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REVIEW

Stress proteins in the pathogenesis of spondyloarthritis

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Abstract
Spondyloarthritis is an autoinflammatory rheumatic disease in which arthritis and osteoproliferation lead the patients who suffer from it to chronic disability. This disease is associated with the expression of class I MHC molecule HLA-B27, which tends to be misfolded in the endoplasmic reticulum and, therefore, expressed in aberrant forms. This phenomena lead to endoplasmic reticulum stress, which in time, evokes a whole response to cellular injury. Under these conditions, the molecules involved in restoring cell homeostasis play a key role. Such is the case of the "heat-shock proteins", which usually regulate protein folding, but also have important immunomodulatory functions, as well as some roles in tissue modeling. In this review, we attempt to summarize the involvement of cell stress and heat-shock proteins in the homeostatic disturbances and pathological conditions associated with this disease.

Keywords Spondyloarthritis · Heat-shock proteins · Cell stress · HLA-B27 · HSP60

General remarks

Spondyloarthritis (SpA) is the term used to describe a group of clinical entities that share some clinical and pathological features. Originally, the term was used to group psoriatic arthritis (PsA), reactive arthritis (ReA), arthritis related to inflammatory bowel disease (IBD-related SpA), undifferentiated SpA (uSpA) and ankylosing spondylitis (AS) [1], which is the prototype of the group, and the best studied among all. The main clinical feature of SpA is the osteoproliferation at enthesis sites that leads the patients to ankylosis and functional disability, although other symptoms such as peripheral oligoarthritis, uveitis, psoriasis and intestinal inflammation can occur [2].

One of the big problems when studying the SpA is the unification of concepts about the clinical criteria and the limits between the diseases included in the group, so several classification schemes have been suggested to differentiate them. Nevertheless, the currently most accepted classification is the one developed by the Assessment of Spondyloarthritis International Society (ASAS), which classifies the disease in two main subsets: axial SpA (axSpA) and peripheral SpA (pSpA) [3]. These two groups can include all the forms of SpA depending on whether the main clinical features are in the axial or peripheral skeleton [4].

The absence of defined borders among the different types of SpA at the time of diagnosis has led to the formulation of theories that suggest that all the varieties are alternative presentations of one condition [5]. This fact might be reinforced by a lot of published data that confirm that there are pathogenic mechanisms shared among psoriasis, IBD, and the different varieties of SpA. Some of these elements include the strong relationship with gut microbiota [6], an increased link with the IL-23/IL-17 cytokine axis [7], the association with the HLA-B27 molecule [8] and the absence of a defined autoantigen, considering that, even with all the new information, these inflammatory diseases cannot yet be considered as autoimmune diseases.

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Autoimmunity or autoinflammation? Aetiology of SpA

Although SpA cannot be classified as an autoimmune disease according to current literature, some recent studies have found the presence of autoantibodies against molecules such as CD74 [9], an important molecule for the function of MHC class II molecules that seemed to be good biomarkers for axial SpA. A recent study on a big cohort found that these antibodies do not have enough specificity for diagnosis [10].

Very little is known about the aetiology of new bone formation in SpA, although the Wnt/β-catenin and the bone morphogenic protein (BMP) pathways seem to be highly involved [11]. Interestingly, important levels of autoantibody complexes against noggin (an inhibitor of the BMP pathway) and sclerostin (inhibitor of the Wnt/β-catenin pathway) are found in the serum of patients with SpA [12]. Despite this, more studies are required to determine the pathogenicity of these antibodies.

Remarkably, the presence of disease activity-related IgG antibodies against self-heat-shock protein 60 (HSP60) has been reported in patients with AS. This immune response against heat-shock proteins will be discussed in more detail afterwards.

This lack of evidence of autoimmunity in SpA leads to question the origin of the inflammation and especially of osteoproliferation in this pathogenic entity. According to the classical theories of immunity, an immune response can be elicited only against foreign antigens or it can be initiated in cases when self-responding cells exceed their activation or proliferation threshold. Following this theory, SpA can only be caused by the aberrant recognition of some peptides that come from a self-tissue or one that shares its structure, issue that was considered in the theory of the "arthritogenic peptide" of SpA aetiology. On the other hand, the "danger theory of the immune system" proposed by Polly Matzinger in 1994 [13] states that the immune system responds to the presence or absence of danger rather than to the discrimination of self and non-self. If we translate this theory to the current knowledge about SpA, it seems more likely that the disease comes from the sensing of danger instead of to any response against specific antigens.

