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Immunopathogenesis and Presumable Antigen Pathway of Sarcoidosis: A Comprehensive Approach

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1. Introduction

Sarcoidosis is a multisystemic disorder of unknown etiology. Formation of non-caseating epithelioid cell granulomas in the involved organs is the main feature. Sarcoidal granulomas may involve any organ, but generally clinical sarcoidosis manifests intrathoracic lymph node enlargement, pulmonary involvement, skin or ocular signs and symptoms, or some combination of these findings. Epidemiologically, sarcoidosis affects people of all racial and ethnic groups, although the incidence of sarcoidosis varies widely throughout the world and is most common in women and in people of Scandinavian or African-American descent. Sarcoidosis may occur at any age, but is usually seen in adults under the age of 50 (Dempsey et al., 2009; Iannuzzi et al., 2007; Fernandez-Faith & McDonnell, 2007).

Sarcoidosis has long been characterized by many unknown variables: antigen, genetic susceptibility, and factors influencing severity (Noor & Knox, 2007). Clinically, non-specific systemic symptoms such as fatigue, night sweats, and weight loss are common in sarcoidosis patients. Tuberculin skin test is classically negative in patients with sarcoidosis, since activated T-lymphocytes are sequestered at the site of sarcoidal granulomas, leading to peripheral depletion (Dempsey et al., 2009). However, a negative result of the tuberculin test is not specific to sarcoidosis. The Kveim-Siltzbach test, in which cutaneous injection of homogenate of human sarcoid tissue extract and subsequent biopsy are performed, is currently less often used because of many constraints and lower sensitivity. Sarcoidal granulomas produce angiotensin I-converting enzyme (ACE), whose levels are elevated in 60% of patients with sarcoidosis, but the importance of using serum ACE levels in diagnosing sarcoidosis remains controversial (Iannuzzi et al., 2007).

Currently, the diagnosis of sarcoidosis is based on three different features: (1) a typical clinico-radiological presentation, (2) the histological evidence of non-caseating granuloma, and (3) exclusion of other possible diseases causing granuloma (Ma et al., 2007). The typical clinico-radiological presentation includes the presence of bilateral hilar adenopathy in chest radiograph of an asymptomatic patient, Löfgren syndrome (combination of erythema nodosum, bilateral hilar adenopathy in chest radiograph, and arthritis), and a gallium-67 uptake in the parotid and lacrimal glands (Panda sign) as well as in the right paratracheal and bilateral hilar (Lambda sign). Diagnostic criteria of sarcoidosis have been thus

established; however, in practice, its diagnosis is made arbitrarily because complete exclusion of other granulomatous disorders is impossible (Baughman et al., 2010). In order to understand and explore the solutions of the problems thus far mentioned, in this chapter, comprehensive approaches from pathological and immunological aspects of sarcoidosis, including the comparison with other granulomatous disorders, are presented. In general, granulomas form as a result of the persistent presence of a nondegradable product or of delayed type hypersensitivity (Kobayashi et al., 2001). The former includes silica, tuberculosis, *Toxoplasma gondii*, and foreign bodies, while the latter includes sarcoidosis, Crohn’s disease, and (tumor-related) sarcoid reactions. It is understood that granuloma-formation is observed in virtually all the hosts in the former, while it is found in limited hosts in the latter. Administration of beryllium oxide or zirconium lactate into subcutaneous tissue usually causes formation of foreign body granulomas, while it may result in hypersensitivity granuloma in a small percentage of individuals (Maceira et al., 1984). Furthermore, most delayed-type hypersensitivity reactions, including contact dermatitis, tuberculin reaction, and tumor immunity, do not form granulomas (Fig. 1).

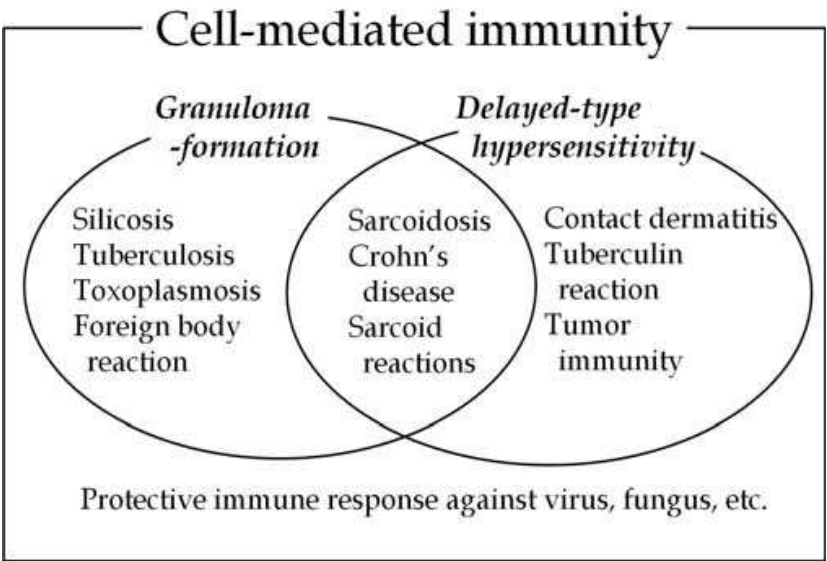


Fig. 1. Sarcoidosis and associated immunoreactions

2. Histology of sarcoidal granulomas and differential diagnosis of granulomatous disorders

Sarcoid lesions vary according to the different stages of the disease. In the earliest stage in the lung, mild alveolitis without granuloma formation is seen. However, characteristic non-necrotizing epithelioid cell granulomas usually occur thereafter. The granulomas have a compact appearance with sharp circumscription from the surrounding lung (Fig. 2a). The granulomas are mainly composed of epithelioid cells, tightly-assembled macrophages with spindle features that are microscopically reminiscent of epithelial cells, and are occasionally surrounded by a rim of lymphocytes. Multinucleated giant cells may be intermingled, which are formed by the fusion of epithelioid macrophages (Ma et al., 2007). Cutaneous manifestations have been classified into nonspecific lesions without granuloma formation such as erythema nodosum and specific lesions with presence of the granulomas (Fig. 2b), similar to the respiratory counterparts (Fernandez-Faith & McDonnell, 2007).

