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Immunology of tuberculosis

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Summary

Mycobacterium tuberculosis (Mtb) infection remains widespread, but the disease is generally limited to the primary infection stage. Patients with an immune defect or impaired immunity are more prone to develop the disease. A total of 8–10 million individuals are affected worldwide every year. A good understanding of Mtb immunity is therefore important to prevent tuberculosis or to develop new vaccines, based on immunomodulators already used for various diseases, and on the knowledge acquired since the unravelling of the genomic structure of Mtb.

Key words: tuberculosis; Mycobacteria; innate immunity; adaptive immunity; vaccines

Introduction

Tuberculosis was a major cause of mortality in Europe up to and including the 19th century. In 1801 for instance, 1000 deaths per 100000 inhabitants were attributed to tuberculosis in England. These cases represented 30% of all deaths [1]. With the improvement of socio-economic conditions and the development of preventive measures against potential infectious agents, mortality due to tuberculosis started to decrease. Since the introduction of antibiotics in 1946, tuberculosis was thought to be no longer a threat in developed countries.

Despite this progress, the World Health Organisation (WHO) estimates that about one third of the world's population is currently infected with Mycobacterium tuberculosis (Mtb), and that 1.4–2.8 million people die of tuberculosis every year [2]. This failure to control the tuberculosis epidemic has been attributed to insufficient use of effective treatment schemes in developing countries, the spread of multidrug resistance and the emergence of AIDS. An HIV positive individual infected with Mtb is estimated to have an 8% per year risk of developing the active disease [3]. By contrast, the lifetime probability for a normal individual to develop active tuberculosis in his lifetime is only 5–10%. HIV infection and the resulting decrease in immunity represent the greatest risk factors with regard to tuberculosis and are far more important than risks such as malnutrition, immunosuppressive drugs, diabetes, silicosis, or gastrectomy.

Young children and elderly people have the highest risk of developing not only active tuberculosis, but also the disseminated form of the infection. This is due to their relatively weak immune defences, as a result of an immature system in the former, and to age-related immune dysfunctions in the latter. In this article, we will review current data and knowledge on the immune mechanisms against tuberculosis, as well as some disorders caused by newly discovered immune defects or HIV infection.

Acquisition of immunity against M. tuberculosis

In 1880, R. Koch described a delayed hypersensitivity reaction to mycobacterial extracts, first in guinea pigs and then in human patients with active tuberculosis [4]. In 1934, Seifert obtained a more purified extract of Mtb proteins (PPD), which later became the reference used in tuberculin tests. Although these bacterial extracts are useful for the diagnosis of latent tuberculosis, as they produce a delayed hypersensitivity reaction in sensitised subjects, they do not confer immunity against the disease. Only infections with attenuated bacillus, such as M. Bovis Calmette-Guérin [5], or with M. tuberculosis itself, confer some degree of protection against a secondary infection with Mtb. Immunity cannot be transferred to animals by immune serum, but requires the transfer of lymphoid cells, as originally demonstrated by M. Chase in 1945. More precisely, the transfer of CD4 but not CD8 T lymphocytes will protect immunodeficient mice [6]. It is therefore clear that memory CD4 lymphocytes are required to maintain immune protection against Mtb.

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Cellular immunity in tuberculosis

Protective anti-mycobacterial immune response involves mainly T lymphocytes activating the macrophages and their microbicidal functions through the release of interferon γ (IFNγ) [7]. This leads to the formation of granulomas, crucial to the containment of mycobacteria. Macrophages/dendritic cells are found in the centre of these granulomas, along with mycobacteria surrounded by T lymphocytes which provide the proper activation.

