Population Ecology Issues in Tumor Growth

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ABSTRACT

Mathematical models developed from population ecology are applied to tumor-host interactions and demonstrate the importance of increased efficiency in substrate absorption as a mechanism enabling tumor cells to (a) proliferate despite inefficient energy production and (b) compete successfully for resources with the numerically superior host cells. As with many biological invasions observed in nature, success of the invaders can be enhanced by disruption of the local ecology if the disruption results in decreased viability of the native populations reducing their ability to inhibit tumor cell growth either directly through an immunological response or indirectly by competition with the tumor cells for available resources.

Following successful invasion and displacement of normal cells from a volume of tissue, tumor cells achieve new equilibrium states with the environment based on their efficiency of consumption and the vascularity of the tissue.

Tumor therapy may be enhanced by reducing available resources below a level which will support growth of the tumor cells or above a threshold which will allow repopulation by normal cells.

INTRODUCTION

The principles of population ecology provide a novel conceptual framework for the examination of tumor-host interaction. Every discrete volume of tissue within an organism can be represented as an ecological domain populated by species of normal epithelial and mesenchymal cells in equilibrium with resources which enter through diffusion or blood vessels. Tumors begin when a single or small number of individuals from a new (tumor) species enter or arise within this domain. Although the causes and manifestation of oncogenesis must be understood on a molecular level, the formation of tumor occurs only when individual malignant cells compete successfully with the host cells allowing them to obtain adequate levels of substrate for proliferation despite the numerical advantage of the preexisting population and the "predatory" effect of the immune system. Interaction of the invading tumor cells with the native host cells may result in three general outcomes: (a) proliferation despite the numerical advantage of the preexisting population and the "predatory" effect of the immune system, (b) competition with the tumor cells for available resources, or (c) extinction of the invading population.

Mathematical models from population ecology, thus, may be applied to tumor-host interaction. Although this approach requires oversimplification of complex biological processes, it may provide useful insight into the basic mechanisms of tumor growth and should make predictions which can be tested both in vivo and in vitro. Previous attempts to model tumor growth have emphasized fitting tumor volume data to Gompertzian (1) or exponential (2) curves. Michaelson et al. (3) applied population ecology principles to competition between tumor subpopulations, but these models have not previously been used to analyze tumor-host interaction.

RESOURCE ASSIMILATION AND UTILIZATION

Each available resource \( R \) is absorbed and used within the cell for maintenance and reproduction:

\[
 c_i = m_i + p_i; \quad i = 1, 2, \ldots, K
\]

where \( c_i \) = consumed resource/individual cell/unit time, \( m_i \) = resource utilized for maintenance/cell/unit time, and \( p_i \) = resource available for reproduction/cell/unit time for \( K \) resources.

Consumption (uptake) of each resource will vary depending on the amount of the resource available and the capacity of the cell to acquire it. Thus,

\[
 c_i = f_i(R)
\]

This analysis will use glucose as a model resource because it is a critical substrate for energy production and thus essential for both maintenance and reproduction. Furthermore, the mechanisms of uptake via glucose transport polypeptides (4, 5) and utilization for energy production (6, 7) are well established.

Holling (8) distinguished three typical shapes for the consumption curve \( c = f_i(R) \) as shown in Fig. 1. In this study, the Holling type III sigmoid response curve will be used as a reasonable approximation of the acquisition of glucose by cells, although the actual shape of the consumption curve does not ultimately affect the conclusions of the analysis.

Returning to Equation A, the total resource absorbed and utilized by a population of \( N \) tumor cells per unit time will be

\[
 Nc = Nm + Np
\]

where \( \bar{c} \) = average consumed resource/cell, \( \bar{m} \) = average resource utilization for maintenance/cell, and \( \bar{p} \) = average resource available for reproduction/cell. For the tumor cell population to grow \( (dN/dt > 0) \), \( \bar{p} > 0 \) and thus \( \bar{c} < \bar{m} \). That is, resource consumption must exceed resource utilization for maintenance if the cell population is to increase.

The relationship of population kinetics \( (dN/dt) \) to consumption and metabolism can assume many forms but may be expressed as

\[
 \frac{dN}{dt} = DN \left( 1 - \frac{N}{N_{max}} \right) \frac{1}{\gamma} \left( \bar{c} - \bar{m} \right)
\]

where \( N_{max} \) is the maximum number of cells that may occupy a given volume of tissue if resources are unlimited and should be related to such constraints as cell volume and cell-cell contact inhibition. \( D \) is the intrinsic rate of growth (e.g., doubling time) if resources are unlimited and is dependent on a variety of factors such as the tumor cell genetics, level of growth factors present, and the number of receptors available for growth factors on cell surfaces. \( \gamma \) is a conversion factor (9) for the transformation of resources into new individuals. In the remainder of this work, \( D/\gamma \) will be expressed as a single constant \( B \).

