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TARGETING THE MULTIDRUG TRANSPORTER PATCHED POTENTIATES CHEMOTHERAPY EFFICIENCY *IN VITRO* AND *IN VIVO*

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One of the crucial challenges in the clinical management of cancer is the resistance to chemotherapeutics. We recently demonstrated that the Hedgehog receptor Patched, which is overexpressed in many recurrent and metastatic cancers, is a multidrug transporter for chemotherapeutic agents such as doxorubicin. The present study provides evidences that Patched is expressed in adrenocortical carcinoma (ACC) patients, and is a major player of the doxorubicin efflux and the doxorubicin resistance in the human ACC cell line H295R. We discovered a drug-like molecule which inhibits the doxorubicin efflux activity of Patched, enhances the cytotoxic, pro-apoptotic, antiproliferative and anticlonogenic effects of doxorubicin on ACC cells which endogenously overexpress Patched, and thereby mitigates the resistance of these cancer cells to doxorubicin. Moreover, we report that in mice the combination of this molecule with doxorubicin prevents the development of xenografted ACC tumors more efficiently than doxorubicin alone by enhancing the accumulation of doxorubicin specifically in tumors without obvious undesirable side effect. Our results suggest that the use of an inhibitor of Patched drug efflux in combination with doxorubicin could be a promising therapeutic option for adrenocortical carcinoma, and most likely also for other Patched-expressing cancers.

BIOGRAPHY

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