Mycobacteriosis in the Compromised Host

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The studies of rare genetic defects, the preliminary results of population-based studies, being validated by the experimental immunocompromised animal models and the current observations accumulated in immunocompromised patients with mycobacterial diseases provide us with insights into the importance of the macrophage activation pathway in controlling human infection with pathogenic and non pathogenic intracellular multiplying mycobacteria.

Initial cytokine production by infected macrophages and/or dendritic cells could be crucial in the overall regulation of self cure, acquired protection or immunopathological sequelae expressing the disease. Knowledge of molecular and genetic cross-talks between phagocytic and specialized antigen presenting cells and different mycobacterial products associated with persistence or replication of the intracellular bacteria, could provide further informations on the global immune regulation of the early host responses to infection and the following events. It seems likely that the development of mycobacterial infections in humans will turn out to be as much dependent on the genetic make up of the host as or the virulence of the bacteria.

Key words: tuberculosis - acquired immunodeficiency syndrome-Aids - atypical mycobacteria - knockout mouse

There is a long history of the association of opportunistic mycobacterial diseases with the immunocompromised hosts. Individual risk factors for tuberculosis (TB) with conditions such as measles, Hodgkin's disease, and corticosteroid immune suppression given during organ transplantation were well recognised. However, other groups of immunocompromised patients are also at risk of TB and mycobacteria other than tuberculosis (MOTT) infections. Recent reports have described several groups of patients with acute leukemia, lymphoma, visceral malignancies and treated with immunosuppressive therapy who have been infected with *Mycobacterium tuberculosis* and others MOTT such as *M. avium*, *M. fortuitum*, *M. chelonae*, *M. scrofulaceum* and *M. hemophilum* (Skogberg et al. 1993, Young 1996). However, it was not until the post-human immunodeficency virus (HIV) era, that renewed interest became widespread in mycobacteriosis (mycobacterial diseases) in the immunocompromised host. Several reasons for such interest are the following. First, re-emergence of TB in countries where TB was in the way of eradication, was puzzling. This being also associated with nosocomial outbreaks, spreading by individuals with acquired immunodeficiency syndrome (Aids) carrying multiple-drug resistant (MDR) strains to others immunocompromised HIV patients but also to normal hosts such as healthcare workers in hospitals or in the community, was frightful. Second, MOTT that were generally quite rarely isolated before the advent of Aids, but represented before the recently used efficient antiretroviral therapies, a considerable role in morbidity and mortality. This was particularly true of the *M. avium* complex (MAC) because these organisms are the single most important cause of disseminated bacterial infection in Aids patients (Benson 1994). Third reason, a newly recognised pediatric syndrome, the idiopathic mycobacterial infection in non immuno-compromised children (Levin et al. 1995), led to the identification of mendelian susceptibility to mycobacterial infection and several specific genetic deficiencies including receptors genes for important cytokines such as IFNγ and IL-12 (interleukin) have been described (Jouanguy et al. 1999).

NATURAL HISTORIES OF MYCOBACTERIAL DISEASES

Among the mycobacterial genus, the vast majority of species are saprophytic belonging to the environmental microflora. They are present at different latitudes, and could be isolated from soil, and water. There are only a limited number of pathogenic mycobacteria for men, as shown in the Table. The natural history of pathological and casual opportunist mycobacteria diseases differ due

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to different tissue tropisms: the MOTT opportunists appear to be more limited than *M. tuberculosis* or *M. leprae* in parallel with the experimental observations of more limited virulence. For instance, experimental infection with *M. tuberculosis* is often lethal in normal non-immuno-compromised mice, in contrast virulent strains of *M. avium* infection are only lethal in immunodeficient mice (Collins 1972). Moreover, among the *M. avium* group, the serovars 1 and 2 have a definite pathogenicity for certain species of domestic animals (Thoen 1994).

