The FEBS Journal

FEBS PRESS science publishing by scientists

COMMENTARY

Discovery of a novel alpha isoform of the long-known enzyme LDHA provides new insights into cancer research

Wonyoung Park[1,2], Shibo Wei[3], Dongryeol Ryu[3] and Ki-Tae Ha[1,2]

1 Department of Korean Medical Science, School of Korean Medicine, Pusan National University, Yangsan, Korea
2 Research Institute for Korean Medicine, Pusan National University, Yangsan, Korea
3 Department of Biomedical Science and Engineering, Gwangju Institute of Science and Technology, Korea

Keywords
c-MYC; FOXM1; glycolysis; LDHA; LDHAα

Correspondence
K.-T. Ha, Department of Korean Medical Science, School of Korean Medicine, Pusan National University, Yangsan, Gyeongsangnam-do 50612, Korea
Tel: +82-51-510-8464
E-mail: hagis@pusan.ac.kr

(Received 6 February 2025, accepted 28 February 2025)

doi:10.1111/febs.70058

Lactate dehydrogenase A is a key enzyme in energy metabolism, with significant roles in cancer progression. Huang *et al.* identified LDHAα, a novel LDHA isoform derived from an alternative transcript initiated at AUG198, producing a protein 3 kDa larger than canonical LDHA. LDHAα exhibits enhanced glycolytic activity and promotes glucose uptake, lactate production, and tumor growth more effectively than LDHA. Regulated by c-MYC and FOXM1, LDHAα is mainly cytoplasmic and serves as a potential cancer biomarker and therapeutic target. These findings highlight LDHAα's unique role in cancer metabolism and its potential for advancing targeted cancer therapies.

Comment on: https://doi.org/10.1111/febs.17374

Lactate dehydrogenase—an overview

Lactate dehydrogenase (LDH) is a critical enzyme in energy metabolism, catalyzing the reversible conversion of pyruvate to lactate, with nicotinamide adenine dinucleotide (NAD^+) and its reduced form, NADH [1]. By modulating the interconversion of these metabolites, LDH helps regulate cellular energy production, linking glycolysis and oxidative metabolism to adapt to varying oxygen levels [2]. LDH exists in five isoenzymes, each composed of different combinations of two subunits: LDH-H (heart type) and LDH-M (muscle type), which are encoded by the *LDHB* and *LDHA* genes, respectively [1]. These isoenzymes include LDH1 (H4), LDH2 (H3M1), LDH3 (H2M2), LDH4 (H1M3), and LDH5 (M4), with their distribution and activity varying across tissues according to metabolic demand [1]. Among these isoenzymes, LDHA (LDH5) is predominantly expressed in muscle tissue, where it supports anaerobic energy production during intense physical activity [3]. LDHB (LDH1) is highly expressed in heart and brain tissues, where it primarily catalyzes the reverse reaction, converting lactate to pyruvate to support oxidative metabolism [4]. The distribution and activity of these isoforms reflect the specific metabolic needs of different tissues, highlighting their critical roles in energy homeostasis.

LDHA and its role in cancer

LDHA is a key enzyme in cancer metabolism that is overexpressed in many types of cancer [5]. By

Abbreviations
ATP, adenosine triphosphate; c-MYC, cellular myelocytomatosis oncogene; EMT, epithelial-mesenchymal transition; FOXM1, forkhead box protein M1; HIF, hypoxia-inducible factors; HREs, hypoxia response elements; LDH, lactate dehydrogenase; NAD, nicotinamide adenine dinucleotide; NSCLC, non-small-cell lung cancer; OCT4, octamer-binding transcription factor 4; SOX2, SRY-box transcription factor 2.

