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Review Article

Cytokine Environment in Tuberculoid Lung Granuloma

Verduzco-Sierra OA and Rosas-Taraco AG*
Department of Immunology, Universidad Autonoma de Nuevo Leon (UANL) and University Hospital, Mexico

***Corresponding author:** Rosas-Taraco AG, Department of Immunology, Faculty of Medicine, Universidad Autonoma de Nuevo Leon (UANL) and University Hospital, Monterrey, Nuevo Leon, Mexico

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Abstract

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), is responsible for about 1.3 million deaths. Mtb is phagocytosed by alveolar macrophages, which trigger an immune response that recruits new cells to the infected tissue. Cytokines produced by local and recruited cells are involved in the host response to Mtb. The newly arrived immune cells are the basis of the granuloma. It is the characteristic lesion of pulmonary tuberculosis. The main function of the granuloma is control the mycobacterial infection but it also may contribute to Mtb survival. The cytokine microenvironment controls granuloma formation and this environment may be associated with the outcome of the disease.

Keywords: Tuberculosis; Granuloma; Immune environment; Inflammatory and anti-inflammatory responses; Cytokines

Abbreviations

TB: Tuberculosis; Mtb: *Mycobacterium Tuberculosis*; LTBI: Latent Tuberculosis Infection; DCs: Dendritic Cells

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (Mtb) that primarily affects the lung and was responsible for about 1.3 million deaths in 2015 (See World Health Organization Tb data). Mtb is a facultative intracellular bacterium that infects and survives inside macrophages and other immune cells [1]. Only 5-10% of individuals exposed to Mtb develop a primary active disease. The majority of infected individuals develop a Latent TB Infection (LTBI) [2]. The control of LTBI cases correlates with a strong immune system response and a balanced cytokine microenvironment in the zone of infection. This review focuses on the cytokine microenvironment of granulomas and how immune-modulation affects the outcome the disease.

Granuloma

Aerosol droplets transmit Mtb and after bacilli are phagocytosed by alveolar macrophages they induce a localized pro-inflammatory response that leads to a systemic immune response that brings new cells to the area [3]. This response is orchestrated by cytokines produced by immune cells in the area of infection [4]. These local and newly arrived cells are the foundation of the granuloma [5], also known as tubercle, which is the characteristic lesion of tuberculosis. The formation of the granuloma is essential for the control of mycobacterial infection but paradoxically, granulomas are also responsible for the typical immunopathology caused by this infection [6,7]. The main function of the granuloma is to contain the bacilli, prevent their spread and also to create a cytokine microenvironment for an optimal immune response. Granulomas are composed of hematopoietic cells, Dendritic Cells (DCs) [8], T cells and B cells but especially mononuclear macrophages including monocytes, tissue macrophages, and transformed macrophages such as foamy or giant cells [9,10], figure 1 shows lung granuloma. In early stages, a pronounced neovascularization caused by Vascular Endothelial Growth Factor (VEGF) can be observed. In humans, three distinct types of granulomas can be distinguished [1]. The solid granuloma correlates with LTBI, this granuloma is composed of infected and non-infected macrophages and lymphocytes and a center without necrosis. The necrotic granuloma is composed of neutrophilic invasion and a necrotic center, which indicates a metabolic reactivation of Mtb. This necrotic granuloma expands and causes tissue damage. With the passing of time the granuloma lacks vascularization. This induces hypoxia that liquefies the necrotic center and a caseous granuloma develops. The caseous granuloma provides a rich environment for the survival and reproduction of Mtb, in addition to the formation of large cavities that cause major tissue damage and the access of Mtb into blood vessels and alveoli.

Development of the TB granuloma

Macrophages infected with Mtb produce cytokine and chemokine involved in the recruitment of monocytes, neutrophils, Dendritic Cells (DCs), and resident tissue macrophages. Pro-inflammatory cytokines (IL-1, IL-6, TNF-α) are produced in the first response of the immune system to Mtb infection causing focal recruitment and accumulation of mononuclear cells [11]; however, Mtb can survive and proliferate in the mononuclear cells by inhibiting their innate immune function [12]. Mtb interferes with phagosome-lysosome and induce an anti-inflammatory response by elevating IL-10 production [13]. Macrophages and DCs by themselves cannot control the infection, however, T lymphocytes (CD4+ and CD8+ T cells) are activated by those cells and work together in granuloma formation [14,15]. Th1lymphocytes produce TNF-α, Interferon Gamma (IFN-γ), Lymphotoxin (LT), and IL-2 [16,17]. These cytokines are important in macrophage activation and lymphocyte proliferation. The granuloma becomes a well-organized structure with recruited lymphocytes and other immune cells, with a central area containing Mtb-infected macrophages surrounded by non-infected macrophages, neutrophils, and lymphocytes. Around the granuloma, macrophages are activated toward M1 phenotype by inflammatory cytokines which drive the infection into a latent stage [6]. Mtb can switch the macrophage phenotype mainly to M2, which is an anti-inflammatory phenotype and is correlated to foamy cell formation by elevating lipid

