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Infusion of mannose- binding ligand (MBL) as therapy against fungal infections

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Abstract
Black fungus, White fungus, yellow fungus, the ones sicknesses have become extra powerful in human beings at some point of Covid-19/20 pandemic, In which black fungus resulting from Mucor my cosisis a life-threatening infection, White fungus resulting from Candida albicans that takes place in sufferers who're immuno compromised due to diabetic ketoacidosis, organ transplantation, and/or accelerated serum levels of available iron. Because of the use of steroids at some point of Covid treatment, growing incidence of diabetes mellitus, cancer, and organ transplantation, the range of sufferers with pre-current headaches are at hazard for this lethal infection. New techniques to save you those fungal infections are urgently needed. The essential aim is to management of Plasma with MBL or purified MBL in MBL poor human beings as immune booster to prompt complement.

Keywords: mannose binding lectin (MBL), complement pathway, replacement therapy

Introduction

Mannose-binding glycoprotein (MBL) is also a soluble lectin of the innate system that's made by the liver and secreted into the circulation wherever it activates the lectin complement pathway, enhances biological process of microorganisms by leukocytes like phagocytosis, and modulates inflammation. MBL will acknowledge patterns on the surface of varied pathogens, in addition as fungus albicans.[1] Mannose-binding lectin (MBL) is an oligomeric calcium-dependent sugar-binding supermolecule containing albuminoid structures. Its overall sertiform structure is incredibly the identical as that of the complement element C1q, and like C1q, MBL mediates the activation of C4 and C2 through 2 associated organic compound proteases (MASPs) when binding to terminal sugar residues gift on the surface of the various micro-organisms [2]. Whereas, MBL shown the action of binding and inducing phagocytosis in killing various microorganisms [3]. The distribution of MBL sequence polymorphisms was considerably totally different between patients with SARS - CoV and control subjects, with the subsequent frequency of haplotypes associated with low or deficient liquid body substance levels of MBL in patients with SARS than up to the mark subjects. bodily fluid levels of MBL were additionally significantly lower in patients with SARS than up to the mark subjects. There was, however, no association between MBL genotypes, that are related to low or deficient bodily fluid levels of MBL, and mortality concerning SARS. MBL may bind SARS-CoV during a dose- and calcium-dependent and mannose-inhibitable fashion *in vitro*, suggesting that binding is through the macromolecule recognition domains of MBL [4].

Role of Mannose Binding Lectin as PRR in PAMP recognition against fungi.

MBL belongs to the category of collectins within the C-type lectin superfamily, whose function appears to be pattern recognition within the first line of defense within the pre-immune host. MBL recognizes carbohydrate patterns found on the surface of an oversized number of pathogenic micro-organisms, including bacteria, viruses, protozoa and fungi. Binding of MBL to a micro-organism leads to activation of the lectin pathway of the complement system.[5] [6] The complement system is often activated through three pathways: the classical pathway, the choice pathway, and therefore the lectin pathway.

Polysaccharides in fungal cell wall:

Almost 90% of the fungal cytomembrane consists of polysaccharides not found in humans. These structures stay an ideal but acts as target for developing new antifungal drugs. The cell membrane structure of medically necessary expedient fungal pathogens has been well delineated (i.e., for fungus, fungus albicans, Pneumocystis spp., Cryptococcus neoformans, Histoplasma capsulatum, and Blastomyces dermatitidis). Fungal cell walls are organized in a very similar way. Indeed, cell membrane consists of two layers: an inner layer that's that the backbone half and an outer layer which can be a quite supermolecule matrix made of carbohydrates. The backbone consists of β-1,3- and/or 1,6-glucan and polyose bound to different polysaccharides or proteins. The outer layer could be a lot of variables among the species. Extremely mannosylated glycoproteins are found on yeast such as Candida sps [7]. However, little or no is assumed concerning the line of the semipermeable

membrane of fungus order spp., a current explanation for mycosis leading to vital morbidity and mortality (Walsh *et al*., 2004), within the main in disorder and diabetic patients. Mucormycosis represents the third invasive mycosis in terms of overall mortality in France (Bitar *et al*., 2014)

Mucorales-Extracellular Polysaccharides

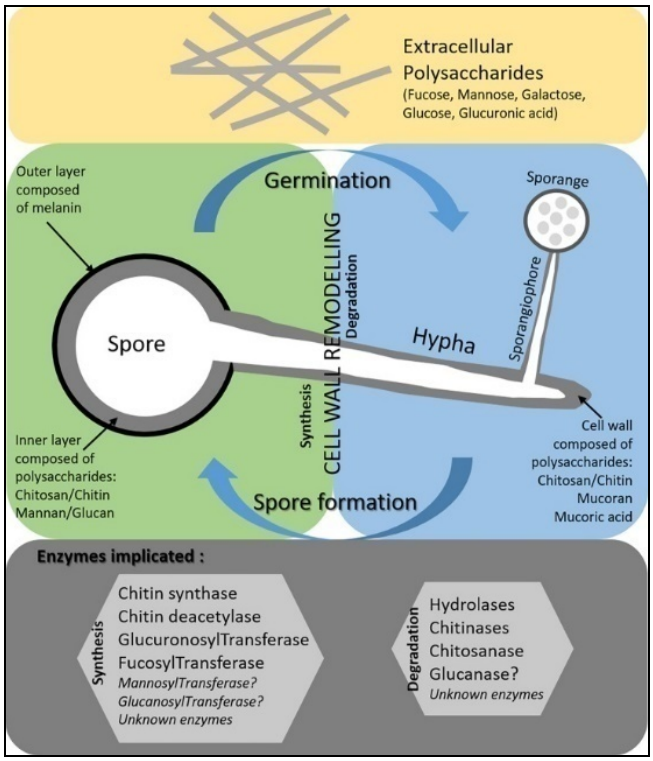

Fig 1: Current knowledge on the cell wall of Mucorales spores (green part) and hyphae (blue part) and gaps (gray part) [7].

Mucorales also secrete extracellular polysaccharides (EPS), few studies have been done on several species of *Rhizopus* and *Mucor*.Eps structure and molecular mass changes based on species and how they were isolated. These polysaccharides are essentially composed of β1,4-linked glucuronic acid. These EPS are composed of mannose varying from 8 to 30%; galactose from 4 to 13%; fucose from 9 to 25%; glucose from 0 to 30%; and glucuronic acid from 32 to 55% (de Ruiter *et al*., 1991, 1992). One study showed that mannose residues could be 2-O-methylated (de Ruiter *et al*., 1994). 2-O-methyl-D-mannose represents 1–2% of the two mannan fractions extracted from EPS of *M. racemosus*. Mannose residues are linked through α1,2 linkages, while 2-O-methyl-D-mannose residues are found at the non-reducing end.[7]

Mannose based Lectin pathway on Mucorales

MBL binds to carbohydrates (to be specific, D-mannose and L-fucose residues) present on the surfaces of many pathogens. MBL in the blood is complexed with (bound to) a serine protease called MASP (MBL-associated serine protease). There are three MASPs: MASP-1, MASP-2 and MASP-3, which have protease domains. There are also sMAP (also called MAp19) and MAp44, which do not have protease domains and are thought to be regulatory molecules of MASPs. MASPs also form complexes with ficolins, Ficolins recognize their targets through fibrinogen domains except the recognition but is similar to MBL both structurally and functions

The MASP protein cleave the blood protein C4 into C4a and C4b to activate the Complement system when target was identified by MBL. The C4b fragments then bind to the surface of the Fungi/bacterium, which initiates the formation of a C3-convertase.

The subsequent complement cascade catalyzed by C3-convertase results creates a membrane attack complex, which causes lysis of the pathogen

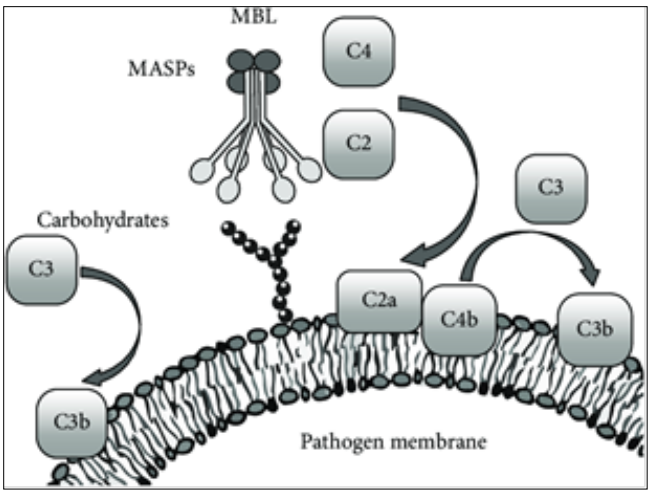

Fig 2: A model illustrates the activation of the lectin pathway by infective agents. MBL recognizes specific carbohydrates such as D-mannose, L-fucose, and N-acetylglucosamine that are represented on the surface of a wide variety of infectious agents. Engagement of ligand by MBL activates MASP2, which then cleaves the C2C4 convertase and results in the cleavage of C3 and the generation of C3b. It has also been proposed that MASP1 can directly cleave C3 [8].

sMBL deficiencies are implicated in infectious diseases

Human sMBL is a {very important} consider Animal weapons system that enables us to fight agaisnt numerous pathogens by direct neutralization and inhibition. In an indirect role, sMBL acts as an antibody like opsonin and as an element in complement activation [9]**.** In general, s MBL concentration in normal serum varies from very low level to l0.0 ng/mL. various studies have reportable that deficiencies in blood sMBL are related to many diseases [9-14]. Infections due to Influenza A virus in Pneumococcal diseases are at higher risk of death from pneumonia. On the opposite hand, sMBL showed a considerably higher incidence of influenza (H1N1) pdm09 virus infection in non-survivors of the disease. Polymorphisms of the MBL gene, a bigger prevalence of haplotypes in respiratory disease patients, are related to low sMBL levels than control. It's been reported, there was no link between genotypes of MBL that were associated with deficient levels of sMBL and SARS mortality. Even then, C4 deposition was multiplied by MBL in SARS-CoV patients. Earlier these findings indicate that MBL could be a susceptibleness issue for the acquisition of SARS **[15]** within the first-line of host defense against SARS-CoV. A greater risk of vulvovaginal candidiasis-Candida canal infections is additionally associated with MBL2 mutations [16].

Supported MBL genotypes (codon fifty-four polymorphism), lower MBL levels have the next risk of cardiovascular disease and hypoglycemic agent resistance in women with post-menopause [16].

Level of MBL's in SARS- Covid-19 patients

It has been reported that the distribution of *MBL* gene polymorphisms was significantly different between patients with SARS and control subjects, with a higher frequency of haplotypes associated with low or deficient serum levels of MBL in those cases. Serum levels of MBL were also significantly lower in patients with SARS than in control subjects [15].

Production of MBL

A manufacturing method for an MBL product from a fraction II + III precipitate obtained by fractionating plasma with ethanol was developed. The MBL process comprises three chromatographic steps, the first and most important step being is affinity chromatography on a cross-linked agarose matrix that selects oligomeric, carbohydrate-binding MBL. Research has shown that the yield from the production process is around 25% of the plasma MBL content and the purity is around 65%. The MBL product shows mannan binding activity and complementarity. A safety study has shown that this plasma-derived MBL is safe and well tolerated in MBL-deficient adult volunteers [17].

Administration of Purified MBL

Individuals with low concentration/levels of MBL within their humorcan be infused with purified MBL in their serum by administration of Plasma with MBL or purified MBL that can flow into in the blood, reach the tissue, and therefore shield against the infections. MBL (plasma-derived or recombinant) medical aid has however to be shown to be safe and effective. probably it should be helpful in MBL-deficient patients to scale back condition to, or enhance recovery from, microbial infection or to change the explanation of a sickness (disease-modifying drug) [18].

Conclusion

Individuals with low tiers of mannan-binding lectin (MBL) appear like liable to infectious diseases. This shows that substitution remedy with MBL is probably a useful remedy of sufferers/ patients with MBL deficiency, in which that they may be save you from fungal infections, recently COVID-19 sufferers are extra touchy to fungal infections, after the remedy of Covid-19 or immune suppressed humans like Diabetics, HIV, consumption of steroids for remedy. Tests need to be achieved to estimate the levels of MBL in a man or woman and administer purified MBL's into them which facilitates to broaden innate immunity. MBL's binds to D- mannose polysaccharides present within the cell-wall of fungal spores ex- Mucorales, Candida sps and turns on C3 complement fixing which destroys fungal spores in an infused person.

Future outcome

Plasma therapy is a therapy by which Covid-19 patients can be cured. Purified MBL from plasma which is collected from Covid-19 cured patients can be administered for black fungus patients. Purified MBL infused with patient's serum can be used as therapy with less concentration of MBL. By this process purified MBL can be used against fungal infection. Covid 19 infected patients are deficient of MBL. Plasma derived from Covid 19 survived patients MBL can be recombined and can be administered into black fungus infected patients. Another option can bethe strain which is responsible for black fungus infection should be sequenced. The goal will be to identify the gene or gene clustered which are responsible for infection. Removing those genes from the genome of Mucor mycosis and administered them as antifungal drug can be an option to cure this disease.

Conflict of Interest

This project is not having any conflict of interest.

Funding Source

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