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Essays

Tuberculosis and multi-drug resistant tuberculosis: immunologic mechanisms and tools for controlling the disease

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Roberta Olmo Pinheiro
Instituto Oswaldo Cruz-Fundação Oswaldo Cruz, Rio de Janeiro, Brazil
rolmo@ioc.fiocruz.br

Margareth Pretti Dalcolmo
Centro de Referência Professor Hélio Fraga, UFRJ, Rio de Janeiro, Brazil
margareth.dalcolmo@saude.gov.br

Elizabeth Pereira Sampaio
Instituto Oswaldo Cruz-Fundação Oswaldo Cruz, Rio de Janeiro, Brazil

Abstract
It is estimated that one third of the world's population is infected with *Mycobacterium tuberculosis.* In 2005, the World Health Organization estimated that eight million people died from tuberculosis worldwide. The official indicators point to a decline in tuberculosis rates in the past century but since 1990 the incidence rates are increasing again. Despite the existence of medicines effective in the control of tuberculosis, the cases of multi-drug resistance have increased worldwide. Recently the problem became even worse with the emergence of strains extremely resistant to drugs, responsible for what the WHO calls XDRTB (extensively drug resistant tuberculosis). The only vaccine available against this disease, the BCG vaccine, is efficient in preventing severe forms of tuberculosis in children. Its efficiency in adults however varies considerably and it has been demonstrated that revaccination does not increase the degree of protection in adolescents and adults. Various studies demonstrated that, in the attempt to contain the infection, the host cells develop immunoregulatory and mycobactericide mechanisms, and that failures in these mechanisms allow the disease to advance. The aim of this article is to review the data related to the immune response in patients with tuberculosis and multi-drug resistant tuberculosis (MDR-TB) and to show how these findings can contribute to the development of new diagnostic strategies and/or vaccines to control the disease.

Keywords
Tuberculosis, multi-drug resistant, diagnosis, IFN-γ, immunologic mechanisms

Introduction
Tuberculosis control

Mycobacterium tuberculosis and HIV are the main agents responsible for deaths caused by infectious diseases in the world (WHO, 1996). The World Health Organization estimates that in 2005 the number of new cases over the world reached eight million and that 1.6 million deaths resulted from tuberculosis (WHO, 2007). Although the official indicators reported a decline in tuberculosis rates over the past century, since 1990 this decline seems to have reverted (LOCH et al., 2007)

The Americas, with 227.551 notified tuberculosis cases in 2003, account for 4% of TB notifications globally. In Brazil, in 2003, 83.575 new cases were notified, corresponding to an incidence rate of 47.3/100.000 inhabitants with variations raging from 18.7/100.000 in the State of Tocantins to 79.6/100.000 in the State of Rio de Janeiro (WHO, 2005). Brazil is among the 22 countries concentrating, in absolute numbers, 80% of the cases, occupying the 15th place in this ranking (WHO, 2005).

It is estimated that one third of the world's population is infected with *M. tuberculosis*. In the greater part of infected individuals however latent tuberculosis infection may last for a lifetime, never developing into disease. On the other hand, diagnosis of latent tuberculosis is important because the infected individuals are at risk of developing the disease, especially when exposed to conditions favoring the development of the mycobacterium, such as HIV co-infection or use of immunosuppressants (LOTCH et al., 2007).

Efficient TB control depends on both diagnosis of the acute disease or latent infection and efficient treatment and/or vaccines in order to prevent that individuals with latent infection develop acute disease.

For improving tuberculosis control, the WHO launched the DOTS strategy (*Directly Observed Treatment Short-Course*) that combines five elements considered pivotal for the control of this disease: political commitment, baciloscopy services, drug supplies, surveillance and monitoring systems and use of highly efficacious regimens with direct observation of treatment (WHO, 2006). The DOTS strategy was adopted by more that 150 countries (RAVIGLIONE et al., 2002) but one quarter of the world's population has still no access to this service.

In most countries with high incidence the diagnosis of active tuberculosis is based on the clinical history of the patient followed by identification of the bacillus in sputum smears under optical microscopy. Nonproductive cough is the most common symptom of the early stage of lung tuberculosis. With the development of the infection, as inflammation and necrosis of the pulmonary tissue advance, mucus begins to be produced. For this reason, baciloscopy is the preferred diagnosis and control method during tuberculosis treatment (TEIXEIRA et al., 2007). The method is inexpensive but its sensibility is extremely variable, reaching rates of less than 20% (STEINGART et al., 2006; URBANZIK, 1985).

