Review

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Stress and atherosclerosis: may Hsp60 be the molecular link?

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Abstract

In last decades, incidence of cardiovascular diseases is increased. Among them, atherosclerosis is one of the most commons. It is a disorder of inflammation and innate immunity following lipid accumulation. From a biologic perspective, the process of adhesion and transmigration of immune cells (monocytes and macrophages) across the endothelium is a crucial step for atherogenesis and mature plaque rupture. Moreover, there is a relationship between inflammation, infection, autoimmunity and atherosclerosis. Inflammation has received increasing attention in recent years as a cause of atherosclerosis and cardiovascular diseases. Autoimmune diseases are characterized by enhanced atherosclerosis. Humoral immune responses to mycobacterial Hsp65, as well as to human Hsp60 and oxLDL, have been established in a number of human autoimmune diseases and are considered to be significantly associated also with atherosclerosis.

Keywords: atherosclerosis, infection, inflammation, chaperonin, cardiovascular diseases

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Introduction

Atherosclerosis (ATS) is a multifactorial disease for which a number of different pathogenic mechanisms have been proposed (1). In the last two decades, attention has been given to the inflammatory processes associated with atherogenesis (2). In addition to classical risk factors for ATS, such as high levels of low-density lipoprotein cholesterol or oxidized LDL, free radicals, hyperglycemia, and genetic susceptibility to endothelial damage, a pathogenic role for infections in ATS has been suggested by the detection of pathogens (e.g., *Chlamydia pneumoniae*, CMV, or herpes virus) in the arterial vessels and the association between ATS and increased antibody levels to these pathogens (3, 4).

Pathogenesis

Observations in humans and animals suggest that atherosclerotic plaques derive from specific cellular and molecular mechanisms that can be ascribed to an inflammatory disease of the arterial wall, the lesions of which consist of macrophages and T lymphocytes. Activated macrophages and T cells would be responsible for *in situ* production of enzymes, cytokines, and chemokines that further expand the process (5). If inflammation continues unabated, it results in increased numbers of plaque -infiltrating macrophages and T cells, which contribute to remodelling of the arterial wall. Within the T cell population of the plaque, most of the cells are activated CD4+ cells expressing HLA-DR and CD25 of the IL-2R (6).

Infections and ATS

C. pneumoniae DNA and *C. pneumoniae*-specific T cells clones were found in the plaques of anti-*C. pneumoniae* sieropositive patients. The specificity repertoire of such CD4+cells included the *C. pneumoniae* 60-kDa heat shock protein (CpHsp60), the 10-kDa HSP (Hsp10), the outer membrane protein 2, or undefined antigens of the *C. pneumoniae* elementary bodies (7). T cell clones recovered from *C. Pneumonia* DNA-negative plaques of anti-*C. pneumoniae* seronegative patients did not react to *C.pneumoniae* Ags. It was demonstrated that anti-mycobacterial Hsp65 antibody levels correlated strongly with human IgA to *C.pneumoniae* and with IgG to H.pylori, suggesting a role for infections in production of mHsp65 antibodies (8). Moreover, two independent groups subsequently went on to confirm that antibody also were elevated in more than 70% of their study population. In these populations, seropositive individuals not only showed a higher prevalence of coronary artery disease but also their disease severity was correlated with antibody titers, independently by traditional risk factors. Therefore, an elevated Hsp60/65 antibody level could be used as a marked for ATS risk prognostica-

