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Editors

Heat Shock Proteins Volume1

Series Editors: Alexzander A.A. Asea · Stuart K. Calderwood

Heat Shock Proteins: Potent Mediators of Inflammation and Immunity

Springer

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Volume 1

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A C.I.P. Catalogue record for this book is available from the Library of Congress.

ISBN 978-1-4020-5584-3 (HB)
ISBN 978-1-4020-5585-0 (e-book)

Published by Springer,
P.O. Box 17, 3300 AA Dordrecht, The Netherlands.

www.springer.com

Printed on acid-free paper

This book is dedicated to our children Ana-Cristina, Alexzander Jr., Edwina and Vanessa

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PREFACE

From their original description as primarily intracellular molecular chaperones involved in cell survival and protection against potentially harmful stimuli, heat shock proteins (HSP) have now been shown to be exit cells and exert profound effects on the host's response to several human diseases as dissimilar as cancer, cardiovascular disease, aging and autoimmunity, and in response to previously unknown stressors like physical exercise and psychological stress including predator fear, confinement and social exclusion. This book reviews the contemporary knowledge on the role of heat shock proteins as mediators of inflammation and immunity. Using an integrative approach to understanding heat shock protein immunobiology, the contributors provide a synopsis of novel mechanisms by which HSP are released from cells, specific binding and resultant receptor-mediated signaling, the process of antigen processing and presentation and finally how HSP stimulate immune responses.

Section I reviews recently discovered mechanisms by which HSP gain access to the extracellular milieu. Classical and unique stressors that stimulate HSP release, as well as pathways by which HSP are delivered to the extracellular milieu are discussed.

Following release of HSP from cells, Section II reviews our recent knowledge of HSP specific binding to cells of the immune system. In addition, the growing number of HSP receptors and the resultant receptor-mediated signaling that occurs is comprehensively reviewed.

In Section III, immune responses elicited by exogenous HSP are reviewed. An up-to-date account of the ability of HSP to act as a danger signal and thereby augment host defense against various diseases or induce devastating autoimmune responses is also discussed in this section.

Finally, in Section IV, the role of HSP in antigen processing, presentation and its effect on inflammation and disease are reviewed. Specifically, the role of HSP-peptide complexes, controlling the inflammatory process and regulatory T cells are comprehensively reviewed.

Heat Shock Proteins: Potent Mediators of Inflammation and Immunity provides the most up-to-date and exciting insights into how heat shock proteins (HSP) modulates the host's immune response. Written by leaders in the field of heat shock protein immunobiology, the chapters systematically and in a step-wise fashion

takes the reader through the fascinating sequence of events by which heat shock proteins activate immune responses and provides answers as to its biological significance to the host. The book takes the reader systematically and in a step-wise fashion, mechanisms of release, to specific binding and receptor-mediated signaling, activation of host defense or initiation of devastating autoimmunity and finally to antigen processing and presentation and its effect on human diseases. This book is a must read for graduate and postgraduates in the field of Biology (plant and mammal), Biochemistry (pro- and eukaryotic), Immunology, Microbiology, Exercise Medicine, Physiology, Inflammatory diseases, Autoimmunity, Pharmacology and Pathology.

Alexzander A.A. Asea and Antonio De Maio

PART I

MECHANISMS OF HEAT SHOCK PROTEIN RELEASE

CHAPTER 1

RELEASE OF HEAT SHOCK PROTEINS: PASSIVE VERSUS ACTIVE RELEASE MECHANISMS

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Abstract: There is now no doubt that heat shock proteins have a profound immunoregulatory effect on the host's immune system. This knowledge has successfully been harnessed to generate a number of important clinical trails. However, one intriguing question that remains to be answered is how heat shock proteins (HSP) which do not have peptide leader sequence targeting secretion can gain access to the extracellular milieu. This chapter will discuss the most recent findings in the area of HSP release and attempts to broadly categorize these findings into two basic mechanisms; the passive and active mechanisms

Keywords: Chaperokine; exosomes; heat shock proteins; inflammation; lipid rafts; protein transport; stress

Abbreviations: eHsp72, extracellular Hsp72; ER, endoplasmic reticulum; Hsp, heat shock proteins; Hsc70; constitutively expressed seventy-kilo Dalton heat shock protein; Hsp72, stress inducible seventy-kilo Dalton heat shock protein; HSF-1, heat shock factor-1; IFN-γ, interferon-gamma; IL, interleukin; LDH, lactate dehydrogenase; MßD, methyl ß-cyclodextrin

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A.A.A. Asea and A. De Maio (eds.), Heat Shock Proteins: Potent Mediators of Inflammation and Immunity, 3–20.

PASSIVE RELEASE MECHANISM: NECROSIS, INFECTION AND TRAUMA

Necrosis

Necrotic cell death is an obvious mechanism by which heat shock proteins escape from cells. However, experimental conditions that conclusively demonstrate necrotic cell killing and the biological significance of the released HSP have been difficult to prove. However, Melcher and co-workers demonstrated that non-apoptotic cell killing induces increased levels of HSP concomitant with enhanced immunogenicity, whereas cells killed predominantly by apoptosis showed low levels of HSP expression and were less immunogenic (Melcher et al., 1998). Inhibition of apoptotic cell death by overexpression of bcl-2 induced increased levels of HSP. Interestingly, stable transfection of B16 and CMT93 cells with cDNA encoding Hsp70 significantly augmented the immunogenicity of both tumors (Melcher et al., 1998). These results were later independently supported by experiments performed by Basu and colleagues who reported that heat shock proteins including gp96, calreticulin, Hsp90 and Hsp72 are released from cells undergoing necrotic but not apoptotic cell death (Basu et al., 2000). These authors demonstrated that necrosis induced by freeze thaw, but not apoptosis induced by irradiation, resulted in the release of HSP into the culture supernatant, respectively. It was further demonstrated that the released HSP stimulates macrophages to secrete cytokines, and induces the expression of co-stimulatory molecules and enhanced antigen presentation by dendritic cells (Basu et al., 2000) a process known as the chaperokine activity of HSP which describes the ability of HSP to act as both chaperone and cytokine (Asea, 2003, 2005; Asea et al., 2000b). The chaperokine activity of HSP has been described in cancer (Facciponte et al., 2005; Facciponte et al., 2006; Gross et al., 2003a; Gross et al., 2003b; Gross et al., 2003c), stem cells (Son et al., 2005), complement activity (Prohaszka et al., 2002), transplantation and allograft injury (Land, 2005), and septic shock (Wheeler et al., 2005), as a trigger for autoimmune reactions (Yokota et al., 2006) and exercise immunophysiology (Fleshner and Johnson, 2005).

Infection

Infection of cells with a variety of microorganisms could result in cell death by apoptosis or necrosis (Fischetti, 2005; Gruenberg and van der Goot, 2006; Mathis et al., 2005; Thorne et al., 2005a; Thorne et al., 2005b). Lytic viruses are known to induce necrotic cell death (Brinkmann and Schulz, 2006; O'Shea , 2005; O'Shea et al., 2005). Infection of SK29-Mel-1 with the lytic parvovirus H1 occurs in the absence of HLA class I or costimulatory molecule upregulation (Moehler et al., 2003). In addition, infection is accompanied by a strong release of the inducible Hsp72, but not the constitutively expressed Hsc73. When compared with the classical non-lethal heat-shock treatment, a known inducer of HSP release (Bausero et al., 2005; Broquet et al., 2003; Gastpar et al., 2005; Lancaster and

Febbraio, 2005), the Hsp72 release is demonstrated to be higher and of longer duration (Moehler et al., 2003). Admixing parvovirus-mediated tumor cell lysate with antigen presenting cells including human dendritic cells (DC) and monocytes resulted in potent chaperokine activity. Further studies by the same group demonstrated that parvovirus-mediated cell killing enhances tumor immunogenicity by Hsp72 release and contributes to the anti-tumor effect of parvoviruses (Moehler et al., 2005). Although these authors did not directly demonstrate that H1-induced cell killing and its associated Hsp72 release promotes the loading and maturation of antigen presenting cells and by extension triggers tumor specific immune responses. One can speculate that the release of Hsp72 can facilitate priming of T cells specific for viral antigens in a similar fashion to that described in autoimmune diabetes and encephalomyelitis (Chandawarkar et al., 2004), and HIV infection (SenGupta et al., 2004).

Other kinds of infection known to stimulate innate and adaptive immune responses might also result in necrotic cell death; namely atherosclerosis. Atherosclerosis is a disease in which the immune response plays a very important role in its pathogenesis (for review see (Hansson and Libby, 2006)). The Wick laboratory was the first to provide evidence that the first stages of atherosclerosis is an autoimmune response against Hsp60 that is expressed by endothelial cells in areas that are subject to increased haemodynamic stress (Wick et al., 1995a; Wick et al., 1995b). Antibody-mediated and T-cell-mediated immune responses against Hsp60 have both been demonstrated early in arthrogenesis (for review see (Wick et al., 1995b)).

Why would the hosts own immune system turn against it in such a fashion? The complete answer has not yet been elucidated. However, there is an indication that the answer might in part be due to molecular mimicry, (for review see (Binder et al., 2002; Rose, 2000; Rose and Mackay, 2000)). Since Chlamydial heat shock proteins are potent antigenic stimuli able to induce specific cell-mediated and humoral immune responses, several studies have proposed a link between Chlamydia pneumoniae and pathologies associated with atherosclerosis and coronary heart disease (CHD) (Ausiello et al., 2005; Hoshida et al., 2005). In addition, Chlamydial heat shock proteins have been suggested to increase the risk of secondary cardiovascular events in patients with coronary heart disease with diabetes (Guech-Ongey et al., 2006).

Trauma

Severe trauma is a clear example by which intracellular Hsp72 gains free and unfettered access to the extracellular milieu. Trauma due to surgery after coronary artery bypass grafting has been shown to result in increased systemic Hsp72 levels (Dybdahl et al., 2004; Dybdahl et al., 2002). In a study designed to determine a correlation between serum levels of Hsp72 with survival of trauma patients and/or the severity of the postinjury inflammatory response, Pittet and colleagues demonstrated a significant upregulation in circulating serum Hsp72 in severely