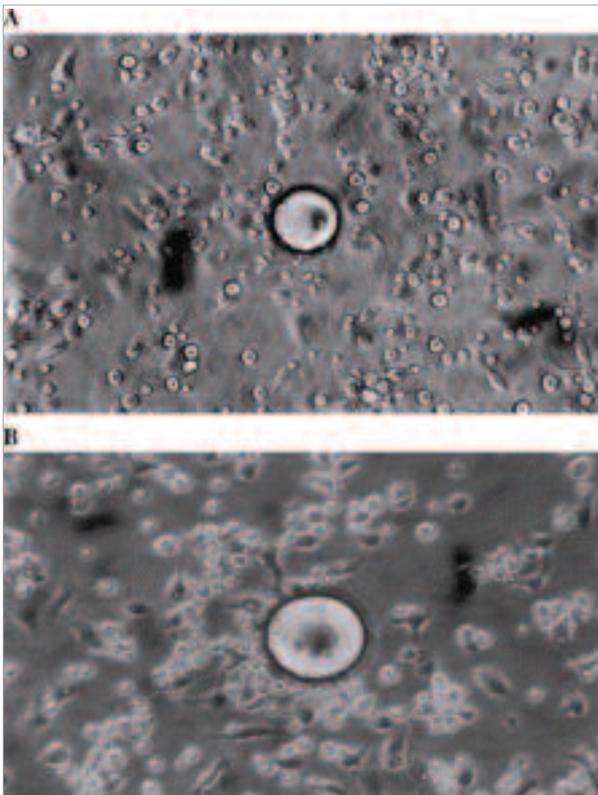


### **B-1 CELLS AND THEIR PARTICIPATION IN THE EXPERIMENTAL MODELS OF MURINE AND *Paracoccidioides brasiliensis* INFECTION**

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Granuloma assays with purified B-1 cells or total adherent cells from Xid mice. gp43-coated polyacrylamide beads incubated with 10<sup>6</sup> cells and with 50 µg/ml soluble gp43. The granulomatous reactions were observed on day 7 of culture. (A) Granuloma-like structures were not formed when isolated B-1 cells were used. (B) Total adherent peritoneal cells from Xid mice were cultured under the same conditions and negative results were also observed. Results are representative of three independent experiments

After more than 20 years since the discovery of B-1 cells, efforts to characterize their origin and function have led to little understanding about their role in phenomena such as inflammation.

B-1 cells constitute a minor fraction of the B-cell population in spleen and lymph nodes of mice, but are the main B-cell population in their peritoneal and pleural cavities. They express high surface IgM, low B220 and IgD, but not CD23. With features of B lymphocytes, they also express markers of monocyte-derived macrophages such as Mac-1. A subset designed B-1a express CD5. Both antigens are lost when B-1 cells leave the peritoneal cavity. These characteristics poise this lineage as a promiscuous one.

B-1 cells spontaneously proliferate in cultures of normal adherent mouse peritoneal cells. Support for this conclusion came when cultivated peritoneal cells from Xid mice showed no B-1 cell proliferation. B-1 cells migrate to a non-specific inflammatory site and differentiate into a macrophage-like cell. Nevertheless, the role these cells play on the inflammatory response and on parasite infection is not yet established. However, Xid mice are more resistant to *T. cruzi*, *P. brasiliensis* and filarial infections. Thus, B-1 cells could down-regulate the efficacy of effector cells to eliminate parasites in the inflammatory milieu. Also, B-1 cells produce and utilize IL-10, a negative regulator of cell mediated immunity, as an autocrine growth factor. We showed that B-1 cells influence macrophages effector functions via IL-10 secretion.

We intend to demonstrate that B-1 cells migrate to inflammatory sites, transforming into a novel type of phagocyte. Characterization of their precursors and their mechanisms of survival in culture will also be addressed. Results will certainly bring new insights on the role these cells could play in inflammatory, degenerative and neoplastic pathologies.

## SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Investigation of the origin, properties and fate of B-1 cells is promising in two guises. First, these cells are known to exist in mammals, mainly in the mice, for a little longer than 20 years. Second, properties of these cells described in the literature point to a still uncovered yet relevant role they may play in physiology and general pathology. For the last 10 years our laboratory has made efforts to build up a comprehensive understanding of the part they play in physiology, basic phenomena as wound healing and graft rejection, models of infection and tumor growth control. Investigation of these themes was possible due to the discovery



(a, b) Giant cells are formed on the surface of glass cover slips implanted for 4 days into the subcutaneous tissue of CBA/J mice (a) and are almost absent on glass cover slips implanted, for the same time, in CBA/N (Xid) mice (b). Mononuclear cell migration and adherence to the glass surface in CBA/N mice is not impaired. Haematoxylin-eosin x400

in our laboratory that B-1 cells grow in cultures of adherent peritoneal cells, and that they are radio-sensitive and migrate from the peritoneal cavity to distant inflammatory foci. Among the most relevant contributions from our group is the unequivocal demonstration that B-1 cells differentiate into a mononuclear phagocyte similar to macrophages. This contribution to the physiology of B-1 cells imposes that nature and function of mononuclear cells, mainly in chronic inflammation, must be revisited. In addition to these observations, the laboratory has demonstrated that B-1 cells are endowed with immunological memory and tolerogenic property when tested in a model of hypersensitivity, and finally, an unexpected effect of B-1 cells was observed when investigated in a model of murine melanoma. B-1 cells have the property of enhancing melanoma transformation, growth and spreading by mechanisms now being uncovered. Attachment of B-1 to melanoma cells parallels ERK activation as demonstrated *in vitro* and *in vivo*. We expect the investigation of B-1 cells in apparently dissimilar models will result in a comprehensive understanding of the origin, properties and fate of these cells.

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