BMC Urology

REVIEW Open Access

# Advancements in research on lactate dehydrogenase A in urinary system tumors

Zhiyuan Zhuo[1†], Yu Wang[1†] and Yifan Xu[1*]

**Abstract**
Tumors of the urinary system, such as prostate cancer, bladder cancer, and renal cell carcinoma, are among the most prevalent types of tumors. They often remain asymptomatic in their early stages, with some patients experiencing recurrence or metastasis post-surgery, leading to disease progression. Lactate dehydrogenase A (LDHA) plays a crucial role in the glycolysis pathway and is closely associated with anaerobic glycolysis in urinary system tumors. Therefore, a comprehensive investigation into the intricate mechanism of LDHA in these tumors can establish a theoretical foundation for early diagnosis and advanced treatment. This review consolidates the current research and applications of LDHA in urinary system tumors, with the aim of providing researchers with a distinct perspective.

## Introduction

Tumors of the urinary system are amongst the most prevalent malignancies, encompassing prostate cancer, bladder cancer, and kidney cancer. Among these, prostate cancer ranks fourth globally in terms of incidence (second among males), while bladder cancer ranks ninth and kidney cancer stands at the 13th position [1]. Despite this, the incidence of these cancers continues to rise annually [2]. Nevertheless, despite the gradual rise in the incidence of tumors in the urinary system, the mortality rate remains alarmingly high. At present, the primary treatment modalities for urological tumors predominantly include early-stage surgery and advanced comprehensive therapy. However, the ultimate goal of fully personalized treatment has not been completely realized. Hence, there is a pressing need for a thorough investigation into the research on various tumor gene expression profiles and the identification of corresponding personalized treatment strategies.

The medical field has recently focused on the application of lactate dehydrogenase A (LDHA). Elevated LDHA levels have been linked to a high tumor burden and are considered both a marker and predictor of poor cancer prognosis [3–5]. In recent years, there has been a growing body of research focusing on LDHA in urological tumors. However, a comprehensive systematic review that consolidates the role and mechanisms of LDHA in urological tumors is currently lacking. As such, this study seeks to elucidate the functions and upstream/downstream mechanisms of LDHA in prostate cancer, bladder cancer, and kidney cancer. By doing so, it aims to offer researchers a more comprehensive understanding and perspective for future investigations in this field.

## The physiological functions of LDHA

Lactate dehydrogenase (LDH) is a nicotinamide adenine dinucleotide (NAD)-dependent enzyme comprised of three subunits, LDHA, LDHB, and LDHC, within the human organism [6]. These subunits have the capacity to

†Zhiyuan Zhuo and Yu Wang contributed equally to this work.

*Correspondence:
Yifan Xu
373659558@qq.com
[1]Department of Urology, Changhai Hospital, Naval Medical University, 168 Changhai Rd, Shanghai 200433, China

assemble into six distinct tetrameric isozymes, distributed across various tissues in the body [7].

LDHA is known to play a critical role in various physiological processes in the human body [6]. It is predominantly found in the cytoplasm, specifically in muscle cells, red blood cells, and certain types of tumor cells. The key function of LDHA is to facilitate the redox reaction between lactate and pyruvate, a vital process that supports energy production and storage [6]. This mechanism is essential for muscle cells to swiftly generate energy during strenuous physical activity and serves as the primary energy source for red blood cells. Thus, LDHA's involvement in cellular metabolism, particularly in energy metabolism, underscores its significant contribution to human health and function.

Furthermore, LDHA is actively involved in the anaerobic glycolysis pathway. In conditions where oxygen is limited, cells rely on glycolysis to generate energy, and LDHA plays a pivotal role in this metabolic process [8]. It facilitates the conversion of pyruvate to lactate, producing NADH, a crucial electron donor for the cellular respiratory chain [9]. This enzymatic activity not only supports energy production but also regulates the balance of NAD+/NADH within the cell, thereby maintaining cellular redox homeostasis [10]. This equilibrium is vital for the stability of cellular metabolism and the efficient production of energy.