For a Holling type III functional response, Equation D can be restated as

\[
 \frac{dN}{dt} = BN \left( 1 - \frac{N}{N_{max}} \right) \left( \bar{m} + \frac{ER^2}{R^2 + R} \right)
\]
TUMOR GROWTH MATHEMATICAL MODELS

TUMOR CELL INTERACTION WITH ENVIRONMENT

In the absence of consumers, the quantity of a resource in any given volume of tissue can be expressed

$$\frac{dR}{dt} = r \left( 1 - \frac{R}{K} \right)$$

(F)

where \( r \) is the rate of resource delivery and \( K \) is the carrying capacity of the environment. When \( R = K \), \( dR/dt = 0 \) because the resource lost because of diffusion to adjacent tissues or outflow in the vasculature is equal to the inflow of the resource. Clearly, \( K \) and \( r \) will decrease substantially if the tissue is hypovascular or if the tumor destroys the vasculature. The dashed curves of Fig. 3 demonstrate two possible resource curves for a volume of tissue with (top line) and without (bottom line) vasculature.

When consumption by a population of cells is considered, the resource kinetics can be expressed as

$$\frac{dR}{dt} = r \left( 1 - \frac{R}{K} \right) - NE$$

(G)

For the Holling type III consumption response this becomes:

$$\frac{dR}{dt} = r \left( 1 - \frac{R}{K} \right) - NE \left( \frac{R^2}{R_0^2 + R^2} \right)$$

(H)

This is illustrated by the solid lines in Fig. 3 which demonstrate the loss of \( R \) because of the presence of varying densities of cells with a Holling type III consumption response. For any level of \( R \) and \( N \), \( dR/dt \) will be the result of subtracting the solid line from the dashed line. Equilibrium is achieved when \( dR/dt = 0 \), which is graphically represented by the intersection of a solid and dashed line.

From Equation D, it is clear that, for a population to grow when \( N < N_{\text{max}} \), it must minimize the resource commitment for maintenance (\( \bar{m} \)) and maximize resource absorption (\( \bar{c} \)) for the ranges of \( R \) within the volume of tissue making up the domain. When this principle is applied to glucose as a model resource, it is clear that the preferential use of aerobic glycolysis (6, 7) poses a problem for tumor cells because it increases glucose requirements for maintenance. Increased absorption (\( \bar{c} \)) of glucose is therefore required if tumor cells are to have adequate energy for proliferation. Furthermore, as this model will demonstrate, this necessary enhancement of glucose absorption will ultimately be critical in allowing tumor cells to successfully compete with normal cells for available substrate.

Finally, in Equations D and E, doubling time (\( D \)) has no relevance to tumor population survival. That is, \( dN/dt \) is positive or negative depending only on the (\( \bar{c} - \bar{m} \)) term. If \( dN/dt > 0 \), however, \( D \) will significantly effect the actual rate of growth of the population.

where \( E \) is the saturation level of \( c \) and \( R_0 \) is the half-saturation density of the resource (i.e., the value of \( R \) at which \( c \) is \( \frac{1}{2} \) of \( E \)).

From Equations D and E, it can be seen that when available resources are less than the requirements for maintenance (\( \bar{m} > \bar{c} \)) \( dN/dt < 0 \) and the population will decline. When \( c = 0 \), \( dN/dt \) will approach \(-NB\bar{m} \) and thus the term \(-B\bar{m} \) can be interpreted as the death rate in the absence of the resource. Fig. 2 examines consumption curves for cells with Holling type III functional response with varying \( R_0 \) and \( E \) and graphically demonstrates the effects of these parameters on the ability of cell populations to compete for a resource.

