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Journal of Clinical Immunology & Microbiology

Review Article

How Fungus Can Debilitate Your Immune System?

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Received Date: 30-01-2021; **Accepted Date:** 19-02-2021; **Published Date:** 26-02-2021

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Abstract

Little is known about the precise mechanism involved in immunity to fungal infections. Researchers discovered that fungal prostaglandins, deactivate immune cells, preventing them from destroying the infection. Fungi are known to make molecules similar to those of our own immune system. Scientists found that the fungus molecules weaken the immune system, which is essential in stopping infections. Opportunistic infections like Cryptococcus which normally pose no threat, but are potentially life-threatening in those with weakened immune systems. Scientists are now working to find the other ways these fungal molecules are affecting immune cells and how the immune cells are deactivated. Antibodies against fungi and yeasts may be

Rao RMV | Volume 2; Issue 1 (2021) | JCIM-2(10)-017 | Review Article

Citation: Rao RMV, et al. How Fungus Can Debilitate Your Immune System? J Clin Immunol Microbiol. 2021;2(1):1-14.

DOI: <http://dx.doi.org/10.46889/JCIM.2021.2104>

found in the sera of many apparently normal people, as well as in those who have overt infections. In presence of clinical fungal infections e.g. due to *Aspergillus fumigatus*, the amount of antibody may be so great as to be readily demonstrable by precipitin tests. Although there is considerable evidence to implicate such antibodies in the pathogenic effects of pulmonary fungal infections, there is no evidence that they hinder their spread once infection is established. However, the very fact that patients with immunoglobulin deficiency diseases are so unduly prone to candida and monilia infections indicates that antibodies must play some part in protecting against initial or reinfection.

Keywords

Fungal Prostaglandins; Th1-Type Cell-Mediated Immunity (CMI); CD4+T Lymphocytes; Cytotoxic-T-Cell (CD8+Tct); T-Cell Mediated Immunity; *Coccidioides Immitis*; *Aspergillus fumigatus*; *Histoplasma capsulatum*; *Blastomyces dermatitidis*; Th1 Immunity; Th2-Immunity

Abbreviations

CMI: Cell-Mediated Immunity; PAMPs: Pathogen-Associated Molecular Patterns; IL: Interleukin; BCR: B-Cell Recognition; TCR: T-Cell Recognition; MHC: Major Histocompatibility; APC: Antigen Presenting Cells; TCT: T Cytotoxic; Igs: Immunoglobulins; Th: T- helper; LPA: Latex Particle Agglutination

Introduction

Candida species cause infections in individuals with deficient immune systems. Th1-type Cell-Mediated Immunity (CMI) is required for clearance of a fungal infection. *Candida albicans* is a kind of diploid yeast that commonly occurs among the human gut microflora. *C. albicans* is an opportunistic pathogen in humans. Abnormal overgrowth of this fungus can occur, particularly in immunocompromised individuals [1].

C. albicans has a parasexual cycle that appears to be stimulated by environmental stress [2].

In humans, *Aspergillus fumigatus* is the most common and life-threatening airborne opportunistic fungal pathogen, which is particularly important among immunocompromised hosts [3].

Inflammatory mediators released by alveolar macrophages lead to the recruitment of neutrophils, which can eliminate the hyphae [4].

The presence of numerous glycosyl hydrolases in the *A. fumigatus* to grow by the degradation of polysaccharides from plant cell walls [5]. Macrophages bind and ingest yeasts via CD11/CD18 integrins, while DCs utilize VLA-5 to recognize *H. capsulatum* ligands heat shock protein 60 and *cyclophilin A*, respectively [6].

CD11/CD18 blockade reduces, but does not prevent, *H. capsulatum* uptake by both human and murine macrophages; this finding suggests that other receptors are capable of driving phagocytosis at least in the absence of CD11/CD18. In contrast to macrophages, human DCs rely on VLA-5 for fungal recognition [7]. Differential recognition of *H. capsulatum* by macrophages and DCs may trigger unique signaling cascades. CD11b/CD18 triggers activation of the tyrosine kinase Syk and downstream production of proinflammatory cytokines in macrophages [8].

The cells recognize Pathogen-Associated Molecular Patterns (PAMPs) present in fungal surface like galactomannan and β -1,3-glucan among others, through Pathogen-Recognition Receptors (PRR) such as Toll-like receptors (specially TLR-1,-3,-4, and-6), the C-type lectin receptor-Dectin-1 [9].

