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The involvement of heat-shock proteins in the pathogenesis of autoimmune arthritis: a critical appraisal

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Abstract

Objectives—To review the literature on the role of heat-shock proteins (HSPs) in the pathogenesis of autoimmune arthritis in animal models and patients with rheumatoid arthritis (RA).

Methods—The published literature in Medline (PubMed), including our published work on the cell-mediated as well as humoral immune response to various HSPs was reviewed. Studies in both the pre-clinical animal models of arthritis as well as RA were examined critically and the data presented.

Results—In experimental arthritis, disease induction by different arthritogenic stimuli, including an adjuvant, led to immune response to mycobacterial HSP65 (BHSP65). However, attempts to induce arthritis by a purified HSP have not met with success. There are several reports of a significant immune response to HSP65 in RA patients. But, the issue of cause and effect is difficult to address. Nevertheless, several studies in animal models and a couple of clinical trials in RA patients have shown the beneficial effect of HSPs against autoimmune arthritis.

Conclusions—There is a clear association between immune response to HSPs, particularly HSP65, and the initiation and propagation of autoimmune arthritis in experimental models. The correlation is relatively less convincing in RA patients. In both cases, the ability of HSPs to modulate arthritis offers support, albeit an indirect one, for the involvement of these antigens in the disease process.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease of global prevalence and afflicts over 1 percent of Americans¹⁻³. The endogenous target antigens involved in autoimmune damage to the joints remain elusive. Identification of the target antigens in autoimmune arthritis is

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vital to advancing the understanding of the etiology of, and the designing of specific immunotherapeutic regimen for, this debilitating disease. Heat-shock proteins (HSPs)⁴⁻⁷ (Table 1) are implicated in the pathogenesis of experimental arthritis in rodents⁸⁻¹⁵ as well as human RA¹⁶⁻¹⁸. The T cells and antibodies from arthritic animals and RA patients are directed against different HSPs^{15,19-23}. Various HSPs share a common characteristic of inducibility by heat-shock or other stressful stimuli, and these HSPs can be categorized into 9 protein families (Table 1). Many of them function as chaperones^{6,24}.

METHODS

We reviewed the literature pertaining to the role of HSPs in the pathogenesis of autoimmune arthritis. We used different combinations of the key words including heat-shock proteins, experimental arthritis, autoantigens, antibodies, T cells, autoimmunity, pathogenesis, immunomodulation, treatment, and rheumatoid arthritis (RA). Our search covered the period from 1975 to 2009, but the majority of the short-listed articles belonged to the period 1985 to 2009. We sought information from published work pertaining to 2 groups. First, the experimental models of arthritis in rodents (Table 2) and second, RA patients (Table 3). Most of the available literature was related to HSP65. We specifically looked for information regarding immune response to HSPs and its correlation with the disease process. The latter included active disease as well as disease remission. Also examined was information about the immunomodulation of arthritis using HSPs.

RESULTS

1. HSPs and experimental arthritis

1.1. Immune response to HSPs in different models of arthritis—HSPs are the major targets of the immune response induced during the course of arthritis in mice and rats. The experimental models of arthritis belong to distinct categories depending on the nature of the arthritogenic stimulus (Table 2). The arthritogens employed include microbial products (e.g., *Mycobacterium tuberculosis* H37Rv (Mtb)^{8,9,25} and Streptococcal cell wall (SCW)^{14,26,27}), oils (e.g., mineral oil, pristane^{13,28}) and synthetic adjuvants (e.g., dimethyl dioctadecyl ammonium bromide (DDA)¹⁵, avridine^{29,30}). Intriguingly, despite the differences both in the nature of the compound/agent initiating the disease process in arthritis and in the rodent species (strains of mice/rats) used, HSPs are one of the prominent antigenic targets of the host immune response. The most studied among them is the mycobacterial HSP65 (BHSP65). Immune reactivity to HSP65 is observed in rodents with adjuvant arthritis (AA)⁹⁻¹², streptococcal cell wall induced arthritis (SCWIA)¹⁴, pristane-induced arthritis (PIA)^{13,28}, dimethyl dioctadecyl ammonium bromide-induced arthritis (DIA)¹⁵ and avridin-induced arthritis (AvIA)³⁰. Other HSPs targeted in 1 or more of these disease models include HSP70³¹⁻³³, HSP40²³ and HSP10^{34,35}. It is noteworthy that although Mtb is used as an arthritogen only for AA, the disease induced by several other arthritogenic stimuli (Table 2) can be experimentally modulated by treatment with certain HSPs. Furthermore, more than 1 HSP can have immunoregulatory effect in a given animal model of arthritis. For example, the arthritis-protective or immunotherapeutic role of HSPs has also been validated in mice/rats with collagen-induced arthritis (CIA). Treatment of animals with recombinant BiP³⁶ or HSP65³⁷ proteins, or with the recombinant plasmids encoding a pathogenic T cell receptor peptide fused with the Hsp70 gene,³⁸ led to the suppression of CIA. This downmodulation of arthritis was associated with a significantly enhanced Th2 cytokine response and reduced CII-specific antibodies.

