Review

Cancer stem cells in solid tumors: Is ‘evading apoptosis’ a hallmark of cancer?

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ABSTRACT

Conventional wisdom has long held that once a cancer cell has developed it will inevitably progress to clinical disease. Updating this paradigm, it has more recently become apparent that the tumor interacts with its microenvironment and that some environmental bottlenecks, such as the angiogenic switch, must be overcome for the tumor to progress. In parallel, attraction has been drawn to the concept that there is a minority population of cells — the cancer stem cells — bestowed with the exclusive ability to self-renew and regenerate the tumor. With therapeutic targeting issues at stake, much attention has shifted to the identification of cancer stem cells, the thinking being that the remaining non-stem population, already fated to die, will play a negligible role in tumor development.

In fact, the newly appreciated importance of intercellular interactions in cancer development also extends in a unique and unexpected way to interactions between the stem and non-stem compartments of the tumor. Here we discuss recent findings drawn from a hybrid mathematical-cellular automaton model that simulates growth of a heterogeneous solid tumor comprised of cancer stem cells and non-stem cancer cells. The model shows how the introduction of cell fate heterogeneity paradoxically influences the tumor growth dynamic in response to apoptosis, to reveal yet another bottleneck to tumor progression potentially exploitable for disease control.

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1. Introduction

1.1. The ‘classic picture’ — hallmarks of cancer

A decade ago, Hanahan and Weinberg (2000) summarized the hallmark cancer cell traits that enable malignant growth and
progression. For a population of cells to exhibit uncontrolled growth, abnormal cell proliferation is necessary but not sufficient. Amongst other things, cells must also escape the induction of apoptosis — programmed cell death — to contribute to a growing population.

Apoptosis, a necessary developmental mechanism, is understood to act as a barrier to cancer (Hanahan and Weinberg, 2000), and defective apoptosis has been argued to compromise treatment (Lowe and Lin, 2000). Mathematical models are often utilized to simulate tumor development or growth dynamics, either at the early, autonomous avascular stage (Anderson et al., 2000; Sherratt and Chaplain, 2001; Ribba et al., 2006a,b), or at the point where the tumor becomes reliant on angiogenesis and other tumor—host interactions for continued growth (Chaplain et al., 1995; Plank et al., 2004; Stamper et al., 2007; Jackson and Zheng, 2010).

In one of the first attempts to mathematically model and simulate the multistep transformation to cancer, Spencer et al. (2004) developed an ordinary differential equation (ODE) system that modulates fitness of cells after acquisition of specific cancer traits. Their model allows investigation of changes in population size when one or a number of tumorigenic traits are acquired. Interestingly, when comparing single phenotypic mutations evading cell death, tumors populations significantly larger than increased proliferation rate. They found the fastest path to a fully developed cancer to be by sequential mutations of apoptotic and proliferation pathways, followed by subsequent acquisitions of angiogenic potential and genetic instability. These findings support previous suggestions that cell proliferation and apoptotic evasion are minimal requirements for tumorigenesis, and that other traits spontaneously emerge on the established cell expansion platform (Green and Evan, 2002). Abbott et al. (2006) proposed a mathematical model that supports evasion of apoptosis as a necessary trait in tumor development, but argued it can confer a selective advantage only if a prior mutation has already occurred.

Many models based on the classical view of cancer presuppose that all cancer cells have acquired the same hallmark identified with the more aggressive attributes of the cancer as a whole, conferring on each cell, among other things, the ability to reinitiate a new tumor locally after inadequate treatment or distally as a metastasis. Accordingly, tumor cells are often represented collectively by a single proliferation term and death term with optional inclusion of one or more specialized functionalities, such as the interaction of tumor cells with their local environment (immune response, chemotactic and haptotactic migration), or induction of angiogenesis under hypoxic conditions. Taken to their limit, such assumptions could leave us with a trivial depiction of tumor growth as

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\frac{dn}{dt} = an - bn ,
\]

where \(a\) and \(b\) are tumor type-dependent proliferation and death rates, respectively (Sachs et al., 2001; Michor et al., 2005; Johnston et al., 2010). Here, it is evident that the tumors can only progress when the proliferation rate is higher than the cell death rate, i.e. \(a > b\), and any increase in cell death rate \(b\) yields a reduction in tumor size. The parameters \(a\) and \(b\) can be replaced by a function of tumor size \(f(n)\) to account for different growth kinetics such as linear, logistic or Gompertzian growth, which is summarized in detail elsewhere (Sachs et al., 2001; Komarova and Wodarz, 2010).