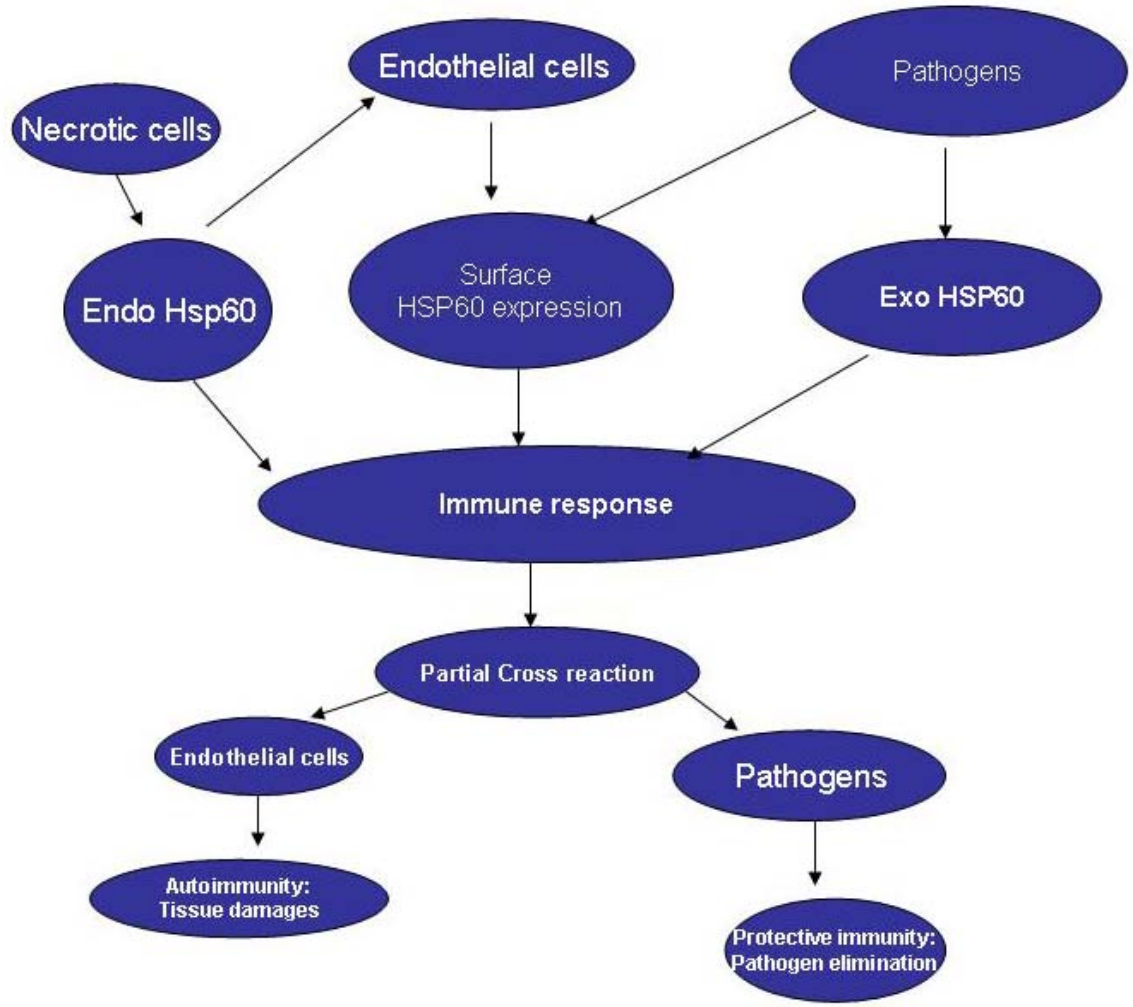

Figure 1: *Schematic representation of the role of autoimmune responses in atherosclerosis. Various endothelial stressors like infections, haemodynamic stress (hypertension), oxidative stress (oxLDL/other free radicals) and other vascular risk factors induce overexpression of HSPs in the cells, especially in the vascular endothelium. HSP being highly immunogenic can be processed by antigen presenting cells like macrophages and presented to T and B lymphocytes. This can cause clonal expansion of autoreactive T cells and B cells, producing autoimmunity. Alternatively, depending on the individual genotype (polymorphism of receptors, viz. MHC, toll-like receptors), the innate immune system can be directly activated by sHSP, causing inflammation within the vascular tissues over expressing HSPs. Both these mechanisms could contribute to atherogenesis.*

tion.

