Global Warming Will Bring New Fungal Diseases for Mammals

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ABSTRACT Fungi are major pathogens of plants, other fungi, rotifers, insects, and amphibians, but relatively few cause disease in mammals. Fungi became important human pathogens only in the late 20th century, primarily in hosts with impaired immunity as a consequence of medical interventions or HIV infection. The relatively high resistance of mammals has been attributed to a combination of a complex immune system and endothermy. Mammals maintain high body temperatures relative to environmental temperatures, creating a thermally restrictive ambient for the majority of fungi. According to this view, protection given by endothermy requires a temperature gradient between those of mammals and the environment. We hypothesize that global warming will increase the prevalence of fungal diseases in mammals by two mechanisms: (i) increasing the geographic range of currently pathogenic species and (ii) selecting for adaptive thermotolerance for species with significant pathogenic potential but currently not pathogenic by virtue of being restricted by mammalian temperatures.

GLOBAL CLIMATE CHANGE

The Earth's climate has suffered major perturbations during its history, presenting periods of global temperate climate (glaciations) followed by warming due to various factors that include accumulation of greenhouse gases (1, 2). The impact of climate changes on the biota can be enormous, and extinction events with subsequent species diversification were each associated with periods of quick planetary overcooling (3–6). Human social evolution has been greatly influenced by climate, and the emergence of agriculture and sedentary settlements dates to the end of the last glacial period around 12,500 years ago (7, 8).

Anthropogenic greenhouse gas generation is expected to increase the mean global temperature by 2 to 5°C in the next decades, leading to the warmest period in the past 40 million years (9). The effect of environment-changing human activities on biodiversity has been extensively documented (see reference 10 for a review), and 41% of all multicellular species are predicted to be impacted by climate change (11). Species disappearance per area was predicted to be 15 to 37% (12) or even higher (13), but global warming will reduce some habitats while favoring others (14). A warmer world may induce geographic expansion of certain groups, such as nematodes, insects, algae, etc., potentially changing the landscape of infectious diseases. Vector-borne diseases are expected to extend by vector expansion, by acquisition of vectorial capacity of new species, and/or by reintroduction of parasites into native insect populations in areas currently free of disease.

FUNGI, TEMPERATURE TOLERANCE, AND ENDOTHERMY

Fungi emerged some 1.6 million years ago (15, 16), and the group is highly diversified. The estimated number of fungal species is 1.5 million, occupying a broad variety of habitats (17), even if only ca. 70,000 fungal species have been formally described. About 300 fungal species are reported to be pathogenic to humans (18), but the majority cause extremely rare mycoses and only a few species are relatively common pathogens. These fungi have the ability to survive and grow at the high body temperatures of endothermic animals (19).

Most fungi thrive in the range of 12°C to 30°C (20), but there are wide temperature tolerances among species, with some growing at temperatures as low as −10°C (21) or as high as 65°C (22). For this essay, which focuses on fungal diseases of mammals, we define thermotolerance as the ability to grow at mammalian and higher temperatures.

Thermotolerant species are scattered in the major groups of fungi. In the Basidiomycota, including several cryptococcal species, this character is not uncommon (20). Among the cryptococci, only *Cryptococcus neoformans* and *Cryptococcus gattii* are common pathogens, but other cryptococcal species express putative virulence factors, such as polysaccharide capsule and melanization (23). In this case, the acquisition of thermotolerance presumably increases their potential to become pathogenic. One such case can be attributed to *Cryptococcus laurentii*, which normally does not grow at 37°C, but thermotolerant strains have increasingly been associated with disease in extremely immunosuppressed hosts (24). Experimentally, heat tolerance can be induced in *Saccharomyces cerevisiae* (25) and in the entomopathogen *Metarhizium anisopliae* without loss of its pathogenic capability (26).

In tropical and subtropical climates, thermotolerant fungi are presumably more abundant. Tropical regions include many fungal pathogens not found in temperate regions, such as *Paracoccidioides brasiliensis*, *Penicillium marneffei*, and *C. gattii* (27, 28). The incidence of fungal infections in these places tends to be higher, possibly due to a higher number of fungi that can cope with human body temperatures. In fact, the incidence of cryptococcosis in AIDS patients in Africa is as high as 30%, whereas in temperate regions, the incidence is seldom higher than 5 to 10% (29).

Even if proportionally low, the absolute number of thermotolerant species in nature is high, and this raises the question of why fungi are relatively rare pathogens of mammals. The rarity of fungal disease in mammals presumably reflects the effectiveness of their immune systems against fungi, but this alone cannot explain it since all jawed vertebrates also have adaptive immunity (30).

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There is evidence that the high resistance of mammals to fungi is a function of both their immune system and their high basal temperature. For example, rabbits are highly resistant to systemic *C. neoformans* infection unless immunocompromised, yet infection can be induced in the cooler testes even in immunocompetent animals (31).

Endothermy is an energy-costly strategy that has evolved only twice in the Metazoa (mammals and birds) and provides the adaptive advantage of sustained levels of high activity and fewer restrictions for the colonization of a broader variety of habitats (32). There is controversy as to how such a complex trait evolved (see reference 33 for a discussion), and whereas endothermy may not have initially been selected as a protection mechanism against infectious agents, it is an extremely efficient mechanism to exclude the majority of fungal species from a mammalian host. Mammals possess not only relatively high body temperatures but also basal temperatures that can be increased in response to infections, producing fever that further limits the opportunities for a pathogen to survive.

POTENTIAL RISKS OF FUNGAL ADAPTATION TO HIGHER TEMPERATURE

Most of the health concerns regarding global warming are focused on vector-borne and parasitic diseases, as they have been long considered tropical-region-associated diseases that might extend to previously more temperate regions (34). However, the potential effects of global warming on the fungi have not been considered.

Global warming could have a significant effect on fungal populations. First, a warmer climate could change the distribution of heat-tolerant and susceptible species by favoring those that are more thermotolerant, and by creating conditions for more environmental fungi to spread and enter into closer contact with human populations, as postulated for *P. brasiliensis* and *C. gattii* (28, 35). Second, under strong selective pressure, the prevalence of species adapted to heat tolerance may increase. There is some evidence for this in the finding that some fungi in urban areas grow faster at warmer temperatures than their rural counterparts (36).

For every 1°C gained in body temperature in the range of 30 to 42°C, approximately 6% of the fungal species are excluded as potential pathogens (20). Global warming means narrowing of the thermal gradient between ambient and mammalian temperatures (Fig. 1). The current gradient is approximately 22°C, and consequently, every degree increase in the global average temperature reduces the gradient by about 5%. We hypothesize that with current global warming, the prevalence of fungal diseases will increase by the mechanisms previously discussed. As thermotolerance is more commonly found within the basidiomycetes (20), this group may be the major contributor of new fungal pathogens.

It may be possible to obtain experimental support for this hypothesis by demonstrating that virulence parallels the emergence of thermotolerance. Furthermore, it may be worthwhile to characterize in detail those fungal species that are close relatives to known pathogens but lack thermotolerance, since these are likely candidates for the emergence of new pathogens. This information could foster increased human preparedness in coping with climate change and add urgency to ongoing efforts to slow global warming. The risk from newly emerged fungal pathogens could be magnified by the fact that there are few antifungal drugs available and

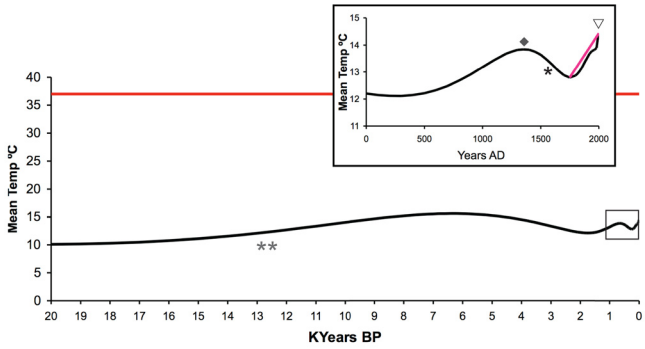

FIG 1 Earth's mean global temperature during the past 20,000 years (38; Goddard Institute for Space Studies, 2010) in relation to human body temperature. The difference between the mean global temperature (black line) and the human body temperature (red line) is ~22°C, but as shown in the inset, the increment in global warming is occurring very rapidly (17 times as fast from 1941 to 2009 AD than from 20,000 to 6,500 years before the present [BP]), making the mammalian-environment gradient smaller. Recent climatic events that have impacted human history are the end of the last glacial period about 12,500 years ago (double asterisks), the medieval warm period (800 to 1300 AD, diamond), the little ice age (1650 to 1850 AD, asterisk), and the current global warming (arrowhead). KYears, Years in thousands.

no licensed vaccines. An increased emphasis on developing vaccines with efficacy against broad fungal classes could help ameliorate new threats from the environment (37).

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