REPAIR OF CHEMICAL DAMAGE IN MAMMALIAN CELLS

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INTRODUCTION

The repair of chemical damage to DNA differs in many ways from the repair of radiation damage and its interpretation is often more complicated. For example, most chemicals of environmental concern do not react directly with cellular macromolecules but must first be activated to nucleophiles [1]. Hence the dosimetry of chemicals is complicated and may vary markedly from tissue to tissue, organelle to organelle [2] or from linker to the core region of DNA [3]. The different reactivities between agents reacting directly and those that react indirectly may give rise to products whose yields as a function of dose are completely different even though the products themselves may be the same. Thus Fig. 1 [4] shows a way of estimating chemical doses in vivo from alkylating agents in terms of the level of specific alkylation of hemoglobin. The direct acting agent methylmethanesulfonate (MMS) yields a linear response curve but alkylation from dimethylnitrosamine (DMN), which needs activation, shows a much lower response and the response increases as some higher power of injected dose measured in mg/kg body weight. On the other hand the development of immunological probes for specific DNA damages offers the possibility of measuring such damages at levels of fmoles [5, 6].

Although one can make a strong argument that damages to DNA are initiating events in carcinogenesis [7, 8] many other factors are important in the carcinogenic process and there is not necessarily a one to one relationship between mutation (damage to DNA) and neoplastic transformation. Moreover because of the multitude of products resulting from chemical treatment it is not easy to decide
Fig. 1. Dose response curves for the appearance of methylcysteine in the hemoglobin of rats injected either with a direct acting agent MMS or an alkylating agent that first needs activation, DMN. Note at zero dose the existence of a high background of methylcysteine, the origin of which is not understood (adapted from 4).

which product is important for a biological endpoint and, indeed, the most plentiful product is not necessarily the one to worry about. One product may be more associated with cell cytotoxicity and another with mutagenesis [9].

Nucleotide excision measurements of DNA repair are used extensively to detect agents that react with DNA and such measurements help identify DNA adducts that are dangerous [7, 8, 10-12]. A number of chemical agents mimic ultraviolet (UV) in the following ways [8, 13]. 1) Xeroderma pigmentosum (XP) cells are more sensitive to the cytotoxic effect of UV and to the chemical than are normal cells. 2) Chemically treated viruses show a higher survival on normal cells than on XP cells. 3) XP cells deficient in repair of UV damage are also deficient in the excision of chemical damage. 4) Excision repair of UV and of chemical damage involves long patches. 5) XP complementation groups observed for the repair of