The above-mentioned observations in different animal models suggest that HSPs comprise an integral component of the effector pathways involved in the initiation and/or propagation of autoimmune arthritis. In addition, reports from several laboratories have documented the

experimental immunomodulation of arthritis by different HSPs, e.g., HSP65^{11,12,32,39-41}, HSP70^{29,32,42} and HSP10^{34,35}, which involved treatment of animals with exogenous HSPs before or after the onset of autoimmune arthritis. The differential role of HSPs can be explained in part by a) a difference in the immunization regimen used, and b) HSPs possess arthritogenic as well as disease-protective T-/B-cell epitopes, and these functionally different sets of epitopes might reside on the same HSP molecule. For example, BHSP65 harbors the arthritogenic epitope 180-188, but also possesses regulatory epitopes in the region 256-270 and the C-terminal region^{9,11,39-41}. Similarly, RHSP65 has regulatory epitopes in regions 31-50, 61-80 and the C-terminus^{10,12,43}. In another study based on the use of small molecule inhibitors of HSP90, SNX-7081 and its analog SNX-4414, has revealed the involvement of this HSP in arthritis. Immunosuppressive effects of these inhibitors on the disease process have been observed in the rat models of CIA and AA¹⁸. Interestingly, SNX-7081 inhibited Hsp90 but induced HSP70. The latter has been shown to induce an arthritis-protective immune response by other investigators. In this regard, it is not clear as to the relative contribution of Hsp70 in the observed anti-arthritic activity of inhibition of Hsp90. The other inhibitor, SNX-4414, inhibited arthritis in vivo, suggesting the potential therapeutic utility of the Hsp90 inhibitors in the treatment of RA.

1.2. Pathogenic versus regulatory attributes of T cells reactive against HSPs—

One perplexing feature common to some of the above-mentioned arthritis models is that despite HSPs serving as targets of immune response, purified HSPs themselves are not arthritogenic⁴⁴. Apparently, the co-presence of a microbial component (e.g., cell wall components of *Mtb/streptococcus*^{8,14}) is necessary for disease induction. Most likely, the microbial component serves as an adjuvant. However, not all bacterial cell walls can induce arthritis. Instead, exposure of mice/rats to certain bacteria can induce protection rather than disease. *Escherichia coli* is 1 example. Unlike, *Mtb* or SCW, *Escherichia coli* does not induce arthritis in rats, but prior exposure to *Escherichia coli* can render the rats resistant to subsequently induced AA^{45,46}. The component of *Mtb* or SCW that is unique in terms of arthritogenicity remains to be determined. Nevertheless, the evidence showing that HSPs are targets of immune response of arthritic animals, and that pre-treatment of rats/mice with HSPs can modulate disease (aggravation in some cases, but downmodulation in most cases (Table 2), shows that apparently disparate immune responses to HSPs are involved in different phases of the disease process, the induction versus the regulation of autoimmune arthritis. The most convincing evidence for the arthritogenicity of HSPs is the BHSP65-reactive A2b T cell clone that was reported to be arthritogenic in Lewis rats and was found to be reactive against the epitope region 180-188 of BHSP65^{8,9}. In comparison, several studies^{11,12,32,39-41} have offered evidence for the immunomodulation of arthritis by treatment with HSPs. Overall, it appears that HSPs are more likely to induce regulation rather than disease induction. The regulatory attribute of HSPs is being exploited for therapeutic purposes.