The cause of SpA is still unknown although it is notorious that there is a strong association of the disease with the HLA-B27 molecule [14] and, in particular, with some alleles such as HLA-B*27:05 and HLA-B*27:02 [15]. The attempts to reproduce the disease in animal models have given much of the actual knowledge about the probable key factors in SpA pathogenesis.

Previously, the disease was only associated with HLA-B27 positivity, without any reason for this relationship. It was assumed that maybe the B27 molecule could be the target of the attack of autoantibodies or autoreactive immune cells as a result of molecular mimicry with enterobacteria [16]. Nevertheless, this theory has not been successfully proven and although the presence of antibodies against bacteria has been evidenced, [16–18], they do not seem to be able to transfer the disease or to be pathogenic to healthy individuals.

Some studies have tried to answer the questions about the relationship between HLA-B27 and enterobacteriae, and so, a strong association between *Klebsiella* and SpA has been suggested. These reports focus on the presence of antibodies against a sequence of amino acids (QTDRED) shared between the B27 molecule and the enzyme nitrogenase of *Klebsiella pneumoniae* [19], or the presence of antibodies against extracts from bacteria [20, 21]. Although it was thought that the induction of pathogenic antibodies with cross-reactivity in B27 positive individuals could be the initiating agent, our group showed that the nitrogenase from *Klebsiella* is not an immunogen in AS patients or B27 subjects and, furthermore, that there is reactivity to a protein of an approximated molecular weight of 60 kDa not related to nitrogenase or any other enzyme [22].

Animal models of SpA, like the one developed by Taurog et al. [23], have significantly contributed to better understand how the HLA-B27 is involved in the pathogenesis of the disease [24]. Now, we know that the B27 molecule is prompt to some alterations. This protein can misfold during its synthesis in the endoplasmic reticulum (ER) before its expression in the cell membrane [25]. This misfolding leads to some significant disturbances, such as the expression of aberrant forms of the B27 molecule forming free heavy chain (FHC) homodimers or other non-canonical structures [26], or the induction of acute ER stress, which can lead to several possible mechanisms to ensure the survival of the cell that suffers from it, including the unfolded protein response (UPR) [27] and the activation of the autophagy system [28].

The importance of proteostasis and stress mechanisms in SpA

The normal homeostasis of the synthesis, quality control, folding and degradation of proteins (also known as "proteostasis") ensures the proper transit of the recently synthesized proteins through the ER lumen and to its target compartment with the help of a series of molecular chaperones that orchestrate this process [29]. The inappropriate folding of proteins during its path through the ER can indeed cause cell stress or death [30], so the cell has to control this possibility using mechanisms such as the "Endoplasmic reticulum associated degradation" (ERAD) that send the unfolded

or misfolded proteins to the ubiquitin proteasome pathway (UPP) for its degradation [31].

UPR and SpA

Once the compensatory capacities of the ER are overcome, the ER stress gets to a point where it needs to be controlled. It is then when the cell uses the "Unfolded protein response" (UPR) system to diminish the protein load that is directed to the ER. The UPR consists of three main branches represented by three main sensors in the ER lumen: the inositol-requiring enzyme 1 alpha (IRE-1α), the protein kinase RNA-like endoplasmic reticulum kinase (PERK) and the activating transcription factor 6 alpha (ATF-6α) [30]. Usually, these three proteins are inactive because of their union with the chaperone BiP (also known as GRP78), which has more affinity to misfolded proteins than for its resting ligands, so when a misfolded protein appears, BiP attaches to it. The release of BiP from these sensors activates some signaling pathways that lead to a decrease in RNA translation, mRNA degradation, ERAD, activation and induction of autophagy, among other processes [30].

