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Inflammation and Immunopathogenesis of Tuberculosis Progression

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1. Introduction

Approximately one third of the human population is infected with *Mycobacterium tuberculosis (Mtb)*. Most individuals establish latent infection. In approximately 10% of infected individuals active disease develops (Raviglione, 2003). It is accepted that the outcome of infection largely depends on the peculiarities of host immune reactivity that are controlled genetically.

A lot of efforts have been made to elucidate immune mechanisms of TB defense. The studies have identified immune cells, molecules and pathways essential for TB protection. It has been demonstrated that protection depends primarily on the activity of Th1 lymphocytes and macrophages (Schluger & Rom, 1998; Flynn & Chan, 2001; Boom et al., 2003; North & Jung, 2004; Kaufmann, 2006). Th1 cells produce immune mediators, such as IFN-γ and TNF-α that activate macrophages. Activated macrophages produce bactericidal molecules (e.g., reactive nitrogen and oxygen species) that kill mycobacteria. Both macrophages and T cells secrete a wide range of soluble factors that promote migration of other immune cells to the site of infection. At the site, immune cells settle to form granuloma that prevents mycobacteria dissemination. Overall, immune protection depends on efficient pathogen killing (i.e., antibacterial response) and efficient concentration of immune cells at the site of infection (i.e., inflammatory response). Multiple studies have demonstrated that deficiency in cells and molecules implicated in either of these responses results in extremely severe TB, supporting a concept that TB develops as a result of immune deficiency. On the other hand, since Koch's studies, TB has been considered as an immunopathological disease. In this concept, disease develops due to uncontrolled inflammatory reactivity of the host to the pathogen. Direct evidences for this concept had not been available, but are now accumulating, raising a general question on the role for immune deficiency and hyperreactivity in the pathogenesis of tuberculosis.

As noted above, the outcomes of *Mtb* infection are very diverse. The diversity consists not only in the establishment of latent infection *vs* progression to active disease, but also in a great variability in the manifestations of active disease. These manifestations differ by the type and the extent of lung tissue pathology, clinical disease characteristics, the rate of disease progression, and patient's responsiveness to treatment. Immune mechanisms operating during the onset of *Mtb* infection and during active disease differ. In particular,

inflammatory response is prerequisite for efficient control of *Mtb* at initial stages of the infection, but may become deleterious at chronic stage of disease. While mechanisms of initial TB control have been studied extensively, pathogenesis of TB progression is much less understood.

This review summarizes recent studies on TB immunopathogenesis focusing on the role for host inflammatory response in TB progression.

2. *Mtb* infection and host immune response in the lungs

2.1 Cellular immune responses to *Mtb* infection

Before considering processes ongoing during TB progression, it is important to summarize current view of the onset of pulmonary *Mtb* infection.

Mycobacteria enter the lungs trough the respiratory tract. Following the inhalation, the bacilli are phagocytosed by alveolar macrophages (AM) and airway dendritic cells (DC). Infected cells migrate to distal sites of the lung and undergo necrosis allowing *Mtb* to enter parenchyma and infect parenchymal phagocytes. Pattern recognition receptors (PRRs) expressed by macrophages, DC and epithelial cells (both on the surface and within the cell) interact with *Mtb* ligands (reviewed in detail in Kleinnijenhuis et al., 2001; van Crevel et al., 2002; Dorhoi et al., 2011; Sasindran & Torrelles, 2011). The interaction drives host cells to enhance the expression of adhesion molecules and produce inflammatory cytokines and chemokines that recruit new immune cells (i.e., neutrophils, monocytes, lymphocytes) to the infectious focus. The accumulating cells initiate formation of granuloma (reviewed in detail in van Crevel et al., 2002; Russel et al., 2009; Flynn et al., 2011).

Infected DC assisted by neutrophils (Abadie et al., 2005; Blomgran & Ernst, 2011) migrate to the lymph nodes and initiate T cell response. Due to a high production of IL-12, the response is largely polarized towards a Th1 type. Th1 cells generated in the lymph nodes migrate to the site of mycobacterial infection.

At the site, effector Th1 cells undergo functional maturation (Kapina et al., 2007) and increase their production of chemokines and effector cytokines. Chemokines attract new immune cells, amplifying local inflammatory DTH-type reaction and promoting granuloma formation. The cytokines IFN-γ and TNF-α activate adjacent macrophages (Schluger & Rom, 1998; Flynn & Chan, 2001; Pearl et al., 2001). Activated macrophages produce reactive nitrogen and oxygen intermediates (RNI, ROI), enhance surface expression of MHC class II molecules and increase secretion of inflammatory mediators, i.e. acquire ability to kill *Mtb*, enhance antigen presentation and propagate local inflammation and granuloma formation.

Besides macrophages and $CD4^+$ Th1 cells, other immune cells accumulate at the infectious focus. $CD8^+$ T cells produce IFN-γ and may exhibit cytotoxic effect against *Mtb*-infected cells (Lalvani et al., 1998; Cooper, 2009); Th17 cells promote Th1 immunity and neutrophil recruitment (Khader & Cooper, 2008); granulocytes phagocyte mycobacteria, mediate bactericidal effect, and contribute to granuloma formation (Korbel et al., 2008; Rivas-Santiago et al., 2008); B lymphocytes together with T cells form follicular structures (so-called "tertiary lymphoid tissues") that orchestrate immune response ongoing in the lungs

(Ulrichs et al., 2004). NK cells, unconventional T lymphocytes, regulatory T cells are also attracted (Cooper, 2009).

Overall, TB protection is achieved by two major mechanisms: *Mtb* killing that, ideally, stops the infection, and formation of granulomas that prevents *Mtb* dissemination. Both processes depend upon proper functioning of sets of surface receptors and soluble factors that provide immune cell activation, migration and effector activity. Factors essential for the current review are briefly discussed below.

