

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Inflammation and Immunopathogenesis of Tuberculosis Progression

Irina Lyadova

Central Tuberculosis Research Institute
Russia

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 through 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-1 β , TNF- α , IL-6. All, IL-1 β , TNF- α and IL-6 promote further activation of macrophages (Kishimoto, 2005). In addition, IL-1 β 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 properties (Orme & Cooper, 1999; Motoo et al., 2009). IL-6 modulates T-cell response, is essential for antibody formation, and stimulates hematopoiesis, in particular, 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 others 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-1 β , 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; Fremont 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 β 1 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 these 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- κ B 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-1 β and TNF- α and increased lung infiltration with neutrophils and macrophages. Blocking IL-1 β 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-1 β , 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-1 β 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-1 β , 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-1 β , 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 Δ SigC mutant had decreased mortality associated with lower numbers of neutrophils and reduced levels of TNF- α , IL-1 β , IL-6 and IFN- γ in their lungs (Khairul-Bariah et al., 2008). Similar results were obtained when SCID mice were challenged with Δ SigC mutant. *whiB3 Mtb* mutant induced milder disease than wild type *Mtb* strain due to reduced granulomatous inflammation in the lungs (Steyn et al., 2002). Δ SigH *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-1 β , 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-1 β , 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-1 β than patients who have small or no cavity. Importantly, the ratios of TNF- α to sTNF-RI and IL-1 β 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-1 β 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 phagocytose 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) hypochlorous acid and chloramines, generated by neutrophil-specific enzyme myeloperoxidase. 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 phagocytose 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-1 β 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 & Kaufmann, 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-1 β 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 phagocytose 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 feature 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 by 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.

Irrespective 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

- Abadie, V.; Badell, E., Douillard, P., Ensergueix, D., Leenen, P., Tanguy, M., Fiette, L., Saeland, S., Gicquel, B. & Winter, N. (2005). Neutrophils rapidly migrate via lymphatics after *Mycobacterium bovis* BCG intradermal vaccination and shuttle live bacilli to the draining lymph nodes. *Blood*. Vol.106, No.5, (September 2005), pp. 1843 - 1850.
- Abdul-Majid, K.; Ly, L., Converse, P., Geiman, D., McMurray, D. & Bishai, W. (2008). Altered cellular infiltration and cytokine levels during early *Mycobacterium tuberculosis* sigC mutant infection are associated with late-stage disease attenuation and milder immunopathology in mice. *BMC Microbiology*. Vol.8, (September 2008), pp.151-164.
- Altare, F.; Durandy, A., Lammas, D., Emile, J., Lamhamedi, S., Le Deist, F., Drysdale, P., Jouanguy, E., Döffinger, R., Bernaudin, F., Jeppsson, O., Gollob, J., Meinel, E., Segal, A., Fischer, A., Kumararatne, D. & Casanova J. (1998) Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. *Science*. Vol.280, No.5368 (May 1998), pp. 1432 - 1435.

- Appelberg, R. & Silva, M. (1989). T cell-dependent chronic neutrophilia during mycobacterial infections. *Clin. Exp. Immunol.* Vol.78, No.3 (December 1989), pp. 478-483.
- Appelberg, R.; Castro, A., Gomes, S., Pedrosa, J. & Silva, M. (1995). Susceptibility of beige mice to *Mycobacterium avium* : role of neutrophils. *Infect Immun.* Vol.63, No.9, (September 1995), pp. 3381 - 3387.
- Argilés, J.; Busquets, S. & López-Soriano, F. (2005). The pivotal role of cytokines in muscle wasting during cancer. *Int J Biochem Cell Biol.* Vol.37, No.10, (October 2005), pp. 2036-2046.
- Barber, D.; Mayer-Barber, K., Feng, K., & Sharpe, A. (2011). CD4 T Cells Promote Rather than Control Tuberculosis in the Absence of PD-1-Mediated Inhibition and Alan Sher. *J. Immunol.* Vol.186, No.3, (February 2011), pp. 1598-1607.
- Barry, S.; Breen, R., Lipman, M., Johnson, M. & Janossy, G. (2009). Impaired antigen-specific CD4(+) T lymphocyte responses in cavitary tuberculosis. *Tuberculosis (Edinb).* Vol. 9, No.1, (January 2009), pp. 48-53.
- Bean, A.; Roach, D., Briscoe, H., France, M., Korner, H., Sedgwick, J. & Britton W. (1999). Structural deficiencies in granuloma formation in TNF gene-targeted mice underlie the heightened susceptibility to aerosol *Mycobacterium tuberculosis* infection, which is not compensated for by lymphotoxin. *J. Immunol.* Vol.162, No.6, (March 1999), pp.3504-3511.
- Bekker, L.; Moreira, G., Bergtold, A., Freeman, S., Ryffel, B. & Kaplan G. (2000). Immunopathologic effects of tumor necrosis factor alpha in murine mycobacterial infection are dose dependent. *Infect. Immun.* Vol.68, No.12, (December 2000), pp. 6954-6961.
- Bilaceroglu, S.; Perim, K., Buyuksirin, M. & Celikten, E. (1999) Prednisolone: a beneficial and safe adjunct to antituberculosis treatment? A randomized controlled trial. *Int J Tuberc Lung Dis.* Vol.3, No.1, (January 1999), pp. 47-54.
- Blomgran, R. & Ernst, J. (2011). Lung Neutrophils Facilitate Activation of Naïve Antigen-Specific CD4 + T Cells during *Mycobacterium tuberculosis* Infection. *J Immunol.* Vol.186, No.12, (June 2011), pp. 7110-7119.
- Boom, W.; Canaday, D., Fulton, S., Gehring, A., Rojas, R. & Torres, M. (2003). Human immunity to *M. tuberculosis*: T cell subsets and antigen processing. *Tuberculosis.* Vol.83, No.1-3, pp. 98-106.
- Bourgarit, A.; Carcelain, G., Samri, A., Parizot, C., Lafaurie, M., Abgrall, S., Delcey, V., Vicaud, E., Sereni, D., Autran, B. & PARADOX Study Group. (2009). Tuberculosis-Associated Immune Restoration Syndrome in HIV-1-Infected Patients Involves Tuberculin-Specific CD4 Th1 Cells and KIR-Negative $\gamma\delta$ T Cells. *J. Immunol.* Vol.183, No.6, (September 2009), pp. 3915-3923.
- Brinkmann, V.; Reichard, U., Goosmann, C., Fauler, B., Uhlemann, Y., Weiss, D., Weinrauch, Y. & Zychlinsky A. (2004). Neutrophil Extracellular Traps Kill Bacteria. *Science*, Vol.303, No.5663, (March 2004), pp. 1532- 1535. ISSN 1095-9203.
- Cardona PJ. (2010). Revisiting the natural history of tuberculosis. The inclusion of constant reinfection, host tolerance, and damage-response frameworks leads to a better understanding of latent infection and its evolution towards active disease. *Arch Immunol Ther Exp (Warsz).* Vol.58, No.1, (February 2010), pp. 7-14.
- Cardona PJ. (2011). A spotlight on liquefaction: evidence from clinical settings and experimental models in tuberculosis. *Clin Dev Immunol.* Vol.2011, ID 868246.

