Local Imbalance of Proangiogenic and Antiangiogenic Factors: A Potential Mechanism of Focal Necrosis and Dormancy in Tumors

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ABSTRACT

Solid tumors produce both stimulators and inhibitors of angiogenesis. The suppression of metastases by some primary tumors has been attributed to the longer circulatory half-lives of the inhibitors. We propose that intrinsic differences in the physicochemical properties of these regulators may also explain focal suppression of angiogenesis within the primary tumor. We present a mathematical framework that describes production, diffusion, and degradation of these factors in tumor and host tissue and their effect on angiogenesis at local and distal sites. Results show focal suppression of angiogenesis, provide an explanation for tumor dormancy and focal necrosis, and predict a suppressive influence of primary tumors on angiogenesis at metastatic sites. They suggest generally that diffusible factors produced by tumors can stimulate responses in adjacent host tissue, preparing it for further tumor invasion. This study presents a new paradigm for the development of tumor necrosis and offers new insight into angiogenesis regulation and therapy. The framework established for modeling the competing effects of diffusible stimulators and inhibitors can be applied more generally to growth factors/inhibitors and other opposing factors produced in the tumor environment.

INTRODUCTION

To grow larger than a few cubic millimeters, solid tumors must generate new vasculature through the process of angiogenesis (1). Prior to neovascularization, human tumors can remain dormant indefinitely until the balance between angiogenic stimulation and inhibition is altered and the tumor switches to an angiogenic phenotype (2–4). This process involves multiple regulatory factors produced by tumor cells, host stromal cells, and/or infiltrating leukocytes (5–8). Among these are angiogenic stimulators such as VEGF (9, 10) and acidic and basic fibroblast growth factors (aFGF and bFGF; Ref. 11). Angiogenic inhibitors, including TSP-1 (12), angiotatin (13), and endostatin (14), are also either produced directly by these cells or as a result of protein cleavage by enzymes produced by the cells. Presumably, angiogenesis in primary tumors is triggered by higher effective local concentrations of angiogenic stimulators than of inhibitors (13, 15). Similarly, growth inhibition of metastases by some primary tumors is attributed to higher distal concentrations of angiogenic inhibitors (13). These contrasting effects imply that tumors produce opposing factors, achieving different outcomes locally and remotely. We propose that this principle, applied within the microenvironment of individual growing tumors, can explain the formation of focal necrosis amid neovascularization. Although imbalances between opposing factors affect tumor growth more generally than in the context of angiogenesis, we focus on competition between proangiogenic and antiangiogenic influences as an important and illustrative case.

Complete suppression of angiogenesis within a primary or metastatic tumor presumably prevents growth by inhibiting neovascularization and maintaining a balance between cell proliferation and apoptosis, resulting in a dormant state (16). In contrast, the focal necrosis commonly observed in solid tumors forms in regions where the vascular network is inadequate or blood flow is impaired in regions of growing tumors, resulting in nutrient deprivation and insufficient waste removal. The reduced perfusion has been hypothesized to result from: (a) solid stress-induced collapse of vessels (17); and/or (b) reduced vascular density attributable to rapid tumor cell proliferation (18).

Expanding on the latter proposition, we present the hypothesis that an excess of antiangiogenic factors in regions of growing solid tumors leads to suppressed angiogenesis and ultimately, as the affected areas become underperfused, focal necrosis. To study this hypothesis, we have developed a mathematical model that illustrates how local variations in the balance of angiogenesis regulators may arise within tumors. Parameters related to the production, diffusion, and degradation of these factors are varied to determine their effect on angiogenesis within the primary tumor, in the peritumor host tissue, and at metastatic sites. The results illustrate possible mechanisms for the dormancy of established tumors, formation of necrosis in solid tumors, suppression of metastases, and stimulation of angiogenic activity in the peritumor host tissue (8).

