

Chapter 2

The Host Support Niche as a Control Point for Tumor Dormancy: Implications for Tumor Development and Beyond

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Abstract An increasingly appreciated focus of carcinogenesis research is on mechanisms governing tumor growth after the fact of cancer cell creation. Of particular interest are dynamical interactions between tumor and host cell populations that can themselves strongly impact the fate of established cancer lesions. Regardless of tumor type, all cancers face the common problem of having to breach the barrier of angiogenic competency in order to advance from a microscopic lesion to symptomatic disease. If pre-angiogenic tumor cells are held in dormancy due to cell cycle arrest, this will postpone the need to traverse this higher-level barrier. On the other hand, the barrier itself may prove limiting to a tumor at its diffusion-limited size, creating a population-level dormancy characterized by balanced proliferation and cell death. In both cases of dormancy, the “angiogenic switch” has not yet occurred. We here describe and mathematically quantify an underappreciated third dormancy state defined by an angiogenic balance following the angiogenic switch. In this state we term “post-vascular dormancy,” a tumor has attained angiogenic competency, but again demonstrates balanced proliferation and cell death because ambient pro- and anti-angiogenic influences are offsetting. Interestingly, autopsies have shown virtually all of us carry latent tumors in pre- or post-vascular states, many of which lie under the threshold of routine clinical detection. We show how, in the post-vascular case, tumor latency can arise from an elaborate mechanism of self-controlled growth, mediated through the tumor–vascular interaction. Underlying this observation is the finding that a tumor produces both angiogenesis stimulators and inhibitors, with the latter having greater influence, both locally and systemically, as the tumor grows—a mechanism we hypothesize is an aberrant co-option of normal organogenic regulation.

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That a tumor can limit its own growth raises the prospect that chronic therapies aimed at suppressing this tumor–host dynamic may compare favorably to current strategies which often yield favorable short-term responses but fail to deliver long-term tumor suppression.

Keywords Angiogenic balance • Tumor–host dynamics • Organogenic regulation • Post-vascular dormancy • Carrying capacity • Logistic growth • Stable disease

Introduction

Against the backdrop of intra- and inter-tumor heterogeneity and genomic instability that are hallmarks of carcinogenesis [1–3], uncovering unifying principles of action that underlie the complex nature of cancer would seem improbable. Yet, there is abundant evidence that tumors are exquisitely dependent on their host environment to manifest the malignant phenotype. The classic experiments of Illmensee and Mintz [4] showed that teratocarcinoma tumor cells can phenotypically revert to contribute to normal mouse development when inserted into blastocysts. More recently, Bhowmick et al. [5] showed that the loss of TGF- β responsiveness in adjacent fibroblasts can result in prostate neoplasia and invasive squamous cell carcinoma of the forestomach. These events show, respectively, that an aberrant, unstable genome is not inconsistent with controlled phenotypic behavior, while conversely cells with no prior overt oncogenic alteration to their genomes can go on to exhibit malignancy. These and other findings [6, 7] demonstrate an overriding ability of the tumor niche to control tumor development. Perhaps the best evidence for the potent role of the tumor/microenvironment dynamic in controlling growth of established tumors comes from the finding that nearly all adults harbor indolent tumor lesions [8, 9]. As the sizes of many of these tumors lie at or somewhat beyond what diffusion of nutrients could accommodate, both pre- and post-vascular forms are likely represented, undergoing balanced proliferation and cell death [10–13] as they await an environmental alteration favoring net growth. Such an alteration could come from increased angiogenic induction by the tumor. But host response is not simply one of accommodating pro-growth tumor cues. Instead, the tumor plays an elaborate role in influencing whether the niche permits or denies tumor growth. Kaplan et al. [14] showed that a certain class of vascular endothelial growth factor receptor-1-positive hematopoietic progenitors must first be recruited by the primary tumor to initiate the “pre-metastatic niche” before a tumor metastasis can seed there and develop. Previously, the revelation that tumors produce both stimulators and inhibitors of angiogenesis [15, 16] had already pointed to a potentially complicated tumor control dynamic. Exploring this possibility, we have shown that tumor growth can be controlled rheostatically by shifting the balance between tumor-derived angiogenesis stimulators and inhibitors [17]. Moreover, as the inhibition is shown to be systemic in scope and would eventually dominate for large enough tumors, we have gone on to propose the tumor-metastasis system should also exhibit asymptotic self-control. This organized growth has

profound implications for the nature of oncogenesis and treatment. Among these is the notion that chronic therapy designed to maintain a cancer as “stable disease” indefinitely might have decided advantage as a therapeutic recourse in those instances where strategies with eradivative intent have typically fallen short of their mark.

