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***In vitro* and *in vivo* profiling of P-glycoprotein in human neuroblastoma and rhabdomyosarcoma cells under simvastatin exposure**

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Background

Drug efflux via ATP-binding cassette (ABC) transporters is one of the main causes for chemoresistance of tumours. P-glycoprotein (ABCB1) is the main representative of these efflux pumps, which needs full glycosylation for proper function. We could previously show that statins have a double impact on P-glycoprotein [1]. Firstly, statins inhibit P-glycoprotein which results in higher intracellular accumulation of chemotherapeutics like doxorubicin. This could be shown in human neuroblastoma and rhabdomyosarcoma cells. Secondly, statins reduce the glycosylation level of P-glycoprotein and thereby also lead to reduced efflux of anthracyclines, which results again in enhanced apoptosis via the mitochondrial pathway. The question arises if these effects are also seen *in vivo* and in other tumour cells.

Methods and results

In a mouse xenograft model, the liver and rhabdomyosarcoma were analysed for P-glycoprotein levels in the absence and presence of simvastatin. On protein level P-glycoprotein was significantly down-regulated in the presence of pharmacological doses of simvastatin. Preliminary data confirm compensatory elevation of mRNA for P-glycoprotein by real time PCR. On cellular level the compensation of mRNA induction of P-glycoprotein is seen only after long-time simvastatin exposure of more than 24 hours. Other ABC-transporters are present in neuroblastoma and rhabdomyosarcoma cells and are currently under investigation, most importantly MRP1 (ABCC1), which allows also doxorubicin export.

Conclusions

Taken together, these data show that pharmacological doses of simvastatin are sufficient to down regulate P-glycoprotein in normal and tumour tissue *in vivo*. Thus, inhibition and down-regulation of an ABC transporter by simvastatin represents a novel mechanism of action which clearly has clinical implications for cancer therapy.

Reference

1. Sieczkowski E, Ambros P, Lehner C, Hohenegger M: **Double impact on P-glycoprotein by statins enhances doxorubicin cytotoxicity in human neuroblastoma cells.** *Int J Cancer*, in press.