- Cardona, P., Gordillo, S., Diaz, J., Tapia, G., Amat, I., Pallares, A., Vilaplana, C., Ariza, A. & Ausina, V. (2003). Widespread bronchogenic dissemination makes DBA/2 mice more susceptible than C57BL/6 mice to experimental aerosol infection with *Mycobacterium tuberculosis*. *Infect. Immun.* Vol.71, No.10, (October 2003), pp. 5845-5854.
- Casanova, J.-L. & Abel, L. (2002). Genetic dissection of immunity to mycobacteria: the human model. *Annu. Rev. Immunol.* Vol.20, pp. 581-620.
- Cassatella, M. A. (1995). The production of cytokines by polymorphonuclear neutrophils. *Immunol. Today.* Vol. Vol.16, No.1 (January 1995), pp. 21-26.
- Castiblanco, J.; Varela, D., Castan˜o-Rodríguez, N., Rojas-Villarraga, A., Hincapié, M. & Anaya, J. (2008) TIRAP (MAL) S180L polymorphism is a common protective factor against developing tuberculosis and systemic lupus erythematosus. *Infect Genet Evol.* Vol.8, No.5, (September 2008), pp.541-544.
- Chang, H. & Bistrian, B. (1998). The role of cytokines in the catabolic consequences of infection and injury. *J Parenter Enteral Nutr.* Vol.22, No.3, (May-June 1998), pp. 56-166.
- Cooper, A. (2009). T cells in mycobacterial infection and disease. *Curr Opin Immunol.* Vol.21, No.4, (August 2009), pp. 378-384.
- Cooper, A.; Dalton, D., Stewart, T., Griffin, J., Russell, D. & Orme, I. (1993). Disseminated tuberculosis in interferon γ gene-disrupted mice. *J. Exp. Med.* Vol.178, No.6, (December 1993), pp. 2243-2247.
- Cooper, A.; Magram, J., Ferrante, J. & Orme, I. (1997). Interleukin 12 (IL-12) is crucial to the development of protective immunity in mice intravenously infected with *Mycobacterium tuberculosis*. *J. Exp. Med.* Vol.186, No.1, (July 1997), pp. 39-45.
- Cooper, A.; Segal, B., Frank, A., Holland, S. & Orme, I. (2000). Transient loss of resistance to pulmonary tuberculosis in p47 (phox-/-) mice. *Infect. Immun.* Vol.68, No.3, (March 2000), pp.1231-1234.
- Corral, L.; Muller, G., Moreira, A., Chen, Y., Wu, M., Stirling, D. & Kaplan, G. (1996). Selection of novel analogs of thalidomide with enhanced tumor necrosis factor alpha inhibitory activity. *Mol Med.* Vol.2, No.4 (July 1996), pp. 506-515.
- Denis, M. (1991). Human neutrophils, activated with cytokines or not, do not kill virulent *Mycobacterium tuberculosis*. *J. Infect. Dis.* Vol.163, No.3, (September 1991), pp.919.
- Di Liberto, D.; Locati, M., Caccamo, N., Vecchi, A., Meraviglia, S., Salerno, A., Sireci, G., Nebuloni, M., Caceres, N., Cardona, P., Dieli, F. & Mantovani A. (2008). Role of the chemokine decoy receptor D6 in balancing inflammation, immune ractivation, and antimicrobial resistance in *Mycobacterium tuberculosis* infection. *J. Exp. Med.* Vol.205, No.9, (September 2008) pp. 2075-2084.
- Divangahi, S.; Mostowy, F., Coulombe, F., Kozak, R., Guillot, L., Veyrier, F., Kobayashi, K., Flavell, R., Gros, P. & Behr, M. (2008). NOD2-deficient mice have impaired resistance to *Mycobacterium tuberculosis* infection through defective innate and adaptive immunity. *J. Immunol.* Vol.181, No.10, (November 2008), pp. 7157-7165.
- Dorhoi, A.; Desel, C., Yeremeev, V., Pradl, L., Brinkmann, V., Mollenkopf, H., Hanke, K., Gross, O., Ruland, J. & Kaufmann, S. (2010). The adaptor molecule CARD9 is essential for tuberculosis control. *J. Exp. Med.* Vol.207, No.4, (April 2010), pp. 777-792.
- Dorhoi, A.; Reece, S.T. & Kaufmann S. (2011). For better or for worse: the immune response against *Mycobacterium tuberculosis* balances pathology and protection. *Immunological Reviews.* Vol.240, No.1, (March 2011), pp. 235-251.