The Bottlenecks of Tumor Dormancy

Histologically confirmed tumors may fail to progress beyond a certain size for a number of reasons. The first to be proposed is the “dormant cancer cell,” a hypothesis advanced by Willis [18] to explain discrepancies between natural progression and observed tumor latency, i.e., the time to recurrence following surgery. The effect has variously been attributed to extended mitotic arrest of tumor-propagating cancer stem cells and their progeny (Fig. 2.1a) [19, 20] and immune response [21, 22]. But interruptions to growth may also occur at the population level. As mentioned, a major barrier to tumor development can be the natural impediment of diffusion-limited nutrient availability. For non-angiogenic tumors, this causes them to become dormant at less than a millimeter or so in size, as cells must lie within ~200 μm or so of the nearest capillary to be adequately nourished. One way this might be realized is through the balanced creation and death of cancer stem cell progeny (Fig. 2.1b). In addition, for those somewhat larger tumors that already evidence a vascular contribution, we propose that a limitation can be the failure to stimulate the additional vascularization required for continued expansion (Fig. 2.1c). Both types of dormancy would be classified as population-level because the cells themselves are quite active, proliferating and dying at balanced rates [10–13]. Apparently, tumors held in one or the other form of population-level dormancy are much more prevalent than overt clinical cancers [8]. Further, it is clear many of these dormant cancers will not progress sufficiently rapidly to ever pose a disease threat [8, 9]. Indeed, in the Mayo lung cancer screening trial, consisting of chest X-ray and sputum cytology testing [23], chest X-ray and sputum testing over 6 years detected 143 lung cancers (90 specifically by screening plus 53 in connection with clinical procedure) compared to just 87 in the control group. Ten more cancers were detected over the next 5 years in the control group, leaving a difference of 46 cancers that persisted over a 16-year follow-up [24]. Similar disparities between prevalence and clinical incidence have been observed in breast cancer. In a consecutive autopsy study of 110 women [25], histologically confirmed breast cancers were detected in 39% of women in the age 40–50 cohort, while only 1% of women in this age group actually suffer from the disease. These results underscore the power of the tumor–host interaction to impede the course of even confirmed cancers.

At the same time, there is no guarantee a given lesion will remain nonthreatening. Almog et al. [26] have shown that a non-angiogenic clone of human liposarcoma can escape dormancy after an extended period (~130 days). In their islet cell RIP-Tag model, Hanahan and Folkman [27] also found a certain percentage of non-angiogenic tumors would spontaneously convert, i.e., “switch,” after 13 weeks. Considering stages of advancing pancreatic disease, we showed at the molecular

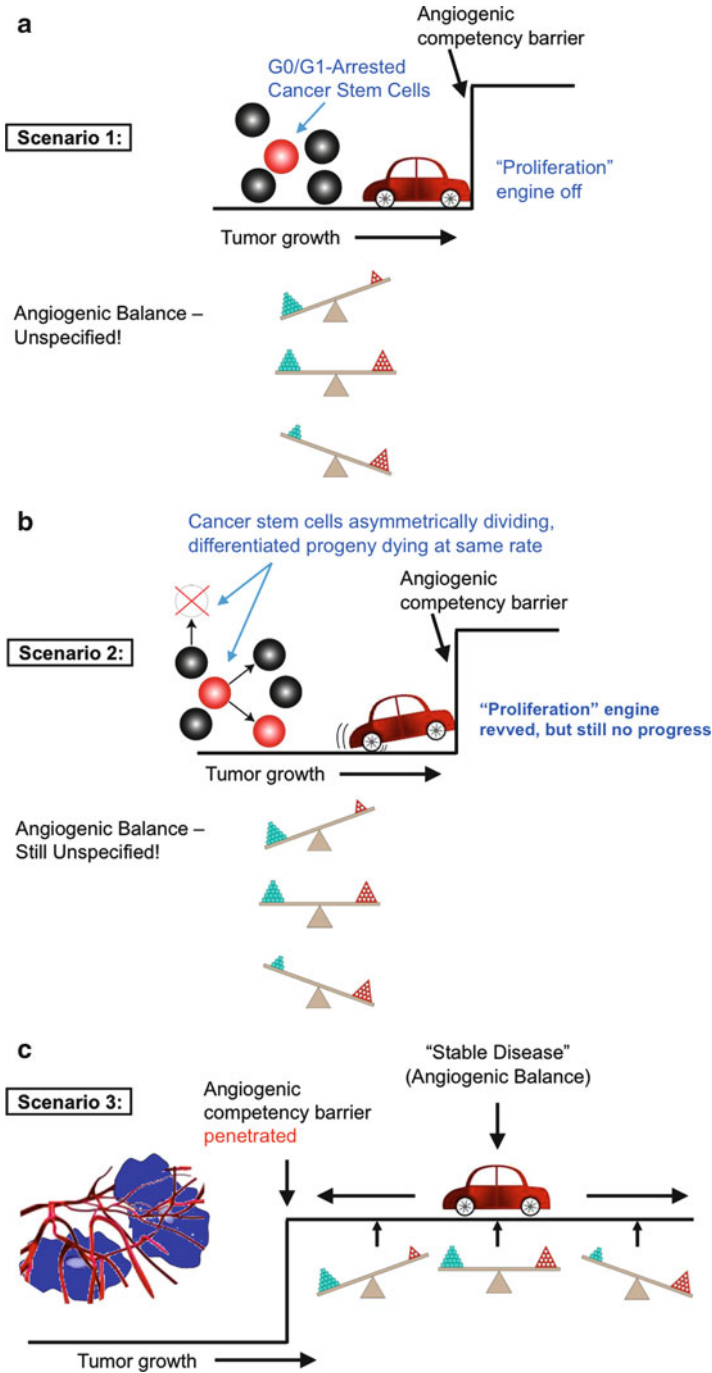


Fig. 2.1 (a–c) Three scenarios for tumor dormancy. In *Scenario 1*, cancer cells are arrested in G0/G1. As the population cannot proliferate, the barrier of angiogenic competency is not tested (the “car” is off). Simple diffusion remains adequate to sustain the population. The population is considered

