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Models of Tumor–Host Interaction as Competing Populations: Implications for Tumor Biology and Treatment

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Population ecology mathematical models examine tumors not as an isolated collection of transformed individuals but as part of a dynamic society of interacting malignant and normal cells. This approach investigates the mechanisms by which a small clone of neoplastic cells is able to replace the much larger and previously stable population of normal cells, despite the numerical advantage of the latter and the inhibitory effects of the host response. The models define a sequence of different stable equilibria with critical mathematical parameters which control the outcome of different stages of the neoplasm-host competition—parameters which can be correlated with cellular physiologic properties. When neoplasm is viewed as a network of interacting tumor and normal populations, a unifying hypothesis can be developed that allows the diverse but inconsistent properties of transformed cells to be understood according to their specific contributions to tumorigenesis within this network. It predicts general sequences of genetic changes necessary for tumor survival and invasion and demonstrates that apparently disparate properties found in different tumor models can be functionally equivalent. The paper proposes novel modes of therapy requiring classification and treatment of tumors according to the strategies they employ, rather than the traditional criteria of cell type and organ of origin.

Introduction

Malignant tumor growth is the result of multiple genetic and epigenetic changes, where each one is insufficient, by itself, to transform the cell but lead to cancer when summed by accumulation. These changes are quite heterogeneous and no single genetic defect, set of defects, or sequence of defects is found in all cells exhibiting a transformed phenotype (Bishop, 1988; Weinberg, 1989; Cho & Vogelstein, 1992).

At a cellular level, each genetic change has the potential to produce a subpopulation with physiologic properties distinctly different from its predecessors. These genetic changes and their physiologic counterparts in turn control the interaction of the developing tumor populations with each other and with normal cells, producing tumor "behavior" ranging from benign, limited growth to gradations of aggressiveness and lethality to the host.

Myriad but inconsistent differences have been reported between transformed and normal cells and, as with changes in the genotype, no single property or set of properties is found in all tumor populations (Fidler & Hart, 1982). The importance of these differences is frequently unclear. It is imperative to separate insignificant, random changes from those which ultimately confer upon a transformed population the characteristics that control its interaction with the host.

Population ecology provides a novel conceptual framework for examination of the tumor–host interface (Gatenby, 1991). Each volume of tissue can be modeled as a cellular community populated by "species" of epithelial and mesenchymal cells that are dynamic equilibrium with each other and the environment. Malignant transformation initially produces a small number of individuals from a "tumor" species, which are immediately enmeshed in

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a complex web of interactions with the normal cells in the community. For tumorigenesis, the transformed cells must evolve properties which allow acquisition of space and resources from the existing population despite the numerical advantage of the latter and the inhibitory activities of the host response.

Models of the tumor–host interaction as competing populations are explored to define the critical parameters that control the outcome, so that the phenotype changes observed in malignant cells can be understood according to their contributions to tumorigenesis.

Mathematical Model

The interaction of populations can be described using the Lotka–Volterra population equations. Although these equations require simplifying assumptions, they have successfully been applied to a large number of complex population interactions in nature (May, 1977; Williamson, 1989; Summers & Wu, 1990). Michaelson *et al*. (1987, 1993) has applied similar population based equations to competing subpopulations within a tumor. Furthermore, clinically measurable tumors exhibit a decelerating pattern of growth (Laird, 1965, 1969; Lala & Patt, 1966; Sullivan & Salmon, 1972; Fearon *et al*., 1987; Spratt, 1992) which is best fit (Spratt *et al*., 1992) by the logistic equation as predicted by the Lotka–Volterra models.

Tumor cells and normal cells are, thus, modeled as populations competing for space and other resources in some small volume of tissue within an organ. In this analysis, the heterogeneity of tumor cell societies and the varied cell types present in normal tissue are simplified by assuming that a dominant normal (N_2) and tumor population (N_1) exist at any given time.

$$\frac{dN_1}{dt} = r_1 N_1 \left(\frac{K_1 - N_1 - \alpha_{12} N_2}{K_1} \right) \tag{1}$$

$$\frac{dN_2}{dt} = r_2 N_2 \left(\frac{K_2 - N_2 - \alpha_{21} N_1}{K_2} \right), \tag{2}$$

where:

