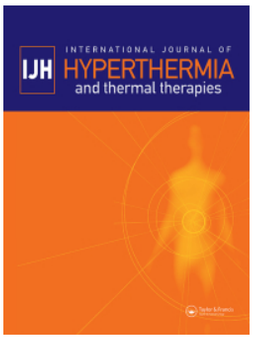

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RESEARCH ARTICLE

Heat shock proteins and immunity: Application of hyperthermia for immunomodulation

TOSHIHIKO TORIGOE, YASUAKI TAMURA, & NORIYUKI SATO

Department of Pathology, Sapporo Medical University School of Medicine, Sapporo, Japan

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Abstract
Heat shock proteins (HSPs) play an important role as 'endogenous danger signals' in the immune surveillance system. Extracellular HSPs released from damaged cells can stimulate professional antigen-presenting cells, followed by cytokine release and expression of cell surface molecules. In addition to such activity stimulating innate immunity, extracellular HSPs can promote the cross-presentation of HSP-bound peptide antigens to MHC class I molecules in dendritic cells, leading to efficient induction of antigen-specific cytotoxic T-lymphocytes. The roles of HSPs stimulating both innate immunity and adaptive immunity can explain at least in part the molecular mechanism by which thermal stress bolsters the host immune system. In the present review, we present novel aspects of the roles of HSPs in immunity and discuss the therapeutic application of hyperthermia for immunomodulation.

Keywords: *heat shock and immune response, immunotherapy, MHC class I, dendritic cells, antigen presentation*

The role of intracellular HSPs in antigen processing and presentation

Heat shock proteins (HSPs) act as molecular chaperones inside cells, regulating conformational change, translocation, assembly and degradation of cellular proteins. They have important roles in cellular protection against various stresses such as ischaemia, heat stress and oxidative stress [1–3]. They are also involved in the antigen processing and presentation machinery as chaperones for antigenic proteins and peptides. A number of studies have shown that the 70 kDa HSP family (Hsp70) and 90 kDa HSP family (Hsp90) are associated with antigenic peptides in the cytosol and mediate their translocation and processing [4]. We have demonstrated previously that Hsp70 is associated with transporters associated with antigen processing (TAP) and mediates ATP-dependent transportation of antigenic peptides from cytosol to endoplasmic reticulum (ER) [5]. The efficiency of the transportation is correlated with affinity of the peptides to Hsp70, indicating that HSPs might serve as intracellular antigen transporters. HSPs are also associated with proteasomes, which degrade cellular proteins and produce antigenic peptides [6] (Figure 1). In virus-infected cells, viral proteins bind to HSPs to utilise the protein folding machinery. However, some HSP-bound viral proteins are degraded by proteasomes and presented to MHC class I, leading to recognition of the infected cells by cytotoxic T-lymphocytes (CTL). Therefore, increased body temperature and the subsequent HSP induction are important reactions in the host defence system.

The role of extracellular HSPs in innate immune responses

Pattern recognition molecules have crucial roles in innate immune responses. So far, a number of Toll-like receptor (TLR) ligands have been reported, including lipopolysaccharides, peptidoglycans, CpG oligodeoxynucleotides and double-stranded RNA [7].

Correspondence: Toshihiko Torigoe, MD, PhD, Department of Pathology, Sapporo Medical University School of Medicine, 060-8556 Sapporo, Japan. Tel: +81-11-613-8374. Fax: +81-11-643-2310. E-mail: torigoe@sapmed.ac.jp

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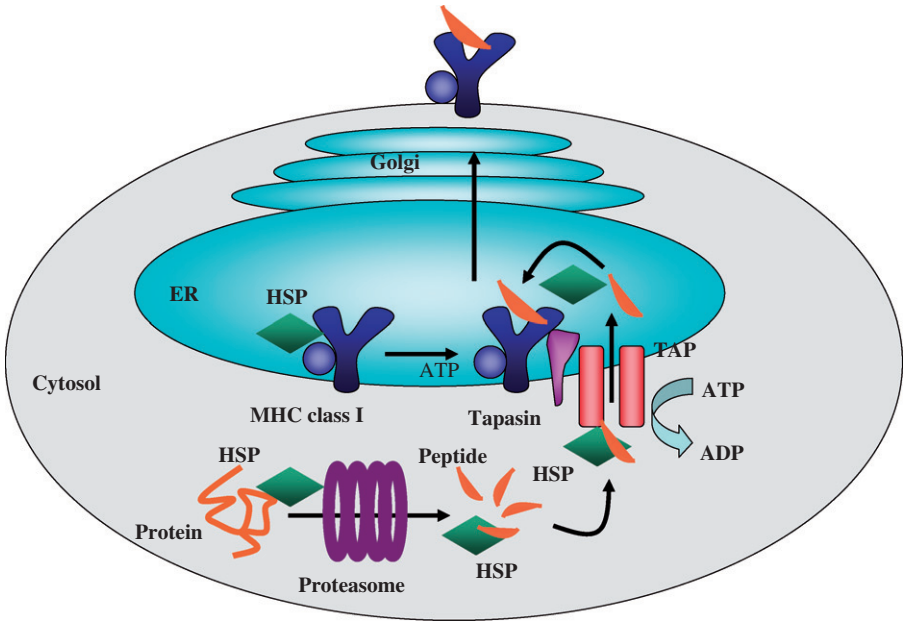

Figure 1. The role of intracellular HSPs in MHC class I antigen presentation. Cellular proteins are degraded by proteasomes, resulting in production of antigenic peptides. The peptides are transported from the cytosol into the endoplasmic reticulum (ER) by transporters associated with antigen processing (TAP), followed by binding to MHC class I molecules and presentation on the cell surface. Molecular chaperone HSPs are associated with antigenic peptides, proteasomes, TAP and MHC class I in this pathway.

In addition to the TLR ligands derived from microorganisms, silica crystals, aluminum salt and asbestos are known to stimulate NOD family molecules [8–11]. It is well known that most of these exogenous foreign molecules activate dendritic cells (DCs) and induce release of cytokines, including TNF-α, interferon and IL-12. Recently, it was revealed that extracellular HSPs could activate DCs as well as exogenous TLR ligands [12, 13]. Hsp70 and Hsp60 are reported to stimulate DCs through TLR4. We have reported that stimulation of DCs with purified Hsp70 results in induction of TNF-α release in a dose-dependent manner, which is inhibited in the presence of Hsp70-targeting polyamine compound deoxyspergualin [14]. Though it has been argued that the pro-inflammatory effects of extracellular HSPs might be mediated through contamination of LPS or other microbial compounds [15], it is true that some aspects of TLR activation by HSPs differ from TLR activation by microbial compounds. For example, activation of TLR signalling by Hsp60 requires endocytosis, whereas that by LPS does not [16]. In another study, it was shown that Hsp70 triggered calcium-mediated signalling in DCs, whereas it was not observed in LPS-triggering signals through TLR [17]. In order to ensure that LPS contamination with Hsp70 was not responsible for the release of cytokines, Hsp70 was either boiled at 95 °C or treated with proteinase K; however, both of these treatments abrogated Hsp70-induced, but not LPS-induced, release of cytokines, providing further evidence against endotoxin contamination contributing to DC activation [17]. Therefore, HSPs are now recognised as 'endogenous danger signals' that can alert the innate immune system in response to cellular damage. The molecular chaperone Hsp70, with cytokine-like activity in relation to DCs, was termed a 'chaperokine' [18]. HSPs released from damaged cells can activate DCs at the site of the injury and induce inflammatory cytokine release (Figure 2). Since the magnitude of the innate immune response is correlated with the amount of extracellular HSPs, more damaged cells and more severe stress can elicit more robust immune responses [14]. Therefore, local hyperthermia treatment might enhance the innate immune response through induction of a heat shock response and extracellular release of HSPs [13].

The role of extracellular HSPs in adaptive immunity

It has been shown that Hsp70 and Gp96, a member of the Hsp90 family, extracted from tumour cells can elicit anti-tumour CTL responses after vaccination in mouse models [19]. The immunogenic tumour antigens recognised by the CTLs are not HSPs themselves, but HSP-bound proteins and peptides [20]. Since HSPs are associated with

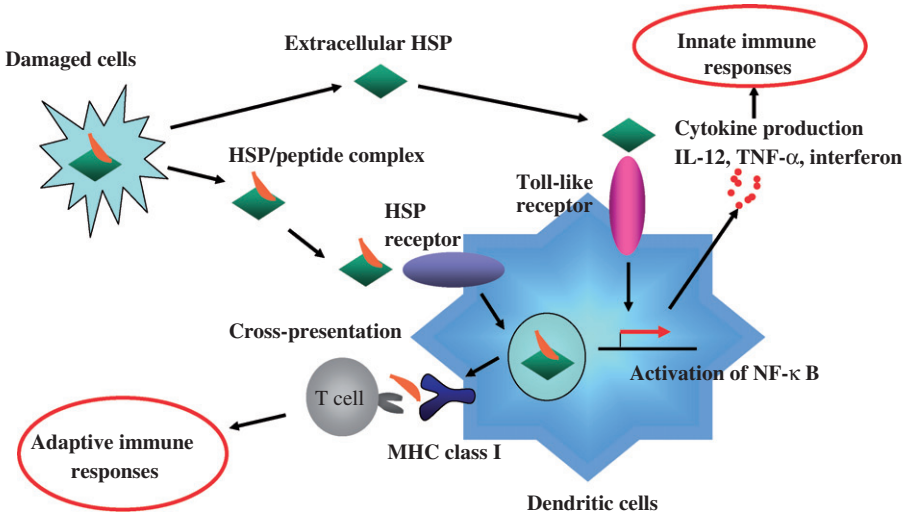

Figure 2. The role of extracellular HSPs in immune responses. Extracellular HSPs can stimulate Toll-like receptors, leading to activation of dendritic cells and release of cytokines such as IL-12, TNF-α and interferon (innate immune responses). Extracellular HSPs can be internalised through HSP receptors with HSP-bound peptides. The antigenic peptides are then cross-presented to MHC class I molecules, leading to induction of peptide-specific CTL responses (adaptive immune responses).

many cellular proteins, especially denatured proteins or mutated proteins in tumour cells, the antigenic proteins can be taken into professional APC in association with HSPs and presented to MHC class I molecules, leading to antigen-specific CTL induction [21, 22]. MHC class I presents peptides derived from endogenous proteins in non-APC. On the other hand, MHC class I can present peptides derived from exogenous proteins in professional APC as well, which is termed 'cross-presentation'. Extracellular HSPs were suggested to enhance cross-presentation of HSP-bound antigens to MHC class I in DCs. However, it remained unclear for a long time how HSPs could facilitate the cross-presentation and induction of CTLs. In 2000 it was reported that a Gp96-peptide complex could be taken into DCs via receptor-mediated endocytosis, and the receptor for Gp96 was CD91, an alpha2-macroglobulin receptor [23]. Basu et al. showed that not only Gp96, but also Hsp90, Hsp70 and calreticulin used CD91 as a common receptor [24]. Following the initial reports, other molecules were shown to be receptors for Hsp70 and Gp96, including CD40 [25] and the scavenger receptor family members LOX-1 [26] and SR-A [27]. Thus, it became evident that DCs could internalise HSP-chaperoned proteins and peptides through various receptors by endocytosis [28, 29]. We have analysed the antigen-processing pathway for cross-presentation after endocytosis. We showed that internalised Hsp70 or Hsp90 was transported preferentially into the early endosome and not to the ER or lysosome in DCs [30]. HSP-bound antigens are then processed in the endosome, followed by presentation through recycling MHC class I molecules (endosomal pathway), or translocated into the cytosol, followed by processing through proteasome-TAP machinery and presentation through MHC class I in the ER (TAP-ER pathway) [31–38] (Figure 3). It is proposed that DCs may have a unique membrane-transport pathway linking the endosomal compartment to the cytosolic compartment [39].

In addition, we have found that HSPs, especially Hsp90, have a potent endosome-targeting capability in professional APCs [38, 40]. Hsp90-chaperoned proteins were presented much more selectively through the MHC class I pathway (early endosomal pathway) than through the MHC class II pathway (late endosomal pathway). In contrast, free proteins are presented preferentially through the MHC class II pathway but not through the MHC class I pathway, resulting in antibody responses rather than CTL responses.

These studies clarified novel roles of extracellular HSPs in adaptive immunity. Professional APCs can present extracellular HSP-bound peptides/proteins to MHC class I and induce antigen-specific CTL responses. The HSP-mediated cross-presentation is more rapid and efficient than free antigens, indicating that extracellular HSPs can activate not only innate immune responses but also adaptive immune responses.

Application of HSPs for vaccine development

On the basis of the immunostimulatory activity of HSPs, we examined the application of HSPs for

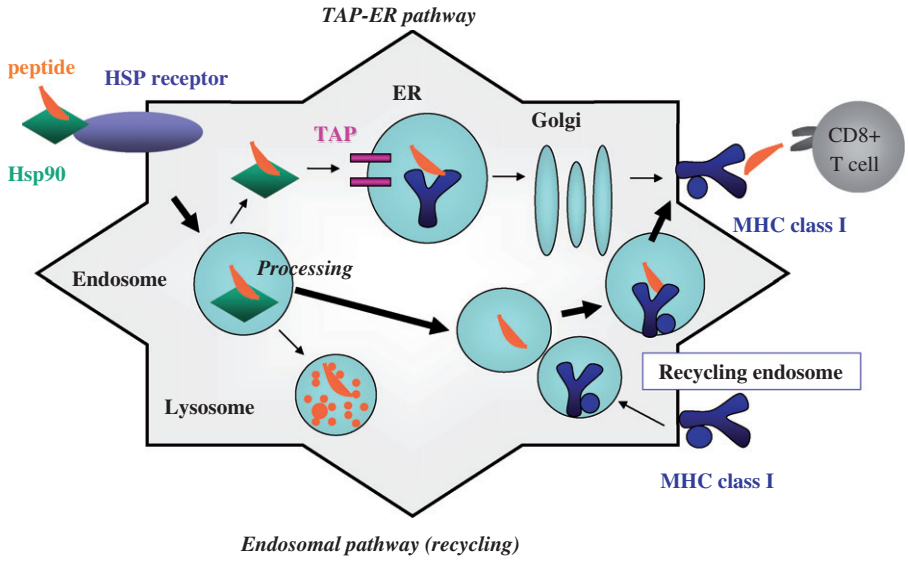

Figure 3. Cross-presentation pathway of Hsp90-antigen complex. HSP-antigen complexes internalised through HSP receptors are transported into the early endosome, followed by processing and presentation through MHC class I in the recycling endosome. Some of the HSP-antigen complexes may be released into the cytosol, followed by transportation through TAP and presentation through MHC class I in the ER.

vaccine adjuvant. Activation of DCs is required to achieve an efficient immune response to vaccination. Thus far, some TLR ligands such as CpG oligodeoxynucleotides and peptidoglycans have been employed as adjuvants as well as classical Freund adjuvants. However, most of the trials failed due to severe adverse effects or lack of effectiveness. The safe and common adjuvants in clinical use at present are mineral oil (Freund incomplete adjuvant) and aluminium. In animal models we compared the efficiency of peptide-specific CTL induction among peptide vaccines with various compositions such as peptide + PBS, peptide + Freund adjuvant, peptide + CpG oligodeoxynucleotide, peptide + Hsp70 and peptide + Hsp90 [38]. It was demonstrated that efficient CTL induction was achieved via vaccination with peptide + Hsp90 or peptide + complete Freund adjuvant (CFA) (Figure 4). However, vaccination with peptide + CFA caused severe local inflammation with skin ulceration. In contrast, there was no obvious side effect in the case of Hsp90 vaccination, indicating the superior safety and immunostimulatory action of Hsp90. Successful immunisation was also demonstrated in a mouse tumour therapeutic model. Vaccination of tumour-bearing mice with peptide + Hsp90 resulted in tumour regression and increased survival [38]. The results represent the greater advantage of utilising 'endogenous danger signals' in the development of vaccine as compared to 'exogenous danger signals', which are less physiological. Our study provides a rationale for a novel vaccine strategy in the field of cancer and infective diseases.

Application of hyperthermia for immunomodulation

It has been reported that hyperthermia in the febrile range could induce heat shock responses and subsequent HSP expression in human cells [41]. Therefore, the roles of intracellular and extracellular HSPs in the immune system can explain at least in part the benefits of fever in infectious diseases [42]. In addition to the HSP-family genes, expression of a number of immunomodulatory genes are induced during febrile-range hyperthermia, including cell adhesion molecules such as ICAM-1/CD54, JAM3, CD11b and CD47, TLRs such as TLR-6 and TLR-7, chemokines such as CXCL-5, CXCL-7 and IL-8, and prostaglandin E synthase [43]. There is accumulating evidence that fever-range thermal stress bolsters primary immune surveillance of lymphoid organs by augmenting lymphocyte extravasation across specialised blood vessels termed high endothelial venules (HEVs) [44–47]. Chen et al. showed that thermal stress enhanced endothelial expression of ICAM-1/CD54 and CCL21 chemokine, leading to increased lymphocyte trafficking across HEVs [48–50]. These mechanisms substantially increase the probability of antigen-specific T cells encountering the APCs in lymphoid organs. They also revealed that one of the important mediators of thermal effects upon lymphocytes and HEVs was IL-6 trans-signalling [48, 49]. These data suggest that hyperthermia treatment that is clinically applied as adjuvant treatment for sarcoma, melanoma and cervical cancer might be effective in the

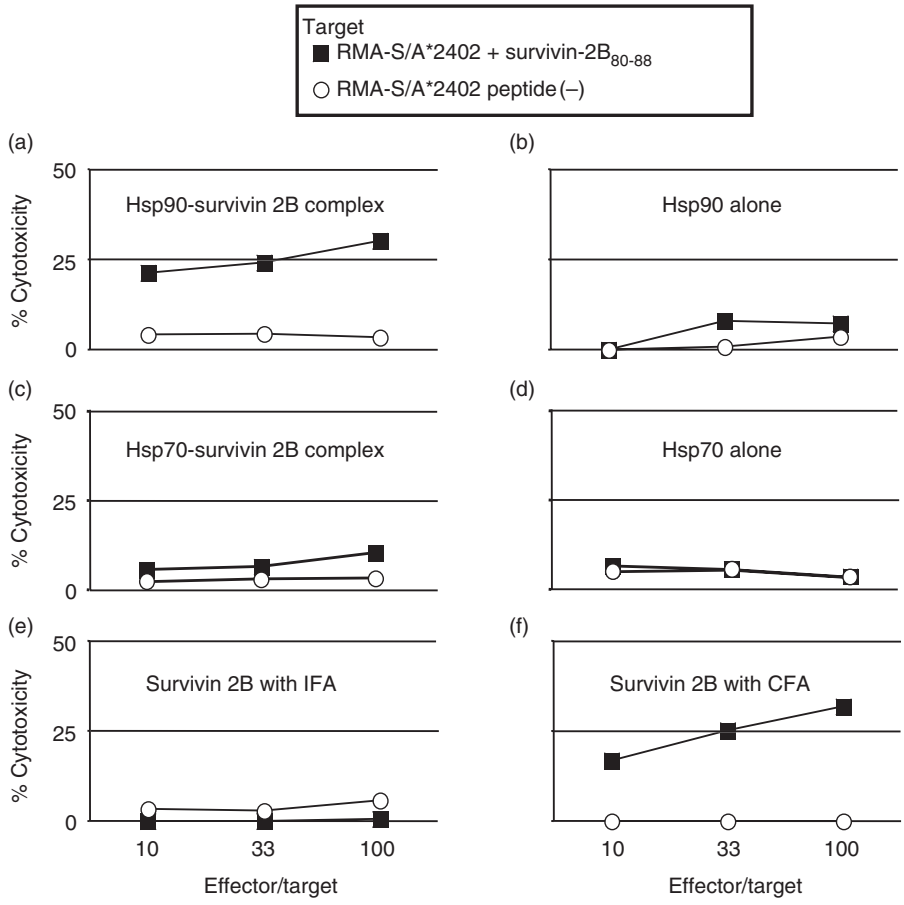

Figure 4. Hsp90-peptide vaccine can induce an efficient specific CTL response. HLA-A*2402/Kb-transgenic mice were immunised four times with the indicated peptide vaccination. Spleen cells were removed one week after the last immunisation, cultured for five days with survivin-2B80–88 peptides, and tested for cytotoxicity. Each line represents the specific lysis of target cells by spleen cells from one individual mouse. Target cells were RMA-S/A*2402 cells pulsed with the survivin-2B80–88 peptide, or without the peptide. Note that CTL were induced in the cases of vaccination with Hsp90 + peptide and complete Freund adjuvant (CFA) + peptide. IFA: incomplete Freund adjuvant. (Figure from reference [38]). Copyright 2007. The American Association of Immunologists, Inc.

enhancement of anti-tumour immune responses [51–53]. CTL-inducible HSP vaccine immunotherapy might be developed in combination with hyperthermia. However, the optimum temperature and duration of hyperthermia for the purpose of immunomodulation remain unclear and have to be determined through further studies, since they are quite distinct from the cytotoxic conditions utilised in the field of cancer therapy. Thermal effects on the immune responses can be achieved in the fever-range temperature (38–41 °C) [48], whereas cytotoxic effects of thermal stress can be achieved in the non-physiological range temperature (over 42 °C). In addition, it has been reported that thermal stress in certain condition can suppress the innate immune responses in macrophages [54, 55].

It is expected that hyperthermia and HSP vaccine might be applicable to the treatment of autoimmune diseases such as type I diabetes and rheumatoid arthritis [56]. The rationale came from the evidence that self-HSP-specific CD4-positive T-cells have been found in association with chronic inflammatory diseases and the HSP-specific T-cells have an immunoregulatory phenotype that can suppress immune responses in autoimmune diseases [56–58]. Indeed, there have been some clinical trials of HSP vaccine for the treatment of rheumatoid arthritis and type I diabetes [59, 60]. There is a report of an animal model showing that whole-body hyperthermia could attenuate autoimmune myocarditis [61]. It is suggested that hyperthermia-mediated induction of endogenous HSPs might facilitate the induction of CD4-positive immunoregulatory T-cells. As we discussed above, Hsp90-bound antigenic peptides could elicit strong peptide-specific CD8-positive cytotoxic T-cell responses through the stimulation of DCs. However, Hsp60 and Hsp70 could induce CD4-positive regulatory T-cell responses in certain conditions [56]. It seems that the direction of HSP-mediated immune response differs among different HSP family proteins and different HSP-bound antigens. Therefore, it is possible that hyperthermia

treatment causes a distinct effect on the immune response, either immunogenic or tolerogenic, depending on the tissue and the temperature. Though further studies will be required to develop a novel therapeutic strategy, there are promising advances in the fields of thermal medicine and immunotherapy.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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