Cellular Players in the Immunopathogenesis of Sarcoidosis

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KEYWORDS

• Saracoidosis • Alveolar macrophage • T cells • TH1 • TH17 • Treg • Cytokines • TNF

KEY POINTS

- Granuloma induction is a coordinated immunologic response requiring the orchestrated action of different cell types.
- The coordination between these cells is regulated by cytokines with tumor necrosis factor as a mediator of high importance.
- The set of immune cells involved and the intensity of the immune reaction induced may determine acute and chronic disease.
- Granuloma induction is elicited by an environmental factor based on and shaped by the genetic background of patients.
- Although several probable sarcoidosis antigens have been identified in the recent past, a single causative, granuloma-inducing agent in sarcoidosis is still lacking.

INTRODUCTION

Every year the knowledge on mediators, receptors, and, during the last years, on genes possibly involved in sarcoidosis is growing. Nevertheless, its cause, its large variability, and the regulatory network involved remains enigmatic. This enigma indicates that, although we know some key players, our view on this disease is merely based on concepts or models than on secure knowledge of the underlying processes and pathways. The main reasons are twofold: the lack of a causal agent and the lack of a reliable animal model in sarcoidosis.

In general, the formation of granuloma requires the presence of activated T cells and macrophages embedded in a specific cytokine milieu. T cells are specifically activated by recognizing antigens with their antigen-specific T-cell receptor (TCR) presented by antigen-presenting cells (APCs). TCRs are highly specific, and the T-cell pool in sarcoidosis discloses signs of TCR enrichment; therefore, the search for a sarcoidosis antigen concentrates on a specific antigen-activating T cells. Although there was some recent progress in identifying T-cell–stimulating peptides in sarcoidosis, their origin is still elusive.

Although the T cells seem to be key players, it is generally accepted that the pathogenesis of sarcoidosis is mediated by a panel of immune reactions mediated by both the innate and the adoptive immune system. This activation is controlled by a plethora of cytokines found to be released in increased amounts by diverse immune cells and by increased expression of activation markers on the cell surface, which might also be released or shed and can be found in body fluids. This rather mechanistic view of the immune processes is shaped by regulatory and cell biological processes and defects as demonstrated by new data from genetic studies.

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From this, the immunopathogenesis of sarcoidosis is driven by a network of cells and processes of the innate and adoptive immune system and their products, which are discussed in the following article.

THE INNATE IMMUNE SYSTEM

Receptors of the Innate Immune System

Throughout the evolution, organisms had to face a potentially hostile environment and defend themselves from invading microorganisms using specialized cells equipped with structures to detect, kill, and eliminate invading microorganisms from the body. These cells are called macrophages, which can be found in all vertebrates and even in invertebrates like the fruit fly *Drosophila*. Cells of the innate immune system detect invading microorganisms using a set of membrane-bound or intracellular receptors called pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like, and retinoic acid inducible gene (RIG)-I like receptors.

Microorganisms exhibit a wide range of invariable molecular patterns, which unambiguously differentiate these cells from cells of the infected host. These structures are called pathogen-associated molecular patterns (PAMPs) and summarize molecules like lipopolysaccharide (LPS), nonmethylated DNA, and others.

TLRs also recognize endogenous ligands. Because these ligands are released in association with tissue injury or trauma, the name damage-associated molecular patterns (DAMPs) or alarmins is suggested. DAMPs are rapidly released by damaged but not by apoptotic cells and may also be released by some living cells (reviewed in[1]).

In sarcoidosis, the plasma level of the S100 acute-phase molecules S100A8 (migration inhibitory factor-related protein [MRP]8, calprotectin)[2,3] and S100A9 (MRP14, calgranulin B)[4] are found to be increased and $S100^+$ cells are involved in early phases of granuloma induction.[5] Both molecules bind to TLR4 and receptor for advanced glycation endproducts (RAGE) and are able to initiate an immune response including nuclear factor kappa B (NFκB) activation and induction of cytokine release.[6,7] Defensins are also increased in sarcoidosis[8] and might also activate the innate immune system via TLR4.[9] Peptides released by neutrophils are rich in defensins and induce tumor necrosis factor (TNF) release in alveolar macrophages from patients with active sarcoidosis but not from controls.[10] Recently it was demonstrated that serum amyloid A is found in sarcoidosis granuloma and activates NFκB via TLR2.[11]

TLR2 also influences adaptive immunity, as the blockade of TLR2 by specific antibodies downregulates T-cell recognition of the mycobacterial antigens like ESAT-6 (early secreted antigenic target 6) and the mycobacterial catalase G (mKatG).[12] It has been shown that recognition of ESAT-6 by TLR2 inhibits MyD88 activation and subsequent interleukin 12 (IL-12) release.[13]

Binding of a ligand to its specific receptor may be modulated by gene modifications. For TLR9, TLR4, or TLR2, it was reported that single nucleotide polymorphisms (SNPs) caused either diminished receptor function leading to reduced mediator production[14,15] or in contrast resulted in increased release of proinflammatory mediators.[16] Thus, TLR polymorphisms might either result in missing detection of an invading pathogen, which would normally be recognized and eradicated by the innate immune system. In this case, the microorganism escapes immune surveillance and persists in the host. In contrast, polymorphisms leading to overstimulation of the immune system the altered TLR might induce an inadequately strong immune response to a normally harmless microbe or a commensal. Thus, polymorphisms in PRRs might be linked to initiation and progress of the disease.[17–23] These differences in activated receptor expression may account for the different reactions to TLR stimulation observed in sarcoidosis.[24]

Neutrophil Granulocytes

An important player of the innate immune system is the neutrophil granulocyte (NG). NGs are attracted by chemokines like CXCL8 (Interleukin-8 [IL-8]), CXCL5 (epithelial-derived neutrophil-activating peptide 78 [ENA-78]), and others. These mediators are released by monocytes and macrophages but also after adequate stimulation by other cells, for example, alveolar epithelial cells type II.[25] Neutrophils are equipped with a variety of PRRs to detect invading microbes and, therefore, they are very effective in phagocytizing and killing these organisms. However, they also release a wide panel of proteases and reactive oxygen intermediates (ROIs), which damage the lung tissue; therefore, excessive activation of neutrophils may be harmful to the lung.

Although neutrophil accumulation inducing chemokines like IL-8 are increased in sarcoidosis, especially in patients with progressing disease or chest radiograph type II,[26–28] the percentage of neutrophils in the bronchoalveolar lavage is rather low. Interestingly, several studies found a positive correlation of CXCL8 or CXCL5 and the number or percentage of neutrophils in bronchoalveolar lavage (BAL) in idiopathic pulmonary fibrosis (IPF) but not in sarcoidosis.[27,28] Nevertheless, it was