MATERIALS AND METHODS

Local Model. The primary tumor is modeled under steady-state conditions as a uniform sphere of radius \( R \), residing in a semi-infinite medium of host tissue. Different tissues produce different regulators, and multiple regulators may work in concert to stimulate or inhibit angiogenesis via pathways yet to be defined. Therefore, we do not identify specific factors or mechanisms. Instead, we lump together the multiple growth factors that promote or inhibit local vascular development into the categories of proangiogenic and antiangiogenic factors, respectively. Representative parameter values are used for each category. The following simplifying assumptions render the problem tractable: (a) production (activation) rates of proangiogenic and antiangiogenic factors in tumor and host tissue are constant and independent of each other; (b) degradation (deactivation) rates of proangiogenic and antiangiogenic factors follow first-order kinetics with different rate constants in tumor and host tissue; and (c) diffusion coefficients of proangiogenic and antiangiogenic factors are constant but different for tumor and host tissue.

The lack of detailed information on spatiotemporal variation in production and degradation necessitates these simplifications of the true pathophysiology (see “Discussion”). Interstitial convection of factors is not addressed independently but is lumped together with diffusion, characterized by an effective diffusion coefficient, often measured in experiments (19). Conservation of mass defines governing equations for the concentrations of proangiogenic and antiangiogenic factors, under the quasi-steady-state assumption that concentration gradients are established rapidly with respect to subsequent biological response. The formulation and solution of mass balances are standard and are discussed in detail in reference texts such as those by Bird et al. (20) and Deen (21). In spherical coordinates, the governing equations for concentrations \( f_i \) take the form:

\[
D_i \left( \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial f_i}{\partial r} \right) \right) - k_i f_i + g_i = 0
\]

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3 The abbreviations used are: VEGF, vascular endothelial growth factor; aFGF or bFGF, acidic or basic fibroblast growth factor, respectively; TSP, thrombospondin. 

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where the first term describes diffusion, the second term represents concentration-dependent degradation, and the third term represents a constant production rate. Definitions of variables and their dimensionless counterparts are provided in Tables 1 and 2, with subscript $e$ representing environment [malignant ($m$) or host ($h$) tissue] and superscript $f$ indicating regulator identity [proangiogenic (+) or antiangiogenic (−) factors]. Boundary conditions are obtained by matching concentrations and fluxes at the tumor/host interface, by requiring that concentrations reach constant values far from the tumor, and by enforcing spherical symmetry. Concentrations are normalized by the values obtained in tumor-free host tissue ($\theta_f^e = \alpha_f^e / \alpha^e_m$), which we prescribe to be non-zero and finite. In dimensionless variables, the normalized concentrations in tumor and host tissue are:

$$\theta_f^m = A^f \sinh(\kappa_f^m \eta) / \eta + \gamma_f^m / (\kappa_f^m)^2$$

and

$$\theta_f^h = B^f \left( \frac{\sinh(\kappa_f^h \eta)}{\eta} - \cosh(\kappa_f^h \eta) / \eta \right) + \gamma_f^h / (\kappa_f^h)^2$$

with

$$A^f = \frac{1}{\sinh^{2}(\kappa_f^{m})} \left( \frac{\gamma_f^m}{(\kappa_f^m)^2} - \frac{\gamma_f^m}{(\kappa_f^h)^2} \right) \left[ \frac{1 + \kappa_f^{m}}{1 + \kappa_f^{h} + \alpha^e(\kappa_f^{m}) \coth(\kappa_f^{m}) - 1} \right]$$

$$B^f = \frac{1}{\sinh^{2}(\kappa_f^{m}) - \cosh^{2}(\kappa_f^{m})} \left( \frac{\gamma_f^m}{(\kappa_f^m)^2} - \frac{\gamma_f^m}{(\kappa_f^h)^2} \right) \left[ \frac{1 - \kappa_f^{m} \coth(\kappa_f^{m})}{1 + \kappa_f^{h} + \alpha^e(\kappa_f^{m}) \coth(\kappa_f^{m}) - 1} \right]$$

The normalized concentration ratio, $\theta_f^m / \theta_f^h$, represents the local balance between the factors and thereby, the local angiogenic tendency. The balance between the factors in the limit of infinite radius, $(\theta_f^m / \theta_f^h)_\infty = 1$, defines the reference condition for stable vascularization expected in tumor-free host tissue. Wherever $\theta_f^m / \theta_f^h > 1$, angiogenesis is stimulated; elsewhere, angiogenesis is suppressed. No further assumptions are made about the relationship between regulator concentrations and activities. Thus, we circumvent the difficulty of assigning effectiveness or activity parameters to the factors.