The interaction of heterogeneous subpopulations in a tumor with different levels of aggressiveness can be modeled by systems of such differential equations with different parameters (Bearer et al., 2009; Friebes et al., 2010).

1.2. Cancer stem cell hypothesis and phenotypic heterogeneity

Departures from the classic view of cancer have recently emerged. Vital studies of serial re-transplantation of harvested tumor cells into immunodeficient mice repeatedly reveal that large numbers of tumor cells, although apparently transformed, cannot initiate new tumors (Al-Hajj et al., 2003). Initial growth phases are followed by remarkable decreases in tumor size up to complete remission and a burden-free survival of the animal. Distinct cellular subpopulations can be identified through expression of specific surface markers, and the resulting tumors demonstrate persistent surface marker expression heterogeneity (Al-Hajj et al., 2003). The observed heterogeneity in cell phenotype, tumor-initiating potential, and longevity is leading cancer research and treatment into uncharted territory. Currently, the proposed markers for tumor-initiating cells, i.e. cells capable of perpetuating a tumor, are too numerous to offer much categorizational insight but since these cells share markers with and display functionality of somatic stem cells, they are often called cancer stem cells. However, to avoid speculative comparison to somatic stem cells, alternative nomenclatures such as tumorigenic cells, tumor-initiating cells, tumor-rescuing units, or stem-like cancer cells are common (Baumann et al., 2008). For the purpose of consistency, we will henceforth call these cells cancer stem cells (CSCs).

If only CSCs are truly tumorigenic, treatment that aims to reduce tumor volume to below detection thresholds might reduce tumor burden without necessarily controlling or curing the disease. In fact, evidence of reduced sensitivity of CSCs to the most common forms of cancer treatment is accumulating (Bao et al., 2006). Initial susceptibility of tumor cells to apoptosis-inducing treatment can lead to selection and reemergence of a more resistant and aggressive tumor (Green and Evan, 2002).

Exploring the implications of tumor cell heterogeneity in a mutation context, Wodarz and Komarova (2007) used a simple calculation to estimate the death rate-dependent number of mutant cells in a population after a wave of clonal expansion. The expected number of mutants at a specific time is derived from an initial number of cells growing exponentially subject to birth and death rates with a probability of mutation. Regardless of the fitness conferred to the mutant, the number of mutants increased with the death rate, peaking at a large death rate followed by a sharp decrease and mutant extinction as the death rate approached 100%. With a low death rate, tumors grew large in only a few cell doubling times, but at selective barriers the inherent phenotypic variation was not sufficient to progress. With a larger death rate, however, slower growing tumors accumulated a larger pool of mutants that enabled the tumor to pass the selective barrier and initiate a second wave of clonal expansion.

Considering the environment rather than mutation as a selective factor, Anderson et al. (2006) developed a hybrid discrete-continuous mathematical model which showed that if oxygen pressure becomes limiting, a phenotypically heterogeneous population gives way under selective pressure to a population composed of only a small number of phenotypes. The selected phenotypes feature low oxygen consumption and a high proliferation rate, as well as negligible cell—cell adhesion and a high response to haptotactic gradients. It was concluded that a less permissive microenvironment can shape populations into more aggressive and less heterogeneous tumors, as subsequently confirmed by an evolutionary hybrid cellular automaton model with a microenvironment response network (Gerlee and Anderson,
and immersed boundary frameworks (Rejniak, 2007; Quaranta et al., 2008).

Less studied are the ramifications of the heterogeneous cancer stem cell composition inherent in the cancer stem cell hypothesis. Lack of biological markers and experimental systems have complicated laboratory investigation. Meanwhile, a number of mathematical and computational studies have begun to focus on cancer stem cells (Ganguly and Puri, 2006; Michor, 2008; Ashkenazi et al., 2007; Boman et al., 2007), although theoretical models of the CSCs and their impact on tumor growth and progression dynamics remain sparse.