Priming of naive T lymphocytes against mycobacterial antigens is thought to occur in the proximal draining lymph nodes and to rely on a particular subset of phagocytic cells, the dendritic cells (DCs). Indeed, DCs have the unique ability to activate naive lymphocytes after their migration from infectious sites. They capture antigens and take them to the lymph nodes, where they will express high amounts of presentation molecules, such as MHC-I or II, as well as co-stimulatory molecules, such as CD80 and CD86 [8], and soluble factors, such as IL-12, IL-18 or IL-23. DCs provide a tight surveillance network around the airways and the vessels, and in the loose connective tissue. It has been shown recently that Mtb enters DCs after binding to the recently identified lectin DC specific inter-cellular adhesion molecular-3 grabbing non-integrin (DC-SIGN). By contrast, complement receptor 3 (CR3) and the mannose receptors, which are the main M. tuberculosis receptors on macrophages, appear to play a minor role, if any, in mycobacterial binding to DCs [9]. The mycobacterial specific lipoglycan lipoarabinomannan (LAM) is identified as a key ligand of DC-SIGN. Also, it appears that human immunodeficiency virus (HIV) is captured by the same receptor DC-SIGN [10], allowing the entry of both, HIV and M. tuberculosis in DCs *in vivo*. This is likely to influence bacterial persistence and compromise host immunity against Mtb [9]. Therefore, DC-SIGN might account for several pathological and immunological aspects of M. tuberculosis infection in subjects co-infected with HIV and unable to provide an adequate immune response, which leads to enhanced incidence of mediastinal adenitis and disseminated tuberculosis.

Toll-Like Receptor-2 (TLR-2) has been shown to play an important role, as it is able to mature DC myeloid precursors into competent antigen-presenting cells expressing CD1 proteins (a, b, c). Mycobacteria were shown to provide two signals for the activation of lipid reactive T cells: lipid antigens that activate T cell receptors, and lipoid adjuvant that activates antigen-presenting cells (APCs) through TLR-2 [11].

After their priming in lymph nodes, memory CD4 and CD8 T cells become central components of the acquired immune system and are therefore the basis for successful immunity/vaccination. The requirement for DCs to prime the CD4 and CD8 T cell response following Mtb infection was confirmed using selective depletion of these DCs in a murine model (12). *In vitro*, once both CD4 and CD8 lymphocytes have been activated, they become cytotoxic for mycobacteria and the macrophages containing them.

The ability of CD4 and CD8 T cells to kill intracellular pathogens has been shown to depend on their capacity to attract infected cells as well as on their secretion of cytolytic and antimicrobial effector molecules. For instance, CD8 T cells can release chemokines, such as CCL5, which efficiently attract M. tuberculosis infected macrophages. *In vitro*, infected macrophages trigger the expression by CD8 T cells of granulysin and perforin, two compounds which are highly active against drug-sensitive and drug-resistant M. tuberculosis clinical isolates [13].

Natural killer cells (NK cells) are also bactericidal against mycobacteria. These killer lymphocytes can be activated in the presence of foreign antigens, even when APCs are absent. These NK cells are innate immune effectors that produce immunoregulatory cytokines, which are critical to early host defence against viral, bacterial and parasitic pathogens. Recently, it has been reported that reciprocal activation interactions occurred between NK cells and DC cells via mechanisms dependent on cell-cell contact and soluble factors [14].

It is reported, that IFNγ and monokines, such as IL-15 and IL-18, play a crucial role in the regulation of CD8 T cells against Mtb infection by NK cells. NK cells improve also the function of γδ T cells, another type of lymphocytes which play a role in the immune response against Mtb [15]. These cells are cytolytic and could potentially kill mycobacteria. These cells are also potent secretors of IFNγ and might be able to activate macrophages.

Resting monocytes or macrophages cannot kill or inhibit the growth of mycobacteria. Their activation requires the release of a number of cytokines by lymphocytes, such as interleukin 2, IFNγ or Tumour Necrosis Factor (TNF). IFNγ up-regulates a variety of macrophage functions, including production of TNF, toxic oxygen species, and nitric oxide by the induction of nitric oxide synthase. The release of oxygen radicals appears to be only partially correlated with the bactericidal capacity of macrophages. In fact, nitric oxide seems to be more important, at least in mice, although the role of lysozyme, proteases, and hydrolases should not be neglected [7]. TNF by itself does not inhibit the growth of mycobacteria, such as M. avium, but it might be more important than IFNγ in inducing human macrophage bactericidy. Experimental models and clinical trials have accumulated evidence identifying TNF as a key factor in host defences against mycobacteria infections. TNF by itself does not inhibit the growth of

mycobacteria, but it acts as a second signal for T cell activation, as well as for macrophage activation. Impaired granuloma formation, reduced bactericidal mechanisms, and alteration of mycobacterium-induced TH1 type immune response have been observed. Total and partial neutralisation of TNF had different effects on cell-mediated immunity against mycobacteria [16].

