Background: Mesenchymal stromal cells (MSCs) have become a tool not only for tissue regeneration but also for the treatment of inflammatory diseases. Several studies have demonstrated the therapeutic potential of MSCs for the treatment of noninfectious inflammatory diseases, however, they appear to play a dual role in infection diseases. Histoplasmosis is a systemic mycosis caused by Histoplasma capsulatum, which occurs mainly in immunosuppressed individuals; this mycosis can present a severe clinical picture with dissemination to various organs and is associated with an exacerbated inflammatory response and with anemia and pancytopenia if bone marrow is affected. So far, the effect of a possible interaction of Histoplasma with stem cells present in the bone marrow is unknown.

Objectives: To examine, in vitro, the immunomodulatory effect of MSCs in response to H. capsulatum infection.

Methods: MSCs were obtained from bone marrow of C57BL/6 mice, after isolation and purification, they were induced to mesenchymal lineage and characterized by flow cytometry. Lice, the basic expression of red blood cells (TLR2) was inhibited using flow cytometry. MSCs were incubated with H. capsulatum strains (lactate CR1980) in a multiplicity of infection (MOI) of 5 and incubated for 24 h. In addition, some of the co-cultures were previously treated with specific blocking antibodies for TLR2 and TLR4 or with a blocking peptide specific for Dictin 1 (C3CL7A). Furthermore, phagocytes, microvascular, and cell proliferation were assayed, and the expression of the genes encoding the cytokines IL-1β, IL-6, IL-10, IL-17, TNF-α, and TGF-β as well as those for arginase-1 and NO were assayed.

Results: We observed that H. capsulatum has the capability to adhere and internalize within these MSCs, nonetheless, this process did not affect the survival of the fungus. The interaction of H. capsulatum with MSCs induced a slight but significantly increased expression of IL-10 but not TLR4 nor Dictin 1. In addition, the fungal interaction significantly increased an augmented expression of IL-1 and a decrease in the expression of IL-1β, IL-17, TNF-α, and TGF-β, as well as the immune mediators Arg-1 and iNOS. Nonetheless, blockade of these receptors did not affect phagocytosis, but increased IL-1β, IL-17, and TNF-α expression and reduced the expression of IL-10. Noteworthy, H. capsulatum induced apoptosis and inhibited the proliferation of these stem cells; furthermore, this fungus significantly reduced the expression of genes related to adaptive differentiation and increased the expression of genes related to the ontogenic differentiation processes.

Conclusions: The above results suggest that H. capsulatum does not exert a variable adverse effect against H. capsulatum; on the contrary, this fungal pathogen not only modulates the expression of inflammatory mediators in MSCs, by a mechanism dependent on TLR2, TLR4, and Dictin 1, but also affects their viability and their ability to differentiate into a different type of specialized cells. These events could, in principal, either affect hematopoiesis and the immune response in the infected host, and in addition, in these stem cells may provide a niche for this fungus, allowing it to persist and evade host immunity.

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Histoplasma capsulatum modulates the immune response exerted by mesenchymal stem cells

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Histoplasma capsulatum infection on activation and proliferation of hematopoietic stem cells

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Background: Hematopoietic stem cells (HSCs) are considered a multipotent population with high proliferative potential, and are widely used in the treatment of leukemias, multiple myeloma, and some lymphomas. In the context of infectious diseases, some microorganisms have been reported to induce changes in the expression of surface markers in HSCs by a direct effect or through the induction of cytokines. Systemic infections are characterized by inducing stress on the bone marrow, which is reflected in an increase in leukocytes in leukocytes and platelets in peripheral blood, a process known as "emergency hematopoiesis". Histoplasmosis is a systemic mycosis caused by Histoplasma capsulatum, which occurs mainly in immunosuppressed individuals; this mycosis can present a severe clinical picture with dissemination to various organs, including the bone marrow, and is associated with anemia and pancytopenia. So far, the effect of a possible interaction of Histoplasma with HSCs is unknown.

Objectives: To evaluate, in vitro, the effects of Histoplasma capsulatum infection on activation and proliferation of HSCs.

Methods: HSCs were obtained from bone marrow of C57BL/6 mice after isolation and purification, they were characterized by flow cytometry. Lice, the basic expression of red blood cells (TLR2) was inhibited using flow cytometry. MSCs were incubated with H. capsulatum strains (lactate CR1980) in a multiplicity of infection (MOI) of 5 and incubated for 24 h. In addition, some of the co-cultures were previously treated with specific blocking antibodies for TLR2 and TLR4 or with a blocking peptide specific for Dictin 1 (C3CL7A). Furthermore, phagocytes, microvascular, and cell proliferation were assayed, and the expression of the genes encoding the cytokines IL-1β, IL-6, IL-10, IL-17, TNF-α, and TGF-β as well as those for arginase-1 and NO were assayed.

Results: We observed that H. capsulatum has the capability to adhere and internalize within these MSCs, nonetheless, this process did not affect the survival of the fungus. The interaction of H. capsulatum with MSCs induced a slight but significantly increased expression of IL-10 but not TLR4 nor Dictin 1. In addition, the fungal interaction significantly increased an augmented expression of IL-1 and a decrease in the expression of IL-1β, IL-17, TNF-α, and TGF-β, as well as the immune mediators Arg-1 and iNOS. Nonetheless, blockade of these receptors did not affect phagocytosis, but increased IL-1β, IL-17, and TNF-α expression and reduced the expression of IL-10. Noteworthy, H. capsulatum induced apoptosis and inhibited the proliferation of these stem cells; furthermore, this fungus significantly reduced the expression of genes related to adaptive differentiation and increased the expression of genes related to the ontogenic differentiation processes.

Conclusions: The above results suggest that H. capsulatum does not exert a variable adverse effect against H. capsulatum; on the contrary, this fungal pathogen not only modulates the expression of inflammatory mediators in MSCs, by a mechanism dependent on TLR2, TLR4, and Dictin 1, but also affects their viability and their ability to differentiate into a different type of specialized cells. These events could, in principal, either affect hematopoiesis and the immune response in the infected host, and in addition, in these stem cells may provide a niche for this fungus, allowing it to persist and evade host immunity.