Most of the studies about the activation of the UPR in SpA have been done in animal models of transgenic rats, where it has been shown that the misfolding of the B27 molecule is linked to the activation of the UPR and, consequently, to a higher production of IL-23 [32]. This cytokine can induce enthesopathy and bone proliferation when it is overexpressed in mice [33] and is probably the main orchestrator cytokine involved in the pathogenesis of SpA [34]. However, it is not clear in humans whether or not the higher production of IL-23 is strictly associated with the UPR [35]. It is also important to note that the misfolding of HLA-B27 has been demonstrated in the gut of AS patients without a significant UPR induction [36]; although conversely, there is evidence of BiP expression and UPR activation in synovial and cytokine-induced macrophages in patients with AS [37, 38].

Interestingly, some studies claim that in patients with SpA, the autophagy (and not the UPR) is responsible of the production of IL-23 in the inflamed gut [36] although this seems not to be reflected to the synovial tissue, where the activation of autophagy is absent [39].

Autophagy and chaperone-mediated autophagy in SpA

Autophagy is a protector mechanism in which self-proteins or organelles are recycled to ensure the cell survival. There are at least three types of autophagy: macroautophagy, usually referred just as autophagy, microautophagy and chaperone-mediated autophagy [40]. This pathway forms an active part of the proteostasis, together with the UPR, the UPP, the ERAD and the chaperone systems, which has a remarkable relationship with the defense against microorganisms, control of inflammatory responses, maturation of immune cells, antigen presentation and the function of some pattern recognition receptors [41].

Ciccia et al. studied autophagy and UPR in biopsies taken from the gut of patients with AS and Crohn's disease. Surprisingly, they found an outstanding relationship between the expression of ATG16L1 (a crucial molecule for the formation of autophagosomes) and MAP1LC3A with the levels of IL-23p19 in the biopsies of chronic inflamed gut of patients with AS and Chron´s disease (CD). In addition, the levels of molecules associated with chaperone-mediated autophagy (CMA) such as HSPA8 and HSP90AA1 were found to be poorly expressed in the gut of patients with CD and AS (independently of the presence of intestinal inflammation) and negatively correlated with IL-23 expression, suggesting that CMA could play an active role in the regulation of IL23 production [36].

In the study of Ciccia et al., the inhibition of macroautophagy and CMA reduced the number of IL-23p19-positive cells from lamina propria mononuclear cells taken from patients with AS and CD (probably caused by the active release of the cytokine). Nevertheless, the combination of the autophagy inhibitors with lipopolysaccharide (LPS) induced higher levels of the mRNA of IL-23p19s.

Taken together, these studies suggest that autophagy and chaperone-mediated autophagy are differentially regulated depending on the tissue where they have been measured. While macroautophagy and IL-23 are overexpressed in the gut, the PBMCs from patients with SpA show lower levels of autophagy markers and IL23 mRNA when compared to healthy persons [39]. This defective autophagy in the peripheral blood of AS patients has been reported in other studies, which found that the expression of LC3 and beclin 1 is negatively correlated with radiographic scores like mSASSS [42].

The relationship of autophagy with IL-23 needs to be issued in further studies to explain these differences considering that this could be a phenomenon that is regulated in both ways: IL-23 can regulate the autophagy process and autophagy can regulate IL-23 production. These studies must also be designed taking into account the relationship between SpA, enterobacteriae and pattern recognition receptors. In this regard, the intracellular receptor NOD2 can both induce autophagy in dendritic cells [43] and limit the expression of IL-23 through mRNAs [44], so this could be an interesting link between dysbiosis, autophagy and inflammation.

Endoplasmic reticulum aminopeptidases alter the proteostasis and inflammatory response

Genetic studies of SpA have revealed that genes not directly related with HLA-class I or II molecules can confer risk to the development of the disease. Some of these genes include the receptor for IL-23 and proteins related to peptide processing [45]. In this regard, it has been described that polymorphisms in the genes of ER-resident aminopeptidases such as ERAP1 and 2 can have differential effects on the proteostasis and antigen presentation associated with SpA [46]. Some of these polymorphisms, such as the rs30187, have shown to be protective [47] and to interact with some subtype-associated B27 like the 04 and 05 alleles (explaining the predominance of this associations) [48], and with other non-B27 HLA variants associated with SpA like HLA-B*40:01 [49].

