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Application of Competition Theory to Tumour Growth: Implications for Tumour Biology and Treatment

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To assess critical parameters controlling tumour growth and response to therapy, competition theory models the tumour–host interface as a network of interacting normal and malignant cell populations using coupled, non-linear differential equations. When the equations are analysed under conditions which simulate tumour development, three phases of tumour growth, each with different critical parameters, can be predicted. Transitions between these phases correspond to the initiation, promotion and invasion stages demonstrated in experimental models of carcinogenesis. Critical cellular properties for each transition are predicted including phenomena already demonstrated experimentally such as the linkage of invasive tumour growth with acquisition of angiogenesis. The model also predicts the previously unknown phenomenon of "functional equivalence" in which disparate tumour traits can play identical roles in tumour growth and invasion. This approach allows the diverse but inconsistent properties of transformed cells to be understood according to their specific contribution to tumorigenesis. The models have significant implications for treatment strategies. Copyright © 1996 Elsevier Science Ltd

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INTRODUCTION

CARCINOGENESIS IS the consequence of multiple genetic or epigenetic changes. However, no single defect, set of defects, or sequence of defects is observed in all cells exhibiting a transformed morphology [1–3]. Similarly, myriad phenotypic differences have been reported between transformed and normal cells but, as with changes in the genotype, no single property or set of properties is found in all tumour populations [4]. Thus, while multiple genetic, epigenetic and phenotypic differences between normal and tumour cells have been observed, the specific role of each difference in tumorigenesis is frequently obscure. Insignificant, random changes, resulting from the inherent instability of malignant cells, must be distinguished from the critical properties which confer upon a transformed population the characteristics controlling its interaction with the host.

Numerous mathematical models of cancer have been proposed. Some are purely descriptive, such as those which fit tumour growth to Gompertzian [5] or exponential [6] functions. Others are highly mechanistic, generally proposing specific growth controls and examining tumour behaviour within the context of those mechanisms [7–10]. The former method is limited because it gives no insight into critical parameters for tumour growth, while the latter assumes specific mechanisms and excludes many potentially important areas of tumour biology.

Competition theory provides a novel descriptive framework which also allows examination of critical parameters controlling the tumour–host interface by viewing it as a population invasion analogous to those found in nature [11]. Although normal tissue is a co-operative, non-competitive cellular community, genetic or epigenetic changes in a member of this community will produce a new "tumour" species and new population dynamics. The fate of these transformed individuals depends on a complex web of interactions. For tumorigenesis, transformed cells must evolve properties which allow them to acquire space and resources at the expense of the native populations, despite the numerical advantage of the latter and the inhibitory effects of the host. Thus, competition theory may provide insight into critical factors in the tumour–host interaction, through application of mathematical models of competing populations, already well developed in the discipline of population ecology, to the problem of cancer. Although these models require simplifying assumptions, they have successfully analysed a wide variety of complex population interactions in nature [12–14].

MATHEMATICAL MODEL

Tumour cells and normal cells are modelled as populations competing for space and other resources in an arbitrarily small

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volume of tissue within an organ. The hererogeneity of tumour cell societies and the varied cell types present in norml tissue are simplified by assuming that a dominant normal (N_2) and tumour population (N_1) exist at any given time. A common model of interacting populations is:

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

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

where N_1 = tumour population, N_2 = the population of normal cells from which the tumour 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 tumour cells N_1, α_{12} = competition coefficient measuring the effects on N_1 caused by 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 including immunological response, contact inhibition, induction of terminal differentiation or apoptosis, α_{12s} = host produced growth factors which stimulate tumour cell growth.

To examine very early tumour growth, equations (1) and (2) can be rewritten and examined under conditions in which $N_2 = K_2$ and N_1 is very small:

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

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

For N_1 small ($N_1 \ll K_1$) and N_2 at or near K_2

$$\frac{N_1}{K_1} \approx 0$$

$$\frac{N_2}{K_2} \approx 1.$$

This allows equations (3) and (4) to be reduced to

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

$$\frac{dN_2}{dt} = r_2 N_2\left(- \frac{\alpha_{21}}{K_2} N_1\right). \quad (6)$$

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

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

$$\text{and } \alpha_{12} < K_1/N_2 \quad (8)$$

$$\text{or } \alpha_{12i} - \alpha_{12s} < K_1/N_2 \quad (9)$$

if N_2 can be approximated as K_2, then

$$\alpha_{12} < K_1/K_2 \quad (10)$$

and (6)

$$\frac{dN_2}{dt} \leq 0 \text{ if } \frac{\alpha_{21}}{K_2} \geq 0$$

$$\text{and thus } \alpha_{21} \geq 0. \quad (11)$$

This simple analysis yields broad insight into the phenotypic changes required for survival of the transformed clone. First, it defines the requirement that $\alpha_{21} \geq 0$. Biologically, this requires that tumour cells do not enhance growth of normal cells.