- Dorman, S. & Holland, S. (2000). Interferon-gamma and interleukin-12 pathway defects and human disease. *Cytokine Growth Factor Rev.* Vol.11, No.4 (December 2000), pp. 321 – 333.
- Drennan, M.; Nicolle, D., Quesniaux, V., Jacobs, M., Allie, N., Mpagi, J., Frémond, C., Wagner, H., Kirschning, C. & Ryffel B. (2004). Toll like receptor 2-deficient mice succumb to Mycobacterium tuberculosis infection. *American Journal of Pathology*, Vol.164, No.1, (January 2004), pp. 49–57.
- Ellis, T. & Beaman, B. (2002). Murine polymorphonuclear neutrophils produce interferon- γ in response to pulmonary infection with Nocardia asteroides. *J. Leukoc. Biol.* Vol.72, No.2, (August 2002), pp. 373–381.
- Eruslanov, E.; Lyadova, I., Kondratieva, T., Majorov, K., Scheglov, I., Orlova, M. & Apt, A.. (2005). Neutrophil responses to Mycobacterium tuberculosis infection in genetically susceptible and resistant mice. *Infect Immun.* Vol.73, No.3, (March 2005), pp.1744–1753.
- Eruslanov, E.; Majorov, K., Orlova, M., Mishenko, V., Kondratieva, T., Apt, A. & Lyadova, I. (2004). Lung cell responses to *M. tuberculosis* in genetically susceptible and resistant mice following intratracheal challenge. *Clin. Exp. Immunol.* Vol.135, No.1, (January 2004), pp. 19–28.
- Eum, S.; Kong, J., Hong, M., Lee, Y., Kim, J., Hwang, S., Cho, S., Via, L. & Barry, C. 3rd. (2010). Neutrophils Are the Predominant Infected Phagocytic Cells in the Airways of Patients With Active Pulmonary TB. *Chest.* Vol.137, No.1, (January 2010), pp.122–128.
- Fiorenza, G.; Rateni, L., Farroni, M., Bogue, C. & Dlugovitzky, D. (2005). TNF- α , TGF- β and NO relationship in sera from tuberculosis (TB) patients of different severity. *Immunol Lett.* Vol.98, No.1, (April, 2005), pp. 45–48.
- Flynn, J. & Chan, J. Immunology of tuberculosis. *Ann Rev Immunol.* Vol.19, pp. 93–129.
- Flynn, J.; Chan, J. & Lin P. (2011). Macrophages and control of granulomatous inflammation in tuberculosis. *Mucosal Immunol.* Vol.4, No.3, (May 2011), pp. 271–278.
- Flynn, J.; Chan, J., Triebold, K., Dalton, D., Stewart, T. & Bloom, B.(1993). An essential role for interferon gamma in resistance to *Mycobacterium tuberculosis* infection. *J. Exp. Med.* Vol.178, No.6, (December 1993), pp. 2249–2254.
- Flynn, J.; Goldstein, M., Chan, J., Triebold, K., Pfeffer, K., Lowenstein, C., Schreiber, R., Mak, T. & Bloom, B.(1995). Tumor necrosis factor- α is required in the protective immune response against *M. tuberculosis* in mice. *Immunity.* Vol.2, No.6, (June 1995). pp. 561–572.
- Frémond, C.; Togbe, D., Doz, E., Rose, S., Vasseur, V., Maillet, I., Jacobs, M., Ryffel, B. & Quesniaux, V. (2007) IL-1 receptor mediated signal is an essential component of MyD88-dependent innate response to Mycobacterium tuberculosis infection. *J Immunol.* Vol.179, No.2, (July 2007), pp. 1178–1189.
- Fu, L.M. (2003). The potential of human neutrophil peptides in tuberculosis therapy. *Int. J. Tuberc. Lung Dis.* Vol.7, No.11, (November 2003), pp. 1027–1032.
- Garlanda, C.; Di Liberto, D., Vecchi, A., La Manna, M., Buracchi, C., Caccamo, N., Salerno, A., Dieli, F. & Mantovani, A. (2007). Dampening Excessive Inflammation and Tissue Damage in Mycobacterium tuberculosis Infection by Toll IL-1 Receptor 8/Single Ig IL-1-Related Receptor, a Negative Regulator of IL-1/TLR Signaling. *J Immunol.* Vol.179, No.5, (September 2007), pp. 3119–3125.