It should be noted that the most common area of involvement for MOTT after the respiratory tract, is the gastrointestinal tract which occurred after colonisation of the mucosal epithelium followed by endocytosis within mucosal lymphoepithelial sites (Lugton 1999). There is also *in vitro* evidence that mycobacteria can adhere to and penetrate epithelial cells other than M cells of the Peyer's patches. Several human epithelial cell lines are permissive to invasion by *M. avium*, *M. tuberculosis* and other rapidly growing mycobacteria. Local immune non specific or specific defect of the mucosa-associated lymphoid tissues (MALT) could be associated with loss of tolerance to the resident mycobacteria and the establishment of a local granuloma formation and necrosis. Only severe and prolonged immunodepression is associated with atypical mycobacterial dissemination.

In contrast, airborne infection of the lower respiratory tract of humans, cattle or small laboratory animals with *M. tuberculosis*, has been extensively studied and well described, showing the direct involvement of alveolar macrophages as portal of entry of such pathogenic mycobacterial species (Hopewell 1988). Acquisition of tubercle bacilli through the oropharynx and gastrointestinal tract by ingesting contaminated food or milk is much less common. From 3% to 10% of newly infected persons will develop clinically apparent TB. In the other 90 to 97%, host defences are sufficient to prevent progression from infection to disease. Cell-mediated immunity is the most important defense mechanism and it contributes in controlling the infection by killing many organisms and walling off the remainder within immune granulomas. When immunity waves, as by the effects of age, or is suppressed, either by the influence of drugs or diseases, the potential exist for either the reactivation at wherever endogenous sites of dormant persisting viable tubercle bacilli or for the development of newly acquired TB from recently inhaled bacilli from an exogenous source. Undoubtedly, both forms occur and the likelihood of one or the other will depend on the background prevalence of TB in the immunocompromised host group and the risk of contracting active cases of TB in the community.

Worlwide, TB is the most common opportunistic bacterial infection in patients with HIV co-infection. Before the efficient antiretroviral therapies, in developed countries, disseminated MAC disease was the most common systemic bacterial opportunistic infection in patients with Aids. Both contribute substantially to morbidity and mortality in this population. The risk factors, clinical syndromes and development in the investigations, prevention and treatment are discussed in the first part in this review. The second part is devoted to the acquisition of knowledge of immune defences in experimentally and transgenic immuno-compromised mouse models. And finally the third part is reporting new data concerning Mendelian susceptibility to mycobacterial infection in men.

MYCOBACTERIAL DISEASES IN HIV COINFECTED PATIENTS

Since the first publications of increased numbers of disseminated life-threatening infection with *M. avium* in 1982 by Greene et al. (1982) and increased prevalence of tuberculosis in patients

TABLE

Mycobacteria species isolated more frequently in microbiology laboratories

Growers	Highly pathogens	Pathogenic	Casual pathogens (opportunist)	Saprophytic
Slow	*M. tuberculosis*	*M. ulcerans*	*M. avium*	*M. gordonae*
	M. bovis	*M. malmoense*	*M. intracellulare*	*M. terrae*
	M. africanum	*M. szulgai*	*M. scrofulaceum*	*M. nonchromogenicum*
	M. leprae	*M. simiae*	*M. kansasii*	*M. flavescens*
	M. hemophilum	*M. asiaticum*	*M. xenopi*	*M. gastri*
				M. triviale
Fast			*M. marinum*	
			M. chelonae	*M. snegmatis*
			M. fortuitum	