**Dual-Site Model.** A dual-site model is used to study systemic distribution of regulators and their influence on angiogenesis at a metastatic site. The primary (site 1) and metastatic tumors are treated as point locations connected by the circulatory system. Steady-state conditions are assumed so that: (a) concentrations of factors at any given location are constant over time; and (b) the differential amount of factors added to blood traversing the tumor exactly balances the degradation in the blood before it returns again to the tumor. Assuming that its concentration is much lower in the blood than in the tumor, addition of a factor to blood is proportional to its concentration in the tumor ($c_f^1$) and is given by $dc_f^1 / dt$. Degradation in the blood is assumed to be a first-order process with half-life $t^{i/2}$ (rate constant $k_{i/2}^e$) so that blood concentration at time $t$ after leaving the tumor ($c_f^i$) is given by: $c_f^i = c_f^0 e^{-k_{i/2} t}$. The balance between degradation and addition requires that: $a_i c_f^i = c_f^0 (1 - e^{-k_{i/2} T})$, for an average full-body circulation time $T$. The two equations can be combined to determine blood concentration at time $t$. The ratio of normalized concentrations delivered to the secondary site after the average circulatory time delay, $t_{1,2}$, between the sites is then:

$$\frac{\theta_f^2}{\theta_f^1} = \frac{\theta_f^1}{\theta_f^1} \left( \frac{\exp(-k_{i/2} T)}{\exp(-k_{i/2} t_{1,2})} \right) \left( 1 - \exp(-k_{i/2} t_{1,2}) \right)$$

where $\beta = a_f^1 / a_f^1$ represents the efficiency of release of angiogenesis stimulators into blood at the primary tumor site relative to that of inhibitors. This parameter combines both the true release rates and the dilution of regulators in the blood. The concentration ratio at the primary tumor site is approximated using the average concentrations over the primary tumor volume, $U_f^1 / \theta_f^1 = <U_f^m> / <U_f^h>$, determined from the local tumor model. As before, when $\theta_f^1 / \theta_f^1 \approx 1$, the primary tumor has a suppressive effect on angiogenesis at the secondary site, and when $\theta_f^1 / \theta_f^1 > 1$, angiogenesis is favored.

**RESULTS**

A base-case scenario is chosen to illustrate focal suppression, peripheral neovascularization, and distal suppression. Parametric sensitivity analysis is used to investigate other possible scenarios. The model is validated by qualitative comparison with experimental data on perfusion and central necrosis in animal tumors. Implications for multifocal necrosis in spontaneous human tumors are addressed in the “Discussion.”

**Base-Case Yields Centralized Suppression and Peripheral Stimulation of Angiogenesis.** Baseline values for half-lives, molecular weights, and plasma concentrations of proangiogenic and antiangiogenic

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### Table 1. Definitions of model variables

<table>
<thead>
<tr>
<th>Dimensioned variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c_f^m$</td>
<td>Concentration of factor $f$ in blood at time $t$ after leaving primary tumor</td>
</tr>
<tr>
<td>$c_f^h$</td>
<td>Concentration of factor $f$ in tissue environment $e$</td>
</tr>
<tr>
<td>$c_f^{m,h}$</td>
<td>Concentration of factor $f$ in tumor-free host tissue</td>
</tr>
<tr>
<td>$e_f$</td>
<td>Point-source approximation of concentration of factor $f$ in primary tumor</td>
</tr>
<tr>
<td>$D_f^m$</td>
<td>Diffusion coefficient of factor $f$ in tissue environment $e$</td>
</tr>
<tr>
<td>$g_f$</td>
<td>Generation rate of factor $f$ in tissue environment $e$</td>
</tr>
<tr>
<td>$k_f$</td>
<td>Degradation rate constant of factor $f$ in tissue environment $e$</td>
</tr>
<tr>
<td>$r$</td>
<td>Radial distance from tumor center</td>
</tr>
<tr>
<td>$R$</td>
<td>Primary tumor radius</td>
</tr>
<tr>
<td>$t_{1,2}$</td>
<td>Blood circulation time between primary tumor and secondary site</td>
</tr>
<tr>
<td>$k_{i/2}$</td>
<td>Half-life of factor $f$ in blood</td>
</tr>
<tr>
<td>$T$</td>
<td>First-order rate constant for degradation of factor $f$ in blood</td>
</tr>
</tbody>
</table>

**Non-dimensional variables**

| $\alpha_f^m$          | Dimensionless concentration of factor $f$ in tumor-free host tissue |
| $\beta$               | Dimensionless diffusion coefficient of factor $f$ in tumor relative to host |
| $\eta$                | Efficiency of blood uptake of angiostatic factors relative to antiangiogenic |
| $\gamma_f^m$          | Dimensionless radial coordinate |
| $K_e$                 | Dimensionless generation rate of factor $f$ in tissue environment $e$ |
| $\theta_f^m$          | Dimensionless degradation rate constant for factor $f$ in tissue environment $e$ |
| $\theta_f^{m,h}$      | Dimensionless concentration of factor $f$ in tumor free environment $e$ |

### Table 2. Variable definitions and corresponding dimensionless groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dimensionless group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial coordinate $r$</td>
<td>$\eta = \pi r$</td>
</tr>
<tr>
<td>Concentrations $c_f^m$</td>
<td>$\theta_f^m = \alpha_f^m \gamma_f^m / \alpha^m_m$</td>
</tr>
<tr>
<td>Diffusion coefficients $D_f^m$</td>
<td>$\theta_f^m = \alpha_f^m \gamma_f^m / \alpha^m_m$</td>
</tr>
<tr>
<td>Production rates $g_f$</td>
<td>$\gamma_f^m = g_f \mathbf{R}^m / D_f^m$</td>
</tr>
<tr>
<td>Degradation rate constants $\theta_f^m$</td>
<td>$\theta_f^m = (k_f^m \mathbf{R}^m / D_f^m)^{1/2}$</td>
</tr>
</tbody>
</table>

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Angiogenic factors are taken from the literature (Table 3). Values of parameters representing production, interstitial and vascular transport, and degradation, however, are assumed because of the availability of experimental data. As a first approximation, the following conditions were placed on the diffusion of angiogenesis regulators: (a) diffusion coefficients in tumor and host tissue are on the same order of magnitude (22, 23); and (b) diffusion coefficients of angiogenic factors are greater than or equal to those of antiangiogenic factors, reflecting their respective molecular weights (Table 3). Production and degradation rate constants are assumed to be greater than diffusion coefficients, and parameters are chosen based on the following additional restrictions: (a) generation and degradation in the tumor occur at rates greater than (or equal to) those in host tissue; and (b) generation occurs at rates greater than degradation in the tumor, corresponding to a net production of factors by the tumor. The validity of these approximations is not currently verifiable; therefore, parameter values are varied in later simulations to determine the sensitivity of the results.

The resulting base-case parameter values for the local model are given in Table 4. Fig. 1a shows normalized concentration profiles in the tumor and host tissue, with the concentration ratio plotted in Fig. 1b. Central regions of the tumor experience an angiogenic effect \( \frac{\theta^+}{\theta^-} < 1 \). Toward the periphery of the tumor, the behavior reverses \( \frac{\theta^+}{\theta^-} > 1 \), and angiogenic factors predominate, with peak angiogenesis at the tumor surface. The dimensionless radial coordinate at this reversal point, \( \eta = 0.56 \), represents the (fractional) radius of angiogenesis suppression and corresponds to suppression in 17.5% of the tumor volume. Stimulation of angiogenesis persists into the host tissue until \( \sim 40\% \) of the tumor radius before concentrations reach stable balanced conditions. The latter result suggests that factors produced by the tumor may directly influence the adjacent host tissue.

In Fig. 2, the concentration ratio profile is superimposed on the experimental perfusion data of Endrich et al. (24), obtained using window preparations of BA 1112 sarcomas in rats. The agreement between the simulations and empirical results suggests a correlation between angiogenic tendency and perfusion in these tumors and demonstrates the ability of the base-case model to qualitatively capture in vivo behavior.

**Suppression of Angiogenesis Becomes More Prevalent as Tumor Size Increases.** As shown in Fig. 3, concentration profiles generated using base-case parameters show significant differences as the tumor radius increases from 1 to 5 mm. In small tumors, a nearly uniform excess of proangiogenic factors favors neovascularization. As the radius increases, angiogenic suppression arises at the center of the tumor while stimulation of angiogenesis persists near the surface. The region of suppression grows as the tumor radius is increased further. This progression suggests that suppression of angiogenesis develops as tumors grow, consistent with in vivo observations (18). However, not every cell in the suppressed region would experience the level of oxygen/nutrient deprivation that causes death nor would every cell be equally susceptible (25–28). Fig. 3b shows how the region of suppression grows with increasing tumor size and indicates necrotic volume for different extents of cell death within the suppressed region. The results qualitatively describe the data of Hilmas and Gillette (28) in all cases, with quantitative agreement when 47% of the suppressed region is assumed to be necrotic.

**Primary Tumor Outcome Is Sensitive to Parameter Values.** Because many parameter values are yet to be measured and are expected to differ significantly among tumor types and sites, we varied model parameters over several orders of magnitude around base-case values. Sensitivity plots in Fig. 4 show the behavior as the indicated dimensionless groups are varied while remaining parameters are held constant at base-case values. The predicted behavior within the tumor is classified as: (a) full suppression of angiogenesis (dormancy); (b) full stimulation of angiogenesis (progression); or (c) central suppression of angiogenesis (focal suppression). Curves separating the different regimes are obtained by enforcing balanced

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**Table 3. Parameter estimates for the angiogenic stimulators and inhibitors**

<table>
<thead>
<tr>
<th>Angiogenesis regulators</th>
<th>Molecular weight</th>
<th>Half-life</th>
<th>Production ( ^a )</th>
<th>[Plasma]</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulators (aFGF, bFGF, VEGF)</td>
<td>Low (&lt;50,000)</td>
<td>Short (min)</td>
<td>†</td>
<td>Low (&lt;1 ng/ml)</td>
<td>(30, 31, 33, 34, 55, 56)</td>
</tr>
<tr>
<td>Inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSP</td>
<td>High (&gt;450,000)</td>
<td>Long (h)</td>
<td>†</td>
<td>High (&gt;60 ng/ml)</td>
<td>(35, 57)</td>
</tr>
<tr>
<td>Angiostatin, endostatin</td>
<td>Low (&lt;50,000)</td>
<td>Long (h)</td>
<td>†</td>
<td>High (&gt;120 ng/ml)</td>
<td>(13, 14, 32, 58)</td>
</tr>
</tbody>
</table>

**Note:**

1. Angiogenic phenotype.

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**Table 4. Dimensionless variables used to generate base-case results**

<table>
<thead>
<tr>
<th>Proangiogenic factors</th>
<th>Antiangiogenic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative diffusion rates</td>
<td>( \alpha^+ = 1.4^a ) ( \alpha^- = 1.2 )</td>
</tr>
<tr>
<td>Dimensionless</td>
<td></td>
</tr>
<tr>
<td>Tumor: ( \gamma^+_t = 136 ) Tumor: ( \gamma^-_t = 109 )</td>
<td></td>
</tr>
<tr>
<td>Host: ( \gamma^+_h = 31 ) Host: ( \gamma^-_h = 29 )</td>
<td></td>
</tr>
<tr>
<td>Dimensionless</td>
<td></td>
</tr>
<tr>
<td>Tumor: ( K^+_t = 4.8 ) Tumor: ( K^-_t = 4.1 )</td>
<td></td>
</tr>
<tr>
<td>Host: ( K^+_h = 5.6 ) Host: ( K^-_h = 5.4 )</td>
<td></td>
</tr>
</tbody>
</table>

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**Fig. 1.** a, normalized concentration profiles for angiogenesis stimulators (\( \theta^+ \), ———) and inhibitors (\( \theta^- \), ———) in tumor and host tissues for base-case parameter values. b, concentration ratio profile with crossover from net angiogenesis inhibition to stimulation at \( \eta = 0.56 \) and peak angiogenesis stimulation at tumor surface. Region of angiogenic suppression (RAS) is indicated in each graph.
regulation \( u_1 / u_2 \) at the center of the tumor \( h_0 \) or the tumor boundary \( h_1 \). Focal suppression requires a balance between the relative diffusion coefficients, \( a_1 \) and \( a_2 \), or one factor will accumulate in the tumor and dominate the behavior throughout (Fig. 4a). Similar production rates, \( g_e \), of proangiogenic and antiangiogenic factors within the tumor relative to the host are also required for central suppression (Fig. 4b), or again, one factor will dominate throughout. Furthermore, central suppression is favored when production rates of both factors in the tumor are higher than in the tumor-free host tissue (Fig. 4c). Varying the dimensionless degradation rates, \( k_e \), has the reverse effect of varying production rates, as expected for similar but opposing processes (results not shown). In all cases, quantitative, but not qualitative, sensitivity depends on base-case parameter values.