- Hernandez-Pando, R. & Rook, G. (1994). The role of TNF- α in T-cell-mediated inflammation depends on the Th1/Th2 cytokine balance. *Immunology*. Vol.82, No.4, (August 1994), pp.591-595.
- Hölscher, C.; Hölscher, A., Rückerl, D., Yoshimoto, T., Yoshida, H., Mak, T., Saris, C. & Ehlers, S. (2005). The IL-27 receptor chain WSX-1 differentially regulates antibacterial immunity and survival during experimental tuberculosis. *J Immunol.*, Vol.174, No.6, (March 2005), pp. 3534-3544.
- Hunninghake, G.; Glazier, A., Monick, M. & Dinarello C. (1987). Interleukin-1 is a chemotactic factor for human T-lymphocytes. *Am Rev Respir Dis*. Vol.135, No.1., (January 1987), pp. 66-71.
- Juffermans, N.; S. Florquin, L., Camoglio, A., Verbon, A., Kolk, P., Speelman, S., van Deventer, T. & van Der Poll. (2000) Interleukin-1 signaling is essential for host defense during murine pulmonary tuberculosis. 182 (September 2000), pp. 902-908.
- Jung, Y.-J.; LaCourse, R., Ryan, L., & North, R. (2002). Virulent but not avirulent *Mycobacterium tuberculosis* can evade the growth inhibitory action of a T helper 1-dependent, nitric oxide synthase 2-independent defense in mice. *J. Exp. Med*. Vol.196, No.7, (October 2002), pp. 991-998.
- Kapina, M., Shepelkova, G., Bogacheva, P., Mischenko, V., Sayles, P., Winslow, G., Apt, A. & Lyadova, I. (2007). CD27^{lo} CD4⁺ lymphocytes that accumulate in the mouse lung tissue during mycobacterial infection differentiate from CD27^{hi} precursors *in situ*, produce IFN- γ , and protect the host against TB infection. *J. Immunol*. Vol.178, No.2, (January 2007), pp. 976-985.
- Kaufmann, S. (2006). Tuberculosis: Back on Commentary the Immunologists' Agenda *Immunity*. Vol.24, No.4, (April 2006), pp. 351-357.
- Kaushal, D.; Schroeder, B., Tyagi, S., Yoshimatsu, T., Scott, C., Ko, C., Carpenter, L., Mehrotra, J., Manabe, Y., Fleischmann, R. & Bishai, W. (2002). Reduced immunopathology and mortality despite tissue persistence in a *Mycobacterium tuberculosis* mutant lacking alternative sigma factor, SigH. *Proc Natl Acad Sci USA* Vol.99, No.12, (June 2002), pp. 8330-8335.
- Keane, J.; Gershon, S., Wise, R., Mirabile-Levens, E., Kasznica, J., Schwieterman, W., Siegel, J. & Braun M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med.* Vol.345, No.15, (October 2001), pp. 1098-1104.
- Keller, C.; Hoffmann, R., Lang, R., Brandau, S., Hermann, C., & Ehlers, S. (2006). Genetically determined susceptibility to tuberculosis in mice causally involves accelerated and enhanced recruitment of granulocytes. *Infect Immun*. Vol. 74, No.7, (July 2006), pp. 4295-4309
- Khader, S. & Cooper, A. (2008). IL-23 and IL-17 in tuberculosis. *Cytokine*. Vol.41, No.2, (February 2008), pp. 79-83.
- Kindler, V.; Sappino, A., Grau, G., Piguet, P. & Vassalli, P. (1989). The inducing role of tumor necrosis factor in the development of bactericidal granulomas during BCG infection. *Cell*. Vol.56, No.5, (March 1989), pp. 731-740.
- Kishimoto, T. (2005). Interleukin-6: from basic science to medicine-40 years in immunology. *Annu Rev Immunol*. Vol.23, pp.1-21.
- Kisich, K.; Higgins, M., Diamond, G. & Heifets, L. Tumor Necrosis Factor Alpha Stimulates Killing of *Mycobacterium tuberculosis* by Human Neutrophils. *Infect Immun*. Vol.70, No.8, (August 2002), pp. 4591-4599.