N_1 = a population of tumor cells;
N_2 = the population of normal cells from which the tumor arises;
r = the intrinsic rate of growth for each population;
K = carrying capacity or maximum number of cells from each population which could occupy the tissue space and be adequately supported by the environment in the absence of the competing population;
α_{21} = competition coefficient measuring the effects on N_2 caused by presence of tumor cells N_1;
α_{12} = competition coefficient measuring the effects on N_1 caused by the presence of N_2. Because this interaction can be complex and variable, it is divided into growth inhibitors and stimulators;
$\alpha_{12} = \alpha_{12i} - \alpha_{12s}$, with
α_{12i} = quantitation of the host inhibitory effects on the tumor population including immunologic response and contact inhibition;
α_{12s} = interactions with the host (i.e. growth factors) which stimulate tumor cell growth.

As shown in Fig. 1, interaction of the tumor population with the native host cells may result in three non-trivial stable steady states: (1) extinction of the original population; (2) a stable equilibrium in which the transformed cells co-exist with normal cells; or (3) extinction of the invading population. Inspection of Fig. 1 suggests three phases of tumor growth. The first occurs immediately following the emergence of a transformed clone following initiation and determines whether the system will return to its prior steady state in which $N_2 = K_2$ and $N_1 = 0$. That is, it determines the survival of the tumor clone. If the clone persists, the system must move to one of two new steady states: (1) Tumor coexists with normal tissue corresponding to unaggressive tumor growth which may arbitrarily be classified as benign (if a large normal population persists) or indolent cancer (if only a small normal population persists). (2) Tumor entirely destroys the normal population corresponding to aggressive, highly malignant cancer.

To analyze these phases further, the interactions of normal tissue with an emerging tumor population (phase 1) can be modeled by rewriting eqns (1) and (2) with the constraints that N_2 equals approximately K_2 and N_1 is very small:

$$\frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{N_1}{K_1} - \frac{\alpha_{12}}{K_1} N_2 \right) \tag{3}$$

$$\frac{dN_2}{dt} = r_2 N_2 \left(1 - \frac{N_2}{K_2} - \frac{\alpha_{21}}{K_2} N_1 \right). \tag{4}$$

For N_1 small ($N_1 \ll K_1$) and N_2 at or near K_2 then $N_1/K_1 \approx 0$ and $N_2/K_2 \approx 1$, eqns (3) and (4) can be

reduced to

$$\frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{\alpha_{12}}{K_1} N_2\right) \tag{5}$$

$$\frac{dN_2}{dt} = r_2 N_2 \left(-\frac{\alpha_{12}}{K_2} N_1\right). \tag{6}$$

The small transformed population will survive only if $dN_1/dt > 0$ and $dN_2/dt \leqslant 0$ for N_1 small and N_2 near K_2. Using eqn (5)

$$\frac{dN_1}{dt} > 0 \text{ only if } 1 - \alpha_{12} N_2/K_1 > 0 \tag{7}$$

and

$$\alpha_{12} < \frac{K_1}{N_2} \tag{8}$$

or

$$\alpha_{12i} - \alpha_{12s} < K_1/N_2. \tag{9}$$

If N_2 can be approximated as K_2 then

$$\alpha_{12} < K_1/K_2 \tag{10}$$

and eqn (6) becomes

$$\frac{dN_2}{dt} \leqslant 0 \text{ if } \frac{\alpha_{21}}{K_2} \geqslant 0$$

and thus

$$\alpha_{21} \geqslant 0 \tag{11}$$

This is again illustrated in graphs of the isoclines of eqns (1) and (2) shown in Fig. 1. Requirements for initial tumor growth are apparent in the phase plane when N_1 is very small and N_2 is near its equilibrium state K_2. Under these conditions, the system will not return to its prior steady state and tumorigenesis will