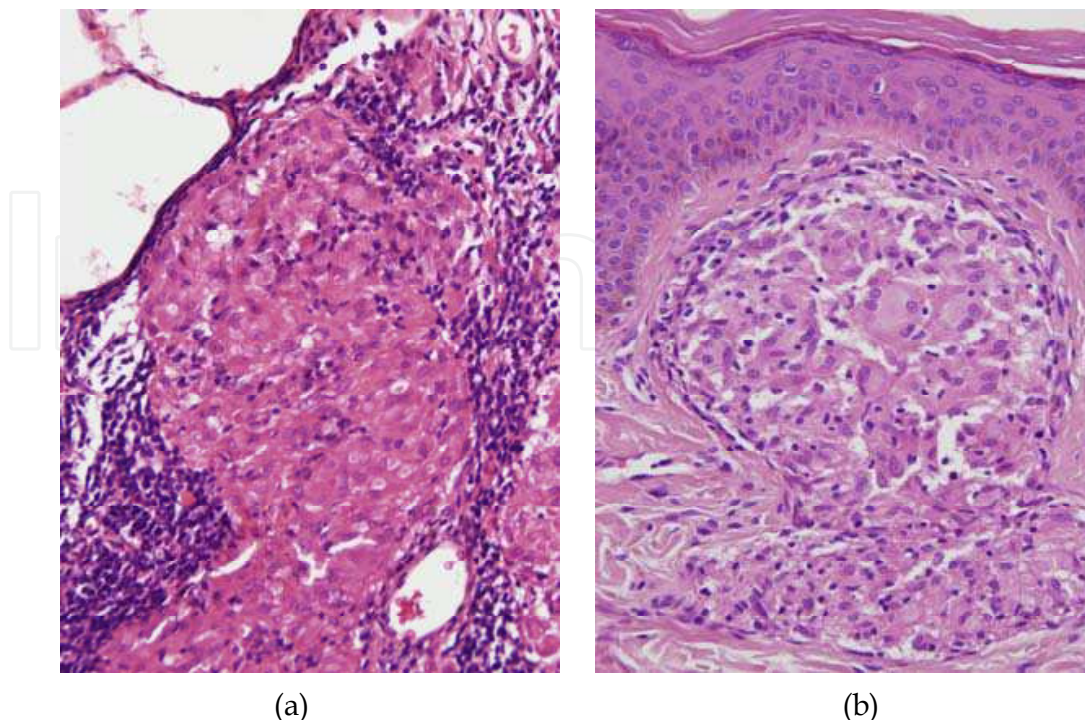


Fig. 2. Typical sarcoidal granulomas in the lung and skin. (a) Non-necrotizing epithelioid cell granulomas in the lung with surrounding lymphocytes. Original magnification: x200. (b) Dermal sarcoidal granulomas formed beneath the epidermis, accompanied by intermingled giant cells. Original magnification: x200.

The subsequent outcome of granulomas seems to be common in different organs of varying etiologies. That is, cellular and discrete granulomas in the early stages of the disease may resolve with little consequence, or become more fibrotic as the disease advances (Fig. 3); eventually they may appear as confluent hyalinized nodules (Iannuzzi et al., 2007; Ma et al., 2007).

Several characteristic histological features have been proposed that are useful in the differential diagnosis of various granulomatous disorders. It is well known that tuberculous granulomas are accompanied by caseous necrosis, and Crohn's disease is usually manifested as small-sized granulomas (Fig. 4a). Toxoplasmic lymphadenopathy is characterized by the presence of microgranulomas without multinucleated giant cells (Fig. 4b) (Eapen et al., 2006).

However, specific features of sarcoidal granulomas have not been identified. Although asteroid and Schaumann's bodies may appear in sarcoidal granulomas (Fig. 5a) (Ma et al., 2007), these may be found in other granulomatous disorders as well (Fernandez-Faith & McDonnell, 2007). Therefore, diagnostic problems occasionally arise. For example, there are difficulties in differentiation of sarcoidosis vs. foreign body granuloma if polarizable foreign body particles are detected in sarcoidal granuloma (Fig. 5b) (Marcoval et al., 2001), and of sarcoidosis vs. sarcoid reactions, which occur in approximately 4% of carcinomas (Brincker, 1986), if a patient with cancer is accompanied by granulomas in lymph nodes or other organs such as the spleen (Marruchella, 2009; Kurata et al., 2010b).

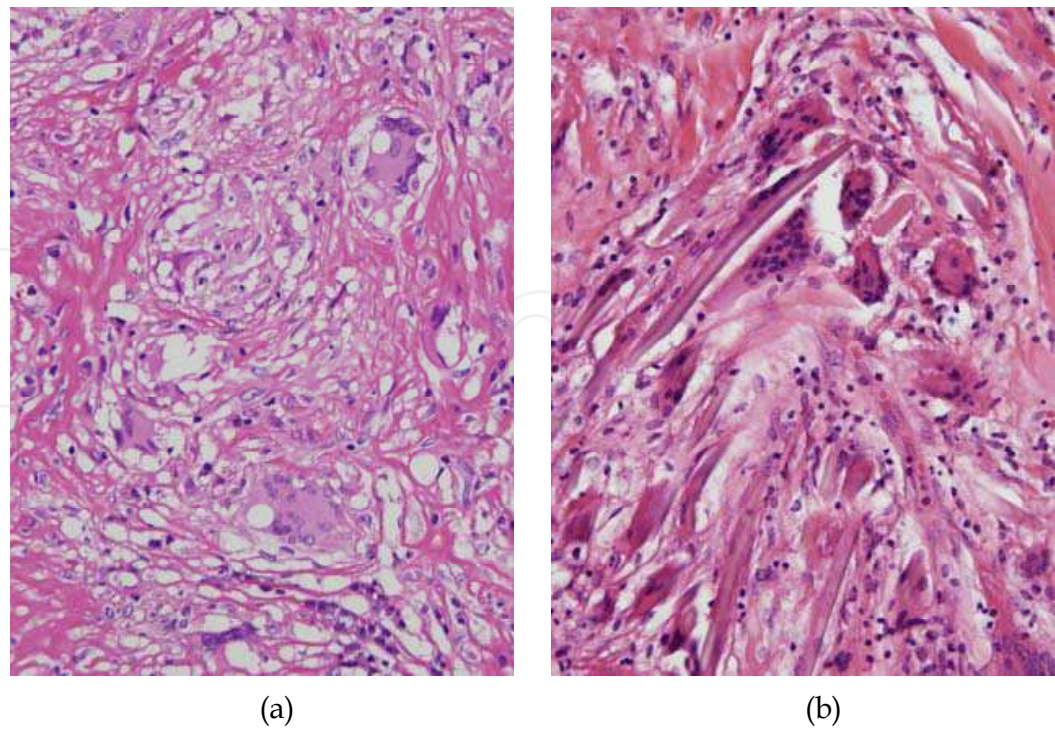


Fig. 3. Examples of old granulomas accompanied by fibrosis in cases other than sarcoidosis. (a) Old granulomas divided by hyaline in the lymph node sarcoid reactions. Original magnification: x200. (b) A thread granuloma, representative foreign body reaction, is tightly packed by fibrotic capsule. Original magnification: x200.