Finally, it is worth noting that LDHA shows aberrant expression levels in specific diseases, particularly tumors, making it a promising candidate for disease diagnosis and therapeutic intervention [11]. To conclude, LDHA plays a crucial role in regulating cellular metabolism, energy generation and storage, as well as maintaining redox balance [12]. Its association with the development and advancement of various diseases underscores the physiological and pathological significance of studying LDHA.

In this study, we explored the mechanisms of LDHA in prostate cancer, bladder cancer, and renal cell carcinoma, and illustrated the upstream and downstream molecules of LDHA in Figs. 1 and 2, respectively.

## The role of LDHA as a biomarker in urinary system tumors

Prostate cancer stands as the most prevalent malignancy within the urinary system, prompting a thorough and intricate exploration of LDHA in the context of this disease. In a study dating back to 2015, Xian et al. [13] observe elevated levels of LDHA expression in prostate cancer tissues compared to benign prostatic hyperplasia tissues. Their investigations on cell lines further demonstrated that inhibiting LDHA activity or expression could impact the invasiveness and Warburg effect of tumor cells. These findings suggest the potential of LDHA as a viable therapeutic target for prostate cancer. Moreover, the groundbreaking study by Mane et al. [14] highlights the remarkable potential of depleting LDHA in not only altering the metabolism and tumor microenvironment of prostate cancer but also advancing CAR-T therapy