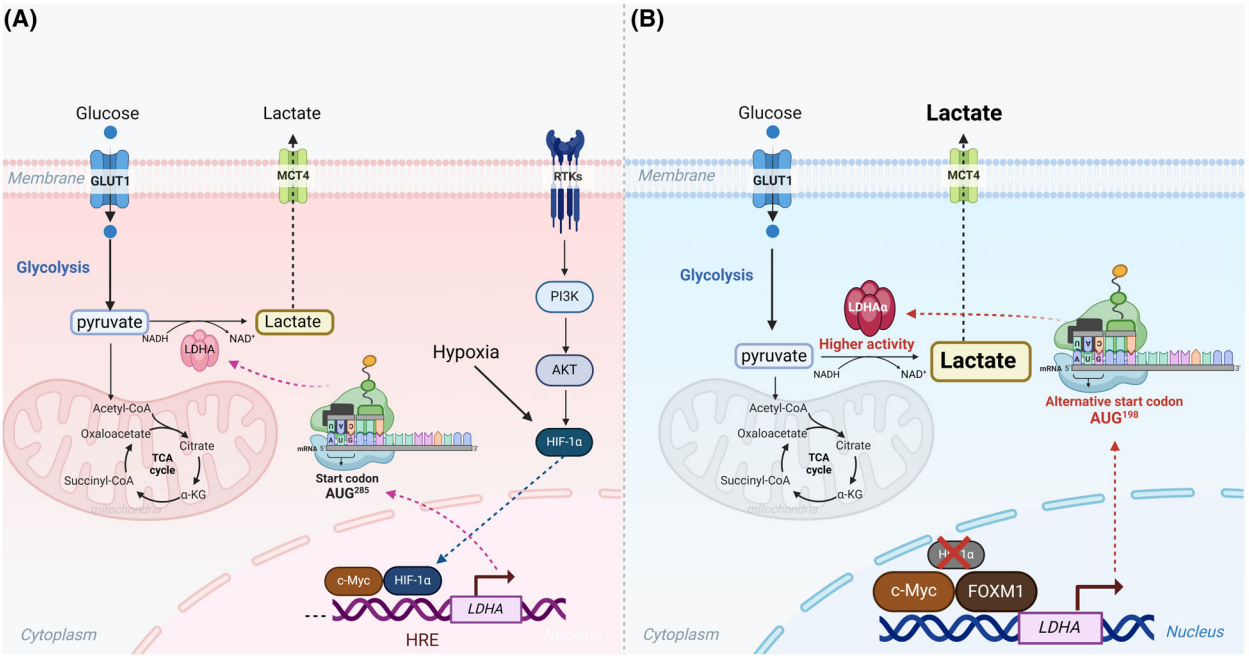

Fig. 1. Transcriptional and translational regulation of LDHA and LDHAα. (A) LDHA is translated from the canonical start codon (AUG^{285}) in the cytoplasm, where it converts pyruvate into lactate using NADH as a cofactor. LDHA transcription is primarily regulated by c-MYC and HIF-1α, which bind to the LDHA promoter and enhance its expression under hypoxic conditions. (B) LDHAα is a novel isoform of LDHA, transcribed under the control of c-MYC and FOXM1, but independent of HIF-1α regulation. LDHAα translation is initiated from an alternative start codon (AUG^{198}), producing a protein with an N-terminal extension of 29 amino acids, making it larger than the canonical LDHA protein. LDHAα exhibits higher enzymatic activity, leading to increased lactate production and enhanced glycolysis, thereby further promoting tumor metabolism and progression.

converting pyruvate to lactate and regenerating NAD^+, LDHA contributes to the Warburg effect, a hallmark of cancer [2]. This metabolic shift sustains glycolytic adenosine triphosphate (ATP) production, promotes cancer cell proliferation, and allows tumors to thrive in hypoxic environments by enhancing survival, rapid growth, and stress adaptation [2]. Since hypoxic conditions are common in solid tumors, LDHA expression is tightly regulated by hypoxia-inducible factors (HIF-1α and HIF-2α), which bind to hypoxia response elements (HREs) in the LDHA promoter, activating its transcription and further promoting cancer progression [6] (Fig. 1A). Beyond its role in metabolic adaptation, LDHA also facilitates tumor progression by modulating epithelial –mesenchymal transition (EMT) and cancer stem cell markers [7]. By influencing key signaling pathways, LDHA regulates EMT-related genes such as Snail, Slug, E-cadherin, N-cadherin, Fibronectin, and Vimentin, while also upregulating stemness-associated factors including octamer-binding transcription factor 4 (OCT4), SRY-box transcription factor 2 (SOX2), Nanog, and cellular myelocytomatosis oncogene (c-MYC), contributing to tumor aggressiveness and therapy resistance [7]. In addition to driving tumor cell plasticity, LDHA significantly shapes the tumor microenvironment. Elevated LDHA activity leads to lactate accumulation and extracellular acidification, which suppresses T-cell responses, enhances immune evasion, and facilitates angiogenesis [8]. This immune-suppressive environment, combined with LDHA-mediated metabolic reprogramming, contributes to treatment resistance, reducing the efficacy of conventional cancer therapies [8]. Given its critical role in cancer progression, LDHA has emerged as a promising prognostic biomarker and therapeutic target. Ongoing research is actively exploring LDHA inhibitors as a potential strategy to suppress tumor growth, overcome treatment resistance, and improve clinical outcomes.

