LINK TO ORIGINAL ARTICLE
LINK TO INITIAL CORRESPONDENCE

Are heat shock proteins DAMPs?

Grace Y. Chen and Gabriel Nuñez

We discuss below the correspondence relating to our Review article (Sterile inflammation: sensing and reacting to damage. *Nature Rev. Immunol.* **10**, 826–837 (2010))[1] by Willem van Eden and colleagues (Heat shock proteins are no DAMPs, rather 'DAMPERs'. *Nature Rev. Immunol.* 25 Jul 2011 (doi:10.1038/nri2873-c1))[2]. We thank Willem van Eden and colleagues for critically discussing their opinion about the role of heat shock proteins (HSPs) as damage-associated molecular patterns (DAMPs). As we discussed in our Review article[1], the evidence that HSPs act as DAMPs to stimulate immune responses during sterile injury is controversial largely owing to the fact that most purified DAMP preparations, including those of HSPs, contain varying amounts of contaminating microbial products. Furthermore, HSPs can bind to several pathogen-associated molecular patterns (PAMPs) and enhance Toll-like receptor (TLR) ligand-induced stimulation[3–5], making the interpretation of published results difficult. Because depletion of microbial products from HSP preparations has been shown to reduce or abolish HSP-induced inflammatory responses[6,7], the evidence that HSPs act as DAMPs is weak at best.

In addition to the immunostimulatory properties of HSPs, we agree that there is also experimental evidence supporting an inhibitory role for HSPs in the activation of autoimmunity, allograft rejection and tumour immunosurveillance. Furthermore, HSPs can contribute to immune responses via several mechanisms, including the delivery of peptides to antigen-presenting cells for presentation by MHC molecules[8]. However, the cellular and molecular mechanisms by which HSPs regulate these activities remain unclear. This is due in part to the fact that HSPs function as ubiquitous chaperones to regulate a wide array of signalling pathways and cellular functions[9]. Thus, whether HSPs truly have a role in sterile inflammation, whether they regulate only certain aspects of the sterile inflammatory response (such as neutrophil recruitment or the modulation of cytokine responses) and whether their role is context dependent remain active areas of investigation.

Grace Y. Chen is at the Division of Haematology/Oncology, Department of Internal Medicine and Comprehensive Cancer Center, University of Michigan, Ann Arbor 48109, USA.

Gabriel Nuñez is at the Department of Pathology and Comprehensive Cancer Center, University of Michigan, Ann Arbor 48109, USA.

e-mails: gchenry@umich.edu; bclx@umich.edu

doi:10.1038/nri2873-c2

1. Chen, G. Y. & Nuñez. G. Sterile inflammation: sensing and reacting to damage. *Nature Rev. Immunol.* **10**, 826–837 (2010).
2. Broere, F., van der Zee, R. & van Eden, W. Heat shock proteins are no DAMPs, rather 'DAMPERs'. *Nature Rev. Immunol.* 25 Jul 2011 (doi:10.1038/nri2873-c1).
3. Habich, C. *et al.* Heat shock protein 60: specific binding of lipopolysaccharide. *J. Immunol.* **174**, 1298–1305 (2005).
4. Warger, T. *et al.* Interaction of TLR2 and TLR4 ligands with the N-terminal domain of Gp96 amplifies innate and adaptive immune responses. *J. Biol. Chem.* **281**, 22545–22553 (2006).
5. Osterloh, A., Kalinke, U., Weiss, S., Fleischer, B. & Breloer, M. Synergistic and differential modulation of immune responses by Hsp60 and lipopolysaccharide. *J. Biol. Chem.* **282**, 4669–4680 (2006).
6. Bausinger, H. *et al.* Endotoxin-free heat-shock protein 70 fails to induce APC activation. *Eur. J. Immunol.* **32**, 3708–3713 (2002).
7. Gao, B & Tsan, M. F. Endotoxin contamination in recombinant human heat shock protein 70 (Hsp70) preparation is responsible for the induction of tumor necrosis factor α release by murine macrophages. *J. Biol. Chem.* **278**, 174–179 (2003).
8. Li, Z., Menoret, A. & Srivastava, P. Roles of heat-shock proteins in antigen presentation and cross-presentation. *Curr. Opin. Immunol.* **14**, 45–51 (2002).
9. Hartl, F. U. & Hayer-Hartl, M. Molecular chaperones in the cytosol: from nascent chain to folded protein. *Science* **295**, 1852–1858 (2002).

Competing interests statement
The authors declare no competing financial interests.