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The role of pattern recognition receptors in lung sarcoidosis



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ABSTRACT

Sarcoidosis is a granulomatous disorder of unknown etiology. Infection, genetic factors, autoimmunity and an aberrant innate immune system have been explored as potential causes of sarcoidosis. The etiology of sarcoidosis remains unknown, and it is thought that it might be caused by an infectious agent in a genetically predisposed, susceptible host. Inflammation results from recognition of evolutionarily conserved structures of pathogens (Pathogen-associated molecular patterns, PAMPs) and/or from reaction to tissue damage associated patterns (DAMPs) through recognition by a limited number of germ line-encoded pattern recognition receptors (PRRs). Due to the similar clinical and histopathological picture of sarcoidosis and tuberculosis, *Mycobacterium tuberculosis* antigens such early secreted antigen (ESAT-6), heat shock proteins (Mtb-HSP), catalase-peroxidase (katG) enzyme and superoxide dismutase A peptide (sodA) have been often considered as factors in the etiopathogenesis of sarcoidosis. Potential non-TB-associated PAMPs include lipopolysaccharide (LPS) from the outer membrane of Gram-negative bacteria, peptidoglycan, lipoteichoic acid, bacterial DNA, viral DNA/RNA, chitin, flagellin, leucine-rich repeats (LRR), mannans in the yeast cell wall, and microbial HSPs. Furthermore, exogenous non-organic antigens such as metals, silica, pigments with/without aluminum in tattoos, pesticides, and pollen have been evoked as potential causes of sarcoidosis. Exposure of the airways to diverse infectious and non-infectious agents may be important in the pathogenesis of sarcoidosis. The current review provides and update on the role of PRRs and DAMPs in the pathogenesis of sarcoidosis.

1. Introduction

The definition of sarcoidosis reported by the American Thoracic Society/European Respiratory Society/World Association for sarcoidosis and by the Granulomatous Disorders Statement on sarcoidosis (Hunninghake, 1999) is merely descriptive. These definitions indicate that sarcoidosis is a multisystem granulomatous disease frequently affecting barrier tissues such as the lungs, eyes, and skin (Iannuzzi, 2007; Haimovic et al., 2012) although the liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones and other organs may also be involved (Costabel, 2001). There is an enormous variety in the clinical presentation of sarcoidosis with most patients

presenting with symptoms such as fatigue, fever, dry cough, dyspnea, chest pain, and malaise or weight loss (Buaghman, 2001).

Pulmonary and mediastinal involvement is found in approximately 90% of the cases, but virtually every organ can be involved in this disease. Pulmonary involvement in sarcoidosis can be categorized using chest radiographs and is classified according to the Scadding criteria (Hunninghake, 1999). Extra pulmonary organ involvement ranges from harmless skin manifestations to life-threatening myocardial sarcoidosis or neuro-sarcoidosis (Perry et al., 1995; Sharma, 1997). Occasionally, sarcoidosis can be found in completely asymptomatic individuals.

Fortunately, in the majority of patients spontaneous remission occurs within 2–3 years. However, approximately 10–20% of patients

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develop pulmonary fibrosis which has a very poor prognosis and high mortality (Crystal et al., 1984). Unfortunately, the course of the disease is difficult to predict although one distinct clinical entity (Lofgren's syndrome) is known to have a favorable prognosis. Lofgren's syndrome was first recognised in 1946 and is characterized with fever, bilateral hilar lymphadenopathy, erythema nodosum and arthralgia (Lofgren, 1946).

Despite being of unknown etiology, environmental factors, infection, genetic factors, autoimmunity and an aberrant innate immune system have been explored as potential causes of the development of the disease (Manju, 2012; Oswald-Richter, 2010; Dubaniewicz, 2010). The possible role of bacteria in sarcoidosis has therefore been extensively studied. Gram positive and intracellular bacteria, such as *Mycobacteria* and *Propioni* bacteria have been suggested to play a role in the etiology of sarcoidosis (Gazouli et al., 2002; Song et al., 2005). There is no convincing evidence, however, of a possible role for Gram negative bacteria in sarcoidosis (Eishi et al., 2002).

Due to the similar clinical and histopathological features of sarcoidosis and tuberculosis (TB), *Mycobacterium tuberculosis* antigens, e.g., early secreted antigen (ESAT-6), heat shock proteins (Mtb-HSP), catalase-peroxidase (katG) enzyme and superoxide dismutase A peptide (sodA) have been considered as infectious factors in the etiopathogenesis of sarcoidosis (Oswald-Richter, 2010; Dubaniewicz, 2006a, 2006b; Bargagli, 2011). In addition, other bacteria, e.g. *Propionibacteria*, *Streptomyces* and *Corynebacteria*, have been found in sarcoid tissue (Oswald-Richter, 2010; Bargagli, 2011). *Propionibacterium acnes* have been described as a potential causative agent in pulmonary sarcoid (Eishi, 2013a, 2013b; Moller, 2007; Abe, 1984). *P. acnes* is a gram-positive bacterium that resides on the skin and was one of the first microorganisms isolated from sarcoid lesions (Moller, 2007; Abe, 1984). It is most common in young adults between the ages of 20 and 40 years, with a number of studies suggesting a second peak after 50 years of age (Henke et al., 1986; Hillerdal et al., 1984; Pietinalho et al., 2000). Furthermore, many non-infectious factors, e.g. metal fumes, pigments with/without aluminum in tattoos, pollen and fire are also considered as potential causes of sarcoidosis (Post et al., 2012; Post et al., 2007).

