

The Clonal Basis of Development

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The Clonal Basis Of Development

James F. Zachary, M. Donald McGavin



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Multidrug Resistance in Cancer: Pharmacological Strategies from Basic Research to Clinical Issues Stefania Nobili, Enrico Mini, Chiara Riganti, 2015-07-06 More than 40 years ago the observation that doxorubicin resistant tumor cells were cross resistant to several structurally different anticancer agents was the first step in the discovery of P glycoprotein P gp P gp belongs to the superfamily of ATP binding cassette ABC transporters its overexpression has become a therapeutic target for overcoming multidrug resistance in tumors However P gp is also expressed in cells of normal tissues where it plays a physiological role by protecting them from the toxic effects of xenobiotics Also ABCB1 gene polymorphisms may influence the response to anticancer drugs substrate of P gp Several strategies to overcome P gp tumor drug resistance have been suggested P gp circumvention is the most explored and is based on the coadministration of anticancer agents and pump inhibitors P gp modulators Despite the positive findings obtained in preclinical studies results of clinical trials are not yet successful and clinical research is still ongoing Other investigational approaches have been studied e g P gp targeting antibodies use of antisense strategies or transcriptional regulators targeting ABCB1 gene expression but their use is still circumscribed to the preclinical setting A further approach is represented by the encapsulation of P gp substrate anticancer drugs into liposomes or nanoparticles This strategy has shown higher efficacy in tumor previously treated with the free drug

The reasons explaining the increased efficacy of liposomal nanoparticle based drugs in Pgp overexpressing tumors include the coating with specific surfactants the composition changes in the plasma membrane microdomains where P gp is embedded the direct impairment of P gp catalytic mechanisms exerted by specific component of the liposomal shell but are not yet fully understood A second strategy to overcome P gp tumor drug resistance is represented by exploiting the P gp presence Actually P gp overexpressing cells show increased sensitivity collateral sensitivity to some drugs e g verapamil narcotic analgesics and to some investigational compounds e g NSC73306 P gp overexpressing cell are hypersensitive to reactive oxygen species to agents perturbing the energetic metabolic pathways changing the membrane compositions reducing the efflux of endogenous toxic catabolites However the mechanisms explaining collateral sensitivity have not been fully elucidated Another approach to exploit P gp is represented by ABCB1 gene transfer to transform bone marrow progenitor cells into a drug resistant state which may allow conventional or higher doses of anticancer drug substrates of P gp to be administered safely after transplantation More recently the development and introduction in the clinics of anticancer drugs which are not substrates of P gp e g new microtubule modulators topoisomerase inhibitors has provided a new and promising strategy to overcome P gp tumor drug resistance P gp evasion This research topic issue aims at exploding the above mentioned matters in particular by retracing the history of the first researches on P gp describing the physiological role of P gp describing the molecular basis structural features and mechanism of action of P gp describing diagnostic laboratory methods useful to determine the expression of P gp and its transporter function describing strategies to overcome tumor drug resistance due to P gp and other ABC transporters indicating novel approaches to overcome P gp multidrug resistance ranging from basic research studies to pre clinical clinical studies

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