Title: Paracoccidioidomycosis patients present increased number of regulatory B cells with an increased capacity to produce IL-10.

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Abstract:

Immunological response in Paracoccidioidomycosis (PCM) is heterogeneous and related to the development of distinct clinical manifestations. In general, more severe and disseminated disease is characterized by the commitment of lymph nodes, liver, spleen and bone marrow; while mild forms present lesions of the skin, mucosa, and lungs. Both clinical forms present a compromised cellular immune response (mediated by T cells) while presenting polyclonal activation of B cells. Overall, resistance to PCM is associated with the development of Th1 and Th17 immune response and low activation of B cells. On the other hand, susceptibility may be associated with a Th2-type response with polyclonal activation of B lymphocytes. Recent studies have shown that a subpopulation of B cells (called Bregs) can exert a regulatory role mainly through the production of suppressive cytokines (IL-10 and TGF-beta). To our knowledge, there are no studies examining the role of B cells as Bregs in fungal infections, particularly in PCM. Therefore, in this study we aimed to characterize, phenotypic and functionally, the B lymphocytes in human paracoccidioidomycosis, evaluating their role as regulatory cells (Breg). We analyzed, by flow cytometry, the number of B cells presenting the stablished Breg phenotipe (CD20+CD38+CD24+) in peripheral blood of PCM patients presenting active disease (before antifungical treatment), as well as, the capacity of purified B cells to produce anti-inflamatory cytokines (IL-10 and TGF-beta) *in vitro* after several stimuli (LPS, CpG ODN, soluble CD40L, and *P. brasiliensis* DNA and gp43). There were included 17 PCM patients (before the antifungal treatment) and 15 healthy donors. Our results showed that PCM patients presented a higher number of circulating B cells (CD19+ and/or CD20+ cells) than healthy controls. Furthermore, there was an increased frequency of B cells presenting Breg phenotype (CD20+CD38+CD24+ cells) in peripheral blood of PCM patients compared with controls. In vitro experiments showed that B cells from PCM patients presented an augmented capability to produce the anti-inflammatory cytokines (IL-10 and TGF-beta), either in unstimulated cells or after all the stimuli utilized. In conclusion, our results, although preliminary, indicate that B cells could participate as regulatory cells in human PCM, contributing to the suppression of the cellular immunological response observed in active PCM patients.

Keywords: Regulatory b cell, IL-10, *Paracoccidioides brasiliensis*.

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