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"A possible mechanism for the spontaneous regression of tumors"

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Abstract

Neither tumor growth nor regression is truly spontaneous, but both may under special circumstances be driven by similar events. We describe a sequence of processes that typically leads to tumor progression but may on occasion inadvertently result in regression. A possible procedure for reducing tumor mass through a controlled intervention is also outlined.

Keywords: spontaneous regression, tumors, cancer, bacterial therapy, Coley, immunotherapy, hyperthermia, oncology

Introduction

The difficulty of characterizing so-called spontaneous regression (SR) is clear already from its definition, which is not unambiguous. SR is often described as the regression of malignancy that occurs in the absense of medical intervention, yet bacterial therapies administered by medical professionals as early as the nineteenth and early twentieth centuries are not necessarily excluded. An interesting introduction to the topic is that of Kucerova and Cervinkova (1).

That a malignant, i.e. growing, tumor should somehow reverse course and regress in the absense of treatment seems implausible, but this phenomenon is abundantly documented in the medical literature (21). That these events apparently occur infrequently makes them challenging to study, but no less interesting as a research topic. Knowledge of the underlying processes could for example guide the development of controlled medical proceedures that lead to partial or complete regression of malignancy without the need for radiation or chemo-therapy.

Given the lack of control that the body has over malignant growth, the case of regression as spontaneous in the sense of not requiring any external input whatsoever is also difficult to justify. In this brief communication we will therefore consider a middle ground in which seemingly innocuous environmental conditions can by accident have a deleterious impart on the viability of a malignancy.

We assume three key attributes for this form of "spontaneous" regression, namely that (1) it possess a high degree of tumor specificity, (2) the processes involved have minimal impact on the body's normal physiology, and (3) no exotic or otherwise rare phenomena are involved, three plausibility conditions that are not overly restrictive.

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The model "spontaneous" regression described here is based on an immune-mediated end to malignant cell proliferation and growth coupled to a deterioration of the tumor's P microenvironment (Fig. 1). Metronomic repetition of these processes could in principle prevent tumor recovery, leading to increasing damage to and death of no longer proliferating cells. The therapeutic goal would be to eliminate the malignant tumor's ability to outgrow a deteriorating microenvironment while concurrently increasing its need for such an escape.

Because of their many pathophysiological features (20), tumors are fragile entities, affected to a greater degree by physiological stress than normal tissues. Their so-called "aggressive" response to therapy reflects a weakness of malignancy in that new growth is a requirement for survival. If such compensatory growth is blocked, net cell death and regression are likely.

Figure 1 shows a symmetric and idealized tumor compartmentalization into proliferating (P), quiescent (Q), and necrotic (N) domains. These three regions are often also characterized by their typical level of oxygenation: normoxic, hypoxic, and anoxic, respectively (18). We limit ourselves to the viable P and Q domains and assume that N has a relatively smaller impact on tumor growth.

To illustrate the above requirements for regression, we consider a model in which two common environmental inputs modulate the tumor microenvironment (TME), namely bacterial colonization with subsequent growth of the colony (2-5, 23), and increased oxygenation caused by hyperthermia (6, 7, 22, 24). Both of these are assumed to recur on a diurnal time scale, matching human activities.

Tumor growth in P is assumed to be stimulated by a deteriorating microenvironment in Q (see also (19)). In other words, P provides a means of malignant escape when the viability of Q is threatened. If Q's impairment is modest, compensatory proliferation in P to enable "escape" is likely to be moderate. If Q on the other hand suffers significant structural and functional damage, the proliferative response is also likely to be elevated, except possibly under certain circumstances. In the last case, proliferation in P may end as a result of cellular debris spilling over from Q. Consequently, deteriorating conditions now in both Q and P would preclude new growth, with the tumor as a whole suffering uncompensated damage and cell death. A probable outcome would be an increase in the necrotic domain N or some degree of tissue regression. If the degradation continues through metronomic repetition, with proliferative compensation disabled throughout, conditions might be favorable for eliminating the malignancy.

