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Innate and Acquired Response on Tuberculosis

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Abstract

Tuberculosis (TB) is a leading cause worldwide of human mortality attributable to a single infectious agent; nevertheless, the infection of human organism with Mycobacterium tuberculosis (Mtb) doesn't lead to disease obligatory, by all means. Recent studies have revealed numerous polymorphisms implicated in host susceptibility to TB. Human organism may have an innate resistance to MTB. A hallmark of Mtb infection is the ability of most (90-95%) healthy adults to control infection through acquired immunity, in which antigen specific T cells and macrophages arrest growth of Mtb bacilli and maintain control over persistent bacilli. Mtb induces vigorous immune responses, yet evades host immunity, persisting within phagosomes of the infected macrophages. Each stage of the host response to Mtb is under genetic control, including the initial encounter with MTB by macrophages, epithelial cells and dendritic cells in the lung, induction of the inductive T cell response, and killing by activated macrophages within granulomas. Thus there is an innate resistance of the human organism to Mtb - and it is a main reason why TB, potentially lethal disease, doesn't destroy all mankind. Mtb itself stimulates acquired response on TB that improves the resistance of the human organism. Special vaccines increase this resistance too. Medical science may help to reinforce both innate and acquired response on TB, nevertheless, genetical predisposition plays important role.

Keywords: Tuberculosis; Immunity; Innate response

Introduction

Tuberculosis (TB) is a leading cause worldwide of human mortality attributable to a single infectious agent [1]; nevertheless, the infection of human organism with Mycobacterium tuberculosis (Mtb) doesn't lead to disease obligatory, by all means. Recent studies have revealed numerous polymorphisms implicated in host susceptibility to TB. Human organism may have an innate resistance to Mtb. Object lesson of this fact was "Lubeck disaster". Between 10 December 1929 and 30 April 1930, 251 infants born in the old Hanseatic town of Lubeck received three doses of BCG vaccine by the mouth during the first ten days of life. Of these 251, 72 died of TB, most of them in two to five months and all but one before the end of the first year. In addition, 135 suffered from clinical TB but eventually recovered; and 44 became tuberculin-positive but remained well. The vaccine used was later found to have been contaminated with a human tuberculosis strain being studied in same lab [2]. Mtb equally infected all children– and some of them died, some of them–got sick with clinical TB, and 17.5% remained healthy, because they had good innate resistance to TB.

A hallmark of Mtb infection is the ability of most (90-95%) healthy adults to control infection through acquired immunity, in which antigen specific T cells and macrophages arrest growth of Mtb bacilli and maintain control over persistent bacilli. In addition to $CD4^+$ T cells, other T cell subsets such as, gamma delta, $CD8^+$ and CD1-restricted T cells have roles in the immune response to Mtb. A diverse T cell response allows the host to recognize a wider range of mycobacterial antigens presented by different families of antigen-presenting molecules, and thus greater ability to detect the pathogen [3].

Mtb Induced Response on TB

Mtb induces vigorous immune responses, yet evades host immunity, persisting within phagosomes of the infected macrophages. Toll-like receptors (TLRs) play an essential role in the recognition of Mtb components by macrophages and dendritic cells, resulting in not only activation of innate immunity but also development of antigen-specific adaptive immunity. Induction of early death of the infected cells may be one of the strategies of host defense against Mtb because macrophages go into apoptosis upon infection with Mtb, resulting in suppression of the intracellular replication. IFN-gamma also plays an important role in protection. The cytokine that is produced from NK cells and dendritic cells at the early period of infection strongly induces not only macrophage activation but also development of antigen-specific IFN-gamma-producing $CD4^+$ T cells. Since antigen-specific $CD8^+$ T cells and CD1-restricted T cells are also reported to contribute to the protective immunity, cooperation of these T cells is essential for the host resistance [4].

Genetic Control of Acquired Response on Tuberculosis

Each stage of the host response to Mtb is under genetic control, including the initial encounter with Mtb by macrophages, epithelial cells and dendritic cells in the lung, induction of the inductive T cell response, and killing by activated macrophages within granulomas. Although environmental factors are important determinants of progression to disease, there is a genetic component underlying susceptibility to TB, the basis of which may vary in different populations [5]. Activation of the P2X7 receptor, an ATP-gated Ca^{2+} channel, leads to the activation of phospholipase D, and the induction of apoptosis with death of the infecting Mtb. Macrophages from subjects who are heterozygote, homozygote or compound heterozygote for these polymorphisms fail to undergo apoptosis and show partial or complete inhibition of mycobacterial killing. One of these non-functioning polymorphisms was significantly associated with increased susceptibility to TB disease, particularly extrapulmonary disease [6].

