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Role of TNF in Host Resistance to Tuberculosis Infection: Membrane TNF Is Sufficient to Control Acute Infection

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1. Introduction

Tuberculosis (TB) infection is a major public health problem caused by *Mycobacterium tuberculosis* (*M.tb*). The present estimate is that one third of the world population harbors *M.tb* in a latent form (http://www.who.int), which may be reactivated when the host immune response is suppressed such as in HIV infection (Dye et al., 2005). Only 10% of the population which has been in contact with the pathogen develop overt clinical symptoms while roughly 90% of the infected persons contain the infection. A recent quantification of bacterial growth and death rates showed that *M.tb* replicates throughout the course of chronic TB infection in mice and is restrained by the host immune system (Gill et al., 2009). Unraveling the host immune response during primary and chronic/latent infection is therefore a major challenge. Prominent mechanisms of the host leading to protective immunity controlling tuberculosis and reactivation of infection are associated with T cells, macrophages, interferon-γ (IFN-γ), TNF, interleukin-12 (IL-12), nitric oxide (NO), reactive oxygen and reactive nitrogen intermediates (RNI), as reviewed (Cooper, 2009; Flynn, 2004; Flynn and Chan, 2001a; North and Jung, 2004). While IL-23 and IL-17 contribute to host resistance (Umemura et al., 2007), they do not seem essential to control acute TB infection (Khader et al., 2007).

2. The TNF family

TNF is the founder member of cytokine TNF-like superfamily (for review see (Locksley et al., 2001; Ware, 2005; Watts, 2005). TNF is expressed by many different cell types including macrophages, dendritic cells, CD4+ and CD8+ T cells, B cells, but also by other cells such as

adipocytes, keratinocytes, mammary and colon epithelium, osteoblasts, or mast cells. TNF is first synthesized as a homotrimeric 26 kDa membrane bound protein or transmembrane TNF (tmTNF). After proteolytic cleavage by TNF-alpha converting enzyme (TACE), 17 kDa soluble TNF is released. Levels of circulating TNF in healthy individuals are nearly undetectable however they increase substantially in pathological situations. Lymphotoxin alpha is a member of TNF superfamily and structurally the closest TNF relative. It exists as a soluble homotrimer (LTα3) or forms a membrane-bound heterotrimeric complex with the anchor LTβ.

TNF, LTα and LTβ genes are tightly clustered within 12kb inside the major histocompatibility complex locus on murine chromosome 17 (human 6), while the receptors (R), TNF-R1 and LTβR genes are clustered on mouse chromosome 6 and human chromosome 13 (Nedospasov et al., 1986; Spies et al., 1986). Membrane-bound as well as soluble TNF interact with two receptors, TNFR1 (p55 in mouse, p60 in humans, CD120a) and TNFR2 (p75/p80, CD120b). TNFR1, the high affinity receptor for soluble TNF, is constitutively expressed in nearly all tissues and cell types. TNFR1 contains a protein module called "death-domain" which is essential for induction of apoptosis, as well as for other non-apoptotic functions (Locksley et al., 2001). The expression of TNFR2 is more restricted to lymphoid tissues (Chan et al., 2000). Soluble LTα3 also binds and activates both TNFR1 and TNFR2, whereas membrane bound LTαβ exerts its unique functions through the engagement of LTβR (for review see Ware, 2005).

Receptor ligation initiates signals through a complex cascade to activate the nuclear factor NFκB, JNK-AP1 and p38 signaling axis resulting in activation of TNF-dependent program of gene expression (for review see (Grivennikov et al., 2006). Both TNR1 and TNFR2 are constitutively shed in substantial amounts *in vivo* and soluble TNF receptor shedding is likely to play an important role in regulating TNF activity under physiologic conditions (Pinckard et al., 1997). Macrophage infection by *M.tb* was shown to induce release of soluble TNFR2 that formed inactive TNF-TNFR2 complexes and reduced TNF bioactivity (Balcewicz-Sablinska et al., 1998). *M. bovis* BCG in vivo infection upregulates soluble TNFR1 and TNFR2 release in the circulation following release of TNF (Garcia et al., 2000).

Thus, tmTNF, soluble TNF and soluble LTα3 appear to mediate both overlapping and distinct physiological responses *in vivo*. Their relative roles in inflammatory models and in host defense have not been fully unraveled, in large part due to the limitations in physiologically relevant *in vivo* models. Membrane-bound TNF mediates cellular responses such as apoptosis, proliferation, B cell activation, and some inflammatory responses. To date, the main evidence for an *in vivo* role for tmTNF has come from genetically modified mice expressing uncleavable membrane-bound TNF {Ruuls, 2001, Alexopoulou, 2006). While the role of TNF in controlling tuberculosis has been extensively studied using a panel of available mouse models (Bean et al., 1999; Kaneko et al., 1999; Roach et al., 2002; Zganiacz et al., 2004), the role of LTα3 had to be implicated indirectly from the comparative phenotypes of mice deficient for LTα versus LTβ or TNFR1/TNFR2 versus TNF and therefore remained much less defined.