Equation (9) defines the additional condition necessary for survival of the tumour clone:

$$\alpha_{12s} > \alpha_{12i} - K_1/N_2. \quad (12)$$

Inspection of this term suggests two phases in early tumour growth. In the period immediately following the initiating genetic events, the clone consists of one or a very 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 vascularised normal tissue ($K_1 \ll K_2$). Under these conditions, K_1/N_2 is relatively insignificant and equation (9) can be approximated as:

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

The biological interpretation of this inequality is that growth of the small tumour clone is entirely dependent on host effects. Thus, initiation will produce a persistent transformed population only if the genetic changes allow the clone to overcome host constraints which restrain growth, such as contact inhibition, immune response, terminal differentiation or induction of apoptosis.

A second phase follows if the surviving clone proliferates because population expansion alters the critical parameters. In this setting, the simplification $N_1/K_2 = 0$ and $N_2/K_2 = 1$ will not hold since the tumour population is both increasing and causing a decline in the normal population. Biologically, this is analogous to the tumour stage following promoter-induced cell proliferation. It demonstrates that promoters must, therefore, induce population expansion by increasing α_{12s} which can be accomplished by enhancing the local or systemic production of positive growth factors or increasing the cell's sensitivity to growth factors.

Of particular interest, the value of K_1/N_2 will progressively increase as the population expands and, when sufficiently large, will dominate the $\alpha_{12i} - K_1/N_2$ term. Thus, the models predict that the immunological and non-immunological host constraint of the tumour (α_{12i}) will become progressively less effective following promoter-induced expansion. Furthermore, as the K_1/N_2 term becomes larger, the dependence on stimulation by the host will also decrease (because $\alpha_{12i} - K_1/N_2$ will get progressively closer to 0). Thus, tumour behaviour following promotion is largely independent of host generated positive or negative growth factors. However, as shown in

Figure 1 the changes necessary for tumour population survival and expansion are still sufficient only to allow limited, non-invasive tumour growth. This stage is analogous clinically to premalignant lesions (i.e. adenoma, papilloma, or carcinoma *in situ*) because, although the tumour population growth is limited, one or more of its members can acquire an invasive phenotype if additional genetic changes confer cellular properties which fulfill the necessary conditions.

The mathematical models can then be examined to predict phenotypic changes necessary to produce invasive malignant behaviour. This is essentially a search for conditions leading asymptotically to tumour population approaching its carrying capacity (K_1) and normal population approaching 0. Requirements for malignant growth can be determined by allowing equations 1 and 2 to approach 0 (an equilibrium state) with the condition that N_2 approaches 0 as the steady state is approached. As N_2 declines, $\alpha_{12}\ N_2/K_1$ approaches 0 and equation (3) becomes:

$$\frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) \tag{13}$$

For $dN_1/dt \geq 0$

$$N_1 < K_1$$

and equation (4) becomes:

$$\frac{dN_2}{dt} = r_2\ N_2 \left(\frac{1 - \alpha_{21}\ N_1}{K_2}\right). \tag{14}$$

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

$$\alpha_{21} \geq K_2/K_1\ .$$

Thus, from the clonal expansion or a pre-malignant stage, an invasive subpopulation will emerge if the clone accumulates phenotypic changes such that the subpopulation displays one of the following strategies: (1) maximise α_{21}, the effectiveness

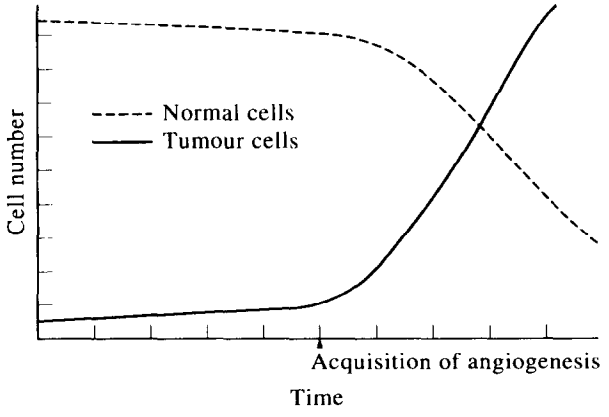

Figure 1. Computer simulation of population dynamics using equations (1) and (2) during the transition from the clonal proliferation to the malignant stage of tumour growth. Clonal proliferation permits only limited tumour expansion with a significant, persistent population of normal cells. Acquisition of a phenotype which permits invasive growth (as an example, development of an angiogenic phenotype is shown) dramatically alters the population interactions with explosive tumour growth and rapid destruction of the normal tissue.