LDHA inhibitors in cancer therapy

LDHA inhibitors have emerged as promising therapeutic agents targeting cancer metabolism by disrupting glycolytic flux and reducing lactate production,

The FEBS Journal **292** (2025) 2219–2222 © 2025 The Author(s). *The FEBS Journal* published by John Wiley & Sons Ltd on behalf of Federation of European Biochemical Societies.

thereby counteracting the metabolic reprogramming characteristic of tumors [1]. By inhibiting LDHA activity, these compounds interfere with the Warburg effect, limiting tumor cell proliferation and survival [1].

LDHA's function is primarily regulated through its active site, where pyruvate and NADH bind to facilitate the conversion of pyruvate to lactate [9]. Traditional inhibitors target this site through competitive inhibition, directly blocking substrate (pyruvate) or cofactor (NADH) binding [10]. However, recent research has identified allosteric sites on LDHA, which serve as alternative therapeutic targets. Unlike active site inhibitors, allosteric inhibitors bind to distinct regulatory regions on LDHA, inducing conformational changes that suppress its enzymatic activity [11].

LDHA inhibitors can be classified based on their mechanism of action into competitive and allosteric inhibitors, as well as by chemical structure into quinoline-based, benzoxazole-based, and benzimidazole-based compounds [1]. Competitive inhibitors bind directly to LDHA's active site, preventing the interaction of pyruvate or NADH. Oxamate, a pyruvate analog, forms an inactive complex with LDHA, effectively blocking pyruvate metabolism and has been shown to reduce LDH levels in tumors, enhancing the effects of pembrolizumab in non-small cell lung cancer (NSCLC) [12]. Similarly, gossypol, a polyphenolic aldehyde, competes with NADH for LDHA binding but has limited clinical application due to toxicity concerns [13]. Additionally, quinoline-based inhibitors, such as quinoline-3-sulfonamides, and benzoxazole-based inhibitors, including FX-11, selectively target the NADH-binding site, thereby reducing glycolytic activity in cancer cells [1,14]. Similarly, benzimidazole-based inhibitors interact with allosteric regions of LDHA, stabilizing an inactive enzyme conformation and exhibiting promising anticancer activity [11]. Regardless of their mode of action, LDHA inhibitors effectively disrupt the Warburg effect and limit tumor progression, while their structural diversity (quinoline-, benzoxazole-, benzimidazole-based) broadens their therapeutic potential [1]. Continued research into LDHA inhibition holds promise for developing novel metabolic-targeted cancer therapies.

Discovery and characteristics of LDHAα

Huang *et al.* [15] identified a novel isoform of LDHA, termed LDHAα, which is initiated from an alternative start codon AUG^{198}, located 87 base pairs upstream of the canonical start codon (AUG^{285}) (Fig. 1B). This produces a protein 3 kDa larger than canonical LDHA. LDHAα arises from a distinct transcript, possibly involving alternative promoters or splicing, and is differentially expressed in various cancer cells, highlighting its unique role in tumor biology. Functionally, LDHAα demonstrates a greater ability to enhance cancer metabolism compared to LDHA. It accelerates glycolysis by increasing glucose uptake and lactate production, promoting tumor cell proliferation, migration, and growth *in vitro* and *in vivo*, and exerting a stronger impact on tumor growth due to its enhanced metabolic activity. Deletion of LDHAα using CRISPR/Cas9-sgRNA reduces cancer cell proliferation and migration, though residual activity from LDHA remains.

Regulation, localization, and therapeutic implications of LDHAα

LDHAα expression is regulated by transcription factors, predominantly c-MYC, with forkhead box protein M1 (FOXM1) playing a supporting role (Fig. 1B). Interestingly, LDHAα expression is independent of HIF-1α, which commonly regulates other metabolic enzymes. Unlike LDHA, which localizes to both the cytoplasm and nucleus, LDHAα is confined to the cytoplasm, suggesting it primarily functions as a metabolic enzyme, while LDHA may have additional roles. Therapeutically, some LDHA inhibitors, such as quinoline 3-sulfonamide-based compounds, effectively suppress LDHAα activity, reducing lactate production and glycolysis. However, not all inhibitors exhibit the same efficacy, underscoring the need for isoform-specific strategies. Clinically, elevated levels of LDHAα, LDHA, and c-MYC were observed in colorectal cancer and acute lymphoblastic leukemia, suggesting LDHAα as a valuable biomarker and therapeutic target for these cancers.

