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Letter to the Editor

Does hypoxia really control tumor growth?

To the Editor,

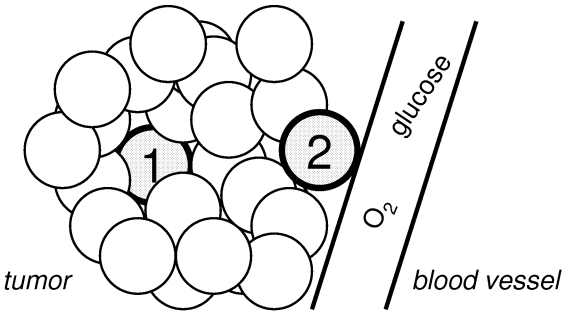
It is becoming widely accepted that tumor growth is controlled by oxygen limitation (hypoxia) [11,17]. There are two lines of evidence that support this idea. On the one hand, it is accepted that oxygen limitation activates hypoxia-inducible factor 1 (HIF-1), a transcription factor that plays a key role in tumor growth. It is considered that cancer is caused by alterations in cancer genes and there is evidence that suggests that the most important cancer gene pathways culminate in HIF-1 activation [22]. HIF-1 activation increases the transcription of many genes that code for proteins that favor tumor growth, including proteins involved in glucose metabolism, cell proliferation, apoptosis resistance, invasion, metastasis and angiogenesis [19,20]. Furthermore, HIF-1 overexpression has been observed in most cancers and has been associated with increased patient mortality [19,20,25]. On the other hand, it is accepted that solid tumors have an inappropriate blood flow that causes a reduced oxygen supply in some cells within the tumor [11]. It is believed, therefore, that HIF-1 activation would occur in cells with reduced oxygen levels, and that the activation of HIF-1 in these hypoxic cells would drive tumor growth.

It is well known that tumor growth requires cell proliferation. It is also recognized that glycolysis is essential for cell proliferation; cell proliferation requires the synthesis of new molecules (S-phase of the cell cycle) and glycolysis provides most of the building blocks required for the synthesis of these molecules [1]. It is also accepted that cells need to take glucose from the blood in order to maintain sustained glycolytic rates. Collectively, these observations imply that tumor growth requires that tumor cells take glucose from the blood. The fact that the blood also supplies oxygen represents an obstacle to accept that tumor growth is controlled by low oxygen concentrations. In other words, it seems contradictory that growing tumors require a blood flow high enough to satisfy their increased glucose demands but, at the same time, low enough to drive hypoxia-mediated tumor growth.

Is it possible to reconcile the experimental evidence that supports that growing tumors need both the activation of HIF-1 and a blood flow high enough to satisfy their increased glucose demands? It is now well established that HIF-1 can be activated in normal and cancer cells under non-hypoxic conditions [10,14,16]. Interestingly, it has been demonstrated that glucose metabolites can keep high HIF-1 levels in cancer cells in the presence of adequate oxygen levels by preventing HIF-1 degradation [15,16]. Furthermore, it has been proposed recently that the key event involved in HIF-1 activation may not be oxygen limitation but an alteration in oxygen metabolism (dysoxia) [14]. This alteration in oxygen metabolism would explain that tumor cells can simultaneously have increased HIF-1 levels and a blood flow high enough to satisfy their increased glucose demands (Fig. 1).

There are experimental data that support that tumor growth may be controlled by the alteration in oxygen metabolism represented in Fig. 1. Tumor cells are known to generate the oxygen-derived species superoxide anion ($O_2^{\cdot -}$) and hydrogen peroxide (H_2O_2) constitutively and in large amounts [4,21]. This high H_2O_2 production may increase the levels of HIF-1 in tumor cells, as H_2O_2 is a key activator of this transcription factor [14]. It has also been reported that cells from the most common cancer types have decreased expression of the oxidative phosphorylation (oxphos) protein ATP synthase [5,6,12,13]. This would cause oxphos repression, decreased ATP generation through oxphos and glycolysis activation to compensate this decreased ATP generation [14]. Accordingly, tumor cells have high glycolytic rates even in the presence of an adequate oxygen supply (aerobic glycolysis) [9], and the activation of glycolysis seems necessary for keeping adequate ATP levels in tumor cells [8,18,23].

It is the author opinion that we should reconsider the idea that tumor growth is controlled by hypoxia. The possibility that tumor growth might be controlled by an alteration in oxygen metabolism instead of a decrease in oxygen levels might modify the therapeutic approaches to achieve tumor regression. For instance,



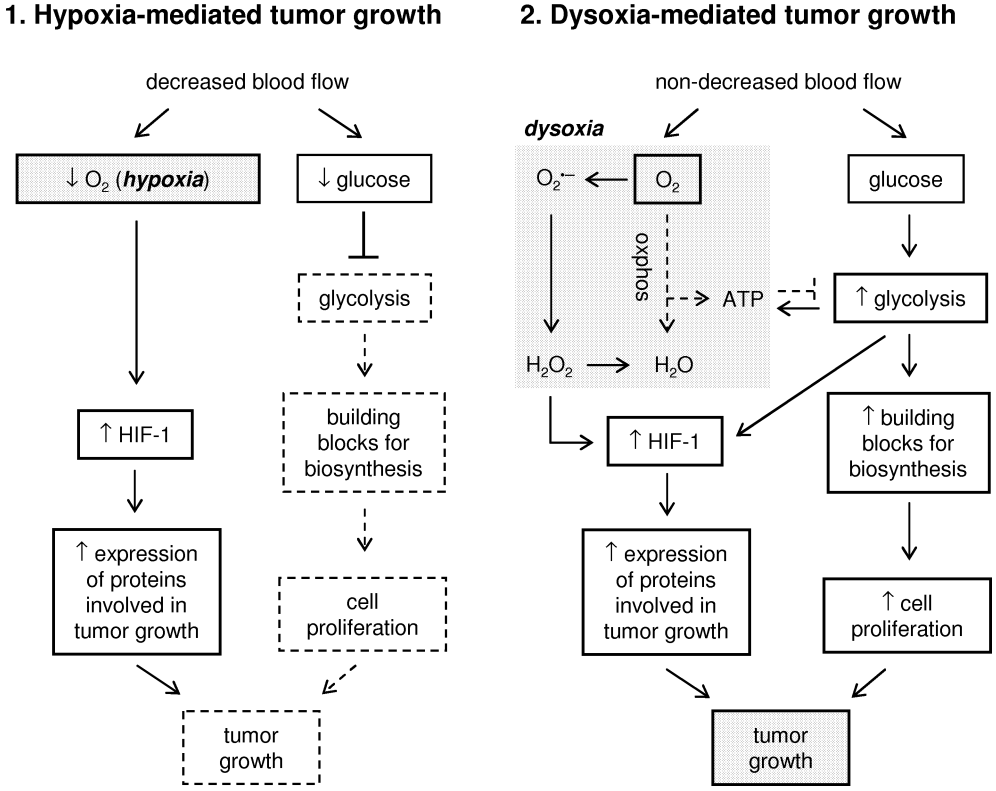


Fig. 1. **Tumor growth may not be controlled by oxygen limitation (hypoxia) but by an alteration in oxygen metabolism (dysoxia)**. This figure represents that a cell with a decreased blood flow (cell number 1) has a reduced supply of both O_2 and glucose. The reduced O_2 supply would cause the activation of HIF-1, a transcription factor that favors tumor growth. However, the reduced glucose levels would restrict the proliferation of this cell. As a result, cell number 1 would not contribute to tumor growth substantially. A cell with a non-reduced blood flow and an alteration in oxygen metabolism (cell number 2) would activate HIF-1 and would not have a restricted proliferative capacity caused by glucose deprivation. Cell number 2, therefore, would contribute to tumor growth.

Pouyssegur *et al.* have recently discussed potential new approaches to enforce tumor regression based on the idea that oxygen limitation plays an important role in tumor growth [17]. They propose that several steps should be combined to enforce necrotic cell death in tumors. One of these steps would be to increase glycolysis; the activation of glycolysis would magnify acidosis-induced necrotic cell death in tumors [17]. However, there is evidence that suggests that the activation of glycolysis may not be an appropriate strategy to induce tumor regression (see Fig. 1). First, if we increased glycolysis we would be giving ATP to

tumor cells. This strategy may be inappropriate, as it seems that tumor cells need glycolytic ATP for their survival [8,18,23]. Second, the activation of glycolysis may result in accumulation of glucose metabolites and HIF-1 activation [14–16]; the activation of HIF-1 would increase the expression of many proteins that favor tumor growth [19,20]. Finally, if we increased glycolysis we would be providing tumor cells with building blocks for biosynthesis. As mentioned before, these building blocks are necessary for cell proliferation and therefore for tumor growth. On the other hand, the new model proposed in Fig. 1 (dysoxia-mediated tumor growth) suggests that tumor growth might be inhibited, for instance, by preventing or reducing the cellular levels of H_2O_2 or by repressing glycolysis. This strategy may prevent HIF-1 activation and therefore inhibit tumor growth. This proposal is in agreement with experimental observations that have shown that tumor growth can be inhibited by reducing the cellular levels of H_2O_2 [2,24] and by repressing glycolysis [3,7,8].

Miguel López-Lázaro
Department of Pharmacology, Faculty of Pharmacy
University of Seville, Spain
E-mail: mlopezlazaro@us.es

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