Chapter from the book *Sarcoidosis*

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1. Introduction

Sarcoidosis is a chronic systemic disorder of an unknown etiology and it is characterized by the presence of noncaseating granulomas in multiple organs. The granulomatous lesion affected by sarcoidosis is marked by the accumulation and activation of CD4+ helper T (Th) cells with the Th1 phenotype and monocytes/macrophages, which suggest that a Th1-type immune response plays a dominant role in the disease pathogenesis [1]. For example, the important roles for IFN-γ and IL-12 were found in sarcoid lung [2], and a genome-wide gene expression analysis of sarcoid lung tissues identified signal transducer and activator of transcription-1 gene (STAT1) as one of the dominant network genes most highly expressed in the sarcoidosis group [3].

IFN-α is known to be a potent stimulator of Th1 immune response, and increased type I IFN signaling has been implicated in a number of autoimmune diseases such as systemic lupus erythematosus (SLE) [4]. On the other hand, type I IFN has been used to treat a variety of diseases, including chronic hepatitis C (HCV) infection. However, due to its immunomodulatory effects, it has also been reported to induce several autoimmune and/or inflammatory disorders [5]. Notably, an increasing number of sarcoidosis has been reported in chronic HCV patients who received type I IFN therapy [6, 7]. In some cases, the sarcoid lesions improved following dose reduction or cessation of the therapy, suggesting the importance of type I IFN in the disease development. Moreover, from a genetic standpoint, we recently showed an association between polymorphisms in the IFNA gene and susceptibility to sarcoidosis [8]. Another recent study found that in an European-American population, serum type I IFN activity was higher in sarcoidosis cases as compared to matched controls [9]. In addition, besides IFN-induced sarcoidosis, a dozen case reports of sarcoidosis have also been reported in patients treated with tumor necrosis factor (TNF) antagonists [10]. A cross-regulation between...
type I IFN and TNF-α pathways has been proposed recently. This review focuses on a potential role of these cytokines, type I IFN and TNF-α, in the pathogenesis of sarcoidosis.

2. Cross-regulation between type I IFN and TNF-α

TNF is a pivotal pro-inflammatory cytokine produced by macrophages, activated T cells, natural killer cells and mast cells, it can also be produced by other non-immune cells such as endothelial cells or stromal cells [11]. Type I IFNs (IFN-α and IFN-β) can be produced by almost every cell type, including leukocytes, fibroblasts and endothelial cells and exert antiviral and multiple immunomodulatory activities [12].

It is well accepted that TNF plays a critical role in the pathogenesis of certain autoimmune diseases such as rheumatoid arthritis (RA), whereas there is growing evidence that IFN-α plays a pivotal role in another set of autoimmune diseases such as SLE [13]. The elevated levels of type I IFN activity in SLE patient sera has been confirmed in the 1980s [14, 15], and it was subsequently shown that overexpression of type I IFN-induced genes, called IFN signature, was a common dominant pattern in human SLE [16]. The role of type I IFN in SLE was further confirmed in the studies demonstrating induction of lupus-like disease during IFN therapy [17].

Recently, anti-TNF agents are found to be associated with the development of drug-induced lupus (DIL) as well. Indeed, a titer of anti-dsDNA antibodies has been found up to 15% of RA patients on anti-TNF therapy [18]. Postmarketing studies on the three anti-TNF drugs have suggested an estimated incidence of DIL of 0.1-0.4% (about 0.2%) [19, 20]. Another intriguing side effect of TNF blockade is the induction of psoriasis-like disease in 3 to 5% of arthritis patients without pre-existing psoriasis, which was also unexpected and paradoxical adverse effect considering the excellent clinical response of psoriasis to TNF blockade [21]. This side effect and the lupus-like syndrome observed in a part of patients undergoing therapy with TNF antagonists led to us hypothesize that TNF might actually act as an antagonist of the type I IFN pathway, further proposing cross-regulation between TNF-α and type I IFN [13].

