Perspectives in Cancer Research

Cancers Beget Mutations versus Mutations Beget Cancers

Richmond T. Prehn

Department of Pathology, University of Washington, Seattle, Washington 98195

Abstract

Despite the plethora of "oncogenes" and "tumor suppressor genes," the hypothesis that cancer is usually the result of genomic mutations may be wrong. We should at least examine the alternative hypothesis, for which there is considerable evidence, that mutations do not commonly beget cancer, but rather that cancer phenotypes result from confused or aberrant patterns of normal-gene expression; the abnormal patterns are postulated to result from epigenetic mechanisms rather than from mutations. The epigenetic hypothesis that I am proposing suggests that cancers may exhibit mutations primarily because replicative errors at inactive sites in the cancer genome may be repaired slowly or not at all, but the mutations so produced, occurring at already inactivated sites in the genome, may have limited biological significance. Thus, it may be more correct to say that cancers beget mutations than it is to say that mutations beget cancers.

Introduction

The general scheme I propose is that epigenetic, not mutational, mechanisms produce neoplastic phenotypes by producing persistent abnormalities in the patterns of gene expression. Furthermore, mutations (defined as errors in DNA of a variety of types) are postulated to accumulate and persist at inactive sites in the genome, owing to a lack of their elimination and/or of their prevention and/or of their repair (1, 2). These lacks allow the accumulation of mutations in those genes whose prior inactivation was, in the first instance, intrinsic to the neoplastic change. According to the hypothesis (as well as to the Ames test which suggested that almost one-half of the carcinogens tested may not have been mutagens; Ref. 3), it is not necessary for a carcinogen to induce mutations; the carcinogen need only turn on, using an epigenetic signal, persistent neoplastic genomic patterns of gene activity, and sooner or later unrepaired errors, arising during the replication of the inactive parts of the genome, will result in mutations at various, already inactive, loci. Thus, a physiological inactivation of a suppressor gene, such as p53, is postulated to precede its mutational inactivation and the mutational inactivation may therefore be largely irrelevant. The postulated failure to repair, eliminate, or prevent errors in the replication of inactive parts of the genome would contribute to energy efficiency; teleologically, why would a cell bother to expend energy to maintain something it has turned off, doesn't use, and doesn't need?

First, I will discuss some of the reasons for believing that cancer may be largely an epigenetic disease and then discuss what the role of mutation might actually be.

Differentiation in Ontogeny

Very diverse creatures may share identical genomes; their diversity resides in diverse patterns of gene activation and inactivation induced by epigenetic information that lies outside of the genome per se, i.e., in the cytoplasm, cytoplasmic organelles, cell membranes, or in the extracellular environment. Thus, the caterpillar and the butterfly use the same genome but are very different creatures, owing to the different patterns of genes that are activated or suppressed by the varied contexts in which the cells find themselves (4).

In complex animals, the cells of the varied organs supposedly share the same genome; the genome of a hepatocyte is presumed to be identical with that of a neuron from the same animal, but during ontogeny, epigenetic mechanisms determine the persistent patterns of gene expression that distinguish the various cell lineages. Nor should it be supposed that organ differentiation simply implies the switching on of a separate part of the genome for each organ; most of the genes used in each organ are the same, and the different patterns of activation overlap.

If the different normal cellular phenotypes are so dependent upon varied patterns of expression in the genome, why is it that when something goes amiss and an abnormal phenotype, a neoplasm, appears, we presume that the cause lies in mutation rather than in an epigenetically induced abnormality in the pattern of gene expression? The reason resides, of course, in the great success that has been experienced in the discovery of a variety of deletions, "oncogenes," and "tumor suppressor genes" as well as in the discovery of cancer- associated chromosomal abnormalities. There is also a general ignorance concerning epigenetic mechanisms that might induce a cancerous pattern of expression among normal genes (5). It should be noted in passing that no cancer exhibits any trait which cannot be found in some normal tissue as the expression of normal genomic activity; thus, for example, no cancer grows faster than an embryo nor is any cancer cell more invasive than a macrophage nor are cancer cell lines more immortal than are germ lines. The only distinction is that, in the cancer, the expression or lack of expression of many traits may be inappropriate for the tissue in which the cancer occurs.