with Aids in 1984 by Pitchenik et al. (1984), several reviews has been published concerning the infections with pathological and opportunistic mycobacteria in HIV coinfected patients. Many of them involved on progress made in defining those at risk, characterising pathogen virulence factors, the host immune responses, development of rapid and sensitive diagnostic tools and therapeutic guidelines. However, natural pathogenic and atypical mycobacteria differ in their relationships with the immunocompromised host. Concerning the natural highly pathogens in immunocompetent hosts, i.e. *M. tuberculosis* and *M. leprae*, only the former was associated with an increased risk for developing the disease in HIV coinfected patients. By contrast, in countries where leprosy is a local endemic disease, no publication is reporting any increase in the prevalence of the disease as such or of any increase of the lepromatous leprosy forms. Such difference in the morbidity between these two pathogens might be explained through different virulence factors, one of them being the very low replicating rate of *M. leprae in vivo* and as such a quite longer incubation period varying from 10 to 15 years in the infected person. Concerning the atypical MOTT, the great majority of species isolated was *M. avium*, and this was observed mainly in developed countries, in contrast to what was reported in Africa, for instance, where such species are very rarely isolated in Aids patients.

M. TUBERCULOSIS AND HIV COINFECTION

Infection with HIV increases the risk of development or clinical TB, either as a result of reactivation of after primary exposure. The emergence and rapid development of the HIV/Aids pandemic has had a devastating impact on the global burden of TB and is now by far the most important predisposing factor for active TB in those individuals infected by the tubercle bacillus.

Clinical presentation and radiological findings are directly dependent upon the level of immunosuppression (Halvir & Barnes 1999). For instance, mycobacteremia and extrapulmonary TB become more common in patients with low CD4 counts. In HIV coinfected patients with TB, who have CD4 cell counts of 200 or more per mm^3, chest radiographic findings include upper lobe infiltrates and cavitation, similar to those in HIV negative TB patients. In HIV TB patients with fewer than 200 CD4/mm^3, mediastinal adenopathy is common (similar to that in HIV-negative patients with primary TB). It should be noted also that approximately 5% of HIV patients with pulmonary TB have positive results on acid-fast straining of sputum, despite normal chest radiographs.

Usually skin testing with 5 TU of PPD is the method by which TB infection is identified. All HIV-infected persons with a positive tuberculin skin test result equal or larger than 5 mn should undergo chest radiography and clinical evaluation in order to exclude active TB, and should receive recommended chemoprophylaxis.

Clinical studies have shown the detrimental effect of TB on the course of HIV infection. The risk of death in HIV-TB patients was reported to be twice than in HIV infected patients without TB, independently of the CD4 counts (Whalen et al. 1995). Such higher mortality rate appeared to be due to progressive HIV infection rather than TB, and the degree of immunosuppression being the most important predictor of survival of HIV-TB patients. *M. tuberculosis* probably increases HIV replication by inducing macrophages to produce transactivating cytokines (TNFα, IL-1, IL-6). New efficient anti retroviral combination regimens associated with anti-TB chemotherapy have shown a dramatic improvement for the pronostic in HIV-TB patients who are infected with drug susceptible tubercle bacillus. Moreover, adjunctive treatments aiming at limiting the hyperproduction of TNFα, such as thalidomide has been used in controlled trials in order to minimise the HIV trasnsactivation during TB (Haslett et al. 1999).

In HIV-infected patients with drug susceptible TB, the standard six month regimen results in prompt sterilisation of sputum, similar to those in HIV-negative TB patients. However, several studies showed higher rates of relapse in HIV-TB patients who received 6 as compared with 9 to 12 months of anti-TB therapy.

The actual guidelines of the Centers for Diseases Control (USA) state that the minimum duration of therapy is 6 months, but if clinical and bacteriological response is slow, treatment should be given for a total period of 9 months, or 4 months after the culture become negative.

MDR TB have been responsible of explosive nosocomial outbreaks in several cities of the world with an unprecedented case fatality rate of 80% in HIV-infected patients. Stringent infection-control policies curtailed these outbreaks in New York city and Miami and a strengthened public health infrastructure and widespread use of directly observed therapy (DOT) resulting in a 44% reduction in MDR TB in New York between 1991-1994. Recommendations on the allocation of adequate public health resources to ensure that every patient complete their anti-TB therapy is urgently needed in countries where prevalences of MDR TB and HIV endemic are growing. Clinicians should strongly consider measuring drugs levels to evaluate the possibility of malabsorption in case

of no response to anti TB therapy in HIV-infected patients who adhere correctly to it.