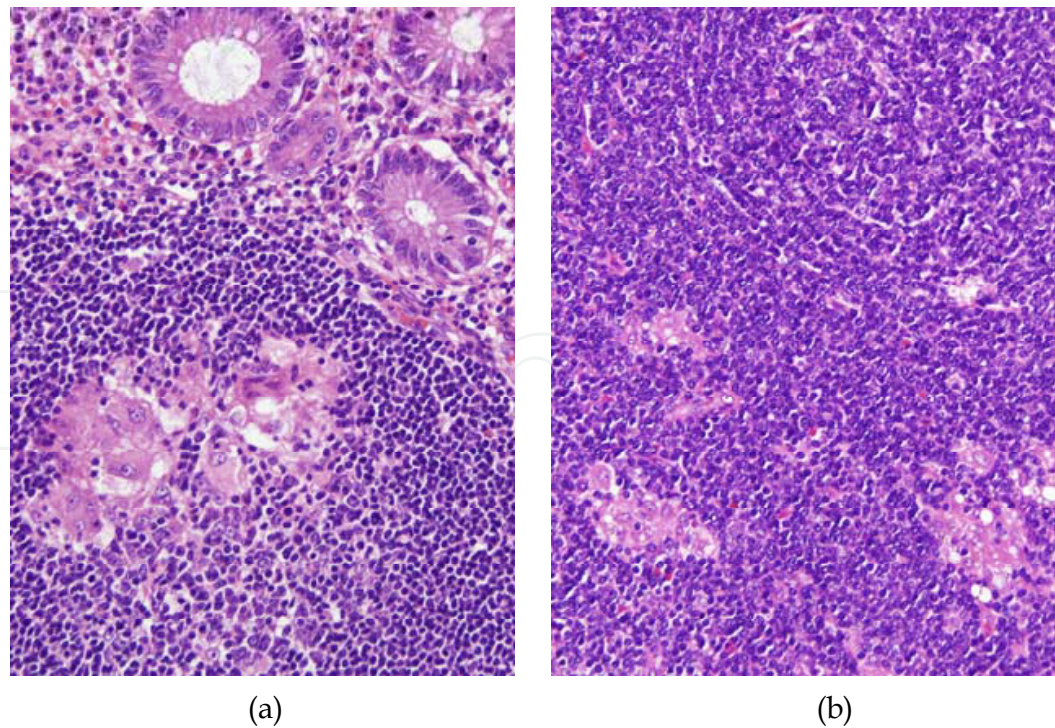


Fig. 4. Examples of small granulomas in cases other than sarcoidosis. (a) Small-sized granulomas in the intestinal mucosa in Crohn's disease. Original magnification: x200. (b) Scattered microgranulomas in Toxoplasmic lymphadenitis. Original magnification: x200.

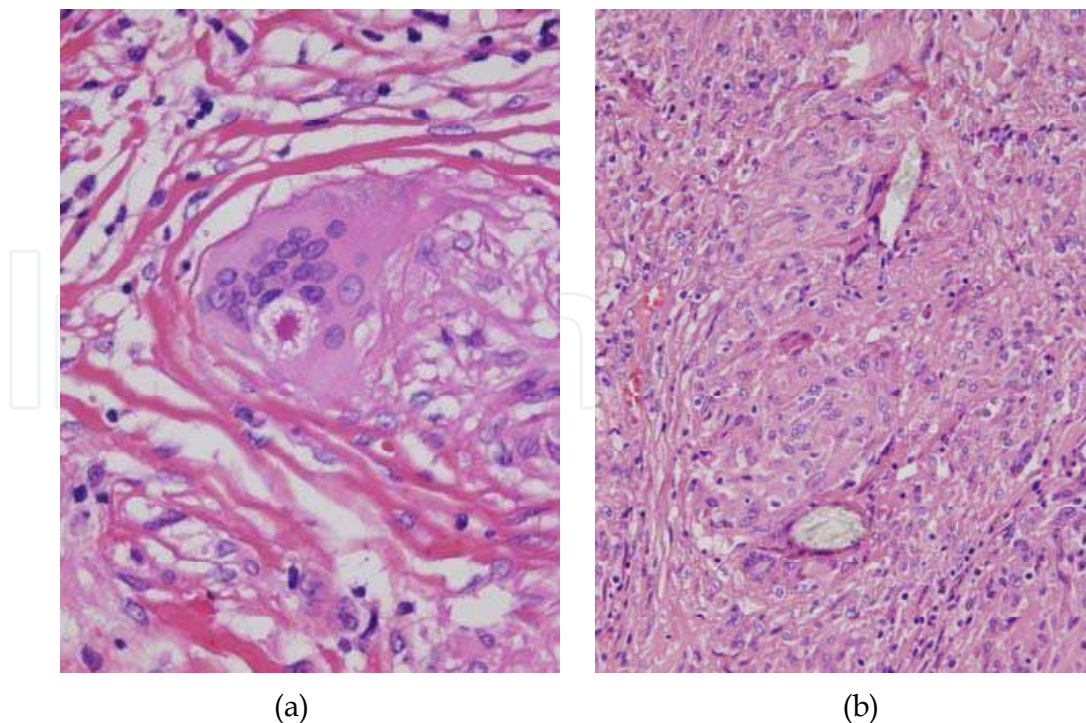


Fig. 5. Examples of inclusions and foreign bodies in sarcoidal granulomas. (a) Asteroid body (arrow), a star-shaped spiculated structure, within multinucleated giant cells of sarcoidal granuloma. Original magnification: x400. (b) Foreign body particles identified in sarcoidal granulomas of the skin. Original magnification: x200.

3. Immunohistochemical characteristics of cells constituting granulomas

Granulomas are usually accompanied by $CD4^+$ T-lymphocytes in the center and $CD8^+$ T-lymphocytes in the periphery (Fig. 6), but B-lymphocytes are rarely observable within granulomas (Kurata et al., 2005; Ma et al., 2007; Noor & Knox, 2007). These observations are compatible with the below-mentioned postulation that granulomas are caused by cell-mediated immunity, and that $CD4^+$ T-lymphocytes are primary cells that recruit other T-lymphocytes and macrophages.

Epithelioid cells and giant cells as well as other macrophages including alveolar macrophages in the lung and sinus histiocytes in the lymph nodes are immunohistochemically positive for CD68, a marker for pan-macrophages. In contrast, macrophages within granulomas are selectively positive for ACE by immunohistochemistry in both sarcoidosis and sarcoid reactions (Fig. 7a), and probably in other granulomas. ACE is selectively expressed in macrophages with particular differentiation including those with epithelioid formation.

The macrophages constituting these granulomas originate from blood monocytes, not from resident tissue macrophages. This was verified by presence of a large amount of mononuclear cells within and around granulomas, regardless of the developmental stage, that were immunohistochemically labeled by myeloid-related protein 8 and 14 (S100A8 and S100A9, respectively), which are only expressed in freshly recruited macrophages (Fig. 7b) (Kurata et al., 2005). Besides T-lymphocytes and macrophages, below-mentioned dendritic cells (DCs) are interspersed within granulomas (Noor & Knox, 2007).

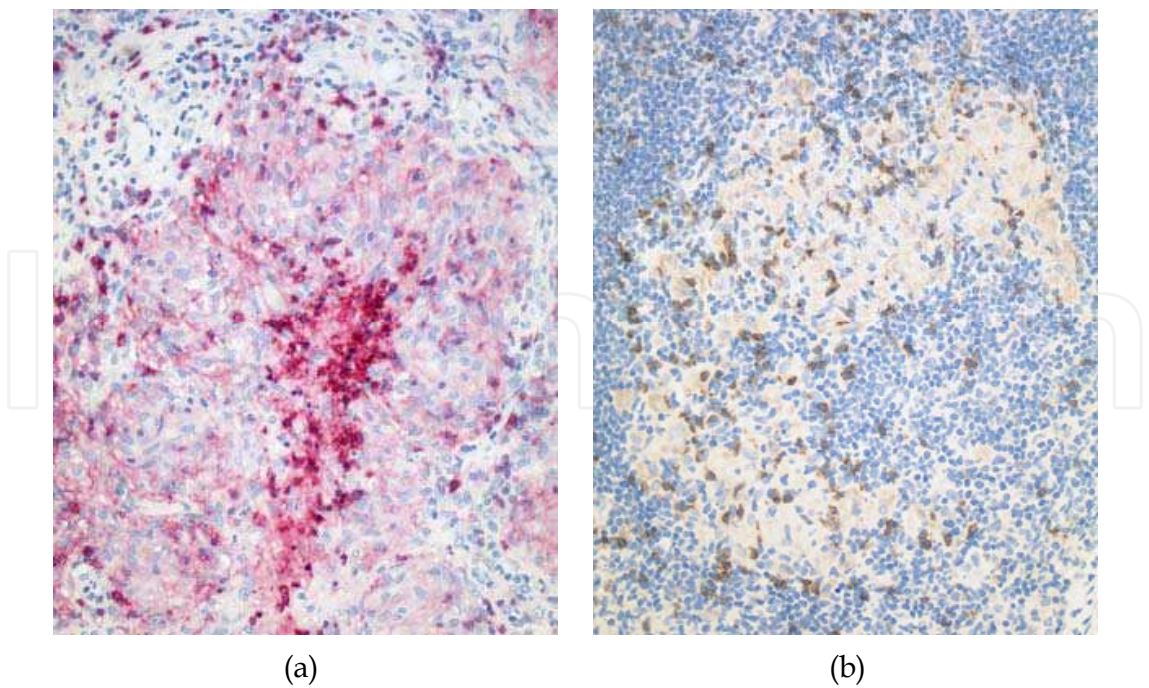


Fig. 6. Immunohistochemitry of lymphocytes in lymph node sarcoid reactions. (a) CD4⁺ T-lymphocytes are abundantly seen especially in the center of the granuloma. Positive signal is red. Original magnification: x200. (b) CD8⁺ T-lymphocytes are scattered especially in the periphery of the granuloma. Positive signal is brown. Original magnification: x200.

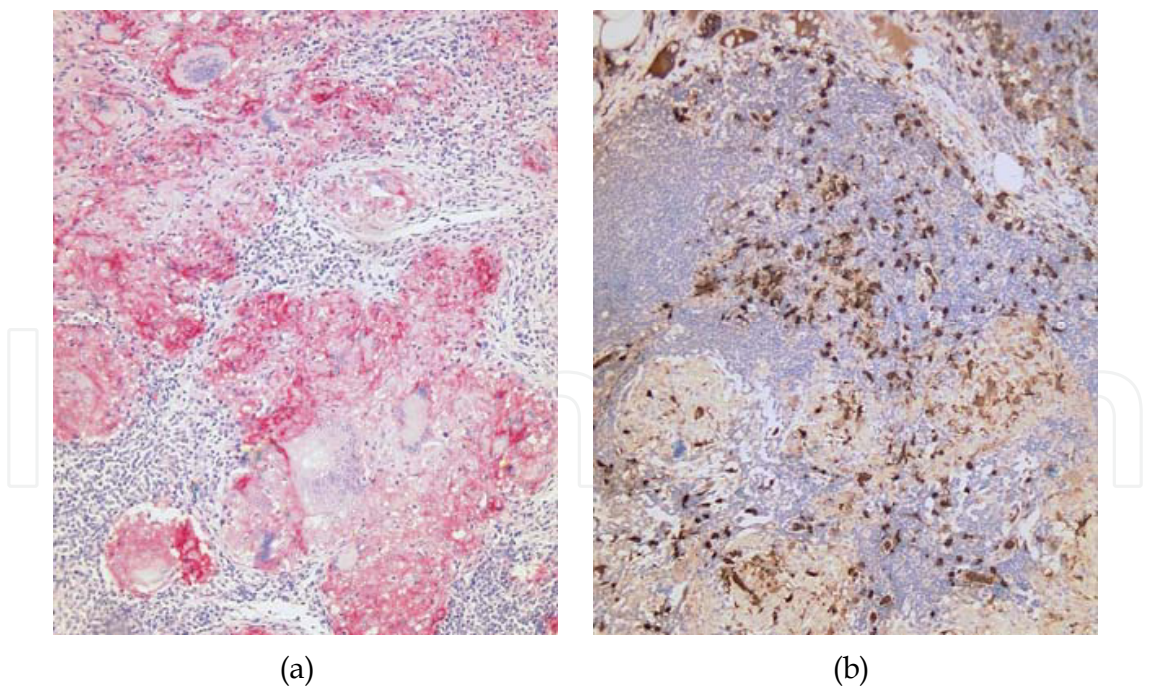


Fig. 7. Immunohistochemitry of macrophages in lymph node sarcoid reactions. (a) Angiotensin I-converting enzyme is selectively expressed in macrophages observed in granulomas. Positive signal is red. Original magnification: x100. (b) Myeloid-related protein 8-positive cells indicating freshly recruited macrophages are abundantly seen in and around the granulomas. Positive signal is brown. Original magnification: x100.

