Cell Proliferation as a Major Risk Factor for Cancer: A Concept of Doubtful Validity

Emmanuel Farber

Introduction

An old idea, now being regenerated anew, focuses a major aspect of risk assessment for cancer on cell proliferation (1–11). It is now being proposed that the presence of cell proliferation by itself or the stimulation of cell proliferation in a quiescent tissue or organ with low mitotic activity should be in and of themselves major concerns for cancer development in the particular tissue or organ. Also, the ability of an agent to induce cell proliferation in a target organ or tissue would be considered to have predictive value as a valid index of the probable carcinogenicity of that agent.

It is axiomatic that cell proliferation plays an important and even critical role in many steps in cancer development. As discussed briefly in a fairly recent article (12), cell proliferation, either of a limited degree (1 cell cycle) or of a more extended degree (12 or more cell cycles), plays a key role in initiation, promotion or selection, and progression during cancer development in several organs and tissues (Table 1). Of course, cell proliferation with altered control is the prime property that is the first characteristic phenotypic feature of a malignant neoplastic cell population.

However, whether cell proliferation, per se, is a risk factor for the long process of cancer development has not been demonstrated scientifically but remains in the realm of conjecture and speculation. No one has yet described a system in which continual cell proliferation can be induced or arrested under controlled conditions so that cell proliferation becomes the only or at least a major variable under study. Until this is done, cell proliferation as a risk factor must remain in the realm of unproven speculation. Of course, a single cycle of cell proliferation without carcinogen exposure, such as in the normal or control adult liver during liver regeneration, has not been shown or proven to be carcinogenic in many hundreds of studies reported over the past several decades.

Theoretical Scientific Bases for Considering Cell Proliferation as a Risk Factor

In addition to the general importance of cell proliferation at all steps in cancer development, there appear to be two other major considerations that underlay this speculation. These are: (a) importance of cell proliferation in initiation of cancer development with carcinogenic agents, especially those that interact with DNA or the genome; and (b) importance of cell proliferation in the genesis of mutations.

Cell proliferation is the central and key phenotypic expression in all types of malignant neoplasia. Cell proliferation in cancer is accompanied not only by disturbances in the fine balance between cell gain and cell loss (Table 1), leading to net growth, but also by two other associated changes: invasion and metastasis.

Because of its pivotal role in cancer, and because of the disturbances in its control in cancer, it is widely assumed that disturbed control of cell proliferation is also the most important and critical property of potential neoplastic cells or so-called "preneoplastic" or "preneoplastic" cells throughout the carcinogenic process. This appears to be an almost universal misconception in studies on cancer. There is neither a rational hypothesis nor any accompanying concrete factual evidence for this concept in cancer development. In fact, as listed in Table 1, and as discussed previously (12), a highly controlled balance between cell proliferation and cell loss is clearly in evidence during the inordinately long process of cancer development until the late appearance of unequivocal cancer with an upset in this normal balance.

Where studied, cancer development in vivo and in vitro with different types of "genotoxic" agents requires a single round of cell proliferation to initiate the process (13–30). Although this dependence on one cycle of cell proliferation has been demonstrated in several tissues and organs in vivo, such as in skin, colon, liver, and urinary bladder, and in different cells in vitro, it is particularly clear-cut and unequivocal in the liver for at least three reasons: (a) the hepatocyte population in the adult is almost totally quiescent with respect to cell proliferation; (b) cell proliferation can be readily induced or stimulated by several types of procedures, both regenerative and primary hyperplastic; and (c) several of the steps between the original hepatocyte exposed to the carcinogen and the ultimate appearance of cancer are highly synchronized during much of the cellular evolution to malignancy but especially during the initiation and promotion–selection periods (31). This synchrony is of the greatest importance because the sequential step-by-step analysis of any multistep process, be it molecular, biochemical, genetic or biological, necessitates a synchronous system if precursor-product relationships are to be established at each major step. This synchrony, together with a short time frame (hours to days instead of many months) makes it feasible to analyze the varying roles of cell proliferation in select models of liver carcinogenesis (12, 31).

Many different carcinogenic agents, including chemicals, radiations, and viruses, interact with the genome of target cells and generate a variety of mutations. The fixation of the genomic changes to generate mutations often requires a round of cell proliferation.

