REPORT

Immunological control of tuberculosis: role of tumour necrosis factor and more

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Therapy of autoimmune diseases with tumour necrosis factor (TNF) neutralising agents has provided a unique opportunity to learn about the significance of TNF in the maintenance of latent bacterial infections in humans. The remarkably high incidence of tuberculosis in patients treated with TNF antagonists raises the intriguing question about the physiological role of TNF in maintaining the lifelong latency of tubercle bacilli in granulomas in infected patients. Basic research during the past decade(s) combined with thoughtful observations in human subjects with tuberculosis and autoimmune diseases has provided several potential explanations for the recurrence of tuberculosis if TNF supply is withdrawn. TNF is involved in at least four key functions that contribute towards beneficial effects on the symptoms of autoimmune disorders on the one hand, and the attenuation of immune responses against *Mycobacterium tuberculosis* on the other hand. These are outlined in this review: induction of apoptosis, maturation of dendritic cells, activation of antimicrobial activity in macrophages, and orchestration of leucocyte movement.

Inhaled *Mycobacterium tuberculosis* is taken up by local alveolar macrophages, which provide the first line of defence for the infected individual. Infected alveolar macrophages release a panel of antimicrobial effector molecules, cytokines, and chemokines, which govern innate immune responses (fig 1) and initiate specific immunity. This complex network of mediators induces activation of antimicrobial activity in macrophages, migration of antigen laden phagocytes to the draining lymph nodes, and finally the influx of antigen specific T lymphocytes to the site of infection (fig 2). Optimally, this results in the formation of a well organised granuloma consisting of central macrophages with surrounding lymphocytes. This cellular micro-environment provides a physical and immunological barrier for the entrapped bacilli thereby preventing multiplication and spread of the mycobacteria. Nevertheless the granuloma contains viable bacilli—most likely throughout the lifetime of the host—and the maintenance of the granuloma is a prerequisite to keep the bacilli in check. Factors disrupting the fine-tuned balance between the low level mycobacterial metabolism and the steady cellular influx to the granuloma will inevitably expose the risk of tipping the balance in favour of the pathogen and result in reactivation of disease.

TNF plays a key role in these processes and mice deficient in TNF fail to control a primary challenge with *M. tuberculosis*.^{1–4} TNF is also essential for maintaining the state of dormancy in mice^{5–7} and humans.^{8–14} The precise mechanisms underlying these findings are yet to be defined but several functions attributed to TNF are potentially relevant for preventing reactivation of tuberculosis.

TNF IS INVOLVED IN THE REGULATION OF APOPTOSIS OF CELLS INFECTED WITH *M. Tuberculosis*

Alveolar macrophages infected with *M. tuberculosis* undergo apoptosis, a process that is at least partially mediated by TNF.^{15–16} Virulent *M. tuberculosis* prevents apoptosis via the suppression of TNF^{16–17} and neutralisation of TNF in cultures of avirulent mycobacteria restores the ability to induce apoptosis in the host cells.¹⁸ This implicates that the prevention of TNF mediated apoptosis is an evasion strategy of virulent mycobacteria. To date there is no clear consensus on whether apoptosis of infected macrophages is beneficial or harmful for the infected organism. The induction of apoptosis could contribute to protection by directly killing the mycobacteria^{19–22} or by strengthening adaptive immunity by inducing the cross-presentation of mycobacterial antigens by dendritic cells (DCs).²³ On the other hand massive apoptosis of macrophages in TNF receptor deficient mice has been described without beneficial effects on mycobacterial killing.²⁴ Taken together, these reports suggest that TNF supports apoptosis of macrophages infected with *M. tuberculosis*, thereby contributing to the clearance of the pathogen.

TNF SUPPORTS THE MATURATION OF DCs

DCs are unique in their ability to ingest pathogens at the site of infection and to migrate to secondary lymphoid organs, where they present pathogen derived antigens to naive T lymphocytes.²⁵ TNF is important for triggering the maturation programme in DCs that induces migration and the upregulation

Figure 1 Innate immunity in tuberculosis. GM-CSF, granulocyte macrophage-colony stimulating factor; IL, interleukin; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; RANTES, Regulated on Activation, Normal T Expressed and Secreted; TGF, transforming growth factor; Th, T helper; TNF, tumour necrosis factor.

Abbreviations: CCL, chemokine ligand; CCR, chemokine receptor; DC, dendritic cell; TNF, tumour necrosis factor

Figure 2 Initiation of adaptive immunity. IFN, interferon; MHC, major histocompatibility complex; TCR, T cell receptor; TNF, tumour necrosis factor.

