

Epidemiologic Evidence for the Increased Cell Proliferation Model of Carcinogenesis

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Recent advances in the molecular genetics of cancer have provided a molecular basis for the concept that cell division is essential in the genesis of human cancer. The activation of oncogenes and inactivation of tumor-suppressor genes allows cancer development. The activation of oncogenes, whether by mutation, translocation, or amplification, requires cell division. Genetic errors that precede the development of a fully malignant tumor also include the loss of inactivation during mitosis of several tumor-suppressor genes that function to control normal cellular behavior (1-3). Most of the models currently favored suggest that the first hit is the inactivation by a mutational event of one of the two alleles of a tumor-suppressor gene present in diploid cells, followed by a reduction to homozygosity of the faulty chromosome (4). The initial mutagenic event and the loss of the wild-type allele of the tumor-suppressor gene both require cell division. Thus, for expression of the full malignant phenotype, cells are absolutely required to divide.

Epidemiologic evidence indicates that increased cell proliferation induced by external or internal stimulation is indeed a common denominator in the pathogenesis of many human cancers. "Increased" may imply division of a subset of cells that would ordinarily not be dividing or increased mitotic activity above the baseline rate. The amount of irreparable DNA damage is a function of the level of cell division. Rapid cell division may "fix" DNA-damaging events by not allowing enough time for normal repair. Cells that would ordinarily not be replicating (e.g., the Schwann cells in the nerve sheath) may at times be stimulated to divide, and when this happens, tumors (e.g., schwannomas) may develop. Nondividing cells in adults, such as nerve cells and cardiomyocytes, never develop tumors.

Cell division increases the risk of errors of various kinds (5). Mutation is more likely to occur in a dividing cell because single-stranded DNA is more sensitive to damaging effects than double-stranded DNA. Cell division also allows mitotic recombination (e.g., nondisjunction, gene conversion), which results in changes more profound than those from a single mutation. Gene duplication that occurs during cell division may cause expression of previously unexpressed oncogenes. Cell division may also involve conversion of adducts to gaps or mutations.

Agents that may lead to increased cell proliferation and eventual neoplastic transformation include a wide variety of physical, infectious, and chemical agents (Tables 1 and 2). The cell proliferation factors listed in Table 1 are those whose primary carcinogenic action is to stimulate cell division. Those shown in Table 2 also seem likely to contribute to neoplasia by stimulating

Table 1. Human cancers associated with agents whose major action is induction of increased cell proliferation.

| Factors causing cell proliferation | Cancer site |
|---|--------------------------|
| Hormones | |
| Estrogen | Endometrium |
| Estrogen and progesterone | Breast |
| Ovulation | Ovary |
| Drugs | |
| Oral contraceptives, anabolic steroids | Liver |
| Infectious agents | |
| Hepatitis B virus | Liver |
| <i>Schistosoma hematobium</i> | Bladder |
| <i>Schistosoma japonicum</i> | Colon |
| <i>Clonorchis sinensis</i> , <i>Opisthorchis viverrini</i> | Biliary tract |
| Tuberculosis | Lung |
| Epstein-Barr virus | Burkitt's lymphoma |
| Chemical agents | |
| Betel nut, lime | Oral cavity |
| Physical or mechanical trauma | |
| Asbestos | Mesothelial tissue, lung |
| Other chronic irritations | |
| Tropical ulcers | Skin |

This paper was presented at the Symposium on Cell Proliferation and Chemical Carcinogenesis that was held January 14-16, 1992, in Research Triangle Park, NC.

Table 2. Human cancers probably associated with increased proliferation.

| Factors causing cell proliferation | Cancer site |
|---|------------------------------|
| Hormones | |
| Testosterone | Prostate |
| Drugs | |
| Diuretics, analgesics | Kidney |
| Chemical agents | |
| Bile and pancreatic juice | Small intestine |
| Animal fat | Colon |
| Salt | Stomach |
| Tobacco | Oral cavity, lung, larynx |
| Physical or mechanical trauma | |
| Hard foods (e.g., coarsely ground corn) | Stomach |
| Gallstones | Gall bladder |
| Loud noise | Acoustic nerve |
| Head injury | Intracranial meninges |
| Other chronic irritations | |
| Reverse smoking | Hard palate |
| Chronic ulcerative colitis | Colon |

cell division, but evidence that the mechanism listed is the one critical to carcinogenesis is weaker. Other agents, including such established carcinogens as tobacco, may exert their effects partly through

increasing cell division. Examples of human cancers have been associated with increased cell proliferation caused by hormones, drugs, infectious agents, chemical agents, physical or mechanical traumas, and other chronic irritations. A fuller account of the role of increased cell division in human cancer has been published (6).

REFERENCES

1. Stanbridge, E. J. Identifying tumor-suppressor genes in human colorectal cancer. *Science* 247: 12-13 (1990).
2. Fearon, E. R., Cho, K. R., Nigro, J. M., Kern, S. E., Simons, J. W., Ruppert, J. M., Hamilton, S. R., Preisinger, A. C., Thomas, G., Kinzler, K. W., and Vogelstein, B. Identification of a chromosome 18q gene that is altered on colorectal cancers. *Science* 247: 49-56 (1990).
3. Sager, R. Tumor-suppressor genes: the puzzle and the promise. *Science* 246: 1406-1412 (1989).
4. Knudson, A. G. Mutation and cancer: statistical study of retinoblastoma. *Proc. Natl. Acad. Sci. U.S.A.* 68: 820-823 (1971).
5. Ames, B. N., and Gold, L. S. Too many rodent carcinogens: mitogenesis increases mutagenesis. *Science* 249: 970-971 (1990).
6. Preston-Martin, S., Pike, M. C., Ross, R. K., Jones, P. A., and Henderson, B. E. Increased cell division as a cause of human cancer. *Cancer. Res.* 50: 7415-7421 (1990).