4. Pathogenesis of granulomatous disorders

It is generally believed that sarcoidosis occurs in genetically susceptible hosts exposed to specific but unknown environmental agents (Dempsey et al., 2009). Pathogenesis of sarcoidosis is thought to be similar to other granulomatous diseases of known cause, such as chronic beryllium disease. That is, the exogenous antigens are phagocytosed and processed by antigen presenting cells, followed by antigen presentation through human leukocyte antigen (HLA) class II molecules to naïve CD4⁺ T-lymphocytes. The immune reaction begets polarization of the T-lymphocytes to a T-helper 1 phenotype (Th1), followed by cellular recruitment and differentiation leading to formation of the sarcoidal granuloma through the secretion of interferon- γ and interleukin-2 (Baughman et al., 2010; Iannuzzi et al., 2007). However, this sequence is identical to delayed-type hypersensitivity in general such as a tuberculin reaction except for the formation of granulomas (Kobayashi et al., 2001). Therefore, the causative factors specific to granuloma formation are obscure (Fig. 8). Although tumor necrosis factor alpha (TNF- α), macrophage inflammatory protein 1 (MIP-1), monocyte chemotactic protein 1 (MCP-1), and granulocyte macrophage colony-stimulating factor (GM-CSF) may be involved in the formation of granulomas (Baughman et al., 2010; Iannuzzi et al., 2007), their decisive roles in the formation of granulomas in comparison with cell-mediated immunity in general have not been proved. Furthermore, although TNF antagonists are effective in treating some patients with sarcoidosis (Baughman et al., 2010), paradoxical occurrence of sarcoid-like granulomas has been reported in patients treated with TNF blockers (Daïen et al., 2009).

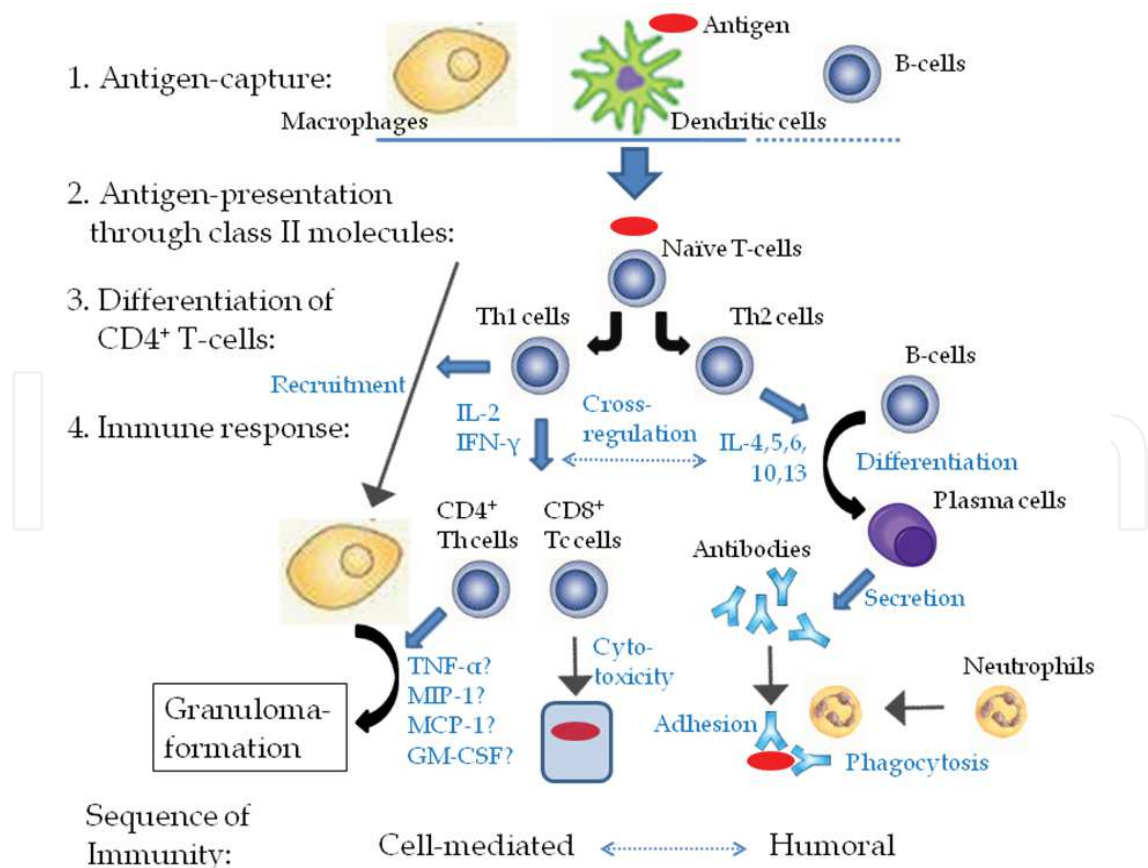


Fig. 8. Paradigm of immunoreactions of Th1 and Th2.

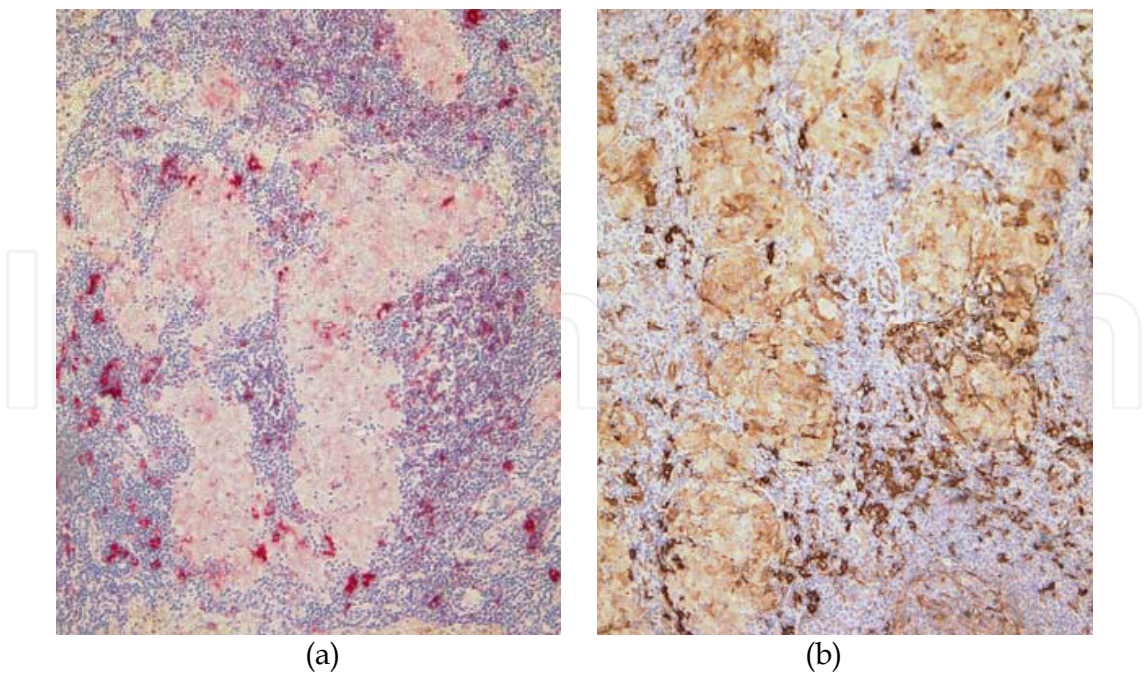


Fig. 9. Immunohistochemistry for antigen-presenting cells in lymph node sarcoid reactions. (a) HLA-DR⁺ antigen-presenting cells in the vicinity and inside the granulomas. Positive signal is red. Original magnification: x100. (b) Fascin⁺ mature dendritic cells in the vicinity and inside the granulomas. Positive signal is brown. Original magnification: x100.