Circulating anti-HSP antibodies discussed above may be induced and maintained by different mechanisms (9). Firstly, infection with microbes containing homologous Hsp60 proteins could induce an anti-self response through molecular mimicry in susceptible individuals. Secondly, the protein itself could become immunogenic because of structural alteration or post-translational modification resulting from oxidation or metabolic alteration (10). Thirdly, other foreign or self-antigens could interact with Hsp60 to form immunogenic complexes in which B cells recognize Hsp60 and T cells direct their response at the associated antigen. Fourthly, soluble HSP (sHSP) might not be recognized as a self-protein by a population of T and B cells, since under physiological conditions HSPs are intracellularly localized (11). During the past decade, it has been noted that infections might contribute to the pathogenesis of ATS. Epidemiological studies suggest an association between several microorganisms and coronary heart disease, including *C. pneumoniae*, *Helicobacter pylori*, and herpes viruses, although controversial reports exist (12). These microbes may directly promote a pro-inflammatory, pro-coagulant, and pro-atherogenic environment, and HSP might serve as a link between infections and the atherosclerotic process. Support for this notion was the fact that a prospective population-based study provided strong evidence of correlation between immune reactions to Hsp65 and bacterial infections

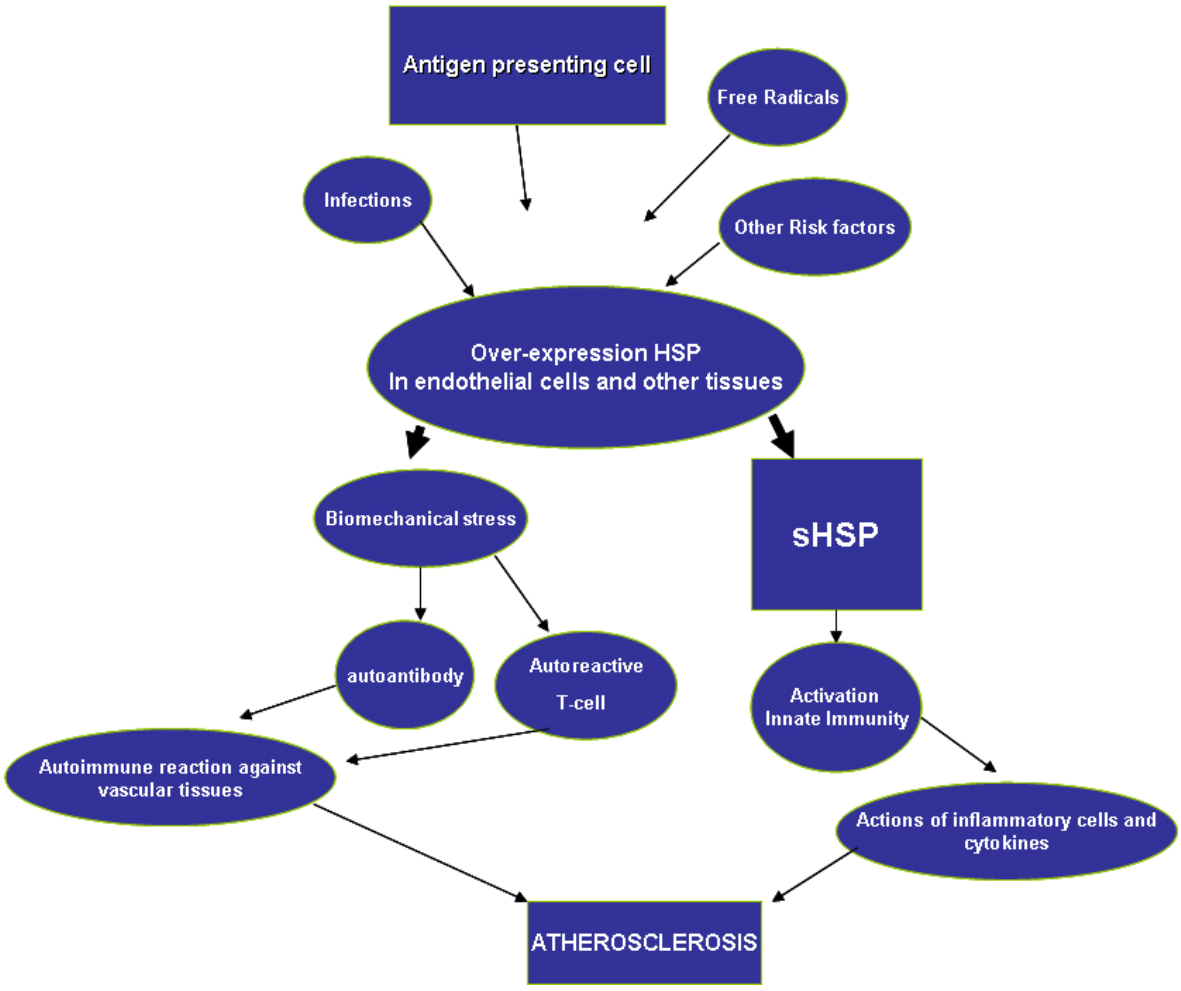

Figure 2. Hsp60-induced immune responses. Stress and aggressions up-regulate Hsp60 expression on membrane cell surfaces and trigger secretion of a soluble form. As exogenous Hsp60, endogenous synthesized molecule play a role in danger signals with activation of the immune system. Anti-Hsp60 antibodies can cross react with both sources of Hsp60. When cells surface Hsp60 is recognized, autoimmune reactions may appear. The soluble form can stimulate regulatory T cells that inhibit alpha/beta T cell-activation. Anti-Hsp60 auto-antibodies may either bind to Hsp60 and then impede the regulatory mechanism or induce cell damages, thus favouring autoimmunity.

in atherogenesis, indicating the impact of infections in HSP induction (13).