It was hypothesized that macrophages from individuals with different clinical manifestations of TB would have distinct gene expression profiles and that polymorphisms in these genes may also

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be associated with susceptibility to TB. Gene expression profiles in Mtb-stimulated and unstimulated macrophages was compared and identified 1,608 and 199 genes that were differentially expressed by >2- and >5-fold, respectively. These results suggest that genome-wide studies can provide an unbiased method to identify critical macrophage response genes that are associated with different clinical outcomes and that variation in innate immune response genes regulate susceptibility to TB [7].

Cellular and Proteins Immune Response on TB

Phagocytosed Mtb either multiply inside the endocytic compartment of mononuclear phagocytes or they are destroyed by the host cell, so TB is controlled by the cellular immune response. Protection against Mtb depends on alpha/beta T-cells expressing the CD4 or CD8 phenotype. T-cell-mediated immunity amplifies macrophage capacities to kill and digest the bacilli. Specific alpha/beta T-cells produce several cytokines that attract and activate macrophages and additional lymphocytes, such as: interferon-gamma (IFN-gamma) which has the capacity to activate several antimicrobial properties of macrophages; tumour necrosis factor-alpha (TNF-alpha) a key cytokine involved in granuloma formation; interleukins 2, 6 and 8 (IL-2; IL-6 and IL-8); and interleukin 12 (IL-12), a candidate cytokine for the induction of Th1 cells. Furthermore, $CD4^+$ and $CD8^+$ T-cells display cytotoxic activity, which permits them to control mycobacterial growth through destruction of the infected cells. Escaping bacteria are subsequently ingested and destroyed by surrounding macrophages activated by T-cells. There is evidence to associate gamma/delta T-cells with antimycobacterial immunity, such as their preferential accumulation in inflammatory lesions, in necrotic areas of tuberculous lymphadenitis, and potent *in vitro* stimulation by Mtb components. In addition, Mtb activated gamma/delta T-cells are cytolytic and secrete several cytokines. Hence, clinical tuberculosis is associated with T-cell reactivity which controls the local concentrations of tubercle bacilli [8].

In TB-induced response participate several types of proteins: macrophage receptors, such as the mannose receptor (MR, CD206), dendritic cell-specific ICAM-3-grabbing nonintegrin (DC-SIGN, CD209), Dectin-1, Toll-like receptors (TLRs), complement receptor 3 (CR3, CD11b/CD18), nucleotide oligomerization domain 1 (NOD1) and NOD2, CD14, P2X7, and the vitamin D nuclear receptor (VDR); soluble C-type lectins, such as surfactant protein-A (SP-A), SP-D, and mannose-binding lectin (MBL); phagocyte cytokines, such as tumor necrosis factor (TNF), interleukin-1β (IL-1β), IL-6, IL-10, IL-12, and IL-18; chemokines, such as IL-8, monocyte chemoattractant protein 1 (MCP-1), RANTES, and CXCL10; and other important innate immune molecules, such as inducible nitric oxide synthase (iNOS) and solute carrier protein 11A1 (SLC11A1). Polymorphisms in these genes have been variably associated with susceptibility to TB among different populations [9,10]. In most of the clinical cases of TB, the production of IL-12, IL-18 and IFN-gamma is increased, however, the group of relatively lower cytokine production did not respond well to the treatment. In addition, the plasma level of one of the chemokines, IP-10, was shown to be an indicator for the severity of the disease [11,12].

Pathognesis of TB Infection

Most common route of transmissions of Mtb is respiratory one, when infectious can be spread by coughing, sneezing, laughing, singing, or just talking. Also are possible alimentary transmission–usually through milk from ill cows; direct and indirect physical contact, including sexual; iatrogenic transmission with BCG instillation for bladder cancer therapy; transplacental transmission (unusual); blood transmission through a mosquito bite (extremely rarely) [13]. Figures 1 and 2 show a case of skin TB.