1.3. Humoral immunity to HSPs in experimental arthritis—

Most of the information described above pertains to T cells. There is limited information about antibodies to BHSP65. We²² and others¹² have shown that arthritic Lewis rats develop antibodies to BHSP65 as well as self (rat) HSP65 (RHSP65). The pattern of response changed with disease progression such that the epitope reactivity profile diversified (epitope spreading) with evolution of the disease course in the Lewis rat^{12,22}. Our results showed that circulating antibodies present in the late phase of the disease can induce protection against AA as evident from the results of serum adoptive transfer experiments^{12,22}. We speculate that the early phase antibodies might instead contain pathogenic attributes; however, this concept needs validation. It is conceivable that the newly emerging antibody specificities may engage new targets for initiation of effector responses, mask certain antigenic epitopes,

induce disease-modulating cytokines or alter the processing and presentation of T cell epitopes^{12,22}. In addition, cross-talk between HSPs might influence immune response to HSPs, disease progression and the outcome of immunomodulatory regimen³².

2. HSPs and human rheumatoid arthritis

Immune reactivity to more than 20 HSPs of mammalian or bacterial origin has been examined in patients with RA (Table 3).

2.1 Gene polymorphisms and their association with the HLA-shared epitope (HLA-SE) and RA—

Some studies have provided evidence for the association between RA and polymorphism in the promoter or the coding region of the genes for HSP70 and HSP32 (HO-1)⁴⁷⁻⁵⁰. However, a similar association reported for the coding region of HSP70-Hom⁵¹, a variant of HSP70, is controversial, and other studies have shown no association between the coding regions of HSP60/HSP70 and RA⁵¹⁻⁵³. Nevertheless, single nucleotide polymorphism analysis indicated an association between HSP70-Hom (in MHC class III locus) and the RA-susceptibility-associated HLA-DR4 (in MHC class II locus)⁵¹. Different RA-associated HLA-DR subtypes possess a shared epitope (SE; HLA-SE) in position 70-74 of HLA-DR β 1 chain⁵⁴. The shared epitope (e.g., QKRAA/QRRAA) is believed to contribute to RA pathogenesis via the binding and presentation of antigenic peptides that induce immune pathology^{54,55}. Several lines of evidence have shown that HSP70 can directly bind to the QKRAA sequence, which is also found in bacterial HSP40 (dnaJ)⁵⁴⁻⁵⁸. Therefore, it was speculated that the interaction and competitive binding to HSP70 of HSP40 versus HLA-SE might influence the efficiency of antigen presentation by HLA-SE^{54,56,57,59} leading to autoimmunity. However, more direct evidence is needed to affirm this speculation. The genetic evidence gathered so far is a strong argument for the involvement of HSP32 and HSP70 in RA pathogenesis, although the detailed mechanisms remain to be unveiled. HSP32 can downregulate the production of reactive oxygen species, but upregulate the production of anti-inflammatory cytokines⁶⁰. In the case of HSP70, in addition to its interaction with HLA-SE, any aberration in the quality/quantity control of this HSP can lead to the creation of neoepitopes on other proteins, which in turn may become targets of immune recognition and thereby contribute to the induction of autoimmunity.

The results of a recent study have offered one of the mechanisms by which HSP90B1, also known as 96-kDa heat-shock glycoprotein (gp96), might promote chronic inflammation in RA. Increased expression of HSP90B1 (HSP96) was observed in the synovial tissue and synovial fluid of RA patients. It was suggested that HSP90B1 acted as an endogenous ligand for Toll-like receptor 2 (TLR2) to activate macrophages for secreting the proinflammatory cytokines⁶¹. The results of another recent study revealed that the exposure in vitro of synovial fibroblasts to geranylgeranylacetone, an inducer of HSPs, leads to cell death⁶². These results suggest that besides the immune-regulatory mechanisms induced by HSPs, HSP-mediated cell death of synoviocytes of arthritic joints represents one of the additional likely mechanisms to account for the arthritis-protective effects of HSPs.

