1

Immunopathogenesis of Sarcoidosis

Giorgos A. Margaritopoulos[1], Foteini N. Economidou[2],
Nikos M. Siafakas[2] and Katerina M. Antoniou[2]
[1]Royal Brompton Hospital, London UK,
[2]Thoracic Medicine Department, University Hospital of Heraklion Crete, Greece

1. Introduction

Sarcoidosis is a multisystemic disease in which inflammatory cells gather and form nodules known as non caseating epithelioid granulomas. The most commonly affected organs are the lungs, the eyes and the skin whereas all the organs can be potentially affected. The disease can develop when genetically susceptible individuals are exposed to environmental agents with antigenic properties. These can be either exogenous agents (infections, antigenic structures) or endogenous agents produced by damaged cells. Usually the immune system is able to eliminate the granulomas over a few years but if this is not the case, a progression to fibrosis and permanent organ damage is observed.
It is commonly accepted that the pathogenesis of the disease is mediated by an interplay of cells of both innate and adaptive immunity as well as by their products. Interestingly, the pathogenetic process is compartmentalized and there is an exuberant immune response occurring in the affected tissues such as increase of lymphocytes in the bronchoalveolar lavage fluid in contrast to the peripheral blood lymphocytopenia and cutaneous anergy to tuberculin and other skin tests (Daniele& Rowlands, 1976; Hunninghake,1979,1981; Siltzbach et al,1974; Winterbauer et al,1993; Yeager et al 1977). The role of the immune cells and cytokines involved in the pathogenesis of sarcoidosis will be discussed in this chapter.

2. Innate and adaptive immune system

Lungs, which represent a frequent site of infections, are constantly exposed to either microorganisms and their by-products or to antigenic structures. Innate immunity represents the first line of host defence against these threats and is able to withhold the majority of them. A vast number of cells such as neutrophil granulocytes, macrophages, dentritic cells and natural killer cells as well as receptors such as toll-like receptors (TLRs), nucleotide-binding oligomerization domain-containing protein (NOD)-like receptors are part of the innate immune system. Should it fail to eradicate the infection or the antigenic structures, a second line of host defence, namely adaptive immune system, is being activated. T-cells, B-cells, antigen presenting cells (APCs) are part of it.

2.1 Receptors

Toll-like Receptors (TLRs) are pattern-recognition receptors that play a key role in the innate immunity and their role in the pathogenesis of sarcoidosis has been investigated in many

studies. TLRs localize to various cellular compartments depending on the nature of the ligands they recognize. Thus, TLRs involved in recognition of lipid and protein ligands are expressed on the plasma membrane (TLR-1, TLR-2, TLR-4, TLR-5 and TLR-6), whereas TLRs that detect viral nucleic acids are localized in endolysosomal cellular compartments (TLR-3, TLR-7, TLR-8, TLR-9). TLRs recognize various conserved pathogen associated molecular patterns (PAMPs) such as viral derived RNA (TLR3-, TLR-7, TLR-8), and DNA (TLR-9), as well as endogenous ligands (TLR-2, TLR-4) called damage association molecular patterns (DAMPs) released following tissue damage, cell death, oxidative stress and decomposition of extracellular matrix (ECM) [Bianchi,2007;Tsan&Gao,2004; Wagner,2006]. Serum amyloid-A has been found to play an important role in the innate immune response in chronic sarcoidosis by inducing the release of TNFa via TLR-2 and nuclear factor kB activation (Chen, 2010). Once TLRs bind to products of various PAMPs and DAMPs, intracellular signaling pathways are being activated and pro-inflammatory chemokines and cytokines are released (Bianchi,2007). TLR-9 has been observed to be overexpressed in the BAL of patients with sarcoidosis compared to normal controls (Margaritopoulos et al,2010). A higher expression of TLR-2 and TLR-4 has been demonstrated in peripheral blood monocytes [Wiken,2009], and linkage analysis has indicated that an unidentified polymorphism of TLR-4 is associated with sarcoidosis [Schurmann et al,2008].

2.2 Neutrophil granulocytes

These cells can detect invading microorganisms through the presence of TLRs and eliminate them through the process of phagocytosis. They are amongst the first cells migrating to the site of infection. They have been identified in granulomas of human lungs affected by tuberculosis and demonstrated to be essential for the initiation of pulmonary granuloma formation in M. Tuberculosis-affected C57BL/6 mice (Seiler et al,2003;D'Souza,1997). Various inflammatory cells such as monocytes and macrophages as well as alveolar epithelial cells type II and fibroblasts produce chemokines such as Interleukin-8 (IL-8) and epithelial neutrophil activating protein (ENA)-78 which can attract neutrophils (Pechkovsky et al,2000;Larsen et al,1989;) which in turn produce IL-1, Tumor necrosis factor-α (TNF-α), IL-12 and CXCR3 ligands resulting in an amplification of the inflammatory response in sarcoidosis. On the other hand, these cells produce reactive oxygen species and proteases which can cause damage to the lung. In accordance with this, the presence of high percentage of BAL neutrophils is associated with disease progression, radiographic evidence of fibrosis and to a more likely IPF-like outcome (Tutor-Ureta et al,2006; Ziegenhagen et al,2003;Borzi et al,1993).

2.3 Alveolar macrophages

Alveolar macrohages (AMs) are part of both innate and adaptive immune system. These cells along with their ancestor cells namely monocytes play an important role in the pathogenesis of sarcoidosis. This is highlighted by various events such as macrophagic alveolitis which is a common finding in sarcoidosis, early migration of monocytes from capillaries to alveolar interstitium (Soler&Basset,1976), and formation of macrophages aggregates and their differentiation into epithelioid and multinucleated giant cells which form the core of granuloma. Moreover, activated AMs produce TNF and other cytokines which promote the formation of granuloma in sarcoidosis (Müller-Quernheim et al,1992; Ziegenhagen& Müller-Quernheim,2003).

Infections have been implicated in the pathogenesis of sarcoidosis. Both AMs and monocytes express CD14 which is a membrane-bound lipopolisaccharide (LPS) receptor. It has no intracellular tail and in order to initiate cell activation acts in synergy with TLR-4 which is in close vicinity. When this complex is activated leads to release of NF-kB dependent cytokines such as IL-1,-6,-8 and TNF-α. Intracellular bacteria such as mycobacteria and propionibacteria have been identified as possible causative agents since DNA has been found in sarcoid tissue (Saboor et al,1992;Abe et al,1984). These bacteria are detected by intracellular PRRs such as NOD-1, 2 and TLR-9.

Activation of PRRs leads to the release of cytokines. TNF-α is a proinflammatory cytokine actively produced by sarcoid alveolar macrophages (Fehrenbach et al,2003). It has an important role in lung injury and in the regulation of fibroblast via induction of IL-6. Chronic overexpression of TNF-α and IFN-γ is crucial for the persistence and progression of inflammation and tissue damage in sarcoidosis (Agostini et al,1996). The release of TNF-α is compartmentalized since it has been observed that it is increased in the cultures of BAL cells whereas it is not in peripheral blood cells of the same patient (Müller-Quernheim et al,1992). This suggests that the trigger for the release of this cytokine should be within the lungs and recently is has been proposed that serum amyloid A induces TNF-α release through activation of the innate immune system via TLR-2 (Chen,2010).

Both IL-12, produced by alveolar macrophages, lymphocytes and NK cells and IL-18, produced by alveolar macrophages and dendritic cells are cytokines which have been found up-regulated in the BAL fluid of sarcoid patients, whereas serum levels of IL-12 was decreased in patients group in accordance to TNF- behaviour (Lammas et al,2002;Antoniou et al,2006). These cytokines are involved in Th1 immune response inducing the Th0 to Th1 shift, and when acting in synergy induce production of IFN-γ from Th1 cells (Shigehara et al, 2001). Other cytokines produced by activated AMs are IL-1, IL-6, and IL-15 which favor T-cell proliferation as well as sarcoid fibroblast proliferation and collagen production.

