Pathogenesis of Fungal Sinusitis

Essay
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بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

رَّبَّنَآ إِنَّنَا سَمِعْنَا مُنَادِيًا يُنَادِى لِلْإِيمَٰنِ أَنْ
ءَامِنُوا۟ بِرَبِّكُمْ فَـَٔامَنَّا ۚ رَبَّنَا فَٱغْفِرْ لَنَا ذُنُوبَنَا وَكَفِّرْ عَنَّا
سَيِّـَٔاتِنَا وَتَوَفَّنَا مَعَ ٱلْأَبْرَارِ

صدق الله العظيم

(آل عمران -193)

To my mother

Acknowledgment

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Table of abbreviations

ABPA	**Allergic Broncho-Pulmonary Aspergillosis**
AFRS	**Allergic Fungal Rhinosinusitis**
AMCase	**Acid Mammalian Chitinase**
APCs	**Antigen Presenting Cells**
BAD1	**Blastomyces Adhesin1**
C4bBP	**C4b Binding Protein**
CF	**Cystic Fibrosis**
COPD	**Chronic Obstructive Pulmonary Disease**
CR3	**Complement Receptor 3**
CRP	**C-Reactive Protein**
CRS	**Chronic Rhino Sinusitis**
CRSsNP	**Chronic Rhino Sinusitis without Nasal Polypi**
CRSwNP	**Chronic Rhino Sinusitis with Nasal Polypi**
DCs	**Dendretic Cells**
EMCRS	**Eosinophilic Mucin Chronic Rhino Sinusitis**
GM-CSF	**Granulocyte Macrophage-Colony Stimulating Factor**
HBD	**Human B Defensin**
HLA	**Human Leukocyte Antigen**
HSD	**Hypertrophic Sinus Disease**
IFN γ	**Interferon γ**
IgG	**Immunoglobulin G**
IL	**Interleukin**
IRAK	**IL-1 Receptor–Associated Kinase**
LPS	**Lipopolysaccharide**
MAPK	**Mitogen-Activated Protein Kinases**

MBL	**Mannan Binding Lektin**
MCP	**Membrane Cofactor Protien**
MHC	**Major Histocompatibility Complex**
MIP	**Macrophage Inflammatory Protein**
NF κ	**Nuclear Factor κ**
PAMP	**Pathogen-Associated Molecular Patterns**
PCR	**Polymerase Chain Reaction**
PG	**Prostaglandin**
PRRs	**Pattern Recognition Receptors**
RANTES	**Regulated on Action Normal T cell Expressed and Secreted**
ROS	**Reactive Oxygen Species**
SAA	**Serum Amyloid A**
SAP	**Secreted Aspartyl Proteinase**
SLPI	**Secretory Leukocyte Proteinase Inhibitor**
SP-A	**Surfactant Protein-A**
SP-D	**Surfactant Protein-A**
T reg	**T Regulatory cells**
TCRs	**T-Cell Receptors**
Th2 cells	**T Helper 2 Cells**
TLRs	**Toll-Like Receptors**
TNF	**Tumor Necrosis Factor**
TRAF	**Tumor Necrosis Factor Receptor–Associated Factor**

INTRODUCTION

Fungal sinusitis is an important clinical problem with diverse manifestations. It should be considered in all immunocompromised patients and in all patients with chronic sinusitis. It is categorized into five manifestations: invasive (fulminant), chronic invasive (indolent), fungus ball, saprophytic, and allergic fungal sinusitis (1).

Non-invasive fungal sinusitis is defined by the absence of hyphae within the mucosal tissue of the paranasal sinuses and it comprises: fungus ball, saprophytic, and allergic fungal sinusitis. Conversely; invasive fungal sinusitis is defined by the presence of hyphae within the mucosal tissue of the paranasal sinuses and it comprises: invasive (fulminant), chronic invasive (indolent) fungal sinusitis (2).

