**Mathematical Oncology**

**Fingerprint of Cell Metabolism in the Experimentally Observed Interstitial pH and pO2 in Solid Tumors**

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**Abstract**

Understanding cancer cell metabolism and targeting associated pathways is a field of increasing interest. Helmlinger and colleagues measured average pH and pO2 as functions of distance from a single blood vessel on the micrometer scale. We show that these results provide unique insight into cancer cell metabolism in vivo when combined with an appropriate mathematical model. We calculate pH as a function of distance from a single blood vessel and for a given metabolism while incorporating a single CO2 buffer with effective diffusion constants. By assuming that cancer cell metabolism is dominated by respiration with a smaller component of glycolysis in the normoxic state, by more balanced respiration and glycolysis in the hypoxic state, and by glycolysis alone in the anoxic state, we are able to semiquantitatively derive the experimental results of Helmlinger and colleagues. We also apply our model to glycolysis-impaired metabolism and show that the low pH and high pO2 observed in these tumors may be related to the substantial shift from a respiration-dominated metabolism to one in which glutaminolysis dominates. Based on this, we propose an in vivo experimental measurement of pH in a glycolysis-impaired tumor to validate the modeling results. [Cancer Res 2009;69(23):9141–7]

**Major Findings**

By proposing a cell metabolism that is a combination of glycolysis and respiration, we are able to describe the experimentally observed pH and pO2 around a single blood vessel in vivo. We also give an explanation for the observed low pH and high pO2 in the glycolysis-impaired tumors. We suggest that multitargeted therapeutic strategies that inhibit both glycolysis and glutaminolysis are necessary in the design of efficient therapies. This work introduces new theoretical and experimental strategies that can be used to create a precise map of cell metabolism in vivo.

**Note:** Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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**Introduction**

Targeting metabolic pathways in malignant tumors increasingly shows promise as an effective therapeutic strategy (1, 2). Thus, unraveling details of metabolic pathways used by cancer cells is of much interest, especially those pathways that are differentially activated or suppressed in tumors. Motivated by this, there have been a number of studies on glycolytic metabolism and its inhibitors, as well as, to a lesser extent, glutaminolysis (1–5).

It was first postulated more than 80 years ago that cancer cells shift their metabolism toward a glycolytic phenotype even under normal levels of oxygen concentration; this phenomenon, dubbed the Warburg effect (6, 7), has since been confirmed by many studies conducted both in vitro and in vivo. In these experiments, the glucose and oxygen consumptions are obtained by measuring these quantities over a large number of cells in either a cell line or a tumor (8–10). These results provide valuable information about cell metabolism and have many clinical implications. However, because these studies draw conclusions by averaging over many cells in a heterogeneous environment, some details of cell metabolism may escape detection. With this in mind, the recent experimental work of Helmlinger and colleagues (11), using a novel and elegant approach to measure pH and pO2 in vivo as functions of distance from blood vessels on a micrometer scale, could serve as the introduction of a new paradigm for examining cell metabolism on the cellular scale. In this experiment, mean values of pH and pO2 were measured over single-scan profiles to find pH and pO2 dependence on distance from a single blood vessel. To ensure that readings were influenced by only one vessel, the authors took measurements up to distances D/3 from a vessel, with D being the distance between that vessel and its nearest neighboring vessel. Measurements taken at a given distance were then averaged.

The impact of this experiment by Helmlinger and colleagues (11) lies not just in the interpretation of their observations but also in the way in which these observations were made: Their methods allow us to probe on a length scale, which was previously inaccessible for in vivo tumor investigation. This is significant because, first, the scale of measurement is comparable with cellular dimension—hence, physical quantities such as pH and pO2 can be directly linked to cell metabolism. Second, on this scale, the system does not have the complexity of larger systems involving many parameters, and hence the creation of a physical model that quantitatively describes the system becomes feasible. Third, the cell metabolism observed at this scale depends on the local microenvironment of the cell rather than on the geometry of the vascular network. Hence, these experimental results, when interpreted with the aid of a mathematical model, can provide unique information...
Quick Guide to Equations and Assumptions

