BLY RECENT ADVANCES WITH IMMUNOTOXINS

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Antibodies with precisely defined specificities, derived from the hybridoma technology, are used as carriers of enzymatically active natural toxins. Both moieties are chemically linked, with integrity of each biological component. Large-scale production by improved methods allows the clinical application in the treatment of malignant disorders. In the laboratory, in vitro and in vivo studies have established the following facts: a) the antibody class as well as the toxin type, influence immunotoxin activity; b) a disulphide link is needed for efficient cell killing; c) improved cytotoxicity can be obtained by addition of lysosomotropic amines (i.e. NH_4Cl) or carboxylic ionophores (i.e. Monensin), leading to the elimination of the last out of 10^6 cells in a clonogenic assay; d) this improved cytotoxicity appears to be due to accelerated cell killing kinetics; e) the type of antigen receptor and its density on the cell surface play an important role. Clinical trials for toxicity and efficacy in purging autologous and allogeneic bone marrow before transplantation are currently under way.

BOE ENZYMATIC METHYLATION OF DNA CYTOSINES IN CHEMICAL CARCINOGENESIS

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Previous experiments from our laboratory have suggested that a number of chemical carcinogens alter the extent of enzymatic methylation of DNA cytosines. Recently, we have studied the neoplastic conversion of mouse C3H 10T1/2 fibroblasts. After treatment with MNU and BPDE, individual foci were scored for tumour formation in nude mice. DNAs isolated from the resulting tumours and the parental cell lines were assayed for DNA methylation patterns in individual genes. The results indicate a considerable heterogeneity among tumours induced by the same carcinogen and a tendency for hypomethylation of DNA in tumours. We have also analysed the c-ras-Ki-1 locus in human melanoma cell lines. Although no gross structural alterations were present, we found variable methylation patterns with no obvious correlation to the expression of this gene. These results exemplify our previous hypothesis (J.Nat.Cancer Inst. 71, 429, 1983) that an altered process of enzymatic methylation of DNA cytosines may be involved in the initiation of chemical carcinogenesis and suggest further that the induction of cellular heterogeneity with respect to DNA methylation patterns may provide the basis upon which selection may operate in the progression of initiated cells.
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BRA CORRELATION OF ANTITUMOUR PROPERTIES OF PLATINUM COMPOUNDS WITH THEIR REACTIVITY TOWARDS DNA: AN ELECTROCHEMICAL STUDY

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Conformational changes in double-helical calf-thymus DNA induced by various types of platinum compounds were studied by means of differential pulse polarography. The investigations were performed at relatively low level of platinum binding (1 Pt atom fixed per 100 nucleotide residues). It was found that the binding of platinum compounds having antitumour activity induced changes in polarographic behaviour of DNA that corresponded to the origin of premelted regions in DNA molecules. On the other hand, attack by inactive platinum compounds induced changes in DNA behaviour indicating the formation of single-stranded denatured regions in DNA molecules. The results of electro-chemical investigations were confirmed by measurement of circular dichroism spectra.