level that as disease transits from chronic pancreatitis to pancreatic cancer to metastatic disease, there is a progressive upregulation of the large class of pro-angiogenic genes, with a simultaneous downregulation of a class of anti-angiogenic genes [28]. The work demonstrated that the angiogenic switch may be triggered over the course of an *en masse* pro-angiogenic regulation by the tumor of a large network of normal genes associated with vascular control. The extent of genetic involvement in the switch would be consistent with a finding by Indraccolo et al. [29], who showed that a more intense pro-angiogenic stimulus may be required for a pre-vascular lesion to breach the diffusion limitation barrier than is required to drive a post-angiogenic lesion after the fact (Figs. 2.1b,c). If so, this does not appear to be an obstacle that limits growth of subsequent metastases. The frequent observation of explosive growth of pre-vascular metastases after excision of the primary [15, 30, 31] is comparatively easy to reconcile with the idea that the loss of primary tumor-derived angiogenesis inhibitors is sufficient to release the metastases from dormancy. In this scenario, no second burst of angiogenic activity at the pre-vascular metastatic sites is required. On the other hand, it may be argued that the metastatic sites have already been pre-conditioned so as to obviate the need for the burst [14]. A second possibility for why a pre-vascular lesion may need more angiogenic stimulus is because it is nowhere near the tipping point of angiogenic balance in the first place, so that induction of angiogenesis may require more stimulatory upregulation than would otherwise be required for growth after a switch. In any event, escape from pre-vascular dormancy arguably constitutes a major step in cancer progression. At the same time, there is no reason to think the original notion of angiogenic balance in the post-switch context has now become irrelevant—in fact, the meaning becomes more important than ever.

The Post-vascular Dormant Tumor

Inherent in the notion of a post-vascular dormant tumor is the notion of an ongoing, balanced expression of angiogenesis stimulators and inhibitors in the tumor milieu. Putting this another way, a dormant tumor that has switched at the level of a pre-vascular lesion could in principle be restored to a dormant status as a larger, post-vascular

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Fig. 2.1 (continued) pre-vascularly dormant at the cell level. In terms of an angiogenic balance, just where the population is relative to the tipping point is unspecified. In *Scenario 2*, there is no cell cycle arrest, but cells are proliferating and dying as the population attempts to breach the angiogenic competency barrier (the “car” is running and pushing against the barrier, but cannot surmount it). The population cannot grow, and so is considered pre-vascularly dormant at the population level. Again, while the population awaits angiogenic competency, it still remains unspecified how close it is to actually crossing the switch. In *Scenario 3*, the population has previously attained angiogenic competency and breached the angiogenic switch barrier. Because it is now equipped with vasculature and in a position to readily grow or regress in response to either a net pro- or an anti-angiogenic stimulus (the “car” is free to move forward or backward in response to any forward or reverse throttle), a state of neither growth nor shrinkage (stable disease) implies an angiogenic balance

lesion through a suitable re-balancing of factors in the niche (Fig. 2.1c). If this were to happen spontaneously, or if the tumor/niche system were to hover at the point of angiogenic balance for prolonged periods of time, larger but dormant or very slowly growing variants of many clinical tumors should be observable. Such is the case. In the breast cancer microlegal autopsy study of 110 women aged 20–54 years [25], 20% had occult tumors, with some reaching >5 mm in size, well beyond the size where vascularization would be required. In a directed study of growth rates of 147 breast cancers based on mammography scans, von Fournier et al. [32] found a remarkable distribution of doubling times, ranging from 44 to 1,869 days. Tumors at the higher end would be considered dormant by most standards. Moreover, at detection, the mean diameter of the 147 tumors was 17 mm (95% confidence limits: 15–18 mm), so the dormant and slow-growing lesions observed were certainly post-vascular. These data suggest that a tumor that escapes pre-vascular dormancy by undergoing an angiogenic switch [10, 26, 27, 33] may potentially remain near or be restored to a dormant or near-dormant state, even as a post-vascular lesion. This is important from the standpoint of competing risks, in the sense that the growth may be slow enough for the tumor to no longer pose a risk of compromising morbidity or survival in that person's lifetime (Fig. 2.2) [9].

Nevertheless, the potential for macroscopic, post-vascular dormancy remains to be recognized in the general literature. This is especially curious given that the concept of angiogenic balance [34] has often been used to characterize pre-vascular dormancy (e.g., [13]), a state where the proximity to the precise tipping point of angiogenic induction is quite unclear (Fig. 2.1a, b). In point of fact, the concept may better apply to what Kerbel and Folkman [35] have termed “stable disease.” This is a form of clinically evident dormancy that, because it already possesses a vascular component poised to expand or shrink in response to even slight shifts in the angiogenic state of the microenvironment, is more arguably in a state of angiogenic balance (Fig. 2.1c).

A Dynamic Carrying Capacity Representation for Angiogenesis-Dependent Tumor Growth

In a typical ecological system consisting of a population and a defined level of environmental support, various quantitative relationships, including the Verhulst equation and its logistic variants, have been used to describe population growth over time [36]. These generally show the population size $V(t)$ to be exponential initially (reflecting abundant support vs. demand), but later to exhibit growth deceleration in the form of an asymptotic approach to some final value K . K reflects the maximum population size the environment can support, otherwise known as the carrying capacity of the environment. Models generally presume the level of support K is fixed, with some functional deviations to adjust for technical features, e.g., the point of inflection (the point $(t_0, V(t_0))$ where $d^2V(t)/dt^2=0$) or the rate at which the population

