Heat-shock proteins in stromal joint tissues: innocent bystanders or disease-initiating proteins?

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Abstract
Heat-shock proteins (HSPs) are molecular chaperones that are highly conserved between species. In recent decades it has become clear that these proteins play an important role in the pathogenesis of inflammatory and degenerative joint diseases by (dys)regulating the immune system and by direct effects on the stromal tissues of the joint. In this review we discuss current insights into the expression pattern of HSPs in connective tissues, the direct biological role of HSPs in stromal tissues and the potential clinical applications.

Key words: stress response, arthritis, tissue inflammation, osteoarthritis, connective.

Introduction
The name heat-shock proteins (HSPs) originates from their initial identification as stress-inducible proteins that act as an intracellular defence mechanism against thermal stress. Functionally, stress-inducible proteins can be classified into seven classes, including chaperones, cytoskeletal proteins and metabolic enzymes (for an overview, see Richter et al. [1]). The predominant class, in terms of expression level, across species is the initially discovered HSPs [2]. In this review we will specifically focus on this class. The primary characterization of HSPs suggested that they were largely regulated at the transcriptional level, however, subsequent mechanistic data have shown that HSPs have multiple levels of regulation, such as phosphorylation, oligomerization and protein interactions [3]. At the transcriptional level, the primary stress-inducible transcription factor is heat shock factor 1 (HSF1). Many HSPs also contain alternative promoter recognition sites, allowing for transcriptional activation via multiple signalling pathways [3]. The HSPs show a remarkable sequence homology between species, emphasizing their important biological role throughout evolution. In humans, the HSPs can be further subdivided into five classes: chaperonins (HSP10/HSP60, primarily located in the mitochondria), the HSP70 (HSPA/HSPH) family, the HSP40 (dnaJ) family, the HSP90 (HSPC) family and the small HSPs (HSPb) [4].

HSPs have a long history in the arthritis research field. Ever since the discovery that T cells recognizing HSPs may elicit an arthritic phenotype, a lot of research has been conducted to study the role of HSPs in arthritis and how these can be used as diagnostic and/or therapeutic tools. This initial discovery described the role of T cells recognizing HSP65 in eliciting arthritis [5]. It has been shown that T cells and antibodies isolated from arthritic animals and arthritis patients recognize different HSPs [6–8]. Surprisingly, despite the fact that HSPs are a major immune target, administration of purified bacterial HSPs does not induce arthritis [9]. It is now clear that self HSPs are not immunogenic per se, but that the immunodominance of bacterial HSPs may induce cross-reactivity with self HSPs. Moreover, HSPs may associate with danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) or other antigenic peptides and thus alter the immune response to DAMPs and PAMPs, further emphasizing their immunological significance [10]. Recently it has become clear that immune responses to HSPs are very complex and may be arthritogenic as well as protective. This complex behaviour may be explained by the presence of different epitopes, the method of immune activation and the administration route. How HSPs interact with the immune system in autoimmune diseases and arthritis has been extensively reviewed elsewhere [11, 12]. In this review we will mainly focus on altered expression of HSPs by stromal joint compartments and how these can affect tissue biology and/or immune activation. An intriguing feature of HSPs is that these are located intracellularly, at the cell surface or even in the extracellular environment. Given the intimate contact between immune and stromal cells in the joint, the presentation of HSPs in the extracellular environment.
space by stromal cells may thus modulate the immune system and contribute to joint inflammation (Fig. 1). In contrast to the research focused on regulation of the immune system by HSPs in arthritis, studies on the direct biological function of HSPs in cells from the joint are rather limited, but they provide exciting avenues for future research.

HSPs: a collection of multiple protein families with pleiotropic effects in joint diseases