AMs can also act as antigen presenting cells and take part in the adaptive immune response. In sarcoidosis, they develop an increased antigen presenting capacity compared to controls and furthermore, this happens only in AMs from patients with active sarcoidosis and non in AMs from patients with inactive disease (Lem et al,1985;Venet et al,1985;Ina et al,1990;Zissel et al,1997). When in contact with the antigen, the process of phagocytosis begins. T cells recognize the antigen through a T cell receptor, when it is presented within the binding groove of the major histocompatibility complex (MHC) molecule. What follows is a subsequent expansion of antigen specific CD4+ T-cells. It has been observed that the number of MHC II molecules is increased in the surface of AMs of patients with active sarcoidosis, something that has been also related to increased antigen–presenting capacity and moreover that some HLA-DR subtypes are associated with the clinical course of sarcoidosis (Rossi et al,1986;Berlin et al,1997;Martinetti et al,2002; Schürmann et al,2002). Several co-stimulatory molecules expressed on AMs and involved in the interaction between AMs and T-cells are found increased in patients with sarcoidosis. These include CD154 (ligand for CD40), CD72 (ligand for CD5), CD80 and CD86 (ligand for CD28), CD153 (ligand for CD30L) (Wahlström et al,1999;Hoshino et al,1995;Nicod&Isler,1997;Kaneko et al,1999;Agostini et al,1999;Zissel,1999). Adhesion molecules such as CD54 and CD11a-c are also expressed highly in epithelioid cells forming sarcoid granulomas (Zissel,1997).

AMs can be activated by different stimuli and produce different types of cytokines and costimulatory molecules with different actions. Activation by LPS or IFN-γ leads to

inflammatory response and production of proinflammatory cytokines and increased expression of CD16, CD32 and CD64. On the other hand, activation by IL-4, IL-10 and IL-13 leads to a fibrotic response and production of CCL17, CCL18, CCL22, IL-1Rα (Prasse,2006).

2.4 Dendritic cells

Dendritic cells (DCs) are antigen presenting cells and have the ability to induce primary immune response in T cells (Banchereau et al,2000). Two subtypes have been identified, the CD11c+ subtype which belongs to the myeloid lineage and the CD11- subtype which belongs to the lymphoid lineage (Ito et al,1999;Siegal et al,1999). The CD11+ myeloid subset has been found to be able to polarize naïve CD4+T cells towards IFN-γ producing – Th1 cells, depending on IL-12 production whereas the CD11c- plasmacytoid subset drives IL-4 producing-Th2 cells upon IL-13 exposure (Rissoan et al,1999). Pulmonary DCs are functionally immature whereas in case of inflammation express high surface amounts of MHC class II and costimulatory molecules and mature into functional APCs (Banchereau&Steinman,1998;Sallusto et al,1998). They also express CCR7 in their surface and under the influence of its ligands such as CCL19 and CCL21 they migrate into the T-cell areas of regional lymphnodes replaced by peripheral blood precursors (Jang et al,2006;Legge&Braciale,2003). Therefore, lymphadenopathy seen in sarcoidosis can be the consequence of the accumulation of DCs in hilar lymphnodes. DCs are components of granuloma observed in sarcoidosis and studies have shown a premature and rapid involvement of these cells at the sites of inflammation and in the formation of granuloma (Iyonaga et al,2002;Ota et al,2004;Chiu et al,2004).

2.5 T-cells

The presence and accumulation of T-cells is critical for the granuloma formation and this is supported by the fact that T-cell depleted mice are incapable of granuloma formation. Lung T-cells from patients with pulmonary sarcoidosis express markers of activation such as IL-2R, CD69 and CD26 (Semenzato et al,1984; Wahlström et al,1999). IL-2R is found to be related with disease severity (Ziegenhagen et al,1997). These activated T-cells are predominantly CD4+, produce mainly IFN-γ and IL-2 and thus belong to the Th1-cell subtype (Pinkston et al,1983;Robinson et al,1985). They represent the immunological hallmark of the disease. Even though in tissues affected by sarcoidosis has been observed that the ratio CD4/CD8 is extremely high, CD8+ cells are capable of releasing IFN-γ and IL-2 as well, adding to the overall Th-1 associated cytokine release in sarcoidisis (Prasse et al,2000). On the contrary, marker cytokines of Th2 cells such as IL-4, IL-5, IL-10, IL-13 are not elevated in sarcoid body fluids or cell culture supernatants of sarcoid T-cells.

T-cell activation occurs when antigens are internalised by APCs, digested into small fragments and loaded into the peptide binding groove of MHC molecules. The variable portions of the T-cell receptors (TCR) are then able to bind to MHC-antigen complex and are clonally expanded (Moller,1998). The cell surface TCR number is then down-regulated and serves as a marker of recent engagement (DuBois et al,1992). Moreover, activation of T-cells requires binding of costimulatory molecules on the cell surface to the appropriate ligand on the APC. The most important molecule expressed by T-cells is CD28 which interacts with CD80 and CD86 on APCs to effectively stimulate T-cells (Pathak et al, 2007).

Both Th1 and Th2 lymphocytes produce cytokines which are responsible for driving the development of granulomatous reactions in the sarcoid lung. IL-2 is released by pulmonary T-cells and acts as a local growth factor for lung T-cells in sarcoidosis (Moller et,1996). Addition of IL-2 in AMs leads to their activation and production of granulocyte-macrophage-colony stimulating factor (GM-CSF). Binding sites for IL-2 have also been observed in human lung fibroblasts and the addition of this cytokine leads to an increased expression of the gene coding for monocyte chemoattractant protein-1 which is involved in fibrosis. IFN-γ, which is expressed by Th1-cells infiltrating the sarcoid tissue, favours the development of the hypersensitivity reaction and on the other hand can inhibit the development of fibrosis. It also regulates the expression of costimulatory molecules such as CD80 and CD86 on accessory cells (Agostini et al,1999). It also induces the release of ELR-chemokines such as CXCL9, CXCL10, CXCL11 and CXCL16 by AMs and alveolar epithelial cells type II (Sugiyama et al,2006;Agostini et al,2005;Takeuchi et al,2006,Morgan et al,2005). Th1-cells expressing receptors for these chemokines such as CXCR3 and CXCR6 are then recruited in the inflamed tissues. IL-4 is released by Th-2 cells and acting in synergy with IL-2 stimulates the growth of T-cells. It has been related to the development of pulmonary fibrosis in sarcoidosis (Gurrieri et al,2005;Wallace&Howie,1999;Tsoutsou et al,2006). IL-10 is released by Th2-cells as well as by CD4+CD25+T regulatory cells (Freeman et al,2005). IL-13 is considered a major inducer of fibrosis and is released by Th0 and Th2-cells. Together with TNFα, induces the release of TGF-β1 in AMs through a process that involves the IL-13rα receptor. Blockade of this receptor signaling results to a decreased production of TGF-β1 and collagen deposition in bleomycin-induced lung fibrosis (Fichtner-Feigl et al 2008).

3. Granuloma

Granuloma is a feature of many chronic interstitial lung diseases, e.g. sarcoidosis, hypersensitivity pneumonitis, berylliosis and histiocytosis X. Granulomas are highly organized structures created by macrophages, epithelioid cells, giant cells, and T cells. It is generally accepted that initiation of granuloma formation requires T cell activation. In contrast, diminished T cell response inhibits granuloma formation. This is shown by Taflin et al who demonstrate that functional regulatory T cells diminish in vitro granuloma formation (Taflin et al,2009). In addition, TNF released by alveolar macrophages is also required for the induction and maintenance of granuloma, as sarcoid patients with macrophage aggregates in their lung parenchyma, which may be regarded as granulomas in status nascendi, disclosed higher levels of TNF release than patients with differentiated granulomas (Fehrenbach et al,2003). In contrast, blockade of TNF in granuloma inducing conditions inhibits granuloma formation (Smith et al,1997).Thus the development of granuloma requires the finetuned interplay of a variety of cell types and cytokines.