What is the mechanism of cross-regulation between IFN-α and TNF-α pathways? Recent study demonstrated that TNF regulates IFN-α production either by inhibiting the generation of plasmacytoid dendritic cells (pDCs), a major producer of type I IFN, from CD34+ hematopoietic progenitors in vitro or by inhibiting virus-induced IFN-α release by PBMCs. In addition, neutralization of endogenous TNF sustained IFN-α secretion by pDCs [13]. Also, TNF can induce the differentiation of the potent IFN-α-secreting immature pDCs to become mature pDCs [22], which may cause downregulation of IFN-α production [23, 24]. These might explain why a deficiency in TNF related to treatment with anti-TNF inhibitors can trigger a syndrome that shares a number of features with SLE.

The relative balance between IFN-α and TNF-α has been also studied genetically and ethnically. In the study showing serum levels of TNF-α and IFN-α in sarcoidosis, significant differences in cytokine levels were found between sarcoidosis patients of different ancestral
backgrounds [9]. In this study, African-Americans had higher TNF-α levels than European-American patients or matched controls, and patients with neurologic disease had significantly higher TNF-α than patients lacking this manifestation. In a European-American population, serum type I IFN activity was higher in sarcoidosis cases as compared to matched controls, and patients with extra-pulmonary disease represented a high serum IFN group [9]. This study demonstrated ancestral and subphenotype correlations with serum cytokine levels in patients with sarcoidosis. On the other hand, however, in patients with SLE, serum TNF-α levels were high in many SLE patients, and the high serum TNF-α levels were positively correlated with high serum IFN-α levels across different ancestral backgrounds [25]. A genetic association study demonstrated that the PTPN polymorphism was associated with skewing of cytokine profiles toward higher IFN-α activity and lower TNF-α levels in vivo in patients with SLE. Moreover, in untreated patients with juvenile dermatomyositis (JDM), serum IFN-α levels was shown to be associated with the TNF-α G-308A promoter polymorphism [26]. In sarcoidosis, the presence of a TNF-α -308A variant allele was also reported to be associated with the susceptibility to and risk of sarcoidosis [27, 28].

While some studies suggest cross-regulation between IFN-α and TNF-α, not all studies of autoimmune diseases fit this model. As in the example above, a positive correlation between serum IFN-α and TNF-α in SLE was observed [25]. In JDM, the TNF-α -308A allele that has been linked to higher TNF-α production [29] was associated with increased serum IFN-α levels [26, 30]. In addition, besides known up-regulation of TNF-α in RA synovium, the increased expression of type I IFN has been also reported in the synovium of patients with RA [31]. Therefore, it is likely that cross-regulation of IFN-α and TNF-α in humans may be more complex.

In clinical settings, systemic juvenile arthritis treated with TNF antagonists display increased transcription of IFN-α-regulated genes in their blood leukocytes compared with untreated patients [13]. Further analysis revealed that infliximab (IFX) treatment induced an upregulation of the type I IFN genes in RA compared with untreated patients, whereas type I IFN response genes were not affected in patients with a good response to TNF-α blockade [32]. In addition, TNF-α blockade with etanercept (ETN), but not IFX, induced a persistent upregulation of type I IFN serum activity from 4 to 12 weeks of treatment in spondyloarthritis [33]. Similarly, in patients with Sjögren’s syndrome, a significant increase in IFN-α activity was detected after treatment with ETN [34]. Meanwhile, in patients with inflammatory myopathies, there was a significant increase in the type I IFN serum activity after IFX treatment without any clinical improvement [35]. However, the relationship between type I IFN and TNF-α appears to be complex and may be influenced by timing and disease progression.

Collectively, although there may exist the trend of a reciprocal regulation between type I IFN and TNF-α in human autoimmunity, these studies as well as the cellular studies and experimental data indicate that the effect of TNF-α blockade on type I IFN is not universal and may depend on the disease, the type of TNF-α blocker, as well as the clinical response to treatment [11]. There are several hypothesis regarding cross-regulation between type I IFN and TNF-α. The original hypothesis proposes that both cytokines can be regarded as opposite vectors and both vectors are normally in balance. A shift towards the one arm may create a permissive
environment for TNF-mediated inflammation (RA) or IFN-driven autoimmunity (SLE) [11]. Alternatively, type I IFN and IFN-α are influencing each other but the balance will be lost in a pathological condition. In addition, an alternative hypothesis proposes that type I IFN plays an important role in the initiation of autoimmunity, while the role of TNF-α increases during the secondary effector phase of the disease [11].

