Parallel Symposium No. 5

Molecular Basis of Drug Resistance

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PS 5.1

A ROLE FOR PLATINUM-DNA DAMAGE IN CISPLATIN RESISTANCE?
Anne Marie J. Fichtinger-Schepman.
The drug cisplatin is believed to express its antitumor activity through the formation of DNA adducts in the cells. In all (tumor) cells studied, the same spectrum of adducts has been found, but the platination levels are not always correlated with cell survival.
One of the major problems in cisplatin chemotherapy is the occurrence of acquired resistance of the tumor to cisplatin. For several drugs, resistance can be ascribed to a single cause, e.g. the activity of P-glycoprotein. However, no uniform explanation for the occurrence of cisplatin resistance has been found. Factors that may contribute to a reduced sensitivity to cisplatin are differences in uptake and/or efflux of the drug, changes in glutathione and metallothionein concentrations or DNA-repair capacities of cells, which may result in different DNA-platination levels. Also the involvement of e.g. oncogenes and protein kinases have been reported. In some cases the phenomenon of "tolerance" was introduced to explain resistance. The study of the nature of acquired cisplatin resistance is complicated by the fact that in vivo and in vitro acquired resistance seem to have different origins.

PS 5.2

P-glycoprotein mediated multidrug resistance.
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The simultaneous acquirance of resistance to unrelated compounds (MDR), has been related to the appearance of a membrane transport glycoprotein, the P-glycoprotein (PGP), sharing high similarities with a series of membrane carriers. PGP would act as an efflux pump, lowering availability of the drug for intracellular targets. It can be induced, simultaneously with MDR, by gene tranfection and it has been related to a series of genetic mutations. Phosphorilation has been described as an important mechanism for the functional control of the protein.
The existence of non-PGP-mediated MDR pointed the attention to the mechanisms involved in the regulation of PGP overexpression. Emergency of MDR phenomena is a multistep process in which the overexpression of the protein would be one of the last aspects. The models of the role and control mechanisms of PGP in MDR constructed sofar, represent guidelines for understanding mechanisms which cause the appearance of MDR phenotype in clinical reality.

PS 5.3

ALTERED DNA TOPOISOMERASE II IN MULTIDRUG RESISTANCE (MDR). WT Beck[1], MK Danks[1], JS Wolverton[1], M Chen[1], BY Bugg[1], DP Suttle[1], CV Catapano[2], and DJ Fernandes[2], [1]St. Jude Children's Research Hospital, Memphis, TN 38101, and [2]Bowman Gray School of Medicine, Winston-Salem, NC 27103.

One form of "natural product" MDR is associated with drugs that interact with DNA topoisomerase II (topo II); its characteristic feature is altered topo II (at-MDR). Our at-MDR human leukemic cells also exhibit altered nuclear matrix topo II, decreased topo II phosphorylation, and a single base mutation resulting in a change of Arg_{449} to Gln at a conserved position in an ATP-binding consensus site in topo II; we do not yet know whether this mutation confers at-MDR. Topo II has two forms: α (170 kd) and ß (180 kd). Topo ß is susceptible to proteolysis, but can be seen after treatment of CEM cells with VM-26 under conditions that promote DNA-protein complex formation, suggesting that the drug protects the DNA-bound enzymes from proteolytic degradation. Other data indicate that the predominant form of the enzyme bound to the DNA of the nuclear matrix is topo α, whereas that bound to the nonmatrix DNA is topo ß, suggesting that the enzymes have distinct cellular functions. Finally, we postulate that at-MDR may have clinical consequences. We are developing assays based on the at-MDR phenotype that may allow us to identify in clinical specimens those cells that express different forms of MDR. (Supported by grants CA-30103, CA-40570, CA-47941, and CORE grant CA-21765, all from NCI, Bethesda, MD, and by ALSAC).

PS 5.4

EXPRESSION OF MULTIDRUG RESISTANCE AFTER IN VITRO EXPOSURE TO FRACTIONATED X-IRRADIATION.
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Since clinical resistance develops after treatment not only with chemotherapy but also after radiotherapy, we have argued that certain cellular and biochemical phenomena mediate the development of this resistance phenotype and these may differ depending on the 'selection' agent used. We have shown that exposure of mammalian tumour cells to fractionated X-irradiation in vitro results in the expression of resistance to a range of antitumour drugs including Vinca alkaloids, the epipodophyllotoxins, but not the anthracyclines. In a series of Chinese hamster ovary sublines this resistance is associated with increased levels of P-glycoprotein, which occurs despite a lack of significant alteration in P-glycoprotein mRNA levels, implicating altered control mechanisms from those operating in the classic drug-selected multidrug resistant cells. Certain similarly-derived human tumour sublines also proved resistant to cisplatin and showed an increased capacity to repair drug-induced DNA damage. These data provide the first evidence that exposure to X-irradiation can result in cell membrane changes and altered DNA damage repair capacity.