2.2 Molecular mediators of immune response

Innate immune cells recognize *Mtb* ligands by a set of PRRs that include Toll-like receptors (TLRs), C-lectin type receptors (CLRs), scavenger receptors (SRs), immunoglobulin Fc receptors (FcRs), NOD-like receptors (NLRs) (reviewed in detail in van Crevel et al., 2002; Sasindran & Torrelles, 2011; Dorhoi et al, 2011). Ligation of PRRs induces gene expression, primarily the expression of genes for early response cytokines IL-1β, TNF-α, IL-6. All, IL-1β, TNF-α and IL-6 promote further activation of macrophages (Kishimoto, 2005). In addition, IL-1β is highly chemotactic for T lymphocytes, stimulates $CD4^+$ T cell proliferation and IFN-γ production, controls early processes of granuloma formation, and stimulates the generation and the recruitment of neutrophils (Hunninghake et al., 1987; Sugawara et al., 2001; Miller et al., 2007; Oliveira et al., 2008; Ueda et al., 2009). TNF-α is critical for the continued organization of the granulomatous lesions (Kindler et al., 1989; Flynn et al., 1995; Bean et al., 1999; Roach et al., 2002) and has immunoregulatory propereties (Orme & Cooper, 1999; Motoo et al, 2009). IL-6 modulates T- cell response, is essential for antibody formation, and stimulates hematopoiesis, in particularly, the myeloid lineage (Liu et al, 1997; Kishimoto, 2005; Walker et al., 2008). All three cytokines may cause severe pathology. They have been implicated in microvascular thrombosis, capillary leak and neutrophilic chemotaxis, produce organ dysfunction, systemic inflammation, acute-phase response, cachexia and fever (Tracey et al., 1987; Hernandez-Pando et al., 1994; Chang & Bistrian, 1998; Bekker et al., 2000; Agriles et al., 2005; Oliveira et al., 2008).

Chemokines are secreted by macrophages, neutrophils, T lymphocytes, endothelial cells and other local cells. CC chemokines CCL2, CCL3, CCL4, CCL5, and other attract monocytes, lymphocytes, macrophages, DC, NK cells to the site of infection and favor Th1 response. CXC chemokines CXCL10 (IP-10) and CXCL9 (MIG) are produced in response to IFN-γ and attract predominantly T-lymphocytes and monocytes, propagating T cell response. CXC chemokines CXCL8 (IL-8), CXCL2 (MIP-2) and CXCL1 (KC) are mainly chemotactic for hematopoietic stem cells and granulocytes and are responsible for neutrophilic inflammation at advanced stages of TB (Rhoades et al., 1995; Sasindran & Torrelles, 2011).

A separate set of molecules mediate *Mtb* killing. IFN-γ activates macrophage for *Mtb* killing. Granzymes and perforin mediate cytotoxicity of $CD8^+$ T cells and NK cells. ROI and RNI, defensins, cathelicidin, proteases and other bactericidal molecules produced by IFN-γ-activated macrophages and by neutrophils mediate *Mtb* killing (Flynn & Chan, 2001; van Crevel et al., 2002; Rivas-Santiago et al., 2008). Of note, these molecules are released not only intracellularly but also extracellularly. Thus, extracellular milieu at the focus of the infection becomes highly inflammatory containing multiple mediators that are not present in healthy lungs and that potentially are highly deleterious. During active TB, cytokines,

chemokines and other mediators released by immune cells, as well as activated immune cells themselves, are found not only at the focus of the infection, but also in the bronchoalveolar fluid (BAL) and in the circulation where they may mediate systemic inflammatory response.

2.3 Granuloma in TB protection and pathology

It is generally assumed that formation of granuloma represents a host strategy to contain the infection and limit pathogen dissemination. However, granulomatous response is observed not only in individuals with latent infection, but also in TB patients, including patients with extremely severe and rapidly progressing TB. Thus, it was suggested that a mere formation of granuloma is not enough to prevent TB, rather it is important how "proper" granuloma is functioning (Flynn et al., 2011).

In humans, granulomas observed during latent infection ("tuberculomas") are usually small, compact, solid and not numerous. They consist of macrophages and lymphocytes and a small amount of neutrophils. A central core contains epithelioid macrophages and a few neutrophils and multinucleated giant cells (Lin et al., 2009). The wall is well organized and contains follicle-like structures, in which proliferating lymphocytes reside (Ulrichs & Kaufmann, 2006). It is believed that such granulomas are able to control the infection and keep *Mtb* in a dormant state (Flynn et al., 2011).

During active disease, the granuloma cannot contain the infection. Immune cells continue to arrive, the granuloma grows and its organized structure disrupts (Ulrichs & Kaufmann, 2006; Russel et al., 2009; Cardona et al., 2011). Macrophages differentiate into epithelioid cells. The neutrophil influx increases and the centrum of the granuloma necrotizes and then caseates resulting in the formation of necrotizing and caseating granulomas. In necrotizing granulomas the central area consists mainly of degenerating neutrophils; in caseating granulomas it is presented by cell debris. The centrum is surrounded by a dense zone of epithelioid macrophages, multinucleated giant cells and lymphocytes (Lin et al., 2009). Eventually, the centrum caseous breaks into the bronchus, releasing bacteria into the respiratory tract and resulting in the formation of cavities. *Mtb* replication goes out of control. It has long been thought that the caseum represents a nutritional site for rapid *Mtb* replication. However, recent data have shown that: (i) many necrotic areas are devoid of *Mtb* (Ulrichs & Kaufmann, 2006), (ii) microbes located in the caseum resemble stationary-phase organisms, whereas replicating *Mtb* are found in sputum and BAL, and in connection with neutrophils (Eum et al., 2010). It is therefore suggested that *Mtb* replication does not occur in the liquefying cavity, but rather starts upon the exit of the bacilli from that cavity into the sputum.

