Editorial

Mycobacterium tuberculosis and Human Macrophage: the Bacillus with "Environment-Sensing"

(*Mycobacterium tuberculosis* / host-pathogen interaction / bacilli gene expression)

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Pathogen and host introduction

Mycobacterium tuberculosis (MTB), the aetiologic agent of tuberculosis, is an obligate pathogen of mammals and is responsible for an incredible toll of human life every year (World Heath Organization, 1999). Even among pathogens, MTB is noteworthy for having selected a particularly difficult lifestyle, inhabiting one of the most inhospitable cell types, the alveolar macrophage. Nevertheless, MTB is able to survive and replicate in such an environment, even in immunocompetent individuals, where it is also able to remain silent, even for lifetime.

The very early phase of interaction between MTB and human macrophage is crucial for the final outcome of the infection: an early and efficient cell-mediated immunity (CMI), exerted by macrophages and antigen-specific T cells, will likely be able to contain the bacterial load to low levels. Differently, if mycobacteria overcome the initial defences, they start to replicate in macrophages until the cell dies, and bacilli are disseminated in the surroundings, giving rise to granuloma formation and to the delayed-type hypersensitivity (DTH), responsible for the immunopathogenic features of TB (Fig.1).

One question then arises: is it possible that the bacillus is capable to distinguish in which type of habitat it is replicating, in order to adapt its metabolism to that? The present article will discuss such a topic.

What we already know about their interplay

Almost a century of international research on tuberculosis has made it possible to clarify the reciprocal strategies adopted by the host (Rook and Bloom, 1994; Kaufmann, 1995) and by the intracellular pathogen (Clemens and Horwitz, 1995) to fight each other. For example, the macrophage that phagocytosed MTB tries to fuse the MTB-phagosome with a proteases-rich lysosome and to acidify the resulting phagolysosome to make the enzymes working. On the other hand, MTB has been shown to be able to evade the phagolysosome (McDonough et al., 1993) and to increase its own inner pH by means of ammonium-ion production. Another important step for this interaction is the competition for ferric iron: IFN-γ-activated monocytes reduce the transferrin receptors on the cell membrane in order to lower the iron content in the cytoplasm (Byrd and Horwitz, 1993). In this context, mycobacteria have developed iron-binding proteins, called mycobactins, with tremendous affinity for this element, which are able to sequester iron either from the cytoplasm or from the host cell ferritin (Gobin and Horwitz, 1996). What is, however, recognized as the most important phase of the protective immune response is the cross-talk between the macrophage and the T lymphocyte (Ladel et al., 1995a; Ladel et al., 1995b; Ladel et al., 1995c). By means of this cell-cell exchange of information, specific antigens of engulfed mycobacteria are presented to $CD4^+$ and $CD8^+$ T effector cells, responsible for the subsequent activation of infected macrophages and of the killing of the non-activated ones.

In any case we should not forget that a principal role in the fight against endemic TB of the fifties has been played by significant amelioration of the lifestyle of the population. It is actually reasonable that a well-fed individual, inhabiting warm and dry houses, and with access to a national sanitary system, is better equipped to fight TB infection by mounting an efficient immune response. The re-emergence of TB in industrialized countries (given that in the "third world" countries it never disappeared), starting from 1985, put in evidence the role of HIV-1 co-infection in MTB-infected individuals, but also the role of the provenance of individuals, mostly living in new "niches" of poverty (Bock et al., 1999; Beckhurst et al., 2000).

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Abbreviations: CMI – cell-mediated immunity, DTH – delayed-type hypersensitivity, MDR – multiple drug resistance, MTB – *Mycobacterium tuberculosis*.