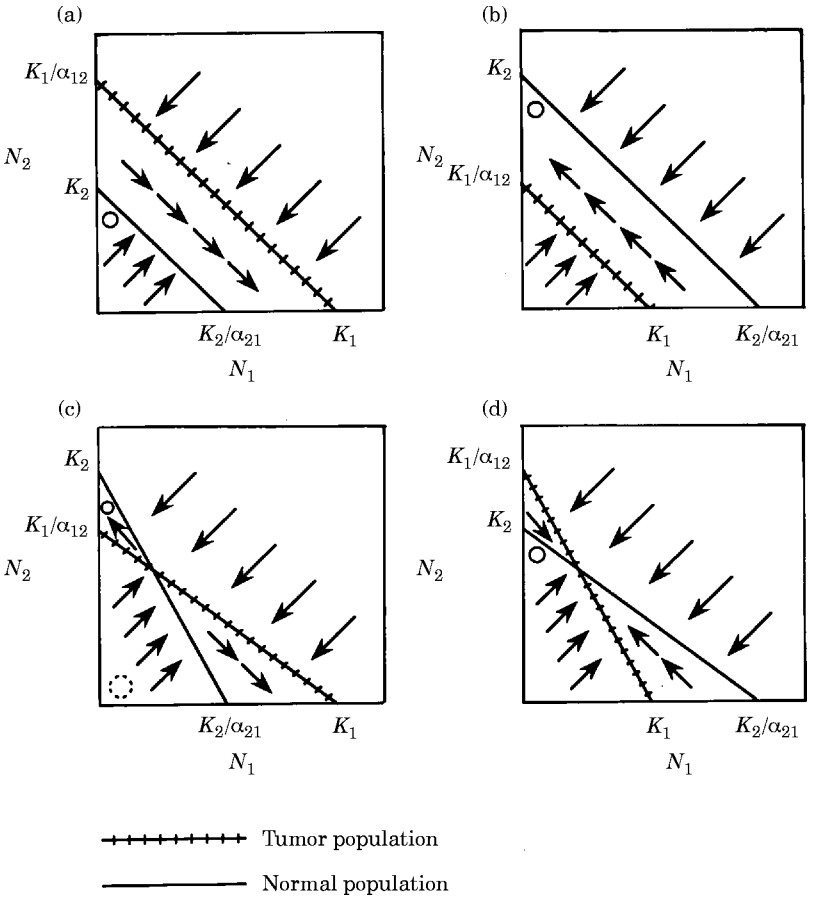

FIG. 1. Four possible arrangements of the isoclines and stable steady states for N_1 and N_2 in eqns (1) and (2) derived by setting $dN_1/dt = dN_2/dt = 0$. The vectors demonstrate the direction of dN_1/dt and dN_2/dt for any point on the phase plane. The solid circles represent sets of points typical in the early phase of tumor growth with N_1 small and N_2 near K_2. Tumor survival from these points occurs in the pairs of isoclines in which $\alpha_{12} < K_1/K_2$ [panels (a), (c)]. Tumor rejection occurs if $\alpha_{12} > K_1/K_2$ [panels (b), (d)]. Following the survival phase, the populations evolve into aggressive, malignant growth patterns in which the normal cells (N_2) are eliminated [panel (a)] or unaggressive growth resulting in a stable combination of N_1 and N_2 [panel (d)]. The former occurs only if $\alpha_{21} > K_2/K_1$. Panel (c) demonstrates that under some conditions tumorigenesis may occur when N_2 is small (dotted circle) but not when N_2 is near K_2 (solid circle).