Many questions regarding the functioning of granulomas remain unclear. What is an association between caseation and TB activity? Caseation is often considered as a hallmark of active disease. However, it has been reported that in non-human primates caseation occurs very early in granuloma formation, shortly after macrophages in the lungs become infected, i.e. during the very early, latent stage of the infection. In this model, caseating granuloma could successfully contain the pathogen and did not necessarily proceed to active TB (Lin et al., 2006), suggesting that it is probably the extent of caseation, but not the caseation itself that determines disease activity. Next, caseous (tuberculous) pneumonia is

an example of active TB disease that is not accompanied by the formation of classical granulomas. In this disease, extensive areas of parenchymal infiltration with multiple necrotizing and caseating foci are observed, but these foci are not structured, instead they extend contiguously in the lung parenchyma. Clinical manifestations of caseous pneumonia are extremely severe with evident signs of severe systemic inflammation; but exact pathways underlying the development of caseous pneumonia (*vs* caseating granulomas) are poorly understood. Another important question is whether caseation (either during pneumonia or in granulomas) represents host response to unlimited *Mtb* growth (i.e., is a result of inefficient *Mtb* control) or whether it is a result of "improper" host reactivity to a relatively small number of dormant *Mtb* persisting in early or mature granulomas. Several recent reviews have discussed these questions and suggested hypotheses to explain the development of active TB in non-immunosuppressed patients (Russel, 2009; Cardona, 2009; 2010; Flynn et al., 2011).

3. TB infection in hosts with immune deficiency

A role for immune deficiency in the pathogenesis of *Mtb* infection has been addressed in multiple studies.

In mice, targeted mutations of PRR genes impaired host resistance to *Mtb* (Drennan et al., 2004; Divangahi et al., 2008; Mayer-Barber et al., 2010). Deficiency on PRR adaptor molecules, e.g., MyD88, CARD9, TIR8, resulted in extremely high susceptibility (Garlanda et al., 2007; Dorhoi et al., 210; Mayer-Barber et al., 2010). Lack of "early response cytokines" (i.e., IL-1β, TNF-α, IL-6) or their receptors impaired granuloma formation, cytokine and chemokine synthesis and rendered mice extremely susceptible to *Mtb* infection. (Ladel et al., 1997; Bean et al., 1999; Juffermans et al., 2000; Yamada et al., 2000; Roach et al., 2002; Fremond et al., 2007).

Defects in acquired immunity also led to disease exacerbation. Mice deficient in T cells, (especially, in $CD4^+$ subset) and Th1 type cytokines (i.e., IL-12p40, IFN-γ) succumbed early to *Mtb* infection with high bacterial loads (Cooper et al., 1993; Flynn et al., 1993; 1995; Cooper et al., 1997; Mogues et al., 2001). Similar effects were observed in mice with defects in enzymes involved in the generation of host bactericidal molecules (e.g., iNOS, p47phox (MacMicking et al., 1997; Cooper et al., 2000; Scanga et al., 2001; Jung et al., 2002).

Observations in humans are in line with results obtained in mice. A role for TNF-α in host defense is supported by reactivation of TB in rheumatoid arthritis patients receiving anti-TNF therapy (Keane et al., 2001). An essential role for $CD4^+$ T cells in anti-TB defense is evident from a high incidence of TB and altered histopathological characteristics of TB (i.e., diffuse necrotic lesions instead of structured granulomas) in humans co-infected with immunodeficiency virus (Chaisson et al, 1987). Finally, humans with mutations in molecules involved in Th1 immunity, i.e., the IL-12p40 subunit, the IL-12 receptor β1 chain, the IFN-γ-receptor ligand binding chain, STAT1, exhibit high susceptibility to mycobacterial infections induced by *Mtb*, BCG or environmental mycobacteria (Altare et al., 1998; Dorman et al., 2000; Casanova & Abel, 2002).

Altogether, multiple studies have associated severe *Mtb* infection with immune deficiency and poor control of pathogen growth. This association explains why hosts with genetic or

acquired immune deficiencies suffer from severe mycobacterial infections. However, it cannot explain why active TB occurs in immunologically-competent hosts, or why TB exhibits so many different clinical manifestations.

4. Inflammation and TB progression

Inflammation always accompanies infection and represents a critical component of host immune defense. However, inflammatory reactions may also be deleterious and promote disease exacerbation. The first indication of a damaging role of host immune response during TB was obtained by Koch who described local and systemic reactions and disease worsening following treatment of TB patients with *Mtb* extract (Koch, 1890, as cited in Moreira et al., 2002). Thereafter, multiple observations have associated severe TB course with high inflammatory reactions. However, it is usually very difficult to dissect whether severe inflammation is a cause or a result of disease severity, i.e., whether it develops due to intrinsic host hyperreactivity to the pathogen or whether it mirrors high pathogen load (i.e. deficient *Mtb* control). Gene targeting approach is not very helpful with this respect as the majority of factors mediating inflammation are prerequisite for the development of protection and therefore their targeting or neutralization results in disease exacerbation and masks potential pathological properties. Yet, several experimental settings made this dissection possible. Detailed analysis of theses studies allows identifying immunological features critical for TB progression.

4.1 *Mtb* infection in mice with deficiency in negative regulators of inflammation

Several studies examined the course of TB in mice with deficiency in negative regulators of inflammation. TIR-8 (Toll/IL-1R), a member of the IL-1R family, is an inhibitor of inflammation. The receptor functions by trapping of TNFR-associated factor 6 and IL-1R associated kinase 1 and inhibiting activation of NF-kB induced by members of the IL-1/TLR family (Polentarutti et al., 2003; Garlanda et al., 2007). In *Mtb* infected Tir-8$^{-/-}$ mice control of mycobacteria growth and T cell responses were unimpaired. Nevertheless, the mice were rapidly killed by low doses of *Mtb*. The disease was characterized by overwhelming inflammatory response in the lungs that manifested as increased production of IL-1β and TNF-α and increased lung infiltration with neutrophils and macrophages. Blocking IL-1β and TNF-α with a mix of anti-cytokine antibodies significantly prolonged survival of Tir-8$^{-/-}$ mice supporting that their exaggerated mortality was associated with exacerbated inflammation and tissue damage (Garlanda et al., 2007).