An initial event triggering granuloma formation in diseases of known origin is the deposition of antigenic substances in the lung, as observed in tuberculosis and hypersensitivity pneumonitis. In berylliosis the triggering event seems to be the binding of beryllium to HLA molecules on the surface of the immune cells (Newman,1993). The immune system, however, recognizes peptides in the context of self on the surface of antigen-presenting cells and the sole binding of beryllium may not be a sufficiently stimulating event. Therefore, other triggers such as an altered cleavage of self-antigens, caused by a beryllium-induced shift of the specificity of restriction proteases, and subsequent presentation of these new peptides in the context of the MHC, are conceivable.

In experimental models such a metal-induced presentation of new self-antigens recognized as nonself by the immune system has been identified as a cause of autoimmunity (Kubicka-Muranyi et al,1995,1996). In sarcoidosis, however, the initiating agent is not known, but it may be found in the membrane of alveolar macrophages, as demonstrated by a granulomatous skin reaction elicited by membrane fragments of sarcoid alveolar macrophages (Holter et al,1992).

Many structurally different agents are known to stimulate the formation of immune granulomas and they share some characteristics. Firstly, in the case of infectious agents their habitat is the macrophage or, owing to their particulate nature, they have the propensity to be phagocytosed by macrophages. Secondly, they have the capability to persist within tissues or macrophages, either because the micro-organisms involved are resistant to intracellular killing or because the materials resist enzymatic degradation. Thirdly, without a specific T-cell response immune granuloma cannot be generated and therefore, the inducing agents have to be immunogenic. The unknown aetiological sarcoidosis-inducing agent should fulfil these three criteria.

One of the major impediments to studying sarcoidosis is the lack of a widely accepted animal model. In many murine models, granulomas are induced by injection of tail vein with antigens, a route of antigen exposure that does not employ the airway (as is thought to be important in sarcoidosis). Infection model studies with organisms that produce granulomatous inflammation typically study the course of infection that can be either self-limited or fatal. Thus, models often focus on the acute phase of inflammation and granuloma formation, a time frame that is incompatible with chronic persistent sarcoidosis. Nevertheless, recent findings suggest certain cytokines and antigenic exposures may be more applicable to sarcoid research.

Sequential analysis of the cellular components of the sarcoid granulomas has demonstrated their dynamic nature. An influx, local multiplication and cell death of immune cells can be observed, most probably governed by inflammatory signals. In immune granulomas, as in sarcoidosis, these signals are likely to be cytokines and cell-cell interactions of lymphocytes, macrophages and their derivatives, and fibroblasts (Kunkel et al,1989). Blocking CD80 and CD86, molecules mediating the accessory signals of macrophages in T-cell activation (Zissel et al,1997), by monoclonal antibodies suppressed helminth-induced granuloma formation and cytokine release of T-cells, highlighting the interdependence of these processes in granuloma formation (Subramanian et al,1997).

After phagocytosis of the inducing agent the macrophage releases a number of cytokines which mediate migration of activated lymphocytes and monocytes out of the bloodstream into sites of inflammation. Osteopontin, also known as early T-lymphocyte activation protein 1 (Eta-1),is a cytokine produced by macrophages and other cells which promotes macrophage and T-cell chemotaxis (O'Regan et al,1999). Osteopontin deficient mice are prone to disseminated bacille Calmette-Guérin (BCG) infection, presumably because of inadequate local control by poorly formed granulomas (Nau et al,1999). Eta-1 was released in high quantities by macrophages immediately after the phagocytosis of M. tuberculosis, but only in minute amounts when phagocytosing inert particles. Normal lung and granulation tissue did not stain positive for Eta-1 but it was identified by immunohistochemistry in macrophages, lymphocytes and the extracellular matrix of pathological tissue sections of patients with tuberculosis or silicosis (Nau et al,1997). Finally, osteopontin-deficient mice recruit fewer macrophages and epithelioid cells in a Schistosoma

hypersensitivity pulmonary granuloma model (O'Regan et al,2001). Yamagami et al used Mycobacterium tuberculosis surface glycolipids (cord factor) to induce both foreign body and hypersensitivity type granulomas in mice (Yamagami et al,2001). Mice were first immunized with heat killed M. tuberculosis before intravenous injection of glycolipid cord factor preparations. Immunized mice developed more severe inflammatory lesions suggesting an immune component (in addition to a foreign body type) to granuloma formation (Yamagami et al,2001). Although both aforementioned models developed immunemediated granulomatous inflammation, both used an intravenous injection and/or a sensitization step as a means of forming pulmonary granulomas.

Other animal models use a variety of knockout mice and antigenic stimuli to elicit pulmonary granulomas. In the study of sarcoidosis, the most common pathogen challenges are with Propionibacterium and Mycobacterium (Seiler et al,2003;Co et al,2004;Kunkel et al,1998;Nishiwaki et al,2004;Perez et al,2003;Minami et al,2003). Finally, some early animal models exposed mice to Kveim reagent or homogenates of sarcoid tissue in an attempt to create a "sarcoid mouse." Belcher and Reid followed mice after footpad injection with sarcoid homogenates for up to 1 year (Belcher&Reid,1975). At autopsy, granulomas were observed equally in animals that received sarcoid tissue homogenates and control animals (Belcher&Reid,1975). However, Mitchell et al showed mice inoculated with sarcoid tissue homogenates manifest granulomas in many organs and tissues for up to 15 months (Mitchell et al,1976). Studies using Kveim reagent in an animal model are appealing, in theory, as the granulomatous inflammation would likely mirror that of sarcoidosis.

Granuloma formation in sarcoidosis requires interplay between APCs, antigen, and T-cells . This immune response will occur in a genetically susceptible individual (ie, BTNL2), and severity will depend on disease-modifying genes (ie, HLA, TNF). During the initiation phase of granuloma formation, macrophages undergo "frustrated phagocytosis" when in contact with the inciting antigen. The antigen in sarcoidosis is believed to be processed in a classic MHC-II restricted pathway (taken up by phagocytosis and degraded in the endosome/lysosome compartment) with subsequent expansion of antigen-specific CD4+ T-cells. Activation of these macrophages recruits mononuclear cells, predominantly monocytes, and CD4+ T-cells. These cells accumulate at the site of inflammation in an attempt to wall off the antigen or pathogen. Next, inflammatory cells are recruited to the granuloma by chemokines TNF-α, IL-1, IN-γ and others that regulate trafficking to the site of inflammation. Animal studies of immune and foreign-body granulomas suggest that IL-1 is important in the early recruitment stages of granuloma formation, while TNF-α may take part in later maintenance or effector functions (Chensue et al,1989). This view is supported by the observation that depletion of TNF-α led to a rapid regression of fully developed immune granulomas and suppressed the accumulation of mRNA in macrophages surrounding the granuloma. The latter indicates that TNF-α enhances its own synthesis and release, thus favouring further macrophage accumulation and differentiation leading to bacterial elimination (Kindler et al,1989). The requirement of IFN-γ for granuloma formation is demonstrated by the absence of granulomas in IFN-γ gene knockout mice, which do not respond with a granulomatous reaction after exposure to thermophilic bacteria (Gudmundsson&Hunninghake,1997).

During the effector phase of granuloma formation, specific cells are recruited to the site of inflammation. In the case of sarcoidosis, CD4 T-cells predominate. However, if the granuloma is skewed by the initial antigenic burden, eosinophils and neutrophils can be

aggressively recruited to the site of inflammation, as is the case with some infection models of granulomatous inflammation. Whether granulomatous inflammation resolves, persists, or leads to fibrosis will depend on a delicate balance of inflammatory cells, regulatory cells, apoptosis, and TH1/TH2 cytokine responses.