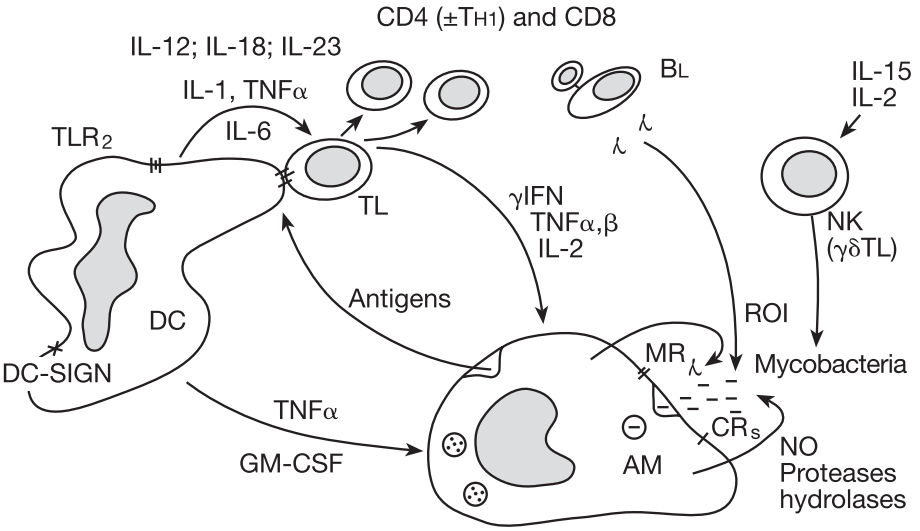

Figure 1

Role of dendritic cells (DCs), alveolar macrophages (AM); T lymphocytes (TL), either CD4, CD8 or Natural Killer (NK) and of B lymphocytes (BL) in defence against mycobacteria TLR-2 = Toll like receptor; DC-SIGN=DC specific intracellular molecular 3 grabbing non-integrin; ROI = reactive oxygen intermediates; NO = nitrogen oxide; TNF = Tumour necrosis factor; IFN = interferon; IL=interleukin

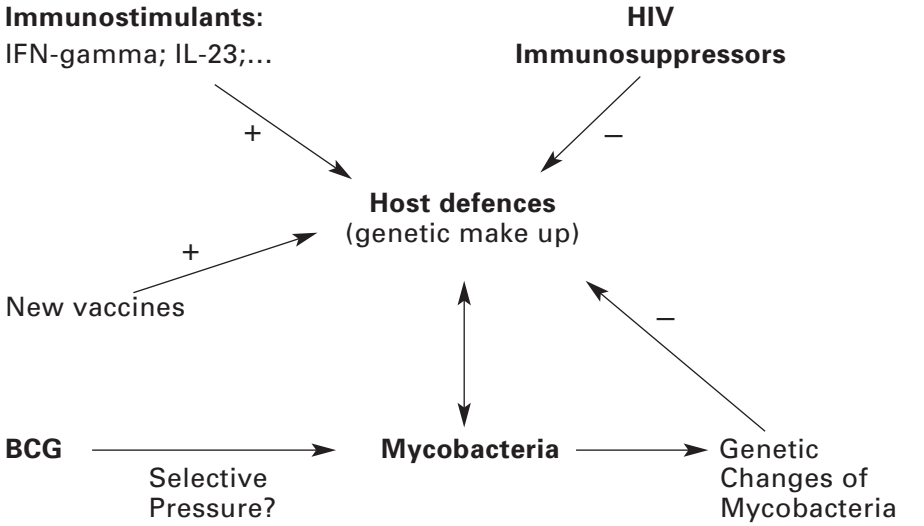

Figure 2

Complex interaction between host defences and elements, which will either up- or down-regulate their efficiency against mycobacteria.

Role of antibodies against mycobacteria

Although antibodies against Mtb may not allow the transfer of immunity against tuberculosis, they seem to have an opsoning role and thereby improve phagocytosis by macrophages or the cytotoxic actions of killer lymphocytes. The ability of human antibodies induced by Mycobacterium bovis bacillus Calmette-Guérin (BCG) vaccination has been studied recently. Serum samples from volunteers, who had been vaccinated twice at a 6-month interval, showed significant increase in lipoarabinomannan specific antibodies. Internalisation of BCG by phagocytic cells was significantly enhanced in post-vaccination serum samples. Furthermore, the inhibition effects of neutrophils and monocytes/macrophages on mycobacterial growth were significantly enhanced by BCG-induced antibodies. BCG-induced antibodies were shown to significantly enhance the cell-mediated immune response with an increased proliferation and IFNγ production in mycobacterium specific CD4 and CD8 T cells. Mycobacterium specific antibodies seem capable of enhancing both innate and cell-mediated immune responses to mycobacteria [17]. It is possible that their absence in the late stage of AIDS could favour the dissemination of atypical mycobacteria, at least those belonging to the M. avium complex [18].