Aspergillus recognition leads to the generation of proinflammatory cytokines like IL-1 α , IL-1 β , TNF- α , IL-8 and MIP-1 α by activation of the NF κ B and inflammasome pathways [10,11]. Granulomas are a sign for control of infections and are composed of macrophages and giant multinucleated cells that contain cryptococcal cells, as well as CD4+ T-cells [12,13].

Macrophages also infiltrate microbial infection sites in response to various inflammatory signals [14]. Proinflammatory cytokines (e.g., interferon- γ (IFN- γ)) guide the polarization of M1 macrophages, whereas Interleukin (IL)-4 mediates the development of M2 phenotypes [15,16]. The ability of macrophages to kill spherule initials and endospores in vitro seems to be dependent on their activation conditions [17]. In the presence of IFN- γ and TNF- α , macrophages are capable of killing *Coccidioides* endospores [18].

Blastomycosis typically presents as a non-specific, febrile illness and is frequently treated as a bacterial pneumonia before *Blastomyces* is identified either by fungal culture, KOH staining, or urine antigen testing. Infections are primarily pulmonary, but can disseminate to skin, bone, central nervous system and other organ systems in 20-50% of cases [19,20].

Immunity

Immunity is concerned with resistance to infection. The non-self is usually the life threatening infectious microorganisms but sometimes it may be tissue grafts taken from other individuals such as the kidney or a piece of skin.

Innate Immunity

Innate Immunity is a form of nonspecific host defense against invading bacteria. It is natural or “innate” to the host, depending, in part, on genetics.

Adaptive Immunity

Adaptive immunity also called acquired immunity. It is mediated by either B-cells (antibody) or T-cells (cell-mediated immunity). As a core function it recognizes antigenic molecules where antigens can be “foreign” or “self” and against that cytokines (messengers) are produced. It generally takes 7-10 days to mobilize on the first encounter. It mobilizes much faster on a second encounter (memory). They use antigen recognition molecules, antibodies on B-cells (BCRs), T-Cell Recognition (TCR) on T-cells. Major Histocompatibility antigens (MHC on antigen-presenting cells). Adaptive immunity can be active or passive. The B or T-cell encounters the antigen for which it is specific. Reaction with the antigen causes cytokines to be produced. Cytokines affect other cells and the cell which produced the cytokine. The cell proliferates into a clone of cells all with the same specificity as the original cell. Thus the response to the antigen is augmented.

Active Immunity

The immunity which results from exposure to an antigen results in natural infection, Vaccination, Passive immunity. Immune components from an exposed individual are transferred to an individual without immunity. Usually antibodies. Occasionally cellular Cytokines.

Cytokines include chemokines, interferons, interleukins, lymphokines and tumor necrosis factors, but generally not hormones or growth factors (despite some overlap in the terminology).

Cytokines are produced by a broad range of cells, including immune cells like macrophages, B-lymphocytes, T-lymphocytes and mast cells, as well as endothelial cells, fibroblasts and various stromal cells; a given cytokine may be produced by more than one type of cell [21,22].

Cytokines are a variety of soluble proteins secreted by monocytes, lymphocytes and other cells exert profound effects on lymphocyte proliferation and terminal differentiation. These soluble proteins include monokine produced by monocytes, interleukins produced by leukocytes (lymphocytes) lymphokines produced by T-lymphocytes. These biologically active substances are collectively known as cytokines. They are not specific for antigens.

The cells of the Immune system express a vast array of surface molecules important in cellular differentiation and cell to cell communication. They are referred as CD (nomenclature - Cluster of differentiation numbers, more than 250 have been identified). These surface molecules are helpful for cellular identity. The cells of Immune system express vast array of surface molecules important in cellular differentiation and cell to cell communication. When T-cells pass thru these areas they are “educated” by the process of positive and negative selection. Involves MHC Class I and II expression in the cells in the thymus.

T-Lymphocytes

Most fungi are highly immunogenic and induce strong antibody and T-cell mediated responses, which can be detected by serology and delayed type hypersensitivity skin reactions.

Antibodies against fungi may be found in the sera of many normal people, as well as those who have overt infections. In the presence of clinical fungal infections, e.g., due to *Aspergillus fumigatus*, the amount of antibody may be so great as to be readily demonstrate by precipitin tests. Although there is considerable evidence to implicate such antibodies in the pathogenic effects of pulmonary fungal infections, there is no evidence that they hinder their spread once infection is established. However, the very fact that patients with immunoglobulin deficiency diseases are so unduly prone to Candida infections indicates that antibodies must play some part in protecting against initial or reinfection 60-70% of peripheral lymphocytes. Formed in Para cortical areas of lymph nodes. T-Cells express as TSR. Paracortical areas of lymph nodes.