Life cycle of Chlamydiae: chlamydial infection and HSP production

In this respect, the life cycle of *Chlamydia*, an obligate intracellular pathogen, appears interesting. During its normal cycle generating infectious progeny, *Chlamydiae* express basal levels of HSP and in the presence of interferon-γ, a product of activated T cells within atheroma, certain *Chlamydiae* can achieve a state of intracellular chronic persistent infection, in which they remain viable but metabolically quiescent and do not replicate. During such chronic and persistent infections, Hsp60 production is abundant. It has been demonstrated that chlamydial Hsp60 co-localized with human Hsp60 within macrophages in atherosclerotic lesions. Non atherosclerotic samples contained neither HSP. These findings suggest that chlamydial infections might exert their role in atherogenesis via HSP production (14)

In fact, during its life cycle, *chlamydia* undergoes both phases of non-lytic infection, in which they remain viable but do not replicate, and phases of lytic infection. During the lytic phase, host cells release their own Hsp60, produced during a chronic phase of infection, and also chlamydial Hsp60, which has been produced from bacteria. A support for this theory is that sHsp60 levels are significantly correlated with anti-chlamydial antibodies, and that chlamydial and human Hsp60s exist at high levels in human atherosclerotic lesions. Second, sHsp60 could be released from the dying cells of tissues during chronic inflammation and from atheroma (15). Finally, surface-expressed HSPs in the cell undergoing apoptosis may be released into blood via the formation of microparticles, which have been identified in the circulating blood of patients with acute coronary syndromes and in non-ischemic patients. These microparticles generated in vitro from activated platelets or leukocytes stimulate cultured endothelial cells to produce prostacyclin and cytokines and to express adhesion molecules. The microparticles circulating in the peripheral blood of patients with acute myocardial infarction affect endothelium-dependent responses in normal blood vessels. sHSPs may be present in the microparticles and serve as active components exerting their role in these processes (16).

Chlamydial and human Hsp60 induces E-selectin, intercellular adhesion molecule-1 and vascular adhesion molecule-1 expression on endothelial cells similar to levels induced by LPS. Each Hsp60 also significantly induces interleukin (IL-6) production by endothelial cells, smooth muscle cells, and macrophages. Many studies have demonstrated that exogenous Hsp70 also acts as a cytokine to human monocytes by stimulating a pro-inflammatory signal transduction cascade that results in an up-regulation of IL-1, IL-6, and TNFα expression (17). Furthermore, it has been show that Hsp60 mediates monocyte adhesion to endothelial cells in vivo and in vitro via CD14.

Despite, it has been reported that human Hsp60 IgA or chlamydial Hsp60 antibodies were a significant risk factor for coronary events. When elevated human Hsp60 IgA antibody levels were present simultaneously with high *C. pneumoniae* IgA antibody levels and elevated C-reactive protein levels, the relative risk was 7.0. Therefore, elevated human HSP60 antibody levels may be a risk factor for atherosclerosis and could be a marker of this disease, especially when it is present with *C. pneumoniae* infection and inflammation (18).

Circulating antibodies to HSPs may be induced or maintained by several different mechanisms. First, infection with agents that contain homologous Hsp60 proteins could induce an anti-self response through molecular mimicry in susceptible individuals. Second, the protein could become immunogenic because of structural alteration or post-translational modification resulting from oxidation or metabolic alterations. Third, other foreign or self-antigens could interact with Hsp60 to form immunogenic complexes in which B cells recognize Hsp60 and T cells direct their response at the associated antigen. Fourth, soluble HSP might be not recognized as a self-protein by a population of T and B lymphocytes, in as much as HSPs being leaked are intracellulary localized in physiological conditions. Finally, genetic variation may also be important for antibody production (19).

Because of the high sequence homology between chlamydial other bacterial, and human HSPs, it is naturally possible that cross-reaction of antibodies and T cells against HSPs between microbes and humans contribute to the development of ATS. Recently, it has been supported that

ATS is an autoimmune disease; although data do not allow us to establish that atherosclerosis is an autoimmune disease, autoimmune reactions to HSPs may contribute, at least in part, to atherogenesis (20). As demonstrated, human serum anti-mycobacterial Hsp65 antibodies react with a recombinant form of human Hsp60 and homogenates of atherosclerosis lesions. Human anti-Hsp65 antibodies react with human Hsp60 present in endothelial cells, macrophages, and smooth muscle cells of atherosclerosis. It has been shown that anti-Hsp65 antibodies are cytotoxic to endothelial cells. By Western blotting analysis, they have demonstrated that such antibodies from patients with atherosclerosis react specifically with recombinant mycobacterial Hsp65, recombinant human Hsp60, chlamydial Hsp60, and E. coli GroEL/Hsp60. Heat-stressed endothelial cells could be lysed by these antibodies in the presence of complement via complement-mediated cytotoxicity or in the presence of peripheral blood mononuclear cells via antibody-dependent cellular cytotoxicity (11). In addition, a population of T cells in atherosclerotic lesions may also play a similar role as auto-antibodies, suggesting that cell-mediated immune responses to Hsp60 are involved in the pathogenesis of this disease. In further support of autoimmunity are findings that rabbits and mice develop ATS after immunization with HSPs. Therefore, serum autoantibodies and T cells react not only with bacterial Hsp65 but also with human Hsp60 in vascular cells. (21). ATS is largely viewed as a chronic inflammatory disease, to which chronic could contribute via elevated lipopolysaccharide (LPS) or endotoxin (22). Endotoxin induces local inflammation and systemic toxicity during Gram-negative infections and results in aortic endothelial injury with or without cell death an replication, followed by increased leukocyte adhesion and cell apoptosis (23).