HSP90 family
The HSP90 protein family consists of 17 gene members divided into four classes based on phylogenetic analysis [13]. The HSP90 family contains five members in humans [4]. This family has been implicated in the physiology of joint tissues in the past, even with therapeutic potential. Interestingly, HSP90 expression varies with age. Moreover, the ability of a cell to respond to cellular stress by up-regulating HSP90 (among other HSPs) expression decreases with age [14]. Such a regulatory mechanism may be extremely relevant in degenerative diseases such as OA. Moreover, it is well known that HSP90 protects cells from apoptosis and interacts with a variety of substrates [15], including signalling proteins such Akt [16] and enzymes such as iNOS [17]. In RA fibroblast-like synoviocytes (FLS) it was shown that HSP90 protects synovial cells from apoptosis and thus contributes to synovial overgrowth via interaction with Akt and Erk [18]. Boehm et al. [19] proposed a role for HSP90 in chondrocyte biology by demonstrating that HSP90 expression regulates MMP13 expression. However, specific blockade of HSP90β (HSPC3) by small interfering RNA (siRNA) induces MMP13 expression. This is probably due to destabilization of a protein complex that interacts with a specific MMP13 promoter site, thereby inhibiting MMP13 expression [20]. As MMP13 is one of the major proteases involved in cartilage breakdown, targeting these proteins was proposed as a potential cartilage repair strategy. Commonly used chemical blocking strategies, such as geldanamycin, do not necessarily have a strong specificity for one of the HSP90 proteins. Thus it is clear that more specific inhibitors await future development [21]. Kimura et al. [22] described a selective HSP90 inhibitor that specifically targets HSPC1 and more specifically induces HSF1 activation, thereby inducing HSP70 expression in cartilage, a protein known to prevent nitric oxide (NO)-induced apoptosis [23].
ultimately leading to reduced MMP13 levels. All of this work clearly suggests an important role for HSP90 proteins in chondrocyte biology. However, the in vivo impact of HSP90 blocking on cartilage metabolism in OA is still unclear. Such in vivo proof of principle was demonstrated in inflammatory arthritis models (CIA and AIA) by a small molecule inhibitor of HSP90 [24]. The authors demonstrate reduced nuclear factor κB (NF-κB) nuclear translocation in synovial fibroblasts and reduced cytokine production upon compound administration.

In conclusion, it is clear that HSP90 directly interferes with important pathological processes in chondrocytes and synovial fibroblasts such as NO synthesis, stabilization of signalling molecules (directly or by mediating other HSP expression) and angiogenesis. However, given the ubiquitous expression of HSP90 and its pleiotropic interaction profile, it remains very questionable whether the HSP90 targeting strategies will have a sufficient therapeutic index, especially given observations that targeting of HSP90 may induce osteoclastogenesis in vitro [25, 26], which could worsen bone destruction in joint diseases. Thus it is likely that targeting HSP90 in one tissue may have beneficial effects, whereas in others detrimental effects may be observed. Overall, the therapeutic potential of HSP90 is therefore uncertain. Indeed, recent clinical studies in multiple myeloma with HSP90 inhibitors report adverse events such as thrombocytopenia, neutropenia and anaemia [27].

HSP90 proteins may also play an important role in the interaction between stromal cells and the immune system. Overexpression and surface presentation of gp96 by stromal tissues under stress conditions such as inflammation may contribute to the chronicity of inflammation in arthritis. Gp96 (or grp94) was shown to be elevated in RA synovial tissue. Moreover, the authors reported gp96 as a TLR2 ligand that activates macrophages and identified the protein as a potential contributor to chronic inflammation in RA [28, 29]. It was shown in vivo that cell surface expression of gp96 elicits a proinflammatory lupus-like phenotype characterized by chronic stimulation of dendritic cells (DCs), which may represent an alternative pathway to initiate spontaneous autoimmune disease [30]. Additionally, fibroblasts overexpressing gp96 elicit a T cell activation involving antigen-presenting cells (APCs) [31]. Such interactions may be of major importance in arthritis pathogenesis given the close proximity of stromal and immune cells in the joint.