Here we review a CSC model we recently developed (Enderling et al., 2009a,b,c), and present novel findings that highlight an altered dynamic progression if tumors are indeed driven by cancer stem cells— one that suggests apoptosis may be more a hallmark of aggressive disease than is ‘evasion of apoptosis’ generally.

2. Materials and methods

We previously developed a cellular automaton model in which we describe the behavior of single cells by a minimal set of parameters and fixed rules. At discrete time points, the state and behavior of all cells is updated based on the internal state of each cell, and the local environment each cell experiences. The advantage of this approach is that no growth behavior is imposed on the tumor as a whole, and population dynamics emerge as a result of single cells interacting with one another and competing for the same environment. Using the cellular automaton we can study how intrinsic cell mechanisms contribute to tumor growth and morphology, with the ultimate aim of understanding which intervention provides the most promising treatment approach.

We adopted a parameter-minimalist approach, focusing on cell proliferation, cell migration and cell death as fundamentally applicable cell kinetics. Other mechanisms, such as cell—cell or cell—matrix adhesion (Anderson, 2005; Gerisch and Chaplain, 2008; Kim et al., 2009a), were omitted here for the sake of inferring a more definite cause-and-effect relationship, and because of their potential overlap in effect on the kinetics, e.g. of migration. Unlimited proliferation capacity ($\rho = \infty$), immortality ($\alpha = 0$), and asymmetric division (Dingli et al., 2007) define CSCs in our model. While two non-stem cancer cells are always the result of non-stem cancer cell proliferation, CSCs can divide either symmetrically to yield two CSCs, or asymmetrically to produce a CSC and a non-stem cancer cell with limited proliferation capacity. Symmetric CSC division occurs with probability $p_i$ and asymmetric division with probability $(1 - p_i)$. For $p_i = 1$, a homogenous population develops that simulates the classic view of cancer as clonogenic expansion. Class diagrams summarizing the intrinsic cell parameters and mechanisms of stem and non-stem cancer cells, the heterogeneous proliferation capacity hierarchy, as well as the simulation flowchart for the model are shown in Fig. 1.

The only additional mechanism considered beyond intrinsic cell kinetics in our model is a natural competition for space. In a growing population, cells populate available space and increasingly push one another, which results in intra-tumoral pressure and inhibited cell proliferation (Brú et al., 2003; Brú and Casero, 2006; Roose et al., 2003; Macklin et al., 2009; Tracqui, 2009). In the simple cellular automaton model, we consider the competition for space that takes place in the local neighborhood of nine (in the three-dimensional model) lattice points. A cell is assumed inhibited, i.e. quiescent, when other cells occupy all neighboring lattice points and cellular proliferation or migration is possible if the local environment is not fully saturated. We simulate tumor growth on a two (or three)-dimensional square lattice, in which each lattice point has the dimensions of $10 \mu m \times 10 \mu m$ and can hold at the most a single cell at any time. The lattice consists of $350 \times 350 \times 350$ lattice points, mimicking a $3.5 mm \times 3.5 mm \times 3.5 mm$ biological domain.

3. Results

3.1. Classic tumor growth

We first simulated growth of a ‘classic’ tumor from one cancer cell in which all progeny are considered immortal with unlimited proliferation capacity, i.e. $p_i = 1$ (100% symmetric division of an immortal cell) and $\rho = \infty$. As one would expect, an initially scattered population quickly forms a sphere-like structure in which a dense population is surrounded by a few migratory cells (Fig. 2). Radial symmetry and a narrow diffusive rim are characteristic morphological features of immortalized in vitro cell populations (Brú et al., 2003; Stein et al., 2007) and of other classical in silico tumor models (Anderson et al., 2000; Enderling et al., 2006). The growth curve of the simulated tumor population is shown in Fig. 2. Although all cells are immortal and have unlimited life span, tumor growth is not exponential. As the number of cells increases, available space is reduced and competition for space arises. Even with ample oxygen and nutrients available throughout populations in vitro, numerous monolayer studies concur that proliferation is limited to the outer rim (Brú et al., 2003; Galle et al., 2009). Cells can actively respond to overpopulation by intrinsic proliferation inhibition, or surrender to mechanical forces (Ribba et al., 2006a,b; Roose et al., 2003). For simplicity we omitted diffusion of oxygen and nutrients in our model simulation. If oxygen-dependent proliferation and hypoxic quiescence had been considered, the tumor would reach a diffusion-limited size. At this stage recruitment of blood vessels (Folkman, 1971; Almoq et al., 2009) or other extrinsic modulation such as tissue-pressure induced morphological instability (Macklin and Lowengrub, 2007) is required to enable further growth.