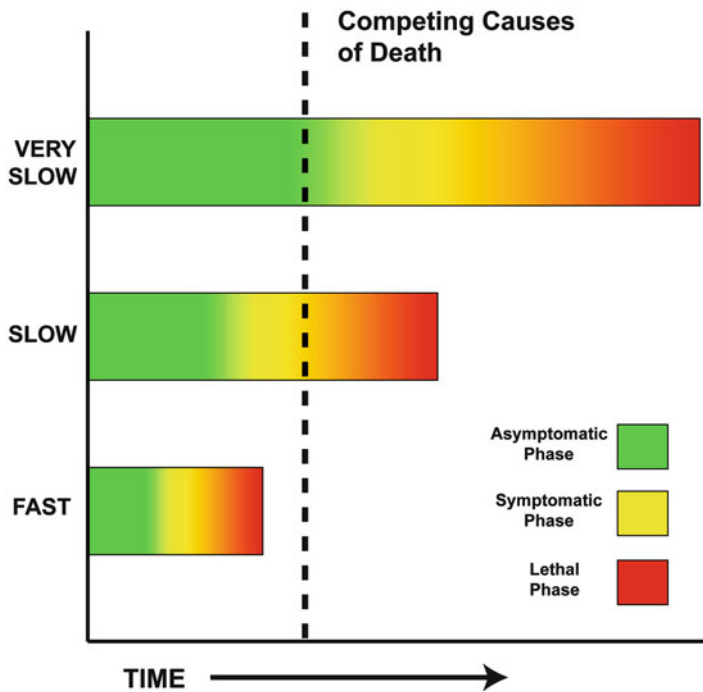


Fig. 2.2 The threat of cancer is determined in the progression phase. Even when the steps leading to cancer are completed and a tumor is growing, whether the cancer will ever present as symptomatic disease is determined by its rate of progression. If the tumor is growing quickly, symptoms followed by potential lethality is a strong possibility. If instead the tumor is growing more slowly, it may reach the point of clinical detection, but may not become life-threatening over the normal life-time of the patient. On the other hand, if the tumor is growing very slowly, such as in the case of dormancy or near dormancy, the tumor may not even be diagnosed. In this case, the patient effectively had no disease, even though from a genetic standpoint a cancer was created. Autopsy data suggest most of us are in this category, carrying latent disease that will not present itself clinically

approaches its carrying capacity. These principles have proven to be robust enough to find application to tumor growth [37].

The generalized logistic equation for tumor size $V(t)$ can be expressed in the form:

$$\frac{dV}{dt} = \frac{\lambda}{\alpha} V \left(1 - \left(\frac{V}{K} \right)^\alpha \right) \quad \text{for } \alpha \neq 0, \lambda > 0, t \geq 0, V(t) < K. \quad (2.1)$$

In the limit $\alpha \rightarrow 0$, this reduces to the Gompertz equation:

$$\frac{dV}{dt} = -\lambda V \log \left(\frac{V}{K} \right). \quad (2.2)$$

The growth rate overall is proportional to λ , and α controls the rate at which tumor size approaches the asymptotic limit, i.e., the steepness of the ascending part of the curve. The parameter α also determines the point of inflection, which occurs at $\frac{V}{K} = \left(\frac{1}{1+\alpha}\right)^{1/\alpha}$ for $\alpha > -1$ (or $\frac{V}{K} = e^{-1}$ in the Gompertz case).

Where we depart from this implementation is in the consideration of the carrying capacity K as variable, rather than fixed. This is necessary to take into account the well-established ability of a tumor to induce angiogenesis, which increases nutrient delivery to the tumor and thereby permits continued tumor growth. Identifying induced vascularization with K , then, leads to a coupled set of differential equations:

$$(a) \frac{dV}{dt} = \frac{\lambda}{\alpha} V \left(1 - \left(\frac{V}{K(t)} \right)^\alpha \right) \quad \text{and} \quad (b) \frac{dK}{dt} = K f(K, V) \quad (2.3)$$

It remains to solve for the K dependence. To do this, we consider the quantitative implications of the fact that tumors produce or activate both stimulators and inhibitors of its vascular niche [15, 16]. Assuming spherical symmetry and a growth rate small compared to the distribution of angiogenesis agent, we can write a diffusion-consumption equation for the concentration m of angiogenesis factor within and outside a tumor of radius r_0 .

$$D^2 \nabla^2 m - cm + s = 0 \quad \text{or} \quad \frac{d^2 m}{dr^2} + 2 \frac{dm}{dr} - \frac{cm}{D^2} + \frac{s}{D^2} = 0. \quad (2.4)$$

where D^2 is the diffusion of agent, c is its clearance rate, and s is its rate of production (we will assume $s=s_0$ inside the tumor and $s=0$ outside).

By making the substitutions

$$(a) r = xD/\sqrt{c} \quad \text{and} \quad (b) m = y/\sqrt{x} + s/c \quad (2.5)$$

the equation reduces to the modified Bessel function of order $1/2$

$$x^2 \frac{d^2 y}{dx^2} + x \frac{dy}{dx} - \left(x^2 + \frac{1}{4} \right) y = 0, \quad (2.6)$$

which has two linearly independent solutions. If we choose the first to be finite at $x=0$, and the other to be finite as $x \rightarrow \infty$, they become:

$$y_1 = \frac{\sinh(x)}{\sqrt{x}} \quad \text{and} \quad y_2 = \frac{\exp(-x)}{\sqrt{x}} \quad (2.7)$$

