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Expression and functional characterization of multidrug resistance transporters in malignant thymomas and thymic carcinomas

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Thymomas and thymic carcinomas are the most common primary mediastinal tumors of the adult. Despite relatively long overall survival and good response rates, a high percentage of thymic tumors, especially in advanced stages, is either not responding or responding insufficiently to cisplatin-based chemotherapy. The responsible mechanisms for treatment failure in thymomas and thymic carcinomas have not yet been fully revealed.

In the first part of this thesis, I used RT-qPCR and Western blot to analyze the expression of 5 ABC transporters, MRP1, MRP2, MRP3, BCRP and PGP, in 46 cases, including thymomas, thymic carcinomas and healthy thymic tissue. In the second part, I induced resistance against cisplatin and etoposide in the human thymic carcinoma cell line 1889c. RT-qPCR, Western blot and confocal microscopy were used to analyze the ABC transporter expression in parental and resistant cell lines. Function of MRP1 and PGP was investigated by efflux assays. A microarray analysis of all three cell lines was performed in the third part of the thesis, since in addition to ABC transporters other factors may play a role in acquiring resistance against the applied cytostatics.

Of the 5 analyzed ABC transporters, MRP1 and PGP appear to be relevant for multidrug resistance in thymoma and thymic carcinoma patients. I think that ABC transporter analysis in selected therapy-refractory patients, as part of a more personalized diagnostic strategy, might help to improve treatment and subsequently survival. In this respect, it appears worthwhile to analyze at least MRP1, PGP and BCRP, since I here demonstrated for the first time that BCRP is also associated with chemotherapy resistance in thymic carcinoma. A broad variety of genes was found to be enriched in the cisplatin- and etoposide-resistant thymic carcinoma cell lines. Future analyses need to identify druggable, clinically relevant targets and prove their role in thymomas and thymic carcinomas.