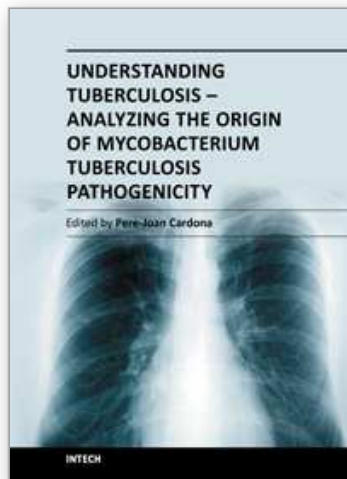
- Kleinnijenhuis, J.; Oosting, M., Joosten, L., Netea, M. & Van Crevel, R. (2011). Innate Immune Recognition of Mycobacterium tuberculosis. *Clin Dev Immunol.* Vol.2011, ID: 405310.
- Koo, M.-S.; Manca, C., Yang, G., O'Brien, P., Sung, N., Tsenova, L., Subbian, S., Fallows, D., Muller, G., Ehrt, S., Kaplan, G. (2011). Phosphodiesterase 4 Inhibition Reduces Innate Immunity and Improves Isoniazid Clearance of Mycobacterium tuberculosis in the Lungs of Infected. *Plos One*, Vol.6, No.2., (February 2011), pp. e17091.
- Korbel, D.; Schneider, B. & Schaible, U. (2008). Innate immunity in tuberculosis: myths and truth. *Microbes and Infection.* Vol.10, No.9, (July 2008), pp. 995-1004.
- Ladel, C.H.; Blum, C., Dreher, A., Reifenberg, K., Kopf, M. & Kaufmann, S. (1997). Lethal tuberculosis in interleukin-6-deficient mutant mice. *Infect Immun.* Vol.65, No.11, (November 1997), pp. 4843-4849.
- Lalvani, A.; Brookes, R., Wilkinson, R., Malin, A., Pathan, A., Andersen, P., Dockrell, H., Pasvol, G. & Hill, A. (1998). Human cytolytic and interferon gamma-secreting CD8+ T lymphocytes specific for Mycobacterium tuberculosis. *Proc Natl Acad Sci U S A.* Vol.95, No.1, (January 1998), pp. 270-275.
- Law, K.; Weiden, M. Harkin, T., Tchou-Wong, K., Chi, C. & Rom, W. (1996). Increased release of interleukin-1 β , interleukin-6, and tumor necrosis factor- α by bronchoalveolar cells lavaged from involved sites in pulmonary tuberculosis. *American journal of respiratory and critical care medicine.* Vol.153, No.2, (February 1996), pp. 799-804.
- Lázár-Molnár, E.; Chen, B., Sweeney, K., Wang, E., Liu, W., Lin, J., Porcelli, S., Almo, S., Nathenson, S., Jacobs, W.Jr. (2010). Programmed death-1 (PD-1)-deficient mice are extraordinarily sensitive to tuberculosis. *PNAS*, Vol.107, No.30, (July 2010). pp.13402-13407.
- Lin, P.; Pawar, S., Myers, A., Pegu, A., Fuhrman, C., Reinhart, T., Capuano, S., Klein, E. & Flynn, J. (2006). Early events in Mycobacterium tuberculosis infection in cynomolgus macaques. *Infect Immun* Vol.74, No.3, (July 2006), pp. 3790-3803.
- Lin, P.; Rodgers, M.; Smith, L., Bigbee, M., Myers, A., Bigbee, C., Chiosea, I., Capuano, S., Fuhrman, C., Klein, E. & Flynn, J. (2009). Quantitative comparison of active and latent tuberculosis in the cynomolgus macaque model. *Infect Immun* Vol.77, No.10, (October 2009), pp. 4631-4642.
- Liu, F.; Poursine-Laurent, J., Wu, H. & Link, D. (1997). Interleukin-6 and the granulocyte colony-stimulating factor receptor are major independent regulators of granulopoiesis in vivo but are not required for lineage commitment or terminal differentiation. *Blood.* Vol.90, No.7, (October 1997), pp.2583-2590.
- Lyadova, I.; Eruslanov, E., Yermeev, V., Majorov, K., Nikonenko, B., Pichugin, A., Khaidukov, S., Kondratieva, T. & Apt, A. (2000). Comparative analysis of T lymphocytes recovered from the lungs of mice genetically susceptible, resistant and hyperresistant to Mycobacterium tuberculosis-triggered disease. *J. Immunol.*, Vol.165, No.10, (November 2000), pp. :5921-5931.
- Lyadova, I.; Tsiganov, E., Kapina, M., Shepelkova, G., Sosunov, V., Radaeva, T., Majorov, K., Shmitova, N., van den Ham, H.-J., Ganusov, V., De Boer, R., Racine, R. & Winslow, G. (2010). In Mice, Tuberculosis Progression Is Associated with Intensive Inflammatory Response and the Accumulation of Gr-1dim Cells in the Lungs. *PLoS One.* 2010; Vol.5, No.5, (May 2010), pp. e10469.

- MacMicking, J.; North, R., LaCourse, R., Mudgett, J., Shah, S. & Nathan, C. (1997). Identification of nitric oxide synthase as a protective locus against tuberculosis. *Proc. Natl. Acad. Sci. USA*. Vol.94, No.10, (May 1997), pp. 5243–5248.
- Martineau, A.; Newton, S., Wilkinson, K., Kampmann, B., Hall, B., Nawroly, N., Packe, G., Davidson, R., Griffiths, C., & Wilkinson R. (2007). Neutrophil-mediated innate immune resistance to mycobacteria. *J. Clin. Invest.* Vol.117, No.7, (July 2007), pp. 1988–1994.
- Matzer, S.; Baumann, T., Lukacs, N., Ro'linghoff, M., & Beuscher, H. (2001). Constitutive Expression of Macrophage-Inflammatory Protein 2 (MIP-2) mRNA in Bone Marrow Gives Rise to Peripheral Neutrophils with Preformed MIP-2 Protein. *J Immunol.* Vol.167, No.8, (October 2001), pp. 4635–4643.
- Mayer-Barber, K.; Barber, D., Shenderov, K., White, S., Wilson, M., Cheever, A., Kugler, D., Hieny, S., Caspar, P., Núñez, G., Schlueter, D., Flavell, R., Sutterwala, F. & Sher, A. (2010). Cutting Edge: Caspase-1 Independent IL-1b Production Is Critical for Host Resistance to Mycobacterium tuberculosis and Does Not Require TLR Signaling In Vivo. *J Immunol.* Vol.184, No.7, (April 2010), pp. 3326–3330.
- McColl, S.; Paquin, R., Ménard, C. & Beaulieu, A. (1992). Human neutrophils produce high levels of the interleukin 1 receptor antagonist in response to granulocyte/macrophage colony-stimulating factor and tumor necrosis factor alpha. *J Exp Med.* Vol.176, No.2, (August 1992), pp. 593–598.
- Miller, L.; Pietras, E., Uricchio, L., Hirano, K., Rao, S., Lin, H., O'Connell, R., Iwakura, Y., Cheung, A., Cheng, G. & Modlin, R. (2007) Inflammasome-Mediated Production of IL-1beta Is Required for Neutrophil Recruitment against Staphylococcus aureus In Vivo. *J Immunol*, Vol.179, No.10, (November 2007), pp. 6933–6942.
- Mogues, T.; Goodrich, M., Ryan, L., La-Course, R. & North, R. (2001). The relative importance of T cell subsets in immunity and immunopathology of airborne Mycobacterium tuberculosis infection in mice. *J. Exp. Med.* Vol.193, No.3, (February 2001), pp. 271–280.
- Mootoo, A.; Stylianou, E., Arias, M. & Reljic, R. (2009). TNF-alpha in Tuberculosis: A Cytokine with a Split Personality. *Inflamm Allergy -Drug Targets*, Vol.8, No.1, (March 2009), pp. 53–62.
- Moreira, A.; Tsenova, L., Aman, M., Bekker, L., Freeman, S, Mangaliso, B., Schröder, U., Jagirdar, J., Rom, W., Tovey, M., Freedman, V., & Kaplan G. (2002) Mycobacterial Antigens Exacerbate Disease Manifestations in Mycobacterium tuberculosis-Infected Mice. *Infect. Immun.*, Vol.70, No.4, (April 2002), pp. 2100–2107.
- Nemeth, J.; Winkler, H., Boeck, L., Adegnika, A., Clement, E., Mve, T., Kremsner, P. & Winkler, S. (2011). Specific cytokine patterns of pulmonary tuberculosis in Central Africa. *Clin Immunol.* Vol.138, No1, (January 2011), pp. 50–59. North, R. J. & Jung Y. (2004). Immunity to tuberculosis. *Annu. Rev. Immunol.* Vol.22, pp. 599–623.
- Oliveira, S.; Canetti, C., Ribeiro, R. & Cunha F. (2008). Neutrophil Migration Induced by IL-1b Depends upon LTB4 Released by Macrophages and upon TNF-a and IL-1b Released by Mast Cells. *Inflammation*, Vol. Vol.31, No.1, (February 2008), pp. 36–46.
- Orme, I. M. & Cooper A. (1999). Cytokine/chemokine cascades in immunity to tuberculosis. *Immunol. Today*, Vol.20, No.7, (July 1999), pp. 307–312.
- Pan, H.; Yan, B., Rojas, M., Shebzukhov, Y., Zhou, H., Kobzik, L., Higgins, D.E., Daly, M.J., Bloom, B.R. & Kramnik, I. (2005) Ipr1 gene mediates innate immunity to tuberculosis. *Nature*. Vol. 434, No.7034, (April 2005), pp. 767–772.

- Pearl, J.; Saunders, B., Ehlers, S., Orme, I. & Cooper, A. (2001). Inflammation and lymphocyte activation during mycobacterial infection in the interferon-gamma-deficient mouse. *Cell Immunol.* Vol.211, No.1, (July 2001), pp. 43-50.
- Pedrosa, J.; Saunders, B., Appelberg, R., Orme, I., Silva, M. & Cooper, A. (2000). Neutrophils play a protective nonphagocytic role in systemic Mycobacterium tuberculosis infection of mice. *Infect Immun.* Vol.68, No.2, (February 2000), pp. 577 - 583.
- Persson, Y.; Blomgran-Julinder, R., Rahman, S., Zheng, L. & Stendahl, O. (2008). Mycobacterium tuberculosis-induced apoptotic neutrophils trigger a pro-inflammatory response in macrophages through release of heat shock protein 72, acting in synergy with the bacteria. *Microbes and Infection* Vol.10, No.3., (March 2008), pp. 233-240.
- Petrofsky, M. & Bermudez, L. (1999) Neutrophils from Mycobacterium avium-infected mice produce TNF-alpha, IL-12, and IL-1 beta and have a putative role in early host response. *Clin Immunol.* Vol.91, No.3, (June 1999), pp. 354-358.
- Polentarutti, N.; Rol, G., Muzio, M., Zoja, C., Benigni, A., Tomasoni, S., Vecchi, A., Garlanda, G. & Mantovani A. (2003). Unique pattern of expression and inhibition of IL-1 signaling by the IL-1 receptor family member TIR8/SIGIRR. *Eur. Cytokine Network*, Vol.14, No.4, (October-December 2003), pp. 1-8.
- Raviglione, M. (2003). The TB epidemic from 1992 to 2002. *Tuberculosis (Edinb)*. Vol.83, No.1-3, pp. 4-14. Rhoades, E.; Cooper, A. & Orme, I. (1995). Chemokine response in mice infected with Mycobacterium tuberculosis. *Infect Immun.* Vol.63, No.10, (October 1995), pp.3871-3877.
- Riedel, D. & Kaufmann S. (1997). Chemokine secretion by human polymorphonuclear granulocytes after stimulation with Mycobacterium tuberculosis and lipoarabinomannan. *Infect. Immun.* Vol.65, No.11, (November 1997), pp.4620-4623.
- Rivas-Santiago, B.; Hernandez-Pando, R., Carranza, C., Juarez, E., Contreras, J., Aguilar-Leon, D., Torres, M. & Sada, E. (2008). Expression of Cathelicidin LL-37 during Mycobacterium tuberculosis Infection in Human Alveolar Macrophages, Monocytes, Neutrophils, and Epithelial Cells. *Infect Immun.* Vol.76, No.3, (March 2008), pp.935-941.
- Roach, D.; Bean, A., Demangel, C., France, M., Briscoe, H. & Britton, W. (2002). TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. *J Immunol.* Vol.168, No.9., (May 2002), pp. 4620-4627.
- Russell, D.; Cardona, P., Kim, M., Allain, S. & Altare, F. (2009). Foamy macrophages and the progression of the human tuberculosis granuloma. *Nat Immunol* Vol.10, No.9, (August 2009), pp. 943-948.
- Sanchez, F.; Radaeva, T., Nikonenko, B., Persson, A., Sengul, S., Schalling, M., Schurr, E., Apt, A. & Lavebratt, C. (2003) Multigenic control of disease severity after virulent Mycobacterium tuberculosis infection in mice. *Infect Immun* Vol.71, No.1, (January 2003). pp. 126-131.
- Sasindran, S. & Torrelles J. (2011). Mycobacterium tuberculosis infection and inflammation: what is beneficial for the host and for the bacterium? *Frontiers in Microbiology*. Vol.2, (January 2011)
- Sawant, K. & McMurray D. (2007). Guinea Pig Neutrophils Infected with Mycobacterium tuberculosis Produce Cytokines Which Activate Alveolar Macrophages in Noncontact Culture. *Infect Immun.* Vol.75, No.4, (April 2007) pp. 1870-1877.