3. Interferon-induced sarcoidosis

A cardinal feature of sarcoidosis is the presence of CD4+ T cells that interact with antigen-presenting cells to initiate the formation and maintenance of granulomas [36]. Activated CD4+ cells differentiate into Th1-like cells and secrete predominantly IL-2 and IFN-γ. Such cytokines maintain the activation of antigen-presenting cells such as macrophages and amplify the local cellular immune response, establishing a vicious cycle that ultimately leads to the formation of granulomas.

The first case of interferon-induced sarcoidosis (IIS) was reported in a patient treated with IFN-β for advanced renal cell carcinoma in 1987 [37]. Since then, there has been an increasing number of reports that supports a possible association between IFN therapy and the development or recurrence of sarcoidosis. Although the incidence of IIS is not known, the prevalence of sarcoidosis in IFN-treated HCV patients has been reported to be rare range from 0.09% to 0.44% [38, 39]. The precise prevalence of IIS, however, may be underestimated and difficult to assess because its clinical presentation mimics the constitutional IFN-related adverse effects [6]. Actually, Hoffman et al. found a 5% incidence of sarcoidosis in a cohort of 60 patients who participated in a randomized trial of IFN-α therapy for chronic HCV [40].

Basically the clinical presentation of IIS resembles that of its idiopathic counterpart. The most commonly affected sites of involvement in IIS are skin and lungs, though many other organ systems have also been involved such as liver, joints and heart. The lungs are the most frequent organ affected in IIS (70%), similar but not as high as the incidence reported in typical sarcoidosis (90%). The most frequent symptoms are dry cough and dyspnea. The second major organ is the skin. The incidence of skin involvement appears to be much higher that reported in natural sarcoidosis (60% versus 25%) [6, 38, 41]. The most common skin manifestation is subcutaneous nodules, whereas erythema nodosum, reported to be the most common cutaneous manifestation in typical sarcoidosis, is less frequently observed in IIS. On the basis of the reported cases, IIS with cutaneous involvement can be expected to resolve within approximately 6 months of treatment discontinuation. Its onset may vary from 2 weeks to 3 years after beginning of treatment. Men and women are equally affected [42, 43], and the mean age of patients was approximately 50 years [39]. The majority (roughly two-thirds) of cases of IIS arise during the first 6 months of IFN therapy, but clinical manifestations may also appear after discontinuation of the antiviral treatment [38].

The pathophysiology of IIS is still unclear, but enhancement of Th1 immune response by type I IFNs may play a crucial role. IFN-α has been shown to promote overexpression of MHC class II antigens as well as upregulation of pro-inflammatory cytokines release by APCs and to
stimulate monocytes to release IL-12. Furthermore, IFN-α, together with IL-12, can induce the expression of the IL-12 receptor (IL-12R) β2 chain after antigen triggering [44]. In contrast to asthma, T cells in bronchoalveolar lavage fluid in sarcoid lungs express a functional IL-12 receptor composed of both the β1 and β2 subunits [45], suggesting a role of IFN-α in sarcoid pathogenesis. So, type I IFN stimulates the differentiation of Th1-type lymphocytes and reduction of the activation of Th2 lymphocytes, favoring the formation of granuloma in susceptible patients. However, among IIS, when compared to IFN-α therapy, IFN-β-acssiated sarcoidosis is relatively rare [46].

The causal link between type I IFN and sarcoidosis is strengthened by the temporal relationship between IFN therapy and appearance of sarcoidosis, by the remission with therapy cessation, and by the recurrence of symptoms on rechallenge with IFN. The occurrence of sarcoidosis during monotherapy for diseases other than chronic hepatitis also supports this relationship. Another recent study found that in an European American population, serum IFN-α activity was higher in sarcoidosis cases as compared to matched controls [9].

Of patients with IIS, the majority of individuals (approximately 80%) received therapy for chronic HCV infection, while sarcoidosis has also developed in association with the management of hepatitis B infection, multiple sclerosis, hematological and other malignant diseases. To date, more than 80 patients cases of sarcoidosis that occurred in association with IFN-α therapy for chronic HCV have been reported [47]. Similar to other species of viruses and bacteria implicated in the etiology of sarcoidosis [48], some reports have suggested a potential role for the HCV itself in the development of sarcoidosis [38, 49-51]. As chronic HCV infection is associated with induction/stimulation of type 1 cellular immune response causing chronic liver damage [52] as well as various immunological diseases [53-56], it is possible that the antigenicity and viral persistence can serve as a trigger factor for the development of clinical sarcoidosis in susceptible individuals [6]. IFN-α may act as an exacerbating factor in this situation.

