Commentary

Impact of Fungi on Immune Responses

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ABSTRACT

Spores and fungal fragments found in indoor and outdoor environments originate from opportunistic fungi and they can contribute to inflammatory responses, causing a broad range of symptoms. Papers were selected and reviewed with an emphasis on the molecular mechanisms involved in the effect of fungi on immune cells, especially mast cells (MCs). Fungi can bind to antibodies and complement them, allowing them to be recognized by cells of the innate immune system, including macrophages, dendritic cells, and MCs, which are then stimulated via Toll-like receptor signaling. Fungi can cause diseases mediated by MCs and aggravate allergic inflammation. Immunosuppressed subjects can be particularly susceptible to developing diseases caused by opportunistic fungi. Mold also liberates mycotoxins that could be on volatile spores and stimulate MCs to secrete pro-inflammatory cytokines/chemokines, but this mechanism is not known. Fungi can activate the immune system directly or through mycotoxins, leading to stimulation of immune cells and chronic neuroinflammatory symptoms. Some of these processes may be inhibited by the new anti-inflammatory cytokine interleukin 37. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮)

Key words: cytokines, fungi, innate immunity, infection, inflammation, macrophages, mast cells, mold, mycotoxins.

INTRODUCTION

Fungi are eukaryotic single-cell or multinucleate organisms that live by decomposing organic material. Molds are fungi growing in the form of multicellular filaments, called hyphae, on damp surfaces in soil, decaying vegetation, as well as in urban and rural settings.[1]

Fungal exposure can lead to an increased risk of respiratory problems, such as asthma attacks, nasal and sinus congestion, eye irritation, sore throat, chronic cough, and sinusitis.[2–5] *Aspergillus fumigatus* is one of the most common fungi that can cause severe pathology in immunocompromised hosts.[6,7]

IMMUNE RESPONSES

Immunity to fungi[8] involves activation of Toll-like receptors (TLRs) generating inflammatory cytokines through pattern-recognition receptors and pathogen-associated molecular patterns.[9,10] In humans, TLRs range from TLR1 to TLR13 proteins, most of which are expressed on the cell membrane; in contrast, TLR3, TLR7, TLR8, TLR9, TLR11, TLR12, and TLR13 are expressed intracellularly on endoplasmic reticulum, endosomes, phagosomes, and lysosomes.[11] Apart from TLR3, all TLRs engage TIRAP, which

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leads to activation of MyD88 and the adaptor molecule IRAK complex.[12] The subsequent phosphorylation cascade engages IRAK4, TRAF6, and TAK, which activate both NF-κB and MAPK, causing gene enhancement that regulates cell differentiation, proliferation, and inflammation.[13,14]

Bacteria, fungi, viruses, and parasites share the capacity to induce a major production of interleukin (IL)-17 during the early innate immune response. T-helper (Th) 17 cells react with IL-1 receptor type 1 by activating the IL-6/STAT3 cascade and generating IL-17A, IL-17F, IL-21, and IL-22.[15] In the innate response, fungal infections provoke the release of IL-17 with consequent inflammatory response.[16] Such responses can be regulated by the cytokine IL-36, which shares the same co-receptor with IL-1, and can regulates Th17 responses,[17] as well as *Aspergillus fumigatus*–induced Th1 and Th17 responses.[18]

CYTOKINES

Cytokines are a family of structurally and functionally related proteins that exhibit pleiotropic effects on the growth and function of a variety of cell types.[19,20] Cytokines orchestrate the host defense against mold by mediating acute and chronic inflammaion.[21]

IL-1 family members[22] are produced in response to fungal infections and promote an innate immune response.[23,24] Fungi-induced allergy and asthma are characterized by stimulation of mast cells (MCs), which generate many inflammatory mediators.[25–27] The allergic reactions to molds are characterized by high levels of IgE and increased numbers of MCs and eosinophils.[28,29] In fact, MCs and dendritic cells communicate for optimal antigen transfer and T-cell activation.[30,31] MCs can respond to many non-immune stimuli, including the cytokines IL-1 and IL-33.[32,33]

MCs may play a major role in the defense against pathogens, but can also contribute to pathogen-associated neurodegenerative diseases.[34,35]

IL-37 as Potential Inhibitor of Inflammation Induced by Fungi

IL-37, formerly IL-1F7, is a natural inhibitor of innate immunity by binding IL-18Rα chain, improving inflammatory diseases.[36–38] IL-37 directly inhibits MyD88, reducing the generation of inflammatory

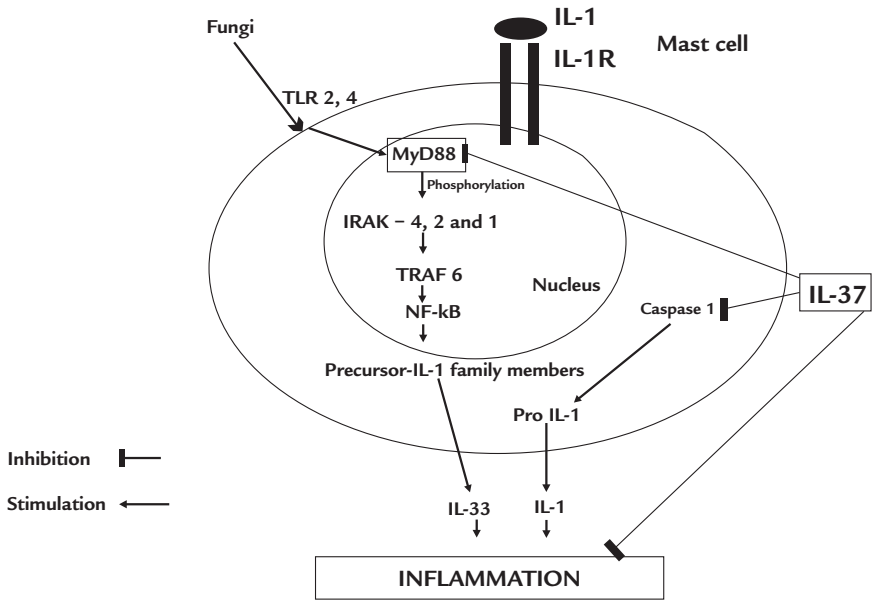

Figure. Diagrammatic representation of a mast cell stimulated by fungi through Toll-like receptor (TLR) 2 and 4, or interleukin (IL)-1 through its receptor, IL-1R, which leads to the release of MyD88 and Caspase 1, generating inflammatory cytokines. Points of potential inhibition by IL-37 are also shown.