CHAPTER 2

IMPLICATIONS OF HEAT SHOCK PROTEINS
IN CARCINOGENESIS AND CANCER PROGRESSION

DANIEL R. CIOCCA¹,*, MARIEL A. FANELLI¹,
F. DARIO CUELLO-CARRIÓN¹ AND STUART K. CALDERWOOD²,³

¹Oncology Laboratory, Institute of Experimental Medicine and Biology of Cuyo
(CRICYT-CONICET), and Argentine Foundation for Cancer Research (FAIC), Mendoza, C. C. 855,
5500 Mendoza, Argentina, e-mail: dciocca@lab.cricyt.edu.ar
²Division of Molecular and Cellular Radiation Oncology, Beth Israel Deaconess Medical Center,
Harvard Medical School, Boston, MA 02215
³Department of Medicine, Boston University School of Medicine, MA 02118, USA,
e-mail: scalderw@bidmc.harvard.edu

Abstract: Heat shock proteins (Hsp) participate in many events related to cancer as molecular
chaperones, starting from the very beginning of carcinogenesis. Several etiological
factors involve the Hsp family in their mechanisms of action, including oncogenic
viruses, hereditary and non hereditary alterations in tumor suppressors or oncoproteins,
hypermethylation, radiation and carcinogenic agents. All of them produce changes
in the Hsp response with consequences in cell proliferation, differentiation, inflam-
mation, apoptosis, DNA repair, angiogenesis, metastasis, and drug resistance and in
the immunological response mounted by the host. In this chapter we will examine the
participation of the Hsp response in tumor cell transformation, either by up-regulation
or down-regulation of specific Hsp. This can explain the variations in Hsp expression
found in pre-neoplastic and neoplastic human tumors in different tissues and organs.
These variations have important clinical consequences in cancer progression, and the
exploitation of such knowledge may improve anticancer treatment strategies

Keywords: Heat shock proteins, cancer, etiology, carcinogenesis, metastasis, drug resistance,
immunity, cancer progression, DNA repair, prognosis

INTRODUCTION

Many of the functions attributed to the heat shock proteins (Hsp) have been obtained
through the study of the role of these proteins in tumor cell biology. For example,
the chaperone activity of Hsp90 is critical to maintain many client proteins that

*Corresponding author: Oncology Laboratory, IMBECU, CRICYT, Casilla de Correo 855, Mendoza
5500, Argentina, Tel: +54-261-5244045, Fax: +54-261-5244001, e-mail: dciocca@lab.cricyt.edu.ar

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are essential for cancer cell growth and survival (See: Pratt et al., Chapter 1, this volume). This has led to the study of a large array of Hsp90 inhibitors that interfere with the chaperone function of this protein causing destruction of mutated proteins, oncoproteins, and also altering the stabilizations of “normal” proteins important for tumor progression/vascularization like hypoxia-inducible factor 1, via ubiquitination and proteasomal degradation (See: Neckers, Chapter 12, Whitesell, Chapter 13, Kamal et al., Chapter 14, Workman, Chapter 15). This form of cancer therapy is under active investigation (Chiosis et al 2006). On the other hand, some Hsp have been unexpectedly linked to cancer, for instance during the search for estrogen-induced proteins in MCF-7 human breast cancer cells, a new 24 kDa protein was identified which later proved to be a member of the Hsp family, Hsp27 (reviewed by Ciocca et al 1993). This protein has been related to anticancer drug resistance, to the prognosis of certain cancer types, and to the inhibition of specific apoptotic pathways (reviewed by Ciocca and Vargas-Roig, 1997, Ciocca and Calderwood 2005, Calderwood et al 2006). In other instance researchers were identifying genes regulated by an antitumor (apoptotic) and anti-angiogenic agent in myeloma cells using oligonucleotide arrays, and among the modulated genes were included several members of the Hsp family (Chauhan et al 2003). Thus, through employing different approaches and techniques, the area of Hsp involvement in tumor biology has expanded to many crucial aspects of tumor development, embodying cell growth and differentiation, apoptosis, metastasis, drug resistance, and anticancer therapies including immunotherapy. These aspects will be covered in the different chapters of this book.

**HEAT SHOCK PROTEINS AND CARCINOGENESIS**

There is a cascade of molecular events that mediate the transformation of a normal cell into a cancer cell. Several etiological agents and factors have been identified as responsible for initiating the carcinogenic process, including are viruses, radiation, carcinogenic compounds, and hereditary and non-hereditary genetic alterations. Thus we aim to know how these cancer etiological agents can modify the molecular milieu of the transformed cells and, in our case, to the role of the Hsp.

Understanding the consequences of such changes are paving the way to cancer prevention, diagnosis and treatment strategies. Among the identified oncogenic viruses are adenovirus, HPV, HBV and HCV; all of them have been related with changes in the expression of certain Hsp (Burdon 1986, Ciocca et al 1991, Ciocca et al 1992, Lim et al 2005). Consequences of such alterations are cytoskeleton modifications characteristic such as seen in HPV infection (collapse of the chaperone-cytoskeleton complex to a perinuclear location seen in koilocytes). The cytoskeleton is very sensitive to different stressors, and the Hsp contribute to cytoskeleton organization (Quinlan 2002). Figure 1 shows the relationship between the oncogenic agents and the Hsp. Another microorganism linked with carcinogenesis is Helicobacter pylori that affects expression of PCNA, p53, c-erbB-2 and Bcl-2 in the human gastric mucosa (Jorge et al 2003). The infection of MKN7