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Review

Microbial and human heat shock proteins as 'danger signals' in sarcoidosis

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ABSTRACT

In the light of the Matzinger's model of immune response, human heat shock proteins (HSPs) as main 'danger signals' (tissue damage-associated molecular patterns-DAMPs) or/and microbial HSPs as pathogen-associated molecular patterns (PAMPs) recognized by pattern recognition receptors (PRR), may induce sarcoid granuloma by both infectious and non-infectious factors in genetically different predisposed host. Regarding infectious causes of sarcoid models, low-virulence strains of, e.g. mycobacteria and propionibacteria recognized through changed PRR and persisting in altered host phagocytes, generate increased release of both human and microbial HSPs with their molecular and functional homology. High chronic spread of human and microbial HSPs altering cytokines, co-stimulatory molecules, and Tregs expression, apoptosis, oxidative stress, induces the autoimmunity, considered in sarcoidosis. Regarding non-infectious causes of sarcoidosis, human HSPs may be released at high levels during chronic low-grade exposure to misfolding amyloid precursor protein in stressed cells, phagocyted metal fumes, pigments with/without aluminum in tattoos, and due to heat shock in firefighters. Therefore, human HSPs as DAMPs and/or microbial HSPs as PAMPs produced as a result of non-infectious and infectious factors may induce different models of sarcoidosis, depending on the genetic background of the host. The number/expression of PRRs/ligands may influence the occurrence of sarcoidosis in particular organs.

Contents

Abbreviations: AIM, absent in melanoma; Ag, antigen; ALR, AIM2-like receptor; APC, antigen presenting cell; CLR, C-type lectin receptor; DAMP, damage-associated molecular pattern; DC, dendritic cell; HMGB1, high mobility group box1; HSPs, heat shock proteins; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; LRR, leucine-rich repeat; Mtb-HSPs, mycobacterial HSPs; MBP, mannose-binding protein; miRNA, microRNA; Mø, monocyte/macrophage; NALP, natch domain-, leucine-rich repeat-, and pyrin-containing domain; NLRP3, NOD-, LRR- and pyrin-domain containing 3; NLR, nucleotide oligomerization domain (NOD)-like receptor; NOD, nucleotide binding and oligomerization domain; PAMP, pathogen-associated molecular pattern; PRR, pattern-recognition receptor; PS, phosphatidylserine; PTP, protein tyrosine phosphatase; RAGE, receptor for advanced glycation endproducts; RIG-I, retinoic acid-inducible gene I; RLR, RIG-I-like receptor; ROS, reactive oxygen species; TLR, Toll-like receptor; TREM, triggering receptor expressed on myeloid cells.

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1. Introduction

Sarcoidosis (SA) is a granulomatous disorder of an unknown etiology. Infectious, genetic factors, autoimmunity, and an innate immune mechanism have been explored as potential causes of SA [1,2,4]. Due to similar clinical and histopathological picture of SA and tuberculosis (TB), *Mycobacterium tuberculosis* antigens, e.g., early secreted antigen (ESAT-6), heat shock proteins (Mtb-HSP), catalase-peroxydase (katG) enzyme, and superoxide dismutase A peptide (sodA) have been often considered as infectious factors in the etiopathogenesis of SA [2,5–7]. Also other bacteria, e.g. propionibacteria, streptomyces and corynebacteria, were discovered in sarcoid tissue [2,7–10]. Many non-infectious factors, e.g. metal fumes, pigments with/without aluminum in tattoos, pollen, fire are also considered as potential causes of SA [11,12]. The innate immune mechanism, possibly involving misfolding and aggregation of serum amyloid A (SAA), might also play a role in the pathobiology of sarcoidosis [7]. Moreover, sarcoidosis fulfills all the criteria needed to recognize a disorder autoimmune in origin [reviewed in 4]. Recently, the American Autoimmune Related Diseases Association included SA in their list [3].

Is there any one explanation of all the considered causes of the same sarcoid granuloma formation?

In my opinion, the Danger Theory, originated by Polly Matzinger, partially supports all my recently published findings and may explain the participation of both infectious and non-infectious factors in the etiopathogenesis of sarcoidosis [5–41]. Prof. Matzinger proposed that antigen presenting cells (APCs) responding to endogenous 'danger signals', that were released from host cells undergoing injury, stress or necrosis caused by different infectious and non-infectious agents, may induce the immune response [13]. In my opinion, heat shock proteins as 'danger signals' released by human and pathogens can induce the sarcoid granuloma formation by both non-infectious and infectious factors.

2. The pathogen-associated molecular patterns (PAMPs), pattern recognition receptors (PRR), and endogenous 'danger signals' – damage-associated molecular patterns (DAMPs) in the immune response

Inflammation results from recognition of evolutionarily conserved structures of pathogens, PAMPs, through a limited number of germ line-encoded PRR receptors and/or from reaction to tissue DAMPs [13,22–25].