3.2. Cancer stem cell model and self-metastatic tumor growth

In a model based on the cancer stem cell hypothesis, only a minority of cells are presumed to be CSCs, the rest being non-stem cancer cells possessing a finite proliferation capacity $\rho = \rho_{max}$ that decrements with every cell division. A cell with $\rho = \rho_i$ gives birth to two daughter cells with $\rho = \rho_i - 1$ until $\rho_i = 0$, at which time a subsequent proliferation attempt results in cell death. We assume cancer stem cells divide symmetrically with probability $p_i = 0.01$ (i.e. 1%), reflecting the correspondingly low fraction of cancer stem cells reported throughout the literature (Vissader and Lindeman, 2008). With probability $1 - p_i = 0.99$, a cancer stem cell divides asymmetrically to produce a stem cell and a non-stem daughter cell. Although the only source of tumor heterogeneity is the mixed stem and non-stem cancer cell content, this interestingly proves sufficient to capture a critical spatio-temporal morphological evolution observed experimentally and in more complicated model systems. In our CSC model, initial tumor growth mimics the early growth phase of ‘classic’ tumors, in which cells proliferate and form an almost spherical population (Fig. 2C). With low $p_i$ (and a wide range of larger $p_i$; Enderling et al., 2009c), cancer stem cells very quickly become a minority surrounded by their progeny. Intra-tumoral competition for space arises and cancer stem cells are forced into quiescence. Proliferation is restricted to the outer rim of the population, which is comprised of almost exclusively non-stem cancer cells. As the population expands the cells at the boundary of the emerging tumor diminish their proliferation capacity and
eventually die. Tumor growth is halted and previously quiescent cells reactivate and repopulate the tumor until their proliferation capacity is exhausted in turn. The interplay of cells dying and cells becoming proliferative again results in tumor size oscillations, a feature intrinsic to the CSC model (Fig. 2D). After successive rounds of cell death and diffusive cell migration, previously quiescent CSCs reenter the proliferation cycle and divide subject to the same rules as before. Following symmetric division, there is

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**Fig. 1.** A) Class diagrams for cancer cells and cancer stem cells. B) Schematic of the cellular proliferation capacity hierarchy. C) Simulation flowchart.

**Fig. 2.** A) Growth of a tumor in the classic cancer view. B) Growth curve of the tumor shown in A (solid line), compared to exponential growth (dashed). C) Growth of a tumor in the cancer stem cell hypothesis. CSCs are shown in yellow, and limited proliferation capacity is shown as a gradient from red \((p = p_{\text{max}})\) to black \((p = 0)\). D) Growth curve of the tumor shown in C.
a tendency for the progeny CSCs to separate spatially via random motility to form independent clusters in the vicinity of one another. Because the separated clusters are less constrained spatially, overall growth is facilitated. Repeated seeding of new tumor clusters, or tumor ‘self-seeding’ (Norton and Massagué, 2006; Kim et al., 2009b), yields a unique intrinsic morphology that may be described as conglomerates of self-metastases (Fig. 2C) (Enderling et al., 2009a).

