
The Immune Response to *Mycobacterium tuberculosis* Infection in Humans

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1. Introduction

The microbe *Mycobacterium tuberculosis* (MTB) is an ancient cohabiter with humans, infecting almost 3 billion people worldwide, 10% of them developing clinical disease. The 20th century dream of eradicating the global scourge of tuberculosis (TB) evaporated with the failure of the old BCG vaccine to protect the populations at greatest risk, low compliance at following the complicated and lengthy treatment in countries with limited resources, which was followed by the spread of multiple-drug resistant (MDR) strains. Actually the situation has worsened with a peak of 9.4 millions of new clinical cases in 2009 and 1.7 million deaths/year [1,2,3].

However, it is intriguing to observe that the incidence and morbidity of the disease varies greatly in different regions of the globe, being highest in Africa and Asia, as well as the response to BCG vaccination [1,4]. That, in spite of the fact that there are no structurally variable strains of MTB, therefore all have a similar virulence capacity. One important factor is the introduction of the human immunodeficiency virus (HIV) into areas and populations already having a high TB incidence [5], the resulting double infections having a disastrous effect. This is especially prominent in sub-Saharan Africa. But that factor alone can not explain the global epidemiological variability in the disease. Also, why only one in ten carriers of the microbe become clinically sick?

In order to address these questions, in the present chapter we will try to delve into the intricacies of the human immune response to MTB infection and to explore possible differences in the genetic regulation of the host immune responses in various human populations.

2. The encounter of Mtb with the innate immune system

Most human infections with MTB occur through inhaled carrier droplets into the lower airways. There the microbe encounters the alveolar macrophage (AMac) and submucosal

dendritic cell (DC). The outcome of the ensuing battle will determine whether the infection will remain locally limited within the engulfing cells of the innate immune system, or will continue to spread, causing the individual to become a clinically active TB patient [1,6,7,8]. During the first contact, the AMac recognizes the microbe through pattern recognition receptors (PRRs), which sense microbial biochemical components, such as outer coat mannose-sylated lipoarabinomannan (ManLam), trehalose dimycolate and N-glycolymuramyl dipeptide. These molecules act as pathogen-associated molecular patterns (PAMPs), which trigger an intracellular signaling cascade in the AMac, which leads to a phagocytic activity, which, if successful, will result into the complete engulfing of the microbe into cytosolic vesicles- the phagolysosomes and secretion of pro-inflammatory cytokines, such as tumor-necrosis factor alpha (TNF α). ManLam also binds directly to mannose receptors on macrophages and DCs.

The best studied PRRs are Toll-like receptors (TLRs) [6,9,10], of which 10 have been identified in humans. TLR- 2 and TLR-4 recognize bacterial products [9,11], TLR-2 having a major role in recognizing MTB in the lung. All contain an intracellular TIR domain, the activation of which initiates a signaling cascade via adapter proteins such as MyD88, interferon-inducing TRIF and TRIF-related adapter molecule TRAM, which results in the recruitment of interleukin-1(IL-1) receptor-associated kinase (IRAK) 4, which phosphorylates IRAK-1. The latter binds to TNF α receptor-associated factor (TRAF) 6, leading to kinase-dependent I κ B α phosphorylation, the degradation of which leads to the activation of nuclear NF- κ B, which is the main nuclear activator of proinflammatory cytokines. Another intracellular PRR is nucleotide-binding oligomerization domain 2 (NOD2), which binds bacterial cell-wall muramyl-dipeptide, eliciting secretion of TNF α , IL-1 β , IL-6 and bacterial LL-37 [12,13]

Neutrophils also play a defensive role, not only as first-line non-specific phagocytes, but also by secreting anti-bacterial proteins, mainly the cathelicidin LL-37 [1,14]. Neutrophils loaded by phagocytized bacteria become apoptotic, thereby eliciting macrophage activation [15].

NK cells, which are large granular circulating lymphocytes, are attracted to the sites of bacterial infections, where they specialize in recognizing and destroying infected host cells. During this process they secrete interferon gamma (IFN γ), which activates macrophages, inducing them to secrete the cytokines IL-12, IL-15 and IL-18, which activate CD8+T-cells, thus forming the link to the adaptive immune system [7,16]

The complement is the humoral arm of the innate immune system. It has been shown that *M. bovis* BCG may activate the three pathways of complement: the classical pathway by binding to the C1q protein, the lectin pathway by binding to the bacterial cell surface mannose-binding lectin (MBL) or L-ficolin and the alternate pathway through the deposition of C3b on the bacterial surface. Mtb can activate the classical and alternate pathways by binding C3. This enables complement to perform its major functions-microbial opsonization, microbial cell lysis through the formation of the attack complex and leukocyte recruitment by eliciting chemokine secretion [7,17].

