Genetic Convergence and Divergence in Tumor Progression

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An essential defect in tumorigenesis is the imbalance between the tendency of neoplastic cells to divide and spread throughout the body, and the capacity of the organism to regulate and restrain such growth. In principle, two main explanatory strategies have in recent medical history been followed when attempting to understand the events of carcinogenesis. In the holistic or integrationist approach, the necessity of viewing the organism as a whole is underscored, and consequently, the emphasis is put on large-scale disturbances (for instance, humoral factors, field effects, topographical disruptions) as causative factors in tumor formation (1–3). The ambition of the reductionist approach, on the other hand, is to dissect accurately the pathogenetic process into component events that at least in principle are simple enough to be comprehended fully within the conceptual framework of biological theory. Since the ascent of cellular pathology 100 years ago, the reductionist position has become more and more cytologic, and today this view dominates most reasoning about oncogenesis (4, 5). Cancer is seen primarily as a cellular disease, in the sense that inherent derangements in the tumor cells themselves, rather than some kind of systematic failure to provide proper proliferation control, are of the essence.

Tumor cells beget other tumor cells. An obvious mechanism for the conservation of neoplastic capacity between cell generations is via a stable genetic alteration that can be faithfully reproduced and passed on to all progeny. Direct evidence of defective genetic material in neoplastic cells dates back to around the turn of the century, when David von Hansemann observed abnormal nuclei in cancers (6). Theodor Boveri in his “Zur Frage der Entstehung Maligner Tumoren” (7, 8) forged these early insights into what has later become known as the paradigmatic view in tumorigenesis. Cancer is not only a cellular disease, it is basically a genetic disease, as it is stable rearrangements of the genetic material that render the cell neoplastic, i.e., enable it to assume a proliferation pattern outside the boundaries set by normal control mechanisms.

Tumor Clonality

If one accepts that cancer is primarily a cellular, and even a genetic, disease, is it of mono- or polyclonal origin? Histopathological examinations and clinical experience indicate that small, originally separate neoplastic foci may coalesce to form carcinomas, and that multiple primaries may originate from outside the boundaries set by normal control mechanisms.

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Tumor Clonality

If one accepts that cancer is primarily a cellular, and even a genetic, disease, is it of mono- or polyclonal origin? Histopathological examinations and clinical experience indicate that small, originally separate neoplastic foci may coalesce to form carcinomas, and that multiple primaries may originate from outside the same epithelial field (9–11). On the other hand, much recent evidence emanating from three main investigative approaches strongly indicates the monoclonality of many tumors.

(a) Neoplasms in women who are constitutionally heterozygous at the G6PD locus have been found to express only one G6PD variant (12, 13). Examinations of DNA from tumors typically yield no more than one band when amplified by the polymerase chain reaction, and the presence of aberrant bands when amplified in neoplastic cells does not seem to be a general feature of malignancies (14, 15). Loss of heterozygosity at the X chromosome is to be expected if a tumor is monoclonal, since all descendants of a single cell have the same X inactivated.

(b) B-cell neoplasms express only one type of immunoglobulin on the cell surface (16, 17). Monoclonality has also been demonstrated, using DNA recombinant techniques, in both B- and T-lineage neoplasms by the finding of unique immunoglobulin and T-cell receptor locus rearrangements in all tumor cells (18–20).

(c) One of the strongest arguments for the monoclonal composition of most tumors derives from cytogenetic investigations (21, 22). Since the development of chromosome banding techniques around 1970, it has become possible to precisely identify chromosomal rearrangements from a growing number of tumor tissues. In the majority of instances, the same karyotypic profile characterizes all analyzed cells from a given neoplasm.