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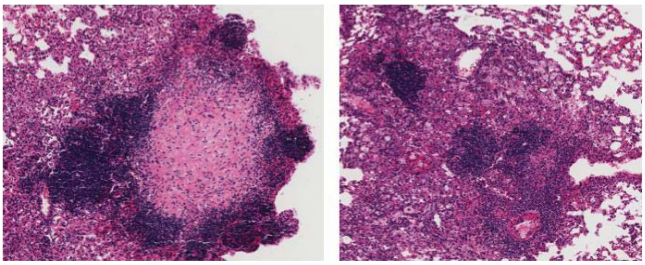

Figure 1: Lung granuloma of mice infected with *Mycobacterium tuberculosis*. Six to eight weeks old C57BL/6 female mice (n=5) were purchased from Jackson (Bar Harbor. ME). The IACUC of Colorado State University approved all animal procedures used in this study. The mice were kept in BSL3 facilities and they were rested for a week prior to infection. The mice were then infected with a low dose aerosol infection using the Glass-Col System to deliver ~50-100 Mtb (Erdman strain, TMC107; ATCC 35801) bacilli per mouse. Necropsy of animals was done at 60 days post-infection; lung samples were collected for bacterial burden determination and histopathological assessment. The post caval lobe of the lung of each mouse was fixed in 4% PFA. Samples were inactivated in 4% PFA solution for 48hrs and transfer to histology cassettes for processing using standard histological protocols for sectioning and staining with Haematoxylin-Eosin (H&E). H&E staining was visualized using the Aperio Digital Scanner (Leica Biosystems) and analyzed with Image Scope software. Photographs show granuloma formations in lung tissue sections stained with H&E. Left photo demonstrate peripheral accumulation of lymphocyte with a core of cells resembling macrophages including foamy cells intermixed with fibroblast type cells. Right photographs show centers of cell aggregations resembling lymphocytes surrounded by foamy macrophage like cells. Photos and descriptions are courtesy of Dr. Mercedes Gonzalez-Juarrero from Colorado State University.

metabolism. This effect may be attributed to ESAT-6 [18-20]. This process leads to caseous granuloma formation and release of Mtb. Although the granuloma is a mechanism of defense in Mtb infection that contains a mycobacterium load, when the immune system fails, and the balance between cytokines disrupts, the granuloma can favor Mtb survival [21]. The complexity of the infected tissue and the heterogeneous vascular supply within the granuloma may impede drug delivery [22].

Cytokines and granuloma

Tumor necrosis factor alpha: TNF-α is one of the key cytokines in granuloma formation. The site of bacterial persistence in pulmonary TB patients is rich in TNF-α. The mononuclear phagocytes are the main source of this cytokine in granulomatous diseases [23,24]. Pathogen Recognition Receptors (PRR) have been implicated in Mtb recognition and follow up TNF-α production [25,26]. Also both CD4 and CD8 T-cells respond and entail a significant source of TNF- α, which regulates phagocytosis and apoptosis [27,28].

Changes in TNF-α levels significantly modify the course of the disease, a report described that low TNF-α levels or even its absence correlates with fatal TB disease outcome [1,29]. This outcome is a consequence of a lack of a mononuclear phagocyte response and granuloma dysfunction. On the other hand, excessive release of TNF-α induces a hyper-inflammatory state, that condition has been associated with a poor prognosis. The role of TNF-α in the development and integrity of the granuloma is well known. TNF-α deficiency murine presented deficient granuloma structure and reactivation of TB [30] also this reactivation phenomenon can be seen in patients treated with TNF-α antagonists [31-34]. Virulent Mtb modulates TNF-α production compared to non-virulent strains. Moreover, TNF-α plays an important role in TB protection or reactivation together with an *in situ* cytokine microenvironment. High rates of TB reactivation have been reported in humans treated with TNF-α inhibitors [35,36].

Other pro-inflammatory cytokines: IFN-γ is a key cytokine released by CD4 T-cells and involved in macrophage activation [2,9]. IFN-γ deficient mice are profoundly susceptible to mycobacterial infections and they present fail to develop granulomas and poor survival rate [37]. IFN-γ interacts with other cytokines such as IL-12 and IL-23 to induce and maintain the Th1 immune profile that plays an important role in the formation of granuloma and containment of TB [38].