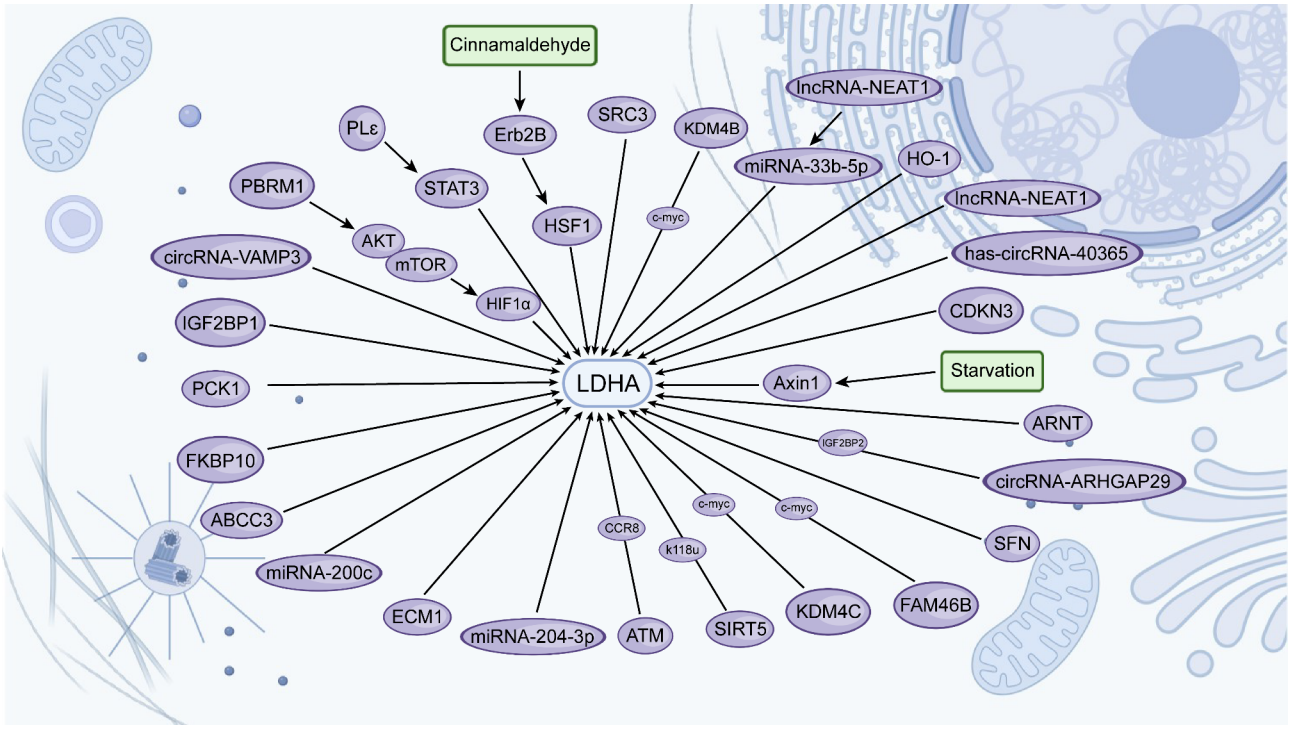


**Fig. 1** Schematic diagram of the upstream mechanism of LDHA

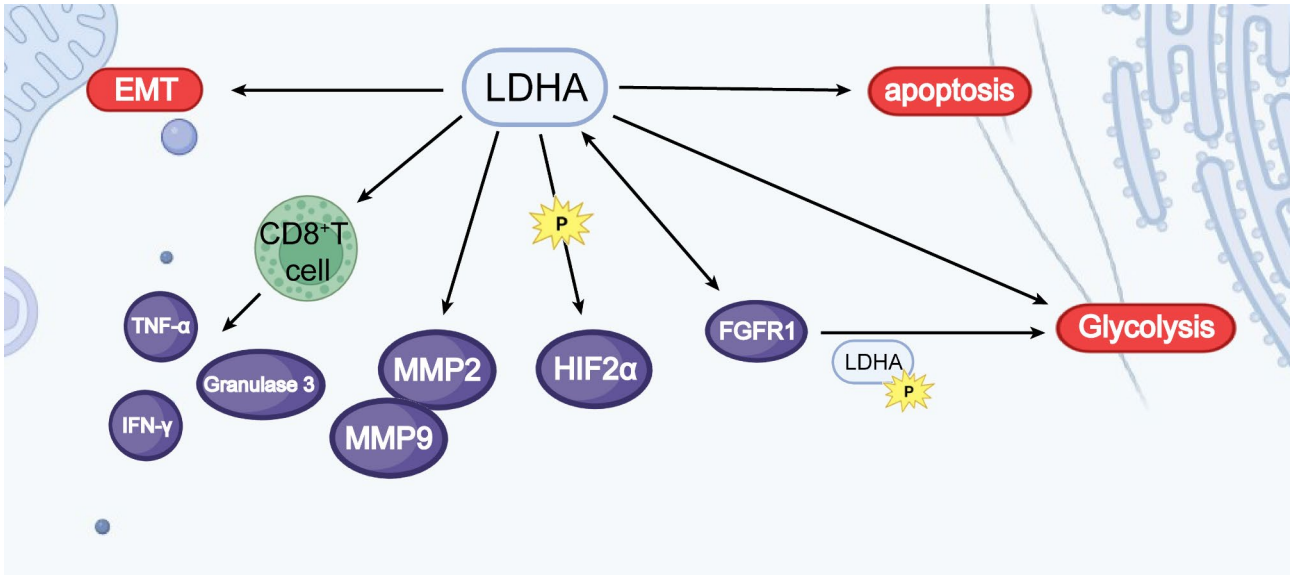


**Fig. 2** Schematic diagram of the downstream mechanism of LDHA

for this malignancy. Castration-resistant prostate cancer (CRPC) denotes a condition wherein prostate cancer continues to advance despite initial hormone deprivation therapy, signifying resistance to hormone treatment. Hiew et al. [15] have recently identified LDH as a dependable prognostic biomarker in advanced CRPC, thus establishing a solid groundwork for further investigations into the role of LDHA in the context of CRPC progression.

It is well established that renal cell carcinoma (RCC) has historically lacked a reliable biomarker, prompting numerous early studies to delve into the search for a distinct biomarker for this disease. White et al. [16] and Song et al. [17] have independently demonstrated through proteomic analyses that LDHA holds promise as a specific biomarker for RCC. Wang et al. [18] have identified a correlation between LDH levels and the prognosis of patients with RCC, delving into the investigation of which gene among LDHA, LDHB, LDHC, and LDHD may serve as a superior marker. Chen et al. [19] delved deeper into the significance of the LDHA to LDHB ratio in ccRCC. Their findings revealed that the LDHA/LDHB ratio served as a standalone predictor of overall survival among ccRCC patients. Moreover, it emerged as a potential player in the pathogenesis of ccRCC, thereby presenting itself as a promising therapeutic target. Concurrently, Girgis et al. [20] have unearthed LDHA as a promising prognostic indicator for ccRCC. In an effort to deepen our comprehension of the biological traits of ccRCC, Soltysova et al. [21] conducted a gene profiling analysis involving 9 cases of ccRCC, 1 case of oncocytoma, and 1 case of renal B-cell lymphoma. Through meticulous experimental validation, they observed a heightened expression of LDHA in the studied cases. In a groundbreaking study, Singer et al. [22] scrutinized the interplay between glucose metabolism and immune cell infiltration in RCC. Their investigation unveiled a notable increase in the expression levels of LDHA and glucose-transporter 1 (GLUT-1) in RCC. Moreover, they identified a negative correlation between LDHA/GLUT-1 levels and CD8+T cell presence. Furthermore, Wu et al. [23] have demonstrated that LDHA combined with CENPE may also serve as a valuable biomarker for chromophobe RCC.