3. Non-redundant role of TNF to control mycobacterial infection

Macrophages, DC and epithelial cells are among the first cells encountering *M.tb* bacilli in the airway. Phagocytosis induces the transcriptional machinery resulting in the secretion of

several proinflammatory cytokines, chemokine, expression of costimulatory molecules and effector molecules including nitric oxide which has mycobactericidal activity (**Figure 1)**. Mycobacterial proteins are degraded and presented by class II proteins to the T cell receptor inducing clonal activation of CD4 T cells. IFNγ derived from T cells and NK or NKT cells is a potent activator of APCs, enhancing the killing of *M.tb* and presentation of mycobacterial peptide to T cells. The concerted action of cytokines and chemokines leads to accumulation of activated macrophages containing a few surviving bacilli surrounded by activated T cells, which constitutes the typical mycobacterial granuloma (**Figure 1)**. Other cell types may participate in this process and include neutrophils, eosinophils, NK, NKT and mast cells and possibly γδ-T cells (Cooper, 2009; Flynn and Chan, 2001a; North and Jung, 2004; Umemura et al., 2007).

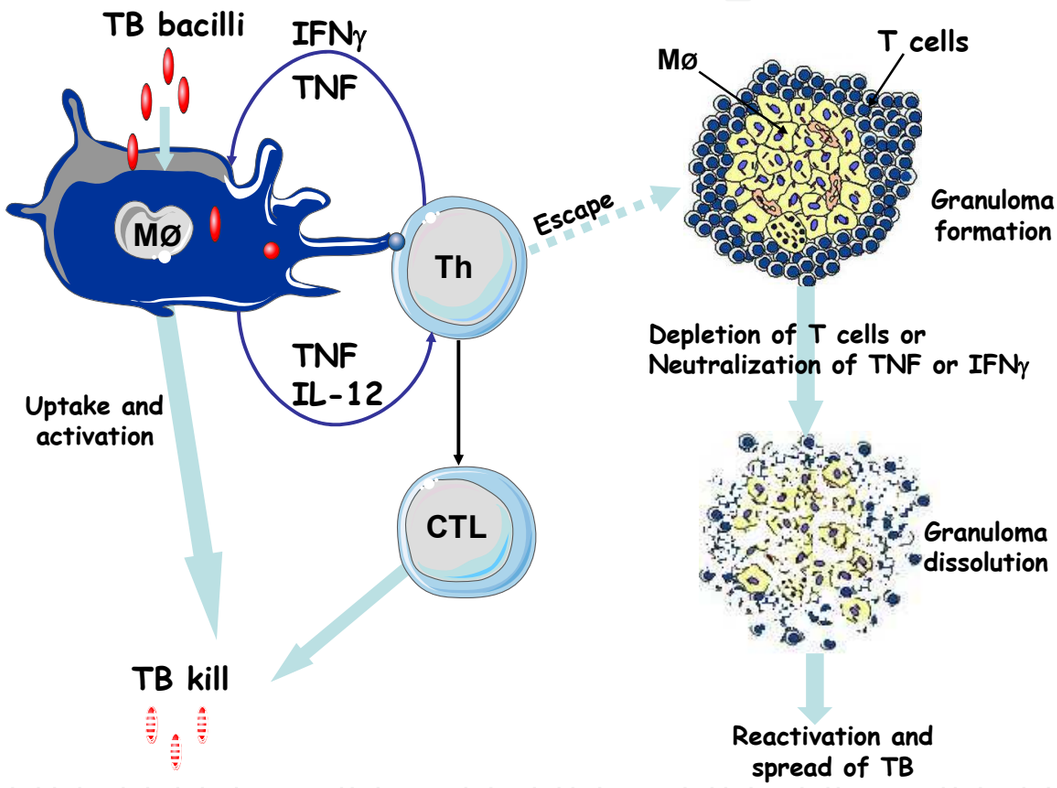

Fig. 1. Macrophage and T cell activation, killing of TB bacilli and granuloma formation. Macrophages are activated by TB bacilli and produce cytokines and T cell activation. Activated macrophages are mycobactericidal, but a few bacilli escape. The cell activation induces lymphocyte recruitment orchestrated by chemokines leading to the formation of granulomas which contain the bacilli. Antibody neutralization of TNF or IFNγ or T cell depletion result in dissolution of the granuloma structure, rescue of surviving bacilli with dissemination of infection.