2.2 The fine characteristics of HSP-reactive T cells in RA—

The majority of studies on HSP-induced T cell activation in RA are focused on the HSP60 family, including human HSP60 and BHSP65⁶³⁻⁷⁴, whereas other studies are directed to bacterial HSP40 (dnaJ)^{55,58,75}, human GRP78 (BiP)^{76,77}, and HSP90^{61,62}. The mononuclear cells in the synovial fluid of RA patients frequently show higher responses after stimulation with HSP (e.g. BHSP65) than those in the peripheral blood^{63,66,67,71,73}. These results apparently offer support to the idea regarding the role of HSP-reactive T cells in RA synovitis. Some investigators have identified specific epitopes of HSPs involved in T cell activation in human RA, such as regions 1–170⁶⁴, 241–255⁷⁴, 303–540⁶⁴ and 451–466⁶⁵ of BHSP65, and

dnaJP1, a peptide fragment of *Escherichia coli* HSP40⁷⁵. It has been proposed that bacterial HSP-induced T cells may cause arthritis through cross-reactivity with the homologous human HSP^{55,56,68,74}. However, the precise significance of this T cell cross-reactivity, at least for HSP60, in the disease pathogenesis has not been fully validated. Also, bacterial HSP-reactive T cells in RA patients showed cross-reactivity with other bacterial antigens, and such T cells were also found in non-RA inflammatory arthritides, including ankylosing spondylitis and reactive arthritis^{63,71,73,78}.

A few studies have refuted any specific association between T cells reactive against HSP (e.g., human HSP60 and BHSP65) and RA⁷⁸⁻⁸⁰. Therefore, the presence of HSP-reactive T cells is not an exclusive finding in RA, and the positive proliferative response of peripheral blood mononuclear cells (PBMC) to human HSP60 has been shown to be unrelated to RA activity and severity⁶⁸. Moreover, recent studies have suggested that both bacterial and human HSPs might be suppressive in RA through the induction of regulatory T cells and the deviation of the cytokine response to T helper 2 (Th2)^{68,72,75,81} (Table 3).

2.3 The presence of HSP-specific antibodies in RA—Antibodies against HSPs belonging to the HSP40^{82,83}, serpin (HSP47)^{84,85}, HSP60^{71,86-92}, HSP70 (including BiP)^{20,76,77,86,89,93,94} and HSP90⁹⁴ family have consistently been identified in sera from patients with RA. One of the target antigens for anti-HSP antibodies in RA is human GRP78 (BiP), which also serves as a T cell target in this disease^{20,76,77,93}. Anti-GRP78 antibody is a reliable marker for RA with sensitivity ranging from 63%~73% and specificity of 65%~96%^{20,76}. This autoantibody was detected about 2.5 years before the diagnosis of RA was made²⁰. A recent study showed that anti-tumor necrosis factor (TNF)- α therapy can lower the titer of anti-GRP78 antibody⁹³, implying a role of this autoantibody in RA pathogenesis⁷⁶. However, no significant correlation was observed among the levels of anti-GRP78 antibody, T cell reactivity, rheumatoid factor (RF) and disease activity in RA⁷⁶. In many studies^{71,86,88,90,92}, anti-bacterial HSP65 antibody was inferred to be specific for RA, and was more abundant in synovial fluid than in peripheral blood of RA patients^{90,92}. Like the bacterial HSP-reactive T cells, anti-bacterial HSP antibodies were also believed to cause RA synovitis through cross-reactivity with the human HSP homologue, but this hypothesis has not yet been confirmed experimentally. Moreover, other investigators^{67,95-98} have argued against any specific role for anti-bacterial HSP65 antibodies in the pathogenesis of RA because no increased antibody titers were detected in RA sera compared with that of control sera. As for the other anti-HSP antibodies, they may have some specificity for RA but their positivity rates in RA patients are not significantly high⁹⁴.

DISCUSSION

1. The T cell and antibody response to HSPs in RA patients

Certain aspects of the role of HSP-reactive T cells in RA patients need clarification. First, what is the predominant phenotype of the HSP-reactive T cells in RA based on the T cell lineage surface markers and function? A few studies^{55,66,75,76,78} have addressed this issue, but no clear consensus has emerged. BHSP65-induced CD4⁺, CD8⁺ as well as $\gamma\delta$ T cells have been implicated as the pathogenic effector cells in RA^{55,66}. HSP40 peptide dnaJP1 was shown to trigger FoxP3 expression in Treg (CD4⁺CD25⁺Foxp3⁺ T cells)⁷⁵. In other studies, GRP78 was suggested to induce either a pathogenic or a regulatory T cell phenotype in different subsets of patients with RA⁷⁶.

