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Immunopathogenesis of Sarcoidosis

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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, dendritic 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 TNF α via TLR-2 and nuclear factor κ B 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 macrophages (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 lipopolysaccharide (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- κ B 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 it 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 not 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-1R α (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 sarcoidosis (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 al, 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 TNF α , induces the release of TGF- β 1 in AMs through a process that involves the IL-13 α receptor. Blockade of this receptor signaling results to a decreased production of TGF- β 1 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 (Bjerner et al,1987;Inoue et al,1996;Agostini&Semenzato,1998). By releasing a number of molecules,

including transforming growth factor (TGF)- β 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- γ , TNF- α 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- β 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) (Bjerner 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).

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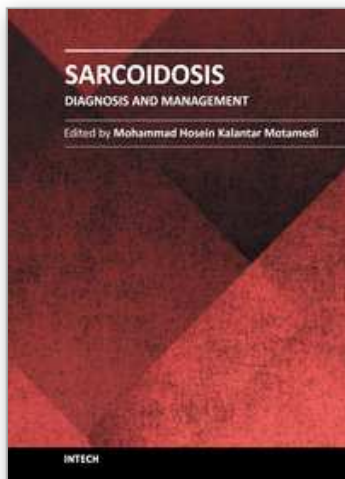
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Sarcoidosis is a type of inflammation that occurs in various locations of the body for no known reason. Normally, when foreign substances or organisms enter the body, the immune system will fight back by activating an immune response. Inflammation 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.

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