Anti-inflammatory cytokines: The intense inflammatory response needs to be regulated to prevent major tissue damage [39]. Release of IL-10 in mycobacterial infections can reduce the production of IL-12, however, IL-10 may deactivates macrophages and reduces the impact of IFN-γ on these [40]. Lung tissue fibrosis is a result of fibroblast activation trigger by anti-inflammatory cytokine Transforming growth factor β (TGF-β) [41]. TGF-β is produced in a basal form and can be activated by different stress situations like hypoxia or low Ph [42]. High levels of TGF-β are correlated with active pulmonary TB [43]. TGF-β stimulates the differentiation of fibroblast to myofibroblast and the production of collagen. Also pulmonary TB fibrosis shows an alternative macrophages phenotype (M2 that interferes with T-cells responses against Mtb).

IL-4/IL-13: IL-4 induces a Th2 response; experimental models of latent TB have revealed that progression to active tuberculosis correlates with high levels of IL-4 gene expression [44,45]. Neutralization of IL-4 results in lower bacterial loads and disease severity compared with wild type mice and also healthy infected TB subjects exhibited a selective increase of message for the IL-4 antagonist [46]. In humans, high IL-4 and IL-13 expression levels have been correlated with lung tissue damage [47]. IL-13 overexpression causes hypoxia in the granuloma that encourages the metabolic activity of Mtb and leads to the formation of necrotic granulomas. Another phenomenon of high IL-13 levels induces the arg-1 gene, which has been correlated with necrotic granuloma formation in TB [48].

Animals Models for the Study of Granuloma

Animal models have been used for a long period of time and those models have provided a lot of useful data in tuberculosis research. Mice are the most common models because of its availability and ease of management, however there is no true latent infection and they develop a progressive infection that eventually leads to death. Moreover, mouse granulomas are different in terms of structure and organization compared to human granuloma. A recent study demonstrated that macaques develop a similar pathology to humans, however some disadvantages are found such as the cost, management, and ethical implications of the use of macaques [4,49,50].

Cytokine Environment in Pulmonary Tuberculosis

Fenhalls et al. describe the lung TB granuloma cytokine microenvironment of 5 human patients; they found IFN-γ expression in 2 of 5 patients, IFN-γ and IL-4 in 3 of 5 patients and TNF-α in

all 5 patients [16]. In another study with macaques, they found a significant relationship between IL-17 and IL-10 and IL-10 *vs*. IFN-γ on sterile granulomas suggesting that a balance of pro-inflammatory and anti-inflammatory effects are required for reducing the pathology [49]. There are a lack of studies in humans because of the lack of noninvasive techniques and the complex management of mycobacteria.

Immunomodulation as a Treatment Option

Anti-inflammatory cytokines are present in the granuloma. IL-10 is a cytokine of interest because of its capacity to down-regulate the production of pro-inflammatory cytokines and chemokines, specifically TNF-α. It has been demonstrated that the balance between pro-inflammatory and anti-inflammatory cytokines is required for an efficient immune response. In a study of an in silico model of the granuloma cytokine environment, researchers performed a series of experiments of the interaction of IL-10 with TNF-α. First, they observed the response of the disease with a virtual deletion of IL-10 at the start of infection and they observed a significant change in the number of granuloma that achieved sterility compared to wild type granulomas. IL-10 inhibition participates in the sterility of granulomas and is only significant in early stages of the disease because patients typically present symptoms months before infection; this treatment is unlikely to be implemented. Also the loss of regulation of the pro-inflammatory response causes great damage to lung tissue. Studies have been demonstrated that TGF-β blocking reduced Mtb bacterial load in an animal model of tuberculosis [51,52]. A recent study demonstrated that TGF-β regulates phenotypic changes in granulomas after drug treatment in pulmonary TB. There are high levels of SMAD-2/3 (an intermediary of TGF-β signaling) in active TB. After two months of drug treatment, TGF-β levels decrease and granulomas show central organization and thickening of a peripheral fibrotic cuff that indicates a healing granuloma phenotype [41].

HIV Infection and TB Granuloma

TB is the leading cause of death among HIV-infected persons [53]. The increase in the Mtb infection ratio in HIV-positive patients correlates with immunological disruptions of granuloma [54]. HIV infection breaks the immunological balance by interrupting the normal function of Tcells and macrophages, destroying CD4+ T cells. This causes disorganization in granuloma structure [55-57]. Lower TNF-α and CD4+ T cells are associated with an increased bacterial count, inflammatory cytokine production by foamy cells, and inadequate granuloma formation [58,59]. More studies about granuloma structure in HIV/Mtb are needed to clarify the effect of HIV in granuloma formation.

Conclusion and Perspectives

In summary, granuloma formation is needed to avoid Mtb expansion and dissemination; however, it has been related with Mtb latency survival and low anti-tuberculosis drugs delivery. Cytokine microenvironment tuberculoid granuloma is important to TB pathogenesis and prognosis. A balance between pro-inflammatory and anti-inflammatory cytokines is key to TB control. Future studies related with lung granuloma immunomodulation will be needed to control TB.

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