The skin test using intra-dermal injection of purified protein derivative (PPD) has low specificity, given that PPD contains antigens are shared among other mycobacteria, including BCG.

Since 1982, the drugs of first choice in the treatment of tuberculosis are isoniazid and rifampicin in a six months regimen in combination with pirazinamid during the first two months. It must be pointed out that the drugs are supplied for free by the government; however, as the therapy is based on self-administration, many abandon their treatment, in part due to the appearance of side effects or simply because they feel better and think they do not need to take the medicine anymore.

Multi-drug resistance is defined as in vitro resistance to both isoniazid and rifampicin (YEW et al., 1995). In Brazil, MDR-TB is defined as resistance of the patients to rifampicin and isoniazid and to a third anti-tuberculosis drug making part of the standard regimens (DALCOLMO et al., 2007).

A multi-centric study aimed at evaluating the efficacy of the treatment regimens for MDR-TB demonstrated that the most important reasons of multi-drug resistance are the use of inadequate treatment regimens and nonadherence to therapy (DALCOLMO et al., 1999). Other factors such as presence of cavitations and HIV co-infection seem also important for the development of resistant strains (GRANICH et al., 2005; VANACORE et al., 2004). However, in Brazil, the rate of co-infection in HIV/AIDS patients has been estimated in 3-4% of cases. The percentage of tuberculosis co-infection in AIDS patients, which was of 30% in the 1990s, tends to decline, a fact that some authors associate with the introduction of antiviral drug therapy (HIJJAR et al., 2005).

Given that the treatment abandonment rates are associated with the occurrence of MDR-TB, different studies sought to assess the level of treatment adherence in tuberculosis patients. In Rio de Janeiro, two studies found nonadherence rates of 30.5 and 28.9% respectively (DINIZ et al., 1995; KRITSKI et al., 2002). In the state of São Paulo, with high MRD-TB rates, DEHEINZELIN et al. (1996) demonstrated a rate of treatment abandonment of 33%.

Data of the World Health Organization indicate a prevalence of acquired drug-resistance of less than 20% and of multi-drug resistance less than 10% in Brazil. However, regional variations must be taken into consideration. Recently BALIZA et al. (2008) reported that in the city of Cabo de Santo Agostino, in the state of Pernambuco, 14% of the total of TB cases were multi-resistant. Another study conducted in the city of São Paulo demonstrated a resistance rate of 15.5%. The present study showed a resistance rate of 27% and multi-resistance of 16.7% among previously treated cases (TELLES et al., 2005).

The types of resistance to *M. tuberculosis* can be classified into: natural (as a result of random mutation, independently of previous exposure to anti-tuberculosis drugs and proportional to the number of bacilli); initial (observed at the moment the patient presents himself

for treatment. This includes patients with primary or secondary (acquired) resistance without history of previous treatment); primary resistance (observed in patients without history o previous treatment, infected with resistant organisms); and acquired or secondary resistance (as a result of nonadherence to therapy or the use of inadequate treatment regimens (MITCHISON, 2005). Earlier studies demonstrated that multi-drug resistant patients transmit and cause the disease in susceptible individuals just like the drug-susceptible patients (SNIDER et al., 1985; VALWAY et al., 1994). The fact of being highly contagious and the consequent dissemination of resistant bacilli in the population turn it difficult to control the disease.

Brazil is currently conducting the *II National Survey of anti-TB Drug Resistance* for updating the multi-drug resistance rates in the country. Despite the great variations between some regions, the rifampicin + isoniazid resistance rates are still expected to be very low. ZAGER et al. (2008) demonstrated in a recent review that the prevalence of MDR-TB expressed as the proportion of resistant cases does not appropriately reflect the occurrence of multi-drug resistance in a community. For obtaining an accurate picture of the incidence or prevalence of the disease in a certain population, the authors suggest to include those cases of multi-drug resistance that appeared in cases with prior treatment.

The treatment recommended for MDR-TB is less effective, less efficient, longer, more likely to cause adverse reactions and more costly than the treatment of drug-susceptible tuberculosis. It requires the use of second- and third-line drugs for 18 to 24 months (ISEMAN, 1993; ZIGNOL et al., 2006, DALCOLMO et al., 2007).