Mycobacterial antigens

Koch obtained the first extracts from mycobacteria in 1880. Nearly 60 years later, in 1949, Siebert described three classes of proteins and two classes of polysaccharides. The recently completed sequencing of the M. tuberculosis genome is seen by many as a turning point in tuberculosis vaccine research [19]. There is no doubt that the identification of approximately 4000 genes will help identify new M. tuberculosis antigens. However, it must be acknowledged that a number of highly immunogenic antigens, such as the culture filtrate protein Ag 85 and ESAT as well as the stress protein hsp 65, had already been identified through intelligent and tenacious research, long before genomic data were available. Clearly, genome sequencing must be followed by comparative and functional genomics to profit from the data that are now available. Specific antigens from Mycobacterium tuberculosis are currently used in clinical settings as new diagnostic tests involving T cell proliferation assays. These tests quantifying the interferon released in supernatants or around the T lymphocytes provide very sensitive and specific tools to detect M. tuberculosis infection [20].

The relevance of comparative genomics for tuberculosis vaccine research has recently been demonstrated. Comparative hybridisation of DNA microarrays showed genetic divergence of M. tuberculosis, evolved during the derivation and maintenance of the BCG vaccine strains [21]. The cause of the genetic divergence might be bi-directional. Progressive attenuating mutations may have been selected over time, when BCG strains with fewer side effects were systematically chosen. At the same time, due to the wide spread use of BCG, M. tuberculosis could have adapted to this vaccine by selective pressure against the strains expressing the same prominent antigens as BCG. The DNA microarray technology might help to develop new vaccines more rationally by identifying specific antigens, and to regularly adapt an existing vaccine to the genetic variations of the pathogens. There is now strong evidence that mycobacterial lineages are adapted to particular human populations. If confirmed, these findings will have important repercussions for tuberculosis control and vaccine development [22].

Mycobacterial capacity to alter immunity

A gene family occupying 2% of the genome is required for synthesis of the complex lipids that play both structural and immunomodulatory roles in Mtb. In the synthesis pathway of the cell wall, associated lipid relevant glycosyltransferase and methyltransferase have been shown to build these lipids. Among these lipids, phenolic glycolipids are only associated with some clinical isolates and they enhance their virulence by modulating host immune responses [23]. These findings should pave the way for new therapeutic approaches.

Mtb infected cells produce methylglyoxal, a tuberculostatic compound, which participates in mycobacteria-induced host cell apoptosis, which is crucial for killing mycobacteria, and which allows cross priming of T cells in tuberculosis [24]. Transcription analyses of Mtb from lung specimens obtained from patients with tuberculosis revealed marked up-regulation of the genes encoding glyoxylase, which detoxify methylglyoxylase and increase resistance of Mtb.

The mechanisms responsible for insufficient T cell-dependent protection in response to BCG vaccination and Mtb infection remain unclear, but regulatory T cells (Treg) may be involved. Specific transcription factors seem in some vaccine components to induce Treg cells. Should Treg cells turn out to suppress optimal immune response to Mtb or BCG, vaccination strategies may have to focus on reduction of Treg cells development [25].

Improved understanding of how Mtb resists and adapts to stress encountered during infection is paving the way toward new interventions. Trehalose, the major intracellular sugar of mycobacteria, protects against cellular stress. It is a component of glycolipids and is involved in the transport of mycolic acids during cell wall biogenesis. Its biosynthesis may provide targets to improve defences against Mtb [25].