Similarly, mice lacking D6, a decoy and scavenger receptor for inflammatory CC chemokines, had normal control of bacteria replication but responded to *Mtb* infection by uncontrolled systemic inflammation and died from a fatal infection (Di Liberto et al., 2005).

WSX-1, a component of IL-27R complex, is another molecule that plays a regulatory role during *Mtb* infection, mainly by dampening Th1 response. In the absence of WSX-1, *Mtb* infection induced elevated production of the pro-inflammatory cytokines TNF-α and IL-12p40. This led to concomitant activation of CD4 T cells, increase in IFN-γ production and macrophage effector functions. Bacterial loads were reduced, but mortality was accelerated, which was attributed to chronic hyperinflammatory response (Holscher et al., 2005).

4.2 *Mtb* infection in mice with deficiency in positive regulators of inflammation

As discussed above, deficiency in molecules mediating inflammatory signals alters host control of *Mtb* replication and exacerbates *Mtb* infection. Strikingly, even when inflammatory pathways are altered, fatal infection is accompanied by overwhelming inflammation, supporting a concept that TB progression and lethality are associated with hyperinflammatory reactions.

Dorhoi and coauthors (Dorhoi et al., 2010) examined *Mtb* infection in mice that lack CARD9, an adaptor molecule that collects signals from several PRRs. Mice developed a lethal infection accompanied by uncontrolled *Mtb* replication, by besides that – by a severe neutrophilic inflammation of the lung tissue and overproduction of factors involved in granulocyte generation and chemoattraction (i.e., G-CSF, KC). Neutralization of G-CSF or depletion of neutrophils reduced lung inflammation and prolonged host survival without affecting bacterial burdens. Thus, dampening neutrophilic inflammation at advanced stage of disease was enough to decrease disease severity.

Mice with a deficiency in IL-1R developed lethal infection characterized by extremely high numbers of *Mtb* in their lungs. Of note, a characteristic feature of lethal infection was an elevated (but not a deficient) production of major proinflammatory cytokines, e.g., IL-1β, IL-6, TNF-α (Fremond et al., 2007).

Mice deficient in TNF-α or TNF-α receptor developed extremely severe disease due to defects in granuloma formation (Bean et al.,1999). Of note, a characteristic feature of this infection was a prominent infiltration of the lung tissue with neutrophils.

In humans, S180L polymorphism in TIRAP gene implicated in the TLR2- and TLR4-mediated signaling, leads to the attenuation of inflammation and decreases the risk of TB development (Castiblanco et al., 2008).

4.3 Anti-inflammatory treatment improves TB outcome

Several groups examined the possibility to improve TB outcome by limiting immune inflammation. In patients with pulmonary TB, treatment with adjunctive corticosteroid therapy together with antibiotics accelerated sputum culture conversion in comparison with patients who received antibiotic treatment alone (Bilaceroglu et al., 1999). Adjunctive treatment with etanercept, a soluble TNF-receptor, reduced time to sputum culture conversion and improved clinical signs of TB in HIV infected patients (Wallis et al., 2004). Thalidomide, an inhibitor of TNF-α production, improved treatment outcome in patients with pulmonary TB (Tramontano et al., 1995; Coral et al., 1996). Recently, an inhibitory effect of CC-3052, an inhibitor of phosphodiesterase-4, on TNF-α production was shown. Co-treatment of *Mtb* infected rabbits and mice with isoniazid plus CC-3052 significantly reduced the level of TNF-α expression and the extent of disease (Koo et al., 2011; Subbian et al., 2011). As mentioned above, simultaneous blocking of IL-1β and TNF-α significantly prolonged survival of Tir-8-/- mice, and neutralization of G-CSF or depletion of neutrophils decreased disease severity in CARD9-/- mice (Garlanda et al., 2007; Dorhoi et al., 2010). In contrast to anti-TNF treatment, treatment of mice with TNF-α or BCG expressing TNF-α significantly increased lung tissue inflammation and resulted in accelerated mortality without affecting the bacillary load (Moreira et al., 2002). Altogether, the studies show that

dampening immune inflammation during TB may significantly ameliorate disease outcome without affecting *Mtb* replication.

4.4 *Mtb* infection in hosts with genetic differences in the extent of inflammation

Studies reviewed above are largely based on the analysis of TB infection in hosts with artificially altered or modulated immune responses. Such interventions may interfere with processes naturally operating in the infected host. To elucidate whether the extent of inflammation affects TB progression in a "normal" population, several groups have compared immune responses in mice genetically resistant and susceptible to TB. In different models, susceptible mice produced more proinflammatory cytokines and developed stronger neutrophilic inflammation than resistant mice (Cardona et al., 2003; Eruslanov et al., 2004; Eruslanov et al., 2005; Keller et al., 2006). To directly address an association between inflammatory reactions and TB progression, we have recently analyzed TB severity and immune reactivity in a panel of genetically heterogeneous (A/SnxI/St)F2 hybrid mice (Lyadova et al., 2010). The hybrids originated from TB-highly-susceptible I/St and more resistant A/Sn mice that following challenge with *Mtb* displayed different rates of TB progression (Lyadova et al., 2000; Sanchez et al., 2003; Eruslanov et al., 2004). In F2 mice, the rate of TB progression did not depend on lung *Mtb* loads or the levels of lung expression of iNOS, IFN-γ, IL-12, or CCL5, i.e. genes controlling antibacterial response. Instead, it directly correlated with high lung expression of inflammation-related factors, such as IL-1β, IL-6, IL-11, CXCL2, several metalloproteinases. Another characteristic feature of rapidly progressing TB was the accumulation in the infected lungs of Gr-1-positive cells (see below for details). Thus, similarly to gene-targeted mice, in F2 mice severe infection was characterized by: (i) overexpression of proinflammatory factors and (ii) excessive infiltration of the lung tissue with neutrophil-like cells. Further analysis suggested that these manifestations were a consequence of increased transcription of proinflammatory factors in host macrophages and were predetermined genetically (Lyadova et al., 2010).