To reduce the complexity of the problem, and also in an effort to avoid obscuring the most relevant parameters affecting acidity, we make the following assumptions: (a) We assume a single, two-dimensional layer of cells, connected on one side to a single blood vessel, with all chemical species diffusing through this layer (Fig. 1). This mimics the experimental setup of ref. (11) in which measurements were carried out on a 25-μm layer of cells. (b) The interstitial fluid pressure seems to be comparable with the microvascular pressure in their experimental setup (20, 21); hence, we assume that the convection is negligible in the system and that movement of chemical species is dominated by diffusion. (c) We replace the net effect of the numerous buffers in the system with a single buffer having hydration and dehydration rates close to those of the CO₂ buffer; we assign effective diffusion constants to this single buffer, which are obtained by fitting the computationally derived pH to the experimental results. Based on these assumptions, we consider our computational framework (Fig. 1) as a two-dimensional automaton model with 20 μm × 20 μm automaton elements and assume that concentrations of all nutrients and chemical species are in steady state.

For noncharged species, the diffusion equation reads

\[ \frac{\partial C_i}{\partial t} - D_i \nabla^2 C_i = P_i \]

where \( C_i \) is the concentration of species \( i \), \( D_i \) is the diffusion constant of species \( i \), and \( P_i \) is the production rate of this species (a negative value means consumption). In Supplement 1, we present the diffusion equation for charged particles, as well as the appropriate boundary conditions used in our calculations. The solution of the diffusion equation 1 (and Eq. 1A for Cl⁻) with boundary conditions gives the species concentration with a given set of consumption rates.

Derivation of Concentration and Consumption Rates:

For a given cell metabolism \( [P_G = P_O (C_G, C_O) \text{ and } P_O = P_G (C_G, C_O)] \), we first simultaneously solve Eq. 1 for oxygen and glucose to derive their consumption rates as functions of distance. Then, we substitute these into Eqs. 4A to 8A and ultimately into Eq. 1 to determine the consumptions of the remaining chemical species. As explained earlier, we apply Eq. 1A for Cl⁻ and use the charge neutrality condition to calculate the concentration of Na⁺. We simultaneously solve these equations iteratively to derive the concentrations and consumptions as functions of distance. All these equations are solved with appropriate boundary conditions (Eq. 2A). The concentration of species in the blood vessel, diffusion constants, and permeability of species are given in Supplement 1 and are assumed to be constant.

For glutaminolysis, we substitute Eqs. 13A, 14A, and 15A into Eq. 1 and solve them simultaneously to derive the concentrations and consumptions of glutamine, oxygen, and glucose as functions of distance. The concentrations of H⁺ and other species are calculated using the same methodology.

Other mathematical work considering tumor acidity has focused primarily on different aspects, such as the effect of acidity on tumor growth and invasion or its role in carcinogenesis (15, 16).

Herein we present a model to compute pH as a function of distance from a single blood vessel for a given set of metabolic pathways. By introducing cell metabolism—which is assumed to be dominated by respiration with a smaller component of glycolysis in the normoxic state, by more balanced respiration and glycolysis in the hypoxic state albeit with reduced rates of oxygen and glucose consumption, and by glycolysis alone in the anoxic state—we semiquantitatively derive the experimental results of ref. (11). We show that the pH plateau observed in the hypoxic region (11) can be explained in terms of reduced oxygen and glucose consumption, and that the presence of this plateau and other qualitative features of the model are independent of the values of the free parameters and driven fundamentally by underlying cell metabolism. We also propose that the observed low pH for glycolysis-impaired tumors (12, 13) could be the result of a metabolic shift from respiration to glutaminolysis. When this metabolic behavior is imposed, the pH drops monotonically as a function of distance from a single blood vessel to values that are about cell metabolism. This emphasizes the importance of additional micrometer-scale experiments on different tumors to confirm the generality of such results.

