Research into targeting tumour metabolism as a therapeutic approach has increased since it was added to the list of hallmarks of cancer in 2011 [1]. Lactate dehydrogenase A (LDHA) is a key enzyme involved in the Warburg effect, a metabolic pathway which appears to be universal in tumours, including primary brain tumours. Most studies on LDHA have been conducted in non-central nervous system tumours, and although studies into inhibiting LDHA as a therapeutic target for brain tumours, presented in brief here, have shown promise in reducing tumour growth and migration, they are few in number and currently no LDHA inhibitors are available for clinical use.

Lactate dehydrogenase metabolism
Lactate dehydrogenase (LDH) enzymes increase the rate of the reaction depicted in figure 1. LDHA has a high affinity for pyruvate, preferentially converting pyruvate to lactate and NADH to NAD$^+$ whereas LDHB has a high affinity for lactate, preferentially converting lactate to pyruvate and NAD$^+$ to NADH [2].

Under normal physiological conditions, pyruvate is used to fuel oxidative phosphorylation and ATP production. However, when oxygen becomes scarce, ATP is produced using anaerobic glycolysis, which requires LDHA to convert pyruvate to lactate (Figure 1). Although it is less efficient at producing ATP, anaerobic glycolysis is 100 times faster than oxidative phosphorylation. Cancer cells upregulate LDHA to convert pyruvate to lactate in order to generate ATP via glycolysis even when oxygen is available, a characteristic termed aerobic glycolysis or the Warburg effect, first observed by Otto Warburg in the 1920s [4].

Brain metabolism is complex and able to respond dynamically to changes in blood glucose and lactate concentrations [5]. In mouse and rat brains, LDHB mRNA expression is predominant with the exception of strong LDHA expression in the hippocampal regions CA1, CA2 and CA4, the ventromedian hypothalamic nucleus, and the dorsal raphe nucleus as well as moderate expression in the cerebral cortex [6]. However, studies have shown that the energy needs of the brain changes over a lifespan. The human brain uses high levels of aerobic glycolysis during foetal growth and development but then switches to oxidative phosphorylation which is seen predominantly in the adult brain [7].

LDHA and tumour malignancy
LDHA over-expression is a common characteristic of cancers; it promotes elevated lactate concentrations which have been shown to predict tumour malignancy, recurrence, survival and metastasis in many types of cancer patients [3,8]. LDHA is also associated with other poor prognostic factors including tumour hypoxia [9], angiogenesis [10], proliferation and glucose uptake [11] as well as resistance to chemotherapy [12] and radiotherapy [13].

Deregulation of LDHA in brain tumours
LDHA has long been known to be regulated by major transcription factors; hypoxia-inducible factor 1 (HIF1) and c-Myc [9, 14]. HIF1 is often stabilised in brain tumours [15] and associated with a significantly poorer survival rate [16]. C-Myc expression is also often deregulated in brain tumour cells, including the medulloblastoma (MB) subgroup with the worst outcome (Group 3) [17], and has been shown to transform rat fibroblasts by up-regulating LDHA [14]. More recently forkhead box protein MI (FOXM1) and Kruppel-like factor 4 (KLF4) have been shown to regulate LDHA transcription [18, 19]. FOXM1 is a marker of poor prognosis in MB [20] and regulates glioma tumourigenicity [21] whereas KLF4 is also suppressed in MB [22] and mutated in meningioma [23]. Like many enzymes, LDHA post-transcriptional activity is regulated by phosphorylation and acetylation of amino-acid residues.

Figure 1: The reaction catalysed by lactate dehydrogenase (LDH). Adapted from Valvona et al [3]. LDH catalyses the reversible conversion of pyruvate and NADH to lactate and NAD$^+$. 
residues. The oncogenic receptor tyrosine kinase FGFR1, expressed in meningioma and glioma [24], has been shown to directly phosphorylate LDHA at Y10 and Y83 [25]. Y10 phosphorylation of LDHA promotes active, tetrameric LDHA formation whereas phosphorylation of Y83 promotes NADH substrate binding [25]. Together these studies suggest that LDHA expression is commonly deregulated in a range of brain tumours.

LDHA and brain tumour growth and survival
Reports predominantly indicate that LDHA suppression inhibits tumour cell proliferation and survival [3, 26]. Aerobic glycolysis benefits cancer cells by avoiding generation of reactive oxygen species by oxidative phosphorylation, and the intermediates of the citric acid cycle (required for oxidative phosphorylation) are utilised to synthesise the lipids, fatty acids and nucleotides required for rapid cell proliferation [27].