From Eq. (2.5) and assumptions about s , these expressions immediately yield the agent concentrations inside and outside the tumor

$$m_{\text{inside}} = \frac{A}{r} \sinh\left(\frac{r\sqrt{c}}{D}\right) + \frac{s_0}{c} \quad \text{and} \quad m_{\text{outside}} = \frac{B}{r} \exp\left(\frac{-r\sqrt{c}}{D}\right) \quad (2.8a)$$

where A and B are constants. The constants are solved for by having the two solutions and their derivatives be continuous across the tumor boundary at $r = r_0$. We obtain

$$\begin{aligned} A &= \frac{-s_0 D}{c\sqrt{c}} \left(1 + \frac{r_0 \sqrt{c}}{D} \right) \exp\left(\frac{-r_0 \sqrt{c}}{D}\right) \quad \text{and} \\ B &= \frac{s_0 D}{c\sqrt{c}} \left(\frac{r_0 \sqrt{c}}{D} \cosh\left(\frac{r_0 \sqrt{c}}{D}\right) - \sinh\left(\frac{r_0 \sqrt{c}}{D}\right) \right). \end{aligned} \quad (2.8b)$$

To assess the action of angiogenesis stimulators and inhibitors, we now take into account the relatively slow clearance of endogenous inhibitors and the relatively fast clearance of endogenous stimulators [15, 16, 38, 39].

We consider the two limiting cases $c \ll D^2/r_0^2$ and $c \gg D^2/r_0^2$ and values of r near or inside the tumor.

$$c \ll D^2 / r_0^2 : m_{\text{inside}} \approx \frac{s_0}{6D^2} (3r_0^2 - r^2) \quad \text{and} \quad m_{\text{outside}} \approx \frac{s_0 r_0^3}{3D^2 r} \quad (2.9a)$$

$$\begin{aligned} c \gg D^2 / r_0^2 : m_{\text{inside}} &\approx \frac{s_0}{c} \left(1 - \frac{r_0}{2r} \exp\left(\frac{-(r_0 - r)\sqrt{c}}{D}\right) \right) \approx \frac{s_0}{c} \quad \text{and} \\ m_{\text{outside}} &\approx \frac{s_0 r_0}{2cr} \exp\left(\frac{-(r - r_0)\sqrt{c}}{D}\right) \approx 0 \end{aligned} \quad (2.9b)$$

The concentration profiles are shown in Fig. 2.3.

It is clear from Case 1 that at any location r_0 , f near or within the growing tumor (i.e., for $0 \leq f < 1$), the concentration of inhibitor is increasing as the square of the tumor radius, or as $V^{2/3}$. The inhibitor term in the growth rate $f(K, V)$ of the carrying capacity K would therefore be expected to be proportional to $V^{2/3}$. By contrast, stimulator concentration does not increase at all anywhere, so can be said formally to increase as V^0 . It could also be said to increase as V/K , which also has zero net volume scale. We decided on the latter because tumors were thought not to display transient oscillation in tumor size for smaller tumors, as the use of V^0 predicts theoretically, although in retrospect, it appears some oscillations in tumor size for small tumors do take place. In any event, the choice of V/K is not expected to alter the results dramatically.

The form for the carrying capacity growth rate $f(K, V)$, then, becomes $aV/K - bV^{2/3}$. Eq. (2.3b) becomes

$$\frac{dK}{dt} = aV - bKV^{2/3}. \quad (2.10)$$

As a confirmation of these results, we previously performed animal experiments where we implanted Lewis lung tumors subcutaneously in the flanks of C57Bl/6