The role of T-cells in the development and maintenance of granuloma can be studied in infectious diseases and their animal models. Experimental infection of susceptible mice with Leishmani major results in a disseminated, lethal disease and the infected animals respond with CD4+ Th2 cells secreting IL4, IL-5, IL-6 and IL-10, promoting a humoral and suppressing a cellular immune response. In marked contrast, CD4+ IL-2, IFN-γ and TNF-β-releasing Th1 cells are observed in resistant strains which respond with a strong cellular immune reaction. Evidence from human leishmaniosis suggests that the Th1 or Th2 polarized response determines whether subclinical or progressive disease develops (Kemp et al,1996). Using mycobacterial and schistosomal antigens Type 1 (IFN-γ and TNF-β dominant) and Type 2 (IL-4 and IL-5 dominant) granulomatous responses can be elicited in normal mice. Knockout of the IFN-γ gene converts the Type 1 response to a response with decreased TNF-β and increased secretion of IL-4, IL-5 and other Type 2 cytokines and eosinophilic infiltration. IL-4 gene knockout exacerbates Type 1 response with compartmentalization of the expected exaggerated IFN-γ release to the lymph nodes and a decrease in IFN-γ transcripts in the lung. Most interestingly, IL-4 gene knockout did not convert Type 2 to Type 1 granulomas (Chensue et al,1997). Along this line a Type 1 cytokine pattern has to be expected in tuberculous and sarcoid granulomas. Bergeron et al analysed the presence of mRNA of 16 cytokines in granulomatous lymph node tissue of patients with tuberculosis and sarcoidosis and found a Type 1 response in sarcoidosis and Type 0 response (less polarized to Type 1) in tuberculosis (Lammas et al,2002). In addition, they demonstrated that distinct histological features were associated with characteristic cytokine patterns, e.g. neutrophilic infiltration heralded the presence of IL-8 transcripts (Bergeron et al, 1997).

4. Fibrosis

In 60% of patients with sarcoidosis, the course of the disease is self-limiting with spontaneous resolution of the granuloma, whereas patients with progressive sarcoidosis show massive development of granulomas and do not recover even if strong immunosuppressive therapy is used. The uncontrolled development of granulomas results in fibrosis. The immune cells composing the granuloma secrete cytokines that attract, stimulate and deactivate fibroblasts, which seems to be dependent on immunological cytokines such as interferon (Subramanian et al,1997;Smith et al,1995,Rolfe,1991). Extracellular matrix is found also in the outer rim of and within the granuloma, indicating that the granuloma is the starting point of fibrosis in sarcoidosis (Limper et al,1994;Marshall et al,1996).

Although the reversible phases of initial alveolar injury in the sarcoid process are mediated by Th1 lymphocytes, the fibrotic changes that follow the sarcoid Th1 immune response are modulated by macrophages, neutrophils, eosinophils and mast cells, which, via overproduction of the superoxide anion, oxygen radicals and proteases, can cause local injury, disruption of the epithelial basement membrane, alteration of epithelial permeability and consequent derangement of the normal architecture of lung parenchyma (Bjemer et al,1987;Inoue et al,1996;Agostini&Semenzato,1998). By releasing a number of molecules,

including transforming growth factor (TGF)-b and the family of TGF-related cytokines, platelet-derived growth factor and insulin-like growth factor I, sarcoid macrophages may mediate fibrosis. These growth factors for fibroblasts and epithelial cells and their receptors are abundantly expressed in fibrotic lung. They cooperate with the TGF family in promoting fibroblast growth and deposition of collagen fibrils. Furthermore, macrophage-derived cytokines which are overexpressed at sites of granuloma formation (including IL-1, IL-6, IFN-c, TNF-a and GM-CSF) and immunoglobulin G immune complexes may upregulate the expression of the inducible form of nitric oxide synthase and nitric oxide production in granuloma cells, thus contributing to the injury and consequent reparative processes (Ishioka et al,1996;Homma et al,1995;Bost et al,1994;Facchetti et al,1999).

Prasse and his colleagues recently demonstrated also, increased release of the profibrotic chemokine CCL18 (a chemokine released by M2 macrophages), by alveolar macrophages from patients with fibrotic sarcoidosis (Prasse et al,2006). The induction of M2 alveolar macrophages in chronic sarcoidosis might emerge due to different mechanisms. First, the activation of alveolar macrophages might be induced in a total lack of T cell activation, possibly because there is no relevant T cell antigen or the T cells are anergic. Engagement of the innate PRRs would induce macrophage activation, which would be boosted by chemokines such as CCL2 released by alveolar epithelial cells type II (Pechkovsky et al,2005). This scenario is rather unlikely because the limited activation of the alveolar macrophages would not result in sufficient granuloma formation. In addition, the involvement of T cells in sarcoid granuloma has been demonstrated (Bergeron et al,1997). Thus, it is more likely that after granuloma formation the T cell activation is downregulated or shifts from a Th1- to a Th2-dominated phenotype. Downregulation of T cell activation but persistent macrophage activation again might result in a shift from classical to alternative activation as already described. A shift from a Th1 T cell activation pattern to a Th0/Th2 pattern can be seen in tuberculosis, but in sarcoidosis IL-4 and Il-10 producing T cells are also present and the contribution of their cytokine release might increase during a downregulation of the Th1 response (Somoskovi et al,1999;Baumer et al,1997;Mollers et al,2001). This shift fosters M2 activation because IL-4 and IL-10 are the main inducers of CCL18 and downregulate M1-related cytokine release (Zissel et al,1996). Besides CCL18, the profibrotic cytokine TGF-b is also found in close proximity to the granuloma, inducing extracellular matrix deposition and downregulating M1-related cytokine release (Zissel et al,1996). CCL18 release is amplified by extracellular matrix, Th2 cytokines, and contact to fibroblasts initiating a vicious cycle and accelerating pulmonary fibrosis.

The recruitment of fibroblasts and the subsequent increased production of matrix macromolecules are crucial to the fibrotic process. The migration of fibroblasts and epithelial cells from the interstitium to the alveolar spaces and adhesive interactions of fibroblasts with the surrounding interstitial matrix are the major factors contributing to the development of fibrosis. The migratory process of fibroblasts reflects the local release of a variety of molecules which can act as chemoattractant factors for fibroblasts, such as chemokines, products of coagulation and the fibrinolytic cascade, as well as matrix proteins (collagen peptides, laminin, fibronectin and elastin-derived peptides) (Marshall et al,1996;Shigehara et al,1998;Probst-Cousin et al,1997;Roman et al,1995). Most of these are actively produced in sarcoid lung. Molecules secreted by sarcoid inflammatory cells are also able to prime fibroblasts to enter the G1 phase of the growth cycle, and thus to proliferate.

A way of estimating the status of fibroblasts is to monitoring the turn-over of cellular matrix in the process of fibrosis. Several parameters have been thoroughly evaluated to serve as markers for pulmonary fibrosis (type III procollagen peptide, collagenase, hyaluronan, and fibrinogen and its degradation products) (Bjemer et al,1991;Mornex et al,1994;Pohl et al,1992;O'Connor et al,1989;Perez et al,1993;Schaberg et al,1994). The problem encountered with this concept is that none of the named markers can differentiate between pathological fibrosis and normal tissue turnover in inflammation, as demonstrated by the fact that some markers correlate with parameters of alveolitis (Perez et al,1993), although conflicting results have been obtained in longitudinal studies (Pohl et al,1992;O'Connor et al,1989).

5. References

Abe C, Iwai K, Mikami R, Hosoda Y. (1984). Frequent isolation of Propionibacterium acnes from sarcoidosis lymph nodes. *ZentralblBakteriolMikrobiolHyg A*, 256:541-547.