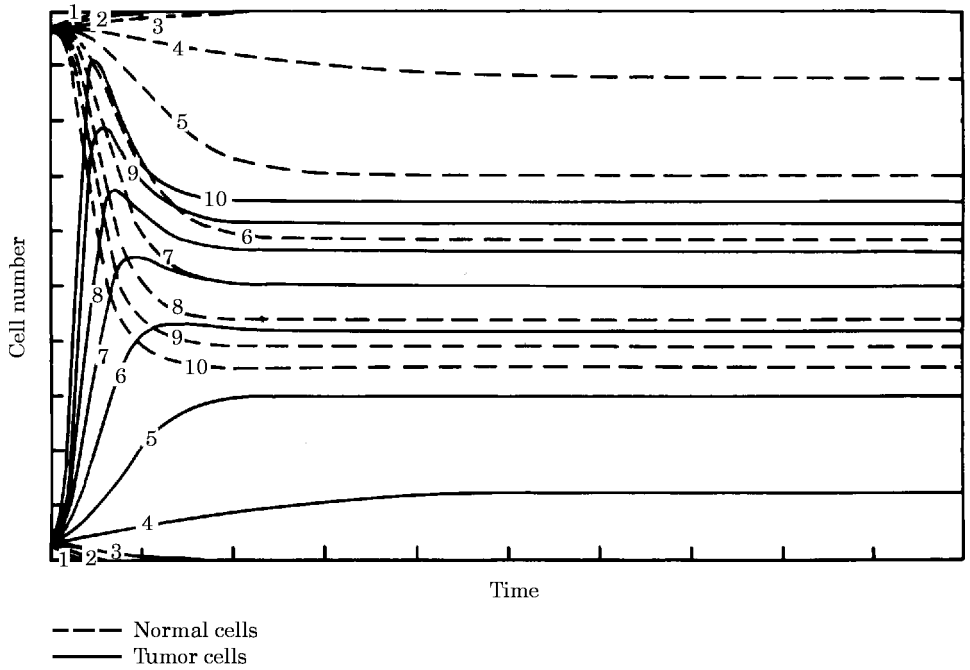

FIG. 2. A family of curves demonstrating the effects of decreasing $\alpha_{12i}-\alpha_{12s}$ of the initial or survival phase of tumor growth. The initial conditions assume that the tumor population is small ($N_1 \ll N_2$) and avascular ($K_1 \ll K_2$). When $\alpha_{12i}-\alpha_{12s} > K_1/N_2$ (curves 1,2,3) the host response destroys the tumor population. As α_{12s} increases, $\alpha_{12i}-\alpha_{12s}$ decreases through the K_1/N_2 threshold (curves 4–10), the tumor population survives despite the host response with a final steady state in which the tumor population can be less than (curves 4–6), the same as (curve 7), or greater than (curves 8–10) the persisting normal population.

occur only if the vector in the adjacent isocline associated with the initial conditions is pointing to the right. As can be seen in Fig. 1, this occurs only when $\alpha_{12} < K_1/K_2$—a conclusion identical to eqn (10).

This simple analysis yields broad insight into the phenotypic changes required for survival of the transformed clone. First, it defines the requirement that $\alpha_{21} \geqslant 0$. This is requires that the tumor cells and the growth factors they produce not enhance growth of normal cells.

Equation (9) and Fig. 1 define the additional condition necessary for survival of the tumor clone:

$$\alpha_{12s} > \alpha_{12i} - K_1/N_2$$

Inspection of this term suggests two phases in early tumor growth. In the period immediately following the initiating genetic events in a single transformed individual, the clone consists of one or a small number of cells with no vascular support. Substrate delivery to the clone is dependent on diffusion from surrounding tissue which results in a smaller carrying capacity than that of vascularized normal tissue ($K_1 \ll K_2$). Under these conditions, K_1/N_2 is relatively insignificant and eqn (9) can be approximated as:

$$\alpha_{12s} > \alpha_{12i}.$$

Thus, survival of the small tumor clone is dependent on factors generated by the host. Clonal persistence occurs only if it is supported by positive growth factors produced by normal cells. This support must quantitatively exceed the negative effects of contact inhibition and other mechanisms by which the normal population might reduce tumor growth. Thus, the initiation events must include genetic changes which allow stimulatory effects produced by the host and acting on the tumor to exceed the host growth constraints.

A second phase of early growth can also be predicted if the transformed clone proliferates—an event analogous to the promotion phase in classic models of carcinogenesis. In this setting, the initial assumptions that N_1 is small and N_2 is large will not continue to hold. Since tumor expansion requires a decline in the normal population, the value of the K_1/N_2 will progressively increase and, when sufficiently large, will dominate the $\alpha_{12i}-K_1/N_2$ term. Thus, the models predict that the host response to tumor will become progressively less significant as the tumor grows. Furthermore, as the K_1/N_2 term becomes larger, the dependence of stimulation by host will decrease because $\alpha_{12i}-K_1/N_2$ will get progressively smaller.

When the two phases of early growth are completed,

the host response has been overcome and some form of tumor growth is assured. The tumor at this point is relatively independent of both positive and negative host effects. However, as shown in Fig. 2 the early genetic changes necessary for tumor population survival are insufficient to allow invasive tumor growth. The changes which have occurred in the transformed population thus far are sufficient only to achieve a steady state in which the tumor coexists with normal cells. This state is, nevertheless, premalignant because one or more of its members can acquire an invasive phenotype if additional genetic changes confer cellular properties which fulfill the necessary conditions. Biologically, therefore, this initial steady state is equivalent to benign tumor growth (but with malignant potential such as a colon adenoma) or noninvasive malignancy such as carcinoma *in situ*.