To exogenous PAMPs, a lipopolysaccharide (LPS) from the outer membrane of Gram-negative bacteria, peptidoglycan, lipoteichoic acid, bacterial DNA, viral DNA/RNA, chitin, flagellin, leucine-rich repeats (LRR), mannans in the yeast cell wall, and microbial HSPs, were mostly included (Table 1) [25–30].

According to characteristics summarized by Bianchi [31], the endogenous danger molecules: (a) should be released immediately after non-programmed cell death via specialized secretion systems; (b) can recruit and activate innate immune cells, e.g. macrophages or dendritic cells (DC), to promote adaptive immune responses; and (c) should also restore homeostasis by promoting the reconstruction of the tissue that was damaged due to direct offense, as well as secondary effects of inflammation. Thus, the endogenous danger molecules have been proposed to constitute a family of so-called 'damage associated molecular patterns' [32].

The heat shock proteins as DAMPs fulfill all the above criteria [28,32,33]. Physiologically, HSPs are involved in cytoprotection in all organisms [4,40]. HSPs are transferring peptides, e.g. antigens (Ag), between cellular compartments, and modulating some proinflammatory and/or anty-apoptotic signaling pathways may be involved in an adaptive response, also autoimmunity [30,34,40].

Despite HSPs, a high-mobility group box 1 (HMGB1), a DNA-binding nuclear protein, mRNA, uric acid, members of the calcium-binding S100 proteins, fibrinogen, C1q, C11b/18, and C5a fragments of complement, apoptotic cells, the nucleotide-binding oligomerization domain 1 or 2 (NOD1/2) ligands, IL-1α, IL-33, and oxidized LDL, are included to endogenous danger molecules' group (Table 1) [22,24–35].

DAMPs can be released in response to a variety of tissue trauma resulting from burns, cold, nutrient depletion, phagocytosis, chemical insults, insecticides, alum, silica, pathogens, tumors, xenobiotics, UV radiation, oxidative stress, and autoimmune tissue destruction. DAMPs have been reported to have pro-inflammatory, chemotactic, proliferative and tissue regeneration properties after binding to the family of pattern recognition receptors [13,23–41].

To PRR receptors richly expressed on monocytes, macrophages, DC were mostly included the *receptor* for advanced glycation end products (RAGE), TLRs, CD14, receptors for Fc fragment of IgG (FcγR) and complement (CR), cytoplasmic nucleotide binding and NOD1/2, NOD-, LRR- and pyrin-domain containing (NLRP), triggering receptor expressed on myeloid cells (TREM1/2), scavenger receptor A, RIG-I-like receptors (RLRs), C-type lectin (CLRs), the macrophage receptor with collagenous structure (MARCO), and DNA-binding HIN domain [22,23,25–27,35–41].

RAGE receptors, encoded within the major histocompatibility class III locus, are constitutively expressed at high levels in lungs, but also in other organs like the heart or liver, and in inflammatory cells [reviewed in 35]. It has been demonstrated that an interaction of RAGE with the endogenous danger signals like peptide family of S100/calgranulins, some species of advanced glycation end products, immunoglobulin light chains, amyloid-β, and HSPs triggers macrophage activation signaling pathways *via*, e.g., NF-κB, mitogen-activated protein kinases (MPKs), phosphatidylinositol 3-kinases/protein kinase B (PI3K/Akt), phosphoglycerate kinases, Janus kinase/signal transducer and activator of transcription (Jak/STAT), and Src family kinases, leading to the chronic inflammation [22,27]. It is possible that multiligand RAGE, localized mostly in lungs, is a cause of predominant pulmonary form of sarcoidosis in Europe but cardiac sarcoidosis in Japan (our study in progress).

Because both endogenous DAMPs and exogenous PAMPs via TLRs often initiate the same signaling cascades and elicit similar responses, Bianchi and Sims et al. suggest that PAMPs can be considered as subgroups of a larger set, DAMPs [31,35]. Also Zhang and Mosser [32] proposed that the term PAMPs is actually a misnomer, since many of these molecules can be expressed on host cells as well as on microbes. Others [34] proposed that some PAMPs and DAMPs act in quite a different manner in order to stimulate an immune response depending on different co-receptors and accessory molecules, like MD-2, dectin-1 or MARCO. They evidenced, that two major intracellular signaling pathways can be activated by TLRs. The first one, a myeloid differentiation factor 88 (MyD88)-dependent pathway, is activated by all TLRs except for TLR3. It involves the IL-1R-associated kinases (IRAK), IRAK-1 and IRAK-4, TNF receptor-associated factor 6, and MPK1 and culminates in the