T-Cells Express TCR

Recognizes linear epitopes, presented by an Antigen Presenting Cell (APC) in conjunction with MHC. Non-covalently bound to CD3 complex, a non-variable protein CD3 does not bind to antigens, but are involved in signal transduction. Each T-cell Express TCR of one structure and specificity. Demonstration of TCR gene rearrangement is a marker for T-cells. Capable of recognizing specific antigens, when expressed on the surface of Antigen Presenting Cells (APC), in conjunction with Major Histocompatibility (MHC) antigens.

Two types of T-Cells

- CD4+ T helper (Th) cells recognize antigen only in the context of MHC class II antigens
- CD8+ T Cytotoxic (TCT) cells recognize antigen only in the context of MHC class I antigens

CD4+T-Lymphocytes

Master regulator (60% of peripheral T-cells), recognize antigen only in the context of MHC class II antigens on APCs (Class II restricted). Thru' cytokines it can influence the function of all other cells of immune system.

Two subsets have been recognized

- Th1 (T helper 1)
- Th2 (T helper 2)

Cytotoxic-T-Cell (CD8+Tct)

An effector cell recognizes antigens only in the context of MHC Class I antigens present on all nucleated cells (Class I restricted). Activated CTL kills target cells (i.e., virus infected cell, tumor cells etc.) cytotoxic T-cell Produces cytokines of Th1 cell type.

B-Lymphocyte

B lymphocytes, named after their site of origin in the bursa of *Fabricsius* in birds or in the bone marrow in humans, form the basis for humoral immunity by their production of Immunoglobulins (Igs). B-cell disorders are divided into defects of B-cell development / immunoglobulin production (Immunodeficiency's) and excessive / uncontrolled proliferation (Lymphomas, Leukaemia's).

Inflammation

Inflammation is one of the first responses of the immune system to infection [23]. The symptoms of inflammation are redness, swelling, heat and pain, which are caused by increased blood flow into tissue. Inflammation is produced by eicosanoids and cytokines, which are released by injured or infected cells. Eicosanoids include prostaglandins that produce fever and the dilation of blood vessels associated with inflammation and leukotrienes that attract certain white blood cells (leukocytes) [24]. Growth factors and cytotoxic factors may also be released. These cytokines and other chemicals recruit immune cells to the site of infection and promote healing of any damaged tissue following the removal of pathogens [25].

T-Cell mediated immunity is critical for resistance to fungi: Most fungi are highly immunogenic and induce strong antibody and T-cell mediated immune responses, which can be detected by serology and delayed-type hypersensitivity skin reactions. Considerable evidence points to the dominant protective role of Th1 and phagocyte activation, rather than antibody mediated responses. Patients with T-cell deficiencies, rather than defect in antibody

production are more at risk of disseminated fungal disease and antibody titers though useful as an epidemiological tool to determine exposure, do not necessarily correlate with prognosis. Nevertheless, fungi can elicit both protective and non-protective antibodies and the protection afforded by some experimental vaccines can be adoptively transferred by immune era. Resistance to most pathogenic fungi, (including dermatophytes and most systemic mycoses including *C. neoformans*, *Histoplasma capsulatum*, etc but not *Aspergillus spp*) is clearly dependent upon T-cell mediated immunity, particularly CD4+ Th1 cells secreting IFN γ and to lesser extent CD8 T-cells. Individuals with mild Paracoccidioidomycosis have Th1 based immune responses [26].

How Fungus Can Cripple Your Immune System?

Life threatening fungal infections have risen sharply in recent years, owing to the advances and intensity of medical care that may blunt immunity in patients [27]. Mice inhalation of *Aspergillus fumigatus* leads to a rapid increase in philosophic numbers in the spleen and blood but also in the lung [28]. IL-3 is important for the recruitment of basophil following *Nippostrongylus brasiliensis* infection [29].

Life-threatening fungal infections have risen sharply in recent years, owing to advances and intensity of medical care that may blunt immunity in patients. Dendritic cells and subsets that are mobilized against fungi in various anatomical components [30]. Susceptibility to fungal disease has greatly enhanced the understanding of the cellular and molecular basis of antifungal immune responses [31].

Immunity to Fungi

Little is known about the precise mechanism involved in immunity to fungal infections. Dermatophytes are usually restricted to the non-living keratinized component of skin, hair and nails.

Immunity in Subcutaneous Mycosis

Saprophytic fungi which can cause chronic nodules or ulcers in subcutaneous tissues following trauma Eg/ *Chromomycosis*, *Sporotrichosis* *Mycetoma*.

S. schenckii complex is composed of closely related fungi that cause sporotrichosis. These organisms are an interesting model to study the biochemical, genetic, molecular and physiological basis of cell differentiation and morphogenesis [32,33].