If it is assumed that such mutations play an important role in initiating the carcinogenic process and in facilitating further progression, the round of cell proliferation is essential for the carcinogenic process with genotoxic agents. Because potential or actual mutagens are widespread in all areas of the human environment, it is assumed that the rate-limiting step in the carcinogenic process is often cell proliferation, not exposure to an adequate level of a carcinogen, and that cell proliferation per se thus becomes a risk factor, providing one
speculates that the possible exposure to potential carcinogens (in the air, food, water, air pollutants etc.) is not often rate limiting (1-11). This simple conjecture concerning how humans interact with the environment is the major basis for the theory that cell proliferation is an important risk factor for cancer development.

Critique

There are at least two serious criticisms of the conjecture that cell proliferation is a risk factor for cancer. These concern: (a) the lack of association between cell proliferation and cancer occurrence in several organs and tissues; and (b) the common property of genotoxic chemical carcinogens as inhibitors of cell proliferation, rather than stimulators, in several organs and tissues.

Cell proliferation is not a risk factor for cancer in several situations in vivo that readily come to mind (the skin in psoriasis, the normal small intestine, the breast, the liver, and the stomach).

Psoriasis is a chronic disease in which focal or regional proliferation of the epidermis is a prominent feature (32-38). This great increase in cell proliferation is of long duration, often lasting decades. Yet, cancer development in psoriatic lesions is uncommon or rare (34, 35, 38, 39), despite the fact that the skin in humans, as in some species of animals (e.g., mouse), is a common target organ for a virtually universal carcinogen (UV light) and for many chemical carcinogens, and is one of the commonest sites for the development of epithelial cancers of several types.

The normal small intestine is the site of vigorous cell proliferation. In fact, Leblond (40) has estimated that the total production of cells by the digestive tract to replace the normal cell loss over a period of 20–30 days is equal to the total number of cells in the body. The small intestine is a major contributor. Despite this enormous cell proliferation, epithelial cancer in the small intestine, especially the jejunum and ileum, is extremely rare and is among the least common types of cancer by far (41, 42). This is in contrast to the segments of the digestive tract immediately below (colon) and above (stomach), sites where malignant disease is very common. Unfortunately, the explanation that is offered as a possible basis for this unusual distribution of cancer evidence is based on a failure to appreciate (43, 44) that the changes in the intestinal epithelial cells in the small and large intestine after the exposure of the organism to various cytotoxic agents are not due to a primary effect in killing the mucosal epithelial cells but are secondary to previous changes in the underlying lymphoid cells (45, 46). The latter, of course, may well vary considerably in different segments of the intestine.

The breasts are common sites for the development of epithelial cancer in women. The epidemiological data on women indicate clearly that the disease is more common in women who have never had children than in women who have (41, 42). This is also true in the mouse models where pregnancy is protective. Pregnancy is associated with a vigorous cell proliferation of all epithelial cells in the breast.

Also, in the development of hepatocellular carcinoma in the rat with initiation-promotion regimens, differential inhibition of cell proliferation, not cell proliferation, is a major mechanism for promotion (31). In addition, one of the promoters used commonly, phenobarbital, has only very limited mitogenic activity for the liver (47, 48). After a brief episode of cell proliferation, this agent is more of an inhibitor of cell proliferation than a mitogen. Visible evidence of promotion can be seen many weeks later. Also, with at least some nongenotoxic carcinogens, such as clofibrate, cell proliferation is seen only transiently during the first week or so and not subsequently during the very prolonged period of cancer development until focal proliferations (nodules, “adenomas”) appear (49).

Another interesting example is the occurrence of epithelial cancers of the stomach in people of certain countries. It is now well documented that atrophic gastritis, with low levels of cell proliferation, not hyperplastic or hypertrophic gastritis, is a risk factor for the development of cancer (50).

Ward et al. (51) have critically reviewed a large body of data in animals, in particular rodents and some in humans, and have concluded that cell proliferation is not a major risk factor for cancer development in many instances. Very recently, Huff (52) has arrived at a similar conclusion.