We first summarize potential circumstances under which each of the two limiting cases described above might occur, and then consider each in detail:

(1) Moderate bacterial colonization of Q, followed by oxygenation of Q via hyperthermia and an immune response to the infection (8-10), with minimal transport of molecular debris from Q to P. Microenvironmental deterioration occurs mainly in Q, with proliferation/growth triggered in P. Tumor progression of this kind might be typical.

(2) Significant colonization and bacterial growth in Q, followed by oxygenation of and immune response in Q, with major degradation in Q as well as Q -> P transport of cellular debris. Due to the latter, an immune-mediated end to proliferation in P via a M2 -> M1 transition in immune polarization (11-13). Complete regression possible if worsening micro-environmental conditions occur over an extended period without possibility of tumor escape.

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Anaerobic bacterial colonization of tumors is possible in immune-suppressing hypoxic and anoxic domains beyond a critical distance from normal vasculature. These bacteria likely find their way to the tumor for a tolerable/hospitable microenvironment and protection against immune attack, and typically infect cells in Q and N.

To add detail to these brief scenarios, we consider a potentially common juxtaposition of bacterial colonization of the hypoxic domain Q and its periodic partial oxygenation through hyperthermia, an example that could serve as a prototype for natural environmental conditions that impact malignant growth. Of special interest will be the possibility that under special conditions of bacterial loading, immune activation, and timing, regression could replace progression in the latter of the above two cases.

We focus in particular on the transition region between P and Q since events there have the greatest impact on P. Q is initially assumed to be hypoxic to an extent that inhibits microbe-related innate immune cell activation, and is consequently a region favored by anaerobic bacteria for colonization and multiplication. Periodically, however, some fraction of Q bordering P is oxygenated from increased tumor perfusion due to hyperthermia. As a result, activated innate immune cells can cross from P to oxygenated regions of Q to attack infected cells there.

For regime (1) this leads to cellular debris that includes PAMPs and DAMPs (14, 15), but with these largely confined to Q. The local microenvironment suffers, potentially resulting in signaling for compensatory growth in P. In this sense, seemingly innocuous environmental effects might stimulate new tumor growth, which could be interpreted as occuring “spontaneously.”

For regime (2) on the other hand, greater quantities of PAMPs and collateral DAMPs are produced in Q, and these are in part transported convectively via interstitial fluid flow from higher pressure (Q) to lower pressure (P), as well as diffusively from greater concentration (Q) to lower concentration (P). The immediate impact in P is a deterioration of microenvironmental quality, which will under the right circumstances result in a transition in immune polarization from M2 (“growth”) to M1 (“clean up”), thereby at least temporarily slowing or ending proliferation.

It is conceivable that such immune-modulated disabling of malignant cell proliferation in P coincident with deteriorating microenvironments in P and Q will gradually damage and/or reduce the size of the tumor over time. A tumor’s raison d’etre is survival, and the means for this are growth, invasion, and/or metastasis. Proliferation plays a key part in all three, and a tumor unable to grow under deteriorating conditions could as a result of accumulating cell damage and death eventually die.

Low level hyperthermia due to for example bathing, exercising, working, or warm weather will increase perfusion of and oxygen delivery to the tumor, resulting in at least partial oxygenation of previously hypoxic Q. A higher oxygen concentration in Q will enable innate immune cell migration from P to clear the infection, generating PAMPs and DAMPs, which in combination can trigger a synergistic immunopathological response (25), with corresponding decrease in microenvironmental quality.

Cellular debris in Q carried along by interstitial fluid into P could through its negative microenvironmental impact there lead to an M2 -> M1 transition in polarization that replaces proliferation with clean up. (Since such debris impedes conventional wound healing via M2 ->

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M1 in normal tissues, we expect a similar effect here. Typically polarization M2 dominates in P, but if an acute immune event in Q should result in deterioration there, one might expect M1 to dominate there as well following an M2 -> M1 transition.) The result would be an end to growth while increasing the need for tumor escape, a possible route to regression.