Cell apoptosis and role of free radicals in ATS

Stimulation of cell apoptosis and proliferation by free radicals is though to be a critical step in atherosclerotic lesion formation (24). The potential role of oxidative stress

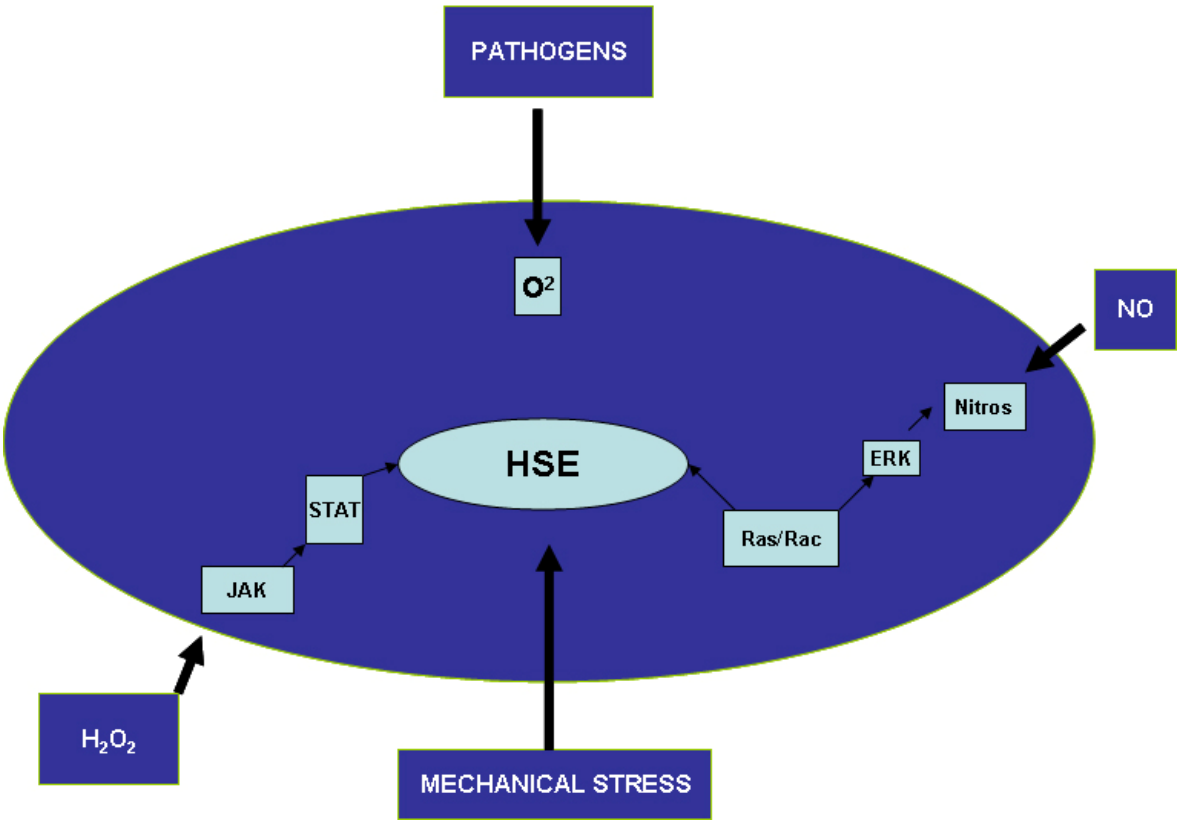

Figure 3: Activation of biochemicals pathways after stimulation of several stress. In particular, exposition of NO stimulate the S-nitrosylation of numerous intracellular proteins by inhibiting DNA synthesis. Exposition of H_2O_2 activates Hsp promoter via enahanced binding of signal transducers and activators of transcription (STAT).