### 3.3. Paradoxical role of apoptosis

In classical tumor models that consist of intrinsically similar cells, a net loss of cells yields a monotonic reduction in population size. In a cancer stem cell model, the net loss of cells due to various forms of programmed or spontaneous cell death results in a short-term reduction in population size, but over the long-term it counterintuitively promotes tumor growth. For successful self-metastatic expansion (Enderling et al., 2009a), CSCs need to proliferate and divide symmetrically with subsequent relocation outside the originating cluster to form new clusters nearby. Both proliferation and migration are inhibited predominantly by non-stem cells occupying the tumor mass. It follows that tumors with low proliferation capacity in cancer stem cell progenies (i.e. low \( p_{\text{max}} = 10 \)) will express a lower non-stem cell fraction and thus grow significantly faster than tumors with more potent non-stem cancer cells (i.e. large \( p_{\text{max}} = 15 \)) (Fig. 3). Although clusters with larger \( p_{\text{max}} \) grow larger initially, the non-stem progeny start to inhibit cancer stem cells inside the population as the tumor grows, slowing progression. By contrast, symmetric cancer stem cell division is a more frequent event and tumor growth more efficient when non-stem progeny are short-lived and low in number.

We next introduced spontaneous cell death \( \alpha = 0.1 \) (i.e. 10%) to the population with large \( p_{\text{max}} = 15 \). At every discrete time point when cell proliferation is considered, non-stem cancer cells can undergo cell death and be removed from the simulation with probability \( \alpha \). Spontaneous cell death, like lower \( p_{\text{max}} \) values, also reduces the number of progeny cells in the cluster and in turn increases intra-tumoral proliferation and migration. The effect of increasing \( \alpha \) is potent – compared to tumors with a relatively low proliferation capacity \( p_{\text{max}} = 10 \), tumors with \( p_{\text{max}} = 15 \) and \( \alpha = 0.1 \) exhibit faster growth (Fig. 3). In general, increasing the rate of spontaneous cell death \( \alpha \) predictably yields a reduction in tumor size in the short-term, but enhances promotion in the long-term emerging population dynamics (Fig. 3). The paradoxical role of apoptosis has been studied extensively for a broad range of parameters elsewhere (Enderling et al., 2009b).

### 3.4. Apoptotic index, mitotic index, stem cell fraction and patient prognosis

With apoptosis counterintuitively promoting tumors driven by a minor subpopulation of cancer stem cells, the advisability of using an increased apoptotic index as a favorable indicator of long-term patient prognosis is put in question (Kuriyama et al., 2002; Gurova and Gudkov, 2002). Exploring this point, we simulated aggressive tumor growth using a low non-stem cancer cell proliferation capacity of \( p_{\text{max}} = 10 \) and a large cancer stem symmetric division probability of \( p_i = 0.5 \) (i.e. 50%), and compared the apoptotic index in a tumor without (\( \alpha = 0 \)) to a tumor with 10% spontaneous cell death (\( \alpha = 0.1 \)).

Due to the aggressive cancer stem cell symmetric division rate, both tumors grow at a comparable rate over the first few weeks (Fig. 4). Without spontaneous cell death the tumor features 58,216 cancer cells and 2942 cancer stem cells. The apoptotic index (due to cells constantly exhausting their proliferation capacity) and the mitotic index are 3.9% and 10.7%, respectively. Spontaneous cell death in the \( \alpha = 0.1 \) case results in an overall reduction in cell number of 16.7% (41,464 cancer cells and 9470 cancer stem cells). The apoptotic index increases to 12.9%, but the mitotic index also increases to 18%. Furthermore, proliferation usually limited to the outer rim is enabled in the tumor core to replace apoptotic cells, allowing for opportunistic symmetric cancer stem cell division. The number of cancer stem cells in the tumor with a higher apoptotic index is increased by more than three-fold, and the cancer stem cell ratio increases from 5% to almost 23% (Fig. 4). One may conclude that, although potentially smaller in size, a tumor with a larger apoptotic index also exhibits a larger mitotic index and a significant increase in the cancer stem cell pool, which renders the tumor less sensitive to current treatment strategies and yields a less favorable prognosis.

