Autoimmune aspects of pulmonary sarcoidosis*

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Despite a plenty of pulmonologic studies, aetiology and pathogenesis of lung sarcoidosis are still insufficiently clear. Most researchers are inclined to speculate about the possible autoimmune/immune-mediated genesis of the disease, finding new evidence of such. The minireview attempted an integral analysis of currently available data suggesting autoimmune origin of sarcoidosis divided into four categories: The role of triggers in the development of sarcoidosis; the presence of immunogenetic susceptibility to the disease; analysis of cellular and humoral immunity in it and evaluation of clinical signs detected in sarcoidosis patients. New original definition of sarcoidosis is suggested. New data are reviewed on the possible autoinflammatory disorder of macrophageal polarization in sarcoidosis distinguishing it from tuberculosis. Author's original hypothesis on possible therapeutic effectiveness of rapamycin in sarcoidosis is first coined.

Keywords: sarcoidosis, autoimmunity, triggers, vimentin, major histocompatibility complex, ASIA-syndrome.

Sarcoidosis belongs to granulomatous diseases with non-caseating granulomas, represented by a conglomerate of epithelioid and multinuclear cells surrounded by CD4 +, CD8 + T– and B–lymphocytes. The most often lungs are altered (90 %), also joints, lymph nodes, in rare cases — bones, integument and liver. Neurosarcoidosis and ocular sarcoidosis also may occur [1]. Regarding its aetiology, nowadays some bacteria, fungi and viruses able to provoke granulomas isolated from sarcoidosis patients [2–3]. The most widely discussed is the implication of *Mycobacteria* and *Propionibacterium acnes* [3–5]. But infectious agents probably act as indirect causal trigger factors, just releasing autoimmune pathogenesis mechanism. Trigger effect may also depend on non-infectious agents: occupational hazards, vaccines, pollutants, xenobiotics — able to be adjuvants. An important place belongs to vaccines containing aluminum. Silicone also holds a special place [4–6].

Sarcoidosis is characterized by 2 acute variants: Löfgren's syndrome, manifested by nodular erythema, fever, polyarthritis, uveitis, and Heerfordt's syndrome, which is char-

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acterized by uveitis, parotitis, fever and facial paralysis [1]. Sarcoidosis has similarities with Sjogren's syndrome: both associated with the HLA-DR3, and proceed with increased content of CD4 + lymphocytes [4]. Pivotal role in autoimmune diseases is played by T-cell immunity, especially driven by Th1 and Th17 subtypes, with T-regulators as autoimmunity inhibitors, and sarcoidosis is not exclusion [7–8]. A distinctive feature of sarcoidosis is the formation of granulomas; the centre of them is reach with macrophages and T-helpers, whereas cytotoxic CD3 + CD8 + T- lymphocytes, Tregs, fibroblasts and B-lymphocytes reside in its peripheral part [9]. In sarcoidosis, an increase in Th17 was found both in peripheral blood and bronchoalveolar fluid, while the number of T regulatory cells in lavage was reduced, although increased in the bloodstream [8–10].

The recent studies suggest that a protein of mesenchymal cytoskeleton intermediate filaments vimentin, taking part in cell-cell interactions in sarcoid and other granulomas [11], may be an autoantigen for sarcoidosis. The role of vimentin in the pathogenesis of sarcoidosis was shown in the studies of T-cell response during incubation of mononuclear cells with vimentin either Kveim's reagent (used for serologic confirmation of sarcoidosis since 1940ies) [10]. Vimentin as a target of autoimmunity has been known for a long time and observed in several autoimmunopathies [5, 11]. The cross-reactivity with mycobacteria, whose proteins may have molecular mimicry with vimentin, is being actively discussed.

Different autoantibodies (anti-nuclear antibodies, anti-dsDNA, anti- citrullinated cyclic peptides, and rheumatoid factors), were found in sarcoidosis, however not diagnostically significant [12].

The activation of the peripheral mononuclears of sarcoidosis patients occurs after stimulation with vimentin and lysylRNA synthetase [13]. Later, the presence of specific CD4 + Th1 with Vα2.3 / Vβ22 receptors interacting with HLA-DRB1*03 proteins was detected in sarcoidosis, and a peptide which coincides with vimentin structure was represented by antigen-presenting cells using HLA-DRB1*03. Specific T-cells and antibodies to vimentin revealed in sarcoidosis patients with HLA-DR-B1*0301 positivity [14]. The role of humoral immunity in sarcoidosis is supported by polyclonal hypergammaglobulinemia. The use of anti-B-cell therapy in its successful treatment suggests mechanistic role of both "naive" and memory B-cells [12]. Proving the nature of disease "*ex juvantibus*", typical treatment of sarcoidosis is similar to many classical autoimmune systemic diseases, including glucocorticosteroids and cytostatics as a second line. In chronic and extrapulmonary sarcoidosis TNF-α inhibitors are in use [12; 15].

The latest advances in models of sarcoidosis give another pathway of its comprehension, interpreting this disease not as a purely autoimmune, but autoinflammatory one. It looks like sarcoidosis may crucially depend on disorder in M1/M2 macrophage polarization process. M2 macrophages, typically involved in aggregation and formation of multinucleate cells, are overexpressed in sarcoidosis granulomata in all tissues involved. The model recently suggested by Crouser et al [16] seems well-explaining early events in granuloma formation in different granulomatoses (e.g., sarcoidosis vs. TB), with a striking M2 macrophage polarization bias in sarcoidosis, but not in tuberculosis. Polarization of macrophages to M2-cells depends on a key mechanism: rapamycin-sensitive signaling pathway [17]. Moreover, chronic signaling *via* mTORC1 kinase, a key element of this pathway, marks granulomata formation and sarcoidosis progression [18].

Due to this, we hereby suggest *a hypothesis that an antibiotic rapamycin prescribed off-label probably can serve as an effective drug against sarcoidosis*. This hypothesis was never

coined or proven before and needs clinical testing, but our analysis of literature revealed at least one case of sarcoidosis occurred *de novo* in a patient with liver transplantation, which resumed after treatment with rapamune (an analogue of rapamycin) by transplantological indications [19].

Conclusion

Summarizing data on sarcoidosis as an autoimmune disease one can observe presence of all their expected features: absence of evident single aetiologic factor, mosaic of triggers with the role of HLA-related predisposal, systemic involvement, disturbance of humoral and cellular immune response, detection of auto-antibodies to targets common for autoimmunopathies, and high efficiency of immunosuppressing versus negliable effectiveness of anti-bacterial therapy.

Thus, it's high time to coin a renewed *definition* of sarcoidosis as: polyetiologic systemic autoimmune/autoinflammatory glanulomatous disease of acute or chronic cause, eliciting on background of genetic predisposition under influence of various adjuvant-like trigger factors, but rarely leading to fatal outcome.

Hence, a lot of new clinical and experimental data put sarcoidosis closer to realm of autoimmune/autoinflamatory diseases and even hint on possible new approaches in its treatment.

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