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Host-iron assimilation: pathogenesis and novel therapies of mucormycosis

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Summary

Mucormycosis is a fungal infection caused by organisms belonging to the order *Mucorales*. Although considered uncommon, mucormycosis has been steadily increasing in incidents for the last two decades. Mortality of the disease is unacceptably high despite antifungal therapy and surgical interventions. The lack of understanding of the pathogenesis of the disease and the absence of rapid diagnostic assay contribute to the poor prognosis of mucormycosis. The hyper susceptibility of patients with elevated available serum iron points to the critical role of the ability of *Mucorales* to acquire host iron as a critical virulence factor. Specifically patients with deferoxamine-therapy, hyperglycaemic with or without ketoacidosis, or other forms of acidosis are uniquely predisposed to mucormycosis. In this review, we discuss the molecular mechanisms of infection in these patient categories in an attempt to identify novel therapies for a disease with poor prognosis. Emphasis on the effect of glucose and free iron on host–pathogen interactions are also covered.

Keywords

iron uptake; mucormycosis; DKA; deferoxamine; CotH; GRP78

Introduction

Mucormycoses are rare life-threatening fungal infections caused by fungi of the order *Mucorales*.[1–3] *Rhizopus* species remain the most common cause of infection, although more mucormycosis cases caused by *Mucor*, *Lichtheimia* and *Apophysomyces* are being reported.[4–7] These infections usually afflict patients with classical immunosuppression due to neutropenia, haematologic malignancies or corticosteroid treatment.[8,9] Additionally,

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Conflict of Interest

The author received research grants or consultancy fees from the following companies to conduct research on mucormycosis: Astellas, Enzon, Gilead, Merck and Pfizer.

hyperglycaemia, diabetic ketoacidosis (DKA) and other forms of acidosis predispose patients to mucormycosis.[3,10] Although burn and trauma patients have long been known to be susceptible to this infection,[9,11] recent data showed that outbreaks of mucormycosis are also associated with natural disasters[12,13] and even in military personnel who are injured in combat operations.[14,15] Therefore, mucormycosis are becoming more prevalent in the last two decades. Indeed, there has been a considerable rise in the incidence of mucormycosis at major transplant centres.[16,17] In fact, in high-risk patients the prevalence of mucormycosis can be up to 8% in autopsied patients with leukaemia.[18] A population-based study carried out in France demonstrated a 70% increase in mucormycosis cases between 1997 and 2006.[19] In addition, data from a tertiary care centre in India demonstrated ≥400% increase in mucormycosis incidence, mainly among DKA patients in a 16-year period.[20,21]

The standard therapy for invasive mucormycosis includes reversal of the underlying predisposing factors (if possible), emergent, wide-spread surgical debridement of the infected area, and antifungal therapy.[2,22,23] Although amphotericin B (AmB) remains the only antifungal agent approved for the treatment of invasive mucormycosis,[2,23,24] it is widely accepted that lipid formulation of AmB are the first line therapy for this disease. This is because *Mucorales* are relatively resistant to AmB, and higher doses (1–1.5 mg/kg/day) are required for effective treatment. Due to the less toxicity of lipid formulations of AmB, it is now possible to administer more effective higher doses of these lipid formulation drugs. However, in the absence of surgical removal of the infected focus (such as excision of the eye in patients with rhinocerebral mucormycosis), antifungal therapy alone is rarely curative.[2,23] Moreover, even when surgical debridement is combined with high-dose lipid formulation AmB, the overall mortality associated with mucormycosis reaches 50%.[2] In patients with prolonged neutropenia and in those with disseminated disease, mortality is 90–100%.[16,17,25] Clearly new therapeutic strategies are required for this deadly disease. Such potential novel therapies can be better designed with comprehensive understanding of the mechanism of infection and its related host defence.