HSP70 family

The HSP70 family is one of the most highly conserved chaperone families. Typically HSP70s never function alone. They require a co-factor such as J protein (HSP40 family) as well as nucleotide exchange factors. These co-factors act together as an HSP70 machine to bind client proteins and nucleotides in an adenosine triphosphate (ATP)-dependent manner [32]. HSP70 has been mainly investigated in the inflammatory arthritis context, based on initial observations that bacterial HSP65 protected rats from adjuvant arthritis [5]. As stated above, in this review we do not focus on how HSPs may modulate the immune system and induce tolerance (see the review by Borges et al. [33]). HSP70 has primarily been investigated in synovial tissue. One of the landmark articles in this field described the enhanced expression of HSP70 in RA synovial tissue compared with OA tissue. In addition, the authors described the induction of HSP70 upon IL-1β and TNF-α stimulation but also under shear stress in synovial fibroblast-like cells [34]. This was later confirmed by Kang et al. [35], who additionally showed that down-regulation of HSP70 may protect synoviocytes from apoptosis. Furthermore, it was reported that HSP70 synovial fluid levels are elevated in RA patients. Indeed, whereas HSPs are generally accepted to act as an intracellular chaperone, the authors showed the release of HSP70 under stress conditions from viable cells [36]. Of great interest, in RA patients surface HSP70 expression was observed in a high percentage of synovial fluid cells, in particular DCs. Based on the known interactions between HSP70 and MHC class II shared epitopes, this may reflect an initiating mechanism in the activation of autoreactive T cells [37]. In contrast to the conventional role of HSPs as intracellular chaperones, Asefa et al. [38] and others have also described a cytokine role for HSP70. However, these reports have been rather controversial. Later on, subsequent studies [39, 40] have shown that lipopolysaccharide (LPS) contamination of HSP preparations may be responsible for these results. Thus caution is needed when interpreting results of data based on recombinant HSP preparations without stringent endotoxin control. Detanico et al. [41] showed reduced TNF-α production by monocytes isolated from synovial fluid upon HSP70 stimulation. Interestingly, Luo et al. [42] confirmed a similar role for extracellular HSP70 in suppressing cytokine release from tissue-derived FLS cultures upon TNF-α stimulation by inhibiting p38, extracellular regulated kinase (ERK) and Jun-N-terminal kinase (JNK) phosphorylation and clearly confirmed that LPS was not involved. These data provided evidence that extracellular HSPs have a direct effect on fibroblast-like synoviocytes. However, the in vivo relevance of these findings still need to be demonstrated.

The HSP70 family contains several more members, including HSP72 (HSPA2). Administration of HSP72 in mice at the onset of arthritis reduced synovial inflammation by reduced NF-κB activation in the synovial tissue [43]. A particular member of the HSP70 family is GRP78. The protein is expressed at the cell surface and can be detected in serum and synovial fluid [44]. Interestingly, the expression of GRP78 is elevated in the synovial lining and sublining of RA patients [45]. A direct pathogenic role on the synovium GRP78 (BiP, HSPA5) was recently demonstrated [46]. The authors confirmed that GRP78 levels are elevated in RA synovium and that in vitro down-regulation of GRP78 abolished TNF-induced synoviocyte proliferation and inhibited angiogenesis. In vivo data confirmed that GRP78 haploinsufficient mice compared with wild-type control mice exhibit reduced arthritic symptoms, including synovial proliferation and angiogenesis.
Induction of GRP78 alone, however, is not sufficient to induce arthritis and thus GRP78 has been suggested to act as an important amplifying factor in synovial hyperplasia and arthritis [46]. Whereas GRP78 has a pathogenic role in the synovium, it has previously been shown that exogenous extracellular GRP78 helps to restore immune system homeostasis and thus resolve acute inflammation, mainly by acting on the myeloid lineage [12]. Overexpression of GRP78 was shown to prolong lifespan and increase the repair capacity of chondrocytes [47], and it might play a crucial role in mineralization events during bone formation [48], thus further demonstrating the pleiotropic effects of HSPs on different tissues. At least in cancer, the subcellular location of GRP78 seems to determine the pro- or anti-tumour activity. Based on the parallels in the tumour environment and the synovial pannus, one can hypothesize that similar phenomena may occur in the joint and may thus explain the contradictory role of GRP78 in arthritis [12].

In conclusion, along with the well-documented role of HSP70 proteins in dampening inflammation by its direct tolerogenic effect on immune cells (primarily DCs and monocytes), HSP70 proteins also have a direct effect on cell metabolism of articular cell types such as FLS and chondrocytes.

