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Research Article

THERAPEUTIC TARGETS OF MUCORMYCOSIS: FTR1 GENE EXPRESSION AND GLUCOSE-REGULATED PROTEIN-78 RECEPTOR IN SARS COV-2 INFECTED PATIENTS WITH UNCONTROLLED DIABETES MELLITUS-A SYSTEMATIC REVIEW

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Abstract

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2) was associated with a significant incidence of both bacterial and fungal probably due to immune dysregulation. Moreover, the main crucial factor for mortality in COVID-19 with Mucormycosis (MCR) was the extensive use of steroids/monoclonal antibodies/broad-spectrum antibiotics as part of the armamentarium against COVID-19 and uncontrolled diabetes may lead to exacerbation of pre-existing fungal diseases. There are still no approved vaccines against fungal pathogens and the availability of drugs for the treatment of MCR is limited to a scarce. Based on the preliminary research and available data the present systematic review mainly aimed to evaluate therapeutic targets of MCR such as the FTR1 gene expression and glucose-regulated protein (GRP78) receptor in uncontrolled diabetes mellitus. Data showed that the gene encoding FTR1 is expressed by R. oryzae during murine infection and inhibition of FTR1 gene expression by RNA-I diminishes the virulence of the MCR. Hyperglycemia induces the over expression of the GRP78 mRNA levels 2- to 5 folds higher in the sinus, lungs, and the brain and also it increased 40% endocytosis of R. oryzae by human endothelial cells. We observed with preliminary evidence that iron chelation therapy showed beneficiary effects in MCR with DKA. FTR1and GRP78 plays a crucial role in MCR patients infected with SARS CoV-2. Large cohorts of genomic studies will be required to enlighten the novel pathways of pathophysiology and their target genes for efficient drug design.

Keywords: Mucormycosis, GRP78, FTR1, SARS-CoV-2, COVID-19, Rhizopus.

INTRODUCTION

Coronaviruses were known to infect a broad spectrum of species, ranging from birds to humans. They were enveloped RNA viruses with large genome sizes of 28–32 kb. At present, coronaviruses are broadly classified into four genera such as Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. The Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2) was under the class of delta virus and first cases of which were reported in Wuhan, China in December 2019. The disease which is still spreading and has affected almost all countries was declared a pandemic by the World Health Organization on 11 Mar 2020 (Yan Y, 2020).

Epidemiology

Globally, there are 169,090,210 confirmed COVID-19 cases worldwide with 3,512,481 deaths as of May 2021 (Worldometer). The major risk factors of COVID-19 were age, diabetes mellitus, cardiovascular disease (CVD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), malignancy, and stroke among others have been associated with severe disease and adverse outcomes. The current therapeutic management of COVID-19 is mainly supportive care (WHO interm guidance, 2020).Meanwhile people are taking a breath in the time of declining phase of first wave of COVID-19 cases proximately they are facing that second wave with raised deadly novel circumstances such as Mucormycosis.

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COVID-19 infected cases in the second wave started rising in the month of February, when India reported an average of about 10,000 infections a day. Then the situation progressively worsened by the end of the Aprilsetting new global records for daily cases. Then the month of May by reported more than 400,000 new COVID-19 cases (Worldometer).COVID-19 is associated with a significant incidence of secondary infections, both bacterial and fungal probably due to immune dysregulation. Moreover, the main crucial factor for mortality in COVID-19 with Mucormycosis was the extensive use of steroids/monoclonal antibodies/broad-spectrum antibiotics as part of the armamentarium against COVID-19 may lead to the development/exacerbation of preexisting fungal diseases (Mishra Y,2020).

Aim of the study: The present systematic review mainly aimed to evaluate the FTR1 gene expression and glucose-regulated protein (GRP78) receptor in uncontrolled diabetes mellitus SARS CoV-2 patients with mucormycosis, and possible therapeutic targets for interventions of the disease in patients with COVID-19.

METHODOLOGY

Electronic searches

In this present study we searched thePubMed, Google Scholar, Scopus, Web of Science database using the following keywords ‘FTR1 gene expression’, ‘glucose-regulated protein (GRP78) receptor, ‘uncontrolled diabetes mellitus’, ‘SARS CoV-2’, ‘COVID-19’, ‘Mucormycosis’, ‘ferritin’ ‘inhibitors’.

Selection of studies

The electronic searches were performed and carefully screened all the articles. All potentially relevant full text articles were investigated. The studies those met the inclusion criteria were included in the study. A total of 330 articles were identified through the electronic database but only 300 were excluded from the study. Potentially relevant articles were found23 others didn't meet the inclusion criteria and PRISMA flow chart was mentioned below (Figure 1).

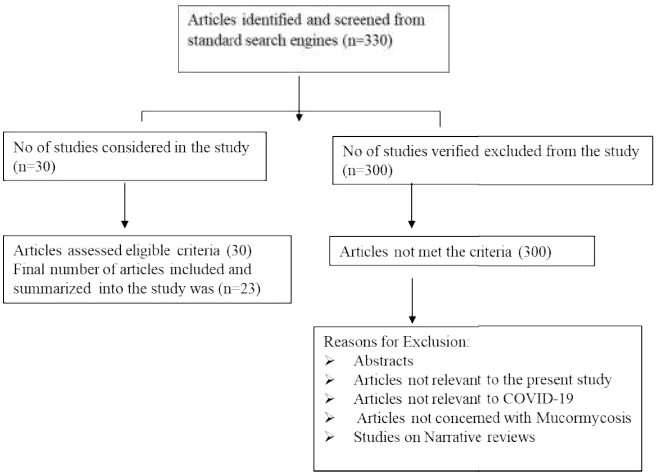

Figure 1. Inclusion exclusion criteria -PRISMA flow diagram

Exclusion criteria

We screened all the articles and the abstracts those didn't have full length articles, studies on narrative reviews, studied parameters of the study were un related to Mucormycosis, therapeutic approach not related to the genes which were involved in the Mucormycosis.

Inclusion criteria

The inclusion criteria of the present review included studies were not restricted to a particular country and studies are concerned majorly with Mucormycosis. For appraisal of the quality of the publications, we considered original studies due to their structure and ability to reduce bias.

DISCUSSION

Mucormycosis, which has an overall death rate of fifty, which can be being triggered by the utilization of steroids, a life-saving treatment for severe and critically ill COVID-19 infected patients. Currently used drugs mainly steroids reduce inflammation in the lungs for Covid-19 patients and appear to benefit stop partial damage that can happen when the body's immune system goes into overdrive to fight off novel corona virus. Nevertheless, they also reduce immunity and push up blood sugar levels in both diabetics and non-diabetic patients with Covid-19. It's thought that this drop by immunity might be triggering these cases of mucormycosis (Mishra, 2020).

Mucormycosis: Mucormycosis (MCR) so called black fungus is a life-threatening infection caused by fungi of the order Mucorales. The most common etiologic species of MCR was Rhizopus oryzae (Figure 2). The most common predisposing risk factor for mucormycosis was diabetes mellitus, and it has been long established that patients with diabetic ketoacidosis (DKA) have a unique predisposition to this MCR infection. Regrettably, despite surgical debridement and first-line antifungal therapy, the overall mortality of MCR remains unacceptably high, and survivors are typically left with considerable disfigurement from the infection and surgery. Early detection of the fatal disease like MCR in COVID-19 infected patients and appropriate treatment plays a crucial role to decrease the mortality rate. Apparently new strategies to prevent and treat MCR are urgently needed especially patients suffering with COVID-19 and such strategies can be facilitated by clear understanding of the pathogenesis of the disease (Howard, 1999 and Artis, 1982).

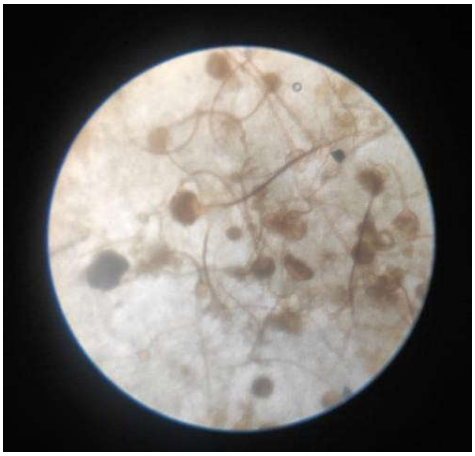

Figure 2. Microscopic picture of Mucormycosis

Risk factors for Mucormycosis

Increased available serum iron for mucormycosis: Iron is a trace element and very little serum iron is available to microorganisms because it is highly bound to carrier proteins such as transferrin. Iron is required by virtually all microbial pathogens for growth and virulence (Howard DH, 1999 and Artis WH, 1982). The organism grows ailing in serum and this growth inhibition is reversed when further addition of exogenous iron(Artis WH, 1982). Consequently, efficacious pathogens use multiple processes for obtaining iron from the host. The obtainable literaturedetermines that the level of available, unbound iron in serum plays a critical factor in uniquely predisposing patients with DKA to MCR(Boelaert JR, 1993).

High-affinity iron permeases (FTR1): In humans, iron is bound to host carrier proteins, such as transferrin, ferritin, and lactoferrin. This impounding avoids toxic effect of free iron (Howard, 1999 and Artis, 1982). Fungi mainly MCR can obtain iron from the host either by using high-affinity iron permeases or siderophores (Howard, 1999). The high-affinity iron permeases (FTR1) are present in fungi that reduce ferric into the more soluble ferrous form which in turn, captured by a protein complex consisting of a multicopper oxidase and a ferrous permease (Ibrahim, 2008, 2006, 2007, and Lewis, 2011). The genome sequencing research identified three ferric reductases, six types of copper oxidases, and one high-affinity iron permease. Certainly, data showed that the gene encoding FTR1 is expressed by R. oryzae during murine infection and inhibition of FTR1 gene expression by RNA-I, or reduction of FTR1 copy number by gene disruption diminishes the virulence of the MCR in animal models (Knight SA, 2005, Jung, 2008, and Ibrahim, 2010). Animal models revealed that passive immunization with anti-FTR1p immune serum

protected mice with DKA from infection with MCR. Consequently, FTR1 is a crucial virulence factor for R. oryzae, and anti-FTR1p passive immunotherapy represents anauspicious strategy to advance outcomes of deadly MCR. Siderophore supplies by Rhizopus with iron through a receptor-mediated, energydependent process (Thieken, 1992). In this process, the genome-sequencing project of R. oryzae identified that thirteen siderophore permeases which act as receptors for siderophores, including rhizoferrin/ deferoxamine. Yet, it is unknown that whether rhizoferrin transports iron by release of iron extracellularly or whether the siderophore is internalized before releasing iron in the cytoplasm. Infact what is known is that rhizoferrin is incompetent in obtaining iron from serum (Thieken, 1992). Consequently, the contribution of the organism's endogenous siderophores to its virulence in a mammalian host is likely to be minimal. The lack of rhizoferrin ability to take iron from serum is also highlighted by the adaptation of the organism to use xenosiderophores, such as deferoxamine, which are more efficient in obtaining iron from the host. A third mechanism by which fungi can obtain iron from the host is through use of heme (Santos, 2003, Worsham, 1988). The Rhizopus genome project revealed that two homologues of the heme oxygenase and which may enable R. oryzae to obtain iron from host hemoglobin (Ma, 2009). Of interest, R. oryzae that had reduced copy numbers of FTR1 also had lagging growth on media supplemented with heme (Schreltl, 2008). Thus, FTR1 may act as a cytoplasmic membrane permease that facilitates heme uptake at intra cellular level, which is followed by release of ferric iron through degradation with heme oxygenases. Other genes likely to be involved SreA, a transcriptional regulator (Schreltl, 2008), and 2 orthologes probably encoding ferritin required for intracellular storage of iron.

Mucormycosis and Uncontrolled Diabetes Mellitus in Severe COVID-19: Diabetes mellitus, a traditional risk factor for MCR, is associated with increased morbidity and mortality in patients with COVID-19. Patients with diabetes mellitus in COVID-19 have a high risk to admission in ICU. The management of diabetes in ICU is always challenging, however, when diabetes is present in COVID-19 the situation seems even more complicated and prone to serious complications and to die. The severity of the MCR disease was significantly higher in patients with diabetes compared with non-diabetes (34.6% vs. 14.2) (Ceriello, 2020). It was observed that India has the highest burden of MCR in the world with estimated prevalence of 140 cases per million population, and moreover about 71% of MCR cases were reported from India(Prakash, 2019). Besides that, India was the second-largest number of adults population aged 20–79 years with DM (Federation International Diabetes, 2019). Recently, it was found that multi-center study on MCR in Indian population, 57% of patients had uncontrolled diabetes mellitus and 18% had diabetic ketoacidosis (Prakash 2019). 67% of uncontrolled DM patients with DKA and as with any other serious infection, patients with COVID-19 are predisposed to DKA (Farmakiotis D, 2016, Singh AK, 2020). Recent scientific evidence showed that SARS CoV-1 induces damage of pancreatic islets resulting in acute DM and DKA (Yang JK, 2010). The conceivable elucidation for the diabetogenic state in COVID-19 infection, as there is a high expression of ACE-2 receptors in pancreatic islets, along with increased insulin resistance due to cytokine storm (Kothandaraman, 2021). A study done from UK observed that prevalence of DM (31%) and DKA (2%) in COVID-19 were higher compared to the national prevalence of type 2 DM and DKA in the general population in a UK study (7%) (Goldman N, 2020). It was found recently, euglycemic DKA patients also being reported in COVID-19 (Oriot, 2020). The causative factor for MCR in COVID-19 was frequent use of corticosteroids that exacerbated glucose homeostasis, may have predisposed to MCR. Corticosteroid use was a key risk factor for opportunistic mycoses. In addition to hyperglycemia, an alteration of iron metabolism occurs in severe COVID-19 (Perricone, 2020). Severe COVID-19 was a hyper-ferritinemic syndrome, but whether high ferritin is a marker of a severe systemic disease versus a modulator of pathophysiology was unknown. Regardless of its role, high levels of ferritin lead to excess intracellular iron that generates reactive oxygen species resulting in tissue damage.

Mucormycosis and Cytokines

Cytokines, mainly Interleukin-6 (IL-6) stimulate ferritin synthesis and down regulate iron export resulting in intracellular iron overload, further exacerbating the process due to severe infection and DKA (Perricone, 2020). The consequential tissue damage leads to the release of free iron into the circulation and that excess free iron seen in acidemic states are one of the key and unique risk factors for MCR (Edeas, 2020; Ibrahim, 2012). Another significant observation was seen in severe COVID-19 was endothelialitis. Previous autopsy series have shown more severe pulmonary vascular endothelial injury in patients who died of COVID-19 than patients with influenza A (Ackermann, 2020). Another postmortem series found thatextensive endothelial injury in patients who died of multi-organ failure. It was reported that endothelial adhesion and penetration were critical early steps in MCR (Ackermann, 2020; Varga, 2020). Remarkably, acidemic states and high glucose levels were induce the enthodelial receptor glucose-regulated protein (GRP 78) (receptors responsible for SARS-CoV-2 entry)and the coat protein homologs, which increased adhesion and penetration of Mucorales to the endothelium (Sabirli, 2021).

Overexpression of GRP78 Protein is Suitable for Host invasion by Rhizopus: Glucose-regulated proteins (GRPs) were first observed in transformed fibroblasts, in which the synthesis of these proteins increased when glucose depletion was induced (Shiu RPC, 1977). The most abundant GRP is a 78-kDa glucose-regulated protein (GRP78), also known as immunoglobulin-binding protein, located in the lumen of the endoplasmic reticulum and expressed in mammalian cells. GRP78 is encoded by the HSPA5 gene, assigned to chromosome 9q34. GRP78 structure shows that which consists of two functional domains such as a nucleotide-binding domain (NBD) and a substrate-binding domain (SBD). The domines activity is regulated by the allosteric ATPase cycle, where NBD binds and hydrolyzes ATP, and SBD binds to polypeptides (Ting, 1988, Handershot, 1994; Yung, 2015).

Endoplasmic reticulum stress on GRP78: While new features have come to light in recent years, GRP78 has been traditionally considered a molecular chaperone belonging to the HSP70 family. GRP78 acts to control (endoplasmic reticulum) ER stress through regulation of the unfolded protein response (UPR), and it plays a key role in the folding, assembly, and quality control of proteins and misfolded protein degradation (Roller, 2013; Know, 2018). GRP78 is mainly

originate in the ER, but it also has the ability to translocate and accumulate in other intracellular locations (Ni, 2011). The cytosolic GRP78 protein is found as GRP78va, an isoform generated by alternative splicing and alternative translation, which absences the ER signal peptide. GRP78va has cytoprotective properties and besides that which possess potential to regulate signaling to the UPR, promoting cell survival (Ni, 2009). The expression of GRP78 in the intermembrane space, internal membrane, and the matrix of mitochondria is triggered by ER stress, and it participates in UPR signaling inside the organelle (Sun, 2006). The recent relevance of GRP78 expression is its translocation to the surface of the cell membrane, where it has receptor and regulatory functions in cell signaling by the formation of complexes with extracellular ligands and proteins anchored to the cell surface (Gonzalez-Gronow, 2009).

GRP78 protein was identified in 1997 on the cell surface of malignant lymphocytes in patients with acquired immunodeficiency syndromeand cutaneous lymphoma (Berger, 1997). Subsequentlyat that moment, this protein has been constantly analyzed and is now known to be involved in the proliferation of various types of carcinoma, chronic or inflammatory diseases, as well as the invasion by fungi and some viruses (Ni, 2011). Thus, the stress in the ER, caused by many pathologies, is known to trigger the GRP78 translocation to the cell surface, where it is called csGRP78, and it can even have antigenic properties inducing the production of anti-GRP78 autoantibodies and it also acts as an associated signal receptor to the membrane (Crane, 2018). Previous studies have shown that hyperglycemia was a stress trigger in the endoplasmic reticulum, which consequently induces the overexpression of the GRP78 protein and has been proposed that GRP78 is translocated to the cell surface from the ER through a mechanism regulated by the MTJ-1 chaperone. Once GRP78 expressed on the cell surface, it interacts with the β1 integrin in charge of mediating phosphorylation of kinases. Later, fibrosis occurs through the expression of extracellular matrix proteins (ECM), such as fibronectin and type I collagen by the activation of the Kinase of Focal Adhesion (FAK) and downstream protein kinase Akt causes (Van Krieken, 2019). Besides that, previous research hasbeen shown that the over expression of csGRP78 plays a vital role as the entry receptor of Dengue virus, Ebola virus, Coxsackievirus, and the novel SARS-CoV2, and Rhizopus spp. Animal models of mucormycosis model had shown that high glucose levels increase 2- to 5-fold higher levels of GRP78 mRNA in the sinus, lungs, and the brain when compared with normal mice and also it increased 40% endocytosis of R. oryzae by human endothelial cells (Van Krieken, 2019). This preliminary evidence opined that csGRP78 was crucial for invasion but not for adhesion because it is bound by germlings but not by spores. However, limited research has been found in progress in this area in recent years. There are still no approved vaccines against fungal pathogens and the availability of drugs for the treatment of mucormycosis is limited to a scarce. Although promising treatment alternatives such as the use of in vitro-reactivated Tspecific lymphocytes or the use of heat-killed yeast, Saccharomyces cerevisiae, as a candidate vaccine, have recently been reported, there have been no other approaches in recent years. It is necessary to continue deepening knowledge about the pathogenic mechanisms, the relationships between Rhizopus, and the microenvironment found in the human body. This knowledge, as well as the use of cutting-edge techniques such as CRISPR/Cas9 for the genetic modification of the complex genome of R. oryzae, will undoubtedly contribute to develop better antifungal agents, treatment alternatives, and vaccine development (Van Krieken, 2019).

Benefit of iron chelation therapy for mucormycosis (Preliminary evidence)

Iron metabolism plays a central role in pathogenesis of MCR, which suggests the possibility of utilizing effective iron chelators as adjunctive antifungal therapy such as deferoxamine, other experimental iron chelators which have been studied in vitro against R. oryzae. In contrast to deferoxamine, these other iron chelators did not allow the organism to take up iron, and did not support its growth in vitro in the presence of iron. Furthermore, in animal models while deferoxamine significantly worsened disseminated R. oryzae infection (Boelaurt, 1994). After that deferiprone, is approved for clinical use as an iron chelator in various countries (Europe and India, and US) is available on a compassionate use basis for iron overload. The ability of deferiprone to inhibit growth of Zygomycetes in vitro and confirmed its efficacy in our diabetic-ketoacidotic murine model of R. oryzae infection (Ibrahim, 2006). Deferasirox became the first orally bioavailable iron chelator approved for use by the US approved by Food and Drug Administration (FDA), with an indication for treatment of transfusion-dependent iron overload. Research showed that deferasirox to be effective at chelating iron from R. oryzae and demonstrated fungicidal activity in vitro against Zygomycetesat concentrations well below clinically achievable serum levels. In addition to that, deferasirox significantly improved survival of DKA or neutropenic mice with MCR, with efficacy comparable to that of liposomal amphotericin B and showed synergistically improved survival rate (Ibrahim, 2007). A recent study using Drosophila melanogaster as a model host also demonstrated that deferasirox significantly protected wild-type flies infected with R. oryzae when compared with placebo-treated flies (Chamilos, 2008). Finally, deferasirox was recently successfully used as a salvage therapy to treat a patient with rhinocerebral mucormycosis who was failing months of polyene treatment (Reed, 2006). The use of therapeutic agents of COVId-19 should be monitored to achieve a therapeutic effect at the lowest dose and shortest durations. The use of broad-spectrum antibiotics, especially in the absence of infection, should be re-evaluated (Mehta S, 2020).

Limitations

- We acknowledge the limitations of our review is MCR incidence in patients with COVID-19due to difficulty making a histopathological or microbiological diagnosis in patients with a contagious infection in a pandemic situation.
- Inability to assess attributable mortality of MCR due to the lack of appropriate controls.
- Finally, the nature of our study does not allow us to determine if uncontrolled diabetes plus COVID-19 is associated with a higher risk of MCR than diabetes alone.

Summery and Conclusion

We observed by previous research that the gene encoding high-affinity iron permease (FTR1) is expressed by R. oryzae

during murine infection and inhibition of FTR1 gene expression by RNA-I, or reduction of FTR1 copy number by gene disruption reduces the virulence of the fungus in animal models of MCR. Hyperglycemia was a stress trigger in the endoplasmic reticulum, which consequently induces the overexpression of the GRP78 protein depending on glucose concentrations and the persistence of hyperglycemia. The therapeutic inhibitors of FTR1 and GRP78 protein might be essential to control MCR in patients with COVID-19. The possible benefits of interventions that would complement existing therapies would be profound for patients with MCR. The logical extension of the observations of the roles of key virulence factors, such as iron use by R. oryzae, is to develop therapeutic strategies that will translate to interventional clinical trials. Large cohorts of genomic studies and interventional studies will be required to enlighten the novel pathways of pathophysiology and their target genes for efficient drug design.

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