The spectrum of fungal involvement in chronic rhino sinusitis (CRS) runs from benign colonization to potentially life-threatening invasive disease. Fungal colonization of the nose and paranasal sinuses appears to be a common finding in both normal and diseased states, although there is considerable debate over the prevalence of colonization (3).

Fungal colonization is presumed to be due to the ubiquitous nature of fungal spores in ambient air and the propensity of these spores to germinate in nasal and sinus mucus. In rare circumstances this leads to macroscopic fungal proliferation in the form of ***fungus balls*** (formerly referred to as mycetomas) or ***saprophytic*** growth of fungus. In these cases fungal mycelia accumulate and occupy available spaces within the nose and paranasal sinuses in the absence of significant mucosal inflammation.

Occurring more commonly than in the case of fungus balls, microscopic quantities of fungal hyphae in sinus mucus elicit an intense local immune response. In ***allergic fungal rhinosinusitis (AFRS)*** this

gives rise to the pathognomonic feature of the disease, namely the presence of allergic mucin (4).

Acute fulminant invasive fungal rhinosinusitis is an acute disease that affects immunocompramized patients. It is usually caused by fungi such as Absidia species, Aspergillus species, Basidiobolus species, Mucor species, and Rhizopus species (5). However, in patients whose immunologic deficiency is mild or unapparent, invasive fungal rhinosinusitis might run a more indolent chronic course leading to what is known as ***chronic invasive (indolent) fungal rhinosinusitis***. It has been specifically associated with Aspergillus species, Mucor species, Alternaria species, Curvularia species, Bipolaris species, Candida species, Sporothrix schenckii, and Pseudallescheria boydii (4).

An important function of the sinonasal mucosa is to protect the lower respiratory tract and the host from inhaled pathogens and potentially harmful particulates. A complex set of innate and adaptive immune pathways are active at the mucosal surface both constitutively and in response to specific challenges. Hypo-function of these critical processes may lead to infection and endanger the health of the host. On the other hand, over-activity or dysregulation of these same mucosal immune mechanisms could lead to damaging persistent inflammation. Disruption of normal mucosal functions caused by ongoing inflammation eventually leads to impaired immune capabilities and possible infectious injury to the host (6).

In eosinophilic CRS, a T helper 2 (Th2)-dominated inflammatory cascade exists in the absence of an identifiable trigger. Although it has been suggested that a microbial element (eg, fungi or toxin-producing straphylococci) may be the underlying target of the immune system in

CRS, no consistent agent has been identified to this point. Moreover, the suggested microbial triggers are fairly ubiquitous, existing in healthy individuals as well as in CRS patients. For this reason, theories of CRS pathogenesis have invoked the concept that it is the abnormal host response to the trigger, rather than the trigger itself, that is ultimately responsible for the disease process. To address this hypothesis further, it is necessary to understand the manner in which the sinonasal mucosa interacts with the external environment (7).

It is now clear that the activation of the innate immune system through dendritic cells and toll like receptors (TLRs) is a critical event that shapes the emerging response, thereby controlling the course of infection and thus may influence allergic diseases such as allergic fungal rhino sinusitis (8).

The regulation of fungal pathogens by the innate immune system and dendritic cells is well recognized (will be discussed in chapter 2), although the signaling processes required to discriminate and mount an appropriate response to the vast array of fungal pathogens has been speculated and is currently the focus of many research groups. Signaling from different groups of microbes can be mediated via the TLRs, which lead to the activation of conserved host defense signaling pathways that control the expression of a variety of immune response genes. Different dendritic cells express various recognition molecules, which indicate that they are more or less efficient when responding to certain pathogens (9).