of the molecular pattern required for the activation of T cells.²⁶ DCs are present in epithelial layers, including alveolar spaces in the lung, where they create a tight surveillance network.²⁷ This localisation suggests that they present a first line of defence against inhaled foreign particles, including microbial pathogens. Recent work has demonstrated that DCs infected with mycobacteria accumulate in the spleen in *M. tuberculosis* infected mice²⁸ and are detectable in granulomas of infected rats²⁹ and humans.³⁰ In vitro experiments revealed that *M. tuberculosis* is phagocytosed by human DCs,^{32–35} mainly by the interaction between the mycobacterial lipoarabinomannan and DC specific C-type lectin (DC-SIGN).³¹ This indicates that the interaction of mycobacteria and DCs plays a special role because macrophages, the major host cells of *M. tuberculosis*, do not express significant levels of DC-SIGN.³⁷ DCs have a special role in initiating T cell responses in tuberculosis. They are essential for activating conventional T cells in the lung, because the local alveolar macrophages are poor antigen presenting cells.^{38–41} In addition, DCs are unique in their ability to activate unconventional subsets of T cells via the antigen presenting molecules, human leucocyte antigen (HLA)-E⁴² and CD1,⁴³ which are not present on macrophages. A subset of *M. tuberculosis* reactive cells is CD8+ cytotoxic T cells²¹ that may be particularly important because these cells release granulysin and directly kill intracellular bacteria.⁴⁹ In summary, TNF promotes the maturation of DCs, thereby inducing the transport of mycobacterial antigens to the lymph nodes and the priming of T cell subsets that traffic to the site of infection to complement effector mechanisms of innate immunity.

TNF INDUCES ANTIMICROBIAL ACTIVITY OF MURINE MACROPHAGES

There is striking evidence that TNF in combination with the T cell derived cytokine interferon γ (IFN γ) induces antimicrobial activity in murine macrophages⁵⁰ via the induction of reactive nitrogen intermediates.⁵¹ Accordingly, TNF deficient mice produce insufficient amounts of nitrogen radicals during tuberculosis and fail to control disease.³ The regulation of antimicrobial effector mechanisms in humans is distinct and the combination of TNF and IFN γ fails to induce

nitric oxide or antimycobacterial activity in alveolar macrophages,⁵² even though nitric oxide activity is detectable at the site of disease.^{53–55} In vitro, TNF even supports the growth of virulent mycobacteria in human monocytes,⁵⁶ alveolar macrophages,⁵⁷ and DCs.³⁵ Therefore the induction of direct antimicrobial activity in infected host cells does not appear to be an effector mechanism of TNF in humans.

TNF DIRECTS THE MOVEMENT OF LEUCOCYTES

One of the major functions of TNF is the recruitment of monocytes and circulating antigen specific T lymphocytes to the site of infection. The mechanisms by which TNF directs leucocyte movement include its action on the vascular endothelium (for example induction of the intercellular adhesion molecule (ICAM)-1) and the capacity to establish gradients for chemokines such as chemokine ligands CCL2 (MCP1), CCL3 (MIP1 α), CCL4 (MIP1 β), CCL5 (RANTES), CXCL10, and CXCL13.^{58–62} TNF also modulates the migration of B lymphocytes and the development and function of B and T zone stromal cells required for lymphocyte compartmentalisation in the spleen.⁶³ Finally, TNF influences the expression of chemokine receptors (CCRs) such as CCR2⁶⁴ and CCR5.⁶⁵

Formal proof for a direct link between the lack of TNF, altered chemokine/CCR expression, and increased susceptibility to tuberculosis is lacking but there is abundant circumstantial evidence to support this hypothesis:

- TNF deficient mice fail to develop^{1–3} and maintain^{3–7} granulomas
- CCL2 (MCP1) deficient mice,⁶⁷ CCR2 deficient mice,⁶⁸ and CCR5 deficient mice⁷⁰ infected with *M. tuberculosis* demonstrate severe alterations in the cellular influx to the lung. However, the overall effect on the outcome of disease is variable highlighting the promiscuity and redundancy of the chemokine/CCR network
- lymph node tissue and blood monocytes isolated from patients with tuberculosis express more CCL2 (MCP1) than controls⁷¹
- neutralisation of TNF production by peripheral blood cells following stimulation with mycobacterial lipoarabinomannan reduced the release of CXCL8, CCL2, and CCL4.⁷²

Figure 3 Key functions of tumour necrosis factor (TNF) in tuberculosis. DC, dendritic cell, IFN, interferon.

Given the profound effects of TNF on the regulation of adhesion molecules, chemokines, and chemokine receptors it is tempting to speculate that neutralisation of TNF will disrupt the delicate cellular architecture of the tuberculous granuloma and permit resuscitation of latent *M. tuberculosis*.

CONCLUSIONS

TNF is critical for prevention of establishment of mycobacterial infection and the maintenance of latent tuberculosis. Likely mechanisms include the induction of apoptosis, the maturation of DCs and induction of antigen specific T cell responses and most importantly directing the movement of leucocytes (fig 3). The relevance of these mechanisms in human tuberculosis is strongly supported by immunological studies in patients with autoimmune diseases receiving therapy with TNF neutralising agents. Anti-TNF therapy modulates apoptosis,^{73–77} reduces the release of macrophages activating cytokines by antigen specific T cells^{78–79} and the production of nitric oxide,⁸⁰ and interferes with leucocyte movement.^{81–84} This grave intervention in the delicate balance between *M. tuberculosis* and the local immunity may also account for the frequent extrapulmonary spread, the severe clinical course and the difficulties in therapy of patients developing tuberculosis during therapy with TNF antagonists.^{85–88} Stringent attention to available guidelines is essential for identification of patients at risk for reactivation of tuberculosis under therapy with TNF antagonists.^{89–90}

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