Figure 1. The simulation box and appropriate boundary conditions.
comparable with the average observed pH level in these tumors. Furthermore, pO₂ as a function of distance drops at a slower rate than in glycolysis-enabled tumors, which accounts for the higher observed values of pO₂ in glycolysis-impaired tumors. Hence, our results suggest that multitargeted therapeutic strategies that inhibit both glycolysis and glutaminolysis may be crucial in the design of effective cancer treatments. Experimental measurements of pH and pO₂ levels as functions of distance from single blood vessels in glycolysis-impaired tumors are required to confirm our model predictions.

This model can be used to predict some of the tumor microenvironmental factors, such as pH, produced as a result of various metabolic scenarios. Conversely, it can be used to deduce the underlying cellular metabolic state of tumors based on experimentally or clinically measured data. We suggest that a significant benefit of this model is its ability to interpret results on both the micrometer and millimeter scales and to play a role in the design and testing of new targeted treatment strategies (see Results and Discussion).

Materials and Methods

In this section, we present a model to compute acidity based on cell metabolism, with a single blood vessel as a nutrient source (Fig. 1). We start with a set of diffusion equations in the extracellular space with given production rates (Quick Guide). A minimal cell metabolism model is considered, wherein glucose, oxygen, CO₂, bicarbonate and lactate are the only species that play any role (17). Using the above chemical reactions, the consumption rates of oxygen and glucose, and the production rates of CO₂ and bicarbonate are computed; these production (consumption) rates are given in Supplement 1. For a given cell metabolism, we solve the model equations (Quick Guide; Supplement 1) to determine the concentrations and consumption of chemical species as functions of distance.

Results and Discussion

pH and cell metabolism. We used a mathematical model to calculate pH = −log[H⁻] as a function of distance from a blood vessel for a spectrum of different cell metabolisms, varying from the extremes of pure glycolysis to combinations of both. In Supplement 2, we present simulations of these alternate metabolic scenarios by plotting pH as a function of distance for different ratios of glycolysis to respiration, parameterized by the ratio r between oxygen consumption and glucose consumption (see below). By increasing the strength of glycolysis (smaller r), the plateau, which is the reminiscent feature of the experimental results, steepens and finally disappears. Hence, our numerical simulations indicate that the only metabolic scenario that captures the experimental results of ref. (11) is the following: Under normoxic conditions close to the blood vessel, cells use a respiration-dominated metabolism and generate CO₂, which acidifies the extracellular environment. In soft tissue, the most prominent buffering system is the interconversion of CO₂ and bicarbonate. We assume that the effect of all other buffers can be included in the CO₂-bicarbonate buffer by fitting the hydration-dehydration rates and diffusion constants of CO₂ and bicarbonate such that we quantitatively derive the experimental data of ref. (11). The chemical reaction for the CO₂ buffer reads

\[ CO₂ + H₂O \rightleftharpoons HCO₃⁻ + H⁺ \]

The effective forward and backward rates for this reaction are determined to be \( k_f = 5.8 \times 10^4 \text{ mol/L/s} \) and \( k_r = 7.4 \times 10^7 \text{ mol/L/s} \), respectively, which are close to the associated experimental values for the bicarbonate system alone (18). Indeed, the experimentally observed pH around a single blood vessel can be replicated quantitatively by incorporating this single buffer with the effective diffusion constants chosen to be \( 8.9 \times 10^{-3} \text{ cm²/s} \) and \( 2.2 \times 10^{-2} \text{ cm²/s} \) for CO₂ and bicarbonate, respectively. The ions Na⁺ and Cl⁻ maintain the charge neutrality condition in the model and avoid the application of any extra forces to the other ionic species. Also, these ions are important in intracellular pH regulation through Na⁺/H⁺ and bicarbonate/Cl⁻ exchange (17). Using the above chemical reactions, the consumption rates of oxygen and glucose and the production rates of waste in the intracellular and extracellular space are computed; these production (consumption) rates are given in Supplement 1. For a given cell metabolism, we solve the model equations (Quick Guide; Supplement 1) to determine the concentrations and consumption of chemical species as functions of distance.