Independent of the route of infection Mtb is spread by bloodstream and lymphatic system throughout the body (so-called primary dissemination). Of course, direct contact more often leads to the skin TB, alimentary route–to intestinal TB, prostate TB may be a cause of a genital TB in sexual partner etc. But after respiratory contamination lungs may by intact, and kidney or lymphonodal TB develops, as well as TB meningitis after alimentary contamination is possible [14,15].

Since the main route of entry of the causative agent is the respiratory route, alveolar macrophages are the important cell types, which combat the pathogen. There are various aspects of macrophage-mycobacterium interactions. The role of macrophage in host response such as binding of Mtb to macrophages via surface receptors, phagosome-lysosome fusion, mycobacterial growth inhibition/killing through free radical based mechanisms such as reactive oxygen and nitrogen intermediates; cytokine-mediated mechanisms; recruitment of accessory immune cells for local inflammatory response and presentation of antigens to T cells for development of acquired immunity is very important. The macrophage apoptosis in containing the growth of the bacilli as well as other components of innate immune response such as natural resistance associated macrophage protein, neutrophils, and natural killer cells play the role too. The specific acquired immune response through CD4 T cells, mainly responsible for protective Th1 cytokines and through CD8

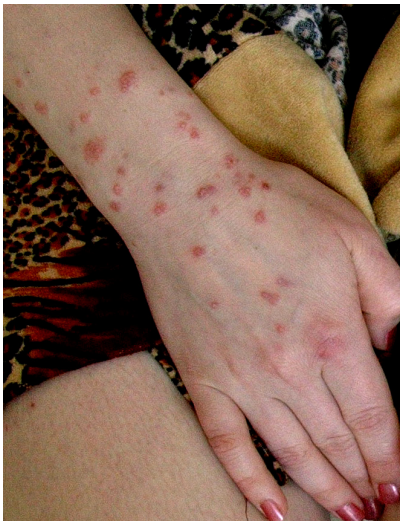

Figure 1: Young woman with skin TB.

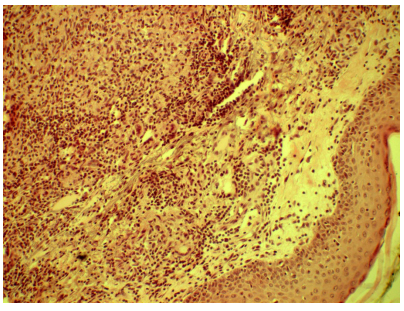

Figure 2: Cutaneous TB. Confluent epithelioid granulomata are in all layers of derma. x200, Hematoxylin and eosin

cells bringing about cytotoxicity, also has been described. Humoral immune response is seen though not implicated in protection. Mtbs are endowed with mechanisms through which they can evade the onslaught of host defense response: diminishing the ability of antigen presenting cells to present antigens to CD4(+) T cells; production of suppressive cytokines; escape from fused phagosomes and inducing T cell apoptosis [16].

The Role of Macrophages and Apoptosis

Alveolar macrophages (AMs) are exposed to frequent challenges from inhaled particulates and microbes and function as a first line of defense with a highly regulated immune response because of their unique biology as prototypic alternatively activated macrophages. Lung collectins, particularly surfactant protein A (SP-A), contribute to this activation state by fine-tuning the macrophage inflammatory response. During short-term (10 min-2 h) exposure, SP-A's regulation of human macrophage responses occurs through decreased activity of kinases required for proinflammatory cytokine production. However, AMs are continuously exposed to surfactant, and the biochemical pathways underlying long-term reduction of proinflammatory cytokine activity are not known. Exposure of human macrophages to SP-A for 6-24 h upregulates expression of IL-1 receptor-associated kinase M (IRAK-M), a negative regulator of TLR-mediated NF-κB activation. In contrast to TNF-α and IL-6, the surfactant components upregulate LPS-mediated immunoregulatory IL-10 production, an effect reversed by IRAK-M knockdow [17].

Microarray analysis of infected human alveolar macrophages found serine protease inhibitor 9 (PI-9) to be the most prominently expressed of a cluster of apoptosis-associated genes induced by virulent Mtb. Inhibition of PI-9 by small inhibitory RNA decreased Mtb-induced expression of the antiapoptotic molecule Bcl-2 and resulted in a corresponding increase in production of caspase 3, a terminal effector molecule of apoptosis. Thus PI-9 induction within human mononuclear phagocytes by virulent Mtb serves to protect these primary targets of infection from elimination by apoptosis and thereby promotes intracellular survival of the organism [18].