Host genetics favouring Mtb infections

Susceptibility to tuberculosis in humans is a polygenic trait, including increased concordance of disease in monozygotic compared to dizygotic twins and increased susceptibility among given populations. Numerous genes have been identified, each of which contribute to the susceptibility, to varying degrees, of a given population. Genes encoding HLA-DRB1, Vitamin D receptor and Natural Resistance-Associated Macrophage Protein – 1 (NRAMP-1) have all been found to play a role in human susceptibility to develop mycobacterial disease. Similarly, mutations in IFNγ recep-

tor 1 or 2, STAT 1, IL-12 p40 and IL-12 R β_1 all lead to a decrease in IFNγ production or efficiency in humans and favour pathogen virulence. Promoter variation in the DC-SIGN, the major receptor for Mtb, is associated with tuberculosis in European and Asian populations. Cathepsin Z expressed in early phagosomes, the adaptor of toll-like receptor signalling MAL (TIRAP), complement receptor 1 (CR1 or CD35) or intracellular pathogen resistance (Ipr1), which appears to foster macrophage apoptosis and confers resistance to Mtb, have been found to play a role in polymorphism or defects leading to increased risk for active tuberculosis in single studies [26]. Recent studies in Korean patients have shown that micro satellite polymorphism in intron II of the human toll-like receptor 2 gene is associated with the development of tuberculosis disease [27]. Finally, autoantibodies directed against IFNγ have recently been associated with the infection of 3 patients with non-virulent mycobacteria [28].

Lung immunity and HIV

Selective depletion of CD4 lymphocytes is a hallmark of HIV infection, which destroys CD4 lymphocytes by its own cytopathic effects. T cells of HIV-infected individuals have an impaired production of IL-2 and of IFNγ [29]. These cells can also be targeted by antibodies directed against the protein gp120.

Monocytes and macrophages have CD4 receptors and can therefore be infected by HIV. HIV infection of monocyte / macrophages reduces the cells' chemotaxis as well as the use of their Fc and C3 receptors, which in turn hinders their recruitment and their ability to clear bacteria. However, their production of superoxide and TNF appears to be preserved. As mentioned above, DCs can be infected and can disappear due to the cytotoxic effect of lymphocytes targeting them or to the cytopathic effect of HIV itself. The number of DCs is decreased in asymptomatic HIV-infected individuals and in patients with AIDS, but more importantly, they are also functionally impaired [30].

Pulmonary disease may occur in HIV-infected individuals as a result of a CD8 T cell influx into the lungs, clinically diagnosed as lymphoid interstitial pneumonitis. Late in the course of HIV infection, the number of CD8 T cells declines. Depletion of CD8 T cells may be associated with the development of cytomegalovirus and mycobacterial infections.

HIV infection also impairs the functional capacities of CD8 T cells. CD8 T cells obtained from the lungs of HIV-infected individuals do not lyse appropriate targets *in vitro*.

Antibody responses to specific antigens are impaired in HIV-infected individuals. B cell abnormalities begin early in HIV infection with failure to produce antibodies in response to mitogen at the time of HIV seroconversion, before T cell function is affected [29].

New vaccinal and immunomodulatory approaches

The combination of antigens provided by "natural" pathogens may not be suitable to induce a specific and efficient immune defence. Indeed, it has been demonstrated that Mtb produces at least one potent antigen (19 Kd lipoprotein), which induces an immune response that actually weakens defences against infection in an animal model. Other attenuated mycobacteria have so far not shown better protective efficacy than BCG itself.

DNA vaccination has an impressive effect in mice but not in humans so far, and the risk of triggering autoimmunity has not been cleared up to date. A gene vector carrying the genetic information directly into the antigen-presenting cells could greatly improve the efficacy of DNA vaccination. Both adenoviral and lentiviral vectors achieve efficient gene transfer to human dendritic cells and are therefore considered as potential vaccine vectors. However, the efficacy of these viral gene vectors must be weighed against safety concerns, which are even more relevant in prophylactic vaccination than in gene therapy [32]. Recently, immunisation against Mtb was achieved in mice, reducing infection and wasting, using dendritic cells retrovirally transduced with mycobacterial antigen 85A gene, and eliciting a specific cellular immunity including cytotoxic T lymphocyte activity specific to an epitope on antigen 85A [31].

Plasmid and replication defective adenovirus vectors encoding IL-23 greatly stimulated defences against aerosolised Mtb in murine models. Interleukin-23 is a heterodimeric cytokine that shares IL-12 p 40, but contains a unique p19 subunit similar to IL-12 p 35. Il-23 increases T cell response like IL-12, as shown by elevated levels of IFNγ and IL-17. IL-23 gene delivery in the lung is well tolerated in these models and also opens new therapeutic avenues [33].

The use of biodegradable plastic microspheres can help target antigen-presenting cells and thereby enhance the immune response involving cytokines or DNA vectors.

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