## LDHA regulates the metabolic characteristics of tumor cells in urinary system tumors

Cellular energy dysregulation is a hallmark feature of prostate cancer. Liu et al. (29891507) have conducted a comprehensive study on the impact of fibroblast growth factor receptor 1 (FGFR1) on the energy metabolism of prostate cancer cells by modulating LDHA. Their findings reveal that FGFR1 boosts the stability of LDHA via tyrosine phosphorylation, prompting a transition in cellular metabolism from oxidative phosphorylation to aerobic glycolysis. This metabolic shift amplifies the tumorigenic potential of prostate cancer cells. In their research, Cascardo et al. [24] have showcased the anti-tumor potential of heme oxygenase 1 (HO-1) in prostate cancer cells. Following induction by hemin, HO-1 effectively suppresses LDHA expression and modulates the metabolic landscape of prostate cancer cells. The Warburg phenomenon, also referred to as the "Warburg effect" or "oxygen-consuming effect", denotes the capability of cancer cells to generate energy by breaking down glucose even in conditions of low oxygen levels. Singh et al. [25] have uncovered that sulforaphane (SFN) has the ability to revert the Warburg effect by reducing the

expression of LDHA, thereby exhibiting a preventive effect on prostate cancer. This discovery indicates that sulforaphane could hold promise as a therapeutic option for prostate cancer through the regulation of cancer cell metabolism.

Anaerobic glycolysis stands out as a key metabolic trait of bladder cancer cells. In their research, Cheng et al. [26] discovered that Phospholipase C epsilon (PLCε) is significantly upregulated in bladder cancer tissue and shows a positive correlation with LDHA at the transcriptional level. Their experiments confirmed that PLCε influences the glycolytic activity of bladder cancer cells by acting upstream of LDHA through STAT3 regulation. Hypoxia is a crucial factor in the development of bladder cancer. In a study by Wei et al. [27], they discovered a circular RNA-403,658 that is triggered by hypoxia and is found to be elevated in bladder cancer cells when exposed to low oxygen conditions. By silencing this circular RNA, the researchers were able to suppress LDHA-mediated aerobic glycolysis, ultimately leading to the inhibition of bladder cancer cell growth. In bladder cancer cells, aberrant autophagy and glycolysis are observed. Li et al. [28] revealed that hunger-induced autophagy leads to the degradation of Axin1 and β-Catenin nuclear translocation, subsequently enhancing LDHA regulation of glycolysis, providing new insights into the cellular metabolic changes occurring in bladder cancer. In the context of the Warburg effect, LDHA holds a pivotal position as the ultimate rate-limiting enzyme [29]. Concurrently, Extracellular matrix protein 1 (ECM1) emerges as a malignant contributor in a broad spectrum of epithelial malignancies, bladder cancer being no exception. A pivotal study by Wang et al. [30] revealed a striking correlation between high ECM1 expression in bladder cancer and adverse prognosis. Moreover, upon inhibiting ECM1, a marked reduction in LDHA expression, which is intricately involved in the Warburg effect, was observed, accompanied by a substantial decline in lactic acid production.