### 3.5. Self-metastases and metastases

The course to final metastasis, the life-threatening event for most solid tumors, is rife with obstacles, any one of which could be
defeating. To even become tumor cells, a number of mutative ‘hits’ to a single cell must presumably occur first. As discussed, the nascent tumor must then expand against a powerful, self-imposed space competition among stem and non-stem cells to reach a state where acquisition of vessel-recruiting ability will then sustain the tumor beyond nutrient diffusion limitations. Should this be successful, the tumor must then negotiate entry into the bloodstream to circulate throughout the body, and extravasate at a distant site. Successful growth at the distant site is far from certain. As Paget proposed some 120 years ago, the tumor ‘seed’ must find a favorable ‘soil’ to establish a viable metastasis (Paget, 1889). As all these steps are rate-limiting, it is not surprising metastasis formation on aggregate is a very inefficient process (Weiss, 1990, 1996; Luzzi et al., 1998).

The cancer stem cell hypothesis, paired with the self-metastatic growth model, invaluably augments our understanding of one rate-limiting process on the course to final competency to metastasize to distant locations, while offering a novel, local version of the metastatic process that illuminates our understanding of how the source primary tumor develops. In the process, it stands to offer a potentially unifying understanding of primary ‘self-metastatic’ growth and distant metastatic escape. To track this coupling, we extended the CSC model. We simulated tumor growth for \( t = 2 \) years using two different non-stem cancer cell proliferation capacities of \( p_{\text{max}} = 10 \) and \( p_{\text{max}} = 20 \), with a symmetric stem cell division rate of \( p_s = 0.01 \) (1%), a migration rate of \( \mu = 15 \) cell widths per day (Maini et al., 2004), and a spontaneous stem cell death rate of \( \alpha = 0.05 \). We introduced a blood vessel into the computational domain and assumed invasion into the blood vessel to be trivial such that the vessel serves as a local sink. As previously shown (Enderling et al., 2009a,b), a low \( p_{\text{max}} = 10 \) enables self-metastatic tumor progression while tumors with larger \( p_{\text{max}} = 20 \) remain dormant in the simulated time interval (Fig. 5). With the given parameter set, none of the dormant tumors were able to shed cells into the blood vessel distant to the initiating cancer stem cell (\( n = 10 \) independent simulations) due to intrinsic self-inhibiting dynamics. Self-metastatic growth, however, enabled shedding of single cells into the vasculature after successful initial growth. On average, \( 30.925 \pm 6114 \) (\( n = 10 \)) cancer cells escaped into the blood vessel sink, of which \( 29 \pm 6 \) cells (0.09%) were cancer stem cells. Reducing spontaneous cell death to \( \alpha = 0.01 \) or \( \alpha = 0 \) reduced the number of metastatic cancer cells to \( 16,187 \pm 3234 \) (9 ± 2 CSC) and \( 6212 \pm 1631 \) (4 ± 1 CSC), respectively. Altering intrinsic tumor parameters toward more favorable self-metastatic directly translated into more metastatic spread and vice versa (Fig. 5C). In contrast to CSCs, non-stem cancer cells could only initiate a size-limited tumor cluster that persisted for many years or even decades, but inevitably these clusters exhausted their proliferative potential and completely regressed (Enderling et al., 2009b). Our simulation results are in good agreement with the literature describing the low efficiency of distant metastases. If only cancer stem cells are capable of initiating secondary macroscopic tumors, and the ratio of cancer stem cells to non-stem cancer cells that escape into the bloodstream is very low, then the vast majority of circulating tumor cells can only initiate populations of a few cells or dormant micrometastasis.

4. Discussion

The application of a cellular automaton model to the cancer stem cell hypothesis allows definition of properties at the single cell level, and observation of emergent properties in the evolving population. Based on simple, clearly stated assumptions one can derive mechanistic insights into complex biological system bounded by these assumptions. Although much attention is paid to potent cancer stem cells, the role of non-stem cancer cells that make up the bulk of the tumor is underappreciated. Stochastic simulations of tumor growth reveal an unexpected, paradoxical contribution of intrinsic and spontaneous cell death in non-stem cancer cells to tumor progression (Enderling et al., 2009b). Although net loss of cells occurs, the growth rate of the tumor population as a whole counterintuitively, increases. Arising quiescence in cancer stem cells due to intra-tumoral competition for space (Brü et al., 2003; Roose et al., 2003) leads to inhibition of the tumor by its own mass (Prehn, 1991) and halted tumor progression. In turn, mechanisms that relax this intrinsic bottleneck facilitate tumor growth (Enderling et al., 2009a). Different approaches reveal the necessity of cancer stem cells to divide symmetrically to expand a tumor (Morrison and Kimble, 2006; Boman et al., 2007), and that many cancer stem cells are likely to be located in the quiescent core.
of the tumor, where their ability to expand is curtailed by the non-stem cells that surround them (Enderling et al., 2009c).