Population models can again be examined to predict the physiologic changes that will produce malignant or invasive behavior. This is essentially a search for conditions which produce asymptotic behavior approaching a new steady state with the tumor population completely replacing the normal population. Requirements for malignant growth can be determined by allowing eqns (1) and (2) to approach 0 with the condition that N_2 declines toward 0 as the steady state is approached. Because, as N_2 declines $\alpha_{12}N_2/K_1$ approaches 0, eqn (3) becomes:

$$\frac{dN_1}{dt} = r_1 N_1\left(1 - \frac{N_1}{K_1}\right)$$

For $dN_1/dt \geqslant 0$, $N_1 < K_1$ and eqn (4) becomes:

$$\frac{dN_2}{dt} = r_2 N_2\left(1 - \frac{\alpha_{21}N_1}{K_2}\right).$$

For $dN_2/dt \leqslant 0$ as K_1 approaches N_1:

$$\alpha_{21} \geqslant K_2/K_1$$

Identical conclusions can be derived by inspection of Fig. 1.

Thus, from the initial pre-malignant tumor, an invasive subpopulation will emerge if the clone accumulates genetic changes such that the subpopulation displays one of the following strategies: (1) Maximize α_{21}, which requires tumor cells to be extremely successful in competing with normal cells for available substrate and space. (2) Maximize K_1, which requires that the tumor cells create an environment which increases the carrying capacity for the tumor population (Fig. 3). (3) Minimize K_2 by reducing the carrying capacity of the environment for normal cells (Fig. 4).

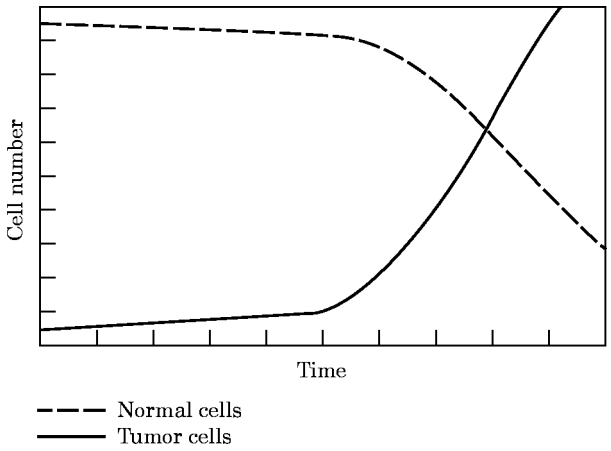

FIG. 3. The first half of the curve represents the early phases of tumor growth with parameters identical to curve 4 in Fig. 2. Although tumor survival is achieved, it is relatively unaggressive and coexists with a persistent population of normal cells. Acquisition of angiogenesis is modeled by a stepwise increase in K_1, at time 0 and results in exponential tumor growth with destruction of the host population.

An interesting exception to the constraints on tumorigenesis is seen when transformation occurs in tissue which has been damaged by trauma, infarction or inflammation. This produces initial conditions in which $N_2 < K_2$. Thus, in eqn (9) the K_1/N_2 term is substantially increased and dN_1/dt can be greater than 0 under conditions that would have produced $dN_1/dt < 0$ if $N_2 = K_2$. This is illustrated in Fig. 5. Thus, the models predict that pre-existing damage to normal tissue creates a cellular ecology that is relatively permissive for tumor growth.

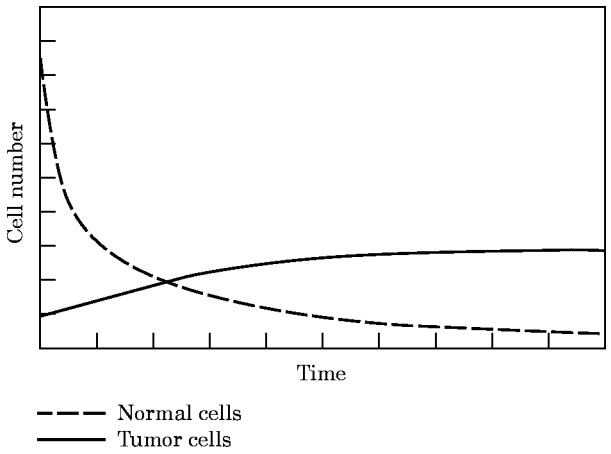

FIG. 4. Tumor–host interaction with initial conditions identical to the steady state of curve 4 in Fig. 1. In the second phase of tumor growth the tumor cells are non-angiogenic but develop phenotypic changes that cause a decline in N_2 either because of a large α_{21} or by decreasing K_2. Both strategies result in a rapid decrease in the host population but somewhat limited tumor growth because of the persistently small K_1. Morphologically, this tumor, although malignant, would be hypocellular with areas of necrosis.

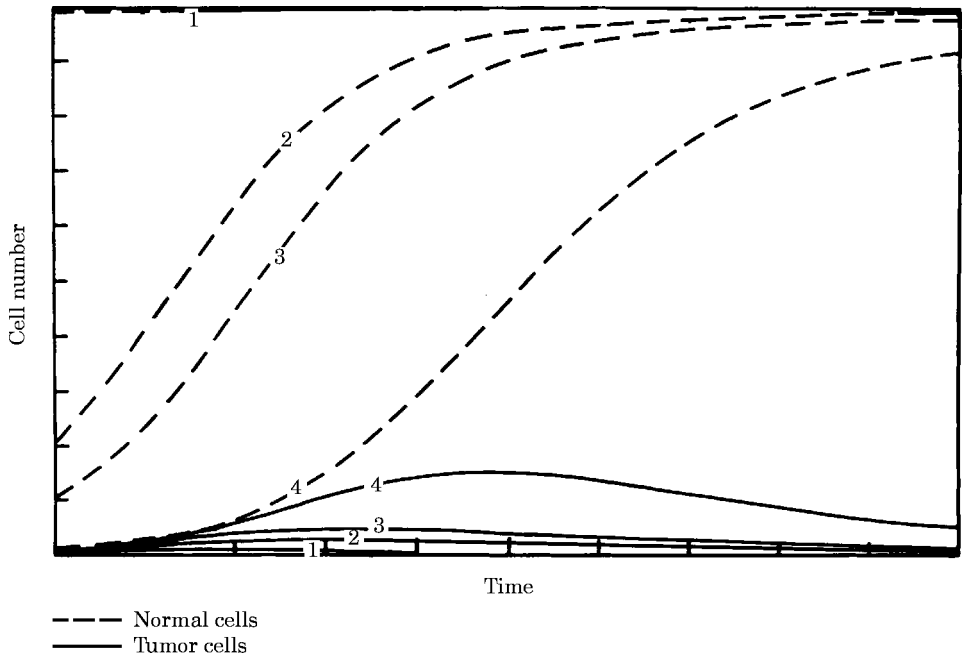

FIG. 5. A family of curves showing the permissive effects of a decline in the normal population on tumor growth following transformation. With the given initial conditions, tumorigenesis does not occur if the normal cell population is near its carrying capacity (curve 1). If the normal population declines prior to transformation (curves 2, 3 and 4), tumor growth occurs in the damaged tissue even though the other parameters are unchanged from curve 1.

Discussion

The monoclonal origin of tumor has been demonstrated in multiple studies (Fearson *et al*., 1987; Korczak, 1988). Although clinically evident neoplasms are usually the product of a single cell, accumulated genetic changes allow multiple phenotypic iterations producing evolving subpopulations with different physiologic properties and capable of different interactions with host. Each tumor population can either be driven to extinction by the immune system and other host response, proliferate and drive the normal cells to extinction, or achieve a stable equilibrium with the normal cells. Population ecology examines tumor in terms of competing populations and defines parameters which control the fate of the tumor–host dynamics.

The model predicts three phases of clonal growth each dominated by a different set of parameters. This first phase occurs immediately after the initiation events in carcinogenesis and determines the survival of this small transformed population. Under the conditions expected in very early tumor growth (N_2 large and K_1 and N_1 small) clonal survival is dependent entirely on its response to host-generated effects (α_{12}). The emerging tumor population, therefore, must accumulate genetic changes which produce a phenotype with enhanced responsiveness to the stimulatory effects of host growth factors and decreased responsiveness to growth constraints such as contact inhibition. At this stage, immunologic response can suppress tumor growth, consistent with the concept of immune surveillance. However, even a substantial immunologic attack can be overcome if the transformed population is sufficiently supported by growth factors.