Second, are the HSP-reactive T cells RA-specific? The relatively high frequency of HSP-reactive T cells might simply reflect the selection of T cells from an inflammatory (stress) site with an up-regulated expression of HSP, and these T cells may modulate immune reactivity under stressful conditions⁷⁶. This speculative scenario needs to be confirmed.

Finally, how can HSPs enforce T cells to secrete different cytokines or to differentiate into either suppressive or pathogenic phenotypes? A recent study has identified 2 proteins belonging to the small HSPs family, HSP22 (HSPB8) and α A-crystallin, that are endogenous toll-like receptor 4 agonists and can activate dendritic cells derived from RA patients⁹⁹, thereby bridging innate and adaptive immunity⁶. Although HSP22 was abundantly expressed in the synovium of RA patients⁹⁹, the in vivo evidence for its role in autoimmune arthritis remains to be clarified.

Evidence for the role of anti-HSP antibodies in RA is largely based on their association with the disease process. Considering the ethical issues in conducting human studies, any inference about the in vivo effects of anti-HSP antibodies in autoimmune arthritis can be delegated in part to the animal models of experimental arthritis. In a couple of studies in AA^{12,22}, both anti-BHSP65 and anti-self (rat) HSP65 antibodies were detectable during the course of arthritis. Interestingly, there was diversification of the humoral response to new epitopes (epitope spreading) of BHSP65 with the progression of arthritis^{12,22}. Further, the adoptive transfer of these antibodies afforded protection against AA in recipient rats. The change in humoral immunity to various citrullinated antigens has been observed in the CIA model as well¹⁰⁰. For RA, at present no firm conclusion can be drawn regarding the roles of anti-HSP antibodies in disease pathogenesis. Nonetheless, anti-HSP antibodies may serve as a diagnostic marker for RA, but the sensitivity and the specificity of the assays for these antibodies need to be increased before they can be considered as an alternative to other currently employed markers, such as anti-cyclic citrullinated peptide antibodies^{101,102}.

2. The disease-modulating activities of HSPs

The results of several studies have suggested potential roles of the major HSPs, such as HSP32, HSP40, HSP60, and HSP90 in affecting disease activity in RA based on in vitro evidence of HSP-induced modulation of T cell responses or cytokine profiles^{55,68,72,75,81,103}. The in vitro stimulation of mononuclear cells of RA patients with human HSP60 and BHSP65 has also been shown to induce a T helper 1 to Th2 cytokine shift^{72,81}. In another study, RA patients with T cells that were reactive against human HSP60 or BHSP65 and produced Th2 cytokines had less disease activity compared with those who did not⁶⁸.

Convincing evidence for the in vivo effect of HSPs on disease activity in RA is based on human HSP10, a mitochondria protein belonging to the GroES chaperonin family¹⁰⁴. A double-blind randomized phase II trial of HSP10 in RA patients¹⁰⁴ showed that intravenously administered HSP10 was well tolerated and reduced disease activity during the entire course of treatment, as well as suppressed TNF- α , interleukin-1 β and interleukin-6 production¹⁰⁴. HSP10 inhibited toll-like receptor 4-mediated nuclear factor kappa B activation by lipopolysaccharide as well as the production of TNF- α and interleukin-6 in human PBMC¹⁰⁵. Because of the relatively small sample size of this study, a larger confirm trial is needed to consolidate the initial findings. Furthermore, the mechanisms underlying the inhibitory effect of HSP10 on various inflammatory mediators need to be defined. HSP40 peptide fragment dnaJP1 from *Escherichia coli* administered orally to RA patients was shown to induce epitope-specific CD4⁺CD25⁺FoxP3⁺ regulatory T cells as well as immune deviation with increased IL-4 and IL-10 but decreased IFN- γ and TNF- α production⁷⁵. Recently, a phase II trial with dnaJP1 in RA¹⁰⁶, showed that the clinical improvement was associated with immune deviation.