Infection with the vaccine strain *M. bovis* BCG is well controlled in normal C57Bl/6 mice. However, the control of *M. bovis* BCG infection is TNF dependent as mice treated with anti-TNF antibodies showed impaired granuloma formation and increased bacillus content (Kindler et al., 1989). Transgenic mice expressing soluble TNFR1-Fc fusion protein

neutralizing TNF and LTα succumbed to *M. bovis* BCG infection (Garcia et al., 1997; Guler et al., 2005). Using the originally available TNF-LTα double deficient mice (Eugster et al., 1996), we showed that TNF and/or LTα signaling is required to activate cells of the immune system (Jacobs et al., 2000). TNF-LTα double deficient mice display high susceptibility and succumb to BCG infection between 8 and 10 weeks. The granuloma response was severely impaired with reduced T cell recruitment and macrophages expressed reduced inducible nitric oxide synthase (NOS2), a key mediator of antibacterial defense (Jacobs et al., 2000). We and others further compared the susceptibility of single TNF and LTα deficient mice, and showed that both single gene deficient mice succumbed to *M. bovis* BCG infection, suggesting that both TNF and LTα are necessary and non-redundant to control *M. bovis* BCG infection (Bopst et al., 2001). Reintroduction of LTα as a transgene into TNF-LTα double deficient mice prolonged survival but failed to restore resistance to *M. bovis* BCG (Bopst et al., 2001).

Although *M. bovis* BCG is an attenuated strain, the absence of TNF or TNF signaling induced a phenotype essentially similar to an infection with virulent *M.tb*. Indeed, mice deficient for TNF (Bean et al., 1999; Kaneko et al., 1999; Roach et al., 2002; Zganiacz et al., 2004), or TNF-R1 (Flynn et al., 1995), or mice treated with soluble TNFR1 or TNFR2 to neutralize TNF (Adams et al., 1995; Garcia et al., 1997; Smith et al., 2002) have poorly formed granulomas with extensive regions of necrosis and neutrophilic infiltration of the alveoli, and an inability to control mycobacterial replication upon infection with virulent *M.tb* strains. Bean et al. found comparable MHC class II and inducible nitric oxide synthase expression, serum nitrite levels, and normal activation of T cells and macrophages, while the organization of granulomas was clearly defective and not compensated by LTα (Bean et al., 1999). TNF was not required for granuloma formation, but rather for maintaining granuloma integrity indirectly by restricting mycobacterial growth within macrophages and preventing their necrosis in *M. marinum*-infected zebrafish (Clay et al., 2008). Similarly, in a murine model of *M. bovis* BCG infection, established hepatic granuloma showed a profound decrease in size and in their population of non-infected macrophages within 2-4 days of anti TNF treatment (Egen et al., 2008).

As observed in *M. bovis* BCG infection studies, both TNF and LTα seemed necessary to control infection with virulent H37Rv strain of *M.tb* (Roach et al., 2002; Roach et al., 2001). However, the very close mutual proximity of genes coding for TNF, LTα and LTβ on mouse chromosome 17 raises the issue of collateral gene damage in mouse models employing targeted modifications of TNF/LT genomic locus. For example, independently generated mouse strains with TNF deficiency behave identically in a number of infection and stress models but demonstrate discrepant phenotypes with regard to the development of Peyer's patches, apparently due to differences in the configuration of the targeted locus (Kuprash et al., 2005). Based on published reports, both removal of a regulatory element controlling transcription of the LT genes and their compensatory upregulation by the actively transcribed neo resistance cassette can be envisioned. Since LT expression essential for the development of Peyer's patches has to be cell type specific and may be subject to autoregulatory feedback loops, concluding resolution of these discrepancies proved to be a technically challenging task.

Another example of collateral gene damage, probably more relevant to TB research, is dysregulation of TNF expression in LTα knockout mice. Recently generated $LT\alpha^{\Delta\square\Delta}$ mice were fully capable of producing TNF at normal levels, whereas "conventional" LTα KO animals displayed significant decrease in TNF synthesis in several critical types of leukocytes both *in vitro* and *in vivo* (Liepinsh et al., 2006). In conventional LTα KO mice, TNF deficiency could be corrected by transgenic TNF expression (Alexopoulou et al., 1998). In agreement with the results of TNF promoter studies, the deficiency appears to be restricted to macrophages and neutrophils (Liepinsh et al., 2006). Defective TNF production has been noted, to various extent, by several published reports utilizing conventional LTα KO mice (Bopst et al., 2001; Schluter et al., 2003). Once again, cell type-specific collateral damage to transcriptional initiation may be difficult to unambiguously discriminate from physiological mutual regulation of two closely related cytokines sharing some of their receptors. Nevertheless, any conclusions indicating an independent protective role of soluble LTα in intracellular infections based on experiments with conventional LTα KO mice should be taken with certain caution. Our recent study comparing "conventional" LTα KO mice and $LT\alpha^{\Delta/\Delta}$ KO mice during *M.tb* and *M. bovis* BCG infections demonstrated that LTα might have a less essential role than anticipated for the control of acute infection, and the phenotype previously observed might indeed result at least in part from additional defects such as reduced TNF expression (Allie et al. 2010).