A new threat for the control of tuberculosis is the appearance of extremely resistant (XDRTB) strains. XDRTB is defined as resistance to rifampicin, isoniazid, one injectable second-line medication (amikacin, kanamycin, capreomycin) and one **fluoroquinolone** (ESPINAL et al., 2001; CDC, 2007).

Despite the already existing knowledge about the immunological mechanisms associated with the pathogenesis of the disease, there is still no complete comprehension of the signaling mechanisms, the transcriptional responses of the host, the adaptation of the bacteria to the host or the cell-cell interactions that follow *M. tuberculosis* infection. Some studies sought thus to assess the immunological mechanisms associated with the infection and with the development of resistance in some individuals.

Immunological mechanisms associated with tuberculosis and multi-drug resistant tuberculosis control

Tuberculosis is a disease affecting predominantly the lungs, being responsible for 80% of notified cases in Brazil; however, the bacillus can invade the organism through the bloodstream and lymphatic system causing disease in virtually any organ of the human body. Immediately after primary infection through bacilli inhaled with the air, the host phagocytes of *M. tuberculosis*, namely alveolar macrophages and dentritic cells, migrate through the lymphatic system in direction of the regional lymph node and form the Ghon's complex. At the same time the phagocytes can penetrate the pulmonary parenchyma initiating and inflammatory focus around the microorganism leading to granuloma formation in a process coordinated by T lymphocites (TEIXEIRA et al., 2007). Studies analyzing the interaction between *M. tuberculosis* and antigen-presenting cells demonstrated that the dentritic cells impede the intracellular growth of *M. tuberculosis* to the contrary to what is observed in macrophages (HERMANN et al., 2006). In the macrophages, the mycobacteria resides in the initial phagosomes and escapes from the immune system by inhibiting phagosome maturation and phagosome-lysosome fusion (RUSSELL, 2003; 2007). *M. tuberculosis* phagosome maturation arrest includes the action of mycobacterial lipid products, which mimic mammalian phosphatidylinositols, targeting host cell membrane trafficking processes (VERGNE et al., 2004).

The adaptive immunity against *M. tuberculosis* involves principally the T $CD4^+$ cells. The importance of the cytokine IFN-γ producing T $CD4^+$ cells in primary resistance to *M. tuberculosis* has already been described (COOPER et al., 1997). However, the T $CD8^+$ cells seem to play an important role in the control of the disease, since loss of T $CD8^+$ cells leads to greater susceptibility to the mycobacterial challenge (KAUFMANN, 2001).

The mycobactericide effect of the IFN-γ produced by the T lymphocytes involves the production of nitric oxide and other nitrogen and oxygen-reactive radicals of the host cell (macrophages) but, according to recent findings, this can only in part explain the action of this cytokine (MACMICKING et al., 2003). It has been demonstrated that the effects of the IFN-γ occur at least in part through a GTPase, the LRG-47 (GUTIERREZ et al., 2004). The LRG-47 is a member of the family of resistance GTPases, which has been described as one of the main factors of protection against *M. tuberculosis*. Is has also been demonstrated that **LRG-47** participates in IFN-γ-dependent induction of **autophagy and that this process is related to the decrease in the intracellular mycobacterial viability** (GUTIERREZ et al., 2004).

As was confirmed by observations made in the murine model, IFN-γ is critical for mediating protection. The relevance of the protective response of IFN-γ is reinforced by the information that natural mutations in human genes codifying IFNγ-R, IL-12, IL-12R or STAT-1 and consequently leading to IFN-γ-mediated immunity, increase the susceptibility to infections by mycobacteria (SAHIRATMADJA et al., 2007; HWANG et al., 2007; OTTENHOFF et al., 2003).

At the same time an IFN-γ response seems to be associated with the control of the disease, different studies demonstrated that human tuberculosis is associated with an increase in the Th2 response, involvement of the cytokines IL-4 and IL-13 as well as IL-4 dependent

IgE secretion (YONG et al., 1989; SEAH et al., 2000). Furthermore, the pulmonary infection leads to increased IL-10 e TGF-γ cytokine production that promote an environment, in which the recently recruited cells of the immune system become refractory to stimulation by the immunological activation signals (BONECINI-ALMEIDA et al., 2004).

Another cytokine important in tuberculosis control is TNF-alfa. It has been observed that patients treated with TNF-alfa antagonists exhibited increased risk of mycobacterial disease, a fact that indicates TNF-alfa as an important molecule in the defense of the host against intracellular pathogens (BOURIKAS et al., 2008; JOLOBI, 2007; STRADY et al., 2006).

In recent years, a great number of studies sought to characterize *M. tuberculosis* molecules for inclusion in a new vaccine against tuberculosis and new diagnostic methods. Our preliminary studies showed an increased IFN-γ production in response to the antigens 85B and ferritin in tuberculosis patients, when compared with controls (ANTAS et al., 2002; CARDOSO et al., 2002). Earlier studies demonstrated ESAT-6 (early secreted antigenic target 6-kDa) to be one of the mycobacterial antigens that determine the production of IFN-γ producing T lymphocytes.The ESAT-6 antigen contains a great number of B and T cell epitopes, which are recognized by the immune serum of tuberculosis patients, suggesting its role in inducing immune memory against the bacillus (HARBOE et al., 1998; MUSTAFÁ et al., 1998). The genes ESAT-6 and CFP-10 (culture filtrate protein 10 kDa) are codified in the RD1 region of the mycobacterial genome. This region is only present in *M. tuberculosis*, *M. africanum* and *M. bovis* (*M. tuberculosis* complex) and in some environmental mycobacteria (*M. kansasii*, *M. marinum* and *M. szulgai*). It is absent in the BCG vaccine and in the majority of environmental mycobacteria, a fact that turns these molecules into important targets for studies evaluating their immunomodulating capacity and their capacity to distinguish latent disease.

In the attempt to evaluate the antigen-specific immune response in a population in Rio de Janeiro, the IFN-γ production in the supernatant of mononuclear cell cultures of peripheral blood (PBMCs) of patients with non-resistant tuberculosis and with MDR-TB was evaluated. It was observed that patients with MDR-TB show low IFN-γ production in response to ESAT-6, when compared with patients with non-resistant tuberculosis before and after treatment (FORTES et al., 2005). These data observed in MDR-TB patients in Rio de Janeiro are in agreement with other studies in the literature that demonstrate that PBMCs of MDR-TB patients show a decreased TNF-alfa response to 30 kDa antigens of *M. tuberculosis*. In this study the authors demonstrated that the reduced response to *M.* tuberculosis antigens of MDR-TB patients is modulated by the cytokine IL-10 (LEE et al., 2003). A recent study evaluating the immune response of MDR-TB patients to lipid antigens revealed that the PBMCs and T $CD4^+$ cells of these patients have a weaker response to the lipid antigens than the cells of PPD-positive individuals. Furthermore it was observed that the IL-4 production in response to lipid antigens was higher in MDR-TB patients, with low IFN-γ response, than in PPD-positive individuals, suggesting that the T $CD4^+$ cells of MDRT patients polarize to Th2 response (SHAHEMABADI et al., 2007).

Although different studies are pointing to the dichotomy Th1 (IFN-γ) -Th2 (IL-4, IL-10) as factors associated with TB resistance or susceptibility, further studies are necessary for a deeper understanding of the immunoregulatory mechanisms involved in the control of tuberculosis. Even with the countless evidences pointing to the importance of IFN-γ in the control of the disease in experimental models and in patients with non-resistant tuberculosis, PARK et al. (2007) demonstrated that in patients with advanced or chronic MDR-TB subcutaneous treatment with IFN-γ did not result in an improvement of the clinical, radiological, microbiological, and immunological parameters, suggesting that other factors might be involved in the control of the disease in these patients. Thus, the understanding of the immunological mechanisms involved in the different clinical and temporal forms of the disease can be helpful in the development of more effective prophylactic and even therapeutic measures against this disease.

New strategies for tuberculosis control

The diagnostic aid used for detecting latent TB infection is the PPD-based intra-dermal Tuberculin Skin Test (TST). It can be affirmed that the TST has low specificity and is of difficult interpretation (BLANC et al., 2007; MENZIES, 1999). Two diagnostic tests based on the production of IFN-γ - T-SPOT.TB and Quantiferon-TB Gold – were licensed recently. These tests only require a blood sample and the interpretation of the results does not depend on the examiner. Based on the antigens ESAT-6 and CFP-10, the specificity of these tests is higher than that of the TST for not presenting cross reaction with the BCG vaccine and with the greater part of environmental mycobacteria. These assays also present a better correlation with the exposure to *M. tuberculosis* than the TST. The capacity of these two tests to detect TB however is reduced in HIV patients, especially those receiving treatment (BLANC et al., 2007). Moreover, it is still unknown if these assays can be easily performed in countries with lack of structure. Thus, other new diagnostic methods are still necessary.