Differentiation of the Incipient Cancer

A tendency of the initial oncogenic lesion to regression by differentiation might suggest that the lesion was probably not caused by mutation. Observation suggests that regression is indeed characteristic of some, perhaps even of all tumor types, early in the course of their progression. This tendency to regression and related observations have led a few investigators to question the role of mutation in the carcinogenic process. The arguments have been elegantly presented by Farber and Rubin (6); I will present here only a brief summary that cannot do justice to their work.

The studies of Farber and Rubin (6) were concerned largely with the biology of chemically induced liver cancers in rodents. The initial effect of carcinogen treatment was a generalized toxicity, followed by what was probably a compensatory type of hyperplasia which, on subsidence, left focal nodules of more persistent hyperplasia. Advanced carcinogen-induced cancers are generally resistant to the toxic effects of carcinogens, and these liver nodules of incipient or precancer shared this attribute (6). The nodules responded with abnormal vigor to proliferative stimuli (6). Although induced by a variety of oncogenic regimens, the nodules showed a common biochemical pattern incorporating "decreases in several phase 1 components in the replication of inactive parts of the genome would contribute to energy efficiency; teleologically, why would a cell bother to expend energy to maintain something it has turned off, doesn't use, and doesn't need?"

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characteristic alterations in glucose metabolism, and a reproducible pattern of iron and heme metabolism” (6). The most striking feature of the nodules was that, in a majority, the abnormal architecture of the nodule underwent spontaneous differentiation to normal-appearing liver; a very small minority developed into overt hepatoma (6). The complex but common biochemical pattern possessed by the nodules, their resistance to the toxicity of a variety of chemical toxins, and their tendency to differentiation suggests that they represented a genetically programmed adaptation to injury; in fact, nodule-bearing animals were resistant to the systemic toxicity of the carcinogenic agent (6). Although the nodules were clonal, they certainly did not seem to be caused by random mutation.

The liver system may closely resemble other oncogenic systems, about which less detail is available. The appearance of numerous nodules or papillomas, of which a minority progress to cancer, is a common feature, for example, of systems as diverse as colon cancer, mammary cancer, and skin cancer. I will discuss the skin system at some length, since it is generally interpreted as being dependent upon mutations for “initiation” and a nonmutagenic stimulator of hyperplasia for “promotion” (7).

The idea that skin oncogenesis, and by inference other types of oncogenesis, involve at least two qualitatively distinct steps was championed, perhaps most notably if not initially, by Berenblum (8). He presented data to show that if mouse skin were painted once with a subcongenenic concentration of a chemical carcinogen, an invisible but permanent change took place such that subsequently repeated treatments, weeks or even months later, of that skin with any of a variety of noncarcinogenic irritants resulted in the rapid appearance of clonal papillomas. Reversal of the sequence, i.e., applying the suboncogenic dosage of carcinogen after the irritant, produced no papillomas. However, somewhat different observations have been made by others to the effect that application of the promoter before the carcinogen is “not innocuous,” from which observation Iversen (9) concluded that initiation and promotion are only quantitatively rather than qualitatively distinguished.

The usual interpretation of “two stage” oncogenesis, as I have said, is that initiation is a mutational event whereas promotion is a non-specific, hyperplasia-producing irritation that “develops” the latent papillomas (7). Such an interpretation is obviously inconsistent with the interpretation derived by Farber and Rubin (6) from the studies of liver oncogenesis. The reasons for the widespread belief that initiation is mutational are probably that it is long-lasting, that seemingly only scattered cells are affected, and a mutagen is usually used as the initiator. Furthermore, a ras mutation is a common early feature (7). However, the impression that only scattered cells are altered is apparently not correct since several studies have shown that a high proportion of the treated epithelial cells are persistently altered; thus, despite 5 weeks of cell turn-over after initiation, most basal cells in a treated area responded to the classical promotion with croton oil with a faster than normal onset of DNA synthesis, albeit that only a rare cell formed a papilloma (10). When a chemical carcinogen was applied repeatedly to the hamster cheek pouch producing a localized carcinoma, there was a large increase in proteolytic activity, both in the carcinoma and in the surrounding, normal-appearing tissues, indicating a high frequency of persistent change in the whole treated area (11). Such a high rate of change, involving virtually all treated cells, is not the usual expectation from a mutational mechanism and suggests an epigenetic adaptation.