Moreover, some studies have indicated that the immune response of the host determines the degree of invasion [34]. The innate immune response plays a key role in establishing an anti-Sporothrix protective response [35]. Phagocytosis by macrophages and neutrophils as well as the production of reactive oxygen species are mechanisms by which cells of *S. schenckii* are eliminated [36].

Immunity to *Coccidioides immitis*

Following recovery from primary infection with *Coccidioides immitis* there usually is immunity to reinfection. Macrophages also infiltrate microbial infection sites in response to various inflammatory signals [37]. Proinflammatory cytokines (e.g., interferon- γ (IFN- γ)) guide the polarization of M1 macrophages, whereas interleukin (IL)-4 mediates the development of M2 phenotypes [38,39].

Immunity to *Histoplasma Capsulatum*

Most cases of *Histoplasma capsulatum*, infections are asymptomatic or show only fever and cough for a few days or weeks. Following initial infection with *Histoplasma capsulatum*, most persons appear to develop some degree of immunity. Immunosuppression may lead to dissemination. Infection is believed to confer long-lasting immunity the most important component of which is T-mediated. In experimental infections macrophages activated by T-lymphocyte-derived cytokines are able to inhibit intracellular growth of *Histoplasma capsulatum* and thus control the disease. Neither B-cell nor antibody have a significant influence on reinfection.

While macrophages and Dendritic Cells (DCs) exhibit overlapping expression of many surface receptors, those utilized for phagocytosis of *H. capsulatum* are cell specific. Macrophages bind and ingest yeasts via CD11/CD18 integrins, while DCs utilize VLA-5 to recognize *H. capsulatum* ligands heat shock protein 60 and cyclophilin A, respectively [40]. CD11/CD18 blockade reduces, but does not prevent, *H. capsulatum* uptake by both human and murine macrophages; this finding suggests that other receptors are capable of driving phagocytosis - at least in the absence of CD11/CD18. In contrast to macrophages, human DCs rely on VLA-5 for fungal recognition [41].

Differential recognition of *H. capsulatum* by macrophages and DCs may trigger unique signalling cascades. CD11b/CD18 triggers activation of the tyrosine kinase Syk and downstream production of proinflammatory cytokines in macrophages [42].

Immunity to *Candida Albicans*

Animals can be immunized actively and are then resistant to disseminated *candidiasis*. Human sera often contain IgG antibodies that can clump *Candida albicans*, *in-vitro* and may be candidacidal. The basis of resistance to Candidiasis is complex and incompletely understood [43].

The cutaneous fungal infections are self-limiting and recovery is associated with certain limited resistance to reinfection. Resistance is apparently based on cell mediated immunity since patients develop DTH reactions fungal antigens and occurrence of chronic infections is associated with lack of these reactions. T-cell immunity is also implicated in resistance to other fungal infections. Since resistance can sometimes be transferred with immune T-cells. It is presumed that T-cells release lymphokines which activate macrophages to produce the destruction of the fungi. In respiratory mycosis, spectra of disease activity somewhat similar to the spectrum of activity in leprosy can be seen.

Immunity to *Blastomyces Dermatitidis*

The principle host defence mechanisms against *B. dermatitidis* have not been clearly defined. The fungal cells activate the complement system by both classical and alternate pathways and antibodies directed against a glucan component of the cell wall have been identified.

Evidence of T-Cell immunity in *Chromomycosis*

Pigmented cells of *chromomycosis* are visible in giant cells in the dermis of a patient. The area is surrounded by mononuclear cells. Evidence to neutrophil-mediated immunity to *mucormycosis*. Section through lung of a patient suffering from mucormycosis an opportunistic infection in an immunosuppressed subject. The inflammatory reaction consists almost entirely of neutrophil polymorphs around the fungal hyphae [44].

Fungi possess many evasion strategies to promote their survival *Cryptococcus neoformans* produce polysaccharide capsules, which inhibits phagocytosis. This helps to escape from the opsonic effect of complement and antibodies.

Candida albicans conceal the beta glucans of their cell wall which would otherwise be efficiently recognized by host dectin-1 underneath an external coat of mannan, a molecule which is considerably less immune-reactive. *Histoplasma capsulatum* is an obligate intracellular pathogen that evades macrophage killing by entering the cell via CR3 and then altering the normal pathway of the phagosome maturation, in parallel to the strategies of intracellular bacteria such as *Mycobacterium tuberculosis*.

Dermatophytes suppress host T-cell responses to delay cell mediated destruction [45].