Conclusion and future directions

This study provides the first report of LDHAα as a distinct isoform of LDHA with enhanced metabolic and tumorigenic activity. The findings underscore the complexity of cancer metabolism and reveal new opportunities for therapeutic intervention. Targeting LDHAα, particularly through c-MYC and FOXM1 pathways, could offer a promising strategy for cancer treatment. Future research should explore the structural and functional differences between LDHA and LDHAα in greater depth and investigate potential mechanisms driving the alternative transcription of LDHAα. Screening small-molecule inhibitors that

specifically target LDHAα, while minimizing off-target effects on LDHA, may enhance the efficacy and specificity of metabolic-based cancer therapies.

Acknowledgements

The figure was created using BioRender.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

WP drafted the manuscript. SW and DR contributed to the writing and revision of the manuscript. K-TH conceptualized and refined the manuscript.

References

1 Han JH, Lee EJ, Park W, Ha KT & Chung HS (2023) Natural compounds as lactate dehydrogenase inhibitors: potential therapeutics for lactate dehydrogenase inhibitors-related diseases. *Front Pharmacol* **14**, 1275000.
2 Claps G, Faouzi S, Quidville V, Chehade F, Shen S, Vagner S & Robert C (2022) The multiple roles of LDH in cancer. *Nat Rev Clin Oncol* **19**, 749–762.
3 Han JH, Kim M, Choi HJ, Jin JS, Lee SO, Bae SJ, Ryu D & Ha KT (2021) The Oral Administration of Sanguisorba officinalis extract improves physical performance through LDHA modulation. *Molecules* **26**, 1579.
4 Urbańska K & Orzechowski A (2019) Unappreciated role of LDHA and LDHB to control apoptosis and autophagy in tumor cells. *Int J Mol Sci* **20**, 2085.
5 Feng Y, Xiong Y, Qiao T, Li X, Jia L & Han Y (2018) Lactate dehydrogenase a: a key player in carcinogenesis and potential target in cancer therapy. *Cancer Med* **7**, 6124–6136.
6 Cui X-g, Han Z-t, He S-h, Chen T-r, Shao C-h, Chen D-l, Su N, Chen Y-m, Wang T & Wang J (2017) HIF1/2α mediates hypoxia-induced LDHA expression in human pancreatic cancer cells. *Oncotarget* **8**, 24840–24852.
7 Mishra D & Banerjee D (2019) Lactate dehydrogenases as metabolic links between tumor and stroma in the tumor microenvironment. *Cancers (Basel)* **11**, 750.
8 Wang ZH, Peng WB, Zhang P, Yang XP & Zhou Q (2021) Lactate in the tumour microenvironment: from immune modulation to therapy. *EBioMedicine* **73**, 103627.
9 Valvona CJ, Fillmore HL, Nunn PB & Pilkington GJ (2016) The regulation and function of lactate dehydrogenase a: therapeutic potential in brain tumor. *Brain Pathol* **26**, 3–17.
10 Sharma D, Singh M & Rani R (2022) Role of LDH in tumor glycolysis: regulation of LDHA by small molecules for cancer therapeutics. *Semin Cancer Biol* **87**, 184–195.
11 Friberg A, Rehwinkel H, Nguyen D, Pütter V, Quanz M, Weiske J, Eberspächer U, Heisler I & Langer G (2020) Structural evidence for isoform-selective allosteric inhibition of lactate dehydrogenase a. *ACS Omega* **5**, 13034–13041.
12 Qiao T, Xiong Y, Feng Y, Guo W, Zhou Y, Zhao J, Jiang T, Shi C & Han Y (2021) Inhibition of LDH-A by Oxamate enhances the efficacy of anti-PD-1 treatment in an NSCLC humanized mouse model. *Front Oncol* **11**, 632364.
13 Le A, Cooper CR, Gouw AM, Dinavahi R, Maitra A, Deck LM, Royer RE, Vander Jagt DL, Semenza GL & Dang CV (2010) Inhibition of lactate dehydrogenase a induces oxidative stress and inhibits tumor progression. *Proc Natl Acad Sci U S A* **107**, 2037–2042.
14 Billiard J, Dennison JB, Briand J, Annan RS, Chai D, Colón M, Dodson CS, Gilbert SA, Greshock J, Jing J *et al*. (2013) Quinoline 3-sulfonamides inhibit lactate dehydrogenase a and reverse aerobic glycolysis in cancer cells. *Cancer Metab* **1**, 19.
15 Huang B, Shen W, Jia Y, Qin L, Wang H, Sun Q, Xiao Z, Zhang R & Wang H (2025) LDHAα, a lactate dehydrogenase a isoform, promotes glycolysis and tumor progression. *FEBS J* doi: 10.1111/febs.17374