Mtb interacts with macrophages and epithelial cells in the alveolar space of the lung, where it is able to invade and replicate in both cell types. Both virulent and attenuated Mtb induce apoptosis in macrophages; however, the attenuated strain–H37Ra resulted in significantly more apoptosis than the virulent strain H37Rv after 5 days of infection. In contrast, cytotoxicity of alveolar cells was the result of necrosis, but not apoptosis. Although infection with Mtb strains resulted in apoptosis of 14% of the cells on the monolayer, cell death associated with necrosis was observed in 59% of alveolar epithelial cells after 5 days of infection. Infection with Mtb suppressed apoptosis of alveolar epithelial cells induced by the kinase inhibitor, staurosporine. Mtb can modulate the apoptotic response of macrophages and epithelial cells. Inhibition of replication of intracellular bacteria resulted in an increase in apoptosis in both cell types: macrophages and alveolar epithelial cells [19]. Anti-apoptotic Bcl-2, Mcl-1, Bfl-1 and Bcl-xL in the cells were significantly upregulated following infection with K-strain (belongs to the Beijing family, is the most frequently isolated clinical strain of Mtb in Korea) compared with H37Rv, whereas Bax was slightly upregulated in response to infection with both H37Rv and K-strain. The highly virulent K-strain keeps cellular apoptosis as a host defense mechanism to a minimum and induces necrosis in macrophages [20].

Mtb and *M. avium* replicate in human macrophages and induce apoptosis. Incubation of freshly added uninfected autologous macrophages with apoptotic *M. avium*-infected macrophages results in 90% inhibition of bacterial growth. Apoptosis also prevents the release of intracellular components and the spread of mycobacterial infection by sequestering the pathogens within apoptotic bodies. Consistent with the model that host cell apoptosis is a defense mechanism against mycobacteria is the finding that the virulent Mtb strain H37Rv induces substantially less macrophage apoptosis than the attenuated strain H37Ra [21].

The Role of the Lung Epithelium during TB

Lung epithelial cells (A549) were used as a model in which to examine cytotoxicity during infection with either virulent or avirulent mycobacteria in order to further establish the role of the lung epithelium during TB. Infection of A549 cells with Mtb strains Erdman and CDC1551 demonstrated significant cell monolayer clearing, whereas infection with either Mycobacterium bovis BCG or *Mycobacterium smegmatis* LR222 did not. Clearing of Mtb-infected A549 cells correlated to necrosis, not apoptosis. Treatment of MBT-infected A549 cells with streptomycin demonstrated a significant reduction in the necrosis of A549 cell monolayers [22].

Coculture of PBMC from TB patients with neutralizing antibodies to TGF-beta or TNF-alpha decreased spontaneous (P<or=0.05) and Mtb-induced (P<or=0.02) T-cell apoptosis by 50-90%, but effects were not additive. During TB, predisposition of CD4 T-cells to apoptosis may involve both low expression of Bcl-2, and excessive expression of TGF-beta TNF-alpha and FasL [23].

Other Factors of Acquired Response on TB

Granulysin is an important defensive molecule expressed by human T cells and NK cells and has a cytolytic activity against microbes including Mtb and tumors. Expression of 15kD (15K) granulysin protein and mRNA in CD8 positive T cells in the patients infected with drug sensitive TB or MDR-TB. *M. tuberculosis* was lower than that in the healthy volunteers, suggesting that granulysin treatment might improve the TB disease in human [24].

CK are potent leukocyte activators and chemoattractants and participate in granuloma formation, functions critical for the immune response to Mtb. It was hypothesized that infection of AM with different strains of Mtb elicits distinct profiles of CK, which could be altered by human immunodeficiency virus (HIV) infection. Macrophage inflammatory protein-1 alpha (MIP-1 alpha), and MIP-1 beta were the major beta-CK produced in response to MTB infection. Virulent Mtb (H37Rv) induced significantly less MIP-1 alpha than did the avirulent strain (H37Ra), while MIP-1 beta production was comparable for both strains. MIP-1 alpha and MIP-1 beta were induced by the membrane, but not cytosolic, fraction of Mtb. Mtb-induced CK secretion was partly dependent on tumor necrosis factor alpha (TNF-alpha). MIP-1 beta suppressed intracellular growth of Mtb two-to threefold. Thus, beta-CK contribute to the innate immune response to Mtb infection [25].