A role for host genetic factors in the control of inflammation and TB progression was directly demonstrated in the studies by Kramnik's group (Pan et al., 2005; Yan et al., 2007). The authors identified *sst1* genetic loci on mouse chromosome 1 that controls progression of pulmonary TB. Different susceptibility of *sst1* congenic mice to *Mtb* infection was associated with neither Th1 cell activation nor with iNOS/NO responses but was due to different host capacity to mount necrotic lung inflammation and was mediated by macrophages.

4.5 T lymphocytes in TB exacerbation

T lymphocytes are responsible for efficient protection against mycobacteria. However, they may also contribute to TB exacerbation. A series of recent studies performed in programmed death-1 (PD-1) knockout mice has clearly demonstrated that (Lázár-Molnár et al., 2010; Barbar et al., 2011).

PD-1 is an inhibitory receptor expressed on exhausting T cells; its engagement inhibits T cell proliferation and cytokine secretion. PD-1-deficient mice infected with *Mtb* developed unaltered or even increased $CD4^+$ T cell and NO responses. Yet, they died because of severe infection characterized by uncontrolled bacterial proliferation, increased lung tissue pathology, neutrophilic infiltration, and high lung expression of proinflammatory cytokines

TNF-α, IL-1β, IL-6 and IL-17 (Lázár-Molnár et al., 2010; Barbar et al., 2011). Depletion of $CD4^+$ T cells ameliorated TB course, indicating that $CD4^+$ T cells themselves drove the increased bacterial loads and pathology seen in infected PD-1-deficient mice. In contrast to *Mtb* infection, resistance to viral infections was increased in PD-1 deficient mice (Velu et al., 2009). Thus, in TB imbalanced T cell responses are more deleterious than during other infections.

Our observations made in F2 model support the involvement of T cells in TB exacerbation (Lyadova et al., 2010). In this model, susceptible mice displayed first signs of TB progression (i.e., wasting) on day 16 post-challenge and died on days 26-35 post-challenge. Mice that had not succumbed to infection by the end of week 5 survived for as long as 140 days (the time of observation). It is well established that *Mtb*–specific Th1 response appears at week 2 and reaches its plateau at week 4 post-challenge. Thus, the most susceptible F2 mice succumbed to *Mtb* infection at a time when T cell response started to operate; mice that survived this period, lived for a long time. We believe that the onset (or a sudden increase, as in Koch's studies) of T cell response represents a risk factor that may provoke disease exacerbation. The underlying mechanism likely involves T-cell dependent propagation of inflammation mediated by innate immune cells.

The role for T cells in hyperinflammatory reactions and TB exacerbation is also supported by the immune restoration syndrome (IRS) observed in patients co-infected with HIV-1 and *Mtb* and initiating highly active antiretroviral therapy. The syndrome is characterized by the exacerbation of granulomatous lesions and massive inflammatory and Th1 cytokine storm. The syndrom has been associated with a sudden restoration of immune competence, i.e. an increase in the numbers of activated tuberculin-specific effector memory CD4 T cells (Autran et al., 2009).

4.6 Infection induced by *imp Mtb* mutants

Recently, several mutant *Mtb* strains bearing immunopathology (*imp*) phenotype have been generated. The mutants have unaltered capacity to grow and persist in mouse lungs, but induce poor inflammation and attenuated disease. TB-susceptible DBA/2 mice challenged with ΔSigC mutant had decreased mortality associated with lower numbers of neutrophils and reduced levels of TNF-α, IL-1β, IL-6 and IFN-γ in their lungs (Khairul-Bariah et al., 2008). Similar results were obtained when SCID mice were challenged with ΔSigC mutant. whiB3 *Mtb* mutant induced milder disease than wild type *Mtb* strain due to reduced granulomatous inflammation in the lungs (Steyn et al., 2002). ΔSigH *Mtb* mutant produced high bacterial counts in the lungs, but recruited fewer $CD4^+$ and $CD8^+$ T cells and was nonlethal in TB-susceptible C3H mice (Kaushal et al., 2002).

Thus, peculiarities of infecting *Mtb* strain represent another factor that determines TB outcome by affecting inflammatory reactions.

4.7 Inflammatory responses in patients with pulmonary TB

In TB patients, severe infection is also associated with excessive inflammatory reactions. Patients with pulmonary TB have higher levels of proinflammatory cytokines IL-1β, IL-6, TNF-α, IL-8, and their inhibitors TNFRI, IL-1Ra and TGF-β in sera and BAL fluid than

healthy controls and TB contacts (Zhang et al., 1995; Tsao et al., 1999; Tsao et al., 2000; Nemeth et al., 2011). Among TB patients, serum levels of TNF-α and TGF-β are significantly higher in patients with advanced TB compared to patients with mild-moderate TB (Fiorenza et al., 2005). In involved sites of TB, spontaneous release of IL-1β, IL-6 and TNF-α is significantly higher than in uninvolved sites and in miliary TB (Law et al., 1996). Patients with large TB cavity have much higher concentrations of TNF-α and IL-1β than patients who have small or no cavity. Importantly, the ratios of TNF-α to sTNF-RI and IL-1β to IL-1RA in the BAL fluids are also higher in patients with large cavity. Thus, a role for the relative abundance of TNF-α and IL-1β in tissue necrosis and cavity formation was suggested (Tsao et al., 2000).

Besides high levels of proinflammatory factors, a characteristic feature of progressing pulmonary TB is high numbers of granulocytic cells in the BAL fluid (Law et al., 1996; Barry et al., 2008). It was demonstrated that in sputum and BAL fluids of patients with pulmonary TB neutrophils are more abundant and contain more intracellular bacilli than macrophages (Eum et al., 2010).

In summary, hyperinflammatory reaction is a characteristic feature of progressing pulmonary TB in both humans and experimental animals. The reaction manifests as high expression of proinflammatory cytokines and prominent neutrophilic influx to the lung tissue. These manifestations develop irrespectively on exact pathways that have led to severe TB (e.g., defects in host capacity to control *Mtb* growth, host hyperreactivity to pathogen-derived signals, or peculiarities of infecting *Mtb* strain).