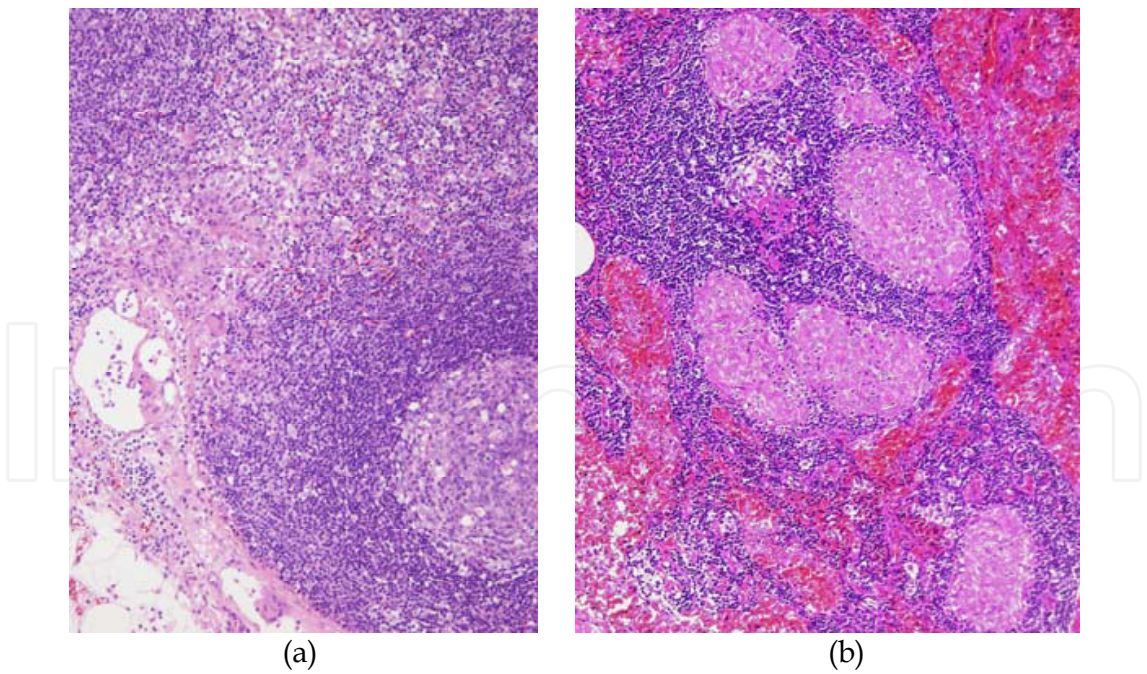


Fig. 10. Pathogenesis of granulomas of lymph nodes exemplified by sarcoid reactions. (a) Solitary granuloma being formed between sinus and T-zone. Original magnification: x100. (b) Multiple granulomas in the T-zone around the lymph follicles. Original magnification: x100.

Emergence of HLA-DR⁺ antigen-presenting cells in the vicinity and inside the granulomas has been shown in sarcoidosis (Ota et al., 2004) and in lymph node sarcoid reactions (Kurata

et al., 2005) (Fig. 9a). These cells grossly corresponded to mature DCs, which are representative antigen presenting cells, as verified by expression of below-mentioned fascin and CD83 (Fig. 9b). Further, cell-to-cell contact between T-lymphocytes and HLA-DR⁺ mature DCs in sarcoidal granulomas has been demonstrated by immunohistochemical double staining (Ota et al., 2004).

Although granulomas in the lymph nodes are usually of the large confluent type in systemic sarcoidosis, some of those in sarcoid reactions are solitary or of multiple types. Solitary type is formed between sinus and T-zone (Fig. 10a), while multiple type occurs exclusively in the sinus or T-zone (Fig. 10b). These data are consistent with the contribution of T-cell-mediated immunity in granuloma formation. However, we have not yet identified any specific feature(s) that can differentiate sarcoid reactions from sarcoidosis by immunohistochemical analysis of lymphocytes, DCs, and macrophages (Kurata et al., 2005).

5. Maturation of dendritic cells above granulomas and with relation to lymphatic vessels in cutaneous sarcoidosis

As mentioned earlier, DCs play central roles in antigen presentation. CD1a⁺ immature DCs, a subpopulation of which is also known as Langerhans cells, are capable of antigen uptake and processing, but unable to present antigens to naïve T-lymphocytes. Immature DCs, after the capture of antigens, generally begin to mature en route through the lymphatic vessels. After maturation, they can express antigen molecules to naïve T-lymphocytes in the lymph nodes. In contrast, some DCs that are activated in the peripheral tissues stay at the site of activation, where they mature and may contribute to the initiation of local inflammation (Wilson & Villadangos, 2004; Kurata et al., 2010b).

