This work has focused on study of processes involved in apoptosis induction by various stimuli in cancer cells. In our case we induced programmed cell death in cancer cells by iron deprivation, commercially available taxanes docetaxel (Taxotere®) and paclitaxel (Taxol®) and application of novel porphyrins derivates P(β-CD)l and P(β-CD)2.

From presented publications we can conclude:

Studies dealing with iron deprivation clearly demonstrated participation different signal pathways which lead to apoptosis induction in mouse and human cancer cell lines. We used for study of apoptosis induction B lymphom cell line sensitive to iron deprivation in both mouse and human experiment model.

In the case of sensitive mouse tumor cells (38C13), we have described a significant portion of the apoptotic pathway leading to apoptosis induction by iron deprivation. Iron deprivation in these cells leads to translocation of proapoptotic Bax protein from the cytosol to mitochondria which is succeeded by mitochondrial membrane potential disruption due to mitochondrial permeabilization, cytochrome c release from mitochondria, activation of caspase-9 and subsequent activation of caspase-3.

In the case of sensitive human tumor cells (Raji) we detected as well apoptosis induction by iron deprivation, however, in character of mechanism different from apoptosis induced in mouse tumor cells (38C13). In human Raji cells sensitive to apoptosis induction by iron deprivation happened only caspase-3 activation and but not caspase-9 activation and mitochondrial alternations. The way how caspase-3 is activated remained unknown.

Significant findings we gained by creation of Raji cell clone resistant to apoptosis induction by iron deprivation. Resistant Raji cells clone were derived from original Raji cells by subsequent adaptation to the medium with lower iron concentration in culture medium with the help of ferric citrate. Finally, Raji clone adapted for non-transferrin bound iron source of iron became resistant to the induction of cell death by iron deprivation. However, readaptation of this resistant Raji clone to transfer in iron (optimal source of iron) caused renovation of sensitivity of this clone to apoptosis induction by iron deprivation. This findings demonstrates that cell sensitivity to certain stimuli can be dependent on particular metabolic status of the cell.

Studies focused on the transporter of non-transferrin bound iron (NTBI) have led to the identification of HSP90 as an iron-binding protein. We also showed its association with the plasma membrane. However, the question whether HSP 90 is someway involved in non-transferrin bound iron transport requires further studies.

Studies concerning apoptosis induction by taxanes were based on comparison of the cell line highly susceptible to taxanes (MDA-MB-435) and a cell line highly resistant to taxanes (NCI-ADR-RES). The efficient concentration of taxanes which induced cell death was 300-fold higher in resistant cell line in comparison with sensitive cell line.

Cell death induced by the taxanes in both sensitive and resistant cells was preceded by the accumulation of cells in the G2/M phase what is typical effect of taxanes on cell cycle. In both cell line p53 and p21 levels did not change so it seems that cell death is independent on p53 activation. Next, both MDA-MB-435 and NCI-ADR-RES did not produced any oligonucleosomal DNA fragmentation even if caspase-3 was activated. Both tested cell line activates caspase-9 after application of effective concentration of taxanes, nevertheless only in resistant NCI-ADR-RES cell line occurred cytochrome c release from mitochondria required for caspase-9 activation via apoptosome. This results demonstrated different mechanisms of cell death induction by taxanes in both cell line and therefore requires further study.

In the study focus on PDT we investigated the photosensitizing properties of two novel mono- and bis-cyclodextrin tetrakis (pentafluorophenyl) porphyrin derivatives for their employing in photodynamic therapy. Both derivates were tested in several tumor cell lines and in BALBk mice bearing subcutaneously transplanted syngeneic mouse mammary carcinoma 4T1. Both studied sensitizers P(β-CD)1 and P(β-CD)1 were localized mainly in lysosomes, however, the final effect on tumor cell was a little bit different. In vitro experiments P(β-CD)1 proved such better properties than P(β-CD)2 like lower light doses, lower effective concentration and faster kinetics of sensitizer uptake by tumor cell. However, in vivo experiments, P(β-CD)2 exhibited complete elimination of tumour with no detectable relapse of primary tumor. Moreover, P(β-CD)2 exhibited favorable accumulation ratio in skin and tumor. In contrast, irradiation of P(β-CD)l treated mice never resulted in complete regression of tumor, moreover, there was fast unfavorable accumulation of P(β-CD)l in the skin.

Therefore we suggest that P(β-CD)2 derivate showed due to its photosensitive properties, rapid distribution throughout the body and preferable early localization in tumors, an early elimination of the drug from the body and low systematic toxicity as suitable drug for in vivo PDT application.