conditions in the induction of HSPs has been reported. Treatment of endothelial cells with H2O2 or xantine oxidase has been shown to increase Hsp70 mRNA levels.(25). Nuclear runoff transcription data and kinetics of mRNA decay have indicated that the observed increase in Hsp70mRNA levels in H2O2 treated cells is mainly due to a transcriptional induction (26). Furthermore, a similar effect of H2O2 on HSP expression in smooth muscle cells has been observed. It has been demonstrated that H2O2 activates the Hsp70 promoter via enhanced binding of signal transducers and activators of transcription (STAT) to cognate binding sites in the promoter. Because janus kinase (JAK)2 is activated rapidly in smooth muscle cells treated with H2O2, STAT1 and AST3 were tyrosine-phosphorylated and translocated to the nucleus in a JAK2- dependent manner. Inhibition of JAK2 activity with AG-490 partially inhibited H2O2 induced HSP production. Thus, regulation of Hsp70 expression via activation of the JAK/STAT pathway suggests that this pathway is responsible for Hsp70 induction in response to oxidative stress (27).

Current data suggest that NO is a double-edged sword that could result in relaxation and/or cytoxicity of vascular smooth muscle cells via cGMP-dependent or independent signalling pathways. NO can stimulate the S-nitrosylation of numerous proteins and also binds to the non heme iron of ribonucleotide reductase to inhibit DNA synthesis. In vivo, increased production of NO has been observed in response to hemodynamic stress, sepsis shock, and endotoxin. It is not yet clear whether NO increases the expression of HSP in smooth muscle cells or whether HSP acts in conjunction with NO (28). A recent report has demonstrated that NO leads to the induction of Hsp70 protein and mRNA in cultured smooth muscle cells and other cells. Induction of Hsp70 mRNA was associated with the activation f heat shock transcription factor 1 (HSF1). HSF1 activation was completely blocked by hemoglobin, dithiothreitol, and cycloheximide, suggesting that the protein damage and nascent polypeptide formation induced by NO may initiate this activation. Thus, NO induces Hsp70 expression in smooth muscle cells via protein nitrosylation-initiated HSF1 activation (29).

In vivo, the vessel wall is exposed to two main hemodynamic forces or biomechanical stress: shear stress and mechanical stretch. Shear stress stimulates endothelial cells to release NO and prostacyclin, resulting in vessel relaxation and protection of vascular cells, whereas smooth muscle cells are stimulated by cyclic strain stress. In humans, atherosclerotic lesions occur preferably at bifurcation and curvatures where hemodynamic force is disturbed; i.e., there is lower shear stress and higher mechanical stretch. Although veins do not develop spontaneous ATS-like lesions, accelerated ATS occurs rapidly in venous bypass grafts, which bear increased biomechanical forces that are due to alterations in blood pressure, i.e. vein (0 to 30 mmHg) versus artery (120 mmHg). Another typical example for mechanical force involvement is hypertension-induced ATS. Therefore, mechanical stress could be a crucial factor in the pathogenesis of ATS. (30)

HSP: autoimmune reaction with anti-HSP antibodies

Augmented expression of the HSP is shown in atherosclerotic coronary arteries, and may provoke an autoimmune reaction with anti-HSP antibody. A strong association has also been demonstrated between anti-human Hsp60 IgG antibody and the severity of coronary ATS, although there was no evidence of an increase in serum levels of anti-chlamydial Hsp60 antibody in patients with IHD. The fact that Hsp60 can induce production of pro-inflammatory cytokines, such as tumor necrosis factor-α and matrix -degrading metallo-proteinases, suggests that this may be a mechanism of plaque instability (31). Hsp60 has also been found to induce cellular oxidation of low-density lipoprotein, macrophage activation, and production of interleukin-6. High levels of antibodies to human Hsp60 and *C.pneumoniae* have been shown to be independent risk factors for coronary ATS, and their simultaneous presence substantially increases the risk of disease development. These findings put together suggest that the inflammatory response associated with Hsp60 related immunologic reaction may play a crucial role in progressive plaque destabilization (32).