A strong cell-mediated immune reaction, which is essential for combating viruses or intracellular bacteria, has been reported in sarcoidosis (Eishi et al., 2002). High levels of TNF- α and IL-12 in the serum of sarcoid patients have been reported, possibly released from peripheral blood monocytes, a similar high levels of these mediators are found in alveolar macrophages (Prior et al., 1996). Macrophages are important defense cells in the lungs and are critical for initiating an inflammatory response to inhaled microbes and toxins. This is facilitated through recognition of pathogen-associated molecular patterns (PAMPs) through pattern-recognition receptors (PRRs) such Toll-like receptors (TLRs) and NOD-like receptors (NLRs) (Rastogi et al., 2011). The high cytokine expression levels detected in patients with sarcoidosis results from stimulation of alveolar macrophages by TLR4 and NOD1 agonists. This, in turn, leads to sustained p38 mitogen activated kinase (MAPK) phosphorylation and increased transcription of IL-12, TNF α , and IL-1 (Dong et al., 2002; Inoue et al., 2006).

TNF- α maintains the integrity of the granuloma and limits the influx of inflammatory cells to the granuloma to prevent escalation of the inflammatory process. However, paradoxically, anti-TNF α -induced sarcoidosis has also been reported which mainly affects the lungs, parotid and skin (Massara et al., 2010). The condition resolves following withdrawal of anti-TNF- α therapy and it is thought that the cytokine imbalance experienced with prolonged TNF- α blockade favours the disease. Corticosteroid therapy has also been shown to be detrimental in recent onset disease (Reich, 2003, 2012).

Dendritic cells play a central role in granuloma formation by directly recruiting immune cells via TNF- α secretion and indirectly through the activation of T cells via antigen presentation within the

surrounding lymph nodes. Patients with sarcoidosis have a deficit in delayed type hypersensitivity reactions through impairment of dendritic cell functioning (Mathew et al., 2008). These patients have comparable levels of circulating dendritic cells to that of healthy controls, but their dendritic cells display anergy to microbial challenge despite the presence of upregulated costimulatory and maturation markers (Mathew et al., 2008). This dysfunction is mild and does not predispose these individuals to severe microbial infections as seen with those with primary immunodeficiency. The same study also demonstrated a correlation between the degree of dendritic cell dysfunction and severity of pulmonary sarcoidosis.

A number of hereditary and acquired immunodeficiency disorders present with granulomatous inflammation at a variety of body sites. Granuloma formation in patients with these disorders is due to failure to clear the infective organism results in persistence and subsequent granuloma formation to try to contain the infection. The aim of this review is to explore the role of the innate immune system in the formation of the granuloma.

2. Pathogenesis of sarcoidosis

Sarcoidosis is a granulomatous disease of unknown etiology with a great diversity in clinical manifestations. The current understanding of its pathogenesis is that several immunological events are involved in sequential manner that finally results in granuloma formation: (1) exposure to one or several unknown antigen(s), (2) activation of macrophages, (3) acquisition of T cell immunity against the antigen(s) following antigen processing and presentation by macrophages, (4) generation of specific T-effector cells and (5) impaired immune regulatory mechanisms involved in repressing immune responses (Baughman, 2011) (Fig. 1). These events take place on the background of a spectrum of genetic polymorphisms that influence disease susceptibility or outcome (Grunewald, 2010). The purpose of the granuloma formation is to isolate the antigen/microorganism from the body to facilitate its eradication and protect the body from dissemination of the antigen/microorganism. This is more important in mycobacterial infections. Many immune defects associated with sarcoidosis, especially those affecting the innate immune system; result in poor granuloma formation. Finally, sarcoidosis is characterized by an exaggerated local Th1/17 immune response, initiated by APCs, and maintained due to the presence of malfunctioning Treg cells. Overall, CD4+ T cells are over-stimulated by the persistent presence of an unknown antigen(s) and this is amplified by a significant reduction in the numbers of regulatory CD8+ cells which drives the formation of granulomata (Poulter, 1988).

On the other hand there is an increased expression of proinflammatory cytokines in sarcoidosis, (Ziegenhagen, 1998). Two key cytokines implicated in sarcoidosis are TNF α and granulocyte macrophage colony stimulating factor (GM-CSF). TNF α is required for granuloma formation in mice (Smith, 1997) and GM-CSF is able to induce the transformation of alveolar macrophages into multinucleated giant cells (Lemaire, 1996). Importantly, both granulomas and multinucleated giant cells are hallmark histopathological features of sarcoidosis.

3. Role of pattern recognition receptors in sarcoidosis

Considering the infectious trigger hypothesis of disease pathogenesis the detection of *Mycobacteria*, *Propionibacteria* and other pathogens within sarcoidosis tissue suggests that PRRs, particularly TLRs, are important in sarcoidosis as they are key players in innate immunity and the initial response to bacterial infection (Song et al., 2005a, 2005b; Ishige et al., 1999, 2005). PRRs comprise several receptor families which recognize microbial structures or host-derived danger signals, and trigger an immune response. TLRs and NLRs are found both in leukocytes and structural cells throughout the airways and are becoming increasingly implicated in airway inflammation. TLRs can

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