Agostini C, Zambello R, Sancetta R, Cerutti A, Milani A, Tassinari C, et al.(1996). Expression of tumor necrosis factor-receptor superfamily members by lung T lymphocytes in interstitial lung disease. *Am J Respir Crit Care Med*, 153:1359-1367.

Agostini C, Semenzato G.(1998). Cytokines in sarcoidosis.*SeminRespir Infect*,13: 184–196.

Agostini C, Trentin L, Perin A, Facco M, Siviero M, Piazza F, et al.(1999). Regulation of alveolar macrophage-T cell interactions during Th1-type sarcoid inflammatory process. *Am J Physiol*, 277:L240-250.

Agostini C, Cabrelle A, Calabrese F, Bortoli M, Scquizzato E, Carraro S, et al.(2005). Role for CXCR6 and its ligand CXCL16 in the pathogenesis of T-cell alveolitis in sarcoidosis. *Am J RespirCrit Care Med*,172:1290-1298.

Antoniou KM, Tzouvelekis A, Alexandrakis MG, Tsiligianni I, Tzanakis N, Sfiridaki K, et al. (2006). Upregulation of Th1 cytokine profile (IL-12, IL-18) in bronchoalveolar lavage fluid in patients with pulmonary sarcoidosis. *J Interferon Cytokine Res*, 26:400-405.

Banchereau J, Steinman RM. (1998). Dendritic cells and the control of immunity. *Nature*, 392:245-52.

Banchereau J, Briere F, Caux C, Davoust J, Lebecque S, Liu YJ, et al.(2000). Immunobiology of dendritic cells. *Annu Rev Immunol*, 18:767-811.

Baumer I, Zissel G, Schlaak M, Mu¨ller-Quernheim J. (1997). Th1/Th2 cell distribution in pulmonary sarcoidosis. *Am J Respir Cell MolBiol*, 16:171–177.

Belcher RW, Reid JD. (1975). Sarcoid granulomas in CBA/J mice.Histologic response after inoculation with sarcoid and nonsarcoid tissue homogenates. *Arch Pathol*, 99:283-285.

Bergeron A, Bonay M, Kambouchner M, et al. (1997). Cytokine patterns in tuberculous and sarcoid granulomas: correlations with histopathologic features of the granulomatous response. *J Immunol*, 159: 303–443.

Berlin M, Fogdell-Hahn A, Olerup O, Eklund A, Grunewald J. (1997). HLA-DR predicts the prognosis in Scandinavian patients with pulmonary sarcoidosis. *Am J RespirCrit Care Med*, 156:1601-1605.

Bianchi ME. (2007). DAMPs, PAMPs and alarmins: all we need to know about danger. *J Leukoc Biol*, 81:1-5.

Bjermer L, Engstrom-Laurent A, Thunell M, Hallgren R. (1987). The mast cell and signs of pulmonary fibroblast activation in sarcoidosis. *Int Arch Allergy ApplImmunol*, 82: 298–301.

Bjermer L, Eklund A, Blaschke E.(1991). Bronchoalveolar lavage fibronectin in patients with sarcoidosis: correlation to hyaluronan and disease activity. *EurRespir J*, 4:965–971.

Borzì RM, Grigolo B, Meliconi R, Fasano L, Sturani C, Fabbri M, et al.(1993). Elevated serum superoxide dismutase levels correlate with disease severity and neutrophil degranulation in idiopathic pulmonary fibrosis. *ClinSci (Lond)*, 85:353-359.

Bost TW, Riches DW, Schumacher B, et al. (1994). Alveolar macrophages from patients with beryllium disease and sarcoidosis express increased levels of mRNA for tumor necrosis factor-a and interleukin-6 but not interleukin-1b. *Am J Respir Cell MolBiol*, 10: 506–513.

Chen ES, Song Z, Willett MH, Heine S, Yung RC, Liu MC et al. (2010). Serum amyloid A regulates granulomatous inflammation in sarcoidosis through Toll-like receptor-2. *Am J RespirCrit Care Med*, 181:360-373.

Chensue SW, Otterness IG, Higashi GI, ShmyrForsch C, Kunkel SL. (1989). Monokine production by hypersensitivity (Shistosomamansoni egg) and foreign body (Sephadex bead)-type granuloma macrophages. Evidence for sequential production of IL-1 and tumor necrosis factor.*J Immunol*, 142: 1281–1286.

Chensue SW, Warmington K, Ruth JH, Lukacs N, Kunkel SL.(1997). Mycobacterial and schistosomal antigen-elicited granuloma formation in IFN-gamma and IL-4 knockout mice: analysis of local and regional cytokine and chemokine networks. *J Immunol*, 159: 356–573.

Chiu BC, Freeman CM, Stolberg VR, Hu JS, Komuniecki E, Chensue SW.(2004). The innate pulmonary granuloma: characterization and demonstration of dendritic cell recruitment and function. *Am J Pathol*,164:1021-1030.

Co DO, Hogan LH, Il-Kim S, Sandor M. (2004). T cell contributions to the different phases of granuloma formation. *Immunol Lett*, 92:135-142.

Daniele RP, Rowlands DT Jr. (1976) Lymphocyte subpopulations in sarcoidosis: correlation with disease aetivity and duration. *Ann Intern Med*, 85:593-600.

D'Souza CD, Cooper AM, Frank AA, Mazzaccaro RJ, Bloom BR, Orme IM. (1997). An anti-inflammatory role for gamma delta T lymphocytes in acquired immunity to Mycobacterium tuberculosis. *J Immunol*, 158:1217-1221.

Du Bois RM, Kirby M, Balbi B, Saltini C, Crystal RG. (1992). T-lymphocytes that accumulate in the lung in sarcoidosis have evidence of recent stimulation of the T-cell antigen receptor. *Am Rev Respir Dis*, 145:1205-1211.

Facchetti F, Vermi W, Fiorentini S, et al. (1999). Expression of inducible nitric oxide synthase in human granulomas and histiocytic reactions. *Am J Pathol*, 154: 145–152.

Fehrenbach H, Zissel G, Goldmann T, Tschernig T, Vollmer E, Pabst R, et al. (2003). Alveolar macrophages are the main source for tumour necrosis factor-alpha in patients with sarcoidosis. *Eur Respir J*, 21:421-428.

Fichtner-Feigl S, Young CA, Kitani A, Geissler EK, Schlitt HJ, Strober W. (2008). IL-13 signaling via IL-13R alpha2 induces major downstream fibrogenic factors mediating fibrosis in chronic TNBS colitis. *Gastroenterology*, 135:2003-2013

Freeman CM, Chiu BC, Stolberg VR, Hu J, Zeibecoglou K, Lukacs NW, et al. (2005). CCR8 is expressed by antigen-elicited, IL-10-producing CD4+CD25+ T cells, which regulate Th2-mediated granuloma formation in mice. *J Immunol*, 174:1962-1970.

Gudmundsson G, Hunninghake GW. (1997). Interferon-γ is necessary for the expression of hypersensitivity pneumonitis. *J Clin Invest*, 99: 2386–2390.

Gurrieri C, Bortoli M, Brunetta E, Piazza F, Agostini C. (2005) Cytokines, chemokines and other biomolecular markers in sarcoidosis. *SarcoidosisVasc Diffuse Lung Dis*, 22Suppl 1:S9-14

Holter J, Park H, Sjoerdsma K, Kataria Y. (1992). Nonviable autologous bronchoalveolar lavage cell preparations induce intradermal epithelioid cell granulomas in sarcoidosis patients. *Am Rev Respir Dis*, 145: 864–871.

Homma S, Nagaoka I, Abe H, et al. (1995). Localization of platelet-derived growth factor and insulin-like growth factor I in the fibrotic lung. *Am J Respir Crit Care Med*, 152: 2084–2089.

