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Plenary Paper

Microbial pathogens in the fungal kingdom

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ABSTRACT

The fungal kingdom is vast, spanning ~1.5 to as many as 5 million species diverse as unicellular yeasts, filamentous fungi, mushrooms, lichens, and both plant and animal pathogens. The fungi are closely aligned with animals in one of the six to eight supergroups of eukaryotes, the opisthokonts. The animal and fungal kingdoms last shared a common ancestor ~1 billion years ago, more recently than other groups of eukaryotes. As a consequence of their close evolutionary history and shared cellular machinery with metazoans, fungi are exceptional models for mammalian biology, but prove more difficult to treat in infected animals. The last common ancestor to the fungal/metazoan lineages is thought to have been unicellular, aquatic, and motile with a posterior flagellum, and certain extant species closely resemble this hypothesized ancestor. Species within the fungal kingdom were traditionally assigned to four phyla, including the basal fungi (Chytridiomycota, Zygomycota) and the more recently derived monophyletic lineage, the dikarya (Ascomycota, Basidiomycota). The fungal tree of life project has revealed that the basal lineages are polyphyletic, and thus there are as many as eight to ten fungal phyla. Fungi that infect vertebrates are found in all of the major lineages, and virulence arose multiple times independently. A sobering recent development involves the species *Batrachochytrium dendrobatidis* from the basal fungal phylum, the Chytridiomycota, which has emerged to cause global amphibian declines and extinctions. Genomics is revolutionizing our view of the fungal kingdom, and genome sequences for zygomycete pathogens (*Rhizopus*, *Mucor*), skin-associated fungi (dermatophytes, *Malassezia*), and the *Candida* pathogenic species clade promise to provide insights into the origins of virulence. Here we survey the diversity of fungal pathogens and illustrate key principles revealed by genomics involving sexual reproduction and sex determination, loss of conserved pathways in derived fungal lineages that are retained in basal fungi, and shared and divergent virulence strategies of successful human pathogens, including dimorphic and trimorphic transitions in form. The overarching conclusion is that fungal pathogens of animals have arisen repeatedly and independently throughout the fungal tree of life, and while they share general properties, there are also unique features to the virulence strategies of each successful microbial pathogen.

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1. Introduction

Infectious diseases remain one of the most significant threats to human health (Cohen, 2000; Jones *et al.*, 2008; Morens *et al.*, 2004). In contrast to chronic diseases such as heart disease and cancer, infectious diseases represent a threat capable of causing extinction and thus have the capacity to threaten the very survival of our species. In addition, microbes that cause infectious diseases are subject to rapid evolution and emergence, given the rapidity of their life cycles and large population sizes. Among pathogenic microbes, the eukaryotic pathogens (fungi, parasites) are increasing in incidence, drug resistance is of mounting concern, and there are fewer drugs or vaccines available compared to bacteria and viruses.

The emergence of microbial pathogens involves several routes, including zoonotic transmission from animals to humans, changes in host or vector range, environmental change, and changes to the pathogen *via* genetic exchange. Genome reassortment of influenza leads to antigenic shifts, necessitating annual changes in vaccine strains and which can lead to pandemics (Lambert and Fauci, 2010). Bacteria predominantly exchange genetic material *via* horizontal gene transfer (transformation, conjugation, transduction). In both fungi and parasites, genetic exchange is mediated *via* sexual reproduction (Heitman, 2006, 2010). Sex generates genetic diversity, can promote and transmit drug resistance, and plays roles in pathogenesis and virulence cycles including infectious propagule production.

