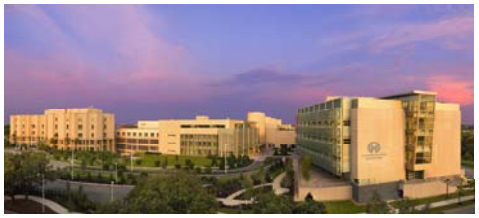

A Theoretical Quantitative Model for Evolution of Cancer Chemotherapy Resistance

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Introduction

Disseminated cancer remains a nearly uniformly fatal disease. While a number of effective chemotherapies are available, tumors inevitably evolve resistance to these drugs ultimately resulting in treatment failure and cancer progression.

We propose that in order to understand the evolutionary dynamics that allow tumors to develop chemo resistance, a comprehensive theoretical quantitative model must be used to describe the interactions of cell resistance mechanisms and tumor microenvironment during chemotherapy.

Goals

1. Understand how tumor chemo resistance is enforced by microenvironment
2. How the use of maximum tolerated dose selects for resistant cells in tumor and may promote tumor resistance
3. How manipulation of tumor microenvironment and use of therapies adjusted to tumor response may lead to control of tumor growth

Methods

In order to achieve this goal we built a computational model of tumor microenvironment as an avascular spherical tumor mass embedded in a volume of well vascularized tissue and simulated different tumor progression and therapy strategies (chemotherapy protocol and glucose restriction) and selected those that led to tumor eradication or prolonged survival in case of resistant tumors.

Tumor population was composed of cells presenting different values for the following phenotypes: glucose consumption, acid resistance, drug resistance and proliferation rate.

We expect that the use of minimum amount of drug sufficient to keep tumor size stable will yield better results than MTD in tumors presenting a resistant subpopulation[3]. We also expect that restriction of glucose availability through 2-Deoxyglucose or other non-metabolizable glucose analog will reduce viability and ATP-dependent chemo resistance of cells in hypoxic regions of tumor and, together with systemic administration of pH buffers, reduce glycolysis mediated acidification and acid mediated apoptosis of host cells in tumor-host interface.

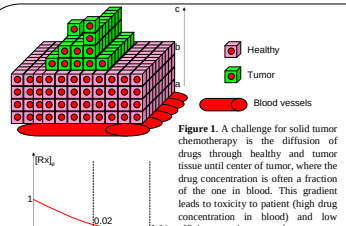

Figure 1. A challenge for solid tumor chemotherapy is the diffusion of drugs through healthy and tumor tissue until center of tumor, where the drug concentration is often a fraction of the one in blood. This gradient leads to toxicity to patient (high drug concentration in blood) and low efficiency against tumor.[1]

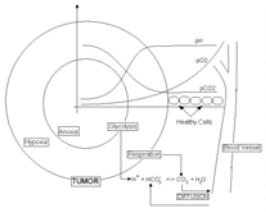

Figure 2. The model implemented in this work represents a solid avascular tumor embedded in healthy tissue[2]. Oxygen and glucose diffuse from blood vessels and consumed by tumor, which in turn generates CO_2 and lactic acid. Bicarbonate plays the role of pH buffer, converting free protons into CO_2 and water.

In hypoxic regions, acidity will be most present due to anaerobic glycolysis and is responsible for both tumor invasion and a necrotic or quiescent tumor core.

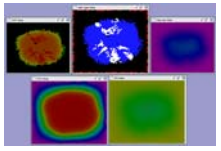

Figure 3. These preliminary results were obtained from simulations of a bidimensional version of the model. The entire simulated space is a lattice with an area equivalent to 90,000 cells.

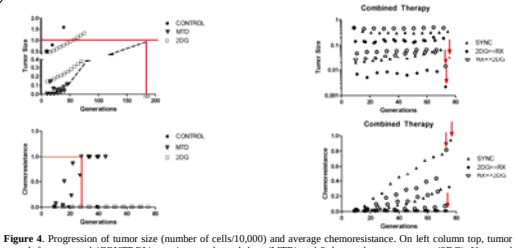

Figure 4. Progression of tumor size (number of cells/10,000) and average chemoresistance. On left column top, tumor growth for untreated (CONTROL), maximum tolerated dose (MTD) and 2-deoxy-glucose treatment (2DG). Untreated tumors reach lethal size after 26 generations; 2DG reaches this size after 57 generations and MTD after 183 generations. On left column bottom, average tumor chemoresistance for untreated (CONTROL), maximum tolerated dose (MTD) and 2-deoxy-glucose treatment (2DG). Only tumor treated with chemotherapy will "develop" chemoresistance to treatment as the treatment will change adaptive landscape of tumor to favor cells with resistant phenotype. The untreated tumor also contains resistant cells but these are kept in small numbers in absence of therapy. On right column top, comparison of tumor size in different combined therapies. SYNC stands for simultaneous administration of 2DG and Rx, 2DG=>Rx corresponds to administration of 2DG followed by Rx, and Rx=>2DG corresponds to administration of Rx followed by 2DG. Red arrows represent final high Rx dose of MTD in one unique dose in order to try tumor eradication. On right column bottom, comparison of tumor average chemoresistance in different combined therapies. Chemoresistance steadily increases in simultaneous administration, but still more slowly than MTD. After final high dose bolus only 2DG=>Rx strategy's tumor remains sensitive.