Peginterferon (plus ribavirin) has recently been used to treat HCV infection. Pegylated IFN-α is the result of adding a polyethylene glycol (Peg) moiety to the standard IFN-α molecule. This modification reduces the clearance rate of the protein from the blood and extends the half-time of IFN-α, providing a constant viral suppression which entails a more sustained virological response [57]. Ribavirin, a synthetic guanosine analogue, has been successfully used in conjunction with peginterferon in the treatment of chronic HCV infection due to its ability to inhibit RNA viral replication [58]. Although no cases of sarcoidosis that occurred with ribavirin monotherapy have been reported, ribavirin might be a contributory factor in the development of sarcoidosis via inhibiting Th2 cytokine response, and preserving or enhancing the Th1 immune reaction [59, 60]. This may explain why combination therapy with IFN-α and ribavirin is more efficacious in treating HCV and, conversely, why it also may further predispose patients to immunological disorders such as sarcoidosis [42]. Thus, enhanced clinical efficacy of peginterferon plus ribavirin possibly results from the skewing Th1 response, favoring the appearance of IIS with a greater likelihood than with conventional IFN-α [61].

Most patients with IIS had resolution of their disease without immunosuppressive treatment. Half of the cases in the literature report spontaneous remission, over the course of a few
months, after stopping IFN without further therapy. There are even some reports of remission despite continuing IFN therapy. There was, however, a report showing that approximately 11% of cases, usually those with extracutaneous involvement, can have a chronic course and 6% may even reactivate after an initial improvement [38].

From a genetic stand of view, we previously showed an association between a polymorphism in the IFN-α gene (IFNA), namely IFNA17, and susceptibility to sarcoidosis in the Japanese population [8]. Then, we identified 2 major haplotype of the IFN-α gene and found that an IFNA allele, overrepresented in patients with sarcoidosis, was subsequently associated with increased IFN-α and IL-12 production in vitro [8]. Moreover, in a recent reported case of IIS, HLA typing was performed and revealed that the patient was positive for HLA-DRB1*03 and HLA-DQB1*02 [62], which have a correlation with the disease course or prognosis in sarcoidosis [63-65]. The authors hypothesized that this HLA profile predisposed the patient to IIS development [62].

In summary, the immunopathogenesis of sarcoidosis is not fully understood, but it is likely that the T cell response is biased toward a Th1 phenotype. To date, many cases of IIS have been reported, suggesting a relationship between sarcoidosis and IFN therapy in patients with a variety of diseases, especially chronic HCV infection. In addition to this, many lines of evidence support the idea that IFN-α appears to play a role in the pathogenesis of sarcoidosis by promoting Th1 immune response.

4. Anti-TNF-associated sarcoidosis

In the recent decades, TNF-α antagonists have made significant therapeutic milestones in the treatment of various inflammatory diseases such as RA, psoriasis, and inflammatory bowel disease. It has been suggested that CD4+ T-helper 1 cells and alveolar macrophages, which secrete IFN-γ and TNF-α, play a pivotal role in the induction and maintenance of sarcoid granuloma [66, 67]. Because of this, it has been postulated that TNF antagonists could be useful for the treatment of granulomatous diseases like sarcoidosis. Indeed, in a multicenter randomized double-blind placebo controlled study of IFX in 138 patients with chronic sarcoidosis, the efficacy of IFX was confirmed [68]. Moreover, case series with a total of 50 patients reported a positive treatment outcome with IFX in different type of sarcoidosis [69]. In contrast, the soluble TNF receptor ETN failed to show therapeutic efficacy in both an open-label trial in progressive pulmonary sarcoidosis and a double-blind randomized trial in refractory chronic ocular sarcoidosis [69-71].