Although studies on the polymorphism rs30187 for ERAP1 and the polymorphism rs2248374 for ERAP2 (which generates a truncated and nonfunctional molecule) did not show differences in FHC, HLA class I and ER-stress markers expression between cases and controls [50, 51], it has been shown that the siRNA silencing of ERAP-1 induces an increase in FHC expression in HLA-B*27:05- and 04-transfected lymphocytes [48]. In addition, patients with AS lacking the expression of ERAP2 and cells with shRNA silencing of the same molecule showed a greater FHC expression accompanied with an up-regulation of the UPR as measured by XBP-1s, CHOP and BiP expression [52].

Stress proteins and spondyloarthritis: the role of HSP60

One of the most important elements that regulate the proteostasis is the chaperone system, represented by the heat-shock proteins (HSPs), that coordinates the traffic and folding of proteins in different cellular compartments [53] and protect cells against the ER stress and other insults [54].

The heat-shock proteins constitute a group of highly conserved molecules among species whose main function is to work as chaperones to guide several proteins across the cell [54], although other functions like immunomodulatory molecules have been studied [55, 56]. These molecules have distinct effects in the immune system according to their origin (bacterial or endogenous) [55, 57], but they are generally overexpressed in different types of stress conditions [56]. The HSPs are highly immunogenic proteins, which have even been proposed as candidates to be "arthritogenic peptides"[58] or autoantigens [57]. Furthermore, they were one of the first molecules considered to act as "danger signals" that alarm the immune system, indicating stress or tissue injury [13, 59].

Our group demonstrated that the majority of HLA-B27-positive patients with AS and their first-degree relatives have IgG antibodies against a 60-kDa protein of *Klebsiella*, regardless of the disease status [17]. This 60-kDa protein was later characterized as a GRO-EL-like heat-shock protein (HSP60Kp) [60]. The fact that this molecule was recognized by sera of the patients with AS and their relatives led us to the idea that the recognition of this antigen was related to the B-27 molecule and to the pathogenesis of AS. To prove this, we cloned and sequenced the gene of HSP60Kp and deduced the aminoacid sequence to determine possible epitopes for B cells by a bioinformatic approach [61]. Then, we found that the 389–397, 360–368 and 282–290 residues could be candidates of B cell recognition and that the antibodies of the patients did not recognize the protein lacking the 282–290 residue. Interestingly, this residue (282–290), which was potentially recognized by the antibodies of the patients, and the 360–368 one have an arginine in the position two of their sequence, which is crucial for every peptide to be presented in the B27 pocket [62]; so, apart from being recognized by antibodies, this peptide can indeed be presented to T cells.

In addition, we also found that the 117–125 peptide could have a stronger recognition by B cells and could be a motif for HLA-B*27:05. The differential response to HSP60Kp between B27-positive and -negative subjects could suggest that HLA-B27-positive but not -negative individuals are able to recognize peptides such as the 117–125 one from the protein and that this response could result in the interaction of T and B cells required for antibody production. Hence, considering the importance of enterobacterial HSPs in cellular immune responses, we analyzed the lymphoproliferative response of peripheral blood mononuclear cells (PBMCs) of HLA-B27 + patients that had shown positive serum reactivity against the whole extract of *Klebsiella pneumoniae* and against HSP60Kp. Our results showed that HSP60Kp can indeed induce the proliferation of PBMCs from the patients, although a more extensive study needs to be done to determine which cells are the main responders [63]. Furthermore, we found that both CD4 + and CD8 + T cells proliferated in response to HSP60Kp [64].

The humoral response against bacterial HSP60 is not restricted to *Klebsiella pneumoniae*, since we described that HLA-B27-positive and -negative patients with AS have elevated levels of IgG antibodies against the HSP60 from *K. pneumoniae*, *Y. enterocolitica*, *S. flexneri*, *E. coli* and *S. typhi* in peripheral blood [65] and in synovial fluid [66]. Importantly, three of these bacteria have a high homology in three regions that are highly antigenic for B cells. The

humoral response against bacterial HSP60 can be somehow related to previous reports in which the synovial fluid mononuclear cells of patients with AS possess DNA from *Salmonella, Shigella* and other enterobacteria [67]. Together, these data suggest a role of previous bacterial infections or gut microbiome interaction, although their specific role is still a topic open to discussion.