HIV-infected patients with recent or remote TB infection are at extremely high risk for the development of active TB disease, and the efficience of chemoprophylaxis has been demonstrated. Isoniazid (INH) for 6 months reduced the risk of TB by approximately 70% in HIV-positive patients with positive PPD skin test. Preliminary data suggest that the efficacy of daily rifampin and pyrazinamide for 2 months is similar to 12 months of INH (Rose 1998). Because HIV-infected patients have defective cell-mediated immunity, and those with a CD4/mm^3 lower than 200, have quite often false negative tuberculin skin tests, it has been recommended that skin testing be performed with PPD and other antigens to detect anergy. However, the great variability of anergic responses and the fact that chemoprophylaxis with INH does not reduce the incidence of TB in HIV-infected persons with anergy, anergy testing is no longer recommended to assess the risk of TB infection. An ongoing study is performed in our laboratory to evaluate a new surrogate marker for infection. It consist of testing for specific IgG antibody detection against *M. tuberculosis* glycolipids in HIV infected patients at risk of TB, since it has be shown that such antibodies were present in serum of HIV-TB patients, long before the clinical diagnostic of TB (Simonney et al. 1995).

TB is often the initial clinical manifestation of HIV coinfection, and all patients with TB should be tested for HIV because of the potential benefits of an early diagnosis of HIV infection. Also, all patients with recently diagnosed HIV infection should be skin tested with tuberculin.

Highly active antiretroviral therapy (HAART) employing both the protease inhibitor (PI) class of drug and the nonnucleoside reverse transcriptase inhibitors has come into wide care among HIV-infected individuals, and this HAART might impact in two ways on TB treatment in Aids patients. The first one is related to the risk of substantial drug interactions between the PI antiretroviral and the rifamycins. The second involved the development of paradoxical reactions during anti-TB therapy. Such paradoxical worsening of the disease develop in up to 36% of these patients, characterised by fever, peripheral and mediastinal lymphadenopathy or worsening chest infiltrates or radiography (Narita et al. 1998). Such reactions suggest reactive inflammation from a stronger immune response to *M. tuberculosis* during effective antiretroviral therapy. Usually self-limited, these reactions generally last 10 to 40 days, but in case of severe reactions, they may require a short course of treatment with glucocorticoid (Narita et al. 1998).

Immunomodulating agents have been tested in order, either to compensate deficiency or to modulate excessive cytokine production. Recently, Condos et al. (1997) reported some success on the administration of IFNγ via aerosol to five patients, with refractory MDR-TB, one patient was HIV coinfected. Thalidomide has recently been given in a group of TB patients being HIV-non infected and HIV-infected. Levels of IFNγ increased, stimulated TNFα production decreased and weight gain was enhanced during thalidomide treatment (Tramontana et al. 1995). No follow-up was reported concerning the viral load and pronostic of HIV infected patients. At least, immunotherapy using an injection of a killed suspension of a non-pathogenic environmental mycobacteria *(M. vaccae)* has been evaluated in several trials with some beneficial effects. However, the last study done in South Africa (Durban Immunotherapy Trial Group 1999) showed that *M. vaccae* immunotherapy has no benefit when added to standard anti-TB chemotherapy.

ATYPICAL MYCOBACTERIA AND HIV COINFECTION

Previously a rare cause of pneumonia in patients with pre-existing lung disease, MAC was recognised early in the Aids pandemic as a cause of serious disseminated infection (Greene et al. 1982) and was the most common cause of systemic bacterial infection in Aids, affecting more than 50% of patients in the developed countries. Primary prophylaxis was recommended on the basis of CD4$^+$ cell threshold (less than 50/mm^3) in all HIV persons for increased risks of specific opportunistic infections, such as MAC disease. However, more potent antiretroviral regimens have been introduced recently that suppress HIV replication and increase the CD4$^+$ cell counts, and marked decrease in the incidence of major infectious complications, especially MAC disease, have been observed everywhere in patients treated with these regimens (Palella et al. 1998).