Figure 2. Simulated plots of pH (solid line with circles) and oxygen concentration (dashed line with circles) as functions of distance from the blood vessel. The experimental data of Helmlinger and colleagues (11) are also included for comparison (solid and dashed lines with squares). Inset, ratio of oxygen to glucose consumption.
space, thereby reducing the pH at short distances from the blood vessel. Based on our results, we cannot reach any definitive conclusion as to whether cell metabolism must have a glycolytic component in the normoxic region; however, as we discuss below, the metabolism here has to be respiration dominated. In hypoxic regions (i.e., at intermediate distances from the blood vessel), cells shift their metabolism to a combination of glycolysis and aerobic respiration, but with reduced rates of glucose and oxygen consumption. This reduction in glucose and oxygen consumption results in a reduction in CO₂ and H⁺ production, giving rise to a flattening of the pH curve over a range of distance between 113 and 133 μm from the blood vessel as shown in Fig. 2, consistent with the experimental observations (11). Under anoxic conditions at very long distances from the blood vessel, cells are forced to rely entirely on a glycolytic metabolism. This causes the pH to again drop until it reaches saturation point. Biologically, this saturation may be due either to a shortage of glucose or to metabolic shutdown resulting from an intolerably low pH level. Here, we define the hypoxic and anoxic regions in terms of oxygen consumption (see Supplement 2 and the next paragraph). The hypoxic region is where oxygen consumption is less than the normoxic state and the anoxic region is chosen as a region where oxygen consumption is less than 0.2% of the normoxic condition. The oxygen partial pressures corresponding to these metabolic transitions are 4 and 0.2 mm Hg, respectively (Fig. 2). Note that ref. (11) uses values of 5 and 1 mm Hg to define these transitions.

The cell metabolism described above gives a pH pattern, for a wide range of parameter values, with the same qualitative behavior as observed in ref. (11). To recapture their results quantitatively, we propose, based on Michaelis-Menten kinetics, that the consumption rates of glucose and oxygen are $P_0 = p_G \frac{C_G}{C_G + k_G} f_1(C_G)$ and $P_0 = rP_0 \frac{C_O}{C_O + k_O} f_2(C_O)$, respectively, where $r$ is the ratio between glucose to oxygen consumptions; in the following, we chose the value of $r = 5$. The values of other constants, the functional forms of $f_1(C_O)$ and $f_2(C_G)$, and their plots are given in Supplement 2.

We now address the question of why cells consume less glucose and oxygen while continuing to make use of both the glycolytic and respiratory pathways in the hypoxic region rather than switching to a completely glycolytic metabolism. To do so, we notice that in the hypoxic region, cells still have (limited) access to oxygen for respiration, which produces energy (in the form of ATP) much more efficiently than glycolysis. Furthermore, increased glycolysis would result in production of a particularly toxic environment. Therefore, the most favorable response to hypoxia for cells is to decrease their rates of both respiration and glycolysis such that they rely primarily on respiration for ATP production while producing less toxic waste. As available oxygen is depleted, cells activate the glycolysis pathway to satisfy part of their energy requirements, but not to the extent that the environment becomes highly toxic. In the anoxic region, oxygen concentration is zero; hence, cells must use glycolysis as their means of energy production. We note that these results may not be valid for tumors and cell lines characterized by constitutive upregulation of glycolysis regardless of local oxygen concentration.

Figure 2 shows the simulated oxygen concentration and pH as functions of distance from a blood vessel—the experimental data (11) are included for the purpose of comparison (the experimental pO₂ are scaled by a factor). In this figure, three distinct regions of pH behavior are evident. (a) From 1 to 113 μm, pH decreases; (b) between 113 and 133 μm, the pH remains stable or in a "plateau" phase; (c) for distances larger than 133 μm, the pH decreases and finally saturates to pH 6.7 at distances larger than 350 μm. To better understand the mechanisms responsible for these results, the consumption rates of oxygen and glucose, and the production rate of ATP, are depicted in Fig. 3 [ATP production for respiration and glycolysis metabolisms are $-36P/O_2/6$ and $-2(P_0 - P/O_2/6)$, respectively]. These results are consistent with our proposal that in the hypoxic region, the energy is predominantly produced by respiration (blue dashed line, inset) and that, although the consumption of glucose increases in the anoxic region (red dashed line), ATP production here decreases compared with the hypoxic region because of the low production of ATP by glycolysis. Under hypoxic conditions with higher values of pH (close to vessels that do not carry oxygen but can transport H⁺), cells may consume more glucose to produce energy.

