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Chapter 3

Regulation of the Immune Response by *Mycobacterium tuberculosis* Beijing Genotype

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1. Introduction

Tuberculosis (TB) is an old infectious disease that has affected humans for millennia [1]. This disease is caused by infection with bacilli belonging to the *Mycobacterium tuberculosis* (Mt) complex and is responsible for 1.3 million deaths around the world, making TB the second leading cause of death by infectious disease caused by a single pathogen. In addition to this high number of deaths, a large proportion of individuals present latent TB infection (LTBI): it is estimated that at least one third of the human population could have LTBI [2]. Why more than 90% of the individuals infected with Mt do not develop the active form of the disease is unclear, although the immune status of the individual seems to play a crucial role for Mt containment [3]. This is evident in individuals with Human Immunodeficiency Virus co-infection, who are more prone to develop active TB: a quarter of TB deaths occur in individuals co-infected with HIV [2].

However, other factors are associated with TB development, such as the host environment and the genetic diversity of Mt. This genetic diversity has been organized into genotypes and lineages, according to the genetic profiles obtained by techniques such as IS6110 fingerprinting, spoligotyping and mycobacterial interspersed repetitive units-variable number of tandem repeats (MIRU-VNTR). Interestingly, these genotypes show a differential distribution around the world and exhibit different levels of virulence [4]. One of the genotypes that has attracted more attention in recent years is the Beijing family, because it is highly prevalent among TB
patients, it favours the spread of multidrug-resistant tuberculosis, and it has been suggested that BCG vaccination confers poor protection against it [5].

It is not clear why the Beijing genotype prevails in infected individuals. One factor that could be responsible for this phenomenon is the interaction that Mtb Beijing establishes with the immune response. In this chapter, we analyze and discuss current knowledge regarding the cellular and molecular mechanisms of the immune response to Mtb, and how these mechanisms are affected by the Beijing genotype in relation to human infections.

2. Immune response to *Mycobacterium tuberculosis*

Mtb can enter the body through several routes, but the most usual one is through the airways [6]. This process is initiated by the release of small saliva droplets containing Mtb bacilli that are expelled by active TB patients [7]. Some droplets are small enough to cross the mucociliary barrier and reach the alveoli, where they interact with the first cellular element of the immune response, the alveolar macrophage [8]. Macrophages are armed with a vast array of innate immune receptors that allow direct recognition of Mtb; these receptors include Toll-like receptors (TLR), Nod-like receptors (NLR), C-type lectin receptors (CLR) and scavenger receptors [9]. After recognition, macrophages ingest bacilli by phagocytosis, but they are unable to kill them due to the evolutionary mechanisms acquired by Mtb that actively inhibit phagosome maturation and protect Mtb from destruction by toxic compounds, such as reactive nitrogen and oxygen intermediates and hydrolytic enzymes from lysosomes; these mechanisms allow intracellular Mtb survival and proliferation [10, 11].

In addition to this intracellular proliferation, Mtb also induces a strong inflammatory response, characterized by macrophage production of cytokines like TNF-α, IL-1β and IL-6, which promote the recruitment of more macrophages from the blood [12]. The recruited macrophages are able to ingest bacilli but, like alveolar macrophages, they are unable to eliminate the ingested Mtb. The continuous recruitment of macrophages during these early stages provides a constant supply of cells susceptible to infection, as well as an increase of inflammatory signals that induces the recruitment of more susceptible cells from the blood, without causing significant tissue damage. At the same time, lung resident dendritic cells (DCs) engulf bacilli or their derived products; the inflammatory environment promotes DCs migration from the lungs to the draining lymph nodes, where they activate Mtb antigen-specific naïve T cells and induce a strong T cell response characterized by proliferation and activation of Mtb antigen-specific CD4+ and CD8+ T cells [13]. These T cells travel through the blood and are recruited to the infection site by the ongoing inflammatory process.