A newly emerging approach that might prove beneficial in RA and other autoimmune diseases involves injection of ex-vivo expanded autologous Treg. Tregs have a critical role in immune homeostasis as well as suppression of the activity of potentially pathogenic T cells. The function of Treg in RA has been shown to be compromised¹⁰⁷. This deficiency

might be overcome by identifying the appropriate ligands for the expansion and activation of autologous Treg ex vivo and then injecting the cells back into the patient. In this regard, HSP60 has been shown to enhance Treg function¹⁰⁸, and thereby represents one of the promising arthritis-regulating HSPs. The immunoregulatory attribute of HSPs is also highlighted by the observations in patients with juvenile idiopathic arthritis (JIA) that high T cell reactivity to self hsp60 correlates with disease remission¹⁰⁹⁻¹¹². Moreover, the T cells reactive against self hsp60 mediate disease regulation in part via the secretion of anti-inflammatory/immunoregulatory cytokines. We have limited the detailed discussion to RA, and therefore the details regarding JIA and HSPs are not presented.

3. The role of host genetics and environmental factors on the pathogenesis of arthritis

The susceptibility/resistance to autoimmunity is determined by multiple factors¹¹³. The most prominent among them is host genetics. The strong association of particular HLA alleles with RA and other autoimmune diseases highlights the influence of genetics on autoimmunity¹⁻³. Furthermore, we have elaborated above the proposed role of the HLA-SE in the induction and propagation of arthritis^{54,55}. By selecting and presenting antigenic determinants to T cell receptors, the HLA molecules play a pivotal role in the initiation of immune responses to potential arthritogens, including HSPs. Understandably, the outcome of antigen presentation depends on the fine attributes of the T cell repertoire, whose selection in the thymus is governed by the host HLA haplotype.

Studies in diverse models of autoimmunity have unraveled the critical interplay between genetic and environmental factors¹¹³. In this regard, one of the important components of the host environment is the microbial agent. Infections can trigger as well as aggravate various autoimmune diseases, including RA^{1,3,114,115}. Besides foreign microbes infecting the host, the body's commensal bacteria might also contribute significantly to the susceptibility to autoimmunity^{114,116}. We¹¹⁸ and others¹¹⁷ have shown that the housing environment of inbred rodent strains can have a profound effect on the susceptibility to experimental arthritis. Furthermore, the MHC haplotype can have a significant affect on the composition of gut flora¹¹⁹, and intestinal microbiota may have a major impact on the pathogenesis of autoimmune arthritis^{114,116}. In 1 study, the proportion of certain species of bacteria in feces was significantly less in RA patients compared to that in patients with fibromyalgia¹¹⁶.

The influence of host genetics on the composition of gut flora has recently been documented in a study conducted in patients with familial Mediterranean fever¹²⁰. Here, the gene under study encoded the protein pyrin which is among the genes that regulate innate immunity. Another study^{120,121} highlighted the influence of the metabolic products of the host microbiome on the metabolism of certain drugs, including anti-inflammatory drugs, thereby altering the host response to that drug. It is conceivable that host microbiota might offer one of the targets to alter drug responsiveness and side effects.

4. Concluding remarks

Genetic, biochemical, and immunological studies have pointed out the potential roles of different HSPs in RA. Genetic studies showed that HSP32 and HSP70 were associated with the disease process in RA⁴⁷⁻⁵¹, while biochemical studies indicates that HSP70 and HSP40 might interact with HLA-SE to cause autoimmunity^{54,56-59}, and HSP32 could suppress the production of proinflammatory cytokines and the expression of cyclo-oxygenase-2¹⁰³. Furthermore, immunological studies have indicated that HSP40, HSP60, HSP70, GRP78 and HSP90 were the key modulators of adaptive immunity^{20,55,58,63-73,75-77,82,83,86-94}, whereas HSP22, α A-crystallin and HSP10 were operative in the signaling pathways of innate immune reactions^{99,105}. Finally, HSP10 and dnaJP1 are the only HSPs tested in clinical trials that produced encouraging results regarding modulation of clinical

disease^{104,106} (Table 3). The above-mentioned studies reflect the functional heterogeneity of different HSPs and their multifaceted roles in different stages of the disease process in RA.