Another recently discovered anti-microbial mechanism of phagocytic cells is the use of vital transition metals, such as iron, zinc and copper, to poison intracellular microorganisms. However, mycobacteria have developed a resistance mechanism to such intoxication [18,19].

This contrasts with the function of the phagosomal metal transporter natural resistance-associated membrane protein (NRAMP) 1 to deprive the microorganisms from essential nutrients, such as iron and manganese [20]. Such duality existing in the same cell is of interest.

Virulent Mtb's have acquired the capability to dampen the activity of NF- κ B by some of their antigens [6,7], such as ESAT-6 and ManLAM. The latter also inhibits the secretion of IL-12, an essential cytokine in the anti-MTB inflammatory response. ESAT-6 downregulates MyD88-IRAK 4 interaction, thereby also interfering with TLR signaling to NF κ B. A third antigen-CFP-10 markedly reduces nitric oxide (NO) and reactive-oxygen species (ROS) production by the macrophages, thereby inhibiting their non-specific killing ability. The microbe may also regulate macrophage apoptosis to its advantage and to inhibit IFN γ - mediated macrophage activation [7]. ESX is a recently discovered protein transport system through the outer membrane of the microbe, which is essential for its survival. It has been demonstrated, in an experimental model, that ESX-5 may modulate macrophage reactivity by dampening the inflammasome activation [21]. These mechanisms enable the microbe to survive in the macrophage phagosome in a balance which is precarious to the host. In addition Mtb may escape the phagolysosome into the cytosol by damaging its membrane. Most recently it has been described that the microbe may secrete toxins, such as the newly discovered MtpA protein, through its outer membrane into the macrophage cytosol, which may cause the death of the later by cell necrosis [22].

Vitamin D seems also to play an important role in the microbe-host pull-of-arms [23]. It may modulate the inflammatory effect of some metalloproteinases (MMPs) in the lung [24] and Vitamin D supplementation has hastened bacterial eradication in pulmonary tuberculosis in a clinical trial [25].

Thus, the encounter between MTB and the various components of the innate immune system induce a complicated and sophisticated series of host responses and counter responses by the microbe. The later is one of the most ancient human infections, carried by our ancestors since they fanned-out from Africa across the globe, therefore enabling it to adapt to the human immune response (26-Cole S, Tuberculosis in time and space, Econference).

However, the next long-term phase of the encounter is played by the activation of the adaptive immune system, as described in the next section.

3. The role of adaptive immunity in the outcome of the Infection

In the previous section the importance of the host innate immune response in the encounter with MTB was described. However, it is generally accepted that the long-term outcome of the primary infection is determined by the effective mobilization of the adaptive immune response. Active TB patients, as well as latently infected carriers, do not suffer from a general innate or adaptive immune defect. On the contrary, ex-vivo studies of their immunocyte function demonstrate increased lymphocyte proliferation and the secretion of numerous cytokines [27]. Thus the disease, in people generally healthy, is a result of a very specific immune failure in face of MTB, or other mycobacteria.

It was thought that the CD4+T cell is the omnipotent determinant of the adaptive immune response in TB. However, lately it became clear that more T-cell subsets, including CD8+ and TH17 cells and even B cells participate in the process [1,7,28]. The induction phase seems to be delayed relatively to the response to more common pathogens. It is initiated by signaling and presentation of the microbial peptides by the macrophages and DCs to the CD4+ cells via MHC class II molecules, while mycobacterial membranal lipids are presented through MHC-I molecules of the CD-1 family [29]. The presentation of mycobacterial antigens occurs within the draining lung lymph-nodes to which the macrophages have migrated, followed by the activation of CD4+ and other T cells. These T cells use various receptors, such as TLRs, NOD-like receptors and C-type lectins, for this purpose. The peptides considered as potentially immunodominant are the already mentioned ESAT-6 and CFP10 and others, such as Rv2031c, Rv2654c and Rv1038c. The T cell response to these antigens is not homogenous, various T cell epitopes being engaged during the different phases of the infection [30]. Other Rv proteins are binding to T cells mainly during the latent phase [31]. T cell activation, by the recognition of these antigens in the initiating phase, results in the secretion of numerous cytokines, mostly proinflammatory, such as IL-1 β , IL-6, IL-21 and IL-12p40. The later activates CD4+TH1 cells, but p40 is also a subunit of IL-23, which induces the TH17 cell lineage, which secretes IL-17, IL-21 and IL-22. These cytokines are considered to be essential for anti-microbial protection and IL-17 is thought to have a major role in granuloma formation [32], as well as TNF α , which is also secreted by CD4+ cells and promotes intra-phagosomal killing of the bacteria in macrophages. During an acute mycobacterial infection $\gamma\delta$ T cells secrete much IL-17 [33], which also promotes the secretion of IL-12, thus a self-enhancing inflammatory loop is being formed. This is balanced by the secretion of TGF β , the role of which is to dampen an over-reactive inflammatory response, partly so by inducing T-reg cells. The later may inhibit TH1 responses, thus potentially facilitating mycobacterial replication within macrophages [34]. A high incidence of T reg Foxp3 cells has been found in extra-pulmonary TB [35].