Numerous tumor cells, including those in renal cell carcinoma, exhibit heightened glycolytic activity even in oxygen-rich environments. The N6-methyladenosine (m6A) modification has been implicated in the pathogenesis of ccRCC. In their research, Yuan et al. [31] identified the m6A reader IGF2BP1 as a key player in the energy metabolism of ccRCC. This protein enhances mRNA stability by recognizing the m6A modification site on LDHA mRNA, thereby promoting the energy metabolism of ccRCC. Circular RNAs (circRNAs) are thought to play a role in glucose metabolism and the switch to glycolysis. In their study, Li et al. [32] identified circVAMP3 as a circRNA that interacts directly with LDHA. This interaction allows circVAMP3 to regulate LDHA activity through phosphorylation by fibroblast growth factor receptor type 1 (FGFR1), ultimately promoting glycolysis. PBRM1 is frequently mutated in approximately 40% of ccRCC. In a study by Tang et al. [33], the role of PBRM1 in the Warburg effect was investigated. The findings revealed that PBRM1 deficiency results in the upregulation of AKT/mTOR signaling, leading to increased LDHA expression in response to hypoxia-induced elevation of HIF1α levels, ultimately enhancing glycolysis. Similiarly, Ashrafian et al. [34] observed an upregulation of LDHA contributing to the Warburg effect in Hereditary leiomyomatosis and renal cell carcinoma (HLRCC).

## LDHA affects drug resistance in the treatment of urinary system tumors

In addition to its role in regulating tumor cell metabolism, LDHA can exert varying degrees of influence on the treatment outcomes of urological tumors. LDHA has been identified as a factor contributing to radiotherapy resistance in tumor cells. Hao et al. [35] conducted a proteomic analysis revealing increased LDHA expression in tumor tissues of radiotherapy-resistant mice. Their study demonstrated that targeting LDHA in combination with radiotherapy could enhance the radiosensitivity of tumor cells, thus highlighting LDHA as a promising therapeutic target for overcoming radiotherapy resistance. Docetaxel is the established treatment for advanced prostate cancer, and overcoming its drug resistance is a significant clinical hurdle. In a recent study, Jiang et al. [36] examined the aberrant expression of circARHGAP29 through RNA sequencing, which can contribute to drug resistance in prostate cancer cells to docetaxel. CircARHGAP29 can promote the interaction between LDHA mRNA and insulin-like growth factor 2 mRNA binding protein 2, thereby boosting glycolysis metabolism, which suggests that circARHGAP29 could serve as both a prognostic biomarker and a potential therapeutic target for chemotherapy-resistant prostate cancer. Cakici et al. [37] conducted a study to explore the impact of LDHA inhibitors in combination with docetaxel on epithelial-mesenchymal transition in mouse prostate cancer treatment. The findings revealed that the combination therapy led to enhanced tumor cell apoptosis, decreased tumor size, and mitigated the development of docetaxel resistance. Prior research has demonstrated the potential role of long non-coding RNA DANCR (lncRNA-DANCR) in driving prostate cancer progression. Wang et al. [38] delved deeper into its molecular pathways within the context of paclitaxel sensitivity. Their study unveiled a significant upregulation of lncRNA DNCR in paclitaxel-resistant prostate cancer cell lines. This upregulation was linked to the increased expression of LDHA, facilitated by the downregulation of miRNA-33b-5p. Consequently, this mechanism bolstered resistance to paclitaxel.

Aerobic glycolysis emerges as a pivotal player in the progression and development of chemotherapy resistance in bladder cancer, with LDHA standing at the forefront as a critical enzyme orchestrating these processes. Within the ABC transporter family, ATP-binding cassette, subfamily C, member 3 (ABCC3) exhibits robust expression in tumor cells. Liu et al. [39] delved into the functional implications of ABCC3 in bladder cancer, revealing a profound attenuation in tumor cell proliferation and drug resistance following ABCC3 knockout. This observed phenomenon was intricately linked to the downregulation of LDHA expression. In bladder cancer tissues, the cyclin-dependent kinase inhibitor-3 (CDKN3) exhibits a notable overexpression. The findings of Li et al. [40] demonstrate that the downregulation of CDKN3 leads to a suppression of LDHA expression in bladder cancer cells, thereby mitigating glycolysis and effectively converting chemotherapy-resistant cells into a chemotherapy-sensitive phenotype.