HSP40 family
The dnaJ, or HSP40 family, is functionally related to the HSP70 family since the dnaJ proteins are necessary for HSP70 chaperone function. The dnaJ proteins have an HSP70 binding domain and activate the ATPase activity required for chaperone function. It is probably the largest HSP family in humans, although very little is known in arthritis and joint diseases. The dnaJ family was first introduced by the discovery that RA patients show strong immune responses to bacterial dnaJ while normal subjects do not [49]. Based on the sequence homology between peptide sequences encoded by HLA genes and dnaJ genes, it has been proposed that in arthritis an interplay between HLA and dnaJ-derived peptides maintains and stimulates T cells, which participate in autoimmune inflammation [50]. Nowadays it is known that differential recognition of epitopes from human and bacterial dnaJ proteins may be a natural mechanism for amplifying and subsequently down-regulating inflammation [51]. Further research has indicated that tolerization with peptides derived from the dnaJ family is feasible [52]. Increased expression in synovial tissues of arthritis patients of dnaJ proteins has been reported by several authors and may further contribute to the regulation of immune responses [51, 53]. Interestingly, HSP40 (dnaJB1) has been reported to be a mechanosensitive gene [54] that may be extremely relevant in linking immune activation and physical stress in the joint.

HSP60 family
Similar to the dnaJ family, research on the HSP60 family in the arthritis field has primarily focused on studying autoimmune responses to self and bacterial HSP60s (reviewed in Vercoulen et al. [55]). It is well known that T cell–recognizing self HSP60 plays a role in disease protection by inducing a tolerogenic effect in arthritis [56]. However, very little is known about how these proteins function in stromal tissues of the joint and how changing expression levels in stromal tissues may influence immune responses. HSP60 has been reported to regulate osteoblast survival [57] and bone marrow mesenchymal cell apoptosis [58]. Interestingly, HSP60 induces pro-inflammatory cytokine secretion through mitogen-activated protein kinase (MAPK) activation in other mesenchymal stem cell (MSC)-derived cell types, such as adipocytes [59]. This might be important in the context of the elevated levels of HSP60 in the synovium [60], suggesting a pro-inflammatory role of HSP60 in the synovium.

Small HSPs
A particular class within the HSPs are the small HSPs (sHSPs). sHSPs are a family of proteins with molecular weights <30 kDa [61]. The proteins are structurally characterized by a conserved α-crystalline domain that is flanked by non-conserved sequences essential for chaperone function [62]. The human genome encodes 10 members of the sHSP family. Some of these are expressed ubiquitously (such as HSPb1, HSPb5, HSPb6 and HSPb8), while others have a more restricted expression pattern [63]. From a structural point of view, the sHSP family is particularly interesting as they show several phosphorylation sites and tend to form oligomeric structures [64]. The phosphorylation status of sHSPs may alter the subcellular localization and the function. For example, in osteoblasts the unphosphorylated HSPb1 acts as a positive regulator of bone calcification, in contrast to phosphorylated HSPb1 [65]. Typically sHSPs, similar to other HSPs, primarily function to protect cells against stress factors. Unlike the large HSPs, the sHSPs do not consume ATP to refold proteins. The expression of sHSPs may be induced by various stresses, such as heat shock, oxidative stress and chemical stresses. Besides, sHSPs show a constitutive expression in particular tissues. In these tissues these molecular chaperones are implicated in many different cellular processes (reviewed in Haslbeck et al. [64]). This is primarily demonstrated by several congenital diseases that are associated with mutations in these proteins. For example, mutations in the HSPb1 and HSPb8 genes are associated with Charcot–Marie–Tooth disease and distal motor neuropathy [66, 67], while mutations in the HSPb5 protein have been associated with myopathy [68] and cataracts [69].

HSPb1, together with large HSPs, was previously shown to be dysregulated in RA synovial tissue [70]. Our own group previously demonstrated that HSPb1 as well as HSPb5 are down-regulated in OA chondrocytes and that the expression is regulated by proinflammatory cytokines [71, 72]. Moreover, it was clearly shown that dysregulation of both HSPb5 and HSPb1 have a major impact on the differentiation status as well as the cytokine secretion of chondrocytes. Indeed, HSPb1 directly influences the IL-1β-induced gene expression in human articular
chondrocytes [73]. A similar relationship between HSPb1 and TNF-α was recently shown in osteoblasts [74]. Our observations of lowered expression of HSPb1 in OA cartilage and the observation that suppressed HSPb1 expression results in a decreased responsiveness towards IL-1β may contribute to the well-known reduced responsiveness of OA cartilage [75] to IL-1β. Such a mechanism may represent another way in which HSPs regulate cell/tissue defence under stress conditions such as OA.

Anti-inflammatory properties for HSPb5 were described through an extracellular mechanism. Indeed, sHSPs are primarily found in the nucleus and cytosol, similar to other chaperones. However, it has been described that HSPb5 may be secreted from cells via exosomes [76], opening new avenues in our understanding of sHSPs. Indeed, Rothbard et al. [77] recently demonstrated that systemic administration of HSPb5 has a therapeutic effect in autoimmune disease [the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis] by binding proinflammatory proteins, in particular acute-phase proteins such as complement factors. Given the increasing evidence for a role of complement factors in degenerative joint diseases [78], studying the interactions between complement and sHSPs may be an interesting avenue for future research, especially given the potential role of sHSP levels in joint diseases. Moreover, the authors reported temperature-dependent binding capacity, which may be extremely relevant at sites of inflammation. Apart from protein–protein interactions of sHSPs with inflammatory proteins, sHSPs such as HSPb8 and HSPb4 may also act as Toll-like receptor ligands [79]. Here the authors propose HSPb8/TLR4 signalling as a potential amplification loop in RA pathogenesis [79]. In this context, Toll-like receptor (TLR) signalling is well known to be involved in the onset and pathogenesis of experimental arthritis [80, 81].

Other HSPs

Several other proteins act as heat-inducible molecular chaperones but are not classified in any particular HSP families. For example, RA-related antigen 47 kDa (RA-A47; HSP47) acts as a collagen-specific molecular chaperone assisting in the maturation of collagen[82, 83], a process that is crucial for normal cartilage development and endochondral bone formation [84]. Indeed, a missense mutation in the gene encoding HSP47 is associated with severe osteogenesis imperfecta [85]. HSP47 has been identified as an antigen expressed by human chondrocytes showing immunoreactivity with sera from RA patients [86]. Interestingly, TNF-α and other proinflammatory cytokines caused down-regulation of HSP47 expression in chondrocytes and an altered subcellular localization (i.e. cell surface appearance), which may represent the mechanism for the recognition of RA-A47 as an autoantigen during RA [87].

Clinical applications

As mentioned earlier, the primary research on HSPs has been done on the immunogenic role of HSP fragments and how these can modulate the immune system and contribute to inflammation. The working mechanism is based on the findings that HSPs may act as bystander antigens that can induce regulatory immune responses. A lot of pre-clinical work has been performed in animal models to induce tolerization, including work on GRP78 [88], HSP60 [89] and HSP10 [90]. This has resulted in a phase II clinical trial with positive results in terms of the impact on inflammation [52]. In another study the chaperonin HSP10, a reported inhibitor of TLR signalling, was administered and resulted in short-term suppression of symptoms in RA [91].

In the cancer field a lot of research effort is put into developing HSP inhibitors. These inhibitors block the anti-apoptotic function of HSPs in tumour cells, thereby making the tumour more sensitive to other anti-cancer agents. Since inflammatory synovia are characterized by high levels of HSPs, such an approach may be useful to dampen synovial proliferation. However, as described earlier, HSPs may have protective effects under some conditions, or in some tissues promoting apoptosis may not be desirable (e.g. chondrocytes). Moreover, their ubiquitous expression and broad interaction profile hamper the development of therapeutic strategies that target HSPs. Limiting the side effects of such therapies remains a challenging task. Further insights into the mechanisms involved in HSP regulation of joint homeostasis are needed to pave the way for future therapeutic applications.

From a diagnostic point of view, altered levels of HSPs [70] or antibodies to HSPs [86, 92–97] occur in several inflammatory joint diseases. Most of these studies compare RA with healthy subjects or non-inflammatory controls or report the presence of autoantibodies in other inflammatory joint diseases (AS, SLE, SS). Although this is interesting from a scientific point of view, it is less relevant in a clinical setting. Real diagnostic tests should be able to discriminate between inflammatory pathologies and be predictive for future disease activity or treatment response. For example, anti-GRP78 (anti-BiP) antibodies have been shown to be elevated in RA patients compared with other inflammatory diseases, healthy controls and non-inflammatory joint diseases [7, 45]. Interestingly, these antibodies appear several years before initial symptom presentation [7]. Currently, however, little or no information is available on the added value of these biomarkers compared with current clinical standards such as RF and anti-CCP tests. Such information is key to evaluating the clinical usefulness of these biomarkers to diagnose disease.