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This is illustrated by the solid lines in Fig. 3 which demonstrate the loss of \( R \) because of the presence of varying densities of cells with a Holling type III consumption response. For any level of \( R \) and \( N \), \( dR/dt \) will be the result of subtracting the solid line from the dashed line. Equilibrium is achieved when \( dR/dt = 0 \), which is graphically represented by the intersection of a solid and dashed line.
Population equilibrium will be achieved when $\frac{dN}{dt} = 0$. From Equation E, it is clear that $\frac{dN}{dt} = 0$ when $N = N_{\text{max}}$ if the population is not resource limited. However, if the population is resource limited and $N_{\text{eq}}$ is $< N_{\text{max}}$, $\frac{dN}{dt} = 0$ when:

$$R < R_{\text{eq}}$$

or

$$R_{\text{eq}} = R_0 \left( \frac{m}{E - m} \right)^n$$

where $R_{\text{eq}}$ is the value of $R$ at equilibrium.

The relationship of the equilibrium values of $R$ and $N$ are shown in Fig. 4. The solid lines are the equilibrium values of $R$ for any given $N$ depending on the presence (top curve) or absence (bottom curve) of tumor vasculature and are derived from Equation H for $\frac{dR}{dt} = 0$ so that

$$N = \frac{r}{E} \left( 1 + \left[ \frac{R_0^2 - R^2 K - R^2}{K^2} \right] \right)$$

The equilibrium values of $R$ ($R_{\text{eq}}$ when $\frac{dN}{dt} = 0$ from Equations E and I) for a resource-limited population with three levels of consumption are shown by the dashed horizontal lines. The entire system is in equilibrium when $\frac{dN}{dt} = \frac{dR}{dt} = 0$ and is shown as the intersection of the dashed lines with the solid lines.

If tumor expansion into a volume of tissue results in destruction of the vasculature in that volume, $K_1$ and $r_1$ in Equation H will be replaced by $K_2$ and $r_2$. Since $K_2 < K_1$ and $r_2 < r_1$, $\frac{dR}{dt}$ will initially be $<0$ (because $R/K_1 < R/K_2$), reducing resources within the domain and resulting in $\frac{dN}{dt} < 0$ (from Equation E). A new equilibrium will then be achieved with $R$ returning to the initial $R_0$, but with a new lower value of $N$ (from Equation J and graphically demonstrated in Fig. 4), resulting in the death of some fraction of the original cell population. This would result in areas of necrosis within the tumor.

Thus, the interaction of the tumor cell population with the host environment can result in multiple possible equilibrium states depending on the carrying capacity (vasculature) of the environment and the capacity of the tumor cells to absorb the available resources. As demonstrated in Fig. 4, vascularized regions of tumor have varying cell densities ($N_{\text{eq}}$) and resource levels ($R_{\text{eq}}$). Devascularized regions of tumor are only able to support cell densities lower than that seen in vascularized areas, resulting in cell death and thus partial or even complete (if $R_{\text{eq}} < K_2$) necrosis.

**TUMOR INTERACTION WITH HOST CELLS**

Until now, we have treated tumors as a species entering an unoccupied environment. In most situations, however, the tumor species enters an ecological domain completely filled by existing species of normal cells at equilibrium with the available resources. Thus, individual tumor cells must compete successfully with normal cells for these resources in order to gain control of this volume of tissue.

Using an analysis similar to Armstrong and McGehee (10) consider two species (Fig. 5) competing for a limited resource with a Holling type III functional response. One population consists of tumor cells ($N_1$), while the other consists of the host cells normally present ($N_2$). In this analysis, the heterogeneity (11) of tumor cell societies and the varied cell types present in...
normal tissue are simplified by “averaging” the various subpopulations. A more realistic approach would expand the number of competing populations into several tumor subpopulations ($N_{1a}, N_{1b}, N_{1c}$) and normal cell subpopulations ($N_{2a}, N_{2b}, N_{2c}, \ldots$). This, however, markedly increases the complexity of the mathematical analysis and will not be pursued further at this time.

In the two species analysis, growth for the tumor population ($N_1$) is:

$$\frac{dN_1}{dt} = B_1N_1 \left[ 1 - \frac{N_1}{N_{1(max)}} \right] \left[ -\bar{m}_1 + E_1 \frac{R^2}{R_{d(1)} + R^2} \right]$$

and for the normal population ($N_2$):

$$\frac{dN_2}{dt} = B_2N_2 \left[ 1 - \frac{N_2}{N_{2(max)}} \right] \left[ -\bar{m}_2 + E_2 \frac{R^2}{R_{d(2)} + R^2} \right]$$

resulting in resource kinetics of:

$$\frac{dR}{dt} = r \left( 1 - \frac{R}{K} \right) - N_1 \left[ \frac{E_1 R^2}{R_{d(1)} + R^2} \right] - N_2 \left[ \frac{E_2 R^2}{R_{d(2)} + R^2} \right]$$