The concentrations of glucose, CO₂, bicarbonate, and lactate are plotted as functions of distance in Fig. 4. As expected, an increase in the distance results in an increase in both CO₂ and lactate concentrations, with a decrease in the concentration of bicarbonate (due to its use in buffering H⁺). In particular, at large distances corresponding to regions of anoxia, the increase in H⁺ and lactate concentrations could be interpreted as the accumulation of metabolic waste products as suggested in ref. (11).
The simulation results suggest that the presence of the pH plateau with increasing distance from the blood vessel indicates a transition from a mainly oxidative metabolism in the normoxic region to a combination of oxidative metabolism and glycolysis in the hypoxic region. The model allows simulation of the Warburg effect by varying the parameter \( r \) in \( Po = rPo \frac{C0}{C0 + k0}f(C0) \), which is the ratio of oxidative phosphorylation to glycolysis in the presence of excess oxygen availability (i.e., in normoxic regions of the tumor). Figure 2A of Supplement 2 shows that the plateau disappears as \( r \) is decreased (i.e., as glycolysis increases in well-oxygenated regions consistent with the Warburg effect). Therefore, the results may suggest that, in the particular experiment performed by Helmlinger and colleagues (11), the Warburg effect does not play a prominent role.

**Glycolysis-impaired tumor.** To extend our cell metabolism model, we calculate the pH of a single blood vessel as a function of distance for a glycolysis-impaired tumor. It has been proposed that glycolysis-impaired cells drastically change their metabolism to include glutaminolysis (13). Thus, we assume that glycolysis-impaired cells generate their energy through respiration and glutaminolysis. It should be emphasized that both of these metabolic mechanisms require oxygen. Ignoring the intermediate states, we can summarize the net reactants and products of a glutaminolysis-driven metabolic pathway in terms of the following chemical reactions,

\[
\text{C}_3\text{H}_6\text{N}_2\text{O}_3 + 2\text{H}_2\text{O} + \text{O}_2 \rightarrow \text{C}_3\text{H}_6\text{O}_3 + 2\text{NH}_3 + 2\text{CO}_2 + \text{H}^+ 
\]

Hence, glutaminolysis contributes to the acidification of the extracellular environment by producing one \( \text{H}^+ \) ion and two \( \text{CO}_2 \) molecules. The production (consumption) rates of different species for this metabolism are given in Supplement 1. We assume \( r = 6 \) (there is no glycolysis) and use the model (Quick Guide) to derive the concentrations and consumptions of glutamine, oxygen, and glucose as functions of distance. The concentrations of \( \text{H}^+ \) and other species are calculated using the same methodology.

The results of these calculations for different values of \( r \) (the ratio of glutaminolysis to respiration) are shown in Fig. 5. By increasing the value of this ratio, the oxygen consumption declines at a slower rate (Fig. 5, dashed lines) and the pH saturates at lower values. These results can be understood based on the fact that in glutaminolysis, one molecule of \( \text{H}^+ \) and two molecules of \( \text{CO}_2 \) are produced per molecule of \( \text{O}_2 \)—this acidifies the environment at a higher rate than respiration (which produces one molecule of \( \text{CO}_2 \) per \( \text{O}_2 \)). The increase in oxygen consumption is related first to the lower rate of glutamine consumption and second to the reaction of one molecule of \( \text{O}_2 \) with one glutamine (compared with six molecules of \( \text{O}_2 \) with one molecule of glucose in respiration). Another interesting feature of this result is the absence of a plateau in pH, which is a sign that there is no shift in metabolism. Hence, our results suggest that the observed high oxygen concentration and low pH in glycolysis-impaired tumors (12, 13) may be explained by a shift in the cell metabolism from respiration to glutaminolysis. An experiment where pH is measured as a function of distance from a single blood vessel using glycolysis-impaired cells could be used to validate our proposal. In particular, the absence of a plateau in pH for glycolysis-impaired tumors would support our hypothesis.