There are other reports of elevated levels of antibodies against human and bacterial HSP60 in patients with SpA that found predominantly IgG3 against human HSP60 and IgG1 against the bacterial one [68]. However, such antibodies did not reflect the disease activity [69]. Although the recognition of both, human and bacterial HSPs, has been described in SpA patients and HLA-B27-positive subjects, cross-reactivity among them still needs to be demonstrated. This would be an important issue given the possible association of endogenous HSP expression with endoplasmic reticulum (ER) stress [30, 70], protein folding and autophagy [41, 71]. In this regard, it was proven that autophagy inhibition affects HSP60 and HSP70 expression and that the absence of HSP60 alters the induction of the autophagy pathway [72]. Also, a co-localization of autophagy elements such as LC3 with HSP60 and their receptors under stress conditions have been found [73].

The HSP60 molecule is mainly located at mitochondria and participates in the proper folding of proteins exported to this organelle [74]. Its chaperone activity requires the union with HSP10 to form a catalytic unit, allowing proper protein folding and unfolding [75]. Captivatingly, it has been shown that HSP60 and other heat-shock proteins can change its location when facing different situations like apoptosis or stress. Therefore, they can either be expressed in the cell membrane or be released to the extracellular media where they can be a target of immune cells [76–78].

Extracellular HSP60 can be sensed by toll-like receptors such as TLR2 and TLR4, CD14 and CD91 receptors and one non-well identified receptor [56, 79–81] both in effector or regulatory cells. In addition, it can interact with elements of the adaptive immune system [82, 83] and interfere with antigen cross-presentation [78, 83].

It has been proposed that the HSP60 can polarize the immune response to the pro- or anti-inflammatory poles according to its concentration and location [84], although there are some controversies regarding this issue [55, 85]. HSP60 is also overexpressed in activated T cells and, according to a theory proposed by the group of Irun Cohen, it can function as an "ergotype" that elicits regulatory actions to control inflammatory responses [82]. Besides, some altered peptide ligands (APLs) like APL2 from HSP60 can induce the production of IL-10 in PBMCs obtained from patients with juvenile idiopathic arthritis that reinforces the immunomodulatory role of these proteins [86]. A summary of the

