Mycobacteria and Biological Response Modifiers: Two Sides of the Relationship

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• Adjunct therapy

Tuberculosis (TB) is one of the oldest diseases known to mankind; humans have adapted to the disease as advances in medicine have been made. Because of its complex immunology, involving the organism and the host, newer treatment modalities in various fields of medicine have affected the outcome of this infection and have caused resurgence of the disease. What makes tuberculosis unique from an epidemiologic standpoint is the large reservoir of infection, consisting of approximately one-third of the world's population.[1] A recent study from Boston showed that overall rates of reactivation TB in that area have declined from 0.10 to 0.16 cases per 100 person-years in the 1950s to 0.040 cases per 100 person-years recently, but reactivation has increased among those individuals older than 50 years (rate ratio [RR], 3.8) and among those born in the United States (RR, 3.2).[2] About 9.2 million new cases of active disease arise every year (roughly 10% of the infected reservoir), many of which are believed to be reactivation disease.[3,4] Some of the causes for reactivation due to immunocompromise include HIV infection, advancing age, use of corticosteroids, organ transplantation (renal, cardiac, liver, and allogenic stem cell), and, more recently, increasing worldwide use of biological response modifiers (BRMs) for the treatment of systemic inflammatory diseases with tissue destruction, particularly rheumatoid arthritis.[5–8] Although BRMs are effective drugs that have revolutionized the treatment of these diseases, there exist considerable adverse effects of BRMs including reactivation of several latent infections. Therefore, their efficacy in disease control needs to be balanced against the risk of development of serious infections,

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particularly TB.[9] The future in treatment of inflammatory diseases includes increased use of recombinant human antiinflammatory cytokines, agents targeting proinflammatory cytokines, and granulocyte-macrophage colony-stimulating factors. The risk of developing reactivation disease with the increased and improved or newer treatment modalities for inflammatory conditions needs to be considered. However, many in vitro and a few in vivo studies have reported benefits of certain BRMs in treatment of TB as adjuncts.[10,11] This article summarizes the different aspects of the relationship between mycobacterial infections and the use of various BRMs (**Table 1**).

IMMUNOLOGY OF TUBERCULOSIS

Only 10% of people infected with *Mycobacterium tuberculosis* develop active disease.[3] For this effective control, innate and adaptive immune responses of the host are operative in mycobacterial infections. Multiple bacterial and host factors determine the outcome of either latent tuberculosis infection (LTBI) or active disease.[12] The immunology of early disease is still not well understood. Mouse studies indicate that the cell type infected initially with *M tuberculosis* is the myeloid dendritic cell (**Fig. 1**).[13]

Macrophages and Mycobacteria

M tuberculosis (an obligatory aerobic and intracellular organism) is acquired by the host through inhalation and infects macrophages early. On infecting the macrophages, multiple macrophage-Mycobacterium interactions occur to evade early intracellular killing. These include binding of *M tuberculosis* to macrophages via surface receptors, inhibition of phagosome-lysosome fusion, inhibition of acidification of the lysosomes, recruitment of accessory immune cells for local inflammatory response, and presentation and modulation of antigens to T cells for development of acquired immunity.[14–16] Mycobacterial growth inhibition and killing can be mediated via free radicals such as reactive oxygen and nitrogen intermediates and cytokines.[17] Within 2 to 6 weeks of infection, cell-mediated immunity develops and a granuloma forms with an influx of lymphocytes and activated macrophages at that site.[18] *M tuberculosis*–infected macrophages have decreased ability to present antigens by major histocompatibility complex (MHC) class II molecules to CD4+ T cells and this can lead to persistent infection.[19] Virulent mycobacteria can escape from fused phagosomes and multiply. Antigen-presenting cells (APCs) contribute further to defective T-cell proliferation and function by the production of cytokines such as transforming growth factor β (TGF-β), interleukin (IL)-10, or IL-6.[20]

Table 1
Mycobacteria: classification of species and primary host

Species oF M TB Complex	Primary Target/Reservoir
M tuberculosis	Human (world wide)
M africanum	Human (mostly in African countries)
M canetti	Human (mostly in African countries)
M caprae	Cattle
M bovis	Cattle
M microti	Rodents
M pinnipedii	Seals

Data from Geyer M, Müller-Ladner U. Rationale of using different biological therapies in rheumatoid arthritis. Arthritis Res Ther 2010;12(4):214.