Of the species composing MAC, *M. avium* is most commonly associated with disease in Aids, and serotypes 1, 4 and 8 are the most commonly isolated from symptomatic patients with Aids (French et al. 1997). Furthermore, epidemiological studies suggest that MAC strains associated with pulmonary disease may differ from those associated with disseminated disease in Aids patients. Moreover, phylogenic analysis of nucleotide sequences data, using the variable 16S-23 rDNA internal transcribed spaces (ITS) in clinical isolates from Aids patients showed that the disseminated disease-associated MAC strains were distinct by ITS sequence analysis from other isolates

(Frothingham & Wilson 1994). Lastly, two particular epidemiological facts are intriguing. First, simultaneous infection of Aids patients with more than one strain appears to be rather common (Arbeit et al. 1993). Second, even if the prevalence of disseminated MAC associated disease was high, great individual susceptibility, geographic and seasonal variations has been described. For instance, disseminated MAC is rare in Africa, although MAC is prevalent in soil and water samples from the area where advanced Aids patients are present (Morrisey et al. 1992). These phenomenon remains unexplained, although it is postulated that widespread previous antimycobacterial immunity from the high rate exposure of Africans to *M. tuberculosis* and BCG vaccination may be responsible. This is supported by data which suggest that prior TB diagnosis may be somehow protective against disseminated MAC (Horsburgh et al. 1996).

The pathogenesis of MAC infection is incompletely understood. Disseminated MAC is believed usually to follow primary acquisition of the mycobacteria. It appears that MAC first colonizes the gastrointestinal (GI) tract or respiratory mucosa, and dissemination follows. Several animal models have shown that dissemination occurs after colonisation of the GI tract. Epidemiological studies in humans did confirm the preceding isolation of MAC from stool or sputum within one year before bacteremia in 60% of patients with $CD4^+$ cell counts less than 50 CD4/mm^3. Individual susceptibility to disseminated MAC disease could be due also to some additive non specific incompetence to kill or to slow down mycobacterial replication. Such hypothesis is reinforced by recent findings showing higher serum levels of both TNFα and soluble TNFα receptors in *M. avium* complex disseminated disease in Aids patients, which is directly correlated with the degree of 1,25 dihydroxyvitamin D3 deficiency (Hang et al. 1996).

In contrast to the immunocompetent host, in which MAC disease is usually limited to the lungs, in patients with Aids, bacteremia is by far the most common syndrome. Frequently, there is wide spread dissemination, often to bone marrow, liver, lymph nodes and spleen. When the clinical syndrome suggests disseminated MAC, mycobacterial cultures of the peripheral blood should be obtained and are often positive. As shown in lepromatous leprosy, if histologic sections are obtained by tissue biopsies, they showed aggregates of foamy histiocytes, in which the organisms can be seen by acid fast staining. Such positive biopsies may be positive before blood cultures.

Several studies have reported negative predictors for survival of Aids patients with disseminated MAC disease: the $CD4^+$ cell counts, and the initial higher level of mycobacteremia (Horsburgh et al. 1994). Moreover, there are also clinical and abnormal laboratory values which are associated with MAC bacteremia, thus being useful to manage the patients in whom this infection is suspected and should be confirmed by blood culture. Such abnormal findings among patients with less 50 CD4 cells/µl are: the documentation of fever on more than 30 days during the preceding 3 months, a previous *Pneumocystis carinii* treated infection, an hematocrit of less than 30%, or a serum albumin concentration of less than 3 g/dl (Chin et al. 1994).

