Published in final edited form as:
Med Hypotheses. 2008 August ; 71(2): 186–189. doi:10.1016/j.mehy.2008.02.010.

Cancer: A *profit*-driven biosystem ?

Thomas S. Deisboeck
Complex Biosystems Modeling Laboratory, Harvard-MIT (HST) Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, 02129, USA

Abstract

The argument is made that solid malignant tumors behave as *profit*-driven biological systems in that they expand their nutrient-uptaking surface to increase energetic *revenue*, at a comparably low metabolic *cost*. Within this conceptual framework, cancer cell migration is a critical mechanism as it maximizes systemic surface expansion while minimizing diffusion distance. Treating these tumor systems with adjuvant anti-proliferative regimen *only* should increase the energetic net gain of the viable cancer cells left behind, hence would facilitate tumor recurrence. Therapeutic attempts to better *control* tumor (re)growth should therefore aim primarily at *containing* its surface expansion, thus reducing its energetic revenue, or increasing its metabolic costs or better yet, *both*.

INTRODUCTION

Amongst the biological mechanisms most often cited as driving malignant tumor expansion is a deregulation of tumor suppressor genes versus proto-oncogenes [1]. While, over the last decade, molecular analysis methods and techniques have undoubtedly increased our understanding of specific aspects involved in carcinogenesis by orders of magnitude, one could argue that in going forward, precisely because of the magnitude of detailed yet fragmented data made available, it may help if not even become critical to keeping a somewhat ‘larger’ picture in mind. That is, much like any other biosystem, tumors need continuous nourishment to sustain their cells’ metabolism, and at the same time, they must dispose of metabolic waste products to avoid the buildup of a hostile microenvironment that would otherwise limit further expansion. However, as solid tumors grow in size their ‘surface-to-volume’ ratio decreases, a fact that leaves the tumor with less exchange area for nutrient intake and byproduct discharge. Consequently, this declining ratio is thought to be responsible for the onset of central necrosis at relatively early growth stages. Solid cancers therefore appear to struggle with balancing a growing intrinsic ‘demand’ with limited microenvironmental ‘supply’. Therefore, based in part on our previous theoretical works [2], I propose here that *a key ‘objective’ of the tumor’s spatio-temporally expansive drive is to increase its surface at a comparably low metabolic cost.*

CONCEPT

Tumors behaving like profit-driven systems, how so? Conceptually, a tumor should be able to increase its surface by a variety of densely investigated, yet commonly separately studied measures:

Thomas S. Deisboeck, M.D., Complex Biosystems Modeling Laboratory, Harvard-MIT (HST) Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital-East, 2301, Bldg. 149, 13th Street, Charlestown, MA 02129, Tel: 617-724-1845, Fax: 617-726-7422, Email: E-mail: deisboec@helix.mgh.harvard.edu.

First, **(1)** in reality, a solid cancer tends *not* to grow as a perfect sphere. Rendering the surface less smooth, with area-increasing bulges and niches, would argue for a selective advantage of a heterogeneous spectrum of tumor clones exhibiting a variety of proliferation rates to dominate the tumor surface. Next, **(2)** cell migration into adjacent parenchyma, i.e. cancer invasion operates with proteases that are degrading extracellular matrix (e.g., [3]), hence can be understood as an attempt to damage neighboring tissue consistency, reduce mechanical confinement, and thus to allow for further local growth of the main mass. Ongoing invasion is therefore advantageous and since these mobile cells derive from cells shed at the proliferative tumor surface, it is this *feedback* (with (1)) that enables the tumor to maintain a rather high regional cell proliferation rate without adding excessively to the regional volume; hence, the tumor system avoids exceeding the diffusion distance limit on site (which would lead to (4) and (5), below) while minimizing diffusion distance at the invasive edges which operate with single cells. Note that (1) and (2) combine to an underlying *minimum energy dissipation* strategy [4]. Equation 1 conceptualizes the relationship between tumor surface expansion and volumetric gain:

$$N_{Total} \approx \frac{(n)\kappa \cdot S}{V} \qquad \text{(Eq. 1)}$$

Here, κ represents the extent of invasiveness (as radial extension of an invasive cell path in [μm], with n representing the number of paths) that expands the tumor surface, S, to compensate for the ever increasing volume, V. It is obvious that the need to raise $(n)\mu$ grows as V increases [more so than S] and that this can be achieved with either a few long invasive paths, or many short ones, or both (i.e., a (n) κ-spectrum or $[(n)\ \kappa]_{1,2\ldots n}$), reflecting a more realistic inhomogeneous microenvironmental permission. Given that all entities in the right-hand term represent cell numbers, (n) κ modulation can lead to an overall increase in [total] tumor cell number, N. Such intuitive idea of increasing the surface roughness in order to optimize the surface-to-volume ratio has been quantitatively confirmed by evaluation of the surface fractal dimension. That is, for a number of malignant tumors it has already been shown that the fractal dimension is much larger than the topological one (which is expected to be 2) [5] and that this fractal surface dimension can in fact be related to histological tumor type and grade [6–7]. Thirdly, **(3)** recruitment or cooption, and tumor cytokine-induced attraction of new blood vessels (i.e., angiogenesis) is necessary early on in the process in an effort to sustain volumetric tumor growth beyond a certain size [8, and references therein].

However, there are quite a few ways a tumor could manage its *onco-economics* favorably, other than simply increasing its overall *intake* via the three strategies listed above. Arguably, its main objective is to secure continued expansion with surplus nutrients, i.e. to turn an energetic net *profit* into net cell growth. As such **(4)** there is the option of facilitating also a 'leaner' structure of the system itself which could be accomplished by furthering *cell loss*. That is, if the costs for maintenance increase dramatically while intake (and/or toxic discharge) stalls, cell loss would have to increase to *reduce demand* or lower *energetic costs* (and because on site toxicity raises beyond a critical level). In other words, a high proliferation rate within a host organ of generally limited nutrient supply (or adaptive capability) will soon have to lead to a high on site cell loss within the tumor. Here, apoptosis and consequently, necrosis, follow primarily an inside-out trajectory, with a central zone of deteriorating cell viability emerging [9]. **(5)** Another option to 'down-size' *temporarily*, without losing its ability to react to the microenvironment once it turns favorably, is to reduce *cell metabolism*, again, in an attempt to control raising energetic costs. Cell quiescence is a well known non-proliferative and non-migratory phenotype that is *reversible* and that is found in the intermediate cell layer between death zone and proliferative tumor surface [9]. The temporal sequence of adjustment options should therefore be reversible cell quiescence, prior to irreversible cell loss. Together, (4) and

(5) result in a layered expansion of multicell-depth shells, rather than a solid core, hence distributing demand more evenly while facilitating diffusion at the same time. Lastly, **(6)** proper *re-investment* of the net gain; that is, placing cell growth areas where they can be managed for some time in going forward, i.e. again, close to the surface (see (1)) and here, close to lesser mechanical resistance areas (see (2)) and neighboring blood vessels (see (3)). Seeding satellite colonies or *metastases* (e.g., [10]) would fall in here also as in theory, Eq. (1)'s $(n)\,\kappa$ term could be modified to account for metastasis, as a means for *systemic* tumor surface increase.

