plays a central role in conversion of carbon dioxide to bicarbonate, and studies by Fritz Muhlschlegel and colleagues have revealed that fungal adenylyl cyclase is directly bound and activated by bicarbonate ions, similar to soluble adenylyl cyclase that is similarly activated in mammals. These studies reveal a virulence signal transduction cascade conserved between two divergent and common human fungal pathogens (*Candida albicans* and *Cryptococcus*) which shares features with conserved signaling cascades in both pathogenic bacteria and mammals.