Infection with Mtb is accompanied by an intense local inflammatory response which may be critical to the pathogenesis of TB. Activation of components of the innate immune response, such as recruitment of polymorphonuclear (PMN) and mononuclear phagocytes and induction of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-alpha), by Mtb occurs early after Mtb infection, however, may persist as the organism establishes itself within granulomas. Mtb and its protein and non-protein components are potent in induction of cytokines and chemokines from PMN and monocytes [26].

Mtb survive inside macrophages by manipulating microbicidal functions such as phago-lysosome fusion, production of reactive oxygen species and nitric oxide, and by rendering macrophages non-responsive to IFN-gamma. Mtb-infected lung tissue does however not only contain macrophages, but also significant numbers of infiltrating polymorphonuclear neutrophils (PMN). These are able to phagocytose and kill ingested Mtb, but are short-lived cells that constantly need to be removed from tissues to avoid tissue damage. Engulfment of Mtb-induced apoptotic PMN by macrophages initiates secretion of TNF-alpha from the macrophages, reflecting a pro-inflammatory response. Moreover, Mtb-induced apoptotic PMN up-regulate heat shock proteins 60 and 72 (Hsp60, Hsp72) intracellularly and release Hsp72 extracellularly. Both recombinant Hsp72 and released Hsp72 enhanced the pro-inflammatory response to both Mtb-induced apoptotic PMN and Mtb. This stimulatory effect of the supernatant was abrogated by depleting the Hsp72 with immunoprecipitation [27].

In addition to direct bactericidal activities, such as phagocytosis and generation of reactive oxygen species (ROS), neutrophils can regulate the inflammatory response by undergoing apoptosis. Infection of human neutrophils with Mtb induces rapid cell death displaying the characteristic features of apoptosis such as morphologic changes, phosphatidylserine exposure, and DNA fragmentation. Both a virulent (H37Rv) and an attenuated (H37Ra) strain of Mtb were equally effective in inducing apoptosis. Pretreatment of neutrophils with antioxidants or an inhibitor of NADPH oxidase markedly blocked Mtb-induced apoptosis but did not affect spontaneous apoptosis. The Mtb-induced apoptosis was associated with a speedy and transient increase in expression of Bax protein, a proapoptotic member of the Bcl-2 family, and a more prominent reduction in expression of the antiapoptotic protein Bcl-x(L). Phagocytosis of Mtb-induced apoptotic neutrophils markedly increases the production of proinflammatory cytokine TNF-alpha by human macrophages [28].

Nitric oxide (NO), synthesized from l-arginine by NO synthases, is a small, diffusible, highly reactive molecule with dichotomous regulatory roles under physiological and pathological conditions. NO can promote apoptosis (proapoptosis) in some cells, whereas it inhibits apoptosis (antiapoptosis) in other cells. This complexity is a consequence of the rate of NO production and the interaction with biological molecules such as iron, thiols, proteins, and reactive oxygen species. Long-lasting production of NO acts as a proapoptotic modulator. However, low or physiological concentrations of NO prevent cells from apoptosis induced by trophic factor withdrawal, Fas, TNFalpha, and lipopolysaccharide [29].

The slow growth and chronic nature of Mtb infection result in prolonged exposure to antigens, and hence further T cell sensitization. To survive in macrophages, Mtb has evolved mechanisms to block immune responses. These include modulation of phagosomes, neutralization of macrophage effector molecules, stimulating the secretion of inhibitory cytokines, and interfering with processing of antigens for T cells. The relative importance of these blocking mechanisms likely depends on the stage of Mtb infection: primary infection, persistence, reactivation or active tuberculosis. The balance of the host-pathogen interaction in Mtb infection is determined by the interaction of T cells and infected macrophages. The outcome of this interaction results either in control of Mtb infection or active disease [3].

Acquired Response on TB in Co-morbid Patients

Any co-morbidity makes worse the response on TB. The association of Mtb with monocytes was significantly lower in diabetics than non-diabetics (p=0.02). Poorly-controlled type 2 diabetes mellitus was significantly associated with the lower interaction of Mtb with monocytes [30,31].