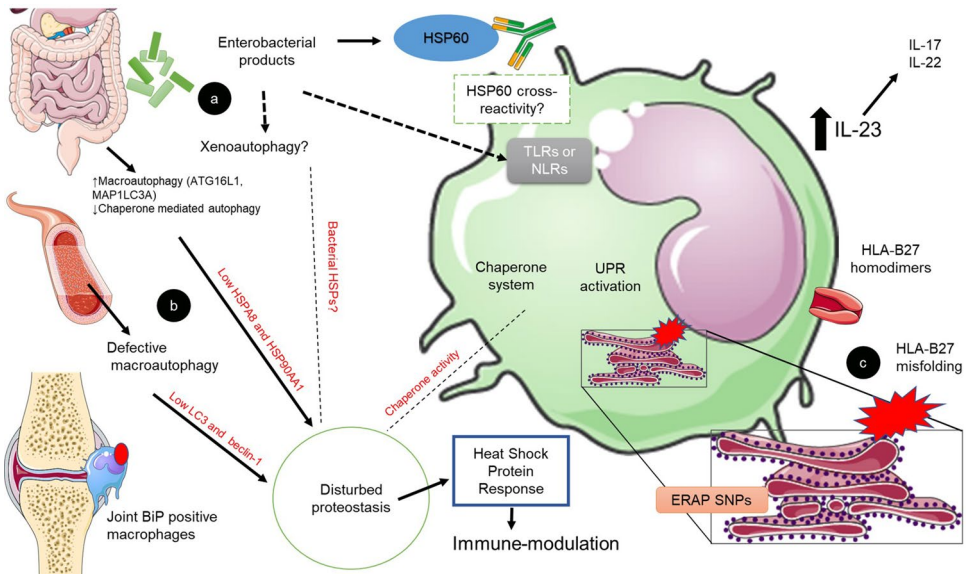

Fig. 1 Network of the interaction between heat-shock proteins and SpA pathogenesis. Stress proteins, either resulting from enterobacteria or from endogenous production can be involved with several mechanisms of inflammation-inducing processes related to SpA. Continuous lines show demonstrated relationships and discontinuous lines show probable or potential interactions. **a** Bacterial products can interact with PRRs like NOD2 or induce xenoautophagy. **b** The autophagy is differentially regulated in the gut, blood and joint of individuals with SpA. **c** The HLA-27 misfolding can induce several regulators like the UPR or the chaperone production and result in homodimer formation and cytokine production. Altogether, these processes confer a disturbed proteostasis or contribute to regulate it, in these conditions, the heat-shock protein response, which has an unexplored role in SpA can be involved. *HSP* heat-shock protein, *TLR* toll-like receptor, *NLR* NOD like receptor, *UPR* unfolded protein response, *ERAP* endoplasmic reticulum aminopeptidases, *SNP* single nucleotide polymorphisms

role of stress proteins and HSP60 in ER-stress, autophagy and inflammation in SpA is shown in Fig. 1.

Other stress proteins related to SpA

Not only the human and enterobacterial HSP60 have been related and studied in SpA for a long time, a molecular mimicry between the HSP65 from *Chlamydia trachomatis* and mycobacteria with endogenous peptides has also been thought to play an important role in the pathogenesis of reactive arthritis [21, 58].

Other chaperones, such as HSP70, have also been related to SpA and genetic polymorphisms have been reported in a Mexican cohort [87]. This protein has been hypothesized to be a core regulator of SpA, possibly by inhibiting the accumulation of unfolded B27 molecules in the ER and to regulate the antigen presentation and even the bone resorption rate [88]. The role of the heat-shock protein response in arthritis was partially assessed in a pilot study in which patients with AS were submitted to hyperthermia. This treatment induced a higher production of IL-10 and a higher expression of TLR4 in monocytes of the studied patients [89].

Remarkably, the group of proteins induced by stress is not only composed of heat-shock proteins but also many other stress-induced molecules have been studied. An interesting research was done regarding the high-mobility group box chromosomal protein 1 (HMGB1), which is a DNA-regulator protein that is released in cases of immune activation and works as an amplifier of inflammatory responses. This protein is found in high concentrations in the plasma of patients with AS and is highly correlated with the basic activity indicators of SpA such as BASMI, C-reactive protein (CPR) and ASDAS [90].

The osteoproliferation and subsequent ankylosis that occurs in patients with SpA is their main problem and, still, one of the least understood phenomena. We know that maybe endochondral bone formation happens in these patients because of the presence of hypertrophic chondrocytes in the synovial tissue of their joints [91]. It has been proposed that cytokines like IL-22 can induce the activation of genes related to bone modeling [33], that mechanical stress can be a pivotal factor in the onset of the disease [11] and that hormonal and growth factors might be involved [92]. Moreover, bone-lineage proteins such as osteopontin and osteocalcin have been found to be overexpressed in the midfoot of SpA patients with severe foot involvement [93].

Some signaling pathways have been anticipated to control the osteoproliferation in SpA, for example, the Wnt and Hedgehog pathways and the bone modeling proteins (BMPs) are some of the main candidates. Remarkably, there is a potential role of stress proteins in the new bone formation of patients with SpA. Actually, it has been proven that XBP1s and ATF6 (two major players in UPR signaling) can regulate in a positive way the hypertrophy of BMP-2 induced chondrocytes [94] and, therefore, enhance the endochondral bone growth. Furthermore, HSP60 can participate in the development of bone, maybe by its anti-apoptotic effect that enhances the proliferation and survival of osteoblasts regulating the bone architecture and mineralization [95], or maybe by its role in tissue modeling and wound healing by promoting the M2 phenotype of macrophages [96] (Fig. 2).