Our understanding of the origins of fungal microbial pathogens begins with the eukaryotic evolutionary tree of life, which has been redrawn over the past decade based on molecular phylogenetic studies (Baldauf and Palmer, 1993; Baldauf, 2003). A key insight was the realization that fungi and animals share a much more recent ancestor than had been appreciated and that the two are sister kingdoms within the opisthokont supergroup lineage of the eukaryotes, which shared a last common ancestor as recently as 1 billion years ago (Fig. 1) (Baldauf and Palmer, 1993; Wainright *et al.*, 1993). The last common ancestor from which all animals and fungi descend is thought to have been unicellular, aquatic, and motile, with a flagellum. There are extant species that closely resemble this hypothesized last common ancestor, and one is the unicellular choanoflagellate *Monosiga brevicolis*. Its genome is ~40 MB and encodes ~9000 genes, which is about the size of a fungal genome but instead this organism is more closely related to the animal kingdom and serves as a pre-metazoan model for the evolution of metazoans (King *et al.*, 2008). There are also extant fungi that look quite similar, and they are called the Chytridiomycetes and are also aquatic with flagella. It is hypothesized that the flagellum was lost once in the fungal kingdom, as fungi exited the oceans and evolved to grow on land as mycorrhiza with the first land plants (Heckman *et al.*, 2001; Liu *et al.*, 2006; Simon *et al.*, 1993). The ongoing UNICORN genome project seeks to understand how unicellular organisms evolved to be multicellular in both the animal and fungal kingdoms, and ten species are being targeted for sequencing (Ruiz-Trillo *et al.*, 2007; Sebe-Pedros *et al.*, 2010a; Sebe-Pedros *et al.*, 2010b). Considering who the fungi are, how they evolved, and their relationships to the animal kingdom will be of general and broad significance.

Traditionally the fungal kingdom has been divided into four phyla: two that share a monophyletic origin (the dikarya: Ascomycota, Basidiomycota) and two considered to be the basal fungi (Zygomycota, Chytridiomycota). However, the fungal tree of life project (AFTOL) revealed that the basal phyla are both polyphyletic, and thus as many as 8–10 phyla

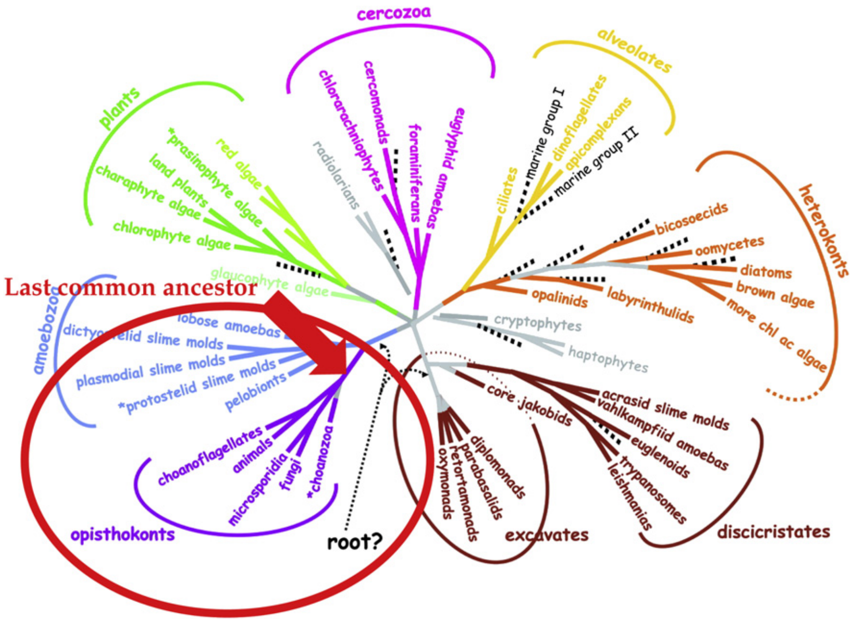

Fig. 1 – The eukaryotic tree of life. Recent molecular phylogenetic studies revealed the organization of the eukaryotic domains of life stemming from a last common ancestor. In particular, this analysis revealed a unique evolutionary relationship of the fungi and the animals as opisthokonts, sharing a more recent last common ancestor with each other to the exclusion of all other groups of eukaryotes. Modified from Baldauf *et al.*, Science 2003.