Numerous local and systemic factors stimulating tumor growth have been identified. Heightened sensitivity to circulating estrogen and progesterone have been reported in some breast cancers (Dickinson *et al*., 1992; Lowry, 1993) and androgens in some prostate cancers (Geller, 1993; Schroder, 1993). Increased expression of the epidermal growth factor receptor (EGFR) has been found on the surface of breast, lung, bladder carcinoma and melanoma cells (Sainsbury *et al*., 1985, 1988; Berger, 1987; Elder *et al*., 1989; Veale *et al*., 1989). Other receptor molecules are also known to be expressed at abnormally high levels in some cancer cells, including the platelet derived growth factor (PDGF) and insulin-like growth factor (ILGF) receptors (Cullen *et al*., 1992). This appears to provide a persistent stimulation for tumor growth.

Alternatively, tumor cells may develop increased responsiveness to as yet unknown local factors such as those produced in bone marrow and bone resorption products which enhance prostate cancer metastases (Chackal-Roy *et al*., 1989; Rossi & Zetter, 1992). Bone and platelet mediated factors are also reported to

promote growth of Walker 256 sarcoma cells (Miller-Brook *et al*., 1990; Kostenuik *et al*., 1992), and normal fibroblasts may stimulate mammary, prostate, and bladder carcinoma and melanoma (Hodges *et al*., 1977; Kabalin *et al*., 1989; Miller *et al*., 1989; Camps, 1990; Cornil, 1991; Cullen *et al*., 1991).

The population ecology model predicts that all *in situ* tumors, benign or malignant, must initially develop at least one of these phenotypic properties to survive. However, these parameters dominate tumor growth only when it is relatively unaggressive, coexisting with normal tissue. After this phase, tumor response to positive and negative effects of the host diminishes. Thus, clinical manipulation of host-generated effects on the tumor, such as through hormone therapy (especially in breast and prostate cancer) or through biological modifiers designed to enhance the immune response, will be effective in the first phase of tumor growth but will become progressively less if new, more aggressive clones emerge allowing the tumor to make the transition from the first two phases of growth into the third.

The genotypic and phenotypic changes required for clonal survival and expansion following initiation and promotion are sufficient only for limited tumor growth (Fig. 2). Invasive tumor will arise from these pre-malignant states only with acquisition of additional phenotypic traits. This allows prediction of genotypic changes necessary (Figs 3 and 4) for the third phase of tumor growth.

Mathematically, tumor invasion of host is dependent on the carrying capacity for tumor (K_1) and normal cells (K_2) and the competitive effects of the tumor on the normal tissue (α_{21}). These yield three equivalent strategies of genotypic and phenotypic changes.

First, the tumor could increase its own carrying capacity (K_1). This can be accomplished through acquisition of angiogenesis. Vascularization of the tumor population increases substrate delivery and therefore increases the carrying capacity. As shown in Fig. 3, this results in explosive growth of a tumor population that has emerged from the survival phase of tumor growth in a relative steady state with the normal tissue.

This is consistent with studies of several tumor models that have shown that non-angiogenic growth is limited but a switch to angiogenic phenotype results in rapid, unrestricted growth (Folkman, 1989, 1992; Folkman *et al*., 1989, 1991). Angiogenesis appears to be a prognostic indicator in human breast cancer (Weidner *et al*., 1991, 1992) and antiangiogenic agents are currently being explored for tumor therapy (Rastinejad *et al*., 1989).

An alternative strategy to increase K_1 is to produce autocrine growth factors. In this case, tumor cells produce growth factors that provide environmental support for further increases in the tumor population. Experimental results have shown that autocrine growth factors may increase the carrying capacity by a factor of 30 (Lippman *et al*., 1986).

The second strategy maximizes α_{21}, which measures the competitive effects of the tumor population on the normal cells. In competing, non-predatory populations, the competition coefficient (α) generally represents the deprivation of resources in one population caused by the presence of the other population. By analogy, the presence of tumor cells may cause a decline in the normal cell populations by acquiring substrate ordinarily available to the normal cells. Numerous investigators dating back to Warburg (Warburg, 1930; Hatanaka *et al*., 1969; Kalckar *et al*., 1973) have observed that tumor cells generally acquire glucose and other substrates more avidly than normal cells, and in at least one system this is linked to oncogene activation (Flier *et al*., 1987). This asymmetric distribution of resources may be sufficient to produce a large α_{21} in some tumor models, as has previously been shown (Basset *et al*., 1990). An alternative tumor trait, which might result in a large α_{21}, is a tumor product that is directly toxic to normal cells. This has been demonstrated in one tumor line (Zucker *et al*., 1993).