Tissue culture studies have also suggested that exposure to a carcinogen produces a high rate of change rather than rare mutants. In apparent parallel with the in vivo skin system, Mondal and Heidelberger (12) found that virtually every cell exposed to methylcholanthrene produced, when cloned, a few variants that formed transformed colonies. A similar conclusion was reached by others using X-rays rather than a chemical carcinogen, and the transformed phenotype could also be reversed (6). Ruben has shown that the rate at which any given clone would produce “foci” could be altered by the environment of the cells, a process he terms “progressive state selection” (13).

Although the initial change produced by the carcinogen or by X-radiation, either in vivo or in vitro, may often be an epigenetic adaptation rather than a mutational event, there are some data to suggest that the second step, papilloma formation in vivo or transformation in culture, is a very rare event that would be consistent with a mutational change. It was shown that the additional treatment of lightly X-rayed cells with the tumor promoter 12-O-tetradecanoylphorbol-13-acetate increased transformation to a very high level and Rubin (6), therefore, concluded that the promoting or second stage, like the initiating or first stage, “could be considered a high frequency process, even although its visible manifestation occurs with low probability.” Which cell actually forms a focus may perhaps be as much a matter of chance as which atom in a group of radioactive molecules will decay. I believe that the high incidence of regression via differentiation and the use of essentially nonmutagenic irritants for promotion also makes it unlikely that promotion would have a mutational basis.

Before leaving the topic of the regression that seems to be so frequent in incipient-cancer systems, the question of the nature of the regressions needs a further word. In the liver system, as explored by Tatematsu et al. (14), it seems clear that nodule regression is associated with differentiation. In the mouse skin system, histology has suggested resolution by differentiation, but the issue remains in doubt. What can be said with some assurance is that regression of the skin papillomas, while influenced by immunity (15), can still occur in the apparent absence of an immune reaction and that regression probably cannot be attributed to cytotoxic immunity. Andrews (16) showed that papillomas induced in skin that had been grafted to an immunodepressed allogeneic recipient underwent regression, even though the immune capacity of the host was incapacitated to such an extent that the papilloma-bearing allografted skin survived (16). The data thus suggest that all of the varied carcinogenic systems may vary only in detail and that they are all characterized by early hyperplastic lesions that have a large predilection to regress by differentiation.

It may be a general rule that a carcinogen of any type produces, after initial toxicity, a persistent increase in mitotic activity and an increased susceptibility to future mitotic stimuli in most or all of the cells with which it comes into contact, and the degree of adaptation can be adjusted forward and back by environmental conditions (13). Any one of the carcinogen-adapted cells can give rise, but very rarely, to clones that proliferate into foci, nodules, or papillomas, most of which will spontaneously regress. Either these incipient lesions are not based upon mutation, or the mutations are inducibly reversible or readily masked by unknown compensatory mechanisms.

The mechanisms by which a carcinogen can produce, by nonmutational means, changes of phenotype that are heritable at the somatic cell level are unknown, but the possibility of such mechanisms is shown by the very existence of heritably stable liver cell lineages as opposed to lineages of neurons. Pitot and Heidelberger (17) presented a detailed hypothetical mechanism as one example of how a carcinogen might be able to induce a heritable change in the pattern of gene expression without producing mutation. The fact that nongenetic surface changes can be propagated indefinitely in Paramecium (18) suggested to Farber and Rubin (6) that carcinogen-induced effects on the cellular phenotype may be mediated through some type of damage or alteration to the membrane. Recently, it has been shown that altered patterns of DNA methylation, producing altered patterns of DNA
silencing, occur increasingly with increasing age in at least one cancer prone tissue (19).

Differentiation of Advanced Cancer

If advanced, as well as incipient, cancers could regress by differentiation, it would suggest that gene mutation is perhaps not the essential determinant of the phenotype of even the more advanced cancers. The literature containing evidence of the differentiation or partial differentiation of the cancer phenotype is vast, and little purpose would be served by attempting to review it in detail, even if I could do so. Rather, I will cite examples of the various types of evidence to an extent that is hopefully sufficient to support the hypothesis I am presenting.

