

MEETING ABSTRACT

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Long-term regulation of ATP-binding cassette transporters on mRNA and protein level by simvastatin in human rhabdomyosarcoma and neuroblastoma cells

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Background

Resistance against chemotherapeutics is still a major problem in cancer therapy. One of the mechanisms of multidrug resistance is up-regulation of ATP-binding cassette (ABC) transporters. HMG-CoA reductase inhibitors have been shown to directly inhibit the main representative, ABCB1 (P-glycoprotein). We have previously shown in rhabdomyosarcoma (RD) and neuroblastoma (SH-SY5Y) cells that simvastatin enhanced the intrinsic apoptotic potential of the anthracycline doxorubicin [1,2]. The aim of the study presented here is to investigate the long-term effect of simvastatin on the expression of ABC-transporters in order to evaluate an adjuvant therapeutic potential of statins in chemotherapy.

Methods

FACS analysis was performed to quantify the accumulation of doxorubicin in RD cells in combinations with simvastatin or verapamil. Several ABC transporters were analysed on mRNA and protein level using real-time PCR and Western blotting in human RD and SH-SY5Y cells. The endogenous level of ABC transporters was also investigated from the livers of simvastatin treated mice.

Results

Here we show that simvastatin led to enhanced accumulation of doxorubicin in RD cells. This was comparable to the effect which was observed for the

coadministration of verapamil, a first generation ABCB1 inhibitor, with doxorubicin. ABCB1 was monitored by Western blot analysis of RD and SH-SY5Y cells upon continuous application of simvastatin. In a time and concentration-dependent manner the ABCB1 transporter was less expressed in both cell lines. Interestingly, real-time PCRs revealed a compensatory elevation of mRNAs for various ABC transporters (ABCB1, ABCC1, ABCC6 and ABCG2). Moreover, the augmented mRNA levels of ABCB1 do not result in more transporters on protein level. *In vivo*, the down-regulation of ABCB1 was confirmed in the liver of simvastatin-treated mice.

Conclusions

Based on our findings, we conclude that simvastatin is able to directly inhibit ABC transporters immediately, but also leads to a long-term down-regulation of various transporters. This feature makes simvastatin a promising candidate for adjuvant chemotherapy to impair transporter-mediated multidrug resistance.

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