4. Molecular mechanisms of mycobacterial killing/resistance

Activation of macrophages and dendritic cells by *M.tb* induces several proinflammatory cytokines including TNF, LTα and IL-12, and expression of costimulatory molecules that enhance antigen presentation and activation of T cells. Activated T cells produce TNF, IFNγ and LTα inducing further activation of macrophages and likely other cells including stroma cells. Activated macrophages express NOS2, producing nitric oxide and reactive nitrogen intermediates (RNI), which are critical for killing and inhibiting growth of virulent *M.tb* and BCG (Chan et al., 1992; Garcia et al., 2000; MacMicking et al., 1995).

Mycobacteria may inhibit phagosomes maturation and fusion with lysosomes, thereby escaping killing (Mwandumba et al., 2004; Russell et al., 1996; Sturgill-Koszycki et al., 1996; Xu et al., 1994). Activated macrophages recruit T cells to form granulomas, which contain bacterial growth. The granuloma is a dynamic structure, which requires a permanent signal from activated T cells and macrophages (Ehlers et al., 1999). Any perturbation of this signaling such as neutralization of TNF causes dissolution of granulomas (Kindler et al., 1989) and allows reactivation and spread of infection (**Figure 1**). Activated T cells not only provide help, but acquire cytotoxic functions, which eradicate bacilli, although the relative contribution of CD4 versus CD8 cells to control TB infection is not fully established.

In order to better understand the effect of TNF on intracellular replication of mycobacteria, we investigated the growth of the vaccine strain BCG in TNF deficient macrophages. *M. bovis* BCG infection resulted in logarithmic growth of the intracellular bacilli, while recombinant BCG-expressing TNF (BCG-TNF) led to bacillary killing associated with production of NO. Therefore, TNF contributes to the expression of NOS2 and to bacterial growth inhibition indirectly (Bekker et al., 2001).

IFNγ has been shown to be an essential component of immunity to tuberculosis. It activates infected host macrophages to directly inhibit the replication of *M.tb* (Flynn and Chan, 2001a). Although IFNγ-inducible NOS2 is considered the principal effector mechanism, other pathways exist. *M.tb* has developed several mechanisms to escape eradication including inhibition of phagosome maturation (Flynn and Chan, 2003). Mycobacteria, blocking Ca^{2+} signaling and phagosome maturation in human macrophages or inhibiting sphingosine kinase, may allow the escape from eradication in the phagocyte (Malik et al., 2000; Malik et al., 2001; Malik et al., 2003). The role of autophagy and ensuing inhibition of phagolysosome formation (Deretic, 2008) may be considered, as well as Coronin-1 inhibition as an alternative pathway to prevent phagosome maturation (Jayachandran et al., 2007).

Defensins such as cathelicidin (LL37) have an important anti-mycobacterium activity in human macrophages. Liu and colleagues have reported that activation of Toll-like receptors (TLRs) up-regulates the expression of the vitamin D receptor and the vitamin D-1-hydrolase generating $1,25(OD)_2D3$, the active form of vitamin D, leading to induction of the microbicidal peptide cathelicidin and killing of intracellular *M.tb* in human macrophages (Liu et al 2006).

Mycobacteria induce apoptosis of macrophages and cause the release of apoptotic vesicles that carry mycobacterial antigens to uninfected antigen-presenting cells, including dendritic cells which are indispensable for subsequent antigen cross-presentation through MHC-I and CD1b. This new pathway for presentation of antigens from a phagosome-contained pathogen illustrated the functional significance of infection-induced apoptosis in the activation of CD8 T cells specific for both protein and glycolipid antigens in tuberculosis (Schaible et al., 2003).

Induction of TNF and other proinflammatory cytokines is mediated through several mycobacterial motives triggering different pattern recognition receptors, including TLR2, TLR4 or TLR9. However, while the control of acute TB infection was severely compromised in the absence of MyD88 (Feng et al., 2003; Fremond et al., 2004), TLR2, TLR4 and/or TLR9 do not seem essential for the control of acute TB infection but may interfere in the control of chronic infection (Bafica et al., 2005; Drennan et al., 2004; Holscher et al., 2008). The MyD88 pathway may thus contribute rather through IL-1R signaling to control acute TB (Fremond et al., 2007). TLR/MyD88 dependent signaling is also required for phagosome maturation (Blander and Medzhitov, 2004).

