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The sigmoidal curve of cancer

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Aneuploidy, although observed in cancerous cells nearly a century ago, and until the 1960s considered the cause of malignant transformation, has been relegated to obscurity for the past 25 years, primarily because no specific chromosomal rearrangements have been described that correlate with specific cancer types. Some of the conflicting views on whether aneuploidy is necessary and sufficient for the initiation and progression of malignant transformation, or whether specific gene mutations initiate and maintain the altered phenotypes of cancer cells, have been recently discussed[1]. Although the vast majority of cancer research continues to focus on particular "cancer genes," the academic debate is far from resolved, and minority views, as illustrated in many cases in the history of science, may well end up at the front of the stage.

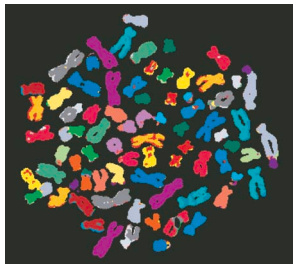
A growing list of papers supports a role for aneuploidy in the genetic underpinning of malignant transformation[2]. Of particular significance is a paper published last year by the Duesberg group[3] that comes very close to showing the existence of hitherto elusive, stage-specific chromosomal combinations (aneusomies). It does so by clearly demonstrating that particular aneusomies appear in nitrosomethylurea-transformed Chinese hamster cells *in vitro,* and in tumors derived from these cells *in vivo,* with a much higher frequency than would be expected based on random chromosome shuffling. For example, 79% of *in vitro*–transformed cells were trisomic for chromosome 3, and 59% were monosomic for chromosome 10; moreover, 52% of the transformed cells shared trisomy 3 and monosomy 10, much higher than the 0.6% expected if the aneusomies were the result of random chromosomal imbalances.

The initial interest of Duesberg and his collaborators in aneuploidy as a cause of the abnormal phenotypes characteristic of the cancer cell arose in part from observations that aneuploidy shows a nearly perfect correlation with neoplasia and malignancy, and that many of the most powerful carcinogens (for example, polycyclic aromatic hydrocarbons) are not mutagenic (genotoxic), as evaluated *in vitro* by any of the numerous variations of the Ames test[3].

In their first experimental exploration of this interest, the authors demonstrated that it is not possible to obtain neoplastic transformation of diploid embryonic cells without aneuploidization, preceding morphological changes that result in abnormal colony formation[4]. Once diploid cells were transformed *in vitro*, detailed study yielded some fascinating results. For example, karyotypes of the transformed cells were unstable to a degree roughly proportional to their distance from simple multiples of the "normal" (diploid) number of chromosomes[5]. Interpretation of this instability also provided a simple explanation for such phenomena as multidrug resistance[6] and the heterogeneity of transformed cell populations upon single-cell cloning[7]. This last phenomenon is familiar to anyone conversant with mammalian cell culture: if the cultured cells are of neoplastic origin, then the heterogeneity of cloned subcultures reveals itself in differing phenotypes (tumorigenicity, metastatic potential, and molecular markers), and if the cultured cells are of embryonic (diploid) origin, then they will eventually stop dividing or, alternatively, a few cells will emerge that will continue to divide but concomitantly will become aneuploid and exhibit aberrant phenotypes.

The mathematical treatment of the "aneuploidy hypothesis of cancer"[8]—to distinguish it in classic fashion from the dominant "gene-mutation hypothesis"—has provided insights into the possible mechanisms underlying all of the above phenomena as well as other properties of the neoplastic cell[9].

For example, derivations of metabolic control analysis formalisms show an outstanding congruence with available cytological data on cancer cells when the evolution of aneuploidy is treated as an autocatalytic process in which each generation of aneuploid cells is succeeded by another with differing degrees and types of aneuploidy and, hence, metabolisms[9]. The use of the logistic equation $\phi_{n+1} = r\phi_n(1 - \phi_n)$ to model the autocatalytic evolution of aneuploidy (where ϕ represents the aneuploid fraction of the genome from one generation to the next) has produced two astounding results: first, a model of the dynamics of the evolution of aneuploid cell populations that is sigmoidal and that fits with high correlation available data on incidence for a variety of malignancies; second, that the evolution of aneuploid malignant cells is chaotic, exploring numerous combinatorial possibilities with an attractor at DNA indices close to that of many observed mature cancers.



A highly aneuploid colorectal cancer cell in which chromosomes have been "painted" with chromosome-specific hybridization probes labeled with distinct fluorochromes. Several chromosomes present in three or more copies can be seen. Reproduced with permission from Jallepalli and Lengauer[14].

The power and appeal of this approach is that it not only models age of onset and DNA content, as reported for several common cancers, but also provides a number of hypotheses that can, and hopefully will, be tested in the laboratory. One example—the experimental exploration of the types of aneuploidy that may, more frequently, lie on those trajectories that lead to neoplasia and malignancy—has already been mentioned[3]. Further analysis of the specific aneusomies uncovered therein by means of the extensive palette available to the modern cytogeneticist should prove extraordinarily instructive.

The cancer cell is generally portrayed as a rogue supercell that somehow not only manages to "disobey" the environmental signals that should check its growth and determine its function, but also succeeds in colonizing other, sometimes very different, tissue environments. In the view of the aneuploidy hypothesis, the transformed cell is a damaged cell trying, against the clock, to resolve the ever-more-complex, irreversible, and unstable gene dosage it accumulated by

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self-complicating mitotic asymmetries. If it manages to do so, the cell will establish itself as, literally, a foreign species (at least karyotypically and in terms of total DNA content[10]) in its host, but the autocatalytic process of karyotypic evolution will continue and will spawn different cells, which ultimately will guarantee the survival of a subpopulation when chemotherapeutic or other challenges appear.

It is now widely accepted that a few genes control the process of malignant transformation, genes whose net output is a highly anomalous metabolism that will permit survival in spite of environmental signals (contact inhibition, endocrine and paracrine regulation, and so on). The hypothesis, however, provides no explanation of how this metabolism arises; it simply states that cell growth is affected by sequence changes in oncogenes or tumor suppressor genes, which results in anomalous proteins, anomalous expression levels, or both. Its main support consists of statistical correlation—by no means as suggestive as the >99% seen with aneuploidy—between various mutations in single or small groups of genes and neoplasia and transformation, clinical or experimental. One of the first "chip" studies on relative expression levels of several thousand genes in normal and malignant colonic cells, however, detected no significant differences in oncogene expression levels, as puzzlingly admitted by the authors[11].

If performing thousands of quantitative northern blots simultaneously does not offer a clear corroboration of the accepted role of the "cancer genes," then what is next? It may well be time to consider the role not of particular genes, but of the altered dosages of thousands of genes resulting from aneuploidy. When the data of the aforementioned chip study were analyzed in the context of the metabolic control analysis–aneuploidy hypothesis, it was quite clear that the largest differences between malignant and normal colon cells related to thousands of genes being expressed with small differences (consistent with chromosome imbalance), rather than a few genes being expressed at very different levels[8].

The sigmoidal curve describes phenomena in which very little change is apparent as a response to stimuli, until a threshold is reached that marks the onset of dramatic transformations (such as a phase transition or the ability to use a language) until a new stable state is reached that is also apparently non-responsive. If that curve reflects the receptivity of the scientific community to new conceptualizations, the distance to the threshold—for the aneuploidy hypothesis at least—looks to be closing fast.

A recent paper by Pollack *et al.*[12] describes the results of performing a highly normalized study of correlation between gene copy number and mRNA levels in breast cancer cells and cell lines. These authors confirm that the main differences between normal and transformed cells lie in the *number* of genes, rather than in the *types* of genes differentially expressed. An even more recent paper from the Vogelstein laboratory[13] also attributes an initiating role to aneuploidy in cancer and develops a mathematical treatment with which to explain it. This model, however, remains rooted in specific gene mutation, and the mathematics is commensurately convoluted and unsatisfying since it provides no obvious experimental insights, as the authors themselves state.

It may take only the realization that individual genes are just parameters in networks, rather than isolated causes, to do away with genocentric models of cancer in particular and life in general.

After over 1,000 years of celestial spheres and epicycles, it needed only the recognition that the circle is a special case of the ellipse to do away completely, in a small fraction of that time, with the geocentric model of the solar system. It may take only the realization that individual genes are just parameters in networks, rather than isolated causes, to do away with obsessive and ever-more-abstruse genocentric models of cancer in particular and life in general.

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