In spite of the credulity these studies lend to the notion of a unicellular origin of cancer, some caution may be warranted. Firstly, the most convincing data indicating tumor monoclonality stem from investigations of hematological and mesenchymal neoplasms, not from carcinomas. This is of particular importance in view of the fact that the contradictory histopathological and clinical evidence (9–11) mainly builds on examinations of epithelial carcinogenesis. Secondly, some results of G6PD studies have indicated that the tumors studied were poly- rather than monoclonal (12, 23–25). Finally, on no occasion has it been possible to monitor the clonality of a human solid tumor longitudinally, to follow directly in time the heterogeneity of the neoplastic cell population. Every investigation is a snapshot that captures only an instantaneous picture of the life of the tumor. Whether the tumor cells evolve towards greater simplicity or complexity at the moment when their genetic constitution is assessed remains conjectural.

Clonal Evolution: The Balance between Genetic Instability and Selection

It is well known that many tumors exhibit pronounced morphological heterogeneity, both as cellular pleomorphism and even in the form of variable tissue differentiation in different tumor parts. Furthermore, neoplastic phenotypes generally undergo changes with time; usually their behavior becomes increasingly aggressive with infiltration of surrounding normal tissues and the setting up of distant metastases. This acquisition of novel phenotypic traits in an expanding population of neoplastic cells is termed tumor progression, and the typical pattern of this process was accurately described by Furth and Foulds during the 1950s (26–28). As tumors progress, their total growth rate increases. This represents the sum of the cells’ intrinsic or independent growth tendency and proliferation induced by stimuli from outside, the responsive growth rate. Foulds also emphasized that the individual steps in the progression process are randomly assorted: not only does the acquisition of new phenotypic traits take more time in some tumors than in others, the order of their occurrence also differs. Is such a dramatic phenotypic heterogeneity compatible with
a unicellular, a monoclonal, tumor origin? Of course, the very existence of multicellular, differentiated organisms is by itself the best example of massive large scale heterogeneity in spite of identical cellular genomes; differential expression of genes can achieve almost any level of phenotypic variability. Additionally, the morphological and functional heterogeneity of tumor cell populations may evolve also through acquired genomic differences, through the establishment of somatic mutations in daughter cells when the neoplastic clone expands. For the latter possibility to be of quantitative importance, it seems necessary, although this conclusion has on theoretical grounds been contested by some (29), that the genomic stability of the cells in question must be less than normal.

The importance of genetic instability in tumor progression has been extensively reviewed by Nowell (30–32). Such instability could conceivably be a constitutional trait in cancer patients, or it could be a feature restricted to the neoplastic cells. The best examples of the first scenario are found in patients with the rare autosomal recessive disorders ataxia telangiectasia, Bloom's syndrome, and Fanconi's anemia, who all have markedly increased constitutional chromosome breakage frequencies and a high risk of developing various malignancies (33, 34). Likewise, measurable increase in constitutional chromosome fragility has also been detected in some dominant cancer diseases, multiple endocrine neoplasia type II and adenomatosis of the colon and rectum being the most extensively investigated examples (35, 36). Although it has been suggested that constitutional genomic instability might be a pathogenetic feature of more general importance in cancer (37), most studies have described normal constitutional chromosome breakage frequencies in patients with sporadic malignancies (38, 39).

The genomic instability of cancer cells must therefore in most cases be an acquired phenomenon, not a reflection of the patient's constitution. In principle, two different kinds of genetic liability are conceivable: either an increased tendency to undergo chromosome-scale rearrangements, in which case the changes would be possible to demonstrate by cytogenetic methods, or the tumor cell DNA might be excessively prone to point mutations. In most cases increased total genetic instability would result from a combination of both, but isolated chromosome-level or DNA-level stability disturbance remains a possibility.

That karyotypic heterogeneity with numerous different but related clones is a regular feature of many advanced neoplasms has been documented in both human tumors (21, 40–42) and in experimental systems (43). Indeed, the detection of microscopically visible disturbances of the mitotic process gave the main impetus leading to the formulation of the somatic mutation theory of cancer. Much less clear is the question of whether tumor cells also have increased tendency to undergo point mutations. Some reports describe enhanced mutability increasing with tumor progression (32, 44, 45), while others maintain the opposite (3, 46–48).