Th1 Immunity

Th1-cells orchestrate antifungal immune responses through the release of proinflammatory cytokines IFN- γ , TNF- α and GM-CSF. The signature TH1 cytokine, IFN- γ manifests pleiotropic effects on cells during infection. It induces the classical activation of macrophages that is crucial for arresting growth of intracellular fungal pathogens including *Histoplasma reticulum*, *Blastomycis dermatitidis*, *Coccidioides immitis*.

Th2-Immunity

For the vast majority of fungal infections, Th2 immunity manifests detrimental influence on the host. These Th2- responses are comprised of CD4+ T cell-derived cytokines IL-4,IL-5 and IL-13 and B-cell-secreted IgE.

T and B-Cell Immunity

The transition from innate to adaptive immunity is facilitated primarily by DCs, although macrophages contribute. These phagocytes process and present fungal antigen to naive CD4 + T-cells in the context of class II MHC. This interaction initiates the commitment to effector Th subsets. DCs also activates CD8+ T-cells by antigen presentation via MHC1. For antigens that enter through the exogenous pathway, engagement of CD8+ proceeds through a mechanism termed cross-presentation in which antigens are shuttled into class II MHC pathway.

Th-17 Immunity

The Th17 lineage provides a unique mechanism for protection against bacterial and fungal pathogens through production and induction of inflammatory cytokines and other proteins [46]. Neutrophil recruitment induced by Th17 cells is also necessary for pathogen protection and clearance in several other models including *Mycoplasma pneumoniae*, *Bordetella pertussis*, *Candida albicans*, *Pneumocystis carinii*, *Francisella tularensis*, *Staphylococcus aureus* and *Citrobacter rodentium* [47,48].

Th17 cells have also been found necessary for complete vaccination protection against the 3 systemic mycoses that are endemic to North America which include *Coccidioides posadasii*, *Histoplasma capsulatum* and *Blastomyces dermatitidis* [49,50].

Research on Circulating Antigens

Research on fungal circulating antigens received considerable attention, principally because of the evolution of systemic opportunistic mycoses in immunocompromised or AIDS patients. Since the First International Symposium on Fungal Antigens held in 1986 at the Pasteur Institute in Paris, during which many problems in isolation, purification and detection of principal fungal antigens were analysed, new tests for the detection of circulating antigens have been developed for *aspergillosis*, *candidiasis* and *cryptococcosis*; these tests are rapid, routine and commercially available, compared with other reference tests.

Historically, the first circulating antigen was the polysaccharide galactomannan from *C. neoformans*, which was detected by Neil and colleagues in infected animals and later in humans. Bloomfield, et al., developed a simple rapid reactive test for antigen detection in body fluids by Latex Particle Agglutination (LPA), using 0.8 mm particles coated with a polyclonal rabbit anti-*C. neoformans* IgG. This was an extremely sensitive and reliable test when standard conditions were used. The monoclonal antibodies, were successfully applied for *C. neoformans* galactomannan antigen detection [50].

Conclusion

Most fungi encountered by man are harmless saprophytes, but some species may in certain circumstances infect human tissue or promote damaging allergic reactions. Predisposing factors include metabolic disorders, such as diabetes mellitus, toxic states such as chronic alcoholism, diseases such as leukaemia and myelomatosis in which immunological responses are disturbed, treatment with corticosteroids and immunosuppressive drugs and radiotherapy. Local factors such as tissue damage by suppuration or necrosis and the elimination of the competitive influence of normal fungal infections.

Summary

Fungi possess many evasion strategies to promote their survival. *Cryptococcus neoformans* produce polysaccharide capsules, which inhibits phagocytosis. This helps to escape from the opsonic effect of complement and antibodies. *Candida albicans* conceal the beta glucans of their cell wall which would otherwise be efficiently recognized by host dectin-1 underneath an external coat of mannan, a molecule which is considerably less immune-reactive *Histoplasma capsulatum* is an obligate intracellular pathogen that evades macrophage killing by entering the cell via CR3 and then altering the normal pathway of the phagosome maturation, in parallel to the strategies of intracellular bacteria such as *Mycobacterium tuberculosis*. The Th17 lineage provides a unique mechanism for protection against bacterial and fungal pathogens through production and induction of inflammatory cytokines and other proteins. For the vast majority

Rao RMV | Volume 2; Issue 1 (2021) | JCIM-2(10)-017 | Review Article

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DOI: <http://dx.doi.org/10.46889/JCIM.2021.2104>

of fungal infections, Th2 immunity manifests detrimental influence on the host. Th1-cells orchestrate antifungal immune responses through the release of proinflammatory cytokines IFN- γ , TNF- α and GM-CSF.

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