Immuno-inflammatory processes have been attracting growing attention as possible pathogenic factors in the development of ATS (33). HSPs have been shown to play a pivotal role in the genesis of autoim-

mune diseases. It is conceivable that HSPs furnish signals that provoke the innate immune system in the presence of infection and cell damage. A strong correlation between serum soluble Hsp60 and ATS has been reported, suggesting that soluble Hsp60 may be important for the activation of vascular cells during the development of ATS. A significant association has also been detected between anti-human Hsp60 IgG antibody and the severity of coronary ATS (34). In same studies it has been reported that no association is found between IgG antibodies to human Hsp60 and levels of coronary calcification. Furthermore, it has been reported that the presence of an elevated level of IgA but not of IgG antibodies against human Hsp60 presages a coronary event several years before it actually occurs (35).

Serum antibody titers against *C. pneumoniae* do not differentiate between severe and mild ATS, and they are not associated with the endovascular presence of *C. pneumoniae* in patients with IHD (36). Moreover, a recent meta-analysis showed that *C. pneumoniae* IgA, but not IgG, antibody and the presence of (ischemic heart disease) IHD yielded a significant association. In some study, no correlation was observed between the serum anti-*C. pneumoniae* IgG or IgA levels and the instability of IHD. However, other study revealed a significant difference in chlamydial IgM titers between acute coronary syndrome and stable IHD patients by using discriminant function analysis, which was independent on the incidence of male gender and/or smoking. Elevation of the chlamydial IgM titers may have resulted from acute *C.pneumoniae* infection. An acute respiratory infection during the two preceding weeks has been shown to be a risk factor for acute myocardial infarction (37).

Correlation between therapy and reduction of cardiac events

Short-term antibiotic treatment of IHD patients did not reduce cardiac events. However, *C. pneumoniae* within monocytes has been shown to resist standard antichlamydial therapy. Antibiotic treatment may have limited effectiveness for the prevention of cardiac events related to acute *C. pneumoniae* infection.

Finally, when acute chlamydial infection has occurred, coronary expression of chlamydial and/or human Hsp60 may be augmented. If these infected patients have high serum titers of anti-human HSP60 antibody, an autoimmunological reaction related to Hsp60 may then occur in an atheromatous plaque and precipitate acute ischemic events (38).

Conclusions

It was demonstrated a strong association between sHSP and ATS is in the general population, this association relates to infection and inflammation. The functional role of circulating sHSP may involve the direct stimulation of vascular cells and the immune system, thus promoting the progression of ATS. sHSP could serve as a diagnostic marker for ATS risk, especially when combined with other infectious and inflammatory markers. The development of new treatments will focus on strategies that decrease the inflammatory response and tip the balance in favour of anti-inflammatory mediators and, therefore, plaque stability. Thus, in the future, this new approach to arterial risk assessment may be useful in clinical approach.

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STRESS E ATEROSCLEROSI: PUÒ L'HSP60 ESSERE IL LEGAME MOLECOLARE?

Negli ultimi anni si è notato un incremento delle malattie cardiovascolari. Tra queste, l'aterosclerosi dei vasi sanguigni è un disordine di natura sia infiammatoria sia autoimmune, caratterizzato da un accumulo di lipidi. Sulla base di conoscenze biologiche, i processi di adesione cellulare, l'accumulo di monociti e macrofagi e la trasmigrazione di cellule appartenenti al sistema immune attraverso l'endotelio sono dei passaggi fondamentali nel processo di aterogenesi e nella rottura della placca aterosclerotica matura. Esiste, altresì, una relazione tra infiammazione, infezione, autoimmunità ed aterosclerosi. L'infiammazione ha ricevuto sempre più maggiore attenzione negli ultimi anni come causa di aterosclerosi e di patologia cardiovascolare, e anche molte malattie autoimmuni sono caratterizzate da aumentata aterosclerosi. Le risposte immuni di tipo umorale nei confronti di Hsp65 micobatterica, Hsp60 umana e LDL ossidate sono state ritrovate in un ampio numero di patologia autoimmuni e sono considerate esser associate con l'aterosclerosi.

Keywords: aterosclerosi, infezione, infiammazione, chaperonine, malattie cardiovascolari

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