It has been clearly shown that the survival of Aids patients with disseminated MAC disease is directly related to the most efficient antimycobacterial chemotherapy given. Curative therapy should include rifabutin, a new macrolide (clarithromycine or azithromycine) and ethambutol. However, designing the ideal therapeutic regimen for disseminated MAC is complicated by the lack of clinically usefull susceptibility testing for most of the available agents. Only clarithromycine susceptibilities have been shown to correlate clinical efficacy. MAC cocultivation within macrophages (Sison et al. 1996a) or MAC infected beige (C57 BL/6/bg/bg) mice gave better clinical correlations (Sison et al. 1996b).

Current guidelines for MAC prevention include the use of rifabutin. In light of current results concerning the new macrolides, clarithromycine or azithromycine, alone or the combination of a macrolide and rifabutin are well considered. Discontinuation of prophylaxis should also be considered if the CD4+ cell counts rise above 100/µl after efficient antiretroviral therapy.

Immune modulators, such as granulocyte-macrophage-colony stimulating factor (GMCSF), granulocyte-colony-stimulating factor (G-CSF), interferon γ and IL-2 may be of benefit in enhancing intracellular killing of *M. avium* (Benson 1995).

IMMUNODEFICIENCY AS A SOURCE OF KNOWLEDGE

Immunological deprivation, using chemotherapeutic regimens or monoclonal antibodies on the susceptibility of animals (mosly done in mice) to mycobacterial disease due to *M. bovis* BCG or to virulent *M. tuberculosis* have shown that the expression of optimal antimycobacterial immunity requires the coordinated activity of a whole range of T-cell and macrophage functions, including those of TCR $\alpha\beta^+$ CD4 and CD8 T cells (Kaufmann 1993). The results from studies with *M. tuberculosis* infection has suggested a major protective role for INFγ, TNFα, IL-12 and inductible nitric oxide synthase (INOS). The use of gene-disrupted mice has

led to new insights into how several immunological effectors protect mice against mycobacterial infections (Cooper et al. 1997). The data from these knockout mice showed that IFNγ and TNFα are the primary mediators of macrophage activation and sterilizing granuloma formation. At least, a primary mechanism of mycobacterial control is the production of nitric oxide (NO) by INOS. As innate production of INFγ is insufficient to control totally *M. tuberculosis* in mice, expansion of INFγ production is needed. The cells considered responsible for such expansion has been shown to be $CD4^+$ and $CD8^+$ lymphocytes. The expression of IFNγ-producing T lymphocytes in these animal models has been shown to be dependent upon the early production of IL-12. Although the $CD4^+$ T lymphocytes is implicated as the primary protective T cell subset, the $CD8^+$ lymphocytes has been also implied later during the infection. However, the absence of any difference between control mice and mice lacking in the common lytic mechanisms (such as granzyme B and perforine) seems to indicate that their role during the first phase of infection is mediated more by the cytokine production than by lysis of infected cells. The putative role of T cell has been highlighted in controlling early aspects of monocytes migration and in aiding maturation of granuloma.

In conclusion, immunodeficient gene-disrupted mice have already contributed a great deal to our knowledge of the nature of immunity to *M. tuberculosis*. Thus, in experimental mycobacterial infection in mice, lack of any of the above mentioned defense mechanisms cannot be fully compensated for by alternative immune mechanisms. These mechanisms appear to have a cascade effect on each other, leading to the generation of an optimal response. However, if the broad components of human antimycobacterial immunity are similar with those of mice, several significant differences in details exist: regulation of NO synthesis, macrophage killing *M. tuberculosis* induced by IFNγ, and the gene coding for the natural resistance associated macrophage protein (NRAMP1) (Kumararatne 1997). Thus it is important to consider not only the acquired immunodeficiency in mice, but also the natural defects associated with higher susceptibility to mycobacterial diseases in humans, in order to better understand the immunological basis of resistance to these diseases.