Hoshino T, Itoh K, Gouhara R, Yamada A, Tanaka Y, Ichikawa Y, et al. (1995). Spontaneous production of various cytokines except IL-4 from CD4+ T cells in the affected organs of sarcoidosis patients. *ClinExpImmunol*, 102:399-405.

Hunninghake GW, Crystal RG. (1981). Pulmonary sarcoidosis: a disorder mediated by excess helper T-lymphocyte activity at sites of disease activity. *N Engl J Med*, 305:429-434.

Hunninghake GW, Fulmer JD, Young RC Jr, Gadek JE, Crystal RG. (1979) Localization of the immune response in sarcoidosis. *Am Rev Respir Dis*, 120:49-57.

Ina Y, Takada K, Yamamoto M, Morishita M, Miyachi A. (1990). Antigen-presenting capacity in patients with sarcoidosis. *Chest*, 98:911-916.

Inoue Y, King TE Jr, Tinkle SS, Dockstader K, Newman LS. (1996). Human mast cell basic fibroblast growth factor in pulmonary fibrotic disorders. *Am J Pathol*, 149: 2037–2054.

Ishioka S, Saito T, Hiyama K, et al. (1996). Increased expression of tumor necrosis factor-a, interleukin-6, platelet-derived growth factor-B and granulocyte-macrophage colony-stimulating factor Mrna in cells of bronchoalveolar lavage fluids from patients with sarcoidosis.*SarcoidosisVasc Diffuse Lung Dis*, 13: 139–145.

Ito T, Inaba M, Inaba K, Toki J, Sogo S, Iguchi T, et al.(1999). A CD1a+/CD11c+ subset of human blood dendritic cells is a direct precursor of Langerhans cells. *J Immunol*, 163:1409-1419.

Iyonaga K, McCarthy KM, Schneeberger EE. (2002). Dendritic cells and the regulation of a granulomatous immune response in the lung. *Am J Respir Cell Mol Biol*, 26:671-679.

Jang MH, Sougawa N, Tanaka T, Hirata T, Hiroi T, Tohya K, et al. (2006). CCR7 is critically important for migration of dendritic cells in intestinal lamina propria to mesenteric lymph nodes. *J Immunol*, 176:803-810.

Kaneko Y, Kuwano K, Kunitake R, Kawasaki M, Hagimoto N, Miyazaki H et al. (1999). Immunohistochemical localization of B7 costimulating molecules and major histocompatibility complex class II antigen in pulmonary sarcoidosis. *Respiration*, 66:343-348.

Kemp M, Theander TG, Kharazmi A. (1996). The contrasting roles of CD4+ T cells in the intracellular infections in humans: leishmaniasis as an example. *Immunol Today,* 17: 13–16.

Kindler V, Sappino A, Grau G, Piguet P, Vassalli P. (1989). The inducing role of tumor necrosis factor in the development of bactericidal granulomas during BCG infection.*Cell*,56: 731–740.

Kubicka-Mulanyi M, Kremer J, Rottmann N, et al. (1996). Murine systemic autoimmune disease induced by mercuric chloride: T helper cells reacting to self proteins. *Int Arch Allergy Immunol*, 109: 11–20.

Kubicka-Muranyi M, Griem P, Lübben B, Rottmann N, Lührmann R, Gleichmann E. (1995). Mercuric-chloride-induced autoimmunity in mice involves up-regulated presentation by spleen cells of altered and unaltered nucleolarself antigen. *Int Arch Allergy Immunol*, 108: 1–10.

Kunkel SL, Chensue SW, Strieter RM, Lynch JP, Remick DG.(1989). Cellular and molecular aspects of granulomatous inflammation. *Am J Respir Cell MolBiol*, 1: 439–447.

Kunkel SL, Lukacs NW, Strieter RM, Chensue SW. (1998). Animal models of granulomatous inflammation. *SeminRespir Infect*, 13:221-228.

Lammas DA, De Heer E, Edgar JD, Novelli V, Ben-Smith A, Baretto R, et al. (2002). Heterogeneity in the granulomatous response to mycobacterial infection in patients with defined genetic mutations in the interleukin 12-dependent interferon-gamma production pathway. *Int J ExpPathol*,83:1-20.

Larsen CG, Anderson AO, Oppenheim JJ, Matsushima K. (1989). Production of interleukin-8 by human dermal fibroblasts and keratinocytes in response to interleukin-1 or tumour necrosis factor. *Immunology*, 68:31-36.

Legge KL, Braciale TJ. (2003). Accelerated migration of respiratory dendritic cells to the regional lymph nodes is limited to the early phase of pulmonary infection. *Immunity*, 18:265-277.

Lem VM, Lipscomb MF, Weissler JC, Nunez G, Ball EJ, Stastny P, et al. (1985). Bronchoalveolar cells from sarcoid patients demonstrate enhanced antigen presentation. *J Immunol*, 135:1766-1771.

Limper AH, Colby TV, Sanders MS, Asakura S, Roche PC, DeRemee RA. (1994). Immunohistochemical localization of transforming growth factor-b 1 in the nonnecrotizing granulomas of pulmonary sarcoidosis. *Am J Respir Crit Care Med*, 149:197–204.

Margaritopoulos GA, Antoniou KM, Karagiannis K, Samara KD, Lasithiotaki I, Vassalou E, et al. (2010). Investigation of Toll-like receptors in the pathogenesis of fibrotic and granulomatous disorders: a bronchoalveolar lavage study. *Fibrogenesis Tissue Repair*, 11;3:20.

Marshall BG, Wangoo A, Cook HT, Shaw RJ. (1996). Increased inflammatory cytokines and new collagen formation in cutaneous tuberculosis and sarcoidosis. *Thorax*, 51:1253–1261.

Martinetti M, Luisetti M, Cuccia M. (2002). HLA and sarcoidosis: new pathogenetic insights. *SarcoidosisVasc Diffuse Lung Dis*, 19:83-95.

Minami J, Eishi Y, Ishige Y, et al. (2003). Pulmonary granulomas caused experimentally in mice by a recombinant trigger-factor protein of Propionibacterium acnes. *J Med Dent Sci*, 50:265-274.

Mitchell DN, Rees RJ, Goswami KK. (1976). Transmissible agents from human sarcoid and Crohn's disease tissues. *Lancet*, 2:761-765.

Moller DR, Forman JD, Liu MC, Noble PW, Greenlee BM, Vyas P, et al. (1996). Enhanced expression of IL-12 associated with Th1 cytokine profiles in active pulmonary sarcoidosis. *J Immunol*, 156:4952-4960.

Moller DR. (1998). Involvement of T cells and alterations in T cell receptors in sarcoidosis. *SeminRespir Infect*, 13:174-183.

Mollers M, Aries SP, Dro¨mann D, Mascher B, Braun J, Dalhoff K. (2001). Intracellular cytokine repertoire in different T cell subsets from patients with sarcoidosis. *Thorax*, 56:487–493.

Morgan AJ, Guillen C, Symon FA, Huynh TT, Berry MA, Entwisle JJ, et al. (2005). Expression of CXCR6 and its ligand CXCL16 in the lung in health and disease. *Clin Exp Allergy*, 35:1572-1580

Mornex JF, Leroux C, Greenland T, Ecochard D. (1994). From granuloma to fibrosis in interstitial lung disease: molecular and cellular interactions. *Eur Respir J*, 7: 779–785.

Müller-Quernheim J, Pfeifer S, Männel D, Strausz J, Ferlinz R. (1992). Lung-restricted activation of the alveolar macrophage/monocyte system in pulmonary sarcoidosis. *Am Rev Respir Dis*, 145:187-192.

Nau GJ, Guilfoile P, Chupp GL, et al. (1997). A chemoattractant cytokine associated with granulomas in tuberculosis and silicosis. *ProcNatlAcadSci USA*, 94: 6414–6419.