What are the mechanisms whereby neoplastic cells become less genetically stable, be it at the chromosomal or DNA level, than their normal counterparts? One possibility is that the neoplasia-producing mutation, as one of its pleiotropic effects, inactivates a repair locus, or phrases differently, activates a "mitotic error locus" (31, 49, 50), thus facilitating later numerical and structural karyotypic changes. Other potential mechanisms for increased genomic instability with time (31) could be the persistence of carcinogens in the tumor, the production of mutagenic or clastogenic agents by the tumor cells or by accumulating stroma cells, or simply that nutritional insufficiency in the microenvironment might predispose to aberrant cell division.

Stating that neoplasia is primarily a cellular disease, i.e., that genetic alterations are the essential pathogenetic requirements in tumorigenesis, is not equivalent to saying that host factors are unimportant in cancer. On the contrary, the milieu in which a population of neoplastic cells proliferates and spreads is presumably crucial in deciding the eventual outcome both at the level of individual cells and clones and for the organism as a whole. The drawing of parallels between evolutionary strategies in the development of species and the competition of evolving clones within a tumor has proved particularly fertile (4, 30–32, 51–54). The application of Darwinian thinking and terminology has lead to the concept of tumor stemlines, and of selection as the main force deciding which of the almost innumerable emerging subclones will prove more fit in tumor evolution. The exact nature of the parameters on which selection depends is not established. Factors like the proficiency of the immune system, the presence of inhibitory or stimulatory growth factors, and the integrity of the tissue microenvironment are undoubtedly of the essence, as are presumably also the general health and nutritional status of the patient and his exposure to infectious agents. Finally, the iatrogenic factor in tumor progression is not to be underestimated; with every new cytostatic agent the patient receives, the tumor cells face a radically altered selective environment.

It follows then that shifts in the balance between the genetic instability of an expanding tumor cell population and the selection pressure the cells confront in principle might lead to increased as well as decreased genetic heterogeneity within the tumor. Even if a neoplasm develops through successive proliferation of a single transformed cell, genomically different subclones will, if genetic instability dominates, soon have introduced considerable genetic complexity. On the other hand, if the selection of different neoplastic cells is strong, genetic heterogeneity within the tumor will inevitably diminish, and the variability between component cells will be reduced. The tendency towards less heterogeneity is irrespective of whether the tumor started out as poly- or monoclonal: in the first case, the number of independent clones will be reduced; in the second, the number of subclones becomes smaller. Flexibility and variety, and thus the ability to rapidly adjust to future environmental changes, is of necessity traded for optimal adaptation to the milieu as it is.

Cytogenetics, with its ability to identify an in principle infinite number of both related and unrelated clones, offers a unique methodology to monitor the waxing and waning of genetic complexity in a tumor cell population. Based on the arguments outlined above and available information on the chromosomal abnormalities of human tumors, we would like to suggest that four scenarios in the clonal evolution of neoplasms are regularly seen:

**Clonal Stability**

In some neoplasms, no karyotypic variability with time is detected (Fig. 1). The tumor is monoclonal at the time of first examination and remains cytogenetically identical until the patient dies. The best evidence for this scenario stems from the hematological disorders, namely from examinations of leukemias, preleukemias, and lymphomas, where the easy access to suitable material and the consistency of cytogenetic success has made longitudinal follow-up of individual patients possible. The situation in CML is particularly well characterized (42, 55). During the chronic phase, which on average lasts for 3
years, CML patients have as the sole cytogenetic anomaly the t(9;22)(q34;q11) that gives rise to the Ph1 marker. With the transformation to blast crisis, 75–80% of the patients develop additional abnormalities. The remaining one-fifth, although clinically and hematologically indistinguishable from the majority of CML blast crisis patients, retain the cytogenetic profile that characterized their chronic phase disease. It is therefore obvious that the phenotypic disease progression in CML is independent of cytogenetically detectable secondary rearrangements. Whether submicroscopic genomic aberrations accrue as the disease goes from bad to worse is still an open question.

Another moot point, in CML as in other neoplasms, is at what time in tumor development the characteristic karyotypic change develops. Although the t(9;22) is almost always detectable at the time of diagnosis, occasional patients exist in whom progression from Ph1-negative to Ph1-positive leukemia has been reported (56). Fialkow and coworkers have used the G6PD assay to find that the leukemic cell in CML is a stem cell capable of differentiation not only to mature granulocytes, but also to erythrocytes, platelets, and B-lymphocytes. The same group has also utilized long-term bone marrow cultures finding that some lymphocytes arising from Ph1-positive clones were Ph1-negative. Combining these results with cytogenetic data, Fialkow has suggested (57) that the acquisition of t(9;22) probably occurs in a clone of proliferating, Ph1-negative bone marrow stem cells that through some unknown rearrangement has become genetically unstable and has achieved selective advantage. This interpretation of the temporal relationship between early events in CML pathogenesis by no means invalidates the hypothesis that t(9;22) with formation of the abl-bcr hybrid gene, a genetic rearrangement now known to be ubiquitous in CML, is essential in leukemogenesis (58, 59). It does illustrate, however, that the first cytogenetically visible aberration need not necessarily be the initiating factor, the change that turns a cell neoplastic. If tumorigenesis is a multistage process, as indicated by most current evidence (32, 60–62), it would indeed be unexpected if all the steps involved genetic changes, let alone chromosomal rearrangements. The sequential order of the various events is obviously a poor guide to their relative pathogenetic importance.

Genetic Convergence

More often than not, clinically recognizable disease progression coincides with growing genetic heterogeneity within the tumor cell population, with genetic divergence (Fig. 2). Again the leukemias are the best examples, and again CML in blast crisis is the most thoroughly investigated (42, 55). The more than three-fourths of blast crisis patients who develop aberrations in addition to t(9;22) do not acquire a mess of random changes; instead, the abnormalities that accrue are remarkably uniform from case to case. The typical secondary changes in CML are +8, +Ph1, and i(17q), and to a lesser degree also +19 and +21. The same principle applies in the acute leukemias: the evolutionary changes are nonrandom, and their relative frequencies are dependent on the nature of the primary anomaly (41). Basically similar results have also been reached in experimental carcinogenesis (43).

What causes the nonrandomness observed in cytogenetic evolution? Is it only a reflection of the selection pressure confronting constantly emerging subclones from the genetically unstable neoplastic cell population, or does perhaps the initial cytogenetic change somehow influence the likelihood with which the various secondary aberrations may be formed? In principle, this dichotomy is not essentially different from the question of whether carcinogenic agents specifically produce the primary karyotypic rearrangements that are associated with neoplasia, or whether all aberrations are initially random but reach specificity through selective sifting. Data could be cited in support of both explanations (63–65), and the questions must remain unresolved pending the acquisition of more conclusive evidence either way.

Genetic Convergence

It is tacitly assumed in both the "stable genome" and the "genetic divergence" scenarios that the neoplasm starts as a monoclonal expansion. Indeed, the overwhelming majority of cytogenetic data seems to support this view (21, 66). In the hematological disorders, the cytogenetically best-characterized malignancies, only 1–4% of all reported cases have contained seemingly unrelated, karyotypically abnormal clones. The majority, or perhaps all, of these situations could be explained by viewing the apparent pleoclonality as a divergence phenomenon where the primary tumorigenic rearrangement has remained undetected. On balance, however, the fact remains that the simplest explanation for some of the data on chromosomally unrelated clones, particularly in myelodysplasia and chronic lymphoproliferative disorders, would be to accept that sometimes these neoplasms can be of polyclonal origin.

A stronger case can be made for at least occasional initial polyclonality in solid tumors. Histopathological examinations and clinical experience (9–11) indicate that carcinomas of some localities may start out as multifocal, but seen against the background of the many cases of tumor monoclonality proven with more sophisticated techniques (13, 15, 21), this evidence is generally regarded as not quite stringent enough to be completely convincing.

The cytogenetic data on solid tumor clonality are not une-
Convergence-Divergence in Tumor Progression

The convergence-divergence situation (Fig. 4) represents a composite of the two preceding scenarios. The initially monoclonal epithelial field undergoes transformation while the cells are still to some extent shielded from the organism's homeostatic regulatory mechanisms, in particular the immune system. This initial heterogeneity is gradually replaced by pseudomonoclonality or oligoclonality later in the disease process. Later still, the balance between the genetic instability of the neoplastic cells and the selection forces is again disturbed, now favoring divergence, and the acquisition of secondary anomalies gains speed. The new imbalance is the result of both the inherent tendency of neoplastic cells to become increasingly unstable, and the organism's diminishing capacity to combat new and more malignant subclones as the disease wears the body down. Thus the secondary genetic complexity is of a principally different kind from the one seen during the convergence phase, and will also be cytogenetically recognizable as such. Whereas the early preconvergence complexity is characterized by clones that have no common karyotypic features, the heterogeneity of tumor progression is created by modifying the already existing clones, and thus some similarity between the various subclones is to be expected.

The essential function of such a neoplastic or preneoplastic focus might be to produce, through autocrine stimulation (71), high local concentrations of growth factors. Alternatively, if one wants to invoke a mechanism that combines cellular and holistic explanations, one could speculate that disruption of the microenvironment's topography (3) is the crucial effect.

Regardless of whether only one or numerous cells are pathogenetically necessary in the initiation process, what heterogeneity there is from the beginning may well be retained throughout the first tumor phases. Epithelial cells, relatively protected as they are from the organism’s defense mechanisms by cell-to-cell specializations and the basal membrane, are presumably less exposed to extensive selection than, for instance, bone marrow stem cells or other mesenchymal cells. Once the basal lamina is penetrated, once invasion starts, the resultant augmented selection will tend to weed out the less fit clones (genetic convergence), leaving the impression that the tumor was monoclonal from the beginning. If very successful, the selection may remove all neoplastic clones, completely ridding the organism of the neoplasm. In most cases, however, one or a few neoplastic clones survive and continue to invade the organism, in a manner indistinguishable from what would be seen if the tumor arose as a monoclonal growth.

Can the situations related above be reconciled with the bulk of cytogenetic, G6PD, and RFLP data (13, 15, 21), which strongly argue that monoclonality is the rule rather than the exception in epithelial tumors? One explanation capable of accommodating both types of evidence would be that the initial heterogeneity encountered in some (many?) epithelial tumors is later on reduced to pseudomonoclonality (“genetic convergence,” Fig. 3) through the influence of more efficient selection.

If this phenomenon is more common in carcinomas than in other types of tumors, this is perhaps no more than what might be expected. Epithelial cells through their location shield the organism from the surrounding sea of chemical and physical carcinogens, and it therefore seems reasonable to assume that early mutagenic (tumorigenic) events may not be as rare here as in for example the bone marrow. After all, most tumors are of epithelial origin. Providing that carcinogen exposure is a quantitatively important factor in this context, as much data indicate (69), simultaneous initiation of several cells in an epithelial field does not appear to be stochastically unlikely. The formation within a confined area of a “critical mass” of appropriately rearranged cells may indeed be an event of rate-limiting importance in the genesis of epithelial tumors (70).

*Unpublished results.*
Predictions Based on the Convergence-Divergence Model

Unquestionably, neoplasia is an exceptionally complex disturbance of cellular differentiation and proliferation and the mechanisms controlling these processes in multicellular organisms. Our understanding of the distinguishing biological features of tumorigenesis is still incomplete. It is quite possible that what we perceive as neoplastic growth constitutes a "final common path" of cellular dysproliferation, an end result that can be reached by several different pathogenetic pathways. In view of this heterogeneity, one may have to accept, as stated by Nowell (32), "some exceptions to any unitary approach." On the other hand, if falsification in the Popperian sense is ever to be achieved when testing theories describing complex biological phenomena, one has to pay heed to especially those instances that do not conform to the paradigmatic view. In Whitehead's words [as quoted by Rubin (72)]; "An unflinching determination to take the whole evidence into account is the only method of preservation against the fluctuating extremes of fashionable opinion." The problem addressed in this context is essentially: are the currently available data on the genetic rearrangements of neoplastic cells solid enough to conclude that some tumors do arise as polyclonal proliferations?