## The mechanistic study of LDHA in urinary system tumors

There have been multiple studies conducted on the mechanisms of LDHA, given its status as an enzymatic protein capable of eliciting diverse biological effects at the terminus of signaling pathways, thus rendering its upstream pathways exceedingly intricate.

Chen et al. [41] report that CC-chemokine ligand-18 (CCL18) is capable of increasing the expression of LDHA. Subsequent investigations demonstrated that the deletion of CC-chemokine receptor 8 (CCR8) decreased the carcinogenic potential of CCL18. Furthermore, depletion of the transcription factor ARNT associated with CCR8 significantly attenuated LDHA expression, thus unveiling the CCR8/ARNT/LDHA pathway. Xia et al. [42] discovered that Long noncoding RNA nuclear enriched abundant transcript 1 (lncRNA NEAT1) is capable of upregulating the expression of LDHA in prostate cancer. This modulation ultimately impacts the secretion of CD8+T cells, TNF-α, granzyme B, and IFN-γ, thereby bolstering the antitumor efficacy. In their study, Liang et al. [43] conduct experiments revealing a decrease in the expression of family with sequence similarity 46 member B (FAM46B) in prostate cancer tissues. They observe that prostate cancer cells exhibiting elevated levels of FAM46B exhibited diminished LDHA activity via MYC signaling, ultimately leading to apoptosis. In a study by Chen et al. [44], it was discovered that the knockout of KDM4C effectively hinders the metastatic potential of prostate cancer cells. Through their experiments, the researchers delved into the KDM4C/c-Myc/LDHA signaling axis, highlighting its critical role in driving prostate cancer metastasis. Targeting this specific pathway emerges as a promising strategy for thwarting the progression of metastatic prostate cancer. Sirtuin 5 (SIRT5), an NAD+-dependent desuccinylase, is recognized as a pivotal regulator in numerous types of tumors. Kwon et al. [45] conducted a study revealing a noteworthy decrease in SIRT5 levels in invasive prostate cancer. Through their investigation, it was unveiled that lysine 118 (K118 su) of LDHA acts as a substrate for SIRT5, leading to heightened succinylation of LDHA. This process ultimately amplifies the metastatic potential of prostate cancer. At present, CRPC remains a major clinical challenge. Wu et al. [46] discover that KDM4B, an enzyme responsible for removing the repressive histone mark H3K9me3/2, acts as a transcriptional activator of androgen receptor (AR) and plays a role in the development of CRPC. Their experiments revealed that silencing KDM4B can impede the proliferation of CRPC cells. Moreover, they unveiled a physical interaction between KDM4B and c-Myc, demonstrating that these proteins collaboratively enhance the transactivation of the LDHA promoter in a demethylase-dependent manner, consequently driving the progression of CRPC. ATM serves as a pivotal regulator in the repair of DNA double-strand breaks, yet mutations in ATM are more frequently detected in CRPC. In a study conducted by Xu et al. [47], ATM-deficient CRPC cells were generated using CRISPR/Cas9 editing techniques, revealing a heightened proliferation of these tumor cells. This observed phenomenon was attributed to the upregulation of LDHA expression induced by ATM deficiency.

Likewise, investigators have uncovered intricate interplays between LDHA and other functional proteins in the context of bladder cancer. Guo et al. [48] found that miR-204-3p is reduced in bladder cancer tissues and cell lines and is related to the poor prognosis of patients. They further found that overexpression of miR-204-3p can reduce the lactic acid production of bladder cancer cells. Therefore, they found that miR-204-3p can combine with the 3 'untranslated region (UTR) of LDHA through experimental exploration to reduce the mRNA and protein expression of LDHA. In the context of human bladder cancer, the steroid receptor coactivator-3 (SRC-3) exhibits a frequent pattern of overexpression. Zhao et al. [48] have unveiled a novel mechanism where SRC-3 contributes to the augmentation of bladder cancer growth through the co-activation of HIF1α and glycolysis-related genes, including LDHA. This finding sheds new light on the potential role of SRC-3 in bladder cancer progression. Yuan et al. [49] found that miRNA-200c can inhibit LDHA-induced glycolysis, cell proliferation, and invasion.