Evidence that gene mutation may not be the basis of the cancer phenotype comes from experiments in a number of laboratories that attempted to ask directly whether the basis of the neoplastic change resides in the cytoplasm or in the nucleus. A number of studies were done that involved the transplantation of a virally induced frog kidney cancer nucleus into the cytoplasm of an enucleated frog egg. The egg’s development was then observed to see what sort of creature, if any, would result. Sometimes the cancer cell nucleus supported development to an overly normal tadpole, although metamorphosis did not occur (20). The reason that development ceased prior to the appearance of a frog is open to speculation; perhaps there were technical difficulties or perhaps the nucleus was incompetent. It seems to me that the important observation is that the cancer nucleus, when placed within a normal cytoplasm, could support overly normal development and differentiation; in the context of egg cytoplasm, it produced nothing that resembled a cancer.

A large variety of other studies has shown that epigenetic influences can profoundly modify the cancer phenotype. Several authors showed that embryonal carcinoma cells might, when transplanted into the developing blastocyst, become incorporated into the developing embryo and result in a mosaic mouse in which, scattered throughout the various organs, seemingly normal cells were of cancer origin (21–23).

Although the blastocyst could produce such modification only in the case of germ cell neoplasms, in the cases of other types of cancer, other environments of the developing embryo, perhaps each peculiar to a particular neoplasm, could apparently normalize neoplastic growth (24); malignant melanoma could, for example, be induced to differentiate by implantation into skin during a short window of time during ontogeny (25). One investigator fused cancer cells in vitro with enucleated but otherwise normal cells and showed that the resulting “cybrids” were no longer malignant or were less malignant (26). Again, these works demonstrate that epigenetic mechanisms are of profound importance; epigenetic signals such as these would be expected to alter patterns of gene expression, but would be unlikely to induce or to reverse mutation.

Cancer regression associated with differentiation can occur spontaneously, most commonly in the neuroblastoma of childhood (24) and more rarely in other cancers (27–29). Regression can sometimes be induced in a number of cancer types by treatment with a variety of simple chemical agents (24, 30), most notably with retinoic acid and its analogues. Although germ cell carcinomas seem, as might be expected, the most easily induced to differentiate, other types are also affected in the right circumstances (31). This approach to cancer therapy is now so popular that conferences are regularly held to promote “differentiation therapy” (30).

It seems that in any organ that is dependent upon a certain hormonal milieu for its maintenance, at least some of the tumors arising in that organ will also be dependent upon that same milieu. Thus, for example, the normal prostate gland undergoes profound regression if deprived of testosterone, and most carcinomas of the prostate will also regress if deprived of that hormone (32). Even prostatic carcinomas that have progressed to the point of extensive bone metastases usually regress temporarily, in the absence of testosterone, via differentiation and apoptosis (33). Another example, perhaps less dramatic, is the temporary regression or retardation of the growth of many breast cancers when treated with an anti-estrogen (34). Dependency, in this usual form, cannot be used as a good argument against the mutational hypothesis; the argument is too easily countered by the suggestion that mutation could still be what distinguishes the cancer cell from the normal cell, but that both cell types, despite their differences, might remain subject to the need to maintain the basic tissue via a proper hormonal environment. However, there is a less widely known facet of dependency that may be more difficult to explain by the mutational hypothesis.

It has been observed that in some cases, even after tumor progression has occurred and the original hormonal dependency has disappeared, epigenetic determinism can still persist. For example, it has recently been found that when progression of the prostate carcinoma has reached the point where the testosterone-blocking agent, Flutamide, is no longer effective, a second remission can often be achieved by withdrawal of the Flutamide; apparently many of the carcinoma cells have now become dependent, not upon testosterone, but upon its absence (35). Likewise, in breast carcinoma in the mouse, the early lesion is characteristically inhibited in its growth by surrounding normal mammary epithelium, but after sufficient progression, it may actually grow better in the presence of such epithelium (36). This plasticity would be, I think, somewhat difficult to explain if the tumor phenotype were determined by mutation. It seems difficult, albeit not impossible, to argue that cancer is caused by mutations but is, nonetheless, reversible with the proper epigenetic influences. The point is that one need not invoke mutation as a cause of cancer if the frequent occurrence of mutations in cancers can be explained in some other way.

Cancer Begets Mutation

When I began to write this paper, being biologically oriented and a stranger to the more intricate glories of molecular genetics, I was uncertain whether the hypothesis I had in mind was molecularly feasible. I was predicting, as part of the hypothesis and from purely biological considerations, that repair of genomic errors would be defective or nonexistent in those inactive genes that help determine the cancer phenotype. Imagine, then, my excitement when I discovered the work of Hanawalt and his associates (1, 2). These investigators showed that nucleotide excision repair was much more efficient at removing UV-induced cyclobutane pyrimidine dimers from expressed genes than from silent partners (1, 2) and, in particular, at repairing errors in the expressed DNA strand (37). More recently, it has been shown by others that in the p53 gene, in UV-irradiated cells, repair at individual nucleotides was variable; only slow repair occurred at positions frequently mutated in skin cancer (38). Perhaps many types of genomic errors go unrepaird or relatively unrepaird at inactive sites in the genome.

Xeroderma pigmentosum is a congenital syndrome characterized by excessive sensitivity to UV light and the development of skin cancers. I believe that these patients may have a pattern of genome suppression and activity that is predisposing to the development of cancer independently of any mutations to which the congenitally acquired pattern of gene expression may also predispose. They have a deficiency in carrying out the incision step of nucleotide excision repair. In some of these cases, repair of the transcribed strand is
normal, but repair of the inactive gene sequences is, as is the case in normal cells, deficient (39). This lack of repair may lead to the mutation of already inactive tumor suppressor genes, but the lack of repair at an already inactive locus, further inactivating it, could not be of much significance for the genesis of cancer. However, mutation at such a site might make regression by differentiation more difficult since a normal pattern of gene activity would, under these circumstances, be difficult to restore.

Patients with Cockayne's syndrome also have a defect in nucleotide excision repair, but in contrast to xeroderma pigmentosa, these patients have a defect in repairing errors in the active strand; apparently, repair at inactive sites is close to the normal low level (40). Also, these patients do not get excessive numbers of skin cancers. I interpret the fact that they do not get cancer to imply that the pattern of genomic activity that they inherited is not a cancer-predisposing pattern. Genetic loci that would often be inactive in a cancer-predisposing genome, such as p53, presumably remain active; their lack of repair and resultant mutation would not easily create a cancer-causing genome inasmuch as numerous changes, to create a distinctive pattern of gene expression, would usually be required.

The Role of Mutation

Even if my thesis should be essentially correct, mutations could, under certain scenarios, still play an important role. One observation that seems to pervade the literature is that there is a tendency for mutations to be seen with increasing frequency as the tumor becomes more aggressive and more malignant. While it may be that tumor progression is characterized in some tumors by a tendency to a certain pattern of mutations, these patterns seem far from clear and rather variable from case to case (41). There seems, as yet, no easily definable one-to-one relationship between a particular set of mutations and a particular tumor phenotype. These observations are explicable in terms of the mutational hypothesis, but I believe they are accommodated even better by the epigenetic hypothesis I am proposing.

The relationship between increased mutation number and the aggressiveness of the tumor, is, according to the epigenetic hypothesis, the result of gene errors going unrepaird at the inactive sites in the genome. It is the presence of a certain pattern of inactive, and therefore mutable, loci induced by the carcinogen, not the mutations that occur at those sites, that produces the cancer and its progression. The stronger the carcinogen, the more malignant the pattern of gene inactivity that is produced and the greater the number of errors that are created. The longer the loci in the genome remain inactive, the greater the chance that a mutation at a particular locus will occur, even if an error-producing carcinogen is no longer present. Progression is postulated to be caused by a succession of activity patterns triggered by epigenetic signals; the mutations simply occur in the genomic pattern at the available inactive sites.

Much of this epigenetic hypothesis was inspired by the various observations showing that cancers, sometimes even advanced cancers, may be induced, to a surprising extent, to differentiate and so undergo at least partial regression. Of course, this argument is not decisive in favor of the epigenetic hypothesis since there probably are compensating mechanisms that might circumvent a particular set of cancer-producing mutations and so permit differentiation and regression, despite the presence of the mutant genes. Nonetheless, I think it probable that such compensatory mechanisms would find it increasingly difficult to offset the effect of increasingly larger and larger numbers of mutations. I have already discussed the fact that regressive behavior is characteristic of the incipient lesion but that regression may be more difficult with advanced cancers. The ever-increasing number of mutations that I postulate occur at inactive loci, after the fact of cancer, might have the effect of making differenti-
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