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Table 1Heat-shock proteins involved in autoimmune arthritis^{4,5,7,60,84,105}

Protein family	HSP (alternative name; origin [*])	Major functions
GroES (chaperonin)	HSP10 (chaperonin 10); HSP10 (rat); HSP10 (GroES; Mtb, <i>E. coli</i>)	Function intracellularly in protein folding in coordination with HSP60
Small HSPs	HSP22 (HSPB8); α -crystallin; HSP27; HSP20 (rat)	A highly diverse group; may be important in thermotolerance
Heme oxygenase	HSP32 (HO-1); HSP32 (HO-1; rat)	Transform heme into iron, biliverdin and CO to reduce oxidative stress and subsequent damage
DnaJ homolog subfamily B	HSP40 (HDJ-1)	Interacts with HSP70 to facilitate peptide loading and stimulate its ATPase activity
HSP40 (dnaJ)	HSP40 (dnaJ; <i>E. coli</i> , <i>A. actinomycetemcomitans</i>)	Binds to HSP70 to stimulate its ATPase activity and facilitate the disassembly of protein complexes to prevent aggregation under stressful conditions.
Serpin	HSP47 (colligin)	Collagen-specific chaperone; may be involved in the biosynthesis of collagen.
HSP60 (chaperonin)	HSP60; HSP60 (HSP65; rat); HSP60 (GroEL; <i>E. coli</i>); HSP65 (GroEL; Mtb, <i>M. bovis</i> , <i>M. vaccae</i>); HSP65 (<i>M. leprae</i>)	Function with HSP10 in the ATP-dependent protein folding and refolding process with high efficiency.
HSP70	HSP70 (HSP72); HSP70 (rat); HSP70 (dnaK; Mtb, <i>M. bovis</i> , <i>E. coli</i>); HSP70-Hom; GRP78 (BiP); HSP73 (HSC70)	High affinity for ATP; disrupt protein-protein interaction to help with various cellular processes, including DNA replication, transport of proteins across membranes, binding of proteins in the endoplasmic reticulum and uncoating of the coated vesicles.
HSP90	HSP90; HSP90B1 (gp96); HSP90 (rat)	Abundantly expressed cytosolic protein; functions to keep various proteins, such as steroid receptors and tyrosine kinases, inactive until the proper signal for activation is received.

Abbreviations: *A. actinomycetemcomitans*: *Actinobacillus actinomycetemcomitans*; ATP: adenosine-5'-triphosphate; ATPase: adenosine-5'-triphosphatase; BiP: immunoglobulin binding protein; CO: carbon monoxide; gp96: 96-kDa heat-shock glycoprotein; HDJ-1: human dnaJ homologue-1; HO-1: heme oxygenase-1; HSC: heat-shock cognate protein; HSP: heat-shock protein; *E. coli*: *Escherichia coli*; *M. bovis*: *Mycobacterium bovis*; *M. leprae*: *Mycobacterium leprae*; Mtb: *Mycobacterium tuberculosis*; *M. vaccae*: *Mycobacterium vaccae*

* Human origin, unless otherwise indicated

Table 2

The Role of Heat-Shock Proteins in Experimental Models of Arthritis

Effect on Arthritis	* Arthritis Model	@HSP / Peptide (source)	Ref
Exacerbation	AA	HSP65, HSP32 (HO-1), OM-89	8,122, 123, 42,124
	PIA	261-271 (HSP65)	16
Protection	AA	HSP10, HSP32 (HO-1),	34,35, 123
		HSP60	99, 12,43, 10,125
		HSP65	12,43, 11,30,39,122,125
		HSP70 (HSP72), HSP71, OM-89,	32, 29,31,126,127, 42,124
		GRP78 (BiP)	77
		HSP90α	32
	DIA	HSP65, 120-134, 213-227 (HSP65)	15
	PIA	HSP65, 261-271 (HSP65), DNA-HSP65	13,28,128-132
	AvIA	HSP65, HSP71, 256-270 (HSP65) 176-190 (HSP60), OM-89	29,30,40,133
	PGIA	HSP70	134
	SCWIA	HSP65	14
	CIA	BiP, HSP65, HSP70	36,37
No significant effect	AA	HSP10, HSP70	34, 31
		211-225 (HSP65)	30
		GroEL, HSP70, 261-271 (HSP58)	28,129
		a nine-amino acid peptide (HSP)	135
		HSP65	14
		HSP71, 180-188 (HSP65)	29,136

* AA: adjuvant arthritis; DIA: dimethyl dioctadecyl ammonium bromide (C₃₈H₈₀NBr)-induced arthritis; PIA: pristane-induced arthritis; AvIA: avridine-induced arthritis; PGIA: proteoglycan-induced arthritis; SCWIA: streptococcal cell wall (SCW)-induced arthritis; ZA: zymosan-induced arthritis.

