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The role of pattern recognition receptors in lung sarcoidosis

Esmaeil Mortaz[a,b], Ian M. Adcock[c], Atefhe Abedini[d], Arda Kiani[d,*], Mehdi Kazempour-Dizaji[e], Masoud Movassaghi[f], Johan Garssen[g,h]

[a] Department of Immunology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Airways Disease Section, National Heart and Lung Institute, Imperial College London, London, UK
[d] Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[e] Mycobacteriology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[f] Department of Pathology and Laboratory Medicine, University of California, Los Angeles (UCLA), USA
[g] Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Sciences, Utrecht University, Utrecht, The Netherlands
[h] Nutricia Research Centre for Specialized Nutrition, Utrecht, The Netherlands

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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 PPRs and DAMPs in the pathogenesis of sarcoidsis.

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

* Corresponding author.
E-mail address: Ardakiani@yahoo.com (A. Kiani).

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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, TNFα, 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-TNFα-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 TNFα and granulocyte macrophage colony stimulating factor (GM-CSF). TNFα 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 aI., 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

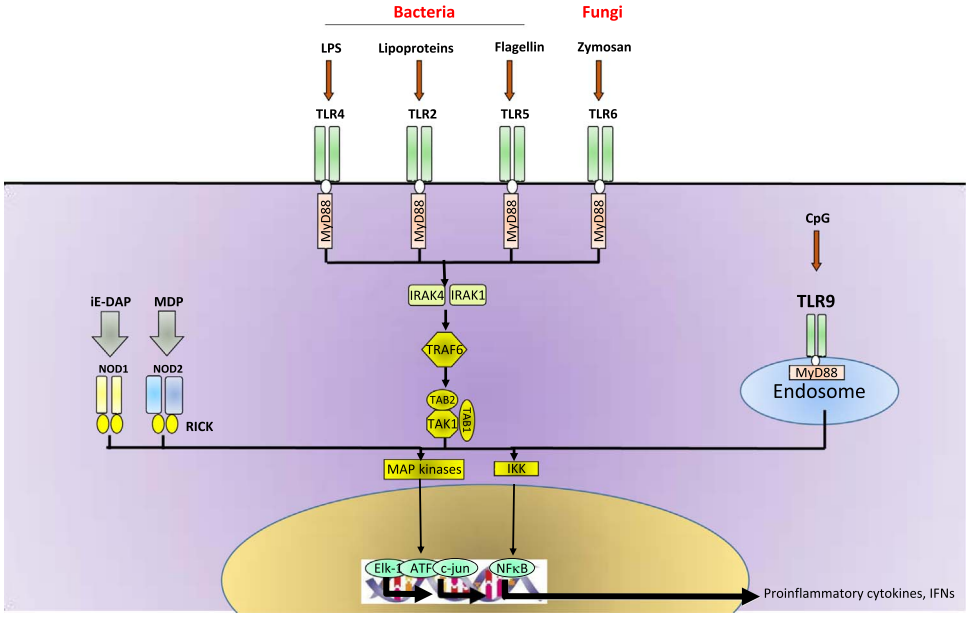

Fig. 1. Pattern recognition receptors (PRRs) involved in recognizing bacteria and viruses. The major PRRs are Toll-like receptors (TLRs). Specific bacterial, fungal and viral components such a bacterial surface products including LPS and nucleic acids (RNA and DNA) activate distinct PRRs. Activation of these PRRs results in stimulation of the canonical or non-canonical nuclear factor-κB (NF-κB) and other downstream pathways including p38 MAPK and this culminates in the production of chemokines, cytokines, and reactive oxygen species. Signal transduction is mainly via the MyD88 adaptor molecule and activation of IRAK/TRAF6. Intracellular bacteria and viruses are detected by NOD receptors that activate several other downstream pathways to activate NF-κB, IFN and IL-1. Abbreviations**:** DAP; diaminopimelic acid, iE-DAP; D-glutamyl-meso-diaminopimelic acid, IRAK; IL-1 receptor-associated kinase, IKK; IκB kinase, LPS; Lipopolysaccharide, MDP, muramyl dipeptide, , MYD88; myeloid differentiation primary response protein 88, NF-κB; nuclear factor-κB, NOD; nucleotide-binding oligomerization domain, RICK; Caspase-recruit-ment domain (CARD)-containing kinase, TAK1; TGF-β-activated kinase, TRAM; TRIF-related adaptor molecule, TRIF; Toll-like-receptor adaptor molecule, TAB2; TAK1-binding protein 2.

initiate inflammatory and anti-microbial innate immune responses, thereby dictating the ensuing adaptive immune response.

The involvement of several TLRs, as well as that of nucleotide-binding oligomerization domain–containing protein (NOD) 1 and 2 proteins, in the immunopathogenesis of other granulomatous diseases such as tuberculosis and Crohn's disease has been explored (Bafica et al., 2005; Kleinnijenhuis et al., 2011; Hampe et al., 2002). These studies indicate the importance of macrophages in pathogen detection. Alveolar macrophages are the first cells that are exposed to inhaled antigens; however, the TLR repertoire and functions in alveolar macrophages during the onset and course of pulmonary sarcoidosis is presently unknown.