On the other hand, there are increasing cases of acute sarcoidosis and sarcoid-like granulomatosis in patients treated with anti-TNF blocking agents have been reported. The frequency of this adverse effect was roughly estimated to be at least 0.04% (1/2800) [72], and this complication has been described in all three major anti-TNF blocking agents (IFX, ETN, and adalimumab), which suggests a class effect [10]. However, while ETN accounted for 27% of patient years of exposure to all three anti-TNF agents as of 2009, it represented 61% of case reports of anti-TNF-induced sarcoidosis at that time, suggesting some
predilection for granuloma formation with this drug [73]. Other studies also suggest an increased risk of sarcoidosis in patients treated with ETN compared to the other two agents [74, 75]. Therefore, it is intriguing that ETN appeared to be more commonly associated with this complication than other anti-TNF drugs and, meanwhile, to be less efficacious in sarcoidosis treatment [70, 71].

The underlying diseases in cases of anti-TNF-associated sarcoidosis include RA, psoriasis/pсорiatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, and Crohn’s disease [19, 76]. The time between initiation of therapy and the onset of signs and symptoms of sarcoidosis is highly variable, with a median duration of approximately 21 months, a range < 1 month to 4 years [76]. Like IIS cases, the clinical picture of this type of sarcoidosis included predominantly pulmonary and cutaneous features. Pulmonary involvement was found in 74% patients, and cutaneous involvement in 29% [76].

The prognosis of sarcoidosis occurring during TNF blockade is generally favorable since almost all patients showed clinical recovery after anti-TNF discontinuation with or without corticosteroid therapy [75, 76]. Therapy with TNF antagonist was discontinued, resulting in spontaneous resolution in some patients, whereas symptoms persisted in others, necessitating corticosteroid treatment (40-50%) [74, 75]. While in some patients recurrence or exacerbations of sarcoidosis after switching to a different TNF antagonist have been reported, other patients were able to switch to a different TNF inhibitor without experiencing recurrences or exacerbations [72, 76].

The pathogenic mechanisms involved in the appearance of sarcoid granulomatosis in patients treated with TNF antagonists are unclear. In addition, there could be notable differences regarding risk of this complication among anti-TNF drugs. Although all the anti-TNF drugs exert their action through blocking TNF-α, they have important differences in their structure and pharmacokinetics, which could explain, in part, the differences that can be observed in clinical efficacy as well as adverse effects, including the risk of granulomatous infections [77]. IFX and adalimumab (ADA) are monoclonal TNF-α antibodies whereas ETN is a TNF-α p75 soluble receptor. ETN binds mainly to soluble TNF-α molecules and interacts with transmembrane TNF with reduced avidity compared with IFX, which binds both transmembrane and soluble TNF. Clearance of ETN is 13 times greater than that of IFX and ADA. Therefore, suppression of TNF-α is greater and more prolonged with IFX and ADA. IFX, therefore, completely neutralizes TNF bioactivity, whereas freely diffusing ETN might be considered to redistribute bioavailable TNF from sites of production to other sites of lower concentration [77]. Also ETN, unlike IFX, does not produce cell lysis, therefore the inhibition of TNF would not be enough to preserve the formation of the granuloma.

Furthermore, a recent study suggested that regulatory T (T reg) cells isolated from patients with active RA were functionally defective in their ability to suppress cytokine production as well as to convey suppressive phenotype to CD4+ effector T cells [78]. Another study showed that sarcoidosis T reg cells, which is globally amplified in circulating blood and BALF of patients, completely inhibit IL-2 production of CD4+CD25- cells, but not that of IFN-γ or TNF-α, suggesting the insufficient ability of sarcoid T reg cells to control local inflammation [79]. Treatment with IFX can restore the number and function of T reg cells [78]. Thus, treatment
with IFX strongly inhibits TNF-α activity, leading to a restoration of T reg cell-mediated inflammatory suppression. In contrast, low levels of TNF-α can persist after treatment with ETN, hence T reg cells may remain down-regulated to some extent and can lead to an sustained Th1 response. Moreover, enhanced IL-17A expression in sarcoid granulomas and in circulating memory T cells from sarcoidosis patients was recently reported [80]. There is a report showing that Th17 responses were inhibited by T reg cells from RA patients responding to the anti-TNF antibody ADA, whereas there was no alteration in T reg number, function or phenotype in ETN treated patients [81].