Among the new proposals for diagnostic tests is the MGIT (*Mycobacterium Growth Indicator Tube*) culture system that permits rapid growth and detection of TB bacteria, reducing average detection time. Another proposal is the Capilia TB assay, a test that confirms the presence of the bacillus in the cultures in 15 minutes. Other tests are being developed for evaluating the drug-resistance in smear-positive patients. Another two tests that have completed development are for drug resistance in smear-positive patients - the *FASTPlaque-Response* test and the GenoType MTBDR test, developed by the Geneva-based Foundation for Innovative New Diagnostics

(FIND) in partnership with private institutions like *Biotec Laboratories* e *Hain Lifescience GmbH* respectively. The knowledge of molecular genetics has led to alternatives ensuring a faster diagnosis; however, the implantation of these molecular tests in the developing countries may be difficult due to the high costs of the equipment and training of personnel (YEW et al., 2008).

In spite of the existence of medications efficient in the control of the disease, the length of the treatment regimen makes many patients break off treatment, a fact encouraging the development of resistant bacteria. Thus, new drugs allowing for shortening the treatment would result in better patient adherence, reduced transmission and less drug resistance and consequently reduce the number of deaths due to this disease.

Two new medicines are in the phase of clinical testing. The first one, moxifloxacin, a drug developed by Bayer and already marketed worldwide, is in phase III clinical trials for tuberculosis. Other drugs are currently being developed. Nitroimidazole (PA-824), developed in partnership between the TB Alliance and Chiron Corporation, USA, is in phase I clinical trials and seems to be one of the most promising drugs since the discovery of rifampicin more than 40 years ago (GARWOOD, 2007).

The BCG vaccine was introduced in 1921 and is still the only available vaccine against tuberculosis. The BCG vaccine is effective in preventing severe forms of tuberculosis in children, its efficiency in adults however varies considerably (NABESHIMA et al., 2005) and it has been demonstrated that revaccination does not increase the degree of protection in adolescents and adults (RODRIGUES et al., 2005). During recent years different vaccine candidates were identified and at least eight vaccines are entering early clinical trials (GUPTA et al., 2007). The characterization of *M. tuberculosis* H37Rv through proteomic methods revealed secretion of various proteins that could be investigated. The development of new vaccines however must take into consideration the effects of central markers for obtaining a better regulation of the immune response (WIKER et al., 2006). Thus, a better understanding of the immunological mechanisms related to tuberculosis and to the development of MDR-TB could be of help in the development of more effective prophylactic tools. The knowledge accumulated in basic research needs to contribute effectively to the development of effective control strategies. Besides, as emphasized by TEIXEIRA et al. (2007), even a vaccine more effective than the BCG vaccine would not be able to prevent the progression of the disease in the 2 million already infected individuals, a fact that reinforces the importance of continuing the search for appropriate diagnostic and therapeutic tools to control the disease.

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About the authors

Roberta Olmo Pinheiro

Graduated in Pharmacy by the Federal University of Rio de Janeiro (1989), she holds a Master's degree (2000) and a Doctor of Science degree (2004) from the Laboratory of Immunopharmacology of the Institute of Biophysics "Carlos Chagas Filho" and made her post-doc in the Laboratory of Immunity Biology of the same university. Currently she is a visiting researcher at the Hansen's disease Laboratory of the Oswaldo Cruz Institute. She has experience in Parasitology and Immunology, with emphasis to Immunology, and her research activities focus mainly infectious diseases, immunoregulation, cell death and vaccines

Margareth Pretti Dalcolmo

Graduated in Medicine by the Medical School of the Holy House of Mercy in Vitória, State of Espírito Santo, Brazil. Doctorate in Medicine (Pneumology) by the Federal University of São Paulo and medical residency at the "Raphael de Paula Souza"-Hospital. Experience in "collective health" with emphasis to Pneumology. Her activities are mainly foicused on tuberculosis.