Mechanisms whereby proinflammatory cytokines mediate their pathological activity have been studied during different pathological conditions and reviewed in detail elsewhere (Chang & Bistrian, 1998; Thacker, 2006; Mootoo et al., 2009; Argiles et al., 2005). In contrast, data on the role for neutrophils in TB pathogenesis are contradictory and require special consideration.

5. Neutrophils

Physiological activities of neutrophils involve adhesion, migration to the site of inflammation, phagocytosis, degranulation, and release of inflammatory mediators. We will briefly review activities related to TB and discuss the controversial results of the studies that addressed the role of these cells in tuberculosis.

5.1 Functional activities

Neutrophils are among the first cells that arrive at the inflammatory focus (Appelberg & Silva, 1989). The process involves adhesion of circulating neutrophils to the endothelial cells and migration through the endothelial barrier and within the inflamed tissues. Neutrophils' migration is driven by the inflammatory cytokines IL-β and TNF-α, the chemokines IL-8, CXCL2, CXCL1, bacteria products and molecules released by dying cells, i.e. it occurs in response to inflammation and tissue injury (reviewed in Witko-Sarsat et al., 2000).

At the site of infection, neutrophils phagocytoze IgG- and complement-opsonized targets and exhibit bactericidal activity. The later is mediated by the production of ROI and release

of bactericidal molecules stored in neutrophils' granules. ROI include: (i) superoxide anion and hydrogen peroxide generated by NADPH-dependent oxidase; (ii) hypochlorus acid and chloramines, generated by neutrophil-specific enzyme metalloperoxidase. Granule-associated bactericidal molecules are numerous and include short bactericidal peptides (e.g., human neutrophil peptides (HNPs) 1–3, cathelicidin LL-37, lipocalin 2); lactoferrin; serine proteases; metalloproteinases (Witko-Sarsat et al., 2000; Fu, 2003; Martineau, et al. 2007; Rivas-Santiago et al., 2008). Macrophages utilize neutrophil bactericidal peptides to increase their antibacterial activity: they phagocyte apoptotic neutrophils and deploy neutrophils' bactericidal peptides to combat intracellular *Mtb* (Tan et al., 2006).

An additional bactericidal mechanism is formation of extracellular traps (NETs) - a web of chromatin fibers that contain serine proteases and can trap and kill extracellular microbes (Brinkmann et al., 2004).

Neutrophils are involved in the formation of granuloma (Seiler et al., 2003) and in the initiation of T cell response: they were shown to transport live mycobacteria from peripheral tissues to the lymphoid organs and to deliver mycobacterial antigens to DC in a form that makes DC more effective initiators of naïve $CD4^+$ T cell activation (Abadie et al., 2005; Blomgran et al., 2011).

An important activity of neutrophils is a secretion of inflammatory mediators and their inhibitors. The list includes proinflammatory cytokines IL-1β and TNF-α, the major neutrophil attracting chemokines IL-8 and CXCL2, growth factors GM-CSF and VEGF, several metalloproteinases, IL-1Ra, TGF-β (McColl et al., 1992; Cassatella, 1995; Riedel & Kaufamm, 1997; Petrofsky et al., 1999; Scapini et al., 2000; Matzer et al., 2001; Sawant & McMurray, 2007; Lyadova et al., 2010). The secretion is not high, but when neutrophils accumulate in high numbers, it may represent an important source of inflammatory factors. Interestingly, many neutrophils contain intracellular IFN-γ. This was shown during *Mtb* infection (our unpublished observations) and also in other models (Terri & Beaman, 2002). Neutrophils not only produce proinflammatory cytokines by themselves, but also stimulate proinflammatory activity of macrophages (Persson et al., 2008).

An important issue is that factors produced by neutrophils are the major positive regulators of their activity: TNF-α and IL-1β enhance neutrophils' migration, degranulation, oxidative and secretory activities; IL-8 and CXCL2 are the major neutrophil-attracting chemokines; IFN-γ promotes secretory activity; metalloproteinases degrade extracellular matrix facilitating cell migration within the inflamed tissue. Thus, neutrophilic inflammation is under an autocrine regulation. The major inhibitors of cytokine production by neutrophils are IL-10, IL-4, and IL-13 (Witko-Sarsat et al., 2000), but they are poorly produced during TB.

Neutrophils release bactericidal molecules and enzymes not only into the phagosome, but also into the extracellular milieu. This allows killing extracellular microbes, but on the other part is detrimental: serine proteinases degrade almost all components of extracellular matrix and a variety of plasma proteins; collagenase (MMP8) and gelatinase (MMP9) cleave different types of collagen; ROI and chlorinated oxidants inactivate inhibitors of proteinases, activate metalloproteinases and may mediate direct cytotoxic effect (Weiss, 1989; Witko-Sarsat et al., 2000)

The only way to resolve neutrophilic inflammation is to clear the infection: in this case emigration of new neutrophils stops; neutrophils that had migrated to the inflamed sites undergo apoptosis and are phagocytosed by macrophages. During chronic infections, neutrophilic inflammation becomes uncontrolled.

5.2 Neutrophils during *Mtb* infection

5.2.1 Antimycobacterial activity of neutrophils and TB prevention

Neutrophils are among the first cells that migrate to the focus of lung *Mtb* infection, and they progressively accumulate at the infectious site during the chronic stage of disease. Human and mouse neutrophils efficiently phagocyte mycobacteria (Kisich et al., 2002; Eruslanov et al., 2005), but their capacity to kill mycobacteria is disputable.

Denis and Andersen reported that human neutrophils stimulated with IFN-γ failed to kill *Mtb* (Denis & Andersen, 1991). In line with this, in our previous studies mouse neutrophils displayed low antimycobacterial activity that could not be enhanced by the addition of exogenous IFN-γ (Eruslanov et al., 2005). In a recent study by Eum and coauthors (Eum et al., 2010), neutrophils present in the sputum and BAL fluids of patients with active pulmonary TB contained *Mtb* that exhibited signs of replication. Based on these observations, it is concluded that neutrophils have poor antimycobacterial activity and during TB act by hiding *Mtb* from macrophages and permitting *Mtb* replication (Eruslanov et al., 2005; Eum et al., 2010).

