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Selective modulators of resistant cancer cells overexpressing ABC transporters: Drug-efflux inhibitors and apoptosis inducers

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Multidrug ABC ("ATP-binding cassette") transporters are involved, upon overexpression, in chemoresistant tumors by pumping anticancer drugs out of the cells. For early discovered ABCB1/"Pglycoprotein", third-generation drug-efflux inhibitors are under clinical development. For more recently identified ABCG2/"breast cancer resistance protein", we have screened different series of flavonoids and derivatives, such as flavones, rotenoids and acridones, and more recently chalcones and chromones, as inhibitors of mitoxantrone efflux from transfected HEK293 human cells and as chemosensitizers of cell proliferation, to establish 3D-Quantitative Structure-Activity Relationships. Two types of selective, non-competitive, inhibitors have been characterized, either inhibiting or stimulating the basal ATPase activity. The most potent inhibitoris indeed efficient *in vivo* on *SCID* mice, xenografted with human ABCG2-transfected cells, by chemosensitizing tumor growth to the drug-substrate irinotecan. These selective inhibitors constitute good drug candidates, with low intrinsic toxicity, as sensitizers of cell proliferation to conventional chemotherapeutics. The "Multidrug Resistance Protein 1" ABCC1 is able to catalyze the efflux of either glutathione conjugates or free glutathione together with hydrophobic substrate drugs. We have identified modulators such as verapamil mimicking substrates and inducing a fast and massive efflux of intracellular glutathione from ABCC1-overexpressing cells, leading to a selective cell death through apoptosis, due to "collateral sensitivity", or hypersensitivity. The overexpressed transporter then constitutes the Achilles' heel of such resistant cancer cells. Since verapamil is known for its cadiotoxic effects, we investigated other types of modulators such as xanthones, flavones and flavonoid dimers. Glutathione efflux appeared to be necessary, but not sufficient alone, to trigger apoptosis, indicating the contribution of other partner(s) or signaling pathway(s). Such apoptosis inducers may 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.

Biograpy

Attilio Di Pietro is heading a group entitled "Drug resistance mechanism and modulation" at the Institute of Protein Biology and Chemistry (IBCP) of Lyon, supported by the National Center for Scientific Research (CNRS) and the University of Lyon. He got a Doctorat d'Etat ès-Sciences from the University of Lyon, at Villeurbanne in 1981, on mitochondrial bioenergetics, and spent a Post-doctoral training with Prof. André Goffeau at the University of Louvain-La-Neuve, Belgium, in 1982-83 on yeast plasma membrane transporters. He became independent in 1992 in studying membrane ATP-binding cassette (ABC) transporters involved in multidrug resistance, especially in cancercells. He chaired a Gordon Research Conference on "Multidrug Efflux Systems" in Oxford, UK, in August 2005, and is organizing the annual French-Belgian meeting on ABC transporters since 2006. He has published around 140 papers in international journals, and deposited several patents. He has given around 70 invited talks to international meetings in the fields of drug discovery and mechanism of cancer cell multidrug resistance. In 2009, his group got Certification by the French National League against Cancer.

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