Primary Tumor Has a Suppressive Influence on Angiogenesis at a Secondary Site. The ability of some primary tumors to suppress growth of distant metastases is a well-documented phenomenon (13–15, 29) commonly attributed to differences in physiological half-lives of proangiogenic and antiangiogenic factors produced by the primary tumor (Table 3). The angiogenic factors VEGF and bFGF have reported plasma half-lives of \( \sim 3 \) min (30, 31), whereas antiangiogenic factors angiostatin and TSP have half-lives of approximately 4 and 9 h, respectively (13, 32). Using these values and assuming an average full-body circulation time \( T \) of 1 min, we applied the dual-site model regulation \( \theta_m / \theta_m = 1 \) at the center of the tumor \( \eta = 0 \) or the tumor boundary \( \eta = 1 \).

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to examine how a primary tumor may influence angiogenesis at a metastatic site.

Critical values of the primary tumor concentration ratio ($\theta^+_1/\theta^-_1$) are determined as a function of the average delivery time $t_{1,2}$ between the sites for various values of the release efficiency ratio, $\beta$. Conditions that yield concentration ratios below the critical value in the primary tumor have a suppressive effect on angiogenesis at a secondary site. In all cases, the critical normalized concentration ratio is significantly $>1$ (Fig. 5a). For comparison, the base-case concentration ratio $\theta^+_1/\theta^-_1 = 1.02$ is well below the critical value at all values of $t_{1,2}$ and $\beta$. This outcome, favoring suppression of angiogenesis at a distal site, results from the large difference in the proangiogenic and antiangiogenic factor half-lives. Even when produced at low levels in the primary tumor, antiangiogenic factors attain higher steady-state concentrations in the blood because of their greater stability. However, an antiangiogenic influence of the primary tumor on a secondary site does not necessarily prohibit development of metastases. High levels of proangiogenic factors produced at or near the metastatic site or a weak response to antiangiogenic factors may overcome the suppressive influence of the primary tumor, allowing metastases to develop.

The size of the primary tumor also significantly influences the extent of distal suppression. As shown in Fig. 5b, the concentration ratio of factors in the blood at the distal site decreases as primary tumor size increases. Because of the longer half-lives of inhibitors compared with stimulators, the ratio also decreases for longer circulation times. Thus, larger tumors and greater circulation times produce a greater suppressive influence on angiogenesis in metastatic tumors, consistent with in vivo observations (29). Values of the normalized effective blood concentration ratios shown in Fig. 5b are also consistent with in vivo measurements of true plasma concentrations of proangiogenic and antiangiogenic factors (Table 2).

DISCUSSION

Using a mathematical model, we present the hypothesis that imbalances between proangiogenic and antiangiogenic agents may be responsible for suppression of angiogenesis within a primary tumor. For the base-case set of parameter values, the model predicts: (a) excess antiangiogenic factors in the central regions of a tumor, suggesting the formation of focal necrosis; (b) net angiogenic stimulus at the surface of tumors that extends into the peritumor tissue, stimulating peripheral angiogenesis; and (c) excess accumulation of antiangiogenic factors at distal sites, suppressing angiogenesis in metastases.

Comparison with Experimental Data. The mathematical model developed here predicts several results consistent with available data. Under the assumption that suppressed regions exhibit low vascular density and hence, low perfusion, the predictions of our local model qualitatively match the tumor perfusion data of Endrich et al. (24) in rat mammary tumors (Fig. 2). The experimental correlation between tumor size and necrotic volume seen in animal models (28) is qualitatively and quantitatively described by model predictions (Fig. 3). Finally, in agreement with several other tumor studies (33–35), we predict that antiangiogenic factors achieve higher steady-state plasma concentrations than proangiogenic factors in a manner dependent on primary tumor size but not strongly on distance from the primary tumor. This result is consistent with current hypotheses for the suppression of metastases by some primary tumors (13, 36) and the effect of primary tumor size on antiangiogenic potency at a secondary site (29, 37). However, as new angiogenesis regulators are discovered, a situation in which the circulatory half-life of the stimulator is greater than that of the inhibitor may arise, in which case, the primary tumor producing these factors could actually stimulate angiogenesis at a peripheral site.