- Scanga, C.; Mohan, V., Tanaka, K., Alland, D., Flynn, J. & Chan, J. (2001). The inducible nitric oxide synthase locus confers protection against aerogenic challenge of both clinical and laboratory strains of *Mycobacterium tuberculosis* in mice. *Infect. Immun.* Vol.69, No.12, (December 2001), pp. 7711–7717.
- Scapini, P.; Lapinet-Vera J., Gasperini, S., Calzetti, F., Bazzoni, F. & Cassatella, M. (2000). The neutrophil as a cellular source of chemokines. *Immunol. Rev.* Vol.177, (October 2000), pp. 195–203.
- Schluger, N. & Rom, N. (1998). The Host Immune Response to Tuberculosis. *Am J Respir Crit Care Med*, Vol.157, No.3 pt1, (March 1998), pp. 679–691.
- Seiler, P.; Aichele, P., Bandermann, S., Hauser, A., Lu, B., Gerard, N., Gerard, C., Ehlers, S., Mollenkopf, H. & Kaufmann, S. (2003). Early granuloma formation after aerosol *Mycobacterium tuberculosis* infection is regulated by neutrophils via CXCR3-signaling chemokines. *Eur J Immunol.* Vol.33, No.10, (October 2003), pp. 2676 - 2686.
- Steyn, A.; Collins, D., Hondalus, M., Jacobs, W.Jr, Kawakami, R. & Bloom, B. (2002). *Mycobacterium tuberculosis* WhiB3 interacts with RpoV to affect host survival but is dispensable for in vivo growth. *Proc Natl Acad Sci U S A.* Vol.99, No.5 (March 2002), pp. 3147–3152.
- Subbian, S.; Tsenova, L., O'Brien, P., Yang, G., Koo, M., Peixoto, B., Fallows, D., Zeldis, J., Muller, G. & Kaplan, G. (2011) Phosphodiesterase-4 Inhibition Combined with Isoniazid Treatment of Rabbits with Pulmonary Tuberculosis Reduces Macrophage Activation and Lung Pathology. *The American Journal of Pathology*, Vol.179, No.1, (July 2011), pp. 289–301.
- Sugawara, I.; Yamada, H., Hua, S. & Mizuno S. (2001). Role of interleukin (IL)-1 type 1 receptor in mycobacterial infection. *Microbiol Immunol.* Vol.45, No.11, pp. 743–750.
- Sutherland, J.; Jeffries, D., Donkor, S., Walther, B., Hill, P., Adetifa, I., Adegbola, R. & Ota, M. (2009). High granulocyte/lymphocyte ratio and paucity of NKT cells defines TB disease in a TB-endemic setting. *Tuberculosis* Vol.89, No.6, (November 2009), pp. 398–404.
- Tan, B.; Meinken, C., Bastian, M., Bruns, H., Legaspi, A., Ochoa, M., Krutzik, S., Bloom, B., Ganz, T., Modlin, R. & Stenger, S. (2006). Macrophages acquire neutrophil granules for antimicrobial activity against intracellular pathogens. *J Immunol.* Vol.177, No.3, (August 2006), pp. 1864–1871.
- Thacker, E. (2006). Lung inflammatory responses. *Vet. Res.* Vol.37, No.3, pp. 469–486.
- Tracey, K.; Fong, Y., Hesse, D., Manogue, K., Lee, A., Kuo, G., Lowry, S. & Cerami, A. (1987). Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature.* Vol.330, No.6149, (December 1987), pp. 662–664.
- Tramontana, J.; Utaipat, U., Molloy, A., Akarasewi, P., Burroughs, M., Makonkawkeyoon, S., Johnson, B., Klausner, J., Rom, W. & Kaplan, G. (1995). Thalidomide treatment reduces tumor necrosis factor alpha production and enhances weight gain in patients with pulmonary tuberculosis. *Mol Med.* Vol.1, No4 (May 1995), pp.384–397.
- Tsao, T.; Hong, J., Huang, C., Yang, P., Liao, S. & Chang, K. (1999). Increased TNF-alpha, IL-1 beta and IL-6 levels in the bronchoalveolar lavage fluid with the upregulation of their mRNA in macrophages lavaged from patients with active pulmonary tuberculosis. *Tuber Lung Dis.* Vol.79, No.5, pp. 279–85.
- Tsao, T.; Hong, J., Li, L., Hsieh, M., Liao, S. & Chang, K. (2000). Imbalances between tumor necrosis factor-alpha and its soluble receptor forms, and interleukin-1beta and

