CHAPTER 11

HSP70 AND HSP27 AS PHARMACOLOGICAL TARGETS IN APOPTOSIS MODULATION FOR CANCER THERAPY

Heat shock proteins and Cancer

M. BRUNET, C. DIDELOT, S. SUBRAMANIAM, A.L. RÉROLE, A. DE THONEL AND C. GARRIDO*  
INSERM UMR-866, Faculty of Medicine and Pharmacy, 7 Boulevard Jeanne d'Arc, 21039 Dijon, France

Abstract: The expression of heat shock proteins (HSP) HSP70 and HSP27 is induced in response to a wide variety of physiological and environmental insults including anticancer chemotherapy, thus allowing the cell to survive to lethal conditions. The cytoprotective effect of HSP70 and HSP27 is related to their ability to disable apoptosis. HSP70 and HSP27 both inhibit key apoptotic proteins at the pre- and post-mitochondrial level. HSP70 and/or HSP27 basal levels are unusually high in malignant cells, and both have been accused of participating in oncogenesis and/or in chemotherapy resistance. In rodent models, HSP70 or HSP27 over-expression increases tumor growth and metastatic potential. HSP70 and HSP27 depletion or inhibition frequently reduces the size of the tumors and even can cause their complete involution (for HSP70). In this chapter we will describe the effectors of the apoptotic machinery that interact with HSP70 or HSP27, and we will discuss the inhibition of HSP70 and HSP27 as a novel strategy of cancer therapy

Keywords: Heat shock proteins, apoptosis, cancer cell growth, cancer cell resistance

Abbreviations: HSP, heat shock proteins; AIF, apoptosis inducing factor; Apaf-1, Apoptosis protease activating factor-1; RO, Reactive oxygen species; PKC, Protein kinase C

*Corresponding author: INSERM UMR-866, 7, boulevard Jeanne d’Arc, Faculty of Medicine, 21039 Dijon, France, Tel: 33 3 80 39 32 84, Fax: 33 3 80 39 34 34, e-mail: cgarrido@u-bourgogne.fr

INTRODUCTION: Hsp70 AND Hsp27 ARE MOLECULAR CHAPERONES

Mammalian HSPs are evolutionary conserved proteins that can behave as molecular chaperones for other cellular proteins. They have been classified into five families according to their molecular size: HSP100, HSP90, HSP70, HSP60 and small HSPs (15 to 30 kDa) including HSP27. Chaperones are instrumental for signaling and protein traffic, even in the absence of stress. However, the need of HSPs increases after proteotoxic damage. HSP70 and HSP27 are the most strongly and universally induced chaperones. They are strongly induced by different stresses such as heat, irradiation, oxidative stress, or anticancer chemotherapy (Garrido et al., 2001).

Under normal conditions, HSP70 functions as ATP-dependent molecular chaperone that assist the folding of newly synthesized polypeptides, the assembly of multi-protein complexes and the transport of proteins across cellular membranes (Beckmann et al., 1990; De Los Rios et al., 2006; Shi and Thomas, 1992). HSP70 contains two distinct functional regions (Carrello et al., 2004): a peptide binding domain (PBD) and the amino-terminal ATPase domain (ABD) (Figure 1A). The PBD, that includes a carboxyl-terminal EEVD motif or chaperone motif, is responsible for substrate binding and refolding. The ABD, in turn, facilitates the release of the client protein after ATP hydrolysis (Mayer and Bukau, 2005) (Figure 1A). HSP70 chaperone activity is regulated by co-chaperones like Hip, CHIP or Bag-1. These co-chaperones bind to HSP70 and modulate its chaperone function by increasing or decreasing HSP70 affinity for substrates through the stabilization of the ADP or ATP bound state of HSP70. Under stressful conditions, elevated HSP70 levels allow cells to cope with increased concentrations of unfolded or denatured proteins (Nollen et al., 1999).

In contrast to HSP70, HSP27 is a ATP-independent chaperone that protect the cells from protein aggregation (Ehrnsperger et al., 1997). An interesting property of HSP27 is its capacity to oligomerize. HSP27 can form oligomers of up to 1000 kDa (Figure 2A). The affinity of HSP27 for the proteins to be chaperoned is modulated by their oligomerization status, the multimer being the binding competent state (Shashidharamurthy et al., 2005). The dimer of HSP27 is the building block for such multimeric complexes. The range of oligomerization size and the magnitude of chaperone activity increases as the temperature is increased (Bruey et al., 2000b; Lej-Garolla and Mauk, 2006). HSP27 oligomerization is a highly dynamic process regulated by the phosphorylation of the protein (Garrido, 2002). Human HSP27 can be phosphorylated at three serine residues, and its dephosphorylation favors the formation of large oligomers (Parcellier et al., 2006; Theriault et al., 2004) (Figure 2A). HSP27 phosphorylation is a reversible process catalyzed by the MAPKAP kinases-2 and -3 in response to differentiating agents, mitogens, inflammatory cytokines such as TNF-α and IL-1-β, some anticancer agents, hydrogen peroxide and other oxidants (Casado et al., 2007; Dorion and Landry, 2002; Vertii et al., 2006). However, phosphorylation is not the only process that modulates HSP27 oligomerization. Cell-cell contact, as that observed in confluent cultures in vitro or solid tumors in vivo, induces the formation of large HSP27 oligomers independently of the phosphorylation status of the protein (Bruey et al., 2000b).