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The transport activity of Patched and its role in chemotherapy resistance

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The Hedgehog receptor Patched regulates Hedgehog signaling by transporting cholesterol. Hedgehog signaling is aberrantly activated and Patched is overexpressed in many recurrent and metastatic cancers. We showed that Patched pumps chemotherapeutic agents such as doxorubicin out of cancer cells using the proton motive force and contributes to chemotherapy resistance of several cancer cell types, and that cells overexpressing Patched at their plasma membrane have persistent (or cancer stem cell) properties.
We identified small molecules which inhibit the doxorubicin efflux activity of Patched and enhance its cytotoxicity on adrenocortical carcinoma and melanoma cells that endogenously overexpress Patched, and thereby mitigates the resistance of these cancer cells to doxorubicin. We also showed that these Patched drug efflux inhibitors enhance the efficacy of kinase inhibitors such as vemurafenib against melanoma cells resistant to the treatment in cellulo and in vivo on xenografts in mice.
Our data suggest that the use of inhibitors of Patched drug efflux in combination with chemotherapy could be a promising therapeutic option to improve chemotherapy efficiency against cancer cells expressing Patched.
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Session

Molecular interactions at the membrane surface

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