Recent studies have been shown selective susceptibility to non classical pathogenic mycobacteria, such as environmental MOTT and BCG vaccine. The selective immunodeficiency has been suspected to be a mendelian disorder, and recent studies were undertaken to demonstrate its molecular basis.

By contrast with the well-known leading causes of disseminated disease in Aids patients, the MOTT and BCG vaccine have been shown also to cause severe disease in otherwise healthy children without any over immunodeficiency (Levin et al. 1995, Casanova et al. 1995, 1996). Unlike severe immunocompromised patients, being highly susceptible to a broad range of opportunistic pathogens, children with disseminated idiopathic BCG and MOTT infections do not have generally associated infections, apart from salmonellosis in less than half of the cases. In the cases of children with the idiopathic disseminated BCG infection, a mendelian disorder of autosomal recessive inheritance was suggested by the high rates of affected siblings and parental consanguinity, together with the equal number of male and female children (Casanova et al. 1996). The same observations were also reported in the Levin's study (Levin et al. 1995). Moreover, the heterogeneity of clinical outcome and its correlation with the histopathological granulomatous type of the lesions, suggested that the underlying potential inherited disorder might be genetically heterogeneous (Jouanguy et al. 1996).

Following a whole genome search, the first gene was mapped to the region of chromosome 6a containing the IFNγ receptor ligand-binding chain gene (R1) and single base substitution in the coding region of this gene, resulting in a new stop codon, and in the complete absence of IFNγ receptor expression on cell surface was identified first in London (Newport et al. 1996). Concurrently, Casanova and collaborators in Paris, sequencing the IFNγ R1 gene in a consanguineous Tunisian family, affected by disseminated BCG infection, identified a frameshift deletion that resulted in the absence of IFNγ R1 (Jouanguy et al. 1999).

Since these two initial reports concerning the IFNγ R1 gene, as a cause of the unique susceptibility to atypical mycobacterial infections in childhood, several other mutations in this gene have been identified that were associated with the complete absence of IFNγ receptor expression on cell surface in patients with severe clinical disease often fatal. The identification of IFNγ R1 deficiency as a cause of susceptibility to mycobacterial infection in humans confirmed indirectly the validity of using knockout mouse model to identify key pathways controlling susceptibility and resistance to these bacteria. Moreover, human equivalents of the murine defects in other key cytokines or their receptors controlling macrophage activation were also identified. For instance, mutations in the IL-12 gene or its receptor were also shown to be associated with susceptibility to disseminated BCG or MOTT infection and do cause clinical syndromes

similar, but milder, to that associated with the IFNγ R1 deficiency (Jouanguy et al. 1999). Furthermore, mutations in the second signaling chain of the IFNγ receptor (IFNγ R2) have been identified in a child with disseminated *M. avium* and *M. fortuitum* infection (Dorman & Holland 1998).

It seems very likely that single gene defects in the different components of the cascade of events involving macrophage activation pathway in humans will be ultimately identified. However, such selective susceptibility associated with gene defects are not representing all the possibilities involved in susceptibility to classical pathogens such as *M. tuberculosis* and *M. leprae*, since higher incidence of TB, or disseminated TB and lepromatous leprosy have not been reported in the preceding described patients.

Individual susceptibility to develop the diseases, such or TB or leprosy, have been suscepted for long time to be associated with genetic factors (Jepson 1998), and functional polymorphims in gene controlling macrophage activation might have an higher numerical implication than gene defects associated with selective susceptibility to atypical mycobacteria or BCG vaccine. The question of functional polymorphims in major genes controlling mycobacterial replication in the host are being assessed in different population-based studies. Some interesting data have been reported concerning the NRAMP gene (Bellamy et al. 1998), and the results obtained with the Belem Family study (Blackwell et al. 1997) are indicative of several putative candidate genes/regions identified through analysis of disease susceptibility phenotypes in murine models of infectious disease as a lead to identification of susceptibility genes in humans.

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