In other studies, neutrophils were shown to kill *Mtb*. The effect was mediated by α-defensins, LL37 and lipocalin and promoted by TNF-α (Kisich et al., 2002). Of note, IFN-γ did not enhance killing, which may explain a failure to detect neutrophil-mediated *Mtb* killing in the studies described above (Denis & Andersen, 1991; Eruslanov et al., 2005). Recently, an association between low plasma levels of HNP1-3 and the development of multi-drug resistant TB has been demonstrated (Zhu et al., 2011), supporting the involvement of neutrophils in TB protection. In line with this, it has been demonstrated that black African participants (known to have a relatively high susceptibility to TB) have lower counts of neutrophils and lower concentrations of circulating HNP1–3 and lipocalin 2 than white participants; in TB contacts, the counts of peripheral blood neutrophils inversely correlated with risk of TB development (Martineau et al., 2007). Thus, multiple studies suggest a role for neutrophils in TB prevention.

5.2.2 Neutrophils and TB progression

In contrast to early stages of *Mtb* infection, at which neutrophils are not numerous and may contribute to *Mtb* control, during active disease neutrophils become more abundant and may cause severe pathology. In humans, high numbers of neutrophils in BAL fluids have been associated with disease activity and lung tissue cavitation (Barry et al., 2009; Sutherland et al., 2009). In mice, neutrophils (Gr-1-positive cells) accumulate abundantly in the lungs of susceptible mice (e.g., I/St, DBA/2) but are less numerous in resistant mice (Eruslanov et al., 2005; Keller et al., 2006). It is believed that neutrophils contribute to disease progression by amplifying local inflammatory reactions and mediating tissue injury.

An important question is whether the propensity to develop extensive neutrophilic inflammation is a primary cause of host susceptibility to the infection. In some studies, granulocytes from susceptible mice were shown to have intrinsically high capacity for migration in response to inflammatory stimuli (Keller et al., 2006). However, neutrophilic infiltration is a characteristic future of severe TB in hosts of different genetic backgrounds, e.g., in DBA/2, C3H, I/St, 129Sv mice. It is unlikely that initial mechanisms of TB susceptibility operating in these mice are identical. Rather, at early stages of infection the disease is driven via different pathways. Such pathways may include defects in host ability to restrict *Mtb* growth, intrinsic hyperreactivity of host macrophages to *Mtb* derived ligands resulting in overproduction of neutrophil-activating factors, or high reactivity of neutrophils to inflammatory stimuli. Ultimately, different pathways converge to induce uncontrolled inflammation, characterized by high local production of proinflammatory factors and extensive neutrophilic infiltration. These inflammatory reactions become a hallmark and an important pathogenic mechanism of TB progression. It would be interesting to know whether "inflammatory" neutrophils (i.e., neutrophils residing in highly inflammatory conditions) retain their antibacterial activity and can, at least in part, mediate *Mtb* control, or whether at this stage of disease they exhibit only inflammatory functions.

5.2.3 Neutrophil depletion experiments

To directly address a role for neutrophils in anti-TB defense, several groups examined how neutralization of granulocytes affected *Mtb* infection in mice.

Pedrosa and colleagues (Pedrosa et al., 2000) found that depletion of neutrophils from TB-resistant BALB/c mice during the first week of *Mtb* infection worsened disease and increased bacillary growth. The effect was due to a decreased production of IFN-γ and NO, i.e. was mediated indirectly. Depletion of neutrophils at late stages of the infection did not have a significant effect on the growth of *Mtb* in the lungs. Appelberg and coauthors (Appelberg et al., 1995) performed studies in B6 and beige mice. Beige mice bear mutation that affects function of leukocytes, including granulocytes, and renders mice susceptible to *M. avium*. Transfusion of beige mice with B6 granulocytes at the early stage of infection increased host resistance. In contrast, depletion of neutrophils from B6 mice increased host susceptibility. Seiler and coauthors (Seiler et al., 2003) reported that early depletion of granulocytes from B6 mice did not affect host survival or *Mtb* burden, but impaired granuloma formation.

In the study by Ehlers' group (Keller et al., 2006), depletion of granulocytes from TB resistant B6 or BALB/c mice did not affect the course of *Mtb* infection. In contrast, in TB-susceptible DBA/2 mice depletion of granulocytes had beneficial effect and prolonged mice survival. In CARD9-/- mice, depletion of neutrophils on days 8-14 post-challenge significantly prolonged mice survival. The effect was due to a reduced inflammation, and was not associated with changes in bacterial burdens (Dorhoi et al., 2010).

The results of these studies are usually interpreted as contradictory. In fact, they are compatible and can be explained by (i) the differential role for neutrophils at early and late stages of *Mtb* infection; (ii) different strength of neutrophilic inflammation in genetically different hosts. We suppose that at the early stage of the infection, when neutrophils are not

numerous and neutrophil-activating proinflammatory cytokines are not abundant, neutrophils contribute to *Mtb* control. At the late stage of the disease, the action of neutrophils depends on the strength of local inflammation: if neutrophils accumulate in high numbers and are in highly inflammatory milieu (conditions usually observed in TB-susceptible mice), they become deleterious. Thus, depletion of neutrophils reduced *Mtb* control and worsened disease in resistant mice, but dampened inflammation and ameliorated disease course in susceptible mice.