There are at least two reasons metronomic repetition of the processes described above may be necessary for complete regression: (1) To end proliferation throughout all of P, and (2) to maintain this condition until all malignant cells in P expire, making regrowth impossible. Given the low risk of toxicity from combined bacterial colonization and mild to moderate hyperthermia, this procedure could in principle be repeated multple times in a therapeutic setting to gradually shrink one or more tumors over time without negative impact on other tissues.

It would be essential to maintain M1 in P for the duration of the therapy, however, to avoid return to tumor growth triggered by an M1 -> M2 reversal. The events in Q should therefore be repeated regularly, which in turn requires (1) ongoing colonization and expansion/growth of bacterial colonies during intervals when oxygenation levels have returned to their hypoxic norm, and (2) correctly timed hyperthermal triggers of immune activation for new rounds of attack of the bacterial colonies once Q is again partially reoxygenated. Since the human cycle of activities is largely diurnal, including the cycle of varying body temperatures, colonizing bacteria able to significantly expand their populations on this time scale should be used. In this case proliferation in P would never be allowed to restart, while TME conditions in both Q and P would deteriorate further with each cycle, making it increasingly more difficult for the malignancy to maintain viability. One would in effect have ongoing "wounding" of the tumor with no opportunity for it to "heal" (regrow or invade).

It would also be important to end proliferation in P before its TME worsens significantly since accelerated growth to escape deteriorating conditions would likely occur otherwise. The transport of debris from Q should therefore occur in a way that it accumulates slowly enough in P so as not to trigger new growth, but quickly enough that the immune system there isn’t able to clear it over one cycle.

Certain other inflammatory conditions should also be avoided. For example, chronic endotoxemia due to e.g. a leaky gut would likely leave the immune system in P in state M2. Also, adaptation to infection (“immune tolerance”) can be circumvented via a minimum recovery period between bacterial colonizations while keeping the period short enough to avoid M1 -> M2 reversion.

Similar to Coley’s therapy (16), the processes described here correspond to a bacteral immunotherapy, but differ from earlier work in that they assume a longer time scale, smaller bacterial loads, milder immune responses, the absense of fever, blood borne transport/homing in place of injected bacteria, and different processes in domains Q and P. There is also no significant risk of sepsis or greatly elevated body temperature here.

It should also be emphasized that the malignancy is not attacked directly. Instead there is periodic collateral damage in response to immune mediated elimination of colonizing bacteria, which crucially inhibits the tumor’s escape mechanisms of regrowth/invasion/metastasis.

Malignant cells need not be identified as special by the immune system. In short, new growth is disabled under conditions during which it is needed most. Stimulated, or controlled, regression in a clinical setting would of course benefit significantly from having all variables controlled and monitored (17, 26) in a medical environment.

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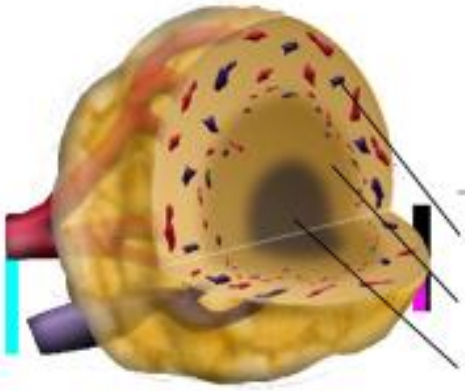
Schematic of three microenvironmental regions in a centrally necrotic tumor.



Tumor Region	Perfusion	Interstitial Pressure	pO_2	Extracellular pH	Proliferation	Drug Delivery
Proliferative	++	+	++	<7.4	++	++
Quiescent	+	+++	+	~6.5 - 7	+/-	+
Necrotic	-	+++	-	~7 - 8	-	+/-

Rakesh K. Jain, and Neil S. Forbes PNAS 2001;98:26:14748-14750

PNAS

Figure 1: Schematic of three microenvironmental regions in a centrally necrotic tumor. A spontaneous tumor may consist of many such necrotic foci. Decreasing magnitude of various physiological parameters is indicated as +++, ++, +, +/−, and −.