In summary, TNF participates in resistance to mycobacteria in the following ways: (1) activation of macrophages, (2) induction of chemokines and cell recruitment, (3) activation of T cells, (4) killing by macrophages, T and other cells and (5) regulation of apoptosis and signals from TLR/MyD88/IL-1R pathway that contribute to the host response. Since separating the effects of these different TNF functions *in vivo* is presently difficult or impossible, a computational model was applied to understand specific roles of TNF in control of tuberculosis in a single granuloma. The model predicted that macrophage activation is a key effector mechanism for controlling bacterial growth within the granuloma, TNF and bacterial numbers represent strong contributing factors to granuloma structure, and TNF-dependent apoptosis may reduce inflammation at the cost of impaired mycobacterial clearance (Ray et al., 2009).

5. Membrane TNF biological activity controls acute M.tb infection

Although a key role of TNF in controlling intracellular bacterial infections is uncontested, it is only recently that the specific function of membrane TNF has been appreciated. Membrane TNF is cleaved by the metalloproteinase-disintegrin TACE (TNF alpha converting enzyme) (Black et al., 1997) into the secreted, soluble trimeric TNF. Several functions of membrane TNF have been described, such as cytotoxicity, polyclonal activation of B cells, induction of IL-10 by monocytes, ICAM-1 expression on endothelial cells and liver toxicity (Decker et al., 1987; Grell et al., 1995; Kriegler et al., 1988; Ruuls et al., 2001). The transgenic expression of membrane TNF suggested an *in vivo* role of membrane TNF (Akassoglou et al., 1997). Olleros et al. investigated the resistance to mycobacterial infection in transgenic mice expressing a membrane TNF (Δ12-10; -1; one substitution, K11E) under the control of proximal TNF promoter and on a TNF-LTα deficient background. In this model membrane TNF had a fully protective effect against *M. bovis* BCG but only partial protective effect against *M.tb* infection (Olleros et al., 2002; Olleros et al., 2005). Mice with functional, normally regulated and expressed membrane-bound TNF represents a major advance and allowed interesting insights in the role of membrane TNF in lymphoid structure development and inflammation. Knock-in mice expressing the uncleavable Δ1-9,K11E TNF (Ruuls et al., 2001) and TNF-deficient mice (Marino et al., 1997) were compared in their resistance to mycobacterial infection. As previously reported for membrane TNF transgenic mice, we and others demonstrated that membrane TNF has important biological functions and substitutes soluble TNF to a large extent (Dambuza et al., 2008; Fremond et al., 2005; Saunders et al., 2005; Torres et al., 2005). Membrane TNF knock-in mice survived a *M.tb* aerosol infection for three months, were able to recruit and activate macrophages and T cells, generate granuloma and partially control mycobacterial infection in the early stage, unlike complete TNF deficient mice (Fremond et al., 2005; Saunders et al., 2005). However, during the chronic phase of infection membrane TNF knock-in mice demonstrated reduced bacterial clearance and succumbed to infection (Fremond et al., 2005). In another model of targeted mutagenesis in mice, the shedding of membrane TNF was prevented by deleting its cleavage site (Alexopoulou et al., 2006). Mice expressing non-cleavable and regulated Delta1-12 TNF allele partially controlled *M. bovis* BCG infection, with recruitment of activated T cells and macrophages and granuloma formation, while mice with complete TNF deficiency succumbed (Allie et al., 2008). It was confirmed that membrane TNF conferred partial protection against virulent *M.tb* infection and inter-crossing these mice with TNF-R1 or TNF-R2 KO mice showed that tmTNFxTNFR2 KO mice were very sensitive, essentially as much as TNF KO mice, while tmTNFxTNFR1 KO mice behaved more like tmTNF mice, suggesting that the protective effect of membrane TNF against acute *M.tb* infection is mediated through TNF-R2 signalling (Allie et al., 2008).

Therefore data from the genetic mouse models suggest that membrane expressed TNF is sufficient and soluble TNF dispensable to control the first phase of acute TB infection. However, during the chronic phase membrane TNF alone is not sufficient and soluble TNF seems to be required to control chronic TB infection. The reason for the progressive loss of infectious control is unclear. As previously discussed, soluble TNF may be required to negatively control the Th1 type cytokines. This TNF function may become important during the chronic phase of infection by regulating excess production of IL-12 and IFN-γ by DC and T cells.

