

Mutagenesis studies with various mutagens in various types of mouse germ cells

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While germ-cell mutagenicity of close to 200 chemicals has been assayed by means of the rather crude dominant-lethal test, the specific-locus test (SLT), which is capable of detecting intragenic mutations as well as larger lesions involving selected genes, has been carried out for only about 30 chemicals. About 20 of these, as well as radiation, have been studied comparatively across arrays of male germ-cell stages, and a handful have been tested in oocytes. In addition, a very large historical control has accumulated over decades. The SLT permits recovery and propagation of mutants, including those that turn out to be recessive lethals, and the wealth of this mutant resource has made it possible to determine the nature of the mutations, in addition to their frequency.

Several germ-cell-stage response patterns have emerged from these studies. Stem-cell spermatogonia have yielded positive results with only five of the chemicals that are mutagenic in other stages, and almost all of this limited number of chemicals have produced stem-cell mutation rates that are lower than (or at most equal to) those recovered from poststem-cell stages. The exceptions are ENU (a point-mutation inducer) and Bleomycin (a deletion inducer). Most of the poststem-cell mutagens produce peak mutation yield from treated spermatozoa and late spermatids; only two from early spermatids, and a small number from differentiating spermatogonia. None was found effective in primary spermatocytes until our recent discovery that etoposide, a topoisomerase-II inhibitor, gave peak mutation (deletion) induction from that stage. Because of the nature of the chemical and the responding stage, etoposide was tested and found positive for effects on crossing over, joining cisplatin in this regard.

The spectrum of relative mutation frequencies at the seven loci of the SLT is characteristic for treated germ-cell stage and mutagen, thus, presumably, for the predominant type of mutation induced. In the case of induced deletions, a high frequency of mutations at a given locus may be explained by a paucity of haplo-insufficient genes in the region surrounding that locus. The spectrum is different for presumed point mutations (ENU- and MNU-induced in spermatogonia), and we will examine whether there is any relation to gene or transcript size. The spontaneous mutation spectrum differs markedly according to whether the mutations arose primarily in mitotic cells or as single-strand events in what we have termed the perigametic interval (which starts with premeiotic DNA synthesis and ends prior to pronuclear DNA synthesis).

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