Results of Bozza et al. (10) and d'Ostiani et al. (11) demonstrate that fungi or possibly fungal derived products provide a powerful activation stimulus to dendritic cells, which results in dendritic cells having functional plasticity and the capacity to distinguish between different

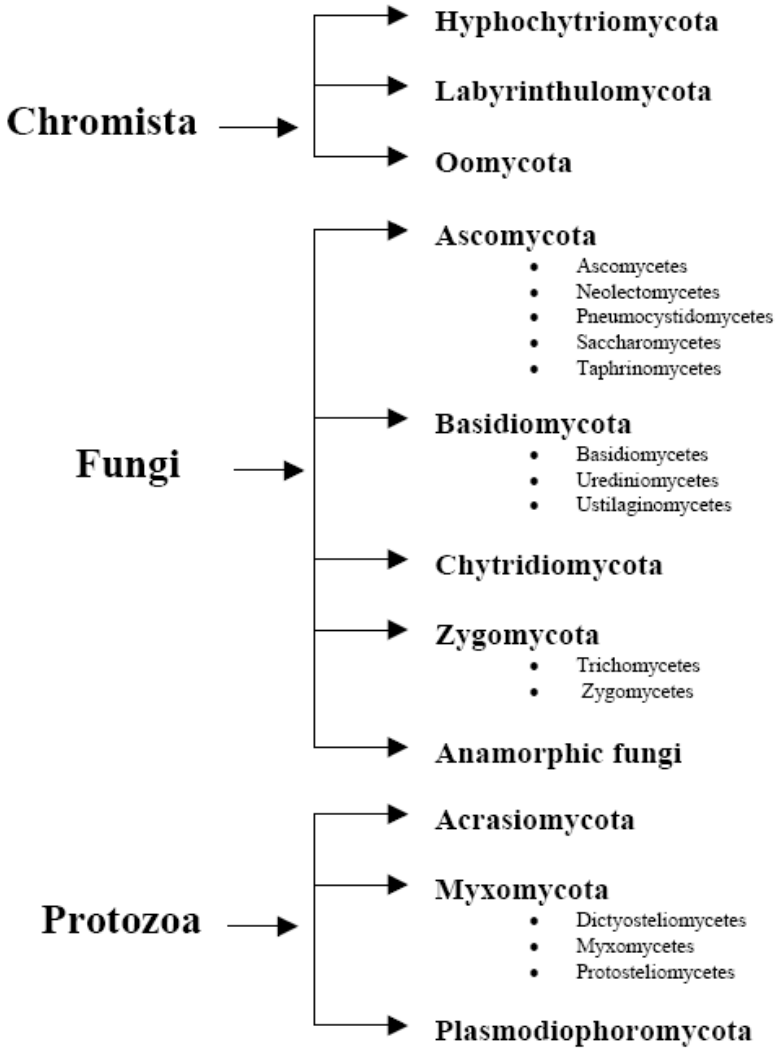
forms of a fungal species prior to differentiating into inter leukin-12 (IL-12) or IL-4/ IL-10 producing cells that support distinct T cell responses. However, the ability of fungi to produce a number of fungal virulence factors during germination and bioactive lipids, such as prostaglandin2 (PG2), that modulate dendritic cell function and TLR4-mediated pro inflammatory signals, in addition to down regulating the maturation of dendritic cells have been recently explored and demonstrated in Aspergillus species ([12, 13]).

As it looks like to be, the process of pathogenesis of fungal sinusitis is the end result of an integrated interaction between fungi and immune system. So we have first to get light on both of these issues to properly understand the pathogenesis of fungal sinusitis.

Chapter 1

FUNGI AND THEIR DISPERSAL

Fungi are a heterogeneous group of non-photosynthetic organisms that are ubiquitous in nature and because of the presence of a cell wall have been grouped in the plant kingdom (table 1), although some authors now place them in a separate lineage because of their ability to synthesize lysine ([14-18]). They are 80-90% polysaccharide in composition and enjoy a relative humidity from 75% to 95% ([19]). Fungi occur naturally throughout the environment and facilitate the aerobic decay of nonliving organic material ([16]). Their activities degrade plant and animal material into carbon dioxide, which is released into the atmosphere in addition to returning nitrogenous compounds back to the soil, where plants and animals can utilize them later ([20]).



(Table. 1) Fungal nomenclature (Ainsworth and Bisby, 2001).