- interleukin-1 receptor antagonist in BAL fluid of cavitary pulmonary tuberculosis. *Chest*. Vol.117, No.1., (January 2000), pp. 103-109.
- Ueda, Y.; Cain, D., Kuraoka, M., Kondo, M. & Kelsoe, G. (2009). IL-1R type I-dependent hemopoietic stem cell proliferation is necessary for inflammatory granulopoiesis and reactive neutrophilia. *J Immunol*. Vol.182, No.10, (May 2009), pp. 6477-84.
- Ulrichs, T. & Kaufmann, S. (2006). New insights into the function of granulomas in human tuberculosis. *J Pathol*. Vol.208, No.2, (January 2006), pp. 261-269.
- Ulrichs, T.; Kosmiadi, G., Trusov, V., Jörg, S., Pradl, L., Titukhina, M., Mishenko, V., Gushina, N. & Kaufmann, S. (2004). Human tuberculous granulomas induce peripheral lymphoid follicle-like structures to orchestrate local host defence in the lung. *J Pathol*. Vol.204, No.2, (October 2004), pp. 217-228.
- van Crevel, R., Ottenhoff, T. & van der Meer J. (2002) Innate Immunity to Mycobacterium tuberculosis. *Clin Microbiol Rev*. Vol.15, No.2, (April 2002), pp. 294-309.
- Velu, V.; Titanji, K., Zhu, B., Husain, S., Pladevega, A., Lai, L., Vanderford, T., Chennareddi, L., Silvestri, G., Freeman, G., Ahmed, R. & Amara, R. (2009). Enhancing SIV-specific immunity in vivo by PD-1 blockade. *Nature* Vol.458, No.7235, (March 2009), pp. 206-210.
- Walker, F.; Zhang, H., Matthews, V., Weinstock, J., Nice, E., Ernst, M., Rose-John, S. & Burgess, A. (2008). IL6/sIL6R complex contributes to emergency granulopoietic responses in G-CSF- and GM-CSF-deficient mice. *Blood*. Vol.111, no.8, (April 2008), pp. 3978-3985.
- Wallis, R.; Kyambadde, P., Johnson, J., Horter, L., Kittle, R., Pohle, M., Ducar, C., Millard, M., Mayanja-Kizza, H., Whalen, C. & Okwera, A. (2004) A study of the safety, immunology, virology, and microbiology of adjunctive etanercept in HIV-1-associated tuberculosis. *AIDS* Vol.18, No.2 (January 2004), pp. 257-264.
- Weiss S.J. (1989). Tissue destruction by neutrophils. *N Engl J Med*. Vol.320, No.6 (February 1989), pp. 365-376.
- Witko-Sarsat, V.; Rieu, P., Descamps-Latscha, B., Lesavre, P. & Halbwachs-Mecarelli, L. (2000). Neutrophils: Molecules, Functions and Pathophysiological Aspects. *Lab Invest*. Vol. 80, No.5, (May 2000), pp. 617, 2000.
- Yamada, H.; Mizumo, S., Horai, R., Iwakura, Y. & Sugawara, I. (2000). Protective role of interleukin-1 in mycobacterial infection in IL-1 alpha/ beta double-knockout mice. *Lab. Investig*. Vol.80, No.5, (May 2000), pp. 759-767.
- Yan, B.-S.; Pichugin, A., Jobe, O., Helming, L., Eruslanov, E., Gutiérrez-Pabello, J., Rojas, M., Shebzukhov, Y., Kobzik, L. & Kramnik, I. (2007) Progression of Pulmonary Tuberculosis and Efficiency of Bacillus Calmette-Guérin Vaccination Are Genetically Controlled via a Common sst1-Mediated Mechanism of Innate Immunity. *J Immunol* Vol.179, No.10, (November 2007), pp. 6919-6932.
- Zhang, Y.; Broser, M., Cohen, H., Bodkin, M., Law, K., Reibman, J. & Rom, W. (1995). Enhanced Interleukin-8 Release and Gene Expression in Macrophages after Exposure to Mycobacterium tuberculosis and Its Components. *J Clin Invest*. Vol.95, No.2, (February 1995), pp. 586-592.
- Zhu, L.; Liu, C., Chen, P., Dai, A., Li, C., Xiao, K., Chen, Y., Cao, J. & Chen, Y. (2011). Multidrug-resistant tuberculosis is associated with low plasma concentrations of human neutrophil peptides 1-3. *Int J Tuberc Lung Dis*. Vol.15, No.3, (March 2011), pp. 369-374.



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>

INTeCH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen