Summary of Ph.D. Thesis

Quantitative and functional analysis of MDR1/P-glycoprotein from human tumors

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Summary

In our experiments we detected the presence and measured the function of the P-glycoprotein (Pgp) using fluorescence and isotope techniques.

We showed for the first time in clinical samples that the Pgp is present in different extent in the ascites cells of patients with ovarian cancer. The percentage of Pgp positive cells in the ascites of patients treated with chemotherapy was between 10-79%. The expression of the Pgp pump was proved by indirect immunofluorescent method while the function of the pump by the detection of the accumulation of rhodamine 123 (R123) fluorescence dye in the cells. We found strong correlation between the rate of expression and the function of the protein.

We observed higher ^{18}FDG PET radiotracer accumulation in the Pgp positive (Pgp^+) human adenocarcinoma-derived ovarian cell line A2780AD than its Pgp negative (Pgp^-) counterpart A2780. Paclitaxel treatment further enhanced the difference in ^{18}FDG accumulation but did not influence the accumulation of the ^{11}C-choline tumor-diagnostic PET radiotracer. The accumulation of the ^{99m}Tc-MIBI Pgp substrate SPECT radiotracer was significantly lower in the A2780AD Pgp^+ cells than in their Pgp^- counterparts. Paclitaxel treatment influenced the accumulation of ^{99m}Tc-MIBI on Pgp dependent and Pgp independent way. Based on our observations we may draw the conclusion that paclitaxel treatment influences the accumulation of the tumor-diagnostic tracers in different ways in Pgp^+ positive and negative cells which should be taken into consideration upon coming to correct diagnostic decision.

We carried out detailed analyses of the same set of data using three different methods to quantitate the ^{18}FDG accumulation in different regions of the human brain. Using correlation analyses we proved, that the simplifying methods such as the SUV and Patlak methods can only be used in certain regions of the brain with good correlation to the general Phelps method. We also proved that both of the simplifying methods lead to distortion in the same regions of the brain. A possible reason of the distortion is that the simplifying methods do not take into consideration the degree of dephosphorilation of FDG-6P and the virtual appearance of the drug which can be relatively high in the vicinity of the vascular compartments.