5.2.4 Not all Gr-1/Ly-6G-positive cells accumulating in the lungs at the advanced stage of *Mtb* infection are neutrophils

To address a role for granulocytes in TB progression, we have recently used our F2 model of *Mtb* infection (Lyadova et al., 2010). In this model, (A/SnxI/St)F2 mice challenged with *Mtb* display different rates of TB progression. We examined the accumulation of cells expressing Gr-1 marker (marker expressed by granulocytes and to a less extent – by monocytes) and Ly-6G molecules (molecules thought to be expressed exclusively by granulocytes) in the lungs of F2 mice at advanced stage of disease (day 24 post-infection). We found that the population of Gr-1-positive cells infiltrating *Mtb*-infected lungs, was not homogeneous, and consisted of two different subsets, Gr-1^{hi} and Gr-1^{dim}. Similarly, Ly-6G-positive cells contained Ly-6G^{hi} and Ly-6G^{low} subsets. In mice with slowly progressing TB all Gr-1/Ly-6G-positive cells were Gr-1^{hi}/Ly-6G^{hi}. In contrast, in mice with severe infection a vast majority of Gr-1/Ly-6G-positive cells were Gr-1^{dim}/Ly-6G^{dim}, whereas Gr-1^{hi}/Ly-6G^{hi} cells were almost undetectable. Further analysis showed that Gr-1^{hi}/Ly-6G^{hi} cells were granulocytes: they expressed F4-80^{neg}CD11b^{hi} phenotype and had segmented nuclei. Gr-1^{dim}/Ly-6G^{dim} cells exhibited characteristics of immature myeloid cells: they had F4-80^{low}CD11b^{hi} phenotype that could be attributed nor to mature granulocytes nor to monocytes. Analysis of nuclear morphology showed that these cells had un-segmented or low-segmented nuclei. At advanced stage of *Mtb* infection, Ly-6G^{dim} cells appeared and accumulated not only in the lungs, but also in the bone marrow (Tsiganov E.N., Lyadova I.V., manuscript in preparation), suggesting that hematopoiesis was altered in mice with progressing TB and that the accumulation of Gr-1^{dim}/Ly-6G^{dim} cells in the lungs was a result of this alteration.

In connection with these data, two points should be discussed.

First, Gr-1 and even Ly-6G expressing cells accumulating in the lungs of *Mtb*-infected mice do not necessarily represent mature neutrophils. Experimental studies in which neutrophils were identified based on their Gr-1/Ly-6G-positivity should be revised to take into account the level of Gr-1/Ly-6G expression. Similarly, several studies identified neutrophils based on the expression of myeloperoxidase. This enzyme is, indeed, synthesized be granulocytes, but also - by their myeloid precursors.

Second, our data suggest that severe TB is accompanied by hematopoietic shifts that result in a progressive accumulation of immature myeloid cells and gradual disappearance of mature neutrophils from *Mtb*-infected lungs. It will be interesting to examine, whether the substitution of neutrophils by immature cells may underlie inability of "neutrophils" to control *Mtb* infection at the advanced stages of TB disease.

6. Conclusion

Inflammation plays a dual role in host immune response to mycobacteria. On the one part, it is prerequisite for successful pathogen elimination. On the other part, it mediates tissue injury and disease progression. At the onset of the infection, inflammatory reactions are largely protective; during active disease, the deleterious effect of inflammation prevails, making inflammation a paramount pathogenic factor of TB progression.

Irrespectively on genetic factors and molecular pathways that have lead to severe TB (that are different in genetically different hosts), pathogenetic mechanisms operating during advanced stage of disease are common. They include overproduction of proinflammatory factors and excessive infiltration of the lung tissue with neutrophils (or their precursors). A positive feedback loop between these reactions exists (proinflammatory factors promote neutrophilic inflammation; neutrophils produce proinflammatory factors; both induce tissue injury, *Mtb* dissemination, and another round of inflammation) making the regulation of the ongoing inflammation difficult. An additional and a new component of TB progression is alteration of host hematopoiesis that results in the generation of immature myeloid cells, their emigration and prominent accumulation in the periphery. The role for these cells in TB progression is yet to be determined.

The fact that mechanisms mediating TB progression are common has an important practical outcome: there is no need to search for exact cause that has driven severe disease in each individual; it might be possible to slow down disease progression by interfering with any of the pathways involved in hyperinflammatory response. With this respect, co-treatment of host with anti-*Mtb* and anti-inflammatory drugs opens new perspectives for efficient TB therapy (Koo et al., 2011).

7. Acknowledgement

This work was supported by the Central Tuberculosis Research Institute of the Russian Academy of Medical Sciences, and by NIH grant AI078899 and Russian Federation of Basic Research grant # 10-04-01128.

8. References

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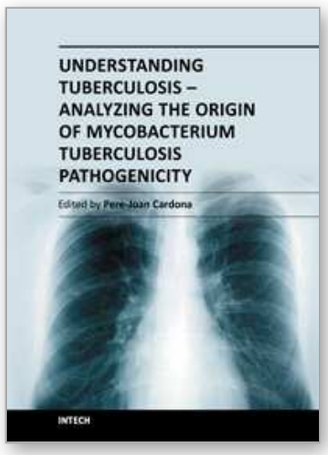

Understanding Tuberculosis - Analyzing the Origin of Mycobacterium Tuberculosis Pathogenicity

Edited by Dr. Pere-Joan Cardona

ISBN 978-953-307-942-4
Hard cover, 560 pages
Publisher InTech
Published online 24, February, 2012
Published in print edition February, 2012

Mycobacterium tuberculosis in an attempt to understand the extent to which the bacilli has adapted itself to the host and to its final target. On the other hand, there is a section in which other specialists discuss how to manipulate this immune response to obtain innovative prophylactic and therapeutic approaches to truncate the intimal co-evolution between Mycobacterium tuberculosis and the Homo sapiens.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Irina Lyadova (2012). Inflammation and Immunopathogenesis of Tuberculosis Progression, Understanding Tuberculosis - Analyzing the Origin of Mycobacterium Tuberculosis Pathogenicity, Dr. Pere-Joan Cardona (Ed.), ISBN: 978-953-307-942-4, InTech, Available from: http://www.intechopen.com/books/understanding-tuberculosis-analyzing-the-origin-of-mycobacterium-tuberculosis-pathogenicity/inflammation-and-immunopathogenesis-of-tuberculosis-progression

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