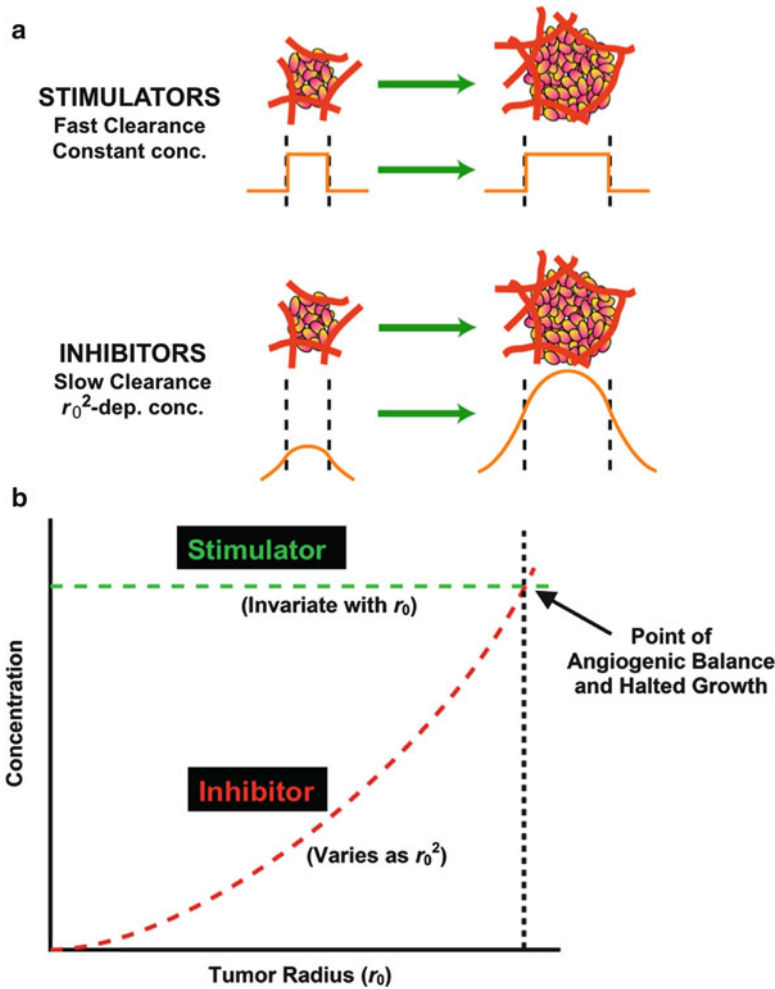


Fig. 2.3 Tumor growth is dictated by the pharmacokinetics of tumor-derived angiogenic stimulation and inhibition. The observation that a tumor produces both angiogenesis stimulators and inhibitors, and that the inhibitors are cleared much more slowly, has important implications for tumor growth. **(a)** Mathematical analysis shows that, in the extreme case of very fast clearance of stimulators and very low clearance of inhibitors, stimulators maintain a constant concentration within the tumor independent of its size. Stimulator concentration away from the tumor is negligible (rectangular function shown in yellow). Meanwhile, inhibitor concentration tends to grow at a rate proportional to the square of the tumor radius r_0 everywhere (bell-shaped function in yellow grows in height as r_0^2). **(b)** The faster accumulation of inhibitor everywhere assures that inhibitor will eventually overtake stimulator, causing the tumor to become dormant (stable disease). While this is a predicted outcome for any tumor, whether this happens before it becomes symptomatic or life-threatening will depend on individual patient circumstance. In any case, shifting the angiogenic state of the tumor environment towards inhibition, e.g., with therapeutic intervention, could cause stable disease to occur at a point consistent with host viability. Such a strategy of chronic tumor maintenance may comprise a favorable alternative to eradication-intent treatments in some situations

mice [17]. This was the model used by O'Reilly et al. [15] in their study of angiostatin, which was actually first isolated from this tumor. We observed tumor growth in a normal setting and in settings where angiogenesis inhibitors (angiostatin, endostatin, and an exogenous inhibitor TNP-470) were introduced exogenously by various schedules. The goal was to see if the model as derived could explain tumor growth and in particular, the effect of angiogenesis stimulation and suppression by the tumor on its own growth. For the purpose of modeling the inhibitor injections, we appended a term $-dKe(t)$ to Eq. 2.10 to account for background antiangiogenic drug administration.

$$\frac{dK}{dt} = aV - bKV^{2/3} - dKe(t), \text{ where } e(t) = \int_0^t r(t') \exp(-c_{\text{inh}}(t-t')) dt' \quad (2.11)$$

Here, $e(t)$ is the concentration of injected inhibitor, $r(t')$ is the rate of injection of inhibitor (in practice, nearly an impulse function), and c_{inh} is the clearance rate of the injected inhibitor. We assumed basic exponential clearance pharmacokinetics.

We fit the model to control growth of tumors, solving for the tumor–host parameters λ , α , a , and b (finding α to be about zero, giving us a Gompertz form for Eq. 2.5a) then tested its predictive power for cases where the systemic environment was artificially made angio-inhibitory by injection, supplementing any tumor-derived angiogenesis inhibition. Tumor responses under the three antiangiogenic agents were used to calculate the inhibitor effectiveness coefficient d and the clearance rate c_{inh} for each agent in the equation for $e(t)$. We were able to confirm that clearance rates for the administered inhibitors angiostatin and endostatin were indeed quite long, supporting the same assumption made for the action of the endogenous inhibitor activated by the Lewis lung tumor (angiostatin). Our data also predicted *de novo* that TNP-470 should be quite effective in terms of its suppression per unit concentration per unit time, but that its effectiveness is likely limited by a relatively fast clearance rate compared to the other inhibitors examined. This is supported by direct pharmacokinetic analysis [40]. The behavior of K/V with time is shown in Fig. 2.4a. Of note, K is not simply advancing marginally ahead of V , as might be expected if it is just accommodating the growing nutritional needs of the tumor, nor is the ratio monotonically decreasing, as would be expected if the growth were in accordance with Gompertz or any conventional logistic form with a fixed carrying capacity. Instead, an entirely new form is revealed, defined by an active advancement of carrying capacity well ahead of growth early on, followed later by an equally active curtailment of carrying capacity, and thus tumor growth.

The Mathematics of Control of Distant Metastases

A basis for thinking about the tumor-metastasis system is laid out in general terms by the finding that tumors are capable of producing stimulators and inhibitors of angiogenesis, with the inhibitors generally having longer half-lives. That this may translate to distant control of a metastatic site is suggested by the solutions to our