In contrast to most TLRs such as TLR2, 4 and 6, which are expressed on the cell surface, NODs are found in the cytosol (Strober et al., 2006) and TLR9 is located in the endosomal compartment (Latz et al., 2004). This indicates that these receptors detect PAMPs originating from intracellular pathogens (Lund et al., 2003; Hemmi et al., 2000) which is important in sarcoidosis where intracellular pathogens are important. However, evidence for a potential role of TLRs is suggested by evidence that BAL cells from sarcoidosis patients exhibit increased cytokine responses to the 19-kDa lipoprotein of *Mycobacterium tuberculosis* (LpqH), a TLR2/1 ligand, and decreased responses to the TLR-2/6 agonist fibroblast stimulating ligand-1 (FSL)-1 (Gabrilovich et al., 2013).

Very recently the role of TLR9 in the pathogenesis of pulmonary sarcoidosis has been described (Schnerch et al., 2016). These authors found increased expression of TLR9 by alveolar macrophages in patients with type I and II sarcoidosis as determined by chest X-ray. In addition, the TLR9 ligands CpG-A and CpG-C preferentially increased the release of CXCL10 by BAL cells from patients with type II sarcoidosis without any effect on the release of CXCL9, CXCL10, TNF, IL-6, or IL-12p40. Thus, TLR9 stimulation might contribute to the Th1-predominant alveolitis found in sarcoidosis by the preferential induction of CXCL10 release from alveolar macrophages.

TLR2 and TLR4 are the most studied among the TLR family (Fig. 2). Numerous agonists for TLR2 have been reported, including lipoteichoic acid (Gram-positive bacteria), lipoarabinomannan (*Mycobacteria*), zymosan (fungi) as well as a number of envelop antigens from viruses (Lien et al., 1999; Drage et al., 2009; Bieback et al., 2002). TLR4 is expressed on a variety of human cells, such as monocytes, mast cells, neutrophils, dendritic cells, T cells and endothelial cells.

TLR4 is well known for its role as a sensor of LPS from Gram-negative bacteria but is also a receptor for heat shock proteins (HSPs), particularly HSPs 60 and 70 in infectious and noninfectious models of sarcoidosis. HSPs are now thought to act as endogenous DAMPs produced by APCs in response to infectious and non-infectious factors (Dubaniewicz et al., 2013). TLR4 is also a receptor for respiratory syncytial virus fusion protein and fungal mannan (Medzhitov and Janeway,1997; Kurt-Jones et al., 2000) (Fig. 2).

However, the main LPS binding receptor is CD14 (Wright et al., 1990), TLR4 acts as a co-receptor for CD14, together with MD-2, and is responsible for activating intracellular signaling pathways resulting in the production of proinflammatory cytokines and upregulation of costimulatory molecules, thereby priming an adaptive immune response (Romics et al., 2005). To date, 3 genetic studies have addressed the role of TLRs in sarcoidosis and the influence of TLR4 polymorphisms on the disease course (Pabst et al., 2006; Veltkamp et al., 2006; Gazouli, 2006).

Huizenga et al. examined the expression of the TLRs 1–9 in cutaneous sarcoid by immunohistochemical staining (Huizenga et al., 2015). They found that TLRs 5 and 6 stained most intensely in both the granulomas and epidermis of the sarcoid cases. The expression of TLRs 2, 3, 4, 5, 6, 7, and 8 was increased in the dermis and epidermis of cutaneous sarcoid compared with normal skin (Huizenga et al., 2015). TLR5 recognizes Gram-positive and Gram-negative bacteria flagellin and is also proposed to play a role in the inflammatory response of cutaneous syphilis (Sieling, 2003).

TLR5 binds to *T. pallidum* only after APCs have phagocytized and digested the bacteria (Hari, 2010; Bouis, 2001). TLR6 forms a