The activated T cells undergo clonal expansion and migrate out of the lymph nodes into the site of the infection in the lung, as effector T cells. This process is driven by chemokines, secreted by various inflammatory cells. Upon arrival to the battle ground they secrete interferon gamma (IFN γ), which is a key cytokine in the ensuing confrontation, by further activating the microbicidal machinery of the macrophage and causing it to secrete IL-18, amongst other cytokines, which seems to be part of the protective TH1 type response. IFN γ also induces the production of toxic NO via inducible NO synthase (iNOS). Casanova et al [36,37,38] have described in detail the importance of the IFN γ -IL-12 cytokines loop, including their receptors, for TB immunity. Furthermore they have described rare Mendelian genetic defects in this system, resulting in susceptibility to serious mycobacterial and sometimes salmonellar infections.

CD8+ T cells also participate in the immune reaction, as they have been found in the mediastinal lymph nodes, mixed with CD4+ cells and later at the infection site in the lungs. Most evidence about them has been collected in mouse and primate models and their role in human infections has not been fully elucidated [7]. It has been demonstrated in vitro that CD8+ cells recognize bacterial peptides and lipids through the MHC-I CD-1 mol-

ecules, which induce a cytotoxic response toward the bacteria and to the phagocytes in which they reside. They also secrete $\text{IFN}\gamma$ and $\text{TNF}\alpha$. Humans with latent TB develop a high level of mycobacteria-specific CD8^+ T cells [39].

From all the above it is clear that the dominant protective response in TB is Th1 type. However in multiple-drug resistant (MDR) [40] and in young children [41] there is a skewing towards a Th2 type response, with greater secretion of IL-4. This may explain why children tend to develop pulmonary milliary and extrapulmonary disease. In addition it seems that the disease in children tends to have a Mendelian heritability of specific defects, while in adults there is no such background, rather some discrete polymorphisms may be found in different populations, such as in the natural resistance-associated macrophage protein 1 (NRAMP1) [42].

For a long time it was generally accepted that B-cells and specific antibodies have no protective role against TB. However monoclonal antibodies against some mycobacterial antigens have shown a clear protective effect in mice [43]. It has been postulated that the unique phenomenon of BCG protection against pediatric TB meningitis may be due in part to specific antibodies. Presently the exact role of B-cells in human TB remains to be determined.

Similarly to the innate immune system, mycobacteria have also developed evasion tactics from the adaptive immune system [44]. They may interfere with the antigen presentation process, promote the secretion of IL-10 by T cells, thereby polarizing them toward a TH2 type response, in which the essential $\text{IFN}\gamma$ secretion is inhibited [7]. They may also attract more T-reg cells to the infection site, thereby further dampening the protective inflammatory response. It was demonstrated in a tuberculosis rabbit model, that mycobacteria may delay the macrophage and T-cells activation process, thereby enabling them to form a permanent infection and damaging pulmonary tissue [45]. More specifically, the bacteria possess a set of genes- *rpf*, which code for the regulatory Rpf proteins, which are believed to be responsible for activating bacteria from a dormant state in latency. In addition the bacteria have also a set of "anti-dormancy genes"-*DosR*, which induce bacterial growth, when appropriate [46].

4. The tuberculous granuloma

The formation of granuloma is the host's containment effort in response to an infection which he can not eradicate. In most cases it results in a state of latency, with dormant, but viable, bacteria residing in it [7, 45, 47]. Therefore the granuloma benefits also the bacteria, who may emerge from dormancy, proliferate again and cause an active disease, if the host's immune system is weakened due to any reason. HIV coinfection, with its damage to T cells, has become the most prominent example of this situation.

The granuloma contains a nucleus of necrotic lung tissue and intraphagosomal bacteria-containing macrophages, surrounded by fibroblasts, DCs, neutrophils, B cells and various subsets of T cells, all of those secreting cytokines, mainly $\text{IFN}\gamma$ and $\text{TNF}\alpha$, and chemokines which ensure a continuous mobilization of granulocytes to the granuloma. $\text{TNF}\alpha$ activates adhesion molecules on the immunocytes [48]. Thus the granuloma is a dynamic and continu-

ous battlefield balancing the bacteria against the immune system. Occasionally, as described before, the bacteria may damage the phagosomal membrane and escape, inducing an apoptotic or necrotic death of the macrophage. This enables the bacteria to proliferate with enhancement of tissue damaging inflammation, which may result in cavity formation.