The identification of LDHA as a biomarker has sparked significant interest among researchers in exploring the upstream and downstream mechanisms associated with LDHA in RCC. In their studies, Wang et al. [50]

discovered that silencing LDHA could effectively impede the proliferation of renal cancer cell lines. This intervention also elicited alterations in cell cycle and apoptosis-related proteins, ultimately diminishing migration and invasion capabilities by downregulating matrix metalloproteinase (MMP)-2 and MMP-9 levels. Liu et al. [51] uncovered the significant contribution of FK506 binding protein 10 (FKBP10) to the hypoxia and glycolysis pathways in the development of ccRCC. Their experiments revealed that FKBP10 actively facilitates the proliferation and metastasis of ccRCC both in vitro and in vivo. Furthermore, they identified that FKBP10 directly interacts with LDHA via its C-terminal domain, consequently influencing the responsiveness of HIF2α inhibitors. Epithelial-mesenchymal transition (EMT) is one of the important pathways for tumor invasion. Zhao et al. [52] conducted experiments revealing a negative correlation between LDHA and E-cadherin, as well as a positive correlation with N-cadherin in renal cell carcinoma. They demonstrated that the suppression of LDHA effectively inhibits the migration and invasion of renal cancer cells by impeding the EMT pathway. Shi et al. [53] delved into the impact of Phosphoenolpyruvate carboxykinase 1 (PCK1) on the glycolysis phenotype, tumor growth, and metastasis of renal cell carcinoma, both in vitro and in vivo. Their findings revealed a significant association between low PCK1 expression levels and unfavorable prognosis in ccRCC patients. Furthermore, they observed a negative correlation between PCK1 expression and LDHA levels. The researchers confirmed that PCK1 diminishes LDHA stability through post-translational modification. Consequently, targeting the PCK1/LDHA pathway may offer a promising therapeutic approach for ccRCC treatment.

## Research progress on LDHA inhibitors as drug treatment for urological tumors

Currently, LDHA inhibitors are not employed as clinical therapeutics for treating urological tumors. This may be attributed to the potential disruption of normal energy metabolism in patients, as LDHA is a critical enzyme in glycolysis. Nevertheless, research on LDHA inhibitors remains robust in the field of basic science.

Muramatsu et al. [54] investigated the role of LDHA in the treatment of castration-resistant prostate cancer (CRPC) with docetaxel. Their study revealed a synergistic cytotoxic effect when prostate cancer cells were treated with a combination of docetaxel and the LDHA inhibitor sodium oxalate. This combination showed pronounced efficacy specifically in CRPC cells, suggesting that LDHA could provide valuable insights for targeted treatment of CRPC.

Bladder cancer is the second most common type of tumor in the urinary system and is associated with high mortality rates. Early studies have shown that combining an LDHA inhibitor with phenformin in the treatment of bladder cancer can effectively suppress tumor cell growth and reduce the toxicity associated with single-drug treatments [55]. This highlights the significant role of LDHA in the development of bladder cancer. In a groundbreaking study, Aminzadeh et al. demonstrated that combining cinnamaldehyde with chemotherapy in bladder cancer treatment led to a substantial reduction in LDHA protein levels and LDH activity. Their rigorous experimental evaluation confirmed that cinnamaldehyde exerts its anticancer effects by inhibiting the ErbB2-HSF1-LDHA pathway, inducing apoptosis in cancer cells. This discovery presents a promising therapeutic approach in combating bladder cancer.

Xie et al. [56] reported that LDHA inhibitors have the potential to induce apoptosis in tumor cells of HLRCC by generating reactive oxygen species (ROS). Subsequent investigations may be directed towards the advancement of pharmaceuticals that target LDHA, without exclusively focusing on LDHA as the main target. Upstream or downstream proteins could also be identified as crucial therapeutic targets in this context.

## Discussion

As widely recognized, LDHA stands out as a pivotal rate-limiting enzyme within the glycolytic pathway. Given the profound reliance of nearly all tumors on glycolysis, LDHA has garnered significant attention in the sphere of tumor research, encompassing a range of malignancies, including those affecting the urinary system such as prostate cancer, bladder cancer, and renal cell carcinoma. Numerous investigations have underscored aerobic glycolysis as a hallmark feature of urinary system tumors, pointing towards the crucial involvement of LDHA in the initiation and progression of such malignancies. