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The Bevacizumab “Pseudoresponse” in Glioma: Disappointment or Opportunity?

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1. Introduction

Cancer biology has focused for years on better characterizing what makes cancer distinctive relative to normal tissue so as to better define targets for treatment. This has resulted in our current cancer paradigm in which cancers arise through an essentially cell autonomous series of variable cellular genetic and epigenetic events that drives the malignant process^{1,2}. The corollary of this model is that cancer is a highly complex process with no two individual cancers being identical leading in turn to the current trend towards “personalizing” therapy. We propose that there is a much simpler way to view cancer, one in which it is viewed from a tissue rather than a cellular perspective. From this vantage point, properties are “distributed” among cell populations, creating a highly integrated cell population and that treatment is better aimed at perturbing the system as a whole rather than a particular gene or receptor target. This physiological approach thus focuses on two universal attributes of malignancy that have not yet been linked experimentally: (i) the need for growing tumors to establish an adequate blood supply, i.e., neoangiogenesis^{3,4}; and (ii) the unique metabolism of tumor tissue in which an inordinate amount of energy is derived through glycolysis (GLY) rather than oxidative phosphorylation (OXPHOS) even in the presence of adequate oxygen (aerobic glycolysis)^{5,6}. Although much research has focused on these two topics, the impact they have upon each other has not been addressed to any extent in living organisms, despite there being substantial information on the relationship between flow and metabolism in normal tissues. Admittedly, one major reason for this lack of study has been technical, i.e., although flow can be assessed, there has not until recently been a way to assess tumor metabolism in intact animals in real time.

The recent introduction of the anti-VEGF monoclonal antibody bevacizumab into the field of brain tumor therapeutics has resulted in an unprecedented rapid improvement in MRI abnormalities and mass effect which led to its fast track approval by the FDA in 2009 based on Phase II studies^{7,8}. While dramatic, this response is transient and associated with late failures that are largely resistant to salvage therapies (Figure 1). This phenomenon has been recently labeled a “pseudoresponse”^{9,10} and has generated a second wave of studies that have been much less optimistic about the prospects of this therapy¹¹.

In this review, we will develop the argument that when viewed from the tissue perspective, the pseudoresponse reflects the effect of blood flow changes that result in a depletion of

nutrients, especially glucose and lactate, that results in increased tissue OXPHOS to maintain energy needs. This results in a “starvation” state within the cancer tissue that temporarily opens a therapeutic window that closes as the tumor tissue adapts to this crisis. We term this the “Warburg-Folkman” effect and postulate that its magnitude will be proportional to the real time lactate/bicarbonate level observed within tumor tissue after anti-angiogenic therapy that can now be visualized in the intact organism with the recent refinement in $^{13}\text{C}_1$ -pyruvate MRS technologies.

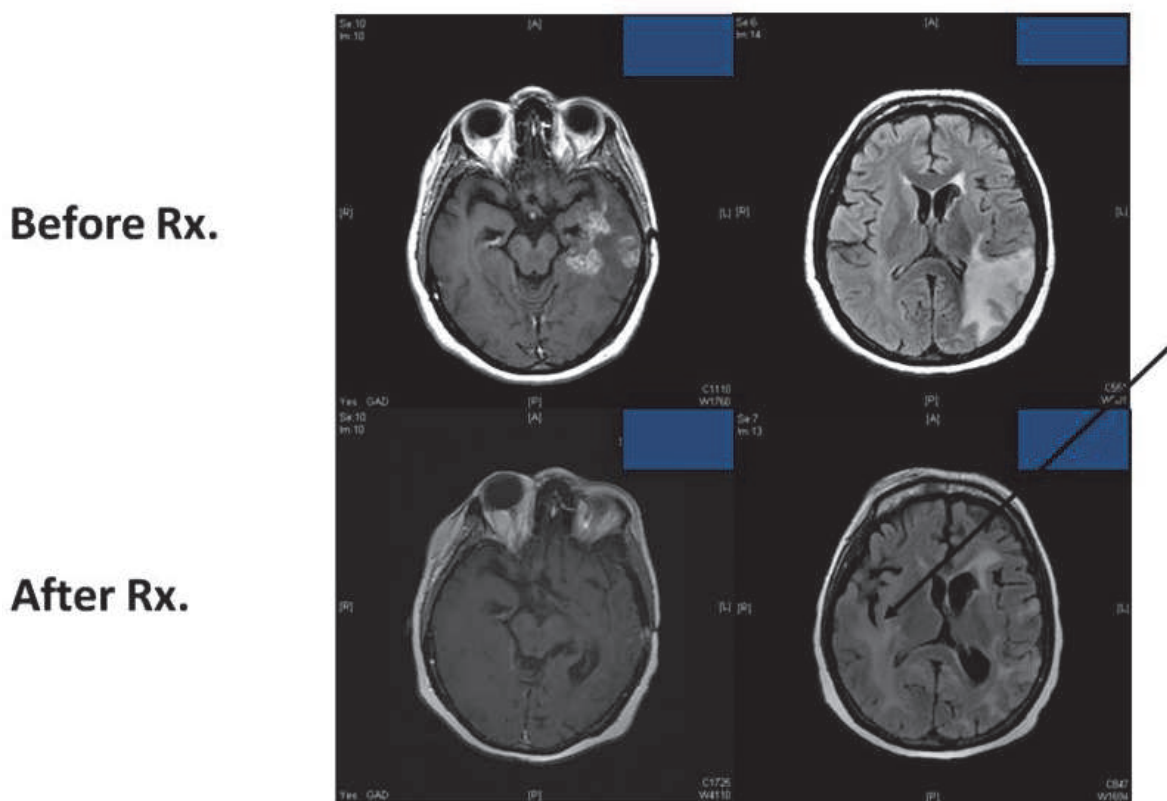


Fig. 1. Demonstration of response to bevacizumab in recurrent glioblastoma. Top two panels reflect an axial T1 enhanced and axial FLAIR image from a 43 year old woman with recurrent GBM before first infusion of BEV while the bottom two panels represent imaging performed after third infusion. Note the marked improvement in enhancement and amount of mass effect after treatment. However, there is now an increased area of T2 FLAIR abnormality distant from original site of relapse (Arrow). This represents new infiltrative tumor.

2. Neoangiogenesis in GBM

Four decades ago, Folkman proposed that all solid tumors are dependent on the formation of new blood vessels (angiogenesis) based on the observation that experimental solid tumors otherwise entered a dormant state or died once their size reached 2-3 mm⁴. In this and subsequent papers (for a review of this work, consult ¹²⁻¹⁴), he noted a strong interaction and counterdependency between endothelium and tumor cells that suggested the presence of a diffusible messenger released from tumor cells was transitioning endothelial cells from a resting state to one capable of forming new capillaries.

Though his hypothesis was initially met with a high level of skepticism, subsequent studies confirmed the relationship between neoangiogenesis and cancer progression as well as characterizing several cytokines that were important in mediating these effects. Numerous pro- and anti-angiogenic mediators are now known that respond to adverse conditions such as hypoxia so that the balance is tipped in favor of angiogenesis (i.e., the “angiogenic switch”). Although a number of these factors have been identified including bFGF and members of the EGF receptor family^{15,16}, the most prominent factor mediating angiogenesis is the family of vascular endothelial growth factor (VEGF) molecules. The VEGF family consists of the VEGF ligands VEGF-A, VEGF-B, VEGF-C, VEGF-D, platelet derived growth factor (PDGF) and placental growth factor. These ligands bind to the VEGF receptor (VEGFR) tyrosine kinases VEGFR-1 and VEGFR-2. The most important of these ligands is VEGF-A which by primarily binding to VEGFR-2 regulates endothelial cell survival, proliferation, vascular permeability and migration. In hypoxic conditions, VEGF-A is primarily induced via hypoxic inducible factor (HIF-1 α), which in the presence of a hypoxic environment is dissociated from the Von Hippel Lindau protein allowing it to bind to promoter regions of several pro-angiogenic factors including VEGF¹⁷.

Among cancers, glioblastoma (GBM) is among the most highly vascularized, the extent of which correlates closely with tumor proliferation and aggressiveness¹⁸. Vascularization occurs via three mechanisms: arteriogenesis (utilizing collaterals from a pre-existing blood supply to augment metabolic demands), vasculogenesis (formation of new vessels via the migration and differentiation of progenitor cells into endothelial cells) and angiogenesis (the production of new blood vessels from pre-existing ones). When the angiogenic cascade is triggered in GBMs, a wide range of cells can become tumor endothelial cells, including circulating progenitor cells that are mobilized from the bone marrow and other tissues as well as other hematopoietic cells and even glioma cells themselves¹⁹⁻²³.

While it is not clear how much tumor vascularization is due to co-option of other vessels relative to the creation of new ones, it is widely accepted that angiogenesis is a key factor in tumor proliferation. Neoangiogenic vessels are tortuous, leaky, and dilated with aberrant interconnections and abnormal basement membranes resulting in inefficient and heterogeneous blood flow as well as increased blood volume within the tumor²⁴. The endothelial cells lining these vessels are abnormal with loosely attached or absent pericytes and basement membranes are often absent or abnormally thickened.

3. Anti-VEGF therapy and the pseudoresponse

The discovery that cancer angiogenesis is dependent on cytokines released by tumor cells spurred interest in developing agents that could interrupt these cytokine loops so as to impact tumor growth via inhibiting vessel formation. After VEGF's identification as perhaps the most important mediator of this process (including one of the seminal papers describing its high concentration in GBM²⁵), a number of strategies were designed to block VEGF's contribution to this process. This led to the development of bevacizumab, the first anti-angiogenic agent to be approved and be widely used.

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds with high affinity to VEGF ligand preventing its interaction with the VEGF-1 and VEGF-2 receptor on the surface of endothelial cells, thus preventing VEGF induced endothelial cell migration, proliferation and vascular permeability²⁶. Bevacizumab (and other anti-VEGF therapies) exerts its effects via multiple mechanisms that block the development of new

aberrant vessels and induce regression of existing aberrant vasculature, thus resulting in tumor growth arrest. This so-called “normalization” of mature vasculature at least theoretically also results in improved susceptibility to treatment via improved delivery of chemotherapeutic agents and via radiosensitization from improved oxygen delivery ²⁴.

Bevacizumab was approved in 2004 for first line use in people with metastatic colon cancer but despite the observation that GBMs were associated with the highest VEGF levels among cancers, its use was delayed in brain tumor patients because of the fear of increasing hemorrhagic risk. The dramatic, immediate effect of bevacizumab on MRI enhancement and clinical status noted when it was finally utilized ^{27, 28} generated an unprecedented initial enthusiasm that led to a fast-track FDA approval for recurrent glioma based on two pivotal Phase II studies ^{7, 8}.

Unfortunately, and perhaps not unexpectedly, despite the impressive radiologic responses with corresponding clinical benefit seen early after BEV treatment, these results were not sustained over long intervals, resulting in only a modest overall survival benefit. What was especially disappointing was the observation of an increased glioma invasiveness that often resulted in the development of a gliomatosis picture ²⁹. This disappointing outcome has tempered enthusiasm concerning the overall role of BEV in GBM therapies and led to intensive research aimed at understanding why this failure occurs. Among the mechanisms invoked for this observation is an up regulation of alternative pro-angiogenic factors such as the pro-angiogenic fibroblast growth factor ³⁰, increased protection of tumor vasculature by increasing pericyte coverage, recruitment of pro-angiogenic inflammatory cells and a cooption of normal vessels by the invading tumor cells ³¹. At the root of most of the explanation for why anti-VEGF therapy is ultimately ineffective is that, by diminishing flow, intratumoral hypoxia is increased, inducing tumor cells to become more aggressive and invasive ³²⁻³⁴.

While the clinical observation of a worsening MRI occurring as a result of treatment effect rather than tumor progression has been well characterized (i.e., pseudoprogression ³⁵), the introduction of anti-angiogenic therapies such as BEV produced a diametrically opposite effect of rapid resolution of MRI abnormalities that, despite its magnitude, is as much of a function of blocking VEGF's effect on permeability as it is on a cytotoxic response. This phenomenon has therefore been labeled a “pseudoresponse” ⁹, in part to reflect the impression that it is similar to what is occasionally seen when steroids are administered to brain tumor patients and is supported by several observations including its association with increased invasive nonenhancing tumor seen on T2/FLAIR imaging representing dispersion of the tumor in an infiltrating pattern ¹⁰ and the demonstration of a rapid radiologic response, rebound enhancement on discontinuation and rapid re-response on recontinuation with anti-VEGF therapy ^{33, 36, 37}.

Within the framework of neoangiogenesis, the pseudoresponse is felt to be a manifestation of an initial “normalization” of perfusion that increases hypoxia, both increasing apoptosis initially as well as upregulating the HIF1 axis. It is through this latter activation that cancer cells initiate cellular programs that increase invasiveness and ultimately lead to a more resistant tumor ³⁸. Such observations have cast a pall over the early excitement generated by the introduction of BEV and have led many workers to question its ultimate value in GBM treatment ^{11, 32}.

While it is certainly valid and reasonable to assess the effects of anti-VEGF therapies in terms of hypoxia, it should be noted that a growing tumor is already adapted to a very low

oxygen tension. It is therefore unclear why any change in oxygen delivery should have such a profound impact. We believe that this concept is misleading and unproven and offer a fundamentally more logical explanation that relates to the cancer’s peculiar metabolism, which we next address.

4. Cancer’s peculiar metabolism

The drive to acquire cell mass and proliferate requires an adequate energy supply and building blocks, underscoring the need for ample amounts of energy in the form of ATP. There are two general ways in which this can be accomplished. Oxidative phosphorylation (OXPHOS), which takes place in the mitochondria, is an oxygen-dependent process in which pyruvate (which can be derived from a number of sources, especially glucose) is converted to acetyl-CoA which is then oxidized to CO₂ and H₂O producing NADH. NADH is further oxidized via the electron transport chain using oxygen as the final electron acceptor, ultimately generating a net of 36 ATP/glucose molecule. Alternatively, cells may use glycolysis (GLY), in which glucose is converted to pyruvate, generating 2 ATP/glucose molecule, completely bypassing the mitochondria. In normal cells, the balance between these two pathways is highly oxygen dependent; in the presence of adequate amounts of oxygen, cells utilize the more efficient OXPHOS while when oxygen is inadequate, the cell transitions to the less efficient GLY (Pasteur Effect)³⁹.

Under optimal conditions, cells derive ninety percent of their energy from OXPHOS and ten percent from GLY. Over 80 years ago, Otto Warburg observed that tumor cells generate an inordinate amount of ATP via GLY, even in the presence of adequate oxygen levels (aerobic glycolysis)^{5, 6, 40}. This preferential shift to the glycolytic pathway is not absolute, instead representing a shift from a baseline glycolytic rate of 10% seen in normal cells to over fifty percent⁴¹ (Figure 2). In association with this shift towards GLY, tumors rely almost exclusively on glucose relative to other substrates (such as fatty acids) for energy needs.

Although it remains unexplained why tumors overutilize GLY, its universal presence that persists even under normal oxygenation and its close correlation with tumor aggressiveness suggests a survival and growth benefit that exceeds the apparent inefficiency of the glycolytic pathway³⁹. Despite its persistence under normal oxygen levels, several studies still point to an important role of hypoxia in this process, perhaps because the byproducts of GLY lead to acidification of the micro-environment. An acidic environment is toxic to adjacent normal cells, assists in destruction of extracellular matrix and triggers angiogenesis, suggesting that the glycolytic shift is necessary for evolution into invasive cancer^{39, 42}. Moreover, as tumor cells proliferate they physically increase their distance from their vascular supply creating additional areas of low oxygen tension that results in activation of HIF1, which in turn upregulates genes that code for proteins important in cancer development and proliferation including glucose metabolism, apoptosis resistance, invasion, angiogenesis and metastasis⁴³.

As tumors become vascularized, the glycolytic phenotype persists despite improved oxygenation. Although the reasons for this remain unclear, one potential explanation relates to the fact that while aerobic glycolysis is much less efficient than oxidative respiration, its kinetics are such that in the presence of excess substrate, it may result in more ATP production as a function of time than can be obtained with OXPHOS^{43, 44}. Vasquez *et al.* studied a model of ATP flux demonstrating that glucose uptake capacity and solvent

capacity of the cytoplasm are important factors. They proposed that at lower levels of glucose uptake OXPHOS is most efficient but once a threshold has been reached, a gradual decrease in OXPHOS relative to GLY results in more efficient ATP production⁴⁴. Alternatively, the reasons underlying the persistent dependence on GLY may be related to the fact that rapidly dividing cells become dependent on this pathway for production of nutrients such as amino acids, nucleotides and lipids needed for development of new cells at a sufficient rate for a rapidly dividing tumor⁴⁵.

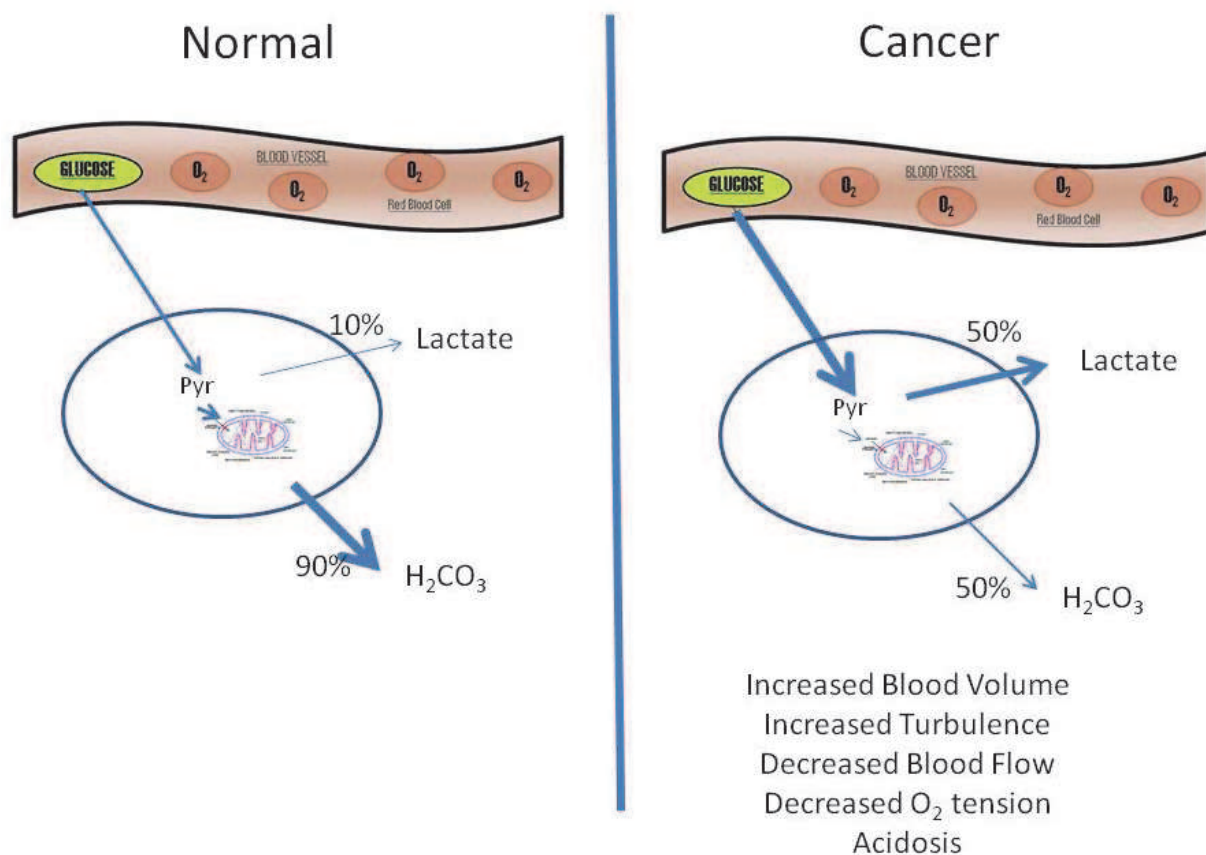


Fig. 2. Simplified graphic that demonstrates some key features of Warburg effect. Under normal conditions, approximately 90% of glucose and other energy substrates are efficiently metabolized via the mitochondria. Only 10% of glucose is metabolized via glycolysis to lactate. In solid cancers, however, there is a shift towards increased glycolysis and now over 50% of ATP is generated through glycolysis. In association with this, the tumor environment is characterized by increased blood volume, stasis and low O₂ tension and pH. For more detailed recent descriptions of tumor metabolism, the reader is referred to^{39, 42, 46, 60}.

Although Warburg proposed that the glycolytic shift related to defective mitochondria, this has proven to be an oversimplification in that this organelle definitely functions in cancer cells, albeit not always at a normal level⁴⁶. In fact, since GLY is a characteristic of normal rapidly proliferating tissues, this shift can occur even in the presence of normally functioning mitochondria⁴⁵. Instead, it is more likely that this shift results from a number of cytokines and oncogenic mutations that combine to effect increased GLY. For instance, HIF1 increases GLY and down regulates mitochondrial function by activating genes involved in

glucose uptake such as GLUT1 as well as enzymes responsible for the glycolytic breakdown of glucose such as phosphofructokinase, aldolase and pyruvate dehydrogenase⁴¹. Mutations that either inactivate p53 or activate NF- κ B can also result in a shift towards producing energy via GLY as do environmental triggers such as acidosis and increased extracellular lactate⁴⁷.

5. Linking blood flow with metabolism to explain the BEV pseudoresponse

In the modern era, cancer is viewed as essentially a cell autonomous phenomenon. In this context, the Warburg effect has therefore been addressed primarily through attempting to ascertain what genetic mutations underlie the shift towards GLY. This has also led many to question its universality for all cancers since it is well documented that at least some cancer cells definitely harness energy via OXPHOS.

In our view, however, the Warburg effect is a tissue not a cell phenomenon, meant to connote the net activity of GLY vs. OXPHOS in the tissue, not the cell. This is in keeping with Warburg’s original descriptions of the process in which he utilized animal preparations to demonstrate the effect⁶. In fact, within the tumor itself, it would be advantageous from the point of view of distributing energy substrates if certain cells used GLY to increase extracellular lactate concentrations that can then be used by other cells for OXPHOS (similar to the astrocyte/neuron relationship⁴⁸; interestingly, a similar distribution of function has been proposed for breast cancers⁴⁹). In steady state, therefore, within cancers including those of the brain, this environment is associated with increased blood volume, increased lactate and decreased blood flow, which results in a substrate “excess”, which as is predicted by models that examine energy utilization within tissues, favors GLY⁴⁴.

Such a steady state requires an adequate amount of blood flow to deliver adequate amounts of glucose to support the process, as well as a high amount of stasis to keep lactate available. It follows therefore that in addition to supporting adequate blood vessel formation to support the growing tumor, VEGF should also be crucial to supporting the cancer’s metabolism. We propose therefore that it is this linkage between VEGF, blood vessel maintenance and tumor metabolism that explains the profound initial effects of BEV on GBM and suggest it be named the **Warburg-Folkman effect** to honor the two scientists whose concepts provide its foundation. We propose that the paring of the tumor vasculature (or “normalization”) after BEV results in a period of acute tumor “starvation” resulting from lowered glucose (delivery of which is decreased due to vascular constriction lowering flow) and lactate (removal of which is increased due to decreased stasis) levels (Figure 3). This creates a situation wherein cells within the cancer must resort to the more efficient OXPHOS in the presence of decreased substrate. This forced utilization of mitochondria results in the exposure of cells to pro-apoptotic factors such as cytochrome C and apoptosis inducing factor and increases reactive oxygen species, increasing susceptibility of these cells to apoptosis^{45,50}.

In effect, therefore, we believe the observed clinical pseudoresponse represents an acute crisis for the cancer tissue, which responds over time by adaptations that favor “dispersion”, a term we prefer to invasion since we believe this represents a compensatory process in which tumor cells migrate to areas where the supply of energetic substrates is more favorable rather than an evolution to a more aggressive tumor. Such a model would suggest that while the effect may be transient, the acute removal of VEGF creates a period in which tumors should be extremely vulnerable to further metabolic perturbations, perhaps to the point where they can be induced to “collapse”.

Warburg-Folkman Effect

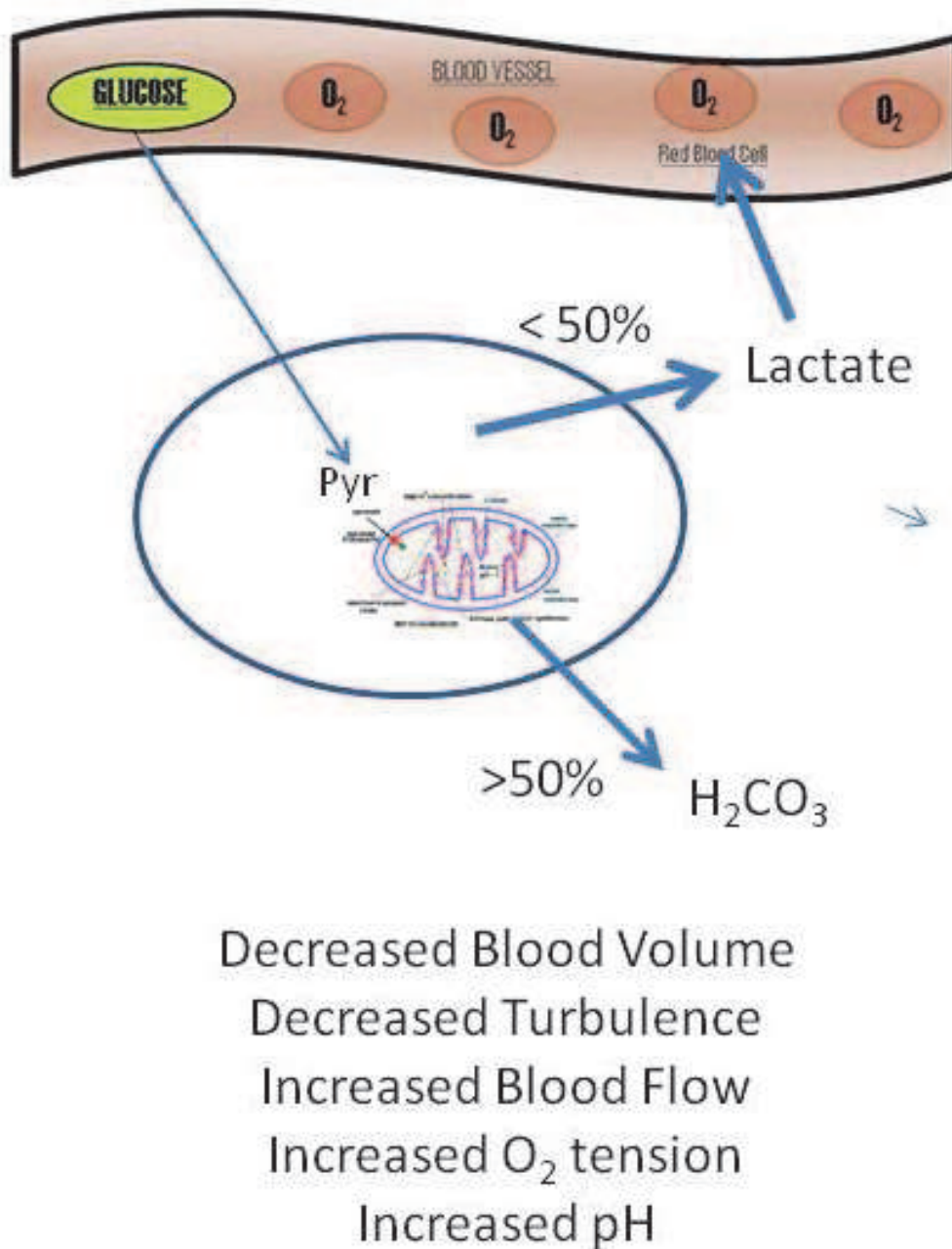


Fig. 3. Proposed early effect of VEGF blockage on the tumor environment: the Warburg-Folkman effect. The effect of removing VEGF is to cause a vessel “paring” that has been proposed to “normalize” flow. We propose that this has the effect of acutely depleting energy substrates – both glucose and lactate – through decreased delivery and increased removal, respectively. This results in increase mitochondrial utilization that results in increased OXPHOS as well as increased ROS production.

6. Measuring OXPHOS and GLY in intact organisms; MRS of hyperpolarized $^{13}\text{C}_1$ -pyruvate

Since our proposal predicts a change in tumor metabolism at the tissue level with the introduction of anti-VEGF therapy, its proof depends on a tool in which the relative amounts of GLY and OXPHOS can be ascertained in the living organism. Until recently, therefore, this question could not easily be addressed. On first glance, one could consider using FDG PET scanning, the importance of which in cancer diagnostics is derived from Warburg's observations and is dependent upon the upregulation of glucose uptake mechanisms in neoplasms compared to normal surrounding tissue. FdG is an analogue of glucose and areas of increased FDG uptake indicate increased tissue metabolic activity and the amount of uptake correlates with tumor aggressiveness⁵¹. However, while FDG PET scanning also indirectly reflects the Warburg effect (because cancers must up regulate glucose transporters to maintain their metabolism), it does not provide a real time picture of the cancer's metabolism and does not measure either OXPHOS or GLY. A similar problem exists with conventional MRI techniques; thus, one can measure total lactate using proton MRS, but this only reflects the total pool, not the throughput.

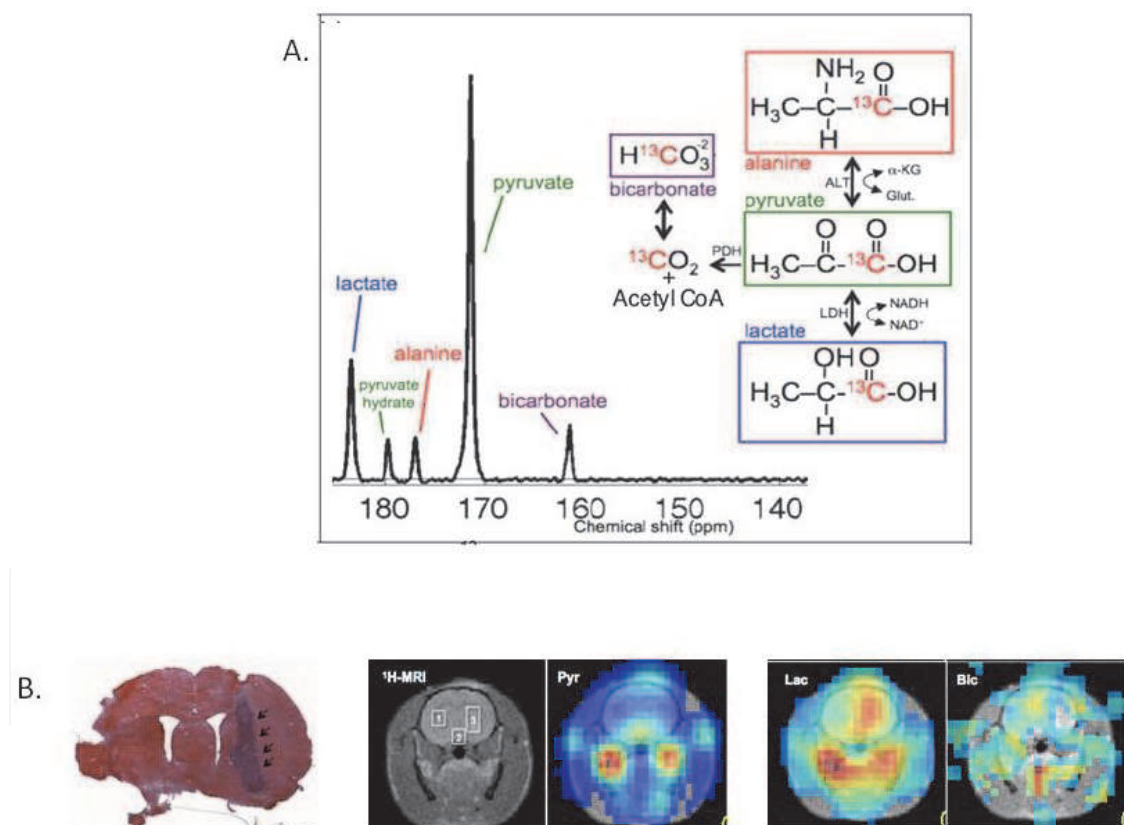


Fig. 4. (A) Single acquisition in vivo ^{13}C spectrum from a rat heart following the injection of hyperpolarized $^{13}\text{C}_1$ -Pyr. ^{13}C -Pyr and its products ^{13}C -Lac, ^{13}C -Ala, and ^{13}C -BiC are easily visualized. A small fraction of the ^{13}C -Pyr is in equilibrium with metabolically inactive ^{13}C -Pyr-hydrate. (B) (left) H&E stained cross-section of rat brain with implanted glioma. (right) Dynamic ^{13}C metabolic imaging results: TR = 3 s, $2.7 \times 2.7 \times 5 \text{ mm}^3$ nominal voxels. ROIs selected for further analysis are shown on the proton images. Elevated lactate is clearly visualized within the tumor.

A novel technology has been developed that can address these important questions, however. *In vivo* hyperpolarized ^{13}C MRS achieves dramatically enhanced signal to noise ratios, thus enabling the real-time investigation of metabolism with more than 10,000-fold signal increase over conventional ^{13}C methods ⁵². It provides unprecedented opportunities for real-time imaging of *in vivo* metabolic pathways critical to the identification and evaluation of cancer ⁵³⁻⁵⁷. In terms of studying the Warburg-Folkman effect, it enables the quantitative assessment of the fate of labeled pyruvate, a key nodal point in the metabolic pathway in which glucose is either converted to lactate (which reflects GLY) or acetyl CoA (which then enters the Krebs cycle, resulting in bicarbonate production, which reflects OXPHOS) (Figure 4). With this technology, the amount of lactate and bicarbonate produced during a 60-90 second period after a labeled injection of pyruvate can be measured, thus permitting generation of a lactate/ HCO_3^- ratio (the Glycolytic Index). Two published studies have already demonstrated increased lactate production in brain cancers this way ^{58, 59}, and this technology is already being tested in the clinic.

This technology therefore offers the prospect of being able to obtain a metabolic “snapshot” at multiple times during the course of cancer and offers an ideal way to assess the BEV’s impact on glioma metabolism. Our prediction is that the Glycolytic Index produced after a pyruvate probe will be significantly decreased during a finite time interval after exposure to BEV. We would also predict that as treatment fails, this ratio will once again increase towards lactate production and believe that the extent to which the ratio trends towards “normal” (i.e., that seen in normal tissue) would correlate with outcome (i.e., it will be a reliable gauge of treatment response).

Ultimately, one could envision such an approach leading to a therapeutic strategy based on physiology rather than genetics. Thus, while it is well known that cancer tissues have a high rate of GLY, it remains unclear whether lowering the amount of GLY relative to OXPHOS would correlate with decreased aggressiveness or whether if the relative amounts were lowered to “normal”, growth would “stall”. We believe this ratio (which can be mathematically expressed as Cancer aggressiveness = $k * \frac{1}{\text{bicarbonate} / \text{lactate}}$) will be a

highly sensitive and rapid readout from which one can repeatedly assess both aggressiveness and treatment effect. In effect therefore, the opportunity is to use this ratio in a way that other physicians may use blood pressure to gauge cardiovascular health.

7. References

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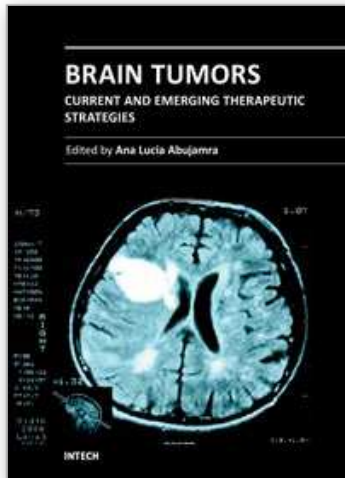
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