of the tumour in competing with normal cells for available substrate and space; (2) maximise K_1, the carrying capacity of the environment for the tumour; (3) minimise K_2, the carrying capacity for normal cells. Malignant tumour morphology is the final steady state of any of these "strategies" which are, thus, functionally equivalent.

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

DISCUSSION

Competition theory models carcinogenesis as a sequence of steady states resulting from many possible combinations of accumulated genetic or epigenetic changes and with multiple potential outcomes. It predicts the general sequence and types of phenotypic changes necessary for each phase of neoplastic growth, but also demonstrates the novel concept of "functional equivalence". That is, diverse, apparently unrelated characteristics found in different tumour populations may actually be mathematically and functionally identical in determining tumour behaviour. At any phase of carcinogenesis, one of several interchangeable phenotypes may be sufficient for tumorigenesis and at least one is necessary.

The model demonstrates a sequence of steady states and transitions in carcinogenesis analogous to the initiation, promotion and invasion observed in experimental systems [15, 16]. Each new steady state is dominated by different mathematical parameters which in turn predict critical biological and clinical factors. The first phase occurs immediately after initiation and determines the survival of the altered population. Under these conditions, tumour survival is shown to be dependent solely on host-generated effects. Initiation must, therefore, produce a phenotype with decreased sensitivity to growth constraints such as contact inhibition, terminal differentiation or apoptosis. At this stage, immunological response (a component of α_{12i}) can suppress tumour growth, consistent with the concept of immune surveillance.

Increased growth stimulation will result in clonal expansion analogous to the promotion stage of carcinogenesis. This defines the role of the numerous local and systemic factors stimulating tumour growth which have been identified [17–20]. Functionally equivalent properties include increased expression of the growth factor receptors [21–25], which provide persistent stimulation for tumour growth. Alternatively, tumour cells may develop increased responsiveness to, as yet, unknown local factors, such as those produced by normal mesenchyma in bone marrow, or bone resorption products [26–34].

The changes leading to clonal expansion will result in a steady state with limited, unaggressive tumour growth in which tumour and normal cells co-exist. A malignant tumour requires transition to a new state in which the tumour invades host tissue. Several functionally equivalent traits can produce this transition.

First, the tumour could increase its own carrying capacity (K_1). Biologically, this is analogous to acquisition of angiogenesis since vascularisation of the tumour population increases substrate delivery and, therefore, the carrying capacity. As

shown in Figure 1, this results in explosive growth of a tumour population, and is consistent with studies of several tumour models, which have shown that non-angiogenic growth is limited, while a change to an angiogenic phenotype results in rapid, unrestricted growth [35–41].

An equivalent strategy to increase K_1 is production of autocrine growth factors which have been shown to increase the maximum obtainable population (the carrying capacity) by as much as a factor of 30 [42].

The second mathematical parameter controlling invasive growth is α_{21}, which measures the effects of the tumour population on 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. Numerous investigators dating back to Warburg [43–46] have observed that tumour cells acquire glucose and other substrate more avidly than normal cells. This asymmetric distribution of resources may be sufficient to produce invasive tumour growth, as the author has previously shown [5].

Finally, a functionally equivalent strategy for invasive growth is reduction of the carrying capacity for normal cells (K_2), such as through lysis of the extracellular matrix by proteinases which the tumour produces directly or induces in adjacent fibroblasts [47–49].

Thus, mathematical analysis of tumour growth demonstrates that no single phenotype or set of phenotypes should be expected in all *in situ* neoplasms. The concept of functional equivalence must be employed to understand the highly diverse and inconsistent properties which are observed in tumour populations.

The behaviour of the mathematical models at each stage of tumour growth is dependent on critical parameters which can be "translated" into clinical factors (Figure 2). This allows predictions of treatment strategies likely to be successful or unsuccessful at each phase of tumour growth.

As previously demonstrated, early tumour growth depends on tumour response to host-generated positive and negative growth factors. Thus, tumour prevention or treatment of subclinical (microscopic) tumour (i.e. adjuvant therapy) should exploit this dependence by: (1) reducing the levels of local or systemic growth factors such as through hormonal manipulation, or block their receptors; (2) increasing the immunological response to tumour antigens; and (3) increasing the levels of negative growth factors or receptors.