Upon recognition of the infected macrophages, T cells produce significant amounts of TNF-α and IFN-γ, the cytokines that characterize a Th1 response. TNF-α and IFN-γ increase the microbicidal mechanisms of the infected macrophages, which eventually leads to the intracellular killing of Mtb. Macrophage activation can be limited by the secretion of IL-4, IL-10 and TGF-β produced by Th2 and T regulatory (Treg) cells [14-16]. The Th1 response, however, does not lead to a complete elimination of Mtb, but to the formation of an organized cellular
structure, the granuloma, where live mycobacteria persist in a dormant state known as latent infection [17]. The structure of the granuloma varies, but usually its center is formed by caseum, a structure that contains abundant remains of dead cells and forms a hypoxic, acidic and lipid-rich environment that limits extracellular Mtb proliferation. The caseum is limited by highly activated macrophages (multinucleated Langhans cells and foamy macrophages) surrounded by CD4+ and CD8+ T cells [18]. While the host immune response is unaffected, the granuloma structure is preserved and Mtb is contained within; however, the alteration of crucial elements of the immune response, such as the decrease of CD4+ T cells during HIV infection or the blockade of TNF-α by therapeutic antibodies, causes disorganization of the granuloma structure, caseum liquefaction and oxygen access, which promotes Mtb extracellular proliferation and dissemination into the airways, from where Mtb can reach susceptible hosts [19-21] (Figure 1).

Figure 1. Development of the immune response to Mycobacterium tuberculosis. The main four stages of the immune response to Mycobacterium tuberculosis (Mtb) are depicted. Macrophages are the first component of the cellular immune response that is encountered by Mtb (top left); they are used by Mtb to replicate and to induce an inflammatory response that allows the recruitment of more macrophages susceptible to infection. Dendritic cells (top right) carry Mtb antigens from the infection site to the draining lymph nodes, to activate antigen-specific T cells. The mycobacterial granuloma (bottom right) plays a fundamental role in Mtb containment. Alterations in the dynamic equilibrium of the granuloma (bottom left) promote disorganization and access of extracellular Mtb to oxygen, which allows its replication and dissemination through the airways.
3. *Mycobacterium tuberculosis* Beijing genotype

Because Mtb strains present over 99% of similarity at their nucleotide sequence level and have identical sequences of their 16S RNAs [22, 23], for several years it was thought that they were genetically homogeneous and lacked genetic diversity. However, the development and use of different genetic tools for the study of Mtb revealed greater diversity. Studies that analyzed repetitive DNA elements in Mtb led to the discovery of high polymorphism in several strains. The study of restriction fragment length polymorphism (RFLP) in IS6110 allowed van Soolingen et al to identify a group of strains, isolated in Beijing, Mongolia, South Korea and Thailand, which shared a unique RFLP pattern. Since the majority of these strains came from Beijing, they became known as the “Beijing family”. Further genetic characterization showed that all these strains shared an identical spoligotyping of the direct repeat (DR) region, and similar patterns of polymorphic GC-rich sequence (PGRS) as well as an IS1081 restriction fragments [24]. Mtb strains with these genetic characteristics were later found outside the Southeast Asian region, in Russia, Spain, the United States, Cuba, Peru, Colombia, Iran, Israel and South Africa [5, 25].

Beijing strains were classified as “typical”, if they presented one or more IS6110 insertions in the noise transfer function (NTF) region, or “atypical”, if they lacked this insertion [26, 27]. Analysis of large sequence polymorphisms (LSP) indicated that Beijing strains could be divided into four different lineages, depending on the presence of RD105, RD142, RD150 and RD181 [28]. Further studies, using PCR to analyze 40 different loci in Beijing strains, showed that this group could also be divided into seven different sub-lineages, thus revealing great genetic diversity in this group [29].

