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RESEARCH ARTICLE

Human MG-63 osteosarcoma cells responses to long and short term hyper- and hypothermia stress

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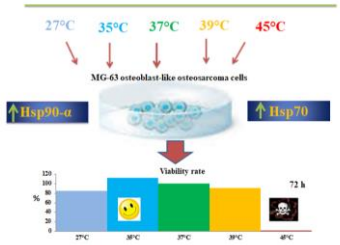
Graphical abstract



Abstract

Hyper- and hypothermia are utilized as treatment modalities in cancer treatment or as a protection against ischemia-reperfusion induced cell damage. The under-lying mechanism of hyper- and hypothermia, on cell death in osteosarcoma cells are not well understood. The aim of this study is to investigate the short- and long-term effects of various severities of hyper- and hypothermia on osteoblast-like osteosarcoma cells (MG-63). MG-63 cells were treated with mild and severe hyper- and hypothermia for short, medium and long-term periods. Severe hypothermia and hyperthermia showed a time-dependent toxicity; hence viability was reduced in a significant manner at all time points and the cells were undergoing apoptosis. Mild hypothermia, on the other hand, showed a protective effect and long term exposure increased the cell viability. Severe hyperthermia induced significant DNA damage at all time points. Caspase 3/7 activity showed a significant increase at 1 h of severe hyperthermia and 72 h of severe hypothermia ($p<0.05$). Hsp90 expression was significantly increased at 72 h of mild hyperthermia ($p<0.01$), whereas Hsp70 showed a significant increase after 24 and 72 h ($p<0.01$ and $p<0.001$). Hsp27 mRNA was increased significantly at 24 h only under mild hyperthermia ($p<0.01$). In conclusion, hyperthermia especially severe hyperthermia induced cellular stress in MG-63 cells leading to apoptosis. Hypothermia, on the other hand caused severe cell stress only when the cells were challenged for a prolonged period with severe low temperatures.

Keywords: hyperthermia, hypothermia, osteosarcoma, heat shock proteins, cold shock proteins

INTRODUCTION

Hyper- and hypothermia are extreme temperatures which can occur physiologically when the body's thermoregulation fails due to e.g. extreme surrounding temperatures in the summer or winter. Hyper- and hypothermia, however, are also treatment modalities. Hypothermia for example is been used to protect the heart and the brain during open cardiac surgery while hyperthermia on the other hand is used as a sensitizer for chemotherapeutic drugs by oxygenating otherwise hypoxic tumor tissue which then leads to increased susceptibility of the tumor to treatment [1,2].

Normal, healthy cells respond to extreme temperatures with a well-orchestrated molecular response involving the up-regulation of heat and cold shock proteins. While the mechanism and function of heat shock proteins are well established, the function and regulation of the cold shock proteins are less well understood. Both, heat and cold shock proteins are molecular chaperones that play an important role in the maintenance of correctly folded proteins. As cancer cells are under continuous stress, certain heat shock proteins are up-regulated to maintain cell viability, drive cancer cell differentiation & cell proliferation, prevent cell death and facilitate metastasis [3]. Zeng et al. (2009) found that the down-regulation of cold shock proteins such as cold inducible RNA binding protein (CIRBP) and RNA binding motif protein 3 (RBM3) with or without temperature treatment increases cell death and susceptibility to cancer drugs in prostate cancer cells [4].

Environmentally caused cell stress for example in form of hypo- and hyperthermia can burden the cells metabolism so much, that the cell death pathway is initiated. As cancer cells are already under a high level of stress, they should be more susceptible to temperature than normal cells, however some cancer cells like A549 (human lung adenocarcinoma) are thermo-tolerant [5]. The reason for different responses to temperature is not clear.

Osteosarcoma, a relatively uncommon malignancy, is a mesenchymal tumor of the bone with an incidence of 0.03–0.2 per 100,000 per year [6]. With this, it is the most common primary malignant bone tumor, which mainly arises from the metaphysis of the long bones of adolescents and young adults [6,7]. Osteosarcoma has a high resistance to chemo- and radiotherapy. Furthermore, it has been demonstrated that osteosarcomas are resistant to anoikis [8], a form of cell death that occurs when the cell looses its adhesion and contact with neighboring cells or the extracellular matrix for example during hyperthermia treatment.

Trieb et al. (2007) reported a significant reduction in cell growth of osteosarcoma cells after a heat shock treatment at 42°C [9]. Rong and Mack (2000) reported that hyperthermia induced apoptotic changes in Dunn osteosarcoma cells [10]. Furthermore, Kanamori et al. (2003)