Although the role of stress-related proteins and alterations in the proteostasis has been studied mainly in relationship with HLA-B27 patients and experimental models, the information about HLA-B27-negative patients has given an interesting switch in the understanding of these phenomena. The unfolded protein response and the autophagy can be important issues in many non-HLA-B27-related diseases and it

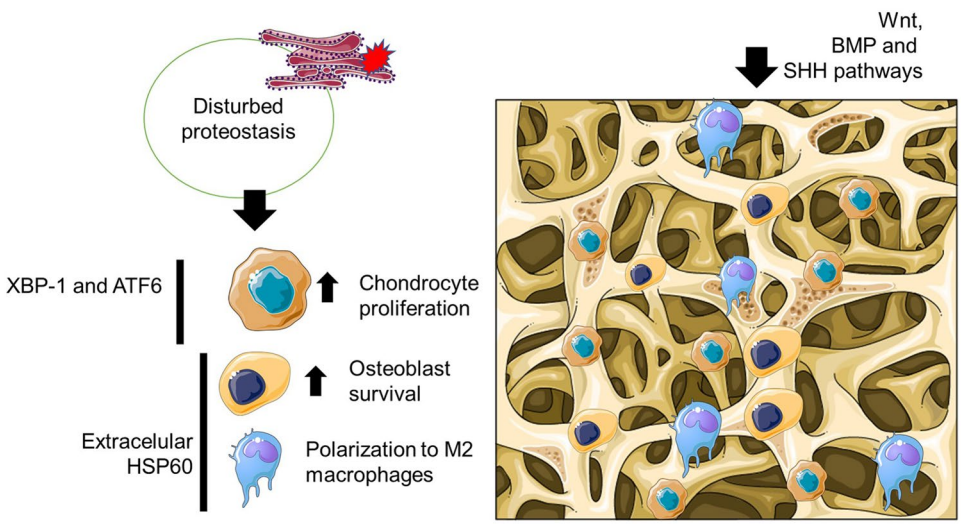

Fig. 2 Possible involvement of stress proteins with bone pathology in SpA. The final consequence of the SpA pathogenesis is bone formation. It is known that an important role of pathways such as Wnt, BMP and Sonic Hedgehog (SHH) can regulate osteoproliferation. Furthermore, it has been described that proteins that result from alterations in the proteostasis can be involved. ATF6 and XBP-1 can regulate the proliferation of BMP-2 induced chondrocytes. Also, HSP60 can regulate the osteoblast function through the modulation of survival genes

is a possibility that this process could be related to SpA in a non-B27-related manner [97]. Our work with HSP60Kp showed that the B27-positive patients have higher titles of antibodies against this protein; nevertheless, both B27-positive and -negative patients showed reactivity against the 282–290 peptide of HSP60 [61]. Also the polymorphisms of HSP70 that were associated with AS showed a high relation to the disease in B27-positive and -negative subjects [87]. Remarkably, the association with protective ERAP2 polymorphisms with AS was found initially in B27-negative patients and afterwards extended to B27-positive and -negative patients [98].

Conclusions and perspectives

The entire system-directed against cellular stress in spondyloarthritis appears not only to be crucial for its onset, but also to be involved in distant elements of its pathogenesis, such as intestinal inflammation or bone proliferation. The identification of specific elements, such as HSP60 or the molecules of the UPR or autophagy pathways, opens the road to get closer to the knowledge of the major pathogenic elements that lead these patients to suffer all the consequences of the disease.

There are still many issues to be solved regarding the pathogenesis of this complex pathogenic entity. However, the involvement of HSPs and other stress proteins in its pathogenesis can open a window to novel research lines and promising therapeutic approaches. The immunomodulatory role of HSP60 has led to a lot of research focused on the possibilities to take advantage of this proteins, either by immunization with complete proteins [99] or with modified peptides [86] that can modulate the inflammatory process, as demonstrated in other types of arthritis such as collagen-induced arthritis or other animal models of rheumatoid arthritis.

Besides, it is very important to note that over time, there have been new functions attributed to stress proteins and their immune network; thus, these attributes might not only be used in arthritis, but also in other research areas like regenerative medicine and tissue engineering.

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Compliance with ethical standards

Conflict of interest All the authors declare not to have any conflict of interests.

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