6. TNF in reactivation of TB infection

Clinical tuberculosis in humans may be due to a primary infection or reactivation of latent controlled infection. Secondary immunosuppression due to HIV/AIDS is the most common cause of *M.tb* reactivation. In recent years, over a million patients received TNF neutralizing therapy for the treatment of severe rheumatoid arthritis, Crohn's disease or severe psoriasis. The most common complication of TNF blockade has been the emergence of opportunistic infection and tuberculosis. Both reactivation of latent tuberculosis and increased susceptibility to new tuberculosis in patients without a clinical history of active TB infection was observed (Wallis, 2008). In some patients, neutralizing TNF antibody, infliximab, or soluble TNFR2-IgG1 Fc fusion protein, etanercept, yielded reactivation of latent TB within 12 weeks and overt clinical disease (Keane, 2005; Keane et al., 2001; Mohan et al., 2004), often with extrapulmonary disease manifestations (disseminated infection in lymph node, peritoneum and pleura). The frequency of tuberculosis in association with infliximab therapy was higher than the reported frequency of other opportunistic infections associated with this drug (Keane, 2005). Reactivation of latent tuberculosis and primary infection in patients treated with TNF inhibitors are still difficult to be clearly defined in many cases. Anti-TNF antibody may be more associated with latent TB reactivation than etanercept. The majority of etanercept-associated cases of TB appears late (90% after 90 days of treatment) suggesting that these cases may have occurred as a result of the inability to control new *M.tb* infection while 43% of infliximab associated cases of TB occurred during the first 90 days of treatment, indicating that they likely represent reactivation of latent infection (Wallis, 2008; Wallis et al., 2005). The reactivation of latent TB under TNF blocking therapy indicates that the normal immune system is able to control, but not able to eradicate a primary infection, and that TNF plays a role in the long term containment of residual *M.tb* in tissues.

In order to study the factors leading to reactivation of chronic or chemotherapy controlled latent infection, several experimental models have been developed (Flynn, 2006). In the Cornell model, after an intravenous administration of *M.tb* H37Rv and treatment with pyrazinamide and isoniazide (INH) for 12 weeks, mice appear to have cleared the bacilli from organs, but a substantial proportion of animals spontaneously reactivate with acute disease upon cessation of chemotherapy. Since the original publication of the Cornell model a few variations have been reported (Botha and Ryffel, 2002; Flynn and Chan, 2001b). In the low-dose model, infection is exclusively controlled by the host in the absence of chemotherapy (Flynn and Chan, 2001b). Although considered to better reflect the human host response, bacterial numbers in the organs of these mice remain high during the chronic persistent phase of infection. To date, these models have yielded significant information on the immune effector mechanisms participating in latent or chronic persistent and reactivated tuberculosis.

We established the first aerosol infection model of drug-induced latent and reactivated murine tuberculosis using rifampicin and isoniazide (Botha and Ryffel, 2002, 2003). In this model, latency was defined as almost undetectable levels of bacilli in mouse organs for a prolonged period of time. Reactivation of infection could be achieved by inhibiting nitric oxide synthase activity by aminoguanidine (Botha and Ryffel, 2002). Using this model, we showed that a 4 weeks rifampicin and isoniazide administration cleared infection as assessed by viable bacterial accounts in the organs in both wild-type and TNF deficient

mice. Upon cessation of therapy massive spontaneous reactivation of *M.tb* infection occurred within several weeks in TNF deficient mice with necrotic pneumonia and death, while wild-type mice displayed mild subclinical reactivation (Botha and Ryffel, 2003). This model allows studying the role of TNF neutralization in a reactivating infection in the presence of an established specific adaptive immune response.

The role of soluble vs membrane TNF was then studied in this model (**Figure 2** and unpublished data). Although TNF KO mice rapidly lost weight and had to be terminated within 6 weeks after the end of the antibiotic treatment with uncontrolled infection, tmTNF KI mice survived as wild-type mice. Therefore, membrane TNF suffices to provide some control of the *M.tb* infection after reduction of the bacterial burden by an antibiotic treatment, while complete absence of TNF results in rapid progression of the infection.

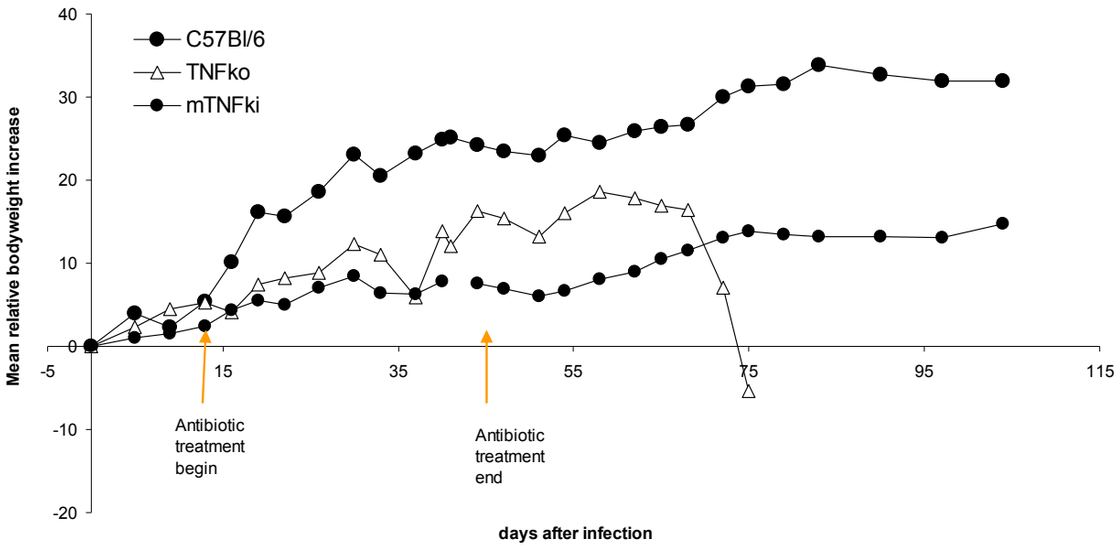

Fig. 2. Comparison of susceptibility of membrane TNF KI and conventional TNF KO reactivating, chronic *M.tb* infection.
Wild-type, TNF KO and mTNF KI mice were infected with *M.tb* (ca 100 CFU i.n.) and treated for 4 weeks with rifampicin and isoniazid (day 14-42) to control the infection. TNF KO mice started to die 6 weeks after the end of the antibiotic treatment while all mTNF KI mice survived as wild-type mice. In parallel groups infected with *M.tb* but not treated with antibiotics TNF KO had to be killed at 3 wk, while 6 out of 8 mTNF KI survived with no marked body weight loss.

7. Pharmacological TNF neutralization and TB control

The experimental models of TB reactivation described above allow to test the potential risk of diverse TNF neutralizing therapies to induce reactivation of TB. Administration of neutralizing TNF antibody but not of soluble TNF receptor was able to reactivate experimental latent infection (Plessner et al., 2007). TNF neutralization resulted in marked disorganization of the tuberculous granuloma and to the enhanced expression of specific proinflammatory molecules. (Chakravarty et al., 2008). A computational approach suggested that TNF bioavailability following anti-TNF therapy is the primary factor for

causing reactivation of latent infection and that even very low level of soluble TNF is essential for infection control (Marino et al., 2007).

Novel approaches to experimentally block soluble TNF are being tested in murine models of TB. One approach is to compete for natural TNF by the use of dominant negative mutant TNF (DN-TNF; see **Figure 3**) reported to block soluble TNF while sparing membrane TNF (Steed et al., 2003). *In vivo*, DN-TNF attenuated arthritis without suppressing innate immunity to *Listeria monocytogenes* (Zalevsky et al., 2007). Similarly, DN-TNF protected mice from acute liver inflammation, without compromising host control of *M. bovis* BCG and *M.tb* infections (Olleros et al., 2009). This was in contrast to TNFR2-IgG1 etanercept that inhibits murine soluble and membrane TNF as well as LTα, which severely compromised the host response to *M.tb* infection (Olleros et al., 2009). Another novel approach is an active immunization selectively targeting soluble TNF. Vaccination with a virus-like particle linked to a TNF N-terminal peptide resulted in high titers of autoantibodies against soluble TNF. It protected mice from arthritis without inducing reactivation of latent tuberculosis (Spohn et al., 2007), while immunization against the entire TNF molecule yielded enhanced reactivation of latent TB. This difference was attributed to recognition of only soluble TNF vs recognition of both transmembrane and soluble TNF by the elicited antibodies. Thus,