5. Shall we ever have an effective immunotherapy or anti-TB vaccine?

Application of highly effective vaccines across the globe is the only way to control and arrest the spread of infectious diseases. So far BCG is the only available anti-TB vaccine. It is one of the oldest vaccines and has remained unchanged for a long time. It does confer reasonable protection to infants at risk and prevents pediatric TB meningitis. However it is ineffective for protection of large adult populations and has failed to prevent the rise in new infections and active disease patients and especially in MDR and extreme drug resistant (XDR) cases [49]. Therefore many efforts have been invested in trying many forms of various extracts of other mycobacteria, such as *M. vaccae*, which may be considered as immunostimulants of TH1 responses or a kind of vaccines. Most have resulted in a transient enhancement of the anti-tuberculous inflammatory response, sometimes with severe side-effects, but without long-term clinical benefit [50]. How can this be explained?

The main reason is that decades of research have not, as yet, demonstrated a universal clearly immunodominant and protective T cell epitope to one of the bacterial antigens—mainly to cell-wall peptides, lipids or glycolipids. An exception may be the 85A and 85B antigens, which may be suitable candidates for a widely used anti-tuberculous vaccine under various constructs [51]. They show enhancement of TH1-type responses, but long-term clinical results are still unknown. Additional vaccines are under trials, such as MTB subunit and DNA preparations [52].

In addition there is the problem in the variability of the host immunogenetic response, both to BCG and to MTB [53]. Therefore various research projects are trying to identify, already mentioned, polymorphisms in immune-associated and other genes, which may increase or decrease the susceptibility to TB, such as the one which has been recently identified in a Moroccan population [54] and another one in a Chinese ethnic group [55]. This subject lies outside of the scope of this chapter, but it may lead to a better understanding of the processes determining the fate of a MTB infection and assist in designing better vaccines, although they may need to be population-targeted.

6. Summary

It has been attempted, in the present chapter, to describe in some detail the arms race between MTB and its ancient human host, who uses the full scope of his sophisticated innate and adaptive immune mechanisms to placate the enemy. The bacteria, which succeed to break the physical barriers in the respiratory tract and reach the lung, are immediately surrounded by residing

DCs and AMa, which recognize the bacterial PAMPs with their PRRs, such as surface TLRs. This recognition triggers DC and macrophage activation, which results in the phagocytosis and internalization of the bacteria in the phagolysosome, where they are submitted to toxic lysis. Meanwhile the macrophages emigrate to the mediastinal lymph nodes, where the bacterial lipid and peptide molecules are presented to CD4+ and CD8+ T cells via MHC-I and MHC-II, causing T cell activation and clonal proliferation. The later return to the battlefield at the site of the lung infection and try to complete bacterial elimination, by intensifying local inflammation. To achieve that, the T cells and the macrophages secrete a series of cytokines, such as IFN γ , IL-12 and TNF α . Secreted chemokines attract more inflammatory cells, such as neutrophils.

Nevertheless, 90% of infected persons, who remain clinically asymptomatic, enter the stage of latency, in which they continue to harbor dormant, albeit viable, bacteria in their macrophages and 10% develop active clinical disease. This is due to numerous evasion tactics from the immune system, that MTB has developed during its long cohabitation with the human host. The bacterium may damage the phagosomal membrane and escape into the macrophage cytosol, inducing necrotic cell death. It may interfere with the signaling to T cells via MHC molecules, downregulate the secretion of IFN γ , promote the secretion of IL-10 and the activity of CD4+Foxp3 T reg cells, thus dampening the protective inflammatory response. A hallmark of the latency stage is granuloma formation, which is a complex structure, containing a core of dormant bacteria in necrotic tissue, surrounded by neutrophils, macrophages, DCs and T cells. This precarious balance may be easily disrupted, if, for whatever reason, immune surveillance is weakened, causing bacterial breakthrough and clinical relapse.

So far, BCG is the only antituberculous vaccine widely available, which does confer a measure of protection in children, but failed to arrest the spread of the infection in adult populations. Many centers around the world are trying to identify immunodominant bacterial epitopes, which could form the basis of a universal efficacious vaccine. So far, the 85A and 85B antigens, in various constructs, seem to be presently the most promising, at least in animal models and limited clinical trials. In addition, since the beginning of the 20th century, many mycobacterial formulations and lately also cytokines, have been tried as specific immune stimulants. In most cases they did induce generalized inflammation with significant side-effects, but with little clinical benefit. However, recent technological developments, such as recombinant preparations and DNA extracts, may obtain better results. To those have to be added numerous projects trying to unravel the immunogenetic susceptibility or resistance factors.

One may estimate that within a decade, or so, better anti-tuberculous vaccines and treatments will be developed, possibly targeted to specific populations.

Author details

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