As previously noted, physiological crosstalk between TNF-α and IFN-α pathways has been reported. There are some indications that type I IFN activity is upregulated during treatment with TNF antagonists in some patients with inflammatory or autoimmune disease [13, 34]. IFN-α can enhance the production of IFN-γ and IL-2, expression levels of both cytokines are elevated in sarcoid T cells [67]. As IFN-γ along with TNF-α is strongly implicated in granuloma formation, the increased production of IFN-γ seen in some patients undergoing anti-TNF therapy [76, 82, 83] may contribute to the development of sarcoid-like granulomatosis. Actually, monoclonal anti-TNF-α antibodies can raise the Th1/Th2 ratio in the peripheral blood [83, 84]. Thus, anti-TNF therapies can modulate the cytokine environment and may restore a Th1 response. IFX and ADA inhibit T cell activation and IFN-γ production, whereas ETN does not [85]. ETN even can enhance T cell production of IFN-γ [84, 86]. This fact could partially explain the greater incidence of sarcoidosis with ETN compared with monoclonal antibody.

It is interesting to note that sarcoid-like granuloma preferentially developed in the skin and lungs, which are in direct contact with exogenous antigen. Several lines of evidence support the idea that sarcoidosis results from exposures to possible environmental agents such as Mycobacterium tuberculosis (M. tuberculosis) and Propionibacterium acnes (P. acnes) [87-89]. M. tuberculosis or P. acnes associated with anti-TNF treatment was also reported [90, 91]. Anti-TNF drugs are known to decrease antigenic clearance and increase infections. Then, mechanisms involved in granulomatosis development during anti-TNF therapy could include increased susceptibility to infection and modification of the cytokine environment and cellular recruitment within the tissues [72]. Among ant-TNF drugs, several studies indicate that infection with granulomatous pathogens such as M. tuberculosis, histoplasmosis, and coccidioidomycosis occur with 2-10-fold greater frequencies in patients treated with IFX than in those treated with ETN [85, 92-94]. Additionally, in most cases of Listeria monocytogenes infection during treatment with anti-TNF agent, IFX or ETN, patients had received IFX [95]. Both IFN-γ and TNF-α are essential for protection against tuberculosis. The higher risk of such intracellular granulomatous pathogens that IFX poses than does ETN is therefore possibly due to the simultaneous suppression of TNF-α and IFN-γ, and may as well explain why IFX, but not ETN, is effective in treatment of sarcoidosis, where the presence of both IFN-γ and TNF-α is necessary.

Together, the development of sarcoid-like granulomatosis during therapy with TNF antagonist is paradoxical in view of the central role of TNF-α in the formation and maintenance of granulomas. There seems to be significant differences between the 2 classes of TNF antagonists in the risk of this complication with the greater incidence of a soluble TNF receptor ETN-associated sarcoidosis. Anti-TNF monoclonal antibody IFX or ADA can suppress TNF-α as
well as IFN-γ and inhibit Th1 (and Th17) response partially through restoring the number and function of T reg cells. IFX and ADA may also eliminate activated T cells and monocyte/macrophage directly either by cell lysis or by inducing apoptosis [96]. On the contrary, ETN therapy may result in an insufficient inhibition of TNF bioactivity and may enhance Th1 response with IFN-γ production causing the formation of the granuloma.

5. Conclusion

Type I IFN and TNF-α are cytokines with important roles in coordinating immune reactions and potentially appear to contribute to the local and systemic inflammatory processes underlying sarcoidosis pathogenesis. The increasing case reports of interferon-induced and TNF-associated sarcoidosis support this idea. A cross-regulation between type I IFN and TNF-α has been proposed in some autoimmune or inflammatory disorders. However, the studies in patients with sarcoidosis show that there is not necessarily a direct balance between the levels of type I IFN and TNF-α, and that the type of clinical manifestations, the disease phase, and patient heterogeneity may contribute to create a complex picture. Ancestral background as well as genetic polymorphisms may influence each cytokine level and clinical manifestations, which can cause heterogeneous phenotype of the disease. Further work regarding sarcoidosis induced by the cytokine/anti-cytokine therapy as well as clinical and in vitro studies in sarcoidosis will help evaluate and treat these patients properly depend on the disease phenotype and disease activity in the future.

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