Nau GJ, Liaw L, Chupp GL, Berman JS, Hogan BL, Young RA. (1999). Attenuated host resistance against Mycobacterium bovis BCG infection in mice lacking osteopontin. *Infect Immun*,67:4223-4230.

Newman LS. (1993). To Be2+ or not to Be2+: immunogenetics and occupational exposure (Comment). *Science*, 262: 197–198.

Nicod LP, Isler P. (1997). Alveolar macrophages in sarcoidosiscoexpress high levels of CD86 (B7.2), CD40, and CD30L. *Am J Respir Cell Mol Biol*, 17:91-96.

Nishiwaki T, Yoneyama H, Eishi Y, et al. (2004). Indigenous pulmonary Propionibacterium acnes primes the host in the development of sarcoid-like pulmonary granulomatosis in mice. *Am J Pathol*,165:631-639.

O'Connor CM, Ward K, van Breda A, McIlgorm A, Fitz-Gerald MX. (1989). Type 3 procollagen peptide in bronchoalveolar lavage fluid.Poor indicator of course and prognosis in sarcoidosis. Chest, 96: 339–344.

O'Regan AW, Chupp GL, Lowry JA, Goetschkes M, Mulligan N, Berman JS. (1999). Osteopontin is associated with T cells in sarcoid granulomas and has T cell adhesive and cytokine-like properties in vitro. *J Immunol*, 162:1024-1031.

O'Regan AW, Hayden JM, Body S, et al. (2001). Abnormal pulmonary granuloma formation in osteopontin-deficient mice. *Am J Respir Crit Care Med*, 164:2243-2247.

Ota M, Amakawa R, Uehira K, Ito T, Yagi Y, Oshiro A, et al. (2004). Involvement of dendritic cells in sarcoidosis. *Thorax*, 59:408-413.

Pathak SK, Basu S, Basu KK, Banerjee A, Pathak S, Bhattacharyya A et al. (2007). Direct extracellular interaction between the early secreted antigen ESAT-6 of

Mycobacterium tuberculosis and TLR2 inhibits TLR signaling in macrophages. *Nat Immunol*, 8:610-618.

Pechkovsky DV, Zissel G, Ziegenhagen MW, Einhaus M, Taube C, Rabe KF et al. (2000). Effect of proinflammatory cytokines on interleukin-8 mRNA expression and protein production by isolated human alveolar epithelial cells type II in primary culture. *Eur Cytokine Netw*, 11:618-625.

Pechkovsky DV, Goldmann T, Ludwig C, et al. (2005). CCR2 and CXCR3 agonistic chemokines are differently expressed and regulated in human alveolar epithelial cells type II. *Respir Res*, 6:75.

Perez RL, Duncan A, Hunter RL, Staton GL. Elevated D dimer in the lungs and blood of patients with sarcoidosis. Chest 1993; 103: 1100–1106.

Perez RL, Rivera-Marrero CA, Roman J. (2003). Pulmonary granulomatous inflammation: from sarcoidosis to tuberculosis. *Semin Respir Infect*,18:23-32.

Pinkston P, Bitterman PB, Crystal RG. (1983). Spontaneous release of interleukin-2 by lung T lymphocytes in active pulmonary sarcoidosis. *N Engl J Med*, 308:793-800.

Pohl WR, Thompson AB, Köhn H, et al.(1992). Serum procollagen III peptide levels in subjects with sarcoidosis. A 5-year follow-up study. *Am Rev Respir Dis*, 145:412–417.

Prasse A, Georges CG, Biller H, Hamm H, Matthys H, LuttmannW,et al. (2000). Th1 cytokine pattern in sarcoidosis is expressed by bronchoalveolar CD4+ and CD8+ T cells. *Clin Exp Immunol*, 122:241-248.

Prasse A, Pechkovsky DV, Toews GB, Jungraithmayr W, Kollert F, Goldmann T, et al. (2006). A vicious circle of alveolar macrophages and fibroblasts perpetuates pulmonary fibrosis via CCL18. *Am J Respir Crit Care Med*, 173:781-792.

Probst-Cousin S, Poremba C, Rickert CH, Bocker W, Gullotta F. (1997). Factor XIIIa expression in granulomatous lesions due to sarcoidosis or mycobacterial infection. *Pathol Res Pract*, 193:741–745.

Rissoan MC, Soumelis V, Kadowaki N, Grouard G, Briere F, de Waal Malefyt R, et al. (1999). Reciprocal control of T helper cell and dendritic cell differentiation. *Science*, 283:1183-1186.

Robinson BW, McLemore TL, Crystal RG. (1985). Gamma interferon is spontaneously released by alveolar macrophages and lung T lymphocytes in patients with pulmonary sarcoidosis. *J Clin Invest*, 75:1488-1495.

Rolfe MW, Kunkel SL, Standiford TJ, et al. (1991). Pulmonary fibroblast expression of interleukin-8: a model for alveolar macrophage-derived cytokine networking. *Am J Respir Cell Mol Biol*, 5: 493–501.

Roman J, Jeon YJ, Gal A, Perez RL. (1995). Distribution of extracellular matrices, matrix receptors, and transforming growth factor-b1 in human and experimental lung granulomatous inflammation. *Am J Med Sci*, 309: 124–133.

Rossi GA, Zocchi E, Sacco O, Balbi B, Ravazzoni C, Damiani G. (1986). Alveolar macrophage stimulation of T-cell proliferation in autologous mixed lymphocyte reactions. Role of HLA-DR antigens. *Am Rev Respir Dis*, 133:78-82.

Saboor SA, Johnson NM, McFadden J. (1992). Detection of mycobacterial DNA in sarcoidosis and tuberculosis with polymerase chain reaction. *Lancet*, 339:1012-1015.

Sallusto F, Schaerli P, Loetscher P, Schaniel C, Lenig D, Mackay CR, et al. (1998). Rapid and coordinated switch in chemokine receptor expression during dendritic cell maturation. *Eur J Immunol*, 28:2760-2769

Schaberg T, Orzechowski K, Oesterling C, Lode H, Schuppan D. (1994). Simultaneous measurement of collagen type-VI-related antigen and procollagen type-N-propeptide levels in bronchoalveolar lavage. *Eur Respir J*, 7: 1221–1226.

Schürmann M, Bein G, Kirsten D, Schlaak M, Müller-Quernheim J, Schwinger E. (1998). HLA-DQB1 and HLA-DPB1 genotypes in familial sarcoidosis. *Respir Med*, 92:649-652.

Schürmann M, Kwiatkowski R, Albrecht M, Fischer A, Hampe J, Müller-Quernheim J, Schwinger E, Schreiber S. (2008). Study of Toll-like receptor gene loci in sarcoidosis. *Clin Exp Immunol*, 152:423-431.

Seiler P, Aichele P, Bandermann S, Hauser AE, Lu B, Gerard NP et al. (2003). Early granuloma formation after aerosol Mycobacterium tuberculosis infection is regulated by neutrophils via CXCR3-signaling chemokines. Eur J Immunol, 33:2676-2686.

Semenzato G, Agostini C, Trentin L, Zambello R, Chilosi M, Cipriani et al. (1984). Evidence of cells bearing interleukin-2 receptor at sites of disease activity in sarcoid patients. *Clin Exp Immunol*, 57:331-337.

Shigehara K, Shijubo N, Hirasawa M, Abe S, Uede T. (1998). Immunolocalization of extracellular matrix proteins and integrins in sarcoid lymph nodes. *Virchows Arch*, 433: 55–61.

Shigehara K, Shijubo N, Ohmichi M, Takahashi R, Kon S, Okamura H, et al. (2001). IL-12 and IL-18 are increased and stimulate IFN-gamma production in sarcoid lungs. *J Immunol*, 166:642-649.