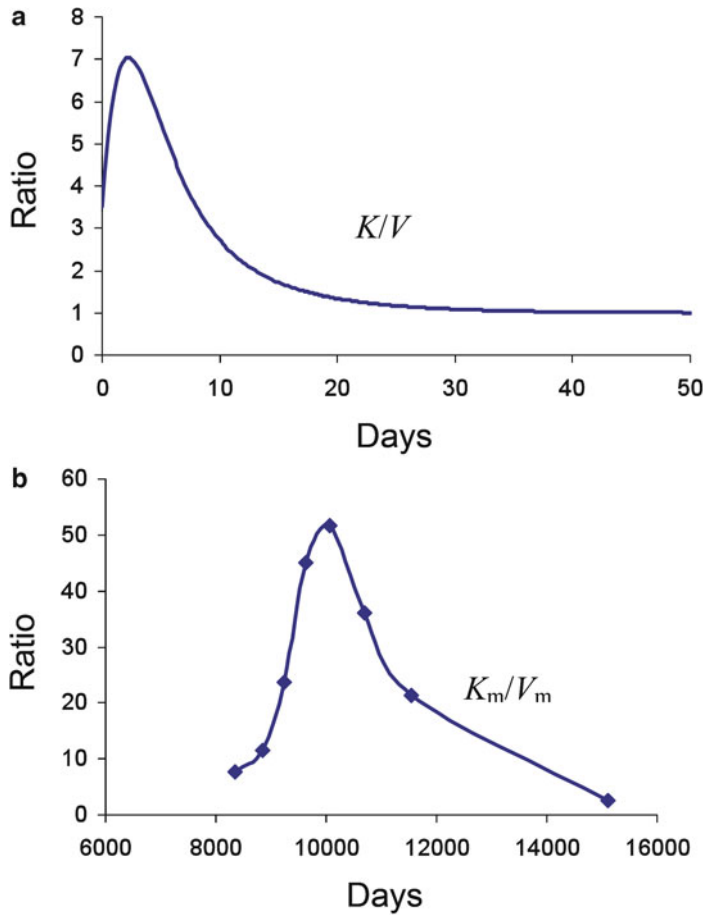


Fig. 2.4 The dynamic carrying capacity model for the progression-level bottleneck of angiogenesis we previously derived based on murine studies (a) was demonstrated to be predictive of angiogenesis-dependent breast tumor growth humans (b). In the human data, growing tumors call for proportionally quickly rising support/tumor ratios K_m/V_m early on (7.62–45.1), then a collapsing ratio later on (45.1–2.5). This reveals an active tumor–host dynamic that is inconsistent with simple vascular induction due to nutrient demand. It is also inconsistent with conventional Gompertz or logistic growth dynamics. That the basic dynamic applies to both mice and humans points to a conserved mechanism that may have an origin in organogenesis

original dynamic carrying capacity construct for the distribution of angiogenesis factor within and outside the tumor. It is seen that the inhibitor can accumulate at some distance from the tumor, while stimulator does not accumulate, despite tumor size. Of course, we used extremes of clearance rate to model this point. In fact, while inhibitors do generally have more persistence, there will be a variation in clearance rates, with some of the stimulators on the more slowly clearing end of the spectrum perhaps having an influence comparable to that of inhibitors that happen

to be on the more quickly clearing end. One would have to consider the details of each instance. For now, we do know there is some connection between the growth of metastasis and signals from the primary. There are a number of reports citing increased vascular density in metastases after removal of the primary [41] and increased detection of metastases overall [42].

Human Cancers

To test how our “dynamic carrying capacity” interpretation of angiogenic control of tumor growth carries over to the human circumstance, we have begun to study the growth of 420 nondormant, untreated breast tumors as part of a study conducted at the University of Heidelberg [37]. As the data for each patient i come in the form of volume scans V_{ij} corresponding to scans $j = 1, \dots, n_i$, with the first scan being assigned a time $\tau_{i1} = 0$ days, the objective was to merge the scan data across patients to permit a global analysis of tumor/vascular development to compare to that performed with the mouse data. To do this, we again applied the general logistic growth relationship Eq. (2.1), but to first derive a sense of absolute times to associate with the scans, we regressed the data onto the solution to Eq. (2.1) expressed as

$$\lambda t = f(K, V_0, a) \quad \text{for} \quad \alpha \neq 0, \lambda > 0, t \geq 0, V(t) < K. \quad (2.12)$$

Here, V_0 is the tumor size at tumor age $t=0$, assumed to be one cell, i.e., $1.0 \times 10^{-6} \text{ mm}^3$. The objective of the regression was to find formal expressions for the overall λ and time offsets $T_i(K, \alpha)$ for the scan data (τ_{ij}, V_{ij}) of Patient i that would translate that patient’s scan times τ_{ij} into estimated absolute tumor ages $t_{ij} (= \tau_{ij} + T_i(K, \alpha))$ based on the collective behavior of the intra-patient tumor volume measurements. We then reinserted these formal expressions back into the solution of Eq. (2.1), now written more conventionally using $\ln(V(t)/V_0)$ as the dependent variable:

$$\ln(V(t)/V_0) = g(K, V_0, \alpha, t). \quad (2.13)$$

Finally, we used Eq. (2.13) to perform another regression of the data $(t_{ij}(K, \alpha), V_{ij})$ to find the best fit with respect to K and α , thereby solving explicitly for K , α , and so the t_{ij} themselves. With the tumor data points thus rendered in the form (t_{ij}, V_{ij}) for the j th scan of Patient i , we then refit to Eq. (2.13) subsets of these data lying in the volume cohorts $0 < V \leq V_m$, for $V_1 = 100 \text{ mm}^3$, $V_2 = 250 \text{ mm}^3$, $V_3 = 500 \text{ mm}^3$, $V_4 = 1,000 \text{ mm}^3$, $V_5 = 2,000 \text{ mm}^3$, $V_6 = 5,000 \text{ mm}^3$, $V_7 = 15,000 \text{ mm}^3$, and $V_8 = 215,600 \text{ mm}^3$ to find analogous parameter values K_m , α_m , and λ_m corresponding to each of these cohorts. These fits included a final one to the full cohort ($V_8 = 215,600 \text{ mm}^3$), which contained all tumor measurements (the largest tumor size measured was $215,600 \text{ mm}^3$). This last fit was not redundant to the original that allowed us to solve for K , α , and t_{ij} in the first place, because the full cohort fit was done with explicit knowledge of the t_{ij} , just as with the other cohort fits. Times corresponding to the arbitrary V_m values were inferred from the full-cohort fit to

Eq. (2.13), and plotted against the ratio of K_m/V_m surmised from each of the cohort fits $m = 1, \dots, 8$. The overall intent of this cohort analysis was to crudely trace out the dynamic behavior of K/V as a function of tumor age by independent methods to compare with that of the animal model.