Before the tumor cells enter, normal cells will have achieved an equilibrium in which

$$\frac{dN_2}{dt} = \frac{dR}{dt} = 0$$

at some values

$$N_2 = \gamma_2$$
$$R_2 = \tau_2$$

where $\gamma_2 = N_{2(max)}$ or, if the population is resource limited, $\gamma_2$ is the population at which

$$-\bar{m}_2 \left( R_{d(2)} \frac{E_2(\tau_2)^2}{R_{d(2)} + (\tau_2)^2} \right) = 0$$

and

$$r \left( 1 - \frac{\tau_2}{K} \right) - \gamma_2 \left( R_{d(2)} \frac{E_2(\tau_2)^2}{R_{d(2)} + (\tau_2)^2} \right) = 0$$

If a small number of tumor cells ($N_1 \ll N_{2(max)}$) enters or arises in this volume of normal tissue, the tumor population will grow if $dN_1/dt > 0$ and thus

$$-\bar{m}_1 \left( R_{d(1)} \frac{E_1(\tau_2)^2}{R_{d(1)} + (\tau_2)^2} \right) > 0$$

If $dN_1/dt > 0$, then $N_1$ will continue to increase until a new steady state is reached ($dN_1/dt = 0$) at equilibrium values of $N_1 = \gamma_1$ and $R = \tau_1$.

This is termed invasability (10) and it is clear from the above that the tumor population ($N_1$) can invade the normal cell population if $\tau_2 > \tau_1$. As shown in Fig. 5, $\tau_1$ will be less than $\tau_2$ if the population $N_1$ is more efficient at resource absorption in the range of $R$ in the domain. The invasability of the normal cells into the tumor cells can be analyzed similarly. If tumor cells are at equilibrium at $R = \tau_1$ and

$$-\bar{m}_2 \left( R_{d(2)} \frac{(\tau_2)^2}{R_{d(2)} + (\tau_2)^2} \right) < 0$$

then $dN_2/dt < 0$ when $N_1$ and $R$ are at equilibrium and $N_2$ cannot invade or even coexist with $N_1$. Thus, if tumor cells can take up resources more efficiently than normal cells and $\tau_1 > \tau_2$, then the tumor population can invade normal tissue and locally drive the normal cells to extinction.

In summary, this analysis predicts that the ability of tumor cells to successfully invade the host is critically linked to their capacity to take up glucose and other resources more effectively than normal cells. This is consistent with and adds significance to experimental observations that the transport of glucose (12–14) and other substrate (15–17) across the cell membrane is significantly increased in transformed cells.

The above model is a laissez-faire (10) analysis because it assumes that the two species do not interfere with one another directly but simply compete for available resources. This is probably not realistic because it neglects the inhibitory effects of the immune system on the invading tumor cells. Mathematical expression of this poorly defined phenomenon is difficult and could undoubtedly assume many forms. One possible general expression is:

$$\frac{dN_1}{dt} = B_1 N_1 - (\bar{m}_1 + c_1) \left( 1 - \frac{N_1}{N_{1(max)}} \right) + dN_1$$

where $D$ is a probability of mortality/unit time caused by the host response. It seems likely that this host interference will depend on the number of host cells present ($N_2$) and the resources available since the vasculature delivers both components of the immune system and the substrate (i.e., oxygen, complement, and antibodies) necessary for the immunological cells to act.
Thus,

$$D = f(N_2, R)$$  \tag{O}

The mortality function will not be further defined in this analysis except to argue that $D$ will probably decrease as both $N_2$ and $R$ decrease. Furthermore (from Equation N), in early tumor growth ($N_1 \ll N_{1\text{max}}$), $dN_1/dt$ will be $>0$ and $D$ will not affect the outcome of the tumor-normal cell competition provided

$$B_1 \left[ -\bar{m}_1 + \frac{E_t R^2}{R^* + R^2} \right] > D$$

or, expressed in terms of resource $R$:

$$R > R_0 \left[ \left( \frac{D}{B_1} + B_1 \bar{m}_1 \right) \frac{E_t - D}{B_1} \right]^{\frac{1}{2}}$$

Thus, minimizing $R_0$ and maximizing $E$ may be adequate to allow tumor survival even in the face of significant predatory activity by the immune system.