However, these strategies will be successful only during the early stages of carcinogenesis. As the tumour clone expands, it becomes increasingly independent of host factors, and biological modifiers (i.e. antibodies, cytotoxic lymphocytes, vaccines etc.) will be progressively less successful.

Cytoreduction remains the standard therapy for invasive tumour but inspection of equations (13) and (14) demonstrates significant limitations in this strategy. Tumour is invasive when the parameters of equations (13) and (14) are such that they approach a stable steady state in which tumour population (N_1) equals carrying capacity (K_1), while the normal population (N_2) becomes 0. Under these conditions, the populations will always return to the steady state following perturbations. Thus, the growth term (dN_1/dt) will remain positive as long as $N_1 > 0$. Clinically, this indicates that the tumour will always repopulate unless the number of tumour cells is reduced to 0. Cytoreductive chemotherapy will always fail in the malignant phase of carcinogenesis unless all of the tumour cells are eradicated.

The mathematical models predict that a more successful strategy would seek solutions to equations (13) and (14) in which $dN_1/dt = 0$ even if $N_1 \neq 0$. This requires treatment that is designed to alter the underlying parameters of the population interaction rather than directly affecting the individual members of the populations and suggests two general approaches: (1) identify the strategy or strategies that the tumour population has evolved in the transition from clonal

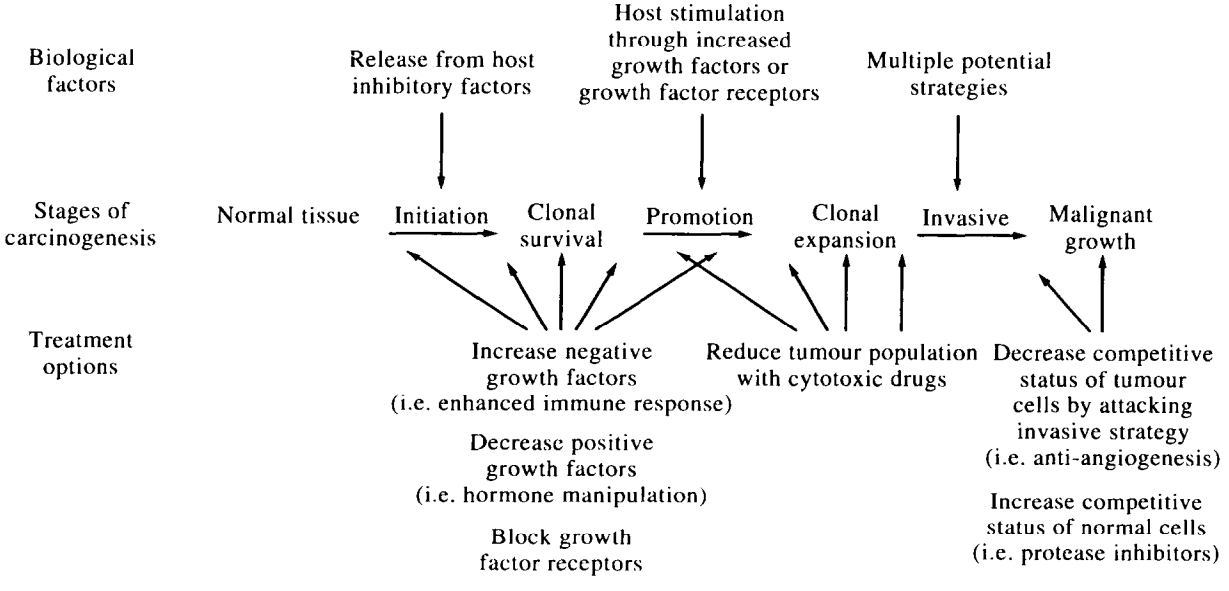

Figure 2. A summary of the stages of tumour development based on mathematical analysis and their clinical and biological significance. As shown, each stage represents the final result of a transition which is analogous to the initiation, promotion or invasive phase in traditional models of carcinogenesis. The summary outlines critical biological changes which must occur at each transition from one stage to the next. Optimal treatment strategies are also shown as the tumour progresses along the multistep process from initiation of a single cell to invasive growth by billions of cells with death of the host.

expansion to invasive growth and reverse those processes; (2) alter the properties of the normal cells adjacent to the tumour to enhance their competitive status.

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