Model Limitations. A number of necessary simplifications made in the model require further consideration. The model does not directly predict the formation of necrosis but assumes that suppression of angiogenesis leads to reduced perfusion and ultimately necrosis. However, several other factors, including cell survival factors, also regulate necrosis, and mechanical collapse of tumor vessels may also reduce perfusion (17, 38).

The assumption of spatiotemporal homogeneity in tumor and host tissue is also limiting (18, 39). Although factors such as TSP-1 are produced throughout tumors (40), others, including VEGF, are spatially regulated (8). Expression of the necessary cellular receptors and susceptibility to physiological stress also exhibit local dynamic variation. The symmetry imposed by the model permits centralized suppression of angiogenesis to develop but not the multifocal necrosis observed in human tumors (41). However, within a predicted region of suppressed angiogenesis, the death of vulnerable cells and survival of resilient cells can also lead to multifocal necrosis. Furthermore, our model can be applied to noncentral regions of a tumor, where local physicochemical properties differ from those in the surrounding tumor tissue. Thus, our hypothesis can explain multifocal necrosis in noncentral regions of heterogeneous tumors. The size of resulting necrotic regions would correlate not with overall tumor size but with the length-scales of tumor heterogeneities.

Even tumors that develop central necrosis display different dependencies of necrotic volume on tumor size (42, 43). These differences correspond in part to variation in the extent of necrosis within an angiogenically suppressed region. Hypoxia-induced up-regulation of
VEGF (44) triggers feedback neovascularization that could also contribute to such differences. Indeed, when we modified our model to simulate this effect, hypoxia-induced up-regulation of angiogenic factors led to a reduction in the size of the suppressed region (data not shown).

Finally, we did not consider the response to angiogenesis regulators at the metastatic site. Our model considers the influence of regulator production in the primary tumor and of their release and degradation in the blood. Therefore, we only predicted a suppressive influence of the primary tumor, which can be overcome by factors at the secondary site. A secondary tumor may even have a suppressive influence on angiogenesis at the primary site.

Despite its limitations, we emphasize that the model presented here is sufficient to illustrate the plausibility of our hypothesis. The assumptions can be relaxed and the model made more comprehensive as relevant data become available.

Implications. The results presented here illustrate a new paradigm for the development of necrosis in tumors. They also indicate that a tumor’s sphere of influence may extend beyond the tumor periphery. Regulatory factors produced by tumors may stimulate host cells in the peritumor region, either directly or through signaling cascades, preparing the host tissue for tumor invasion. This effect may explain the reported up-regulation by tumors of VEGF promoter activity in surrounding host fibroblasts (8).

Although the model has predicted several results consistent with current literature, there is a general lack of published quantitative data on production, transport, and degradation of proangiogenic and antiangiogenic factors. Parametric sensitivity analysis has emphasized the importance of regulator production and degradation rates in determining tumor behavior. Predicted outcomes ranged from angiogenic stimulation throughout the tumor, to inhibition throughout, and to centralized suppression. We would expect highly angiogenic, wellvascularized tumors to fall into the first category. Conversely, pervasive suppression of angiogenesis would inhibit tumor progression, explaining the extended dormancy of many tumors (2, 45–47).

This and other related models (48) are relevant to the design of new antiangiogenic agents, a topic of increasing attention and significance (49, 50), as well as of other anticancer agents (51, 52). They provide insight into physicochemical properties, including bioactivity, that affect the ability of antiangiogenic therapeutics to overcome biophysical barriers in solid tumors and elicit the desired response (53).

Finally, the role of angiogenic factors, the effect of hypoxia, and variations in stromal properties considered here are also important in wound healing. Indeed, tumors may activate the wound healing response of the host (8, 54). More generally, the framework established here applies to competition between other diffusible factors (e.g., growth factors and inhibitors). Thus, this model of regulator imbalances in tumors has implications for various physiological and pathophysiological processes.

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Local Imbalance of Proangiogenic and Antiangiogenic Factors: A Potential Mechanism of Focal Necrosis and Dormancy in Tumors

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