Thus, in several common circumstances, there is no relationship between the degrees of cell proliferation generally in an organ or tissue and cancer development. If anything, negative correlations between cell proliferation and cancer incidence, at least in some instances, can be seen. A key characteristic of almost all examples of cancer development in humans and animals is the focal nature of the few cells in any organ that do show increased cell proliferation in comparison to the vast number of surrounding cells, not apparently directly involved in carcinogenesis, that often show inhibition of cell proliferation.

The animal and human data will have to be much more convincing if the property of inducing cell proliferation is to be considered seriously as an important risk factor of carcinogenicity (e.g., Refs. 53–55).

It is now well documented that many if not all genotoxic carcinogens are inhibitors of DNA synthesis and/or cell proliferation (“mitoinhibition”) in several organs or tissues. Carbon tetrachloride, ethionine, 2-acetylaminofluorene, 4-dimethylaminoazobenzene and derivatives, thioacetamide, aflatoxin B1, 3-methylcholanthrene, benzo(a)pyrene, dimethylnitrosamine, diethylnitrosamine, pyrrolizidine alkaloids, 7,12-dimethyl-benzo(a)anthracene, urethane, and N-methyl-N-nitrosourea are among the many chemical carcinogens that have been shown to inhibit cell proliferation and/or DNA synthesis (see Refs. 56 and 57 for list of references).

These data are consistent with the hypothesis proposed in 1938 by Hadow (58). On the basis of his research on the inhibition of cell growth of normal and cancer cells with some pure polycyclic aromatic hydrocarbons that were being identified and synthesized at the Chester Beatty Research Institute, Hadow suggested that inhibition of cell proliferation could be an early effect of carcinogens and that, in such an environment, resistant cells may arise and be encouraged to proliferate selectively relative to the surrounding cells. This hypothesis was further analyzed in many subsequent reports (e.g., 56, 57, 59, 60). This differential between a focal population and the surrounding cells is also seen when rats are exposed continuously for many weeks to two quite different carcinogens, 2-acetylaminofluorene and ethionine (61). Inhibition of cell proliferation after an initial brief stimulation of cell proliferation is also seen with some nongenotoxic carcinogens, such as clofibrate (49, 62).
shown that cell proliferation does play an important role in the adult, in which cell proliferation is indeed minimal, it can be broad spectrum of cancer developments in a variety of organs and tissues. There are special instances where cell proliferation does appear to be the rate-limiting step or the major determinant for cancer development. For example, in organs such as liver and urinary bladder in the adult, in which cell proliferation is indeed minimal, it can be shown that cell proliferation does play an important role in the carcinogenic process in the presence of nonnecrogenic doses of chemical carcinogens. In experimental animals, single doses of many different chemical carcinogens are or may not be necrogenic and thus may not stimulate cell proliferation. However, I know of no circumstance where stimulation of cell proliferation in such quiescent organs can induce cancer in the absence of an exposure to the appropriate carcinogen, either with a or without prior metabolic activation.

Implications

If it were assumed that cell proliferation is rate limiting in the carcinogenic process, there would follow a totally new and radical orientation to the primary prevention of cancer with known or suspected carcinogens. The vigorous search and elimination of possible primary or even promoting carcinogenic agents becomes of secondary importance in any program for cancer prevention because the number and levels of present carcinogenic agents would already be saturating if cell proliferation is rate limiting. This new emphasis in cancer prevention, as nonexplicitly implied from the writings of Ames et al. (e.g., 1, 2, 63, 64), would encourage us to pay much less attention to our environment, such as smoking and occupation, than we do currently. This new radical suggestion for cancer prevention would demand accurate and detailed factual documentation, rather than the (current) undocumented opinion, if we are to give it serious consideration in the rational development of approaches to cancer control and if we are to redirect an important focus of attention in cancer prevention away from the environment. The justification for this reorientation requires a careful documentation of facts that are unavailable at this time.

References

EGF receptors and the ability of physiological concentrations of calcium to suppress hepatocyte proliferation. Carcinogenesis (Lond.), 9: 479–483, 1988.


Cell Proliferation as a Major Risk Factor for Cancer: A Concept of Doubtful Validity

Emmanuel Farber


Updated version  Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/55/17/3759.citation

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.