A third strategy available to the tumor is reduction of the environmental carrying capacity for normal cells (K_2). This corresponds to findings in some tumor models in which the tumor invades by breaking down the extracellular matrix in adjacent normal tissue through metalloproteinase, which the tumor produces directly or induces in adjacent fibroblasts (Basset *et al*., 1990; Ossowski *et al*., 1992; Pyke *et al*., 1992). The increased interstitial pressure, frequently found in other tumor models, (Less *et al*., 1992) is a mathematically equivalent trait. This results in compression of the adjacent normal tissue resulting in reduced blood flow and increased mechanical stress on the normal cells, both of which will decrease K_2.

As shown in the mathematical analysis, the above three strategies are equivalent. Each can produce malignant growth independent of the other strategies. Thus a set of genetic changes producing one of the above phenotype is necessary but any of the sets is sufficient for invasive growth. All tumor populations that are malignant *in situ* must express one of these phenotypic patterns. Conversely, no single phenotypic patterns should be expected in all tumor models and the concept of equivalent strategies must be employed to understand the highly diverse but inconsistent

properties that are observed in tumor cells. Finally, properties found in tumors which do not fit one of the necessary conditions for the survival or invasion are the result of random genetic events, insignificant in tumorigenesis.

It should be noted that adoption of any one of these strategies does not insure malignant growth. For example, an angiogenic tumor can still behave in a "benign" manner if the increase in K_1 caused by the development of angiogenesis does not exceed the threshold value of K_2/α_{21}.

Population ecology models also have implications for therapeutic strategies in the invasive phase of tumor growth—a phase that without intervention will ultimately be lethal to the host. Malignant growth produces a stable steady state in which N_1 will approach K_1 and N_2 will approach 0, as shown in Figs 1(a) and (c). From this point, even if cytoreductive therapy decreases N_1 substantially, provided $N_1 > 0$, dN_1/dt will remain greater than 0 and the tumor population will regrow [as shown by the phase plane vectors in Figs 1(a) and (c)] until the steady state of $N_1 = K_1$ and $N_2 = 0$ is re-established. This repopulation can be prevented only if N_1 is reduced to 0 or if the isoclines on the phase plane are altered. Inspection of Fig. 1 demonstrates that conversion of the tumorigenic isocline patterns of Fig. (a) and (c) to those which do not allow malignant growth in (b) and (d) can be most simply accomplished by increasing K_2, the carrying capacity for normal cells.

This predicts that therapies directed only at the tumor population will generally be inadequate. Successful tumor therapy requires enhancement of the competitive state of adjacent normal cells. Treatment strategies must, therefore, also be developed to increase the carrying capacity of the environment for normal cells. The specific mode of therapy will be dependent on the strategy employed by the tumor. Infusion of metalloproteinase inhibitors will be effective in tumors which invade using metalloproteinases to breakdown the ECM. Growth factors which stimulate normal cells but not tumor cells, could promote normal cell expansion. Anti-angiogenic approach will be effective in tumors which use the "angiogenic strategy". Reduction of tumor interstitial pressure (if this is the mechanism of invasion), could allow increased blood flow and decreased mechanical stress in normal cells at the tumor–host interface.

Conclusion

Population ecology models view cancer not as the inevitable expansion of a single transformed population but as a web of interacting tumor and normal cells with multiple potential outcomes. They demonstrate malignant tumor as the final common pathway of many possible combinations of accumulated genetic defects and their resulting phenotypic expression that alter the dynamics of the interacting populations. The analysis predicts the sequence and types of phenotypic changes necessary neoplastic growth and thus demonstrates various strategies which may be employed for tumor survival and invasion. Diverse, apparently unrelated characteristics found in different tumor models are shown to be functionally equivalent in promoting tumor expansion. These critical traits in the tumor–host interaction can be separated from those that are not. However, the model concludes that the fundamental defect in cancer is genetic instability and that the observed physiologic traits are selected from multiple genetic iterations because they represent properties which allow subclones successfully to expand within their own unique cellular ecology.

This approach provides a unifying hypothesis that allows the diverse traits of tumor cells to be understood according to their contribution to tumor survival or tumor invasion within the host. It predicts possible new approaches to therapy, emphasizing definition of the tumor strategies employed and designing countermeasures to enhance the competitive status of normal cells at the tumor–host interface, rather than relying exclusively on cytoreductive techniques directed at the tumor populations only.

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