Abstract

Hyperthermia (HT), a term used in general for temperatures higher than 42°C, induces cell stress response in dependence on its intensity, heating duration and target cell type (this is called a thermal dose). *In vitro*, HT causes changes in Ca^{2+} homeostasis as a consequence of endoplasmic reticulum stress and permeabilisation of the outer mitochondrial membrane. The release of cytochrom c further leads to activation of caspases that can result in cell death.

In parallel, the presence of denatured proteins in the cell cytosol leads to the development of the so called unfolded protein response (UPR). UPR is characterized by increased expression and activation of molecular chaperones, increase in the intensity of proteosomal degradation and enhancement in autophagy. This process is accompanied by the attenuation of translation machinery, iniciation of DNA repair and activation of cytoprotective mechanisms leading to cell survival. This highly complex stress response mechanism is regulated mainly by the signalling pathways in the PI3K/Akt/mTOR axis. Cell survival is in the end fully dependent on the amount of energetic substrates, denatured proteins accumulation and on the level of irreversibly demaged DNA. If the termal dose is too high, the cell will ultimatively die.

Hyperthermia is also one of the approved approaches in the therapy of some types of cancer. To further enhance the anti-tumor effect, hyperthermia is combined to administration of small molecule based inhibitors of the aforementioned PI3K/Akt/mTOR signalling pathways. However, nor in combination to hyperthermia, nor when administered alone, using these inhibitors lead to the expected therapeutic effects so far. This is probably caused by the increased basal levels of PI3K in many tumor tissues which then causes the inability to reach the effective therapeutic dose without causing toxicity to the healthy tissue. Together with the other non-neglegible differences between individual patients, these observations are the most important reasons for the loss of success in the therapy of cancer based on the inhibition of PI3K.

Based of the results reached in this diploma thesis, it was shown that partial inhibition of the PI3K activity and its downstream effector molecules leads under specific conditions to the increased survival rate of some of the tumor cell lines treated with HT. Insufficient inhibition then leads to the activation of cytoprotective mechanisms regulated by the molecule of the natural PI3K inhibitor (PTEN, Phosphatase- tensin homologue on the chromosome 10).

The inhibition of the PI3K/Akt/mTOR signalling remains however one of the approaches with a significant potential in the therapy of cancer and further understanding the molecular basis of its regulation is therefore of an essential meaning.