Identification of novel tumor associated proteins affecting cell death

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PhD thesis

Medical University of Pécs
Department of Biochemistry
and Medical Chemistry

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Introduction

Tumor associated proteins are investigated worldwide to obtain a better understanding of the behavior of tumor growth and development or even of tumor therapy. Several proteins have been studied by our team in the last few years such as Heme Binding Protein 2 / SOUL or Heat Shock Protein 16.2 (HSP16.2). In this study the effect of these proteins on cell death is described.

Heme and porphyrines have high chemical reactivity and are poorly soluble in aqueous solutions. They are known to be good catalysts of the formation of activated oxygen species actively promoting free radical reactions leading to damages to biological molecules. Heme and the intermediates of heme synthesis have to be bound by cytosolic heme-binding proteins to avoid the formation of large aggregates in aqueous solutions such as the cytosol. Recently a number of heme-binding and heme-transport proteins have been described that bind heme and porphyrines in sub micromolar concentrations. Heme-binding protein 1 (HBP22) is a ubiquitously expressed protein having high affinity for heme and protoporphyrine. More recently, heme-binding protein 2 (SOUL) was identified. SOUL is expressed just in some specific tissues, has more than 40% sequence homology with HBP22, and has much higher binding affinity for porphyrines than HBP22 does having Kd in the nM range. Although its chemical and heme-binding properties were described, almost no information is available on its physiological function.

Role of heme-containing proteins in the regulation of cell death and survival are well characterized. They can affect formation of reactive oxygen species hence induction of direct oxidative damages as well as induction of mitochondrial permeability transition (mPT). MPT was strongly implicated in both apoptotic and necrotic cell death. Various stimuli,

including elevated intracellular Ca^{2+} concentration, induce the opening of a megachannel in the inner mitochondrial membrane leading to equilibration of the ions within the intermembrane space (and thus the cytosol) and the mitochondrial matrix, dissipation of the mitochondrial membrane potential ($\Delta\psi$) and uncoupling of the respiratory chain. Numerous agents, including CsA can prevent the opening of the PTP. Dissipation of $\Delta\psi$ induces the release of mitochondrial proteins like cytochrome c resulting in activation of the caspase-cascade, and ultimately in apoptotic cell death. The volume disregulation following the opening of the PTP causes swelling of the matrix, leading to membrane disruption and finally necrotic cell death.

Searching NCBI database, we noticed homology between the amino acid sequences of LOC51668 and alphaB-crystallin. Since small heat shock proteins, which interact with various components of the programmed cell death machinery upstream and downstream of the mitochondrial apoptotic events[4,5] are homologous to alphaB-crystallin[1,2], it raised the possibility that LOC51668 may have a physiological role similar to that of small heat shock proteins. To indicate this putative physiological role, we used the name small heat shock protein 16.2 (Hsp16.2) for LOC51668 further on.

Unlike heme-containing proteins, effects of heme-binding proteins on the processes involved in cell survival and death are poorly characterized. For this reason, we studied the effect of SOUL on etoposide-induced, hydrogen-peroxide- or Taxol-induced cell death and compared it to HSP16.2. The effect of SOUL was also evaluated on several phenomena such as ROS formation or the mitochondrial permeability transition both in living cells and *in vitro* in isolated mitochondria.

Study objectives

1. Characterization of SOUL protein to detect it in different tissues, measure its expression, to detect homologies and to find its subcellular localization

2. Describe the effect of SOUL on cell death by measuring cell viability of SOUL or HSP16.2 overexpressing and control cells treated by different types of cell death inducing agents

3. Describe the effect of SOUL or HSP16.2 suppression by siRNA technique on cell death in overexpressing and control cells

4. Elucidate the effect of SOUL on ROS-production in SOUL overexpressing and control cells

5. Describe the effect of SOUL on the mitochondrial permeability transition and on the Mitochondrial Membrane Potential ($\Delta\psi$)

6. Prevention of SOUL-induced sensitization toward oxidative stress by cyclosporine A (CsA)

7. Analysis of both apoptotic and necrotic cell death induced by SOUL

General Conclusions

1. Multiple alignment of SOUL was done with its homologues and forms found in different species. The expression of SOUL was detected in a number of human tissues, and cell lines. It was found, that SOUL is not expressed ubiquitously an all tissue, but rather had differential expression. It was interesting to see, that e.g. normal pancreas tissues had little SOUL expression but in pancreas adenocarcinoma it was greatly elevated. According to this finding SOUL might have an importance in the development of pancreatic cancer. SOUL's subcellular localization was also detected with fluorescent microscope and with Western blot after fractionating cells endogenously producing high amount of SOUL. According to our results SOUL was found mostly in the cytoplasm, but it was also present in the mitochondrial fraction in a smaller quantity, which later proved to be very interesting.

2. Overexpressing a protein in a system can supply us information on the possible function of a protein. Effects of SOUL and HSP16.2 were examined in different conditions by treating cells with cell death inducing agents and detecting the living using MTT assay. Several types of drugs were selected to examine the effect of the two proteins. Hydrogen peroxide causes oxidative stress, Taxol affects the microtubule system, A23187 causes mainly necrosis, and Etoposide causes mostly apoptosis. In the presence of excess SOUL cells seemed to have decreased resistance against the above mentioned drugs in our experiment. This effect of SOUL was moderate, although statistically significant and was detected with all kinds of drugs used. On the contrary, when examining HSP16.2

we found opposite results. HSP16.2 protected cells against cell death in our system. Thus, we found two previously uncharacterized proteins that affect cell death in different ways. In this manner we can state that both proteins have an effect on cell death.

3. Gene silencing became a widely used method for knocking out a specific protein to identify its function from indirect effects caused by the lack of this specific protein. When SOUL was silenced using specific dsiRNAs in cells endogenously expressing it significant resistance was observed against the cell death inducing agents as expected. In the case of HSP16.2 we also obtained the result we expected. Silenced with the method mentioned above the cells suffered a greater damage when they were exposed to those agents. The result of this and the previous thesis unequivocally confirms that, we found two previously uncharacterized proteins that affect cell death in different ways.

4. We hypothesized, that increased ROS formation caused by the presence of excess iron ions possibly bound by SOUL would be responsible for the excess cell death. To test this, the endogenous and induced production of reactive oxygen species was measured in both the aqueous and in lipid phase of cells overexpressing SOUL. We found no evidence that SOUL would influence the production of ROS *in vivo*, therefore we rejected our hypothesis. Now we had to look for a new mode of action.

5. The role of mitochondrial permeability transition in cell death is a well studied phenomenon. To find a possible mode of action for SOUL protein we investigated its effect on mitochondria *in vivo* and also *in vitro*. First we tracked the change of the mitochondrial membrane potential in SOUL-overexpressing NIH3T3 cells using fluorescent microscopy. We detected, that in cells overexpressing SOUL the mitochondrial membrane potential collapsed faster than in control cells. This result raised our interest and mitochondria were isolated from rat liver to detect direct effect of SOUL *in vitro*. Recombinant SOUL, when added alone, had no effect on mitochondria, but when added with sub-threshold concentrations of calcium, SOUL provoked mitochondrial permeability transition. This effect of SOUL was concentration dependent. At the same time intermembrane proapoptotic mitochondrial proteins such as cytochrome c, apoptosis inducing factor or endonuclease G were released to our reaction mixture in concentrations that were proportional to the concentration of SOUL. These data supports our view that SOUL mediates cell death primarily through the induction of mitochondrial permeability transition.

6. Cyclosporine A is a well known and widely used inhibitor of mitochondrial permeability transition. It binds to cyclophilin D in the mitochondrial permeability transition pore hindering its opening. Permeability transition provoked by SOUL could be inhibited by low concentrations of cyclosporine A *in vitro* and also *in vivo*. This points to the fact, that SOUL has specific effect on the mitochondrial permeability transition.

7. We proved that SOUL induces cell death by acting on mitochondria, and provokes mitochondrial permeability transition. Since mPT is involved in both the necrotic and in apoptotic cell death depending on the nature and severity of the stimulus, we were interested whether SOUL overexpression facilitates either of them. Cells were treated with different agent and were stained with propidium iodide and FITC-conjugated Annexin V to distinguish between the two types of cell death. Using flow cytometry it was shown that irrespective of the stimuli SOUL increases the ratio of necrotic cell death even to the detriment of apoptotic one.

Summary

The examined SOUL and HSP16.2 proteins are present in tumor cells, and in some they are overexpressed. Our investigation proved that both of these proteins have function in the process of cell death. We studied the effects caused by these proteins when they were overexpressed or silenced. Our experiments unequivocally confirmed that while the presence of excess SOUL increases cell death, HSP16.2 protects cells against it in our systems. The following part of the research was designed to further investigate the functions of SOUL protein. Since it was found that the presence of excess SOUL is a disadvantage for the cells, I tried to unravel how this protein affects cell death. Using multiple experimental procedures, it was demonstrated that SOUL, although able to bind the highly reactive heme, it doesn't raise the production of endogenous reactive oxygen species. The additional experiments were aimed at the mitochondrion, since this tiny component of the cell has great role in the process of cell death. By means of in vivo and in vitro experiments it was proved that in the presence of SOUL protein the mitochondrial permeability transition is more easily provoked and that this effect can be inhibited with cyclosporine A, hence this effect of SOUL is specific. Keeping in mind, that the mitochondrion can have a role in both the apoptotic and necrotic cell death, the last experiment in this study was planned to decide which type is involved in the death of SOUL-overexpressing cells. Using flow cytometry it was shown that irrespective of the stimuli SOUL increased the ratio of necrotic cell death even to the detriment of apoptotic one. In conclusion SOUL and HSP16.2 exerts their effect on cell death in a different way, and SOUL, although unable to induce cell death by itself, sensitizes cells to necrotic cell death by promoting mitochondrial permeability transition under stress conditions.

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Új, sejthalált befolyásoló tumor-asszociált fehérjék azonosítása

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PhD tézis

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