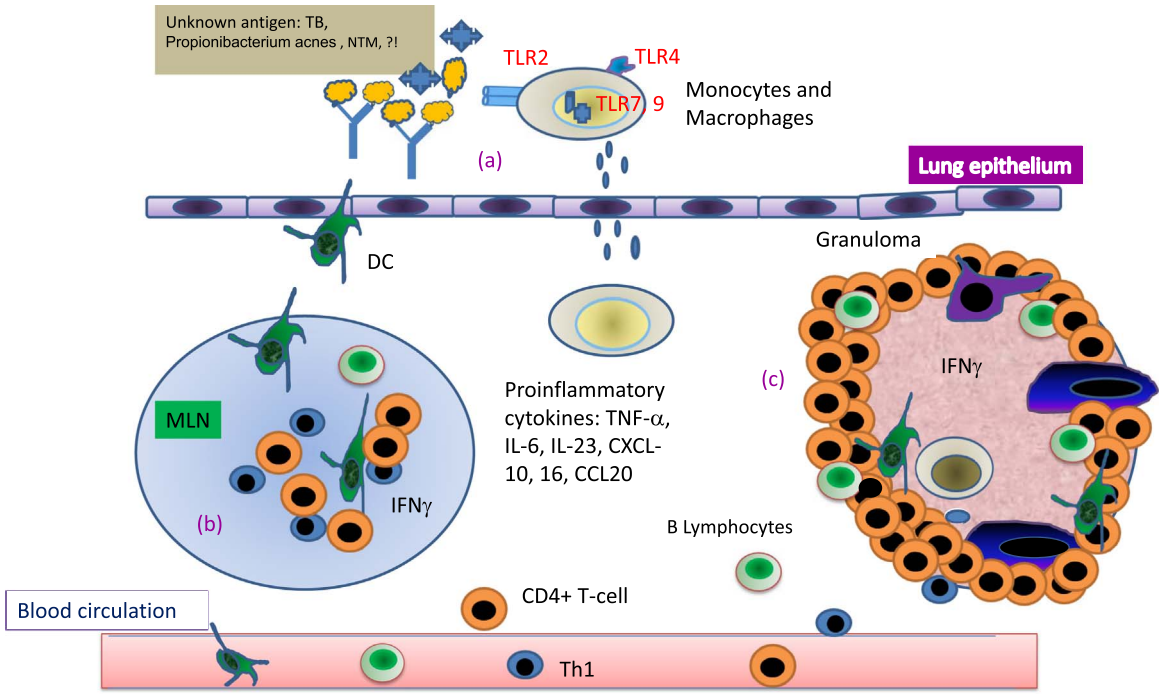

Fig. 2. A schematic model for granuloma formation in pulmonary sarcoidosis and possible role of TLRs. (a) Macrophages and dendritic cells engulf the putative bacterial sarcoid antigen via membrane-bound and intracellular Toll-like receptors (TLRs) within the airway lumen with the subsequent secretion of pro-inflammatory cytokines. They also present antigen derived peptides and lipids via MHC class II and CD1 molecules to T cells, NKT cells, and NK cells. (b) Dendritic cells loaded with antigen migrate to the local mediastinal lymph nodes (MLN) where they present to naïve CD4+ T-cells. Within the lymph node, IL-12 secreted from dendritic cells stimulates naïve cells to differentiate into Thl cells. Th1 cells, in turn, secrete IL-2 to expand their population. (c) At the granuloma site, activated dendritic cells secrete copious amounts of TNFα which activates the endothelium, upregulating the number of adhesion molecules to allow extravasation of Th1 cells and monocytes. Th1 cells secrete IFNγ which stimulates monocytes to differentiate into macrophages. Abbreviations: CCL: CC chemokine ligand; CXCL: CXC chemokine ligand; DC: Dendritic cell; IFNγ: Interferon γ; IL: Interleukin, MLN: Mediastinal lymph node; NK: Natural killer; NKT cells: natural killer T cells; TLRs: Toll-like receptors; TNF-α: Tumor necrosis factor alpha.

heterodimer with TLR2 and binds bacterial lipoproteins (Huizenga et al., 2015). A similar inflammatory response using TLRs 2, 5 and 6 could be involved in the pathogenesis of sarcoidosis. Current theories propose that *P. acnes*, the known cause of acne vulgaris, could be implicated in the pathogenesis of sarcoidosis. The inflammatory response to *P. acnes* is mediated through TLR2 (Kim, 2002). The enhanced TLR2 expression in cutaneous sarcoidosis indicates that a bacterial antigen from *P. acnes* could be an etiologic agent of the disease. These results suggest that a bacterium could be the cause of the granulomas formed in cutaneous sarcoid. Future studies that clearly define the etiology of sarcoid will lead to better therapies and a better prognosis for affected patients (Huizenga et al., 2015).

4. Future perspectives

In this review, we have discussed how the sensing of pathogens and cellular components by PRRs triggers sarcoidosis and its consequences. The cellular mechanisms by which individual PRRs induce pleiotropic outcomes are complex, and we are far from predicting the entire immune response resulting from crosstalk between the various PRRs. Furthermore, we do not know much about the dynamic regulation of immune cell activation or behaviour. Investigations into how inflammation is physiologically controlled to cause sarcoidosis are in the infancy but future research should define the dynamics of immune cell activation in real time in vivo using advanced imaging techniques. Secondly, a systems biology approach may provide greater insight into disease pathobiollogy. There have been several attempts to incorporate systems biology into immunology research. Aderem et al. identified ATF3 and C/EBPγ as a suppressor and amplifier of TLR-mediated gene expression respectively (Gilchrist et al., 2006; Litvak et al., 2009). There have also been attempts to comprehensively understand the transcriptional networks activated in response to PRR stimulation in DCs. Recently, Regev and coauthors identified 125 transcription regulators involved in TLR-mediated gene expression and constructed a network model following sequential knock down of each of them in turn (Amit et al., 2009). However, multiple PRRs are activated simultaneously in the course of microbial infection. Thus, the dynamic changes in transcriptional networks activated in response to inflammatory stimuli are likely to be highly complex. In the future, the merging of imaging, systems biology, and immunology will uncover the dynamics of PRR-mediated inflammatory responses and their role in autoimmune disease.

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