Human macrophages represent the first line of defense for the containment of Mtb infection. After phagocytosis, macrophages express activation surface markers and produce proinflammatory cytokines and chemokines whose main role is to control pathogen spreading by recruiting peripheral lymphocytes and monocytes at the site of inflammation. However, in the case of a concomitant human immunodeficiency virus (HIV) infection, these signals strongly enhance the susceptibility to viral infection both at the viral entry and replication levels. Under these conditions, viral expansion extends beyond tissue macrophages to T cells and vice-versa, according to the emerging viral phenotype. In absence of an efficient immune response, Mtb can replicate in macrophages in an uncontrolled fashion culminating in macrophage death by apoptosis. As a consequence, a more severe form of immunedepression, involving both innate and specific immune responses, could be responsible for both ematogenous mycobacterial dissemination and extrapulmonary form of TB in HIV-infected patients [32]. During HIV/TB, systemic immune activation is dissociated from microbial translocation. Changes in circulating sCD14 and LPS are dependent on CD4 T-cell count [33]. Expression of CycT1 in response to Mtb was assessed in mononuclear cells from pleural fluid (PFMC) and blood (PBMC) from HIV/TB patients with pleural TB, and in blood monocytes (MN) from singly infected HIV-1-seropositive subjects. Higher expression of CycT1 mRNA in PFMCs as compared to PBMCs from HIV/TB-coinfected subjects was found [34]. Concomitant intestinal helminth infection in TB patients had a negative impact ($P < 0.05$) on absolute frequencies of CD3(+), CD4(+), CD8(+), natural killer (NK) T and CD4(+) CD25(high) T cell subsets when compared to either TB patients or healthy controls. In addition to a depressed anti-Mtb immunity, TB+Helm patients also presented with more severe radiological pulmonary disease, with a significant difference (P=0.013) in the number of involved lung zones at the end of TB treatment [35].

Vaccines against TB Infection

To improve an acquired response on TB a special vaccine were created. Infection of human monocytes with *M. bovis* BCG induced macrophage inflammatory protein (MIP)-1alpha and MIP-1beta secretion in a dose-dependent manner. The ability of *M. bovis* BCG to produce CC-chemokines might lead to protection in the acquired immune response of mycobacterial infection [36]. The BCG was initially administered as a live oral vaccine. This route of administration was stopped in 1930 following the Lübeck (Germany) disaster. The intradermal route of administration was later found to be safe for mass vaccination, through studies conducted in the 1930s [37]. Okada has developed a novel TB vaccine; a combination of the DNA vaccines expressing mycobacterial heat shock protein 65 (HSP65) and interleukin 12 (IL-12) delivered by the hemagglutinating virus of Japan (HVJ)-liposome or-envelope (HSP65+IL-12/HVJ). This vaccine provided remarkable protective efficacy in mouse and guinea pig models compared to the BCG vaccine, on the basis of an induction of the CD8 positive CTL activity against TB antigens and improvement of the histopathological tuberculosis lesions, respectively. The ELISPOT assay showed that HSP65+IL-12 DNA/HVJ vaccine induced a greater number of IFN-gamma producing T cells than BCG in the mouse model [38]. This vaccine also provided therapeutic efficacy against multidrug resistant TB (MDR-TB) and extremely drug resistant TB (XDR-TB) in murine models [39-41].

Also recombinant virus-vectored TB vaccine was developed. A recombinant replication-deficient adenoviral (Ad) vector was engineered to express Mtb Ag85A. Single administration of this Ad vaccine via the intranasal route provided potent immune protection from pulmonary Mtb challenge. Respiratory mucosal boosting immunization with Ad vaccine was effective in enhancing T-cell activation and immune protection following parenteral DNA or BCG prime immunization [42,43].

Guinea pigs immunized with extracellular proteins (EP) and then challenged with aerosolized Mtb exhibit protective immunity: they were consistently protected against clinical illness, including weight loss. Actively growing Mtb release immunoprotective molecules extracellularly, that a subunit vaccine against TB is feasible; extracellular molecules of Mtb are potential candidates for a subunit vaccine [44].

Conclusion

Thus, there is an innate resistance of the human organism to Mtb– and it is a main reason why TB, potentially lethal disease, doesn't destroy all mankind. Mtb itself stimulates acquired response on TB that improves the resistance of the human organism. Special vaccines increase this resistance too. Medical science may help to reinforce both innate and acquired response on TB, nevertheless, genetical predisposition plays important role.

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