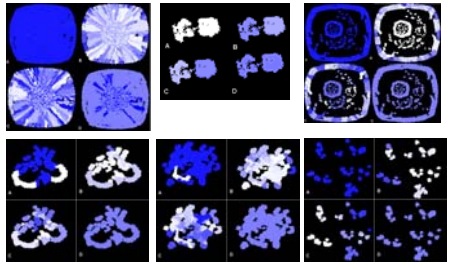

Figure 5. Growth pattern of tumors. A shows chemosensitive cells (blue) and chemoresistant cells (white). B shows distribution of glycolytic phenotype: cells closer to blue have slower metabolic rate while closer to white are more glucose avid. C shows distribution of acid resistance, the closer to white the more resistant, the closer to blue the more sensitive to low pHe. D shows cells in low pHe induced quiescent state in dark blue. On top left, untreated tumor at generation 39. On top center MTD treated tumor at generation 45. On top right tumor treated with 2DG at generation 57. Bottom left, tumor treated with synchronized combined therapy at generation 75. Bottom center, tumor treated with chemotherapy followed by 2DG at generation 72. Bottom right, tumor treated with 2DG followed by chemotherapy at generation 72.

Combined Treatment

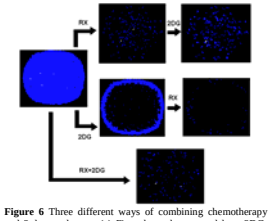

Figure 6 Three different ways of combining chemotherapy and 2-deoxy-glucose: (a) First chemotherapy and later 2DG, (b) 2DG first followed by chemotherapy and (c) both administered at the same time.

Importance of drug half-life

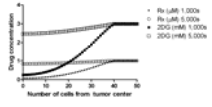

Figure 7 Gradient of drug concentration for both chemotherapy and glucose competitor. The longer the system is exposed to drugs, the higher the concentration in tumor center and more efficient the treatment.

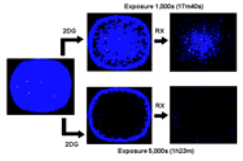

Figure 8 The exposure of the tumor model to 2DG during 5,000 seconds is enough to produce energy depletion in most cells inside tumor but can only kill a fraction of cells in intermediate region if exposed to only 1,000s. This exposure time is crucial for the efficiency of a drug such as 2DG which acts mainly in inner regions of tumor.

Model Parameters

- IC_{50} of resistant cells: 1uM*h
- IC_{50} of sensitive cells: 10uM*h
- Resistant cells proliferative rate: 0.05
- Sensitive cells proliferative rate: 1.0
- Initial tumor number of cells: 5,000
- Tumor doubling time: 1 week
- Rx and 2DG half life: 1h23m (5,000s)
- Simulation space dimension: 300 x 300 cell slots (7.5mmx7.5mm)
- Blood $[Glc]_e$: 5mM
- Glucose diffusion rate: 5x10-6 cm2/s
- Bicarbonate diffusion rate: 5x10-6 cm2/s
- Oxygen diffusion rate: 1.5x10-5cm2/s
- CO2 diffusion rate: 1.5x10-5cm2/s
- Blood [HCO3-]: 33.13 mM
- Blood [CO2]: 1.66mM
- MTDRX bolus=7uM*h
- LowRxbolus=1.4uM*h
- 2DG bolus=3mM

Results

1. Tumors with pre-existing chemo resistant sub-populations will respond poorly to conventional therapy but may be kept stable by using minimum amounts of drug administered with the goal of prolonging patient survival;
2. Concentrations of drug delivered to avascular solid tumors are two orders of magnitude lower in tumor center than in tumor host interface. This gradient depends on drug absorption by exterior layers of cells but also on a combination of half-life and diffusion;
3. Administration of glucose competitors is only efficient if the concentrations are comparable to the one of glucose in blood and if the competitor is kept in system long enough to diffuse to tumor center;

Conclusion

Tumors with resistant subpopulations can have their growth slowed down by a commitment of maintaining a reasonable amount of sensitive cells left to compete with the resistant ones for resources and space. The drugs proposed in this model, however, are not mutagenic.

The results from this work suggest that if moderate amounts of a glucose competitor could be administered to the tumor long enough for it to reach tumor center, better results could be achieved, even tumor resistant population eradication by energy starvation.

Our next steps will be to study how tumor angiogenesis may increase sensitivity to therapy and how normalization of this vascularization could improve chemotherapy results.

References

1. Frieboes H et al., Prediction of Drug Response in Breast Cancer Using Integrative Experimental/Computational Modeling. Cancer Res. 2009; 69: (10)
2. Silva A et al., The Potential Role of Systemic pH Buffers in Reducing Intratumoral Extracellular pH and Acid Mediated Invasion. Cancer Res. 2009; 69: (6)
3. Gatenby R et al., Adaptive Therapy. Cancer Res. 2009; 69 (11)