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Spondyloarthropathies and bone resorption: A possible role of heat shock protein (Hsp70)

(Review)

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Spondyloarthropathies consist of chronic inflammatory disorders genetically linked with each other through HLA-B27 molecules, and are connected with the destruction of periarticular bone and also with systemic bone loss in many cases. Expected molecular mechanisms behind these conditions overlap the functions of Hsp70s, a group of major molecular chaperones and cytokines. Hsp70s may control disease progression via inhibition of unfolded HLA-B27 protein accumulation and alteration of ER stress signaling. Further, Hsp70s may improve disease related malfunction of antigen presentation, and may induce nitric oxide (NO) release from macrophages which probably protective against spondyloarthropaties as well. Considering premised possible influence of Hsp70s on core mechanisms of spondyloarthropaties it may be expected that, increased expression of Hsp70s advantageously retards disease progress, or may lead to remission. On the other hand Hsp70s as danger signals induces the secretion of proinflammatory cytokines playing major role in the progression of spondyloarthropaty induced bone loss. Consequently, the effect of Hsp70s on the progression of spondyloarthropathic bone loss is "Janus-faced" in some respect: increase of Hsp70s' level is likely advantageous regarding to the core of disorder; but it may facilitate existing bone resorption processes.

Keywords: antigen presentation, bone resorption, chaperokine, ER stress, heat shock proteins, HLA-B27, Hsp70, osteoblast, osteoclast, spondyloarthropathy

The disease group of spondyloarthropathies consists of several chronic inflammatory disorders such as ankylosing spondylitis, psoriatic spondylitis, inflammatory bowel disease-related spondyloarthritis and rheumatoid arthritis (28, 29). All premised disorders are genetically linked with each other through a human leukocyte antigen B27 type

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molecule (HLA-B27) of type-1 major hystocompatibility complex (MHC-I) (28, 47, 48), and are connected with the destruction of periarticular bone and also with systemic bone loss in many cases (26, 29). The consequences of bone resorption may include joint destruction, increased bone fracture risk, implant failures and accelerated loss of periodontal (alveolar) bone (6, 29, 50) causing strong difficulties for several medical and dental professionals and their patients. Accordingly, the link between spondyloarthropathy induced inflammation and consequent bone loss has achieved increasing attention over the past decade (28, 29). Growing research on the molecular mechanisms involved in spondyloarthropathies and consequent inflammation induced changes of bone metabolism has revealed a set of expected molecular mechanisms behind premised pathological processes (28, 29). Interestingly, many of expected molecular mechanism overlap the function of 70 kDa heat shock proteins (Hsp70s) which are major molecular chaperones and cytokines/chaperokines (4)/of most cells/tissues (14, 15, 17), extracellular/interstitial fluids (12), blood (43, 58), synovial fluids (37, 49) and also secretory body fluids like saliva (19, 20, 21). Although premised overlap of functions and functional targets is obvious, the possible role of Hsp70s in the pathogenesis of spondyloarthropathies related bone loss was not yet pointed out or discussed in detail. The aim of present review is to stop premised gap of related literature, and to highlight the possible role of Hsp70s in premised pathological processes.

Spondyloarthropathies and the HLA-B27 molecules

Although spondyloarthropaties are known as multifactor disorders; genetic factors are also expected being a major determinant of these disorders (11, 28). Importantly, strong association between spondyloarthropaties and expression of HLA-B27 molecules was clearly confirmed during the past decades (28, 52). Two sets of HLA-B27 related theories are currently being proposed such as antigen specific theories and theories independent of antigen specificity (28). *Antigen specific theories* either predict that the HLA-B27 molecule has a unique ability to bind (and present) joint-specific peptide(s) recognized by autoreactive CD8+ T cells (cluster differentiation 8+ lymphocytes of thymus origin; cytotoxic T cells) responsible for inflammatory disease; or based on cross-reactivity between some bacterial antigens and HLA-B27 leading to inflammatory disease (28, 30, 38). In latter case other cross reactive self-peptides presented by HLA-B27 itself may also be expected (2, 7, 28). *Theories independent of antigen specificity* are based on unusual biochemical properties of the HLA-B27 type molecules characterized by slow folding during its three-dimensional formation, and tendency to dimerize via “aberrant” intermolecular disulfide bonding (16). Premised properties may lead to misfolding and accumulation of HLA-B27 molecules in the endoplasmic reticulum /ER/ (16). Therefore, these theories expect either proinflammatory ER stress response because of unfolded protein accumulation; or *abnormal* reactivity of HLA-B27 dimers with the receptors of CD4+ T cells (cluster differentiation 4+ lymphocytes of thymus origin; T helper cells) and natural killer (NK) cells (3, 8, 28). Although both

premised major sets of HLA-B27 related theories underlie the role of T lymphocytes (i.e. CD4+ and/or CD8+ cells) in the pathomechanism; *malfunction of HLA-B27 coupled antigen presentation* together with *normally functioning T cell response* seems to be the crucial point of disease predisposition (9, 27, 28, 39).

The important role of microbial flora in the development of spondyloarthropaties was also demonstrated via germ-free animal experiments (28, 45, 51). It may be expected that, above mentioned malfunction of antigen presentation impairs immune defense and CD8+ cytotoxic response against microbes (22, 23, 55) which may lead to consequent over-activation ("rebound") of the immune system *in time* leading to impairment of tolerance, particularly towards the microbial flora (27) and cross reactive self-peptides. Further, the possible role of several inflammatory mediators such as interferon gamma (INF-γ), interleukin 2 (IL-2) and also nitric oxide (NO) was also expected (10, 28). The possible role of INF-γ and IL-2 in the pathomechanism is far from being clear, but protective role of nitric oxide (NO) against spondyloarthropaties is likely (10, 28).

Bone loss and spondyloarthropathies

Osteoclast formation and consequent disturbance of the tight balance between bone resorption and bone formation seems to be an essential step in chronic inflammatory bone resorption induced by spondyloarthropaties (29, 44). This unfavorable shift of balance towards bone resorption is the basis for rapid bone loss primarily (29). There could be several mechanisms expected behind osteoclast activation, however the interrelationship between the immune system and the differentiation of osteoclasts seems to be a rather important and determinant one (29). Premised interrelationship may be routed in the fact that, immune cells and osteoclast precursor cells are derived from the same hematopoietic precursor cells (whereas osteo*blast* precursors are cells of mesenchimal origin) (29). Consequently, pro-inflammatory cytokine signaling network responsible for the activation of immune cells exert an activating effect on osteoclast precursor cells (having the same origin like immune cells) rather than on osteoblast precursors; which lead to the shift towards bone resorption (29). Further, certain pro-inflammatory cytokines, such as interleukins (IL) IL-1β (56), IL-6 (57), IL-17 (34) and especially tumor necrosis factor alpha (TNF-α) (36) induce the expression of RANKL (receptor activator of nuclear factor-κβ ligand; a member of tumor necrosis factor superfamily) which is essential for final differentiation steps of osteoclasts as well as for their bone resorbing capacity (33, 35). TNF-α additionally induces the mobilization of osteoclast precursor cells (OCPs) from the bone marrow and their homing and migration to the sites of inflammation (29). Moreover, TNF-α also exerts inhibitory effects on osteo*blasts* via degradation of runt-related transcription factor 2 (Runx2) (32) and inhibition of Wnt (a highly conserved signaling molecule, with a name derived from the first two recognized members of the family) induced osteoblast differentiation (18, 31); which further increases the shift toward bone resorption (29).

Spondyloarthropathies, bone loss and Hsp70s

Until now there heave been described 25 allelic subtypes coding for 23 distinct HLA-B27 molecules (HLA-B2701 to HLA-B2723), and most subtypes heave been disease-associated (28). However, those which seem not to be associated with spondyloarthropaties /such as HLA-B2706 and HLA-B2709 (46)/differ from the others because of amino-acid substitution in position 116 which is involved in the association of HLA-B27 type molecules with chaperones (28) likely including also Hsp70s (41, 54). Considering the antigen specificity independent theories of spondyloarthropaties (see above), and based on premised important finding and known chaperoning and signaling functions of Hsp70 in the ER (40) it is likely that, Hsp70s may play crucial role in controlling disease progression (via inhibition of unfolded HLA-B27 protein accumulation and alteration of ER signaling in response to ER stress). Further, antigen-complexed extracellular Hsp70s enhance the function of antigen presenting cells (i.e., macrophages, dendritic cells) and (cross)presentation of antigens (coupled with either MHC-I or MHC-II molecules) to cytotoxic T cells (CD8+ cells) or T helper cells (CD4+ cells), respectively (12, 53). Although direct links between bone loss and HLA-B27 related ER alterations and/or malfunction of antigen presentation were not yet discussed; it is very likely that premised expected effects of Hsp70s on the core of disease progression decreases the bone-related consequences of spondyloarthropaties as well. Further, uncomplexed extracellular Hsp70s also induce inducible nitric oxide (NO) synthase and NO release from macrophages (42); which is likely to be protective against spondyloarthropaties as well (10, 28). Considering premised possible influence of Hsp70s on core mechanisms of spondyloarthropaties it may be expected that, increase of intra and/or extracellular level of Hsp70s advantageously influences (retards) disease progress, or may lead to remission. It may not be excluded either that, certain effects – like ionic strength, warm or massage etc. (1, 24, 25) – used for physio-therapies may lead to improvement of sypondyloarthropathic symptoms due to the increase of intra- (1, 25) and/or extracellular (19, 20, 24) Hsp70s. On the other hand, uncomplexed extracellular Hsp70s as danger signal induces the secretion of proinflammatory cytokines playing major role in the progression of spondyloarthropaty induced bone loss, such as IL-1β, IL6 and TNF-α (5, 13) as detailed above. Consequently, the effect of Hsp70s on the progression of spondyloarthropathic bone loss is “Janus-faced” in some respect: Increase of Hsp70 level is seems to be advantageous regarding to the core of disorder; but it may facilitate existing bone resorption processes.

Conclusion

Taking together data and considerations above it may be concluded that, Hsp70s likely play an important role in the pathomechanism of spondyloarthropathies and consequent bone loss. Therefore, it would be worth investigating the possible role of intra- and extracellular Hsp70s in the pathomechanism of (as well as possible therapeutic targets for) spondyloarthropaties and related bone loss in detail.

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