Interference in the normal cell populations by tumor cells is also possible. This will not be considered here since the main concern of the analysis is invasability of $N_2$ by $N_1$. When $N_1$ is very small, this interfering term should be negligible.

As with biological invasions observed in nature (18, 19), the models predict that disruption of the local ecology may favor the invader. For example, if local tissue injury, inflammation, or devascularization reduces the resource levels for a prolonged duration, $R$ could decline below $r_2$ resulting in a decrease in the population ($dN_2/dt < 0$) and low levels of resources for the remaining cells. If a tumor population arises in this volume of tissue and if $R$ is $>r_1$, the tumor cells can proliferate unchecked by any competition from the already declining normal host population. Furthermore, from Equation O, limited resources should reduce the mortality function ($D$) associated with the immune response.

**SUMMARY OF TUMOR-HOST INTERACTION**

Tumor and adjacent host tissue can be represented as multiple regions in differing states of equilibrium or transition. As demonstrated in Fig. 6, the host tissue surrounding the tumor contains normal cells in equilibrium with available resources. The tumor-host interface is a site of transition in which a small number of tumor cells invade and compete with the normal cells for resources. The tumor rim is populated solely by tumor cells which are in a new equilibrium with the resources previously used by the normal cells. The tumor core may be identical to the tumor rim if the vasculature remains intact within the tumor. However, if the tumor destroys the host vasculature and fails to promote new vessels, the available resources in the tumor core will decline leading to a new equilibrium state in which the density of tumor cells is less than that in the vascularized rim resulting in varying degrees of necrosis.

As the tumor size increases with time, each volume adjacent to the tumor will experience a transition from normal tissue to competition to tumor rim to tumor core as the “wave” of tumor cells passes through.

**IMPLICATIONS FOR THERAPY**

If tumor cells are killed or damaged by therapy, Fig. 4 demonstrates that, starting from any equilibrium state, $R$ will increase when $dN_1/dt < 0$. Using Equations L and M, we find that during treatment, as long as $N_1 < N_{eq}$, $R$ will be $>r_1$. When therapy is withdrawn, the resources available in the environment will allow $dN_1/dt > 0$ provided $N_1 > 0$. Thus, therapy directed at cancer cells alone will ultimately be ineffective unless $N_1$ can be reduced to 0.

Therapy, however, could be enhanced by the following: (a) reduction in $R$ below $r_1$ will maintain $dN_1/dt < 0$ and add to the negative growth effects of therapy. This would have to be accomplished by destruction of the blood vessels in and adjacent to the tumor; (b) increase $R$ above $r_2$ allowing $dN_1/dt > 0$ and thus proliferation of normal cells (assuming they are not killed or damaged by the tumor therapy) to compete with the remaining tumor cells. Returning to Fig. 4, it is clear that, in vascularized tumors with $N_{eq}$ small and $R_0$ large, this process could occur because even a small percentage kill of tumor cells would allow the $R$ value to increase to high levels (presumably above $r_2$).

For equilibrium states in vascularized tumors in which $N_1$ is large and $R_0$ is small, an equivalent percentage of reduction in $N_1$ will result in a much lower $R$, probably preventing any repopulation by normal cells.

In portions of the tumor which have become devascularized, it is possible that even a maximum reduction in $N_1$ will not allow $R$ to increase above $r_2$. In these regions, therapy will be effective only if $N_1$ is reduced to 0 or if resources are increased by some therapeutic intervention.
CONCLUSION

Population ecology models may be applied to the phenomenon of tumor growth and yield interesting insights into tumor-host interaction. Specifically, the models make the following predictions:

1. Success of tumor cells in gaining dominance is determined substantially by their ability to absorb resources more efficiently than normal cells. In the specific case of glucose used in this analysis, increased uptake provides two advantages: (a) it allows adequate energy for proliferation despite the use of inefficient aerobic glycolysis by tumor cells, and (b) it allows tumor cells to compete successfully with normal cells for available resources enabling them to invade and ultimately destroy the normal cells in a given volume of tissue. This prediction is consistent with experimental evidence demonstrating a significant increase in membrane transport of glucose and other substrate in transformed cells.

2. In the competition between normal and tumor cells, doubling time of the cells is not critical to the survival of the population (i.e., $dN/dt > 0$) and contributes to growth rate only if $dN/dt > 0$.

3. The interaction of tumor cells and host environment can assume several clearly defined patterns with predictable final equilibrium states which depend on the degree of vascularization and the efficiency of resource assimilation by the cells.

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