Endogenous Interleukin-12 regulates macrophage phagocytosis of Sporothrix schenckii

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Context: Sporothrix schenckii is a widespread dimorphic fungus that causes sporotrichosis, an acute and chronic infection of the skin and subcutaneous tissues. It displays a range of clinical forms from fixed cutaneous to systemic infection. Systemic sporotrichosis occurs mainly in immunodeficient patients and can be potentially fatal. In the host defense against S. schenckii, macrophages play an important role through both phagocytosis and oxidative processes.

IL-12 is an immuno-regulatory cytokine mainly produced by phagocytes and dendritic cells in response to different pathogens. Functions of IL-12 include induction of interferon-γ (IFN-γ) production by T and natural killer cells, and polarization of CD4⁺ T cells toward high-level IFN-γ-producing T helper 1 cells. IFN-γ in turn activates macrophages which enhance the clearance of the invading organisms. Moreover, IL-12 can directly stimulate mouse peritoneal macrophages (PMΦ) to produce IFN-γ.

Endogenous IL-12 has been shown to be important for resistance to most bacteria, intracellular protozoa and fungal pathogens. In fungal pathogens, neutralization of endogenous IL-12 increased the severity of experimental infection with Histoplasma capsulatum and Coccidiodes immitis. Previous studies, however, have not investigated the role of endogenous IL-12 in S. schenckii infection. Therefore, in this study we analyzed whether neutralizing antibodies against IL-12 exerts an effect on the phagocytic activity of PMΦ in gerbils infected with S. schenckii.

Methods: A S. schenckii strain was isolated from a patient with lymphocutaneous sporotrichosis at the Department of Dermatology (Hospital Juan I. Menchaca, Guadalajara Jalisco, Mexico). Yeast cells were obtained by culture from a brain-heart infusion and subsequently used to infect gerbils, supplied by the breeding facilities (Centro de Investigación Biomédica de Occidente, Guadalajara Jalisco, México). Ten three-months old male gerbils weighing 60-70 g were infected subcutaneously with 6x10⁶ S. schenckii yeast cells (SsY) in the left hind footpad. Neutralizing antibody against IL-12 (I 7642 SIGMA), were diluted in phosphate buffer solution (PBS). Five infected gerbils were intraperitoneally (i.p.) injected with 250 ng of anti-IL-12 at the same time as infection and two days after infection. Another five infected gerbils were injected with PBS alone. Additionally, five healthy control gerbils received PBS alone. Seven days post-infection, PMΦ were harvested from peritoneal cavities of gerbils. Phagocytosis of SsY by freshly harvested PMΦ was assayed and the Phagocytic Index (PI) was determined. Difference between groups was evaluated by Student’s t-Test, and a p-value < 0.05 was considered significant.

Results: PMΦ from anti-IL-12-treated-infected gerbils displayed a 55% of decrease in number of engulfed SsY compared with PMΦ from untreated-infected gerbils (p< 0.0001*) and a 70% of decrease compared to the healthy control gerbils (p< 0.0001); Figure 1.
Interpretation: The results show that neutralization of endogenous IL-12 decreased macrophage phagocytosis of SsY, indicative of an impairment of host resistance to this fungus. This is in accordance with studies in experimental histoplasmosis and coccidioidomycosis in mice, in which neutralization of endogenous IL-12 increased the severity of infection. Data from this study suggest that endogenous IL-12 can exert an immunoregulatory role on phagocytic activity of PMΦ to eliminate S. schenckii. However, further research is required to elucidate the underlying molecular mechanisms involved in this process.