As outlined above, some G6PD studies have indicated that the neoplasms investigated were probably multiclonal (12, 23-25), and the same applies to a certain percentage of cytogenetically characterized tumors (66). However, mitotic recombination could explain signs of polyclonality in the G6PD assay (73), and an invisible somatic mutation might be the initiating change common to the apparently unrelated clones in cases like the carcinomas described in Ref. 67 and Ref. 68. The data as they exist today are therefore not sufficiently stringent to conclusively falsify the proposition that all cancers are monoclonal from their inception.

Turning the argument the other way round, can the apparent polyclonality of some, mostly epithelial, tumors be disproved? Initial heterogeneity evolving into pseudomonoclonality is a thoroughly logical proposition, and its occasional occurrence would be hard to rule out. The at present most critical testing would be to subject all cases which appear to be polyclonal, by either cytogenetic or X chromosome heteromorphism analysis, also to the other assay. For example, if only a single G6PD or X-linked RFLP variant is found in tumor cells from a constitutionally heterozygous woman, this strongly argues that any apparent cytogenetic polyclonality does not convey a correct picture of the neoplastic cell population. Unfortunately, no tumors with signs of a multifocal origin have as yet been tested in all clonality assays available.

We have suggested that cytogenetic polyclonality indicating multicellular tumor origin is an occasional finding in several tumors, perhaps, in accord with the "field cancerization" concept, especially in early carcinomas. Whether this proposition accurately describes a common pathway in tumor development can only be established when more such tumors are chromosomally characterized. The suggested evolutionary scenario implies that invasive squamous cell cancers may be found to be less karyotypically diverse than early in situ lesions. In later tumor stages, diversity again increases, but now in general some resemblance will be seen between the various subclones, if pseudomonoclonality was reached after the convergence phase. In addition to the importance of accumulating and assessing more cytogenetic data, some predictions inherent in the proposed scenario could be tested in experimental carcinogenesis. Support for the concept of early polyclonality comes from investigations of metastatic phenotype heterogeneity of mouse melanoma cell lines (74), and in particular from studies of X-linked heterozygosity at the phosphoglycerate kinase locus in chemically induced fibrosarcomas of the mouse (75). If evidence of initial pleoclonality developing into pseudomonoclonality and later evolutionary complexity could be detected also by cytogenetic analysis in these and other experimental systems, the credibility of the convergence-divergence model also would be greatly strengthened.

Conclusions

The genetic constitution of a population of neoplastic cells can either evolve toward greater complexity and diversity (genetic divergence), the population can become more homogeneous (genetic convergence), or it can remain genetically unchanged. At any given time in any given tumor, the question as to which of these three evolutionary tendencies is the dominating trend depends on the balance between two opposing influences: the genomic instability of the neoplastic cells and the selection pressure confronting them. In principle, four tumor progression scenarios are likely. (a) Clonal stability may persist from the inception of a tumor until the patient dies. (b) Clonal stability may be followed by divergence, leading to massive genetic heterogeneity in later stages. (c) A state of pseudomonoclonality may have been preceded by genetic convergence that eliminated all but one or a few clones from the initially heterogeneous neoplastic population. (d) Finally, initial convergence in a tumor cell population may give way to later divergence during disease progression.

Data now emerging from cytogenetic studies of neoplastic cells are compatible with all four scenarios. In hematological disorders and mesenchymal tumors, where the amount of information is largest, examples of both genomically stable malignant clones and genetic divergence abound. Recent evidence from epithelial tumors exemplifies early pleoclonality, apparent monoclonality in some tumors, as well as later divergence during tumor progression. The genetic pluralism that can be detected before genetic convergence has narrowed down the range of abnormalities is cytogenetically different from the complexity introduced during later evolutionary divergence. The tumor karyotype data and their interpretation within the convergence-divergence model therefore indicate systematic differences between different types of neoplasia in preferred progression pathways.

References

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