@ HSP: heat-shock protein; HO-1: heme oxygenase-1; BiP: immunoglobulin binding protein; OM-89: an *E. coli* extract containing HSP70 (dnaK) as one of the major immunogenic constituents.

Table 3

The relationship between heat-shock proteins and the immunopathogenesis of human rheumatoid arthritis

Parameter of interest [§]	HSP (alternative name; origin [*])	Ref. [@]
Disease-associated gene polymorphism		
Promoter region	HSP32 (HO-1), HSP70 (HSP72)	47-50
Coding region		
Yes	HSP70-Hom	51
No	HSP60, HSP70 (HSP72), HSP70-Hom	51-53
HLA-SE association		
Homology	HSP40 (dnaJ; <i>E. coli</i>)	55,57,58
Direct binding	HSP70 (HSP72), HSP70 (dnaK; <i>E. coli</i>), HSP73 (HSC70)	5,54,56,57,59
SNP association	HSP70-Hom	51
Increased T cell activation[§]		
Yes	HSP40 (dnaJ; <i>E. coli</i>), HSP60, HSP65 (GroEL; Mtb / <i>bovis</i> [#]), HSP65 (<i>M. leprae</i>), GRP78 (BiP)	55,58,63-77
No	HSP60, HSP65 (GroEL; Mtb / <i>bovis</i> [#]), HSP70 (dnaK; <i>M. bovis</i>)	65,78-81
Increased specific antibodies[§]		
Yes	HSP40 (dnaJ; <i>E. coli</i> & <i>A. actinomycetemcomitans</i>), HSP47 (colligin), HSP60, HSP60 (GroEL; <i>E. coli</i>), HSP65 (GroEL; Mtb / <i>bovis</i> [#]), HSP65 (<i>M. leprae</i>), HSP70 (HSP72), HSP70 (dnaK; Mtb), HSP70 (dnaK; <i>M. bovis</i>), HSP70 (dnaK; <i>E. coli</i>), GRP78 (BiP), HSP73 (HSC70), HSP90	20,71,76,77,82-94
No	HSP60 (GroEL; <i>E. coli</i>), HSP65 (GroEL; Mtb / <i>bovis</i> [#])	67,95-98
Dendritic cell activation		
Yes	HSP22 (HSPB8), αA-crystallin	99
No	αB-crystallin, HSP27, HSP20 (rat)	99
Protein expression		
Synovium		
Yes	HSP22 (HSPB8), HSP32 (HO-1), HSP40 (HDJ-1), HSP47 (colligin), HSP60, HSP70 (HSP72), GRP78 (BiP), HSP73 (HSC70), HSP90B1 (gp96)	17,76,99,103,137-147
No	αA-crystallin, HSP70 (HSP72)	99,147
Synovial fluid	HSP60, HSP70 (HSP72), HSP90B1 (gp96)	148
Peripheral blood	HSP32 (HO-1), HSP60	48,148
Gut	HSP60	149
Decrease RA severity (protective)		
Yes (clinical trial)	HSP10 (chaperonin 10), HSP40 (dnaJ; <i>E. coli</i>)	75,104,106
Possible (suggested by in vitro study)	HSP32 (HO-1), HSP60, HSP65 (GroEL; Mtb / <i>bovis</i> [#])	68,72,81,103
Increase RA severity (pathogenic)		
Possible (suggested by in vitro study)	HSP60, HSP65 (GroEL; Mtb / <i>bovis</i> [#]), HSP90B1 (gp96)	55
No	HSP10 (chaperonin 10), HSP60	68,104

Abbreviations: HLA: human leukocyte antigen; RA: rheumatoid arthritis; SE: shared epitope.

[§] If a specific HSP is not listed under 'Parameter of interest', it indicates that no data is available for that HSP for that parameter.

[§] Compared with normal healthy controls.

^{*} Human origin, unless otherwise indicated.

[#] HSP65 sequences in *Mtb* and *M. bovis* are identical.

[@] Only studies conducted with samples from human RA patients were included, except for the item “HLA-SE association”.