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Macrophages and Mycobacterium Tuberculosis, the Hard Fighting to Preserve Host Protective Immune Responses

Leslie Chavez-Galan
National Institute of Respiratory Diseases
Mexico.

COLUMN ARTICLE

Tuberculosis (TB) is an infection disease caused by *Mycobacterium tuberculosis (M. tuberculosis)* infection. The World Health Organization estimates an incidence of 9 million per year in the worldwide. TB is the leading cause of opportunistic infection and mortality among people living with HIV infection. These epidemiology data prove that to intensify studies providing strategies on how preserving and increasing the functionality of macrophages to control bacterial growth is essential.

M. tuberculosis is an intracellular bacterium and the macrophage is one of the most important phagocytic cells that recognize it. Mycobacterium has the ability to manipulate the activation of bactericidal mechanisms and to stablish a parasitic relation which allow the latent persistence of *M. tuberculosis* in the host for long time.

My research line has as main goal to identify activation pathways of macrophages that favor the development of mycobactericidal mechanisms controlling and eliminating *M. tuberculosis*. In this way, it has been shown that freshly obtained monocytes from TB patients are under a pre-apoptotic primed status with persistent mitochondrial damage which has been suggested to be associated with TLR-2-dependent cell death [1]. Due to this pre-apoptotic status of monocytes in TB patients, recruitment in the lung would result in macrophages that are no entirely functional and this may impair innate and adaptive immune responses. My interest has been the characterization of the mycobacterial cell wall components responsible for the differentiation of monocytes in functional macrophages. Our studies have shown that macrophages differentiated from monocytes that have been exposed to Lipoarabinomannan (LAM), an important lipid from *M. tuberculosis* wall, exhibited a decrease frequency of TLR-2+ macrophages and were less able to phagocyte. Interestingly, macrophages generated under exposure to LAM for long time (4 - 6 days) produced lower amounts of the soluble form of Tumor Necrosis Factor (TNF), a proinflammatory cytokine crucial for the control of *M. tuberculosis* infection [2]. Thus, this work has identified a mycobacterial cell wall component impairing the generation of functional macrophages during the normal course of the disease.

TNF is critical for resistance against *M. tuberculosis* infection as shown in different mouse models. However, a novel mouse model has been required to clarify if new human specific TNF inhibitors can be associated with an increased risk of TB reactivation in pre-clinical tests using a murine model of TB. Recently the group of Irène Garcia (CMU, University of Geneva, Switzerland) validated a mouse model with a replacement of the mouse TNF by the human TNF gene (huTNF-KI). These studies showed that human TNF can replace mouse TNF in term of capacity to efficiently induce host immunity against mycobacterial infection which can be disturbed by human anti-TNF inhibitors in these mice. Thus, huTNF-KI mice represent an useful model system to elucidate potential differences in the

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underlying molecular mechanism of TNF neutralization [3].

Finally, although the pulmonary TB is the most common form of TB, extrapulmonary forms such as pleural TB, are frequent pathology which specific host defense mechanisms are not well elucidated. Our group has been focusing in the study of pleural TB in order to identify how TNF pathways can modulate the disease and the resolution of the infection. Our studies have shown that TNF and TNF receptors are essential to control mycobacterial infections in the pleural cavity. Inability to use TNF results in spread of the infection and military tuberculosis. Macrophages unable to produce or to respond to TNF do not develop iNOS-dependent bactericidal mechanism and failed to eliminate mycobacteria. In addition, absence of TNF favored a proinflammatory environment with an exacerbated cell recruitment and formation of fat-associated lymphoid structures inside the pleural cavity [4].

The understanding of the mechanism whereby *M. tuberculosis* blocks host defense immune responses may help to develop more efficient strategies to eliminate the bacterium and to prevent a TB reactivation.

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