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Targeting overexpressed ABC transporters of multidrug-resistant cancer cells with drug-efflux inhibitors and apoptosis inducers

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Three types of overexpressed ATP-binding cassette (ABC) transporters are strongly involved in tumor resistance to anticancer drugs by pumping out chemotherapeutics: Pglycoprotein/ABCB1, breast cancer resistance protein/ABCG2 and multidrug resistance protein/ABCC1. For ABCB1, third-generation inhibitors are under clinical development. For more recently discovered ABCG2, screening of flavonoids and derivatives, as inhibitors of mitoxantrone efflux from transfected HEK293 human cells and as chemosensitizers of cell proliferation, allowed us to establish 3D-Quantitative Structure-Activity Relationships. The molecular model built for ABCG2-specific inhibitors, which are non-competitive, was different from those previously reported for ABCB1, whereas both polyspecific transporters display strongly-overlapping spectra for transported drug substrates. ABCG2 also appeared polyspecific for inhibitors, with at least three types of inhibitory sites being identified with distinct effects on ATPase activity. The most potent inhibitor, which was active *in vitro* at submicromolar concentration, was indeed efficient *in vivo* on *SCID* mice, xenografted with human ABCG2-transfected cells, by chemosensitizing tumor growth to the ABCG2 substrateirinotecan. These flavonoidic inhibitors therefore constitute good drug candidates, with low intrinsic toxicity, as sensitizers of cell proliferation to conventional chemotherapeutics. On the basis that ABCC1 may catalyze the efflux of either glutathione conjugates or free glutathione together with hydrophobic drugs such as vincristine, we identified verapamil derivatives able to induce a fast and massive efflux of intracellular glutathione from ABCC1-overexpressing cells; this led to selective cell death through apoptosis, characteristic of collateral sensitivity. Since verapamil is known for its cadiotoxic effects, we investigated other types of compounds and identified xanthones and flavones, as well as flavonoid dimers with an even higher efficiency. Despite glutathione efflux was necessay to trigger apoptosis, it was found not to be sufficient alone indicating that other partner(s) or signaling pathway(s) might be also involved. Such apoptosis inducers might constitute a new type of anticancer drugs operating through an original strategy aimed at selectively targeting and eliminating multidrug-resistant tumors overexpressing the ABCC1 transporter.

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