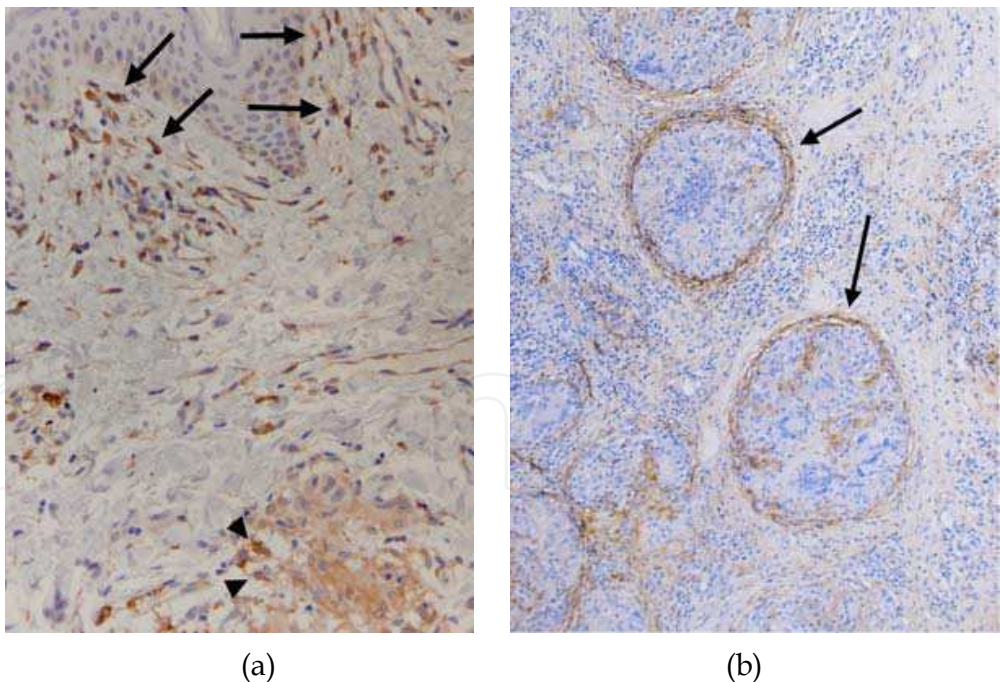


Fig. 11. Immunohistochemistry of cutaneous sarcoidosis (a) Mature fascin⁺ DCs proliferate in the upper dermis (arrows) and appear in dermal granulomas (arrowheads). Blood vessel endothelial cells are also positive for fascin. Original magnification: x100. (b) Granulomas in deeper dermis encircled by D2-40⁺ lymphatic vessel endothelial cells (arrows). Original magnification: x100.

In cutaneous sarcoidosis, it was previously reported that Langerhans cells in the epidermis overlying the dermal granuloma increase in number compared with those in the epidermis of age-, sex-, and race-matched controls (Martin et al., 1986). We have recently identified that mature DCs, which are immunohistochemically positive for fascin and CD83, proliferate in the upper dermis overlying the dermal granulomas (Fig. 11a), compared with other granulomatous skin disorders or various skin diseases. In addition, dermal granulomas, especially those located in the deeper dermis, were occasionally encircled by D2-40⁺ lymphatic vessel endothelial cells (Fig. 11b), whereas no dermal granuloma was encircled by fascin⁺ blood vessel endothelial cells (Kurata et al., 2010a). We have re-checked the granulomas in all 11 specimens of cutaneous sarcoidosis used in the above-mentioned research for CD31, a more specific marker for blood vessel endothelial cells, and confirmed that no granuloma was encircled by blood vessels. Therefore, cutaneous sarcoidosis has common pathogenesis with Crohn’s disease in that granulomas appear to be in and around the lymphatic vessels (Van Kruiningen & Colombel, 2008). These data suggest that the antigen pathway of cutaneous sarcoidosis is from epidermis through dermis to lymphatic vessels, and not from other organs such as lungs through the vascular pathway.

6. Presumable antigen pathway and proposed antigen of sarcoidosis

The hypothesis that the antigen enters through the skin in cutaneous sarcoidosis is in accordance with the observations that cutaneous sarcoidosis is usually seen at the onset of systemic sarcoidosis (Fernandez-Faith & McDonnell, 2007). However, cutaneous manifestation in sarcoidosis occurs in only about 20-35% of patients (Fernandez-Faith & McDonnell, 2007). It is conceivable that antigen enters not from the skin, e.g. through the respiratory tracts, in the other 65-80% of patients. Alternatively, it is also possible to speculate that the initial skin lesions are overlooked in a considerable number of sarcoidosis patients. The supposed antigen pathways are shown in Fig. 12. Granulomas may be formed at arbitrary sites in the course of these pathways. However, bilateral pulmonary hilar lymph nodes may be the most important sentinels against the antigens. Although we have not investigated ocular sarcoidosis, local entry of the antigen in ocular sarcoidosis (“ocular pathway”) is also possible.

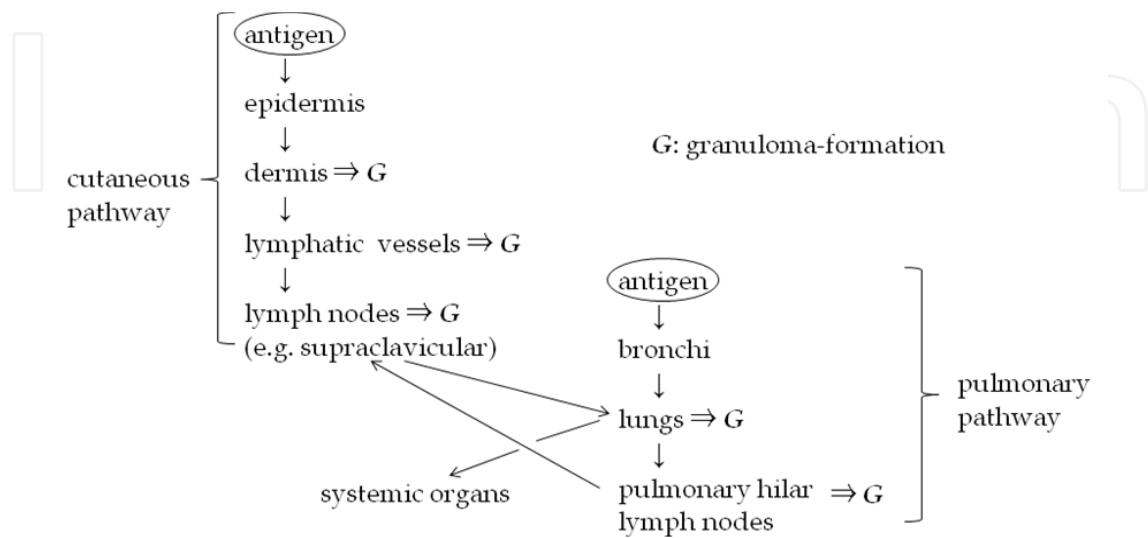


Fig. 12. Presumable antigen pathway of sarcoidosis

The common antigen of sarcoidosis patients remains unknown. Mycobacterium species are suspected in Western countries, and Propionibacterium (P.) species are suspected in Japan. It has been reported that *P. acnes* DNA are highly detected in lymph nodes of Japanese and European patients with sarcoidosis (Eishi et al., 2002). Therefore, *P. acnes* is a likely candidate as the antigen of sarcoidosis. Since *P. acnes* is indigenous to the skin, the “cutaneous pathway” may bring this antigen to systemic organs. Further studies are necessary to investigate the specificity of *P. acnes* in causing sarcoidosis, e.g. if *P. acnes* is more often detected in cutaneous granulomas in sarcoidosis than in other granulomatous skin diseases.