Interestingly, recent studies have demonstrated that LDHA is inhibited in the isocitrate dehydrogenase (IDH) subgroup of glioblastoma (GBM) which characteristically has a slower progression, greater survival rates and better prognosis than the other GBM subgroups [28]. Even brain tumour stem cell (BTSC) lines which once had IDH mutations but lost their mutant IDH allele had silenced LDHA. Analysis of data from The Cancer Genome Atlas and REMBRANDT public databases, revealed that low expression of LDHA and high methylation of the LDHA promoter was found in IDHmt GBM patients and glioma patients whose tumours over-expressed LDHA had a median survival of 16 months whereas patients whose tumour under-expressed LDHA had a median survival of >50 months [28]. These studies suggest that the silencing of LDHA in GBMs with IDH mutations may be responsible in part for the characteristically slow progression of IDH mutant GBMs.

LDHA and brain tumour migration and metastasis
Secondary brain tumours, derived from other cancers such as breast, lung and melanoma, are the most common type of adult brain tumour and the reported incidence is rising. LDHA expression correlates with metastasis and poor patient prognosis in many tumours [11, 29]. The most frequently reported mechanism by which LDHA modulates cell migration and invasion is through lactate production. Lactate causes acidification of the microenvironment which promotes tumour cell invasion by inducing apoptosis of normal cells and pH-dependent activation of metalloproteinases (MMPs) and cathepsins which degrade the extracellular matrix and basement membranes [30, 31]. Seliger et al found that, in high grade glioma cell lines, the knockdown of LDHA resulted in a decrease in lactate concentrations which caused a reduction of THBS-1 and TGF-β2 expression and reduced migration by approximately 40% compared to the control [32]. Furthermore, addition of lactate or synthetic THBS-1 rescued TGF-β2 expression and glioma migration [32]. In another study it was found that MMP-2, which is over-expressed in high-grade glioma, is also up-regulated by LDHA through lactate induction of TGF-β2 [33]. It is probable that reducing lactate production through targeting LDHA would cause a reduction in metastasis and prolong patient survival.

LDHA and brain tumour evasion of the immune response
Again, it is thought that lactate generation, promoted by LDHA, is the predominant cause of LDHA-mediated evasion of the immune response [34]. A study in GBMs revealed that LDHA induced the transcription and expression of natural killer group 2 member D (NKG2D) ligands on circulating monocytes and tumour infiltrating myeloid cells [35]. Chronic exposure to NKG2D ligands expressed by monocytes down-regulates the expression of NKG2D receptors on natural killer cells, preventing their ability to lyse NKG2D ligand-expressing tumour cells [36]. Previous studies in glioma have also shown that TGF-β can decrease NKG2D expression on NK cells in vitro [37]. As discussed previously, lactate production by
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LDH A activates TGF-β in glioma [33]; therefore it is possible that LDHA also activates TGF-β to promote evasion of the immune response.

**LDHA and the brain tumour microenvironment**

LDHA can influence the tumour microenvironment through generation of lactate which lowers pH. Primary brain tumours have been found to have a mean pH of 6.8 and as low as 5.9 compared to normal brain tissue which has a pH of 7.1 [38]. It has also been shown that an acidic pH induces glioma stem cell markers and promotes angiogenesis and malignancy, furthermore in vitro elevation of pH reversed these effects [39]. Angiogenesis is a hallmark of many tumours, including GBMs, and is stimulated by angiogenic factors including VEGF and IL-8. An acute acidic extracellular pH has been shown to promote up-regulation of VEGF in human glioma cells independently of hypoxia and furthermore hypoxia and acidic pH did not have a synergistic effect on VEGF transcription [40].

**LDHA therapy development**

There are several LDHA inhibitors which have been used in vitro and in vivo studies in many types of cancer including oxamate [41]. Galloidavin [42], Mn(II) complexes [43], quinoline 3-sulfonamides [44], azido and alkyne compounds [45] and N-hydroxyindole-based (NHI) inhibitors [46], all of which show promise but still require refinement in terms of specificity, potency and reducing toxic effects.

Unpublished studies by the Pilkington group have also shown that oxamate significantly reduces the proliferation and motility of MB cell lines. However in terms of brain tumours, Gossypol, a derivative of cotton seed oil, which has been shown to be well tolerated in clinical trials and has been completed (NCT00540722 and NCT00390403) but the results have not yet been published.

**Summary**

Research has shown that LDHA and lactate are involved directly and indirectly in many aspects of tumour growth, migration, invasion and maintenance in a wide range of tumours (Figure 2) [3, 34]. Studies of LDHA and lactate in brain tumours have shown promise but the extent of these studies is severely lacking. Furthermore, targeting LDHA and tumour metabolism downstream of pyruvate synthesis is an attractive option as the effect on non-neoplastic cells should be minimal. Brain tumours are often more difficult to treat than other cancers as therapeutic drugs often have limited propensity to cross the protective blood-brain barrier (BBB). Although current available LDHA inhibitors are not approved for clinical use, to our knowledge, no groups have tested whether any potential LDHA inhibitors are even able to cross the BBB. This article is a brief summary of the function of LDHA and brain tumours which has been reviewed more extensively by Valvona et al [3].

**References**


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