4. Clinical importance of *Mycobacterium tuberculosis* Beijing genotype

In addition to the high prevalence of Beijing strains in the Southeast Asian region, Beijing strains have been associated with outbreaks in different parts of the world. The strains that were responsible for a TB outbreak in New York in the 1990’s were from the Beijing genotype, and they were more frequent in patients co-infected with HIV, reaching a mortality rate of more than 80%. Interestingly, strains from this outbreak had multidrug resistance to isoniazid, rifampicin, streptomycin, ethambutol, ethionamide, rifabutin and kanamycin, favouring treatment failure [30-32]. Later studies showed the global emergence of this genotype in different parts of the world [25, 33, 34].

Several epidemiological studies have documented the hyper-virulence of the Beijing genotype. For example, patients infected with Beijing strains have increased rates of treatment failure and relapse [35-39]. In line with these studies, Kong et al showed that patients infected with Beijing strains developed more extra-thoracic TB than patients infected with other genotypes [40]. Other studies demonstrated that individuals infected with strains from the Beijing genotype were more likely to progress to active TB [41, 42] and had increased drug resistance [43, 44]. Furthermore, patients infected with these strains were younger than patients infected
with other genotypes [45], and they developed febrile responses in earlier stages of treatment [46]. Moreover, infection with Beijing strains was associated with HIV co-infection [47] and BCG vaccination [48]. However, others have been unable to find an association between infection with Beijing strains and the aforementioned clinical manifestations of the disease [38, 45, 49-54].

Few studies focused on the immune response have been conducted in patients infected with Beijing strains. Sun et al found that the sera of patients infected with Beijing and non-Beijing strains had similar levels of IFN-γ and IL-18, while peripheral blood mononuclear cells (PBMCs) expressed similar mRNA levels for IFN-γ, IL-2, IL-18. However, patients infected with Beijing strains had decreased levels of IL-4 [55]. In contrast with these results, Rakotosamimanana et al observed that PBMCs from patients infected with the “modern” Mtb strains from Beijing and Central Asia produced less IFN-γ in response to ESAT-6 than PBMCs from patients infected with other genotypes [56]. These results suggest that Mtb Beijing genotype could induce an altered immune response that could favor infection by these strains.

5. Effects of Mycobacterium tuberculosis Beijing genotype on the immune response: in vivo models

The first evidence of the hyper-virulence of the Mtb Beijing genotype came from studies with different mouse models of infection. Manca et al showed that the Beijing strain HN878, isolated from cases from an outbreak in Texas, led to higher bacterial loads in the lungs and to accelerated death in immune-competent mice, compared to a non-Beijing strain. Moreover, the lymph node and spleen cells from HN878-infected mice showed decreased proliferation and IFN-γ production after in vitro re-stimulation, suggesting a defective induction of a Th1 response because of the early induction of type I IFN by HN878 [57, 58]. Later studies showed that the decrease in the Th1 response was associated with the induction of Treg cells in mice and also in guinea pigs, an animal model that resembles human tuberculosis [59, 60]. Intracisternal infection of rabbits with Mtb leads to the development of tuberculous meningitis. In this model of infection, the Beijing strains HN878 and W4 led to higher bacterial loads in the cerebrospinal fluid and brain, increased dissemination to the lungs and liver, earlier leukocytosis, increased levels of TNF-α during the later stages of the infection, and severe clinical manifestations, compared to the low-virulence strain CDC1551 [61].

López et al reported that three Beijing strains, representing the predominant genotypes in Asia, were hyper-virulent in a mouse model of progressive pulmonary tuberculosis, compared to other genotypes (Somali, Haarlem, Canetti and H37Rv). This hyper-virulence was reflected as an increased number of bacteria in the lungs and a rapid death of the mice infected with the Beijing strains. The mice infected with the Beijing strains had altered immune responses: they expressed TNF-α and iNOS in their lungs during the early stages of the disease, but had a defective production of iNOS and IFN-γ during the later stages of the infection [62]. Further studies associated this phenomenon with a decrease in Th1 cells caused by apoptosis and with a defective cytotoxicity, indicative of a deficient CD8+T cell response [63, 64]. A more recent
report with the Beijing strain K1, isolated in Korea, showed that this strain is hyper-virulent, and the lungs of infected mice had a decreased production of Th1 and Th2 cytokines [65]. The hyper-virulence of the Beijing strains was also observed when they were compared to East African-Indian strains in mice [66].