CONCLUSIONS

If so, what are the implications? First, **(A)** if cell loss indeed is a prominent means by which a tumor adjusts readily to deteriorating conditions in its vicinity, there should be clinical evidence of relationships between cell loss, tumorigenesis *and* patient outcome. Indeed, for instance, a recent multivariate analysis reported less TP53 mutations in glioblastomas with necrosis, indicating at least some functionality of the apoptotic loop, while the very presence of such necrosis correlated with poor outcome in these patients [11]. Together with the reported fact that such TP53 mutations play a significantly lesser role in the more rapidly growing primary or de novo glioblastomas [12–13] one would argue that given the proposed concept (particularly, (4) and (5)), topographically, the requirements for a functional apoptosis loop are less so on the tumor surface where cells shed and start to invade the neighboring tissue. Intriguingly, analyzing cDNA microarray data, Mariani et al. [14] already reported a reduced apoptotic activity in such migrating glioma cells. **(B)** Secondly, from a therapeutic perspective, any primarily anti-proliferative treatment modality (such as adjuvant radiotherapy and most chemotherapeutic regimen), if applied *without* targeting microenvironmental nourishment in addition[1], should indirectly yield an *increase* of the remaining tumor's energetic profit or net gain, and would therefore unintentionally *accelerate* re-growth. Recurrence would be further facilitated if sub-total resection leaves a tumor residual behind[2]. **(C)** If the necessity to increase nutrient intake triggers surface expansion, *improving* intake therapeutically may *reduce* the tumor's drive to expand. This may sound paradoxically at first. However, interestingly, there are corroborating reports in the literature that *normalizing* tumor vascularization with anti-angiogenesis regimen indeed is beneficial from a therapeutic perspective (such as for administering adjuvant anti-cancer drugs in a sufficiently high concentration on site) yet reportedly without necessarily increasing tumor cell proliferation [15]. **(D)** The latter notion is important to be confirmed since at the time of diagnosis, the feedback loop described in ((2), above) should be already established and thus every unintended surge in proliferation could potentially lead to an increase in invasion, locally if not globally (and thus also raise the probability of metastases (see (6), above) depending on the cancer type). The need for such a dual anti-proliferation *and* anti-invasion strategy is already supported by data from a clinical retrospective study that analyzed patients with recurrent malignant glioma who received chemotherapy and the anti-angiogenesis agent bevacizumab (a monoclonal antibody against vascular endothelial growth factor, VEGF). While this combination therapy was well tolerated and seemed to fend off local volumetric recurrence at least temporarily, a trend towards non-enhancing, diffuse infiltrative tumor progression was noticeable on MR image [16]. Taken together, **(E)** a treatment regimen that targets *both*, tumor angiogenesis *and* cancer cell motility [3] is needed and recent, promising news on e.g. anti-integrin targeting in treating highly malignant brain tumors seem to support this strategy [17]. Ongoing pharmaceutical strategies

[1]For instance, conventional external radiation therapy is focused on the on-image visible tumor, precisely to *reduce* the burden for the surrounding healthy tissue.

[2]Because of the underlying dynamic surface-to-volume relationship, Eq. (1) suggests that attempting primarily a reduction of V (e.g., through surgery) will have a *relatively* less limiting effect on S (albeit temporarily containing the demand for $(n)\kappa$); it thus may result in a diminished reduction of the [total] number of tumor cells, N, and can facilitate recurrence.

[3]Eq. (1) also indicates that, if such selective treatment would become available, targeting invasion ($(n)\,\kappa$) *only*, without impacting V, will result in an even *more* substantial trigger for invasion once the treatment has faded off.

on targeting simultaneously the angiogenesis system and the hepatocyte growth factor/scatter factor (HGF/SF, and its receptor tyrosine kinase, c-Met [e.g., 18–19]) would fall into the same category.

In summary, Eq. (1) suggests that reducing the [overall] nutrient intaking surface, *S*, through containment of cell invasion ((*n*) κ), while maintaining metabolic demand of the main mass (and thus keeping the denominator, *V*, viable), would result in a decrease in [total] tumor cell number. Eradicating a malignant tumor system completely has all too often proven to be a difficult task, albeit for instance breast and prostate carcinoma as well as melanoma have excellent cure rates if discovered early. In all other cases, the patient's life quality and thus in essence, *sustainability* of the host organ's function remain the main goals. Therapeutic attempts to better *control* tumor (re)growth should therefore aim primarily at *containing* its surface expansion, thus reducing its energetic revenue or increasing its metabolic costs or better yet, *both*.

Acknowledgments

This work has been supported in part by NIH grant CA 113004 and by the Harvard-MIT (HST) Athinoula A. Martinos Center for Biomedical Imaging and the Department of Radiology at Massachusetts General Hospital. I thank Drs. Jose Costa (Department of Pathology, Yale University Medical School) and Caterina Guiot (Dip. Neuroscience-INFM, Università di Torino) for critical review of the manuscript.