Alternatively, since the association with various environmental exposures has been reported in sarcoidosis patients, it has been proposed that “the development of sarcoidosis is probably the end result of immune responses to various ubiquitous environmental triggers” (Iannuzzi et al., 2007). Combining this proposal and the “cutaneous pathway” theory, it is postulated that environmental antigens may often enter through the skin. In this hypothesis, cutaneous sarcoidosis is likely to be the granuloma-forming variant of contact dermatitis, along the same line as sarcoid reactions being the granuloma-forming variant of tumor immunity (Fig. 1). The fact that *P. acnes* is highly detected in sarcoidosis lesions may not indicate that *P. acnes* is a causative agent, rather, it may be the supporting evidence that other antigens enter through the skin along with *P. acnes* that is indigenous to the skin. To confirm this possibility, further experimental research is necessary, such as testing the skin reaction by topical application of various environmental factors to the sarcoidosis patients’ skin in order to identify the antigen.

7. Further hypothesis on susceptibility to sarcoidosis

As mentioned earlier, sarcoidosis is thought to occur in genetically susceptible hosts exposed to specific but unknown environmental antigens. Genetic susceptibility due to particular immunity profiles including expression of specific HLA-molecules and T-cell receptors has been proposed, since the pathogenesis of sarcoidosis seems to involve the interplay between antigens, HLA class II molecules, and T-cell receptors (Baughman et al., 2010). For example, HLA class II antigens encoded by HLA-DRB1 and DQB1 alleles have been reported to be associated with sarcoidosis (Rossman et al., 2003; Iannuzzi et al., 2003). However, no single gene appears to be responsible for sarcoidosis; rather, the susceptibility is likely to be based on more than one gene (Ma et al., 2007).

Alternatively, it is also conceivable that environmental factors may affect the susceptibility. For example, the prevalence of allergic diseases such as wheeze, atopic dermatitis, and rhinitis in children has increased throughout the world in the past 50 years (Yura et al., 2011). This phenomenon cannot be explained only by genetic susceptibility, since the prevalence of susceptible genes has not been changed during these 50 years. Interestingly, it has been reported that infants who received Diphtheria-Pertussis-Tetanus (DPT) vaccination subsequently show significantly higher incidence of bronchial asthma, allergic rhinitis, and atopic dermatitis, compared with those who did not receive it in a remote island in Japan (Yoneyama et al., 2000). This may be explained by the hypothesis that those who received DPT vaccination escaped from natural immunoreaction against these intracellular pathogens, thus the paucity of defense against intracellular pathogens brings about a Th1-less and Th2-dominant constitution, leading to increased susceptibility to allergic pathogens that are associated with humoral immunity because Th1 and Th2 cytokines suppress each other (Kobayashi et al., 2001) (Fig. 13).

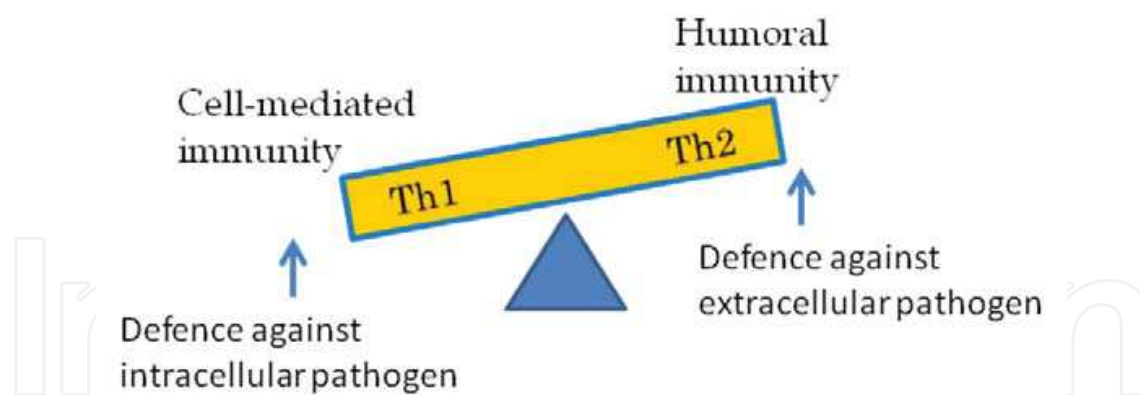


Fig. 13. The interrelation between Th1 and Th2 immunophenotypes.

Contrary to the atopic predisposition, sarcoidosis patients may tend to have a Th1-dominant constitution. This is partially verified by the fact that the incidence of atopic diseases including asthma and allergic rhinitis in sarcoidosis patients is much lower than the usual atopy prevalence (Kokturk et al., 2005). Although highly speculative, Scandinavian people are more often exposed than other Europeans to intracellular pathogens such as viruses that prefer a colder environment, whereas Americans of African descent live in an environment where more viruses are found than their natural environment. These external factors may promote the susceptibility of Scandinavian and African-American hosts to sarcoidosis.

8. Conclusion

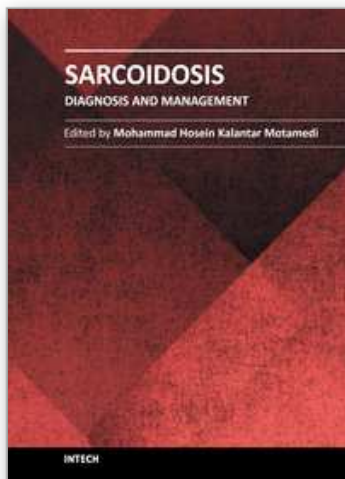
Sarcoidosis is an elusive disorder that has long been characterized by many unknown factors. Although its hallmark feature is formation of non-necrotizing epithelioid cell granulomas in the involved organs, exclusion of other granulomatous disorders is necessary in its diagnosis, and a unique histological feature is lacking. However, due to the recent advances in the fields of immunology and immunohistochemistry, the characteristics of sarcoidosis have gradually emerged. It is obvious that sarcoidal granuloma is formed through antigen presentation by DCs and sequential Th1 immunoreactions. Th1-associated cytokines recruit blood monocytes, leading to granuloma formation, although the critical cytokines are still under discussion. Immunohistochemical characteristics of cells constituting granulomas seem to be common between sarcoidosis and other granulomatous disorders including the expression of ACE and the contribution of mature DCs. Although causative antigens are still unknown, the local antigen pathway in cutaneous sarcoidosis has been proposed, since DCs mature above dermal granulomas and dermal granulomas are often associated with local lymphatic vessels. Environmental factors in addition to genetic susceptibility may be associated with not only the onset of but also the predisposition to sarcoidosis.

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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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