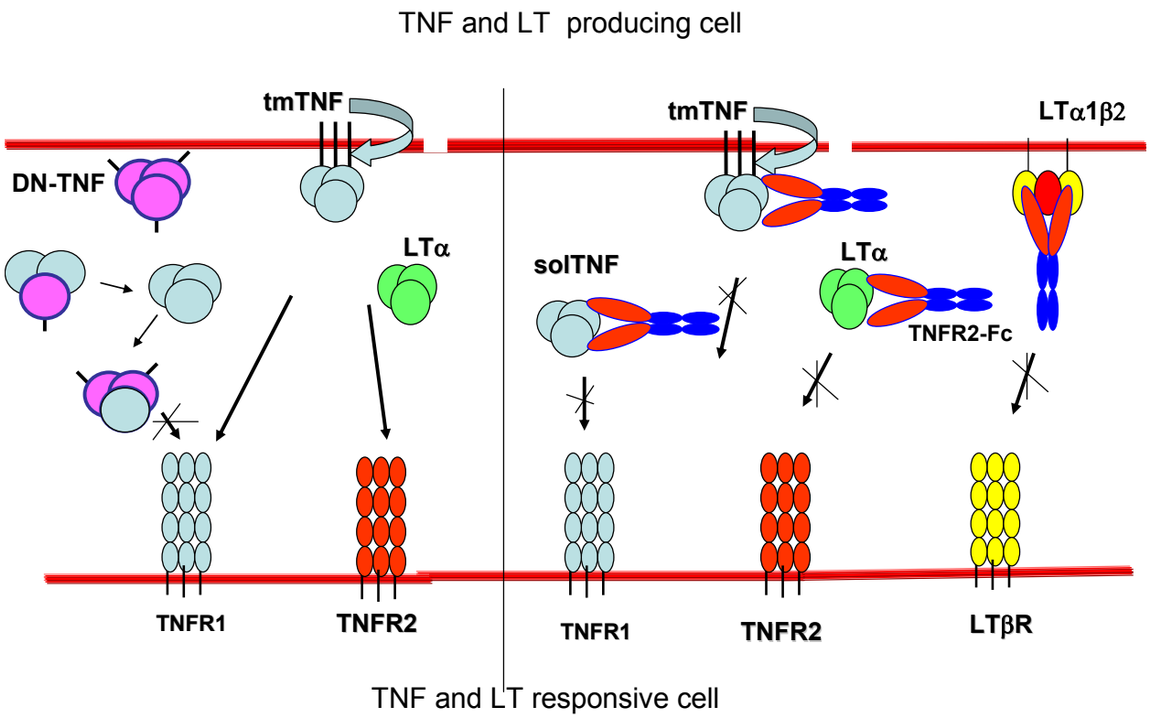

Fig. 3. Mechanisms of action of dominant-negative-TNF (DN-TNF) biologics and soluble TNFR2-Fc (Etanercept). *Left*, DN-TNF, a mutated form of human solTNF with disrupted receptor binding interfaces eliminates solTNF by a subunit exchange mechanism, but is unable to interact with tmTNF and LTα. *Right*, solTNF, tmTNF, LTα and LTαβ can be neutralized by Etanercept, inhibiting interaction with corresponding receptors. Thus, DN-TNF (XENP1595) inhibits solTNF receptor signaling without suppressing tmTNF- or LTα responses to TNFR1 and TNFR2, mediating inflammatory and immune responses

specifically targeting soluble TNF has the potential to be effective against inflammatory disorders while overcoming the risk of opportunistic infections associated with the currently available TNF antagonists.

8. Conclusions and perspectives

In conclusion, TNF is an essential mediator for the integrity of microbiocidal granulomas and the control of *M.tb* infection. Experimental tuberculosis infection of gene deficient mice has demonstrated the non-redundant contribution of several pro-inflammatory cytokines such as TNF, IL-12, IFNγ or IL-1 to the host response to M.tb infection (Flynn, 2006; Fremond et al., 2007). An important notion is the fact that latent mycobacterial infection can be reactivated by TNF neutralization. Sparing membrane TNF in neutralizing TNF therapy used in rheumatic arthritis or Crohn's disease may diminish the infectious complications and reactivation of latent TB infection.

9. Acknowledgments

This work was supported by the "Agence Nationale pour la Recherche" (ANR 2007 MIME-103-02), the "Fondation pour la Recherche Médicale" (FRM allergy DAL 2007 0822007), the "Fonds européen de développement regional" (FEDER Asthme 1575-32168) and Le Studium Orleans, CNRS, Orléans, France, National Research Foundation (South Africa), National Health Laboratory Service (South Africa), Medical Research Council (South Africa) and the University of Cape Town (South Africa)

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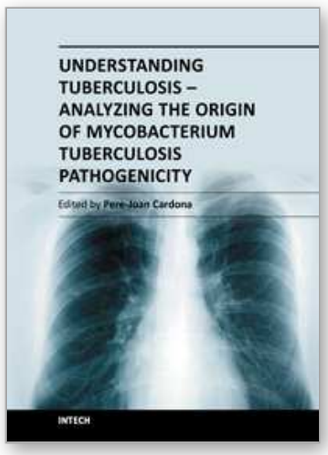

Understanding Tuberculosis - Analyzing the Origin of Mycobacterium Tuberculosis Pathogenicity

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

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Valerie Quesniaux, Irene Garcia, Muazzam Jacobs and Bernhard Ryffel (2012). Role of TNF in Host Resistance to Tuberculosis Infection: Membrane TNF Is Sufficient to Control Acute Infection, 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/role-of-tnf-in-host-resistance-to-tuberculosis-infection-membrane-tnf-is-sufficient-to-control-acute

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