"Endothelial cell metabolism and tumour angiogenesis: glucose and glutamine as essential fuels and lactate as the driving force."

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ABSTRACT

Angiogenic endothelial cells and tumour cells can survive under hypoxic conditions and even proliferate and migrate in a low-oxygen environment. In both cell types, high rates of glycolysis (i.e. conversion of glucose to lactate) and glutaminolysis provide most of the required biosynthetic intermediates and energy to support sprouting and cell division without coupling to oxidative phosphorylation. This metabolic preference is observed under hypoxic conditions, but also in situations in which oxygen is present. In the case of tumour cells, this is known as the Warburg effect and is largely governed by oncogenes. In endothelial cells lining tumour blood vessels, the option of respiration-independent metabolism allows the neovasculature to resist the hostile environment of fluctuating oxygen tension (ranging from severe hypoxia to quasi-normal levels of oxygen). In addition, accumulation in tumours of lactate, the end-product of glycolysis, largely contributes to the angiogenic phenotype through inhibition of prolyl hydroxylase 2 and the activation of HIF1α and NFκB. Activation of the latter in a hypoxia-independent manner leads to the increased production of interleukin-8/CXCL8 which drives the autocrine stimulation of endothelial cell proliferation and maturation of neovessels. In conclusion, the addiction of proliferating endothelial cells for glucose and glutamine as fuels and the driving force of lactate to promote angiogenesis provide novel potential treatment options without the disadvantages of conventional anti-angiogenic drugs.

CITE THIS VERSION

Feron, Olivier; Polet, Florence. Endothelial cell metabolism and tumour angiogenesis: glucose and glutamine as essential fuels and lactate as the driving force.. In: Journal of Internal Medicine, Vol. 273, no. 2, p. 156-165 (Février 2013) http://hdl.handle.net/2078/125552 -- DOI : 10.1111/joim.12016
Endothelial cell metabolism and tumour angiogenesis: glucose and glutamine as essential fuels and lactate as the driving force

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Angiogenic endothelial cells and tumour cells can survive under hypoxic conditions and even proliferate and migrate in a low-oxygen environment. In both cell types, high rates of glycolysis (i.e. conversion of glucose to lactate) and glutaminolysis provide most of the required biosynthetic intermediates and energy to support sprouting and cell division without coupling to oxidative phosphorylation. This metabolic preference is observed under hypoxic conditions, but also in situations in which oxygen is present. In the case of tumour cells, this is known as the Warburg effect and is largely governed by oncogenes. In endothelial cells lining tumour blood vessels, the option of respiration-independent metabolism allows the neovascularature to resist the hostile environment of fluctuating oxygen tension (ranging from severe hypoxia to quasi-normal levels of oxygen). In addition, accumulation in tumours of lactate, the end-product of glycolysis, largely contributes to the angiogenic phenotype through inhibition of prolyl hydroxylase 2 and the activation of HIF1α and NFκB. Activation of the latter in a hypoxia-independent manner leads to the increased production of interleukin-8/CXCL8 which drives the autocrine stimulation of endothelial cell proliferation and maturation of neovessels. In conclusion, the addiction of proliferating endothelial cells for glucose and glutamine as fuels and the driving force of lactate to promote angiogenesis provide novel potential treatment options without the disadvantages of conventional anti-angiogenic drugs.

Keywords: angiogenesis, endothelial cell, glucose, glutamine, hypoxia, lactate, metabolism, metabolism-targeting drugs, prolyl hydroxylase.

Introduction

There are numerous sources of crosstalk between tumour metabolism and angiogenesis; the most obvious link is the role of interface played by blood vessels delivering oxygen and nutrients to all tissues in the organism including tumours. Blood vessels are more than a passive plumbing system and can alter their shape to meet the changing oxygen and energy demands of the tissue [1]. NO produced by the endothelial NO synthase (eNOS) plays a central role in this regulation of blood vessel phenotype; NO not only mediates vasodilation and angiogenesis [2] (and thus influences the supply of oxygen to the surrounding tissues) but also inhibits the respiratory electron transfer chain [3, 4]. Therefore, it has been proposed that mitochondrial oxygen consumption mirrors the NO gradient, thereby allowing oxygen to diffuse from the blood towards the tumour stroma [3]. Recently, however, as cancer metabolism has been further investigated [5], understanding of the reverse dialogue, i.e. metabolism influencing angiogenesis, has increased [6]. Here, we will focus on the conversion of glucose to lactate that occurs in endothelial cells lining tumour blood vessels. In particular, we will provide the rationale to support why glucose fuels glycolysis in endothelial cells without coupling to the downstream tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS); why, instead, glutamine feeds the TCA cycle in these cells and how lactate, the end-product of glycolysis, contributes to the stimulation of angiogenesis in tumours.
Glucose- and glutamine-dependent proliferation of endothelial cells

Endothelial cells are in close contact with red blood cells (RBCs) and thus seemingly have access to a high level of oxygen. As emphasized above, in part because of an NO-driven inhibition of the respiratory chain, most glucose entering endothelial cells is converted to lactate, diverting pyruvate from the TCA cycle. This tendency towards glycolysis in dividing endothelial cells can be interpreted at the light of the concepts of ‘cycling hypoxia’ and of the so-called Warburg effect [7], which describes the preference of some tumour cells for conversion of glucose to lactate even in situations in which oxygen is present.

Hypoxia is a hallmark of cancer, but is recognized as a biologically unstable characteristic [8–11], referred to as intermittent or cycling hypoxia. Two different timescales of fluctuations may be considered: high-frequency cycles (minutes to hours) are directly caused by variations in RBC flux within tumour microvessels [12–14] whereas low-frequency waves (hours to days) are due to remodelling of the angiogenic tumour vascular network (Fig. 1). Although the consequences of cycling hypoxia are usually evaluated in terms of changes in the phenotype of cancer cells [15–18], the different components of the fluctuations in oxygen availability also affect tumour-associated endothelial cells [18–20]. In other words, despite their struc-

Fig. 1 The two main timescales of cycling hypoxia. The complex timescale of fluctuations in oxygen tension in tumours results from the superimposition of low- and high-frequency cycles. The slower cycling timescale (hours to days) is caused by stimulation of angiogenesis in response to the hypoxic tumour environment. Following the development (and possibly maturation) of an efficient vasculature in the previously hypoxic region of the tumour, cancer cells proliferate and reach an imbalance between oxygen delivery and consumption. Proliferating and migrating endothelial cells are exposed to hypoxia during the angiogenic process and are oxygenated only when the neovessel is perfused (a). The higher frequency hypoxic cycles (minutes to hours) are caused by variations in RBC flux within tumour microvessels. Fluctuations in RBC flux can result from the uneven distribution of these cells at microvessel bifurcations because of their reduced deformability in low-oxygen conditions; this may lead to interruption of blood flow in a given tumour area (b). Of note, altering RBC flux in a limited number of vessels can affect the haemodynamics of the entire tumour vascular network.

(a)

(b)
tural location at the interface with blood flow in healthy tissues, tumour-associated endothelial cells are exposed to hypoxia for variable periods of time. This may occur before connection of a neoformed precapillary to pre-existing blood vessels to perfuse the surrounding tumour area (Fig. 1a) or through an unequal distribution of RBCs at the point of bifurcation leading to a temporarily non-perfused vessel (or a vessel perfused with RBC-free plasma) (Fig. 1b).

The capacity of endothelial cells to adapt to excess oxygen as well as to a hypoxic environment requires a particular metabolism suitable for such fluctuations. This metabolic requirement is reminiscent of ‘preconditioning’ of cardiac [21] and vascular cells [22], i.e. the prosurvival mechanisms against ischaemic insults conferred by challenges of repeated short periods of ischaemia. Following exposure to cycles of hypoxia/reoxygenation, tumour-associated endothelial cells become resistant to proapoptotic stresses, including reduced growth factor availability and radiotherapy [19]. In addition, endothelial cells exposed to such hypoxic preconditioning have a higher migratory capacity and an increased tubulogenic potential [19]. These findings demonstrate that endothelial cells can exploit the glycolytic pathway without further need of coupling to the TCA/OXPHOS system (despite their blood-interfacing location), thus showing adaptation to the fluctuating oxygen levels in tumours. Most healthy tissues could not support such a stressful setting of intermittent alterations in the surrounding gaseous environment. It has been proposed that vascular-type proton ATPases in microvascular endothelial cells, in addition to the ubiquitous Na"+/H"+ exchanger and HCO"3"-based H"+-transporting systems, provide these cells with the means to manage acidosis resulting from the production of lactic acid under hypoxic/ischaemic conditions [23].

Evidence supporting the Warburg effect in tumour cells also illuminates the metabolic properties of angiogenic endothelial cells [24, 25]. First, it is noteworthy that as long as glucose and nicotinamide adenine (NAD") are available, glycolytic ATP production can match the ATP yield from oxidative phosphorylation [26]. Because NAD"+ can be generated efficiently from the conversion of pyruvate to lactate, extracellular glucose is critical to maintain high glycolytic rates (Fig. 2). Secondly, lipid and nucleotide synthesis can be derived from the glucose-6-phosphate-fuelled pentose phosphate pathway (PPP) via production of nicotinamide dinucleotide phosphate (NADPH) and ribose-5-phosphate respectively [24]. Moreover, aromatic amino acids can also be synthesized via the PPP and the glycolytic intermediate 3-phosphoglycerate can serve as a carbon source for amino acid synthesis (Fig. 2). Together, these different sources of biosynthetic intermediates contribute to the duplication of cell biomass and the genome at each cell division without the need for coupling to the OXPHOS. In tumour cells, this metabolic preference is observed under hypoxic conditions (see Fig. 2 legend for details), but also in the presence of oxygen (the Warburg effect) because of oncogenic alterations that promote a high glycolytic turnover [24, 27]. In the context of endothelial cells dividing to form new blood vessels, the ability to use glycolysis is not guided by mutations, but by the need for access to increased building blocks for the synthesis of macromolecules (i.e. nucleotides, lipids, sugars and amino acids). It is interesting that the hypoxia-independent activation of these pathways can arise from glycolysis per se, i.e. from the effects of the glycolytic end-product lactate on the activation of key transcription factors such as nuclear factor NF(kB) [28] and hypoxia-inducible factor (HIF)-1α [29] (see below).

Nevertheless, it should be noted that whilst endothelial cells in the arteries are generally quiescent and exposed to high levels of oxygen (and nutrients), those in the venous and lymphatic systems are more prone to sprouting and more likely to encounter hypoxic and nutrient-deprived conditions because of their functions and locations in the vascular tree [30]. Whether endothelial cells express a specific gene programme to deal with different biological situations or conversely whether their fate is determined by their metabolism remains unknown. Furthermore, even if endothelial cells do not fully oxidize glucose via TCA cycle coupling to the OXPHOS, the TCA cycle can still be used to ensure cataplerosis (i.e. the efflux of biosynthetic intermediates for lipid and amino acid synthesis). In tumour cells, glutamine can compensate for the loss of TCA products via the influx of α-ketoglutarate [19], thereby having a role in the so-called anaplerotic process [18] (Fig. 2). In addition, such replenishment of the TCA cycle allows NADPH to be generated from glutaminolysis [31] (Fig. 2). In one of the few studies to focus on endothelial cell metabolism, measurements of the maximum catalytic activities of the major metabolic pathways demonstrated that, in addition to
Glucose and fatty acids, glutamine represents an important fuel for these cells [32]. In particular, the activity of glutaminase is about 20-fold higher in endothelial cells than in lymphocytes (known to exhibit high rates of glutaminolysis) [32]. Furthermore, it was recently reported that the inhibition of glutaminase in endothelial cells induced a senescent-like phenotype [33]. These data confirm that, as in tumour cells, endothelial cells can produce biosynthetic intermediates via the TCA cycle independently of coupling to the OXPHOS machinery (Fig. 2). In this way, tumours also avoid producing excess ATP which is known to have a negative feedback effect on glycolysis. It is interesting that glutamine deprivation was found to exert the same effects as lactate accumulation in tumours: increased NFκB activity and subsequent stimulation of interleukin-8 (IL-8)/CXCL8 expression which, in turn, can promote angiogenesis [34].

### Lactate-driven angiogenesis

Elevated lactate concentration is a good indicator of the glycolytic adaptation of tumours and is...
correlated with clinical outcome in a variety of human cancers [35]. More than a simple waste product, lactate is used as a fuel by glucose-deprived tumour cells [36] and also to initiate signalling after cellular uptake. In tumour-associated endothelial cells, lactate was recently found to inhibit prolyl hydroxylase-2 (PHD-2) activity and thereby facilitate the activation of the NFκB pathway [28]. PHDs are enzymes that, in the presence of oxygen, hydroxylate proline residues within specific consensus sequences leading to proteasomal degradation of the targeted protein (Fig. 3a). Inhibition of PHD2 activity by lactate occurs through direct competition between lactate and the bona fide PHD co-substrate 2-oxoglutarate, leading to accumulation of IκB kinase (IKK) which

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**Fig. 3** PHD2-driven effects of the glycolytic end-product lactate on the NFκB and HIF signalling pathways. (a) PHDs are a family of 2-oxoglutarate-dependent Fe(II) dioxygenases that, in the presence of oxygen, hydroxylate proline residues within specific consensus sequences (such as LxxLAP). This leads to recognition by the von Hippel-Lindau E3 ubiquitin ligase complex which targets the ubiquitinated protein to proteasomal degradation. Elevated lactate concentrations can compete for PHD binding with 2-oxoglutarate, the co-substrate of this enzyme. (b) Inhibition of PHD2 prevents the hydroxylation of IKK leading to its accumulation and consequent phosphorylation of IκBα, which may then dissociate from the RelA and p50 subunits. The resulting translocation of free NFκB into the nucleus promotes the transcription of a specific gene programme, including IL-8. (c) A similar mechanism promotes the stabilization of HIF-1α. After migration to the nucleus, HIF1α forms a heterodimer with the constitutively expressed HIF-1β subunit, leading to the expression of bFGF in endothelial cells. Although mechanistically similar, the processes of NFκB and HIF induction in response to lactate are somewhat different. In particular, in contrast to HIF-1α, IKK is always expressed in basal conditions. Therefore, lactate and even hypoxia modulate rather than absolutely determine the expression and activation of IKK; this may be due to the single LxxLAP motif in IKK (vs. the two motifs present in HIF-1).
may in turn phosphorylate inhibitor of kappa B (IκBα) and thus promote the release of active NFκB (Fig. 3a, b). A major target of NFκB in endothelial cells is IL-8. Using small interfering RNA (siRNA) directed against IL-8/CXCL8 (rescued or not with recombinant IL-8), it was shown that this pathway accounted for most of the proangiogenic effects of lactate in these cells [28]. In addition, the release of lactate by cancer cells effectively contributed to the in vivo development of the tumour vasculature. Moreover, anti-IL-8 antibody could prevent the stimulation of angiogenesis and eventually reduce tumour growth [28].

It has recently been reported that similar mechanism of regulation also leads to the activation of HIF-1α in endothelial cells [29]. Lu and colleagues had shown that a variety of monocarboxylate compounds could inactivate PHD in tumour cells [37]. In endothelial cells, the major HIF-1α target induced in a lactate-/PHD2-dependent manner was basic fibroblast growth factor (bFGF) [29] (Fig. 3c), further supporting the proangiogenic impact of the high glycolytic rates observed in the tumour microenvironment. Although it may be difficult to discriminate between the role of hypoxia and lactate in triggering vascular endothelial growth factor (VEGF) signalling in vivo, the finding that NFκB acts as a lactate-responsive transcription factor explains the presence of an HIF-independent pathway which links increased glucose metabolism with key aspects of malignancy including tumour angiogenesis.

**PHD2 integration of lactate-driven angiogenesis**

Reduction in PHD2 activity is the common cause of both the stabilization of HIF-1α and release of NFκB observed in endothelial cells in response to lactate [28, 29]. This is consistent with the finding of Cummins et al. that hypoxia may activate NFκB in different tumour cells, through decreased PHD1-dependent hydroxylation of IKKβ and the subsequent phosphorylation-dependent degradation of IκBα [38]. More recently, Chan and colleagues proposed that PHD2 could represent a tumour suppressor gene promoting NFκB activation when absent in tumour cells [39]. They showed using PHD2-silenced cancer cells that injection of these modified cells into mice led to the development of more highly vascularized tumours. Thus, PHD2 functions as a tumour suppressor by limiting angiogenesis, but also vasculogenesis, through a reduction in bone marrow-derived cell recruitment.

How PHD2 can be downregulated in some tumours whilst acting as an oncogene in others [40] remains unclear [41]. Mutations in PHD2 associated with increased risk of tumours have been reported [42] and epigenetic silencing has been proposed for PHD3 [43]. However, based on the striking effect of lactate on activation of PHD2 by 2-oxoglutarate [28, 29], it can be postulated that the activity (and not the expression) of PHD2 may be altered in proportion to the extent of lactate production in tumours, or even within a specific tumour area.

Of interest, Chan and colleagues [39] found that silencing HIF did not reduce tumour growth and blood supply in PHD2-silenced cells in multiple cancer types. This indicates that the effects of PHD2 inhibition do not depend solely on the presence of HIF, but that other PHD-dependent pathways such as NFκB/IL-8 activation may be most important under normoxic conditions. It remains to be confirmed whether the extent of hypoxia determines the context in which one PHD function prevails over the other. However, it is most likely that HIF-dependent and -independent pathways cooperate to provide redundant pathways promoting angiogenesis. Furthermore, temporal and spatial variations in oxygen tension are likely to modulate the contribution of both pathways. Mazzone et al. recently reported that endothelial cell-specific heterozygous deficiency of PHD2 normalized the tumour endothelial lining [44]. They observed that these endothelial cells had a cobblestone-like appearance and reported that endothelial haplodeficiency of PHD2 restored tumour oxygenation and thus may induce a metabolic shift to a more oxidative, less malignant phenotype [44]. Of interest, in the study by Vegran et al. [28], lactate-driven angiogenesis led to a net increase in tumour perfusion in vivo indicating that the stimulated NFκB/IL-8 pathway also contributed to make efficient the neovessels; this supports the hypothesis of a role of this pathway to increase vascular maturation. Mazzone and colleagues found that reduced PHD2 levels stabilized HIF-2α in endothelial cells and subsequently enhanced levels of soluble VEGF receptor (VEGFR)1 and vascular endothelial (VE)-cadherin. VEGFR1 is a negative regulator of VEGF signalling, whereas VE-cadherin plays a key role in intercellular junction assembly and endothelial barrier function. In addition, in complex with VEGFR2, VE-cadherin recruits phosphatases that dephosphorylate VEGFR2, thus controlling VEGF signalling. Together, these findings indicate that
Table 1  *Agents that directly interfere with the transport or metabolism of glucose, glutamine and lactate*

<table>
<thead>
<tr>
<th>Molecular target</th>
<th>Drug/compound</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose metabolism</strong></td>
<td></td>
<td></td>
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<tr>
<td>Glucose transporter (GLUT or SLC2A)</td>
<td>Phloretin</td>
<td>Preclinical</td>
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<tr>
<td></td>
<td>2-deoxyglucose (2DG)</td>
<td>Phase I/II</td>
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<tr>
<td></td>
<td>Silybin</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Hexokinase (HK)</td>
<td>2-deoxyglucose</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>3- bromopyruvate (3BP)</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>Lonidamine</td>
<td>Phase I/II/III</td>
</tr>
<tr>
<td></td>
<td>Methyl jasmonate</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Glyceraldehyde 3-phosphate dehydrogenase (GAPDH)</td>
<td>3-bromopyruvate (3BP)</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>Ornidazole, α-chlorohydrin</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Phosphofructokinase (PFK)</td>
<td>3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO)</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Pyruvate kinase-M2 (PK-M2)</td>
<td>TLN-232</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Shikonin</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>Alkannin</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Lactate dehydrogenase A (LDHA)</td>
<td>2,3-dihydroxynaphthalen-1-carboxylic acid (FX11)</td>
<td>Preclinical</td>
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<td></td>
<td>N-hydroxy-2-carboxy-substituted indoles (NHI)</td>
<td>Preclinical</td>
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<td></td>
<td>Oxamate</td>
<td>Preclinical</td>
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<tr>
<td></td>
<td>R-(-)-gossypol or AT101</td>
<td>Phase I/II</td>
</tr>
<tr>
<td></td>
<td>3-hydroxyisoxazole-4-carboxylic acid (HICA)</td>
<td>Preclinical</td>
</tr>
<tr>
<td><strong>Glutamine metabolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutamine transporter (ASCT2 or SLC1A5)</td>
<td>L-γ-glutamyl-p-nitroanilide (GPNA)</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Glutamine bidirectional transporter (CD98 or SLC7A5-SLC3A2)</td>
<td>2-aminobicyclo-(2,2,1)heptanecarboxylic acid (BCH)</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Glutamine analogues</td>
<td>6-diazo-5-o xo-L-norleucine (DON)</td>
<td>Preclinical</td>
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<tr>
<td></td>
<td>Azaserine</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>Acivicin</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Glutaminase (GLS)</td>
<td>bis-2-(5 phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide (BPTES)</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>L-asparaginase (GLS activity)</td>
<td>Clinical use</td>
</tr>
<tr>
<td></td>
<td>6-Diazo-5-o xo-L-norleucine (DON)</td>
<td>Preclinical</td>
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<tr>
<td></td>
<td>Benzophenanthridine (968)</td>
<td>Preclinical</td>
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<tr>
<td>Glutamine plasma depletion</td>
<td>Phenylbutyrate</td>
<td>Clinical use</td>
</tr>
<tr>
<td>Glutamate transaminase</td>
<td>Amino-oxyacetic acid (AOA)</td>
<td>Preclinical</td>
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</table>
PHD2 coordinates angiogenesis and maturation of neovessels through regulation of NFκB, HIF1α and HIF2α. The capacity of lactate to interfere with PHD2 provides a direct link between tumour metabolism and angiogenesis. As a consequence, the observation of hypoxia-independent stimula-
tion of glycolysis in tumours indicates that the metabolism may tune the tumour vasculature according to the fuel requirements for cell proliferation and, importantly, even before the development of hypoxia.

The metabolic regulators of angiogenesis described above are only a fraction of the total [reviewed in [6]]; nevertheless, the increased use of glycolysis/glutaminolysis by proliferating endothelial cells and the signalling pathways activated by lactate, the end-product of glycolysis, already provide considerable opportunities for new anticancer treatments. Compounds targeting glucose, glutamine and lactate metabolism have been found to exert anticancer effects (Table 1) and are therefore likely to also inhibit survival and/or proliferation of tumour-associated endothelial cells. In addition, although further studies are needed to fully understand the mechanism of PHD2 genetic loss or downregulation by lactate, the findings discussed above suggest that this enzyme together with other up- and downstream factors in the glycolytic pathway could provide potential new therapeutic targets (Fig. 4). In particular, inhibiting one or several steps of the lactate/NFκB signalling pathway may represent new possibilities for treatment of tumours that have become resistant to anti-VEGF therapies or HIF inhibitors. MCT1 and MCT4, the main controllers of lactate fluxes in endothelial and tumour cells, as well as IL-8 and its cognate receptor represent new areas of research for anticancer drug development (Fig. 4). More generally, by targeting endothelial cell metabolism rather than proliferation, it may be possible to circumvent adaptive or evasive resistance to conventional anti-angiogenic treatments (i.e. the activation and/or upregulation of alternative pro-angiogenic signalling pathways) [45, 46] and to achieve the ultimate therapeutic goal of blocking pathways to which tumours are ‘addicted’ [47].

Conflict of interest statement
No conflict of interest was declared.

Acknowledgements
This work was supported by grants from the Fonds de la Recherche Scientifique FRS-FNRS, the Télévie, the Foundation Against Cancer, the J. Maisin Foundation, Action de Recherche Concertée (ARC 09/14-020) and the InterUniversity Attraction Pole (IUAP - P7-03).

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