We have summarized a series of findings indicating the positive correlation between cell death and subsequent stem cell proliferation and ultimately tumor progression, and propose that ‘evading cell death’ as a hallmark of cancer should be revisited in light of the cancer stem cell hypothesis. We have shown that tumors can remain dormant for surprisingly long intervals despite constant cellular turnover, and that stimulation of apoptosis can perturb the intrinsic tumor dynamics and shift the population into an aggressively growing domain. By extension, external perturbations such as immune system interactions (Dunn et al., 2002) and cytotoxic treatments (Bao et al., 2006; Baumann et al., 2008; Marcato et al., 2009) may shape the tumor by selecting for aggressive cell types, including cancer stem cells, that go on to facilitate malignant growth. Successful therapy must eradicate tumor stem cells (Dingli and Michor, 2006), but with increasing evidence surfacing that these cells are intrinsically less sensitive to current agents (Bao et al., 2006; Diehn et al., 2008; Deeb et al., 2009) a shift toward controlling the tumor via modulation of the non-stem progeny could emerge. If detected early, tumors could potentially be maintained at a non-advancing equilibrium by reinforcing the ability of non-stem cells to competitively suppress CSC proliferation. Reactivating the senescence program in the active tumor compartment, for example, could disable proliferation without creating voids that can opportunistically be populated by more potent, quiescent cells (Chao et al., 2008). Alternatively, or as an adjuvant approach, cell migration inhibition promises to be an attractive target to inhibit tumor expansion (Roose et al., 2003; Basanta et al., 2008).

Within the cancer stem cell hypothesis, self-seeding of clones to the primary tumor is a morphologically unique phenomenon (Norton and Massagué, 2006; Enderling et al., 2009a; Kim et al., 2009b). The mechanisms underlying the self-seeding phenotype are sufficient to explain the formation of metastases, and may contribute to the frequently observed inefficiency of distant metastatic seeding. Assuming cancer stem cells drive primary tumor growth, tumors do not metastasize because they are big; rather, they are big because they self-metastasize (Norton, 2005), and distant metastasis is a direct result of self-metastasis. By this reasoning, the primary tumor would inherently have metastatic capability, and it would not need to acquire another trait to successfully metastasize. Migrating, self-renewing and symmetrically-dividing cancer stem cells shape the primary tumor,

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{A) Simulation of tumor growth and escape of cells into a blood vessel. B) Prevention of metastatic spread in non-self-metastatic dormant tumors. C) Parameter dependent number of metastatic cancer cells after 2 years of tumor growth.}
\end{figure}
and are also exclusively capable of distant seeding, whereas the majority of non-stem cancer cells (that can be frequently detected as circulating tumor cells) are intrinsically only able to form dormant micrometastases.

The models discussed here were intentionally minimalist to enable conclusions to be drawn about the contribution of intrinsic cell properties to growth dynamics and emerging tumor morphologies. The model is based on simplistic definition of cell–cell interactions. Complex biological models (Rejniak, 2007; Bearer et al., 2009; Frieboes et al., 2010) need to be developed on the presented assumptions to help identifying the extent to which the derived intrinsic dynamics are modulated by tissue biomechanics. We were able to show that in certain tumors, invasive morphology is a logical result of heterogeneous cell phenotypes—a pattern that is often attributed to mutations in the phenotypic landscape, and cell-extrinsic higher order mechanisms such as oxygen and nutrient availability (Bearer et al., 2009; Anderson et al., 2006). With increasing awareness and understanding of intrinsic tumor properties, the model can be extended to study how environmental conditions alter tumor growth (Enderling et al., 2010), and eventually how one might exploit the environment to push the tumor toward a non-progressing, dormant disease.

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