What we found is shown in Fig. 2.4b. Of note, both in this case (Fig. 2.4b) and in the mouse (Fig. 2.4a), there is a slightly left-skewed curve describing how the ratio of carrying capacity (vascular support) K leaps well ahead of tumor size V initially, then almost as rapidly descends so as to cap off the potential tumor size. The human data thus corroborates the finding in mice; that tumor support is not passively controlled (e.g., by need for O_2), as originally believed, but is dynamically reset by the tumor throughout growth, up to a point where a tumor will start to curtail its own growth (approach a dormant state) through active capping of endothelial support. Whether it can attain this state soon enough to be host-viable will depend on the precise case-specific details of the tumor–niche interaction, as modified by therapeutic intervention. The potential significance of this reciprocal tumor–host dynamic is also glimpsed in work by Kaplan et al. [14], where it is shown that homing of VEGFR1-positive hematopoietic progenitors to would-be sites of tumor metastasis (“pre-metastatic niches”), although a tumor-directed event, is a precondition for eventual tumor metastasis to those sites. If the pre-metastatic conditioning program is blocked, metastases do not occur. Suggesting a generalization beyond cancer, Lammert et al. [43] and Yoshitomi and Zaret [44] described a control in line with our proposed “endothelio-centric” paradigm [17] for organ development, in that endothelial growth at the organ site is seen to precede and permit growth of the parenchyma, which in turn controls growth of the supporting vasculature. As further support for our hypothesized connection between angiogenesis and organogenesis, Greene et al. [45] tracked liver regrowth after partial hepatectomy, and showed that the regenerating organ plateaus to a final size that varies with the angiogenic status of the host. Mice given angiogenesis stimulators during regeneration developed larger-than-normal livers, while those given angiogenesis inhibitors had smaller final liver sizes.

Conclusion

The notion that cancer often occurs as “stable disease,” a state of post-vascular dormancy viewable clinically, has vital implications for antiangiogenic therapy, and in particular how we interpret therapeutic progress towards overcoming the original angiogenic switch. Once it is recognized that achieving an angiogenic balance, and thus “stable disease,” may be achievable with a macroscopic tumor without shrinking it to microscopic size, this opens the door for new thinking about what constitutes successful response. Current notions of “complete or partial response,” referring to total or partial tumor shrinkage as measures of the effectiveness of classic maximum tolerated dosing (MTD) regimens, would give way to “failure of the tumor to progress,” the likely hallmark of successful antiangiogenic therapy.

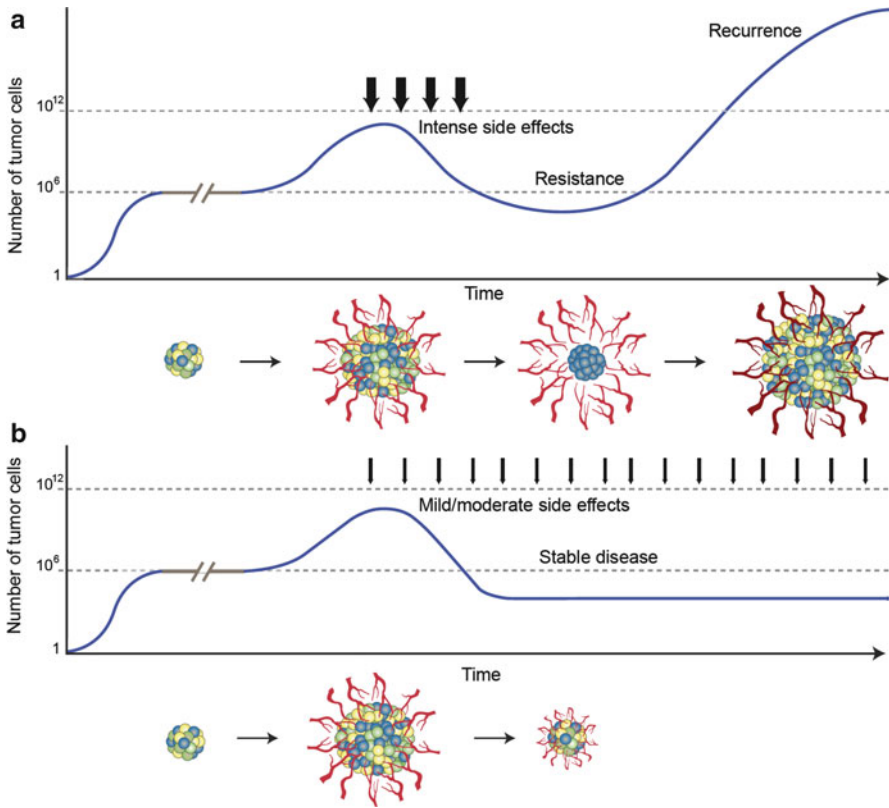


Fig. 2.5 Two strategies for tumor therapy compared. Maximum tolerated dosing (MTD) strategies and targeted strategies aimed at total tumor eradication hold the promise of cure. For some cancers, this is a course with a substantial success rate, albeit often with undesirable side effects. For most cancers, however, good responses are often followed by resistance and tumor regrowth, assisted in rebound by the host support left behind (**a**). Part of the reason may be that the tumor and its vascular niche are not being co-suppressed as a unit, which may be better accomplished using more chronic treatments that include anti-angiogenics. While cures are no longer the goal, stable disease consistent with excellent quality of life may be achievable (**b**)

New therapeutic designs might entail altering the self-imposed theoretical dormancy “set point” of the tumor downward to a level consistent with symptom-free disease over the lifetime of the patient (Fig. 2.5). In this way, the achievement of a tolerable equilibrium between tumor and host could stand quite favorably against eradication-intent strategies whose very aggressiveness may often be the instrument of their own defeat.

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