However, Dormans et al showed that hyper-virulence is not associated with all the Beijing strains. He observed that strain 9402008, isolated from Asia, caused little lung pathology, bacterial load and mortality in mice [67]. Furthermore, Aguilar et al showed that Beijing strains isolated in South Africa, which presented low transmissibility in humans, were less virulent than the Beijing strains that were highly transmissible [68]. The highly transmissible Beijing strains caused an early induction of TNF-α and delayed IL-4 production, as well as defective induction of IFN-γ and iNOS in the lungs during the later stages of the disease, compared to the low-virulence Beijing strains [68]. This difference in virulence among Beijing strains was also observed in a mouse model of infection with seven Beijing strains isolated in Vietnam [69], and in guinea pigs infected with ten Beijing strains isolated in the USA. Interestingly, the lungs of these guinea pigs also showed differential patterns of T cell infiltration and cytokine production: virulent strains induced less IFN-γ during the later stages of the infection, compared to low-virulence strains [70]. A more recent study showed that heterogeneity in virulence was also observed in mice infected with Beijing strains isolated from Brazil and Mozambique [71].

From these in vivo experiments, it is clear that hyper-virulence is not a unique characteristic that applies to all the strains from the Beijing genotype. However, all the hyper-virulent strains from the Beijing group share a common characteristic: they are able to interfere with the Th1 response that is crucial for infection containment, favoring the dissemination of bacilli in the lung and an increased pathology.


6.1. Macrophages

Several studies have analyzed the ability of the Beijing strains to replicate inside macrophages and to induce cytokine production by these cells. One of the first studies that showed a differential response of macrophages to the Beijing strains was performed in human macrophages. The Beijing strain 210, isolated in the USA, grew faster in human macrophages than other Mtb strains tested, but there were no differences among the strains regarding the induction of TNF-α, IL-6, IL-10 or IL-12 [72]. A faster intracellular replication of the bacilli in human macrophages was also observed with four different Beijing strains [73]. In contrast with these results, Manca et al showed that human monocytes infected with the Beijing strain HN878 produced increased mRNA levels for IL-4, IL-11, IL-13, type I IFN, TRAIL and VEGF, compared to monocytes infected with the low-virulence strain CDC1551 [74], and our group reported that the hyper-virulent Beijing strain 9501000 induced higher expression of IL-1β,
Crevel et al found that, in Indonesian patients, the polymorphism D453N G and an insertion in the 3'untranslated region (UTR) of the \textit{slc11a1} gene (formerly known as \textit{nramp1}) were strongly associated with Beijing strains infection \cite{122}; polymorphisms in this gene (which codes for an iron transporter in macrophages) have been associated with TB susceptibility \cite{123}. Salie et al documented an association between MHC class I alleles and infection with Beijing strains in South Africans, where the allele B*07:05 increased the odds of infection with Beijing strains, while the allele B*35:01 had the opposite effect. Interestingly, B*07:05 is a frequent allele in East Asian populations \cite{124}. MHC class I molecules are essential for antigen presentation to CD8+T cells, which are needed for the containment of Mtb infection \cite{125}. These studies provide evidence of a co-evolution between Beijing strains and their hosts.

9. Conclusion

Mtb Beijing genotype has attracted attention because of its high prevalence among TB patients, but despite multiple studies, the causes of this success remain obscure. An interesting aspect of Mtb Beijing genotype infection is the diversity of the immune responses that are induced in humans and in experimental models (\textit{in vivo} and \textit{in vitro}). It is possible that this diversity results from the adaptation of Mtb Beijing genotype to the genetic background of its hosts and to other evolutionary pressures, such as drug treatment, BCG vaccination and HIV co-infection. These factors, and others still unknown, will shape the strategies used by Beijing strains to override the immune response and to establish successful infections in the host.

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