Host iron acquisition is central to the pathogenesis of mucormycosis

Iron uptake from the host by microorganisms is essential for the establishment and progression of infection since this element is required for the survival of living cells.[26] In a normal host, free iron is restricted by highly efficient iron sequesters such as transferrin, ferritin and lactoferrin.[26] Pathogens either devise strategies to obtain iron from the host by stripping iron from these sequesters (e.g. by siderophore production), or the tightly controlled free iron becomes more available in certain medical conditions. The unique susceptibility of certain patient populations to mucormycosis, but not to other pathogenic fungi, point to the importance of iron uptake in the pathogenesis of mucormycosis.[3,23] These include, hyperglycaemic, DKA and other forms of acidosis patients as well as deferoxamine-treated patients. All these patient categories suffer from elevated available serum iron. For example, the excessive glycosylation of proteins such as transferrin and ferritin, due to constant hyperglycaemia result in decreased iron affinity of these sequesters which leads to the release of free ion in the blood stream and in cells.[27] Similarly, DKA and other forms of acidosis cause proton-mediated dissociation of iron from iron-sequestering proteins.[28] The increased levels of available iron enable enhanced growth of *Mucorales* in

serum.[9,28,29] It is also known that DKA mice are more susceptible to mucormycosis infection than normal mice and iron chelation therapy using deferiprone or deferasirox protects DKA mice from mucormycosis.[29,30] Subsequent studies confirmed the efficacy of deferasirox in treating experimental mucormycosis using the *Drosophila* fly model.[31]

Patients with iron overload toxicity were used to be treated with the bacterial iron-siderophore, deferoxamine. These patients were found to be extremely susceptible to deadly form of mucormycosis.[32–34] Subsequent studies demonstrated that although deferoxamine is an iron chelator from the perspective of the human host, *Rhizopus* spp. utilise ferrioxamine (the iron-rich form of deferoxamine) as a xenosiderophore to obtain previously unavailable iron.[35,36] It was found that ferrioxamine binds to a cell surface receptor on the surface of *Rhizopus* and through an energy dependent reductive step releases ferrous iron prior to transporting it across the fungal cell membrane without deferoxamine internalisation.[36] Subsequent studies demonstrated that reduction in the high-affinity iron permease *FTR1* copies (*Mucorales* are multinucleated organisms) in *R. oryzae* almost entirely prevented growth of the fungus on medium supplemented with ferrioxamine as a sole source of iron.[37] Collectively, these studies demonstrate that iron uptake from ferrioxamine is mediated through the reductase/permease system.[37,38] More recently, we were able to identify the *FOB1* and *FOB2* as two closely related genes that encode cell surface proteins involved in binding ferrioxamine to *R. oryzae* cell surface.[39] Attenuation of expression of these two genes results in compromising the ability of *R. oryzae* to take up iron from ferrioxamine *in vitro* and reduces virulence in a deferoxamine-treated mouse model of mucormycosis.[40]

Hyperglycaemia and elevated available serum iron and host-pathogen interactions

A hallmark of mucormycosis is the universal propensity of the infection to invade blood vessels.[1] The *Mucorales* angioinvasion capabilities likely contribute to the capacity of the organisms to haematogenously disseminate to other target organs. Therefore, interactions of invading organisms with endothelial cells and extracellular matrix proteins lining blood vessels represent a critical step in the progression of the disease. Earlier studies demonstrated the ability of *Mucorales* to bind to extracellular laminin and type IV collagen[41] as well as human umbilical vein endothelial cells.[42] Moreover, *Mucorales* appear to damage endothelial cells *in vitro* via a mechanism that involves the induction of their own endocytosis by the mammalian cells.[42] This endocytosis process is mediated by the binding of *Mucorales* to a mammalian Glucose Regulated Protein with the molecular weight of 78 kDa (GRP78).[43] Interestingly, only germlings of *R. oryzae* bind to GRP78 and not spores, thereby fitting the notion that germlings are likely responsible for the haematogenous dissemination during mucormycosis. Thus far in fungal infection, GRP78 appears to be a unique host cell receptor since neither *Candida* nor *Aspergillus* bind to this protein during invasion of host tissues.[43] GRP78 is a heat shock protein that is mainly found in the endoplasmic reticulum acting as a chaperon for facilitating proper protein folding and targeting misfolded proteins for proteosome degradation.[44] It also plays an important role in endoplasmic reticulum Ca^{2+} homeostasis and in serving as a sensor for stress.[45] Finally, GRP78 was reported to be antiapoptotic and plays critical cytoprotective roles in early

