Abstract

Resistance to chemotherapeutics is a widespread phenomenon in cancer cells that may counteract the successful therapy of many patients. In resistant cells, higher level of ABC transporters, among others, often can be detected. This high level of ABC transporters represents a suspected mechanism of acquired cancer resistance. We studied the molecular mechanism of resistance to taxanes in cancer cells using SK-BR-3 and MCF-7 breast cancer cell lines. We analyzed the effect of paclitaxel on apoptosis induction in the originally sensitive cells of these lines as compared to their counterpart resistant cells, developed by gradual adaptation to paclitaxel. In resistant cells of the SK-BR-3 and MCF-7 lines, we did not detected ongoing induction of apoptosis but we did detect significantly increased expression of ABCB1 transporter after paclitaxel application. By silencing the expression of the transport via employment of small interfering RNA (siRNA), we tested the role of the ABCB1 transporter in cells resistant to paclitaxel. We found that resistant cells with silenced expression of the ABCB1 transporter had a statistically significant increase of sensitivity to paclitaxel as compared to control resistant cells with high expression of this transporter. Along with increased sensitivity, we demonstrated that cells resistant to paclitaxel are also partially resistant to doxorubicin. Furthermore, we assessed the persistence of the resistance to paclitaxel in the resistant cells after reverse adaptation to a medium without paclitaxel. After reverse adaptation, cells incubated without paclitaxel exerted nearly the same resistance to paclitaxel and the expression of ABCB1 transporter as resistant cells. Based on our data, we suggest that acquired resistance to paclitaxel is of a persistent character and the increased efflux of paclitaxel resulting from the induction of ABCB1 transporter expression represents a mechanism that is significantly involved in drug resistence of studied breast cancer cells. Given that cell sensitivity of resistant cells after the silencing of ABCB1 transporter expression is only partial, we can assume that there may be more combined mechanisms of the resistance at play.

Key words: SK-BR-3, MCF-7, breast cancer cells, paclitaxel, ABCB1 transporter, cancer resistence