The Effect of Apoptotic Cell Recognition on Macrophage Polarization and Mycobacterial Persistence

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Introduction

The concept of phenotypes, while useful, is oversimplified, because macrophages exhibit substantial plasticity, with markers and functions readily altered by external signals. Previous studies demonstrated increased percentages of apoptotic cells in lesions from paucibacillary when compared to multibacillary leprosy patients (Walsh et al., 2004; Brito de Souza et al., 2010).
In vitro, we have previously demonstrated that *M. leprae* induces monocyte apoptosis by a TNF-dependent mechanism. However, the effect of apoptotic cell removal on *M. leprae*–stimulated cells has not been fully elucidated. Here, we investigate whether apoptotic cell removal (efferocytosis) induces different phenotypes in *in vitro* differentiated pro-(MΦ1) and anti-(MΦ2) inflammatory macrophages.
M. leprae stimulation did not alter the phenotype of in vitro differentiated macrophages.
*In vitro* differentiated МФ2 are more phagocytic than МФ1 cells
The presence of apoptotic cells increases *M. leprae* uptake by МΦ1 cells.
Phagocytosis of apoptotic cells in the presence of *M. leprae* induce МΦ1 polarization toward a МΦ2 phenotype.
The increased SRA-I expression in МФ1 cells stimulated with apoptotic cells and *M. leprae* is dependent on arginase.
Increased IL-10 and TGF-β in ML+Apo stimulated MΦ1 cells
МФ2-derived from МФ1 cells induce the production of the antiinflammatory cytokines IL-4 and IL-13 by T lymphocytes

CD14+ cells GM-CSF 6d ± ML ± Apo ± T LΦ 48h IL-4 and IL-13 measured in the supernatants
These results suggest that M1 cells are more susceptible to phenotype changes after apoptotic stimuli when compared to M2 cells. Based on these data, we may also suggest that in paucibacillary patients, efferocytosis contribute to mycobacterial persistence instead of the presence of an effective cellular immune response by maintaining an M2 phenotype at lower levels in the skin lesions.
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