embryogenesis, oncogenesis, neurodegenerative diseases and atherosclerosis.[46] Fitting with the concept of GRP78 being a stress-related protein is the finding that GRP78 is overexpressed on the host cell surface when endothelial cells exposed to elevated concentrations of glucose and iron consistent with those seen during hyperglycaemia and DKA. This elevated GRP78 expression results in increased ability of *R. oryzae* to invade and damage endothelial cells in a receptor-dependent manner.[43] More recently, the *Mucorales* ligand that binds to GRP78 was identified as the spore coat protein homologs (CotH). Expression of CotH genes, especially CotH3, in the non-invasive *Saccharomyces cerevisiae*, enables the yeast to invade endothelial cells via binding to GRP78.[47] Also CotH colocalize with GRP78 during *R. oryzae* invasion of endothelial cells. More importantly, a mutant of *R. oryzae* with attenuated expression of CotH exhibited reduced ability to invade and damage endothelial cells and had reduced virulence in a DKA mouse model of mucormycosis. Of special interest is the wide presence of CotH among *Mucorales* and its absence from other known pathogens.[47] Collectively, the unique interaction between GRP78/CotH and the enhanced expression of GRP78 by glucose and iron concentrations often seen in hyperglycaemic, DKA and other acidosis patients likely explain the increased susceptibility of these patient populations to mucormycosis.

Potential novel therapies

As mentioned above, patients with elevated available serum iron, be it free iron or ferrioxamine iron, are at high risk of acquiring mucormycosis. Experimental data strongly indicated that the use of iron chelators that are not utilised as xenosiderophores by *Mucorales* can be of benefit in treating the disease alone or as an adjunctive therapy.[29–31,48] In 2005, deferasirox became the first orally bioavailable iron chelator approved for use in the US by the FDA to treat iron overload in transfusion-dependent anaemia. This lead to the off label use of deferasirox in treating advanced cases of mucormycosis with reported success as an adjunctive therapy mainly in diabetic patients with ketoacidosis.[49] However, a subsequent phase II, double-blind, randomised, placebo-controlled trial of adjunctive deferasirox therapy that enrolled a total of twenty patients failed to demonstrate a benefit of the combination regimen in patients with mucormycosis.[50] In fact significantly higher mortality rates were found in patients randomised to receive deferasirox at 30 (45% vs. 11%) and 90 days (82% vs. 22%, $P = 0.01$). It is imperative to note that although this study represents the first completed clinical trial of evaluating a novel treatment option for mucormycosis, it suffered from major imbalances between the two study arms with patients receiving deferasirox were more likely than placebo patients to have active malignancy, neutropenia, corticosteroid therapy and less likely to have received additional antifungal, making the results of this pilot trial hard to interpret.[51] Thus, conclusions regarding the use of deferasirox cannot be drawn from this small study. Indeed subsequent studies to the Phase II clinical trial continue to suggest the successful use of deferasirox as an adjunctive therapy against mucormycosis especially in DKA patients.[52,53] Therefore, only a large, Phase III trial, potentially enrolling only diabetic or corticosteroid-reated patients (as suggested by the animal studies[30] and anecdotal studies [49,52]), and excluding cancer/ neutropenia patients, could further elucidate the safety and efficacy of initial, adjunctive deferasirox (and other iron chelators) for the treatment of mucormycosis.

Other potential novel targets for immunotherapy include the depravation of the invading *Mucorales* of iron uptake *in vivo.* Experimental evidence showed that antibodies targeting the high-affinity iron permease, an iron transporter cell membrane protein, protect DKA mice from infection with *R. oryzae* infection.[37] Moreover, antibodies targeting the GRP78/CotH interactions (i.e. antiGrp78 antibodies[43] or antiCotH antibodies[47]) protected DKA mice from infection with *R. oryzae.* These findings lend support for the future development of novel passive immunisation strategies that target virulence traits of *Mucorales.*

Conclusions and future directions

Mucormycosis is a lethal infection with very limited and mainly ineffective treatment options. Although considered rare, mucormycosis are on the rise and this increase is expected to continue due to the increased number of immunosuppressed patients and the severity in the immunosuppression regimens. Additionally, the increased cases of obesity and unhealthy life style will increase cases of diabetes, which are uniquely predisposed to mucormycosis. Clinical data point to the importance of iron acquisition in the pathogenesis of mucormycosis and subsequent research confirmed this observation. Although mucormycosis pathogenesis studies are at its infancy, recent major discoveries highlight the possibility of translating this knowledge into possible novel therapies urgently needed to improve the outcome of this disease.

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