

Chapter XXXVIII

Fluorescence Imaging of Mitochondrial Long-Term Depolarization in Cancer Cells Exposed to Heat-Stress

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ABSTRACT

*This chapter deals with the mitochondrias' stress response to heat, which is the central agent of thermotherapy. Thermotherapies function by inducing lethal heat inside target tissues. Spatial and temporal instabilities of temperature distributions in targets require optimized treatment protocols and reliable temperature-control methods during thermotherapies. Since solid cancers present predominant targets to thermotherapy, we analyzed hyperthermic stress-induced effects on mitochondrial transmembrane potentials in **breast cancer cells (MX1)**. Heat sensitivities and stress reactions might be extremely different among different tissue species and tissue dignities; therefore it is very important to investigate tissue-specific stress responses systematically. Even though this chapter provides minimal information only to the enlightenment of systemic cellular heat stress mechanisms, it may contribute to deepening the basic knowledge about systemic stress responses. In addition, the data presented here might support optimizing of treatment protocols applied during thermotherapy, particularly LITT and hyperthermia.*

INTRODUCTION

Heat represents a primarily environmental physical stress factor inducing multiform stress reactions in cells and tissues exposed to unphysiologically elevated temperatures. Molecular mechanisms triggered by heat stress include enhanced synthesis of so-called **heat shock proteins (HSP)** providing a limited protection to cells and organisms against heat-induced damages [Lindquist, 1986; Sonna, 2002; Takayama, 2003; Kregel, 2002]. HSP are also involved in other stress responses initiated by non-thermal stress factors, like oxidative stress, energy and nutrient depletions, or drug toxicities [Kregel, 2002]. The effectiveness of HSP-mediated damage protections depend on the stress factor dose, exposure time, and the cell species encountering stress. Especially hyperthermic stress induces cell type individual stress reactions involving complex networks of genetic and biochemical changes [Sonna, 2002]. Detailed knowledge about molecular HSP functions and the resulting metabolic interactions does not really exist so far, although they are under intensive investigation worldwide [Kregel, 2002].

Understanding of HSP regulation by using systems biology tools, HSP interact with multiple key components of signalling pathways that regulate growth and development. The molecular relationships between heat shock proteins and various signalling proteins appear to be critical for the normal function of signal transduction pathways. The relative levels of these proteins may be important, as too little or too much Hsp70 or Hsp90 can result in aberrant growth control, developmental malformations and cell death. Although the functions of HSP as molecular chaperones have been well characterized, their complementary role as 'stress-induced' proteins to monitor changes and alter the biochemical environment of the cell remains elusive. Genetic and molecular interactions between HSP, their co-chaperones and components of signalling pathways suggest that crosstalk between these proteins can regulate proliferation and development by preventing or enhancing cell growth and death, as the levels of HSP vary in response to environmental stress or disease.

The field of clinical cancer therapy comprises two major groups of different ablative thermotherapy methods, 1) **laser-induced thermotherapy (LITT)** working with locally confined temperatures between 50°C and 150°C to induce target tissue coagulation [Gewiese, 1994; Roggan, 2001; Nikfarjam, 2003] and 2) **hyperthermia** working with temperatures below 45°C [van der Zee, 2002]. Combined modality treatments such as hyperthermia-assisted radiotherapy and/or chemotherapy are under intensive scientific investigation today [van der Zee, 2002; Debes, 2004; Hehr, 2003; Colombo, 2003]. Another approach of interstitial thermoablation has been published by Jordan *et al.* (2006) and Johannsen (2007) who suggested injection of magnetic nanoparticles into a tumor followed by application of alternating current magnetic fields inducing elevated temperatures inside the particle-loaded tissue [Campbell, 2007; Johannsen, 2007; Jordan, 2006]. Therapy preconditions for this modern approach of nanomedicine concerning sufficient target loading with nanoparticles as well as feasible opportunities providing homogeneous particle distributions were not discussed in this context.

Generally, if the temperature induced in a target tissue is high enough to cause lethal effects and to induce thermal destruction thermotherapy is successful [Gewiese, 1994; Roggan, 2001; Nikfarjam, 2003; van der Zee, 2002; Debes, 2004; Hehr, 2003; Colombo, 2003]. Since heat transfer and distribution inside a target tissue usually are irregular and exhibit spatial and temporal instabilities, there is always a risk that certain areas of the target will survive the thermotherapeutic intervention to cause persistence or recurrence of disease [Nikfarjam, 2003; Gellermann, 2005; Mack, 2004]. Thresholds for thermal damage in human tissues vary among tissue species as well as among normal and diseased

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