Siegal FP, Kadowaki N, Shodell M, Fitzgerald-Bocarsly PA, Shah K, Ho S, et al. The nature of the principal type 1 interferon-producing cells in human blood.Science. 1999 Jun;284:1835-7.

Siltzbach LE, James DG, Neville E, Turiaf J, Battesti JP, Sharma OP, et al. (1974). Course and prognosis of sarcoidosis around the world. *Am J Med*, 57:847-852.

Smith D, Hansch H, Bancroft G, Ehlers S. (1997). T-cell-independent granuloma formation in response to Mycobacterium avium: role of tumour necrosis factor-alpha and interferon-gamma. *Immunology*, 92:413–421.

Smith RE, Strieter RM, Zhang K, Phan SH, Standiford TJ, Lukacs NW.A role for C-C chemokines in fibrotic lung disease.J LeukocBiol 1995; 57: 782–787.

Soler P, Basset F. (1976). Morphology and distribution of the cells of a sarcoid granuloma: ultrastructural study of serial sections. *Ann N Y Acad Sci*, 278:147-160.

Somoskovi A, Zissel G, Zipfel PF, et al. (1999). Different cytokine patterns correlate with the extension of disease in pulmonary tuberculosis. *Eur Cytokine Netw,* 10:135–142.

Subramanian G, Kazura JW, Pearlman E, Jia X, Malhtra I, King CL. (1997). B7-2 requirement for helminth-induced granuloma formation and CD4 Type 2 T helper cell cytokine expression. *J Immunol*, 158: 5914–5920.

Sugiyama K, Mukae H, Ishii H, Kakugawa T, Ishimoto H, Nakayama S, et al. (2006). Elevated levels of interferon gamma-inducible protein-10 and epithelial neutrophil-activating peptide-78 in patients with pulmonary sarcoidosis. *Respirology*, 11:708-714.

Taflin C, Miyara M, Nochy D, et al. (2009). FoxP3þ regulatory T cells suppress early stages of granuloma formation but have little impact on sarcoidosis lesions. *Am J Pathol*, 174:497–508.

Takeuchi M, Oh-I K, Suzuki J, Hattori T, Takeuchi A, Okunuki Y et al. (2006). Elevated serum levels of CXCL9/monokine induced by interferon-gamma and CXCL10/interferon-gamma-inducible protein-10 in ocular sarcoidosis. *Invest Ophthalmol Vis Sci*, 47:1063-1068.

Tsan MF, Gao B. (2004). Endogenous ligands of Toll-like receptors. *J Leukoc Biol*, 76:514-519.

Tsoutsou PG, Gourgoulianis KI, Petinaki E, Germenis A, Tsoutsou AG, Mpaka M, et al. (2006). Cytokine levels in the sera of patients with idiopathic pulmonary fibrosis. *Respir Med*, 100:938-945.

Tutor-Ureta P, Citores MJ, Castejón R, Mellor-Pita S, Yebra-Bango M, Romero Y et al. (2006). Prognostic value of neutrophils and NK cells in bronchoalveolar lavage of sarcoidosis. *Cytometry B Clin Cytom,* 70:416-422.

Venet A, Hance AJ, Saltini C, Robinson BW, Crystal RG. (1985). Enhanced alveolar macrophage-mediated antigen-induced T-lymphocyte proliferation in sarcoidosis. *J Clin Invest*, 75:293-301.

Wagner H. (2006). Endogenous TLR ligands and autoimmunity. *Adv Immunol*, 91:159-173.

Wahlström J, Berlin M, Sköld CM, Wigzell H, Eklund A, Grunewald J. (1999). Phenotypic analysis of lymphocytes and monocytes/macrophages in peripheral blood and bronchoalveolar lavage fluid from patients with pulmonary sarcoidosis. *Thorax*, 54:339-346.

Wallace WA, Howie SE. (1999). Immunoreactive interleukin 4 and interferon-gamma expression by type II alveolar epithelial cells in interstitial lung disease. *J Pathol*, 187:475-480.

Wikén M, Grunewald J, Eklund A, Wahlström J. (2009). Higher monocyte expression of TLR2 and TLR4, and enhanced pro-inflammatory synergy of TLR2 with NOD2 stimulation in sarcoidosis. *J Clin Immunol*, 29:78-89.

Winterbauer RH, Lammert J, Selland M, Wu R, Corley D, Springmeyer SC. (1993). Bronchoalveolar lavage cell populations in the diagnosis of sarcoidosis. *Chest*, 104:352-361.

Yamagami H, Matsumoto T, Fujiwara N, et al. (2001). Trehalose 6,6′-dimycolate (cord factor) of Mycobacterium tuberculosis induces foreign-body- and hypersensitivity-type granulomas in mice. *Infect Immun*, 69:810-815.

Yeager H Jr, Williams MC, Beekman JF, Bayly TC, Beaman BL. (1977). Sarcoidosis: analysis of cells obtained by bronchial lavage. *Am Rev Respir Dis*, 116:951-954.

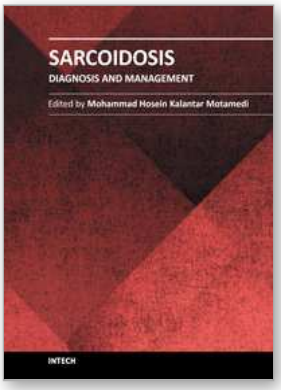
Ziegenhagen MW, Benner UK, Zissel G, Zabel P, Schlaak M, Müller-Quernheim J. (1997). Sarcoidosis: TNF-alpha release from alveolar macrophages and serum level of sIL-2R are prognostic markers. *Am J Respir Crit Care Med*, 156:1586-1592.

Ziegenhagen MW, Müller-Quernheim J. (2003). The cytokine network in sarcoidosis and its clinical relevance. *J Intern Med*, 253:18-30.

Zissel G, Schlaak J, Schlaak M, Mu¨ller-Quernheim J. (1996). Regulation of cytokine release by alveolar macrophages treated with interleukin-4, interleukin-10, or transforming growth factor beta. *Eur Cytokine Netw*, 7:59–66.

Zissel G, Ernst M, Schlaak M, Müller-Quernheim J. (1997). Accessory function of alveolar macrophages from patients with sarcoidosis and other granulomatous and nongranulomatous lung diseases. *J Investig Med*, 45:75-86.

Zissel G, Ernst M, Schlaak M, Müller-Quernheim J. (1999). Pharmacological modulation of the IFNgamma-induced accessory function of alveolar macrophages and peripheral blood monocytes. *Inflamm Res*, 48:662-668.



Sarcoidosis Diagnosis and Management

Edited by Prof. Mohammad Hosein Kalantar Motamedi

ISBN 978-953-307-414-6
Hard cover, 280 pages
Publisher InTech
Published online 17, October, 2011
Published in print edition October, 2011

Sarcoidosis is a type of inflammation that occurs in various locations of the body for no known reason. Normally, when foreign substances or organisms enter the body, the immune system will fight back by activating an immune response. Inflammation is a normal part of this immune response, but it should subside once the foreign antigen is gone. In sarcoidosis, the inflammation persists, and some of the immune cells form abnormal clumps of tissue called granulomas. The disease can affect any organ in the body, but it is most likely to occur in the lungs. It can also affect the skin, eyes, liver, or lymph nodes. Although the cause of sarcoidosis is not known, research suggests that it may be due to an extreme immune response or extreme sensitivity to certain substances. It also seems to have a genetic component as well, and tends to run in families. Sarcoidosis most commonly develops in people between 20 and 50 years of age. African Americans are somewhat more likely to develop sarcoidosis than Caucasians, and females are somewhat more likely to develop sarcoidosis than males. The symptoms of sarcoidosis depend on the organ involved. This book deals with the diagnosis and treatment of this mysterious disease of unknown etiology.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821