One of the therapeutic implications of this discussion is that when one metabolic pathway is blocked (e.g., glycolysis), tumor cells may compensate by switching to another pathway (e.g., glutaminolysis). Hence, any successful metabolism-targeting therapy...
must at least block the main metabolic pathways such as glycolysis and glutaminolysis. In Fig. 6, we plot the oxygen concentration as a function of distance for tumor cells that rely solely on respiration due to the impairment of glycolysis and glutaminolysis; the ATP production rate is depicted in the inset of this figure. For distances from the blood vessel >150 μm, the ATP production reaches zero and hence cells are necrotic. The only living tumor cells are in an oxygenated region; thus, these cells could be targeted by radiotherapy.

In summary, we have presented a set of equations describing the acidity and oxygen concentrations that result from specified cell metabolisms. Applying this model to a variety of possible scenarios, we were able to find a set of metabolic behaviors that produces the experimentally observed pH around a single blood vessel. This metabolism is respiration dominated under normal oxygen levels, features respiration and glycolysis with reduced oxygen and glucose consumption under hypoxic conditions, and is glycolysis driven under anoxic conditions. We have also calculated the pH around a single blood vessel for a glycolysis-impaired tumor and conclude that a metabolic shift from respiration to glutaminolysis can successfully explain the low pH and high pO2 level observed by experimentalists, and, additionally, we have proposed a possible experiment to validate our proposed metabolic scenario. One should note that the faster drop in oxygen concentration in these results, compared with Fig. 2, is related to the higher oxygen consumption (r = 6 for Fig. 6 and r = 5 for Fig. 2).

Although it may seem that these results are based on a specific geometry of a single blood vessel, they can, in principle, be expanded to any arbitrarily complex vascular architecture. In fact, cell metabolism depends on the local concentration of nutrients and wastes rather than on the geometry of the blood vessel network—although the distribution of nutrients ultimately derives from the vasculature. If knowledge of these concentrations can be obtained, then it is feasible sufficient to disregard the underlying vascular geometry.

Thus, given the independence of our model on the precise distribution of blood vessels, we can extend results beyond the micrometer domain to provide information about cell metabolism on a larger scale (0.1–1 mm), e.g., the scale of a biopsy. Hence, currently existing clinical and experimental measurement techniques (such as bioluminescence imaging or magnetic resonance spectroscopic mapping of metabolites) could be used on a tissue sample to provide input to the model, which in turn could predict the average cell metabolism over the sample. Performing this procedure over different regions of the tumor could give useful information about the heterogeneity of cell metabolism within a malignancy. We further suggest that such a technique could have great utility in measuring the effects of a wide variety of anticancer drugs, ranging from cytotoxic chemotherapy to molecularly targeted therapeutics. One could deduce whether a particular candidate drug has an effect on cell metabolism simply by measuring the appropriate concentrations and applying the model.

Tumor metabolism is a complex and dynamic function of many factors, including gene expression. The model in this first iteration was intended to be as simple as possible while still providing unique insights into tumor metabolism for testing in future experimental studies. The objective was to relate measurable parameters in the tumor microenvironment (oxygenation, pH, glucose concentration, and lactate concentration) to the underlying cellular metabolism. The effect of variation in gene expression is embedded in these parameters and in the metabolic state of the tumor as...
predicted by the model. The model is readily expandable to include gene expression profiles and the impact of changes in expression on metabolism, and this will be considered in future work.

In general, this model underlines the importance of in vivo measurements at the micrometer scale where single-cell properties can be directly related to observed physical quantities such as oxygen concentration and pH. It is feasible to model these types of experimental results because of the relative simplicity of the experiment and the (relatively) small number of important parameters involved. We hope that this work sheds light on cell metabolism in vivo and emphasizes the critical importance of experimental measurements at the micrometer scale. Finally, our results suggest the use of multitargeted therapeutic strategies that inhibit both glycolysis and glutaminolysis as a means of enhancing tumor control. By targeting both metabolic pathways, cancer cells in the anoxic region are eliminated directly and the remaining cancer cells (which are in the oxygenated region) could be targeted by radiotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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