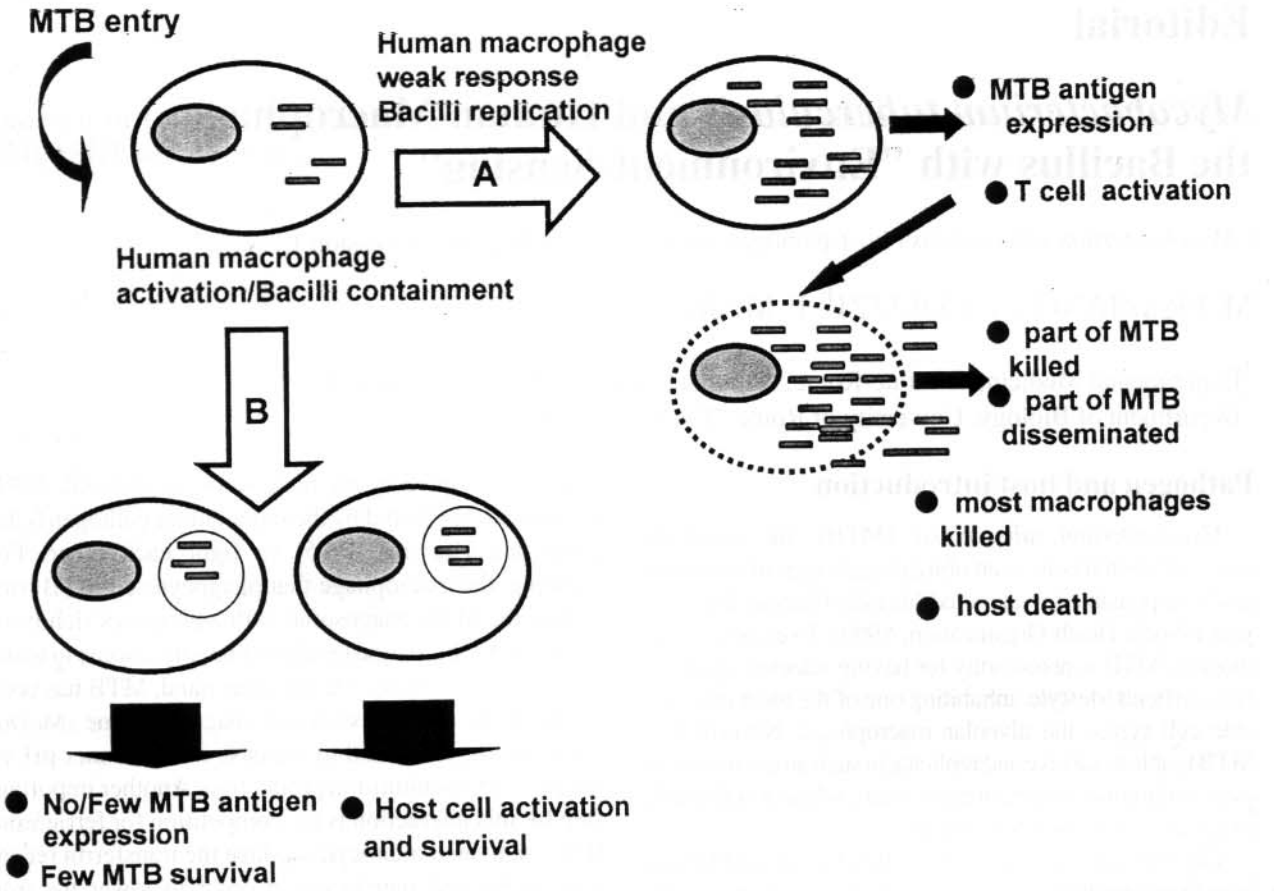

Fig. 1. Cartoon depicting the complex interplay between *M. tuberculosis* and human macrophages. A and B pathways schematize two of the possible final outcomes of the infection, discussed in the text

Such an information presents the host-pathogen interaction as a very delicate and dynamic balance, which can be tipped in favour of either organism, depending also on economic and social factors. With the exception of extreme cases, in which the human host is immunodeficient (AIDS patients) or the *M. tuberculosis* clinical strain displays multiple drug resistance (MDR), bringing the infected host to death, in the majority of individuals MTB infection evolves towards co-existence with the host.

Host cell survival and its relation to the bacillary load

In this scenario, concerning the host side of the interaction, both monocyte activation and death by apoptosis have been observed *in vitro*, being strictly depending on the multiplicity of infection employed. In fact, a low amount of MTB is able to induce expression of a chemokine receptor (Fraziano et al., 1999) and simultaneously to prevent monocyte apoptosis by inducing production of pro-inflammatory cytokines such as TNF-α (Durrbaum-Laudmann et al., 1996), whereas high levels of TUNEL positive cells were observed following infection with high mycobacterial doses (Placido et al., 1997). This latter phenomenon deserves further investigation, given that macrophage apoptosis induced by several stimuli and in the course of low levels of infection has been often associated to mycobacterial killing (Kornfeld et al., 1999). However, the molecular pathway followed by monocytes after MTB-induced apoptosis is not associated to any modification in mycobacterial viability (Santucci et al., in press).

Does *M. tuberculosis* modulate its gene expression *in vivo*?

A recently performed analysis which compared MTB gene expression in synthetic medium and in human macrophages (Mariani et al., submitted) has shown that the bacillus' choice to transcribe genes with different functions depends on the environment in which it replicates, suggesting that it is able to distinguish where it is. In particular, it has been observed that MTB produces mRNAs for a group of genes known by immunologists for their capacity to activate macrophages and T cells in mouse and human, preferentially when it is growing in synthetic medium. Such a group of genes is not detectable in the pool of mRNAs extracted from an MTB-infected human macrophage, whereas in such samples, many genes mandatory for MTB survival are found to be