Conclusion and future perspectives

It is clear that the area of HSPs is a fascinating research domain that includes studying immune responses towards self and foreign HSPs as potential danger signals that may activate or regulate the immune system. In recent years this work has been translated from bench to bedside, with several promising clinical trials published. Given the large amount of data that are available on this topic, it is surprising that much less data are available on
the direct function of HSPs in cell biology of the stromal joint tissues, specific factors that may elicit an altered redistribution or expression of the HSPs and how this altered subcellular location may contribute to the chronicity of inflammation. Indeed, expression and localization of these proteins in stromal tissues are under the control of inflammatory cytokines, hypoxia and heat (Fig. 1). Altered expression patterns and subcellular localization, and knowledge of the factors that induce changes, may be important in understanding regulation and activation of the immune system. Such mechanisms may act through the adaptive immune system and/or via the innate immune system (Fig. 1). For example, HSPs may bind antigenic peptides or PAMPs (e.g. LPS) and contribute to immune activation [98]. In the extracellular environment HSPs are accessible to receptors (e.g. through TLR4 on monocytes or TLR2 on T cells) [99] and subsequently induce cytokine secretion, such as IL-10, and thus explain the anti-inflammatory effect of some HSPs [41]. Alternatively, extracellular HSPs (or bound peptides) may induce the activation of regulatory T cell subsets [100]. An immune response may also be induced via APCs, resulting in activation of NK and cytotoxic T lymphocytes [101, 102] or by chronic stimulation of DCs [30]. The HSPs may thus provide an interesting link between stromal and immune cells, which are in close contact in the joint. Such mechanisms may contribute to the chronicity of inflammation, as observed in arthritis patients. Whereas some initial in vivo findings in tumour biology are promising [31, 101, 102], this remains to be shown in joint inflammation.

Of equal importance are the findings that altered expression patterns have been associated with severe changes in cellular metabolism of synoviocytes, chondrocytes and other connective tissue cells with direct consequences on the integrity of the joint’s connective tissues (see Table 1). HSPs have crucial functions in fundamental processes involved in tissue homeostasis, signalling processes and inflammation, such as protein kinase activity [103], the proteasome [104], autophagy [105] and transcriptional activation [106]. Undoubtedly, future research will disclose whether HSPs are involved in these processes in joint inflammation and degradation.

### Table 1

**Summary of the best described HSPs in arthritis research**

<table>
<thead>
<tr>
<th>HSP family member</th>
<th>Biological effect</th>
</tr>
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<tbody>
<tr>
<td>HSP90 (HSPC1 and HSPC3)</td>
<td>Pleiotropic effects. Targeting HSP90 suppresses inflammation [24], reduces expression of matrix-degrading enzymes [22] and also induces osteoclastogenesis [25, 26]</td>
</tr>
<tr>
<td>TRAP1 gp96</td>
<td>Promotes chondrocyte survival under hypoxic conditions [107]</td>
</tr>
<tr>
<td>TRAP1 gp96</td>
<td>Activates macrophages and is suspected of contributing to the chronicity of inflammation [28, 29]</td>
</tr>
<tr>
<td>HSP70</td>
<td>Extracellular HSP70 suppresses cytokine secretion from FLS [42]; involved in tolerance and autoimmune processes [33, 37]</td>
</tr>
<tr>
<td>HSP72</td>
<td>Reduces synovial inflammation in animal models [43]</td>
</tr>
<tr>
<td>GRP78</td>
<td>Reduces synovial proliferation [46], increases survival of chondrocytes [47] and promotes mineralization [48]</td>
</tr>
<tr>
<td>sHSP HSPb1</td>
<td>Involved in cytokine expression in cartilage [71]</td>
</tr>
<tr>
<td>HSPb5</td>
<td>Involved in regulation of cartilage metabolism [72]</td>
</tr>
<tr>
<td>HSPB8</td>
<td>TLR ligand, may amplify inflammation responses [79]</td>
</tr>
<tr>
<td>Other</td>
<td>Involved in cartilage and bone development [84], may act as an autoantigen in RA [86]</td>
</tr>
</tbody>
</table>

Table indicates the most important role in joint biology. The individual HSPs are classified according to their HSP family.

### Rheumatology key messages

- HSPs contribute to joint diseases by (dys)regulating immune responses and by disturbing stromal cell homeostasis.
- HSPs play a role in the interplay between connective tissue and the immune system.
- Preclinical studies and clinical trials propose HSPs as therapeutic targets in inflammatory joint disorders.

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