



Iron and Fungal Infections

We saw recently that iron is involved, however unlikely it may seem, in producing [dandruff, seborrheic dermatitis, and quite possibly, male pattern baldness](#). These conditions all have in common that a fungus, *Malassezia*, is involved. In this short post I want to take a look at the evidence of a connection between iron and fungal infections.

Malassezia

Dandruff and seborrheic dermatitis are both [associated with several species of fungus of the genus Malassezia](#). They are [specialized to live on human skin](#). Like all other microbial pathogens, *Malassezia* require iron to grow and reproduce, and they obtain iron from their hosts.

Transferrin is the protein molecule in mammals that binds and carries iron. (Ferritin is for iron storage.) [Transferrin is at the center of an evolutionary arms race between microbes and primates](#). Primates try to withhold iron from microbes, and the microbes try to grab it. Each one of them attempts to fight their respective opponents by evolving molecules that have an ever stronger grip on iron.

Iron sequestration provides an innate defense termed nutritional immunity, leading pathogens to scavenge iron from hosts. Although the molecular basis of this battle for iron is established, its potential as a force for evolution at host-pathogen interfaces is unknown. We show that the iron transport protein transferrin is engaged in ancient and ongoing evolutionary conflicts with TbpA, a transferrin surface receptor from bacteria. Single substitutions in transferrin at rapidly evolving sites reverse TbpA binding, providing a mechanism to counteract bacterial iron piracy among great apes... These findings identify a central role for nutritional

immunity in the persistent evolutionary conflicts between primates and bacterial pathogens.

[Transferrin inhibits the growth of *Malassezia*](#). Adding transferrin to a culture of the fungus withholds iron from it so that it can't grow. [Ciclopirox and salicylate](#), both iron chelators, also inhibit *Malassezia* in skin.

Candida

Candida is a genus of fungus with a number of different species and which cause a number of different diseases, including thrush (oral candidiasis), vaginal and skin infections. They can also be invasive and cause blood and other internal infections. Naturally, *Candida* requires iron.

Ciclopirox, the iron chelator, [inhibits *Candida*](#), and the addition of iron reverses the inhibition.

Candida albicans, the major species in this genus, is [the only microorganism known to directly exploit ferritin for its iron](#).

Iron is an essential nutrient for all microbes. Many human pathogenic microbes have developed sophisticated strategies to acquire iron from the host as most compartments in the body contain little free iron. For example, in oral epithelial cells intracellular iron is bound to ferritin, a protein that is highly resistant to microbial attack. In fact, no microorganism has so far been shown to directly exploit ferritin as an iron source during interaction with host cells. This study demonstrates that the pathogenic fungus *Candida albicans* can use ferritin as the sole source of iron. Most intriguingly, *C. albicans* binds ferritin via a receptor that is only exposed on invasive hyphae... Therefore, *C. albicans* uses an additional morphology specific and unique iron uptake strategy based on ferritin while invading into host cells where ferritin is located.

Cryptococcus neoformans

Cryptococcus neoformans is a fungus that causes an often fatal infection of the meninges and brain, especially in HIV patients. [When it senses that iron is available, it grows](#), and elaborates its pathogenic mechanism.

Iron overload is known to exacerbate many infectious diseases, and conversely, iron withholding is an important defense strategy for mammalian hosts. Iron is a critical cue for *Cryptococcus neoformans* because the fungus senses iron to regulate elaboration of the polysaccharide capsule that is the major virulence factor during infection. Excess iron exacerbates experimental cryptococcosis and

the prevalence of this disease in Sub-Saharan Africa has been associated with nutritional and genetic aspects of iron loading in the background of the HIV/AIDS epidemic. We demonstrate that the iron-responsive transcription factor Cir1 in *Cr. neoformans* controls the regulon of genes for iron acquisition such that *cir1* mutants are “blind” to changes in external iron levels. Cir1 also controls the known major virulence factors of the pathogen including the capsule, the formation of the anti-oxidant melanin in the cell wall, and the ability to grow at host body temperature. Thus, the fungus is remarkably tuned to perceive iron as part of the disease process, as confirmed by the avirulence of the *cir1* mutant; this characteristic of the pathogen may provide opportunities for antifungal treatment.

There are many other species of fungi that can cause infections, and this is just a quick look at three of them and how they require iron. All other microbes require it as well.

Keeping iron (ferritin) under control may stop these infections from happening. [Iron supplementation is known to increase the infection rate and exacerbate their severity.](#)

PS: For more on iron, see my book, [Dumping Iron](#).

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