PULSE-CARCINOGENESIS BY ETHYLNITROSOUREA IN THE DEVELOPING RAT NERVOUS SYSTEM: MOLECULAR AND CELLULAR MECHANISMS

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INTRODUCTION

The molecular and cellular mechanisms of malignant transformation and tumorigenesis can probably be best studied in so-called "pulse-carcinogenesis systems", i.e., in systems where, after a single dose of a short-lived carcinogen sufficient to produce a high tumorigenic effect, the process proceeds autonomously without the complication of continued interaction of the target cell population(s) with the carcinogen. In such systems one can operationally separate the process of carcinogenesis into three phase (A,B,C): Phase A, period of carcinogen interaction with target cells; phase B, time interval between phase A and phase C; and phase C, period beginning with the onset of (clonal) proliferation of tumorigenic cells. More or less synonymous terms are "initiation" for phase A and "expression" (of malignant phenotypes) for phase B. In spite of its obvious importance, least is presently known about phase B which often constitutes the longest of the three phases. Phase B appears to encompass a sequence of phenotypic changes (including acquisition of the capacity for continuous proliferation) in the cells which ultimately become tumorigenic and represents the period during which, for instance, tumor promoters can exert their pleiotropic effects, i.e., modify gene expression and induce cell proliferation in the target cell population.

Structural alterations of DNA in the chromatin of target cells are primary events in the multi-step process of malignant transformation and tumorigenesis by most chemical carcinogens. In general, covalent binding occurs between nucleophilic centers (electron-rich N and O atoms) in cellular DNA.
and highly reactive, electrophilic derivatives (ultimate carcinogens) generated from the respective parent compounds (pre-carcinogens) either by enzyme-catalyzed "metabolic activation" or via non-enzymatic decomposition.\textsuperscript{18,19} As a consequence of their reaction with DNA most chemical carcinogens are also mutagenic.\textsuperscript{20,21,22} However, the strong correlation of carcinogenicity and mutagenicity does not constitute proof for an obligatory requirement of mutation (nor even of modification of DNA structure in general) for malignant transformation. Cellular macromolecules other than DNA also contain multiple nucleophilic sites which can, and indeed do, react with carcinogen-generated electrophiles. Nonetheless, the central importance of DNA structure and conformation for the expression of genetic information provides a strong argument for a critical role of DNA alterations as a prerequisite for the initiation of carcinogenesis by chemical agents.

Carcinogen-modified DNA structures can, in principle, lead to local alterations of nucleotide sequence\textsuperscript{11,12,13,15,17,23} and helical distortions,\textsuperscript{13,24} possibly facilitate transition of the B-form of the double helix to a left-handed conformation (Z-DNA),\textsuperscript{25,26,27,28} or, for example, interfere with the patterns of mRNA processing (splicing)\textsuperscript{29} and DNA methylation,\textsuperscript{30,31,32,33} affect the precision of DNA rearrangements (note that transpositional events in the genome may be associated with development/differentiation in mammalian cell systems),\textsuperscript{34} cause inappropriate gene amplification\textsuperscript{35} and rearrangements at the chromosomal level,\textsuperscript{34,36} and perhaps induce error-prone DNA repair.\textsuperscript{37} It is presently still a matter of speculation, whether one or several of these mechanisms are of a predominant importance in terms of malignant transformation. However, there is little doubt that the common denominator is an interference with the genetic programmes of target cells. More information is, therefore, needed on the molecular control of eucaryotic gene expression, on the mechanisms regulating phenotypic differentiation and cell proliferation in developing and mature cell systems, and on the particular combinations of genes involved in these complex processes. Although it is theoretically not excluded that malignant transformation is generally the consequence of alterations in the same (few) specific gene(s), the wide spectrum of differing phenotypes observed in cancer cells (and the specific architectural and microenvironmental properties of each of the respective normal tissues and cell systems of origin) seems to argue against such a "unifying" possibility. The observed variety of malignant phenotypes may indeed not only reflect the different types of the corresponding normal cells of origin and their developmental/differentiation stage and/or the particular phenotypic "plasticity" of cancer cells in general; it could also indicate that a variety of qualitatively different phenotypic alterations may share the property of resulting in a malignant behavior of cells in their respective tissue environment. The DNA