References

1. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100(1):57–70. [PubMed: 10647931]
2. Deisboeck TS, Guiot C, Delsanto PP, Pugno N. Does cancer growth *depend* on surface extension? Med Hypotheses 2006;67:1338–1341. [PubMed: 16828232]
3. Nakano A, Tani E, Miyazaki K, Yamamoto Y, Furuyama J. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in human gliomas. J Neurosurg 1995;83(2):298–307. [PubMed: 7616276]
4. Deisboeck TS, Berens ME, Kansal AR, Torquato S, Stemmer-Rachamimov AO, Chiocca EA. Pattern of self-organization in tumour systems: complex growth dynamics in a novel brain tumour spheroid model. Cell Prolif 2001;34(2):115–134. [PubMed: 11348426]
5. Cross SS. Fractals in pathology. J Path 1997;182(1):1–8. [PubMed: 9227334]
6. Kikuchi A, Kozuma S, Yasugi T, Taketani Y. Fractal analysis of surface growth patterns in endometrioid endometrial adenocarcinoma. Gynecol Obstet Invest 2004;58(2):61–67. [PubMed: 15103231]
7. Kikuchi A, Kozuma S, Yasugi T, Taketani Y. 3-D fractal tumor growth of epithelial ovarian cancer. Eur J Gynaecol Oncol 2006;27(6):561–565. [PubMed: 17290583]
8. Folkman J. Angiogenesis. Annu Rev Med 2006;57:1–18. [PubMed: 16409133]
9. Freyer JP, Sutherland RM. Regulation of growth saturation and development of necrosis in EMT6/Ro multicellular spheroids by the glucose and oxygen supply. Cancer Res 1986;46(7):3504–3512. [PubMed: 3708582]
10. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer 2003;3(6):453–458. [PubMed: 12778135]
11. Homma T, Fukushima T, Vaccarella S, Yonekawa Y, Di Patre DL, Franceschi S, Ohgaki HJ. Neuropathol Exp Neurol 2006;65(9):846–854.
12. Lang FF, Miller DC, Koslow M, Newcomb EW. Pathways leading to glioblastoma multiforme: a molecular analysis of genetic alterations in 65 astrocytic tumors. J Neurosurg 1994;81(3):427–436. [PubMed: 8057151]
13. Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. Am J Pathol 2007;170(5):1445–1453. [PubMed: 17456751]
14. Mariani L, Beaudry C, McDonough WS, Hoelzinger DB, Demuth T, Ross KR, Berens T, Coons SW, Watts G, Trent JM, Wei JS, Giese A, Berens ME. Glioma cell motility is associated with reduced

transcription of proapoptotic and proliferative genes: a cDNA microarray analysis. J Neuro-Onc 2001;53(2):161–176.

15. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogeneic therapy. Science 2005;307(5706):58–62. [PubMed: 15637262]
16. Kesrari S, Norden AD, Young GS, Setayesh K, Muzikansky A, Klufas R, Ross GL, Ciampa AS, Ebbeling LG, Levy B, Drappatz J, Kesari S, Wen PY. Bevacizumab for recurrent malignant gliomas: efficacy, toxicity and patterns of recurrence. Neurology. 2008Personal CommunicationIn press
17. Narbors LB, Mikkelsen T, Rosenfeld SS, Hochberg F, Akella NS, Fisher JD, Cloud GA, Zhang Y, Carson K, Wittemer SM, Colevas AD, Grossman SA. Phase I and correlative biology study of cilengitide in patients with recurrent malignant glioma. J Clin Oncol 2007;25(13):1651–1657. [PubMed: 17470857]
18. Eckerich C, Zapf S, Fillbrandt R, Loges S, Westphal M, Laszus K. Hypoxia can induce c-Met expression in glioma cells and enhance SF/HGF-induced cell migration. Int J Cancer 2007;121(2): 276–283. [PubMed: 17372907]
19. Lal B, Xia S, Abounader R, Laterra J. Targeting the c-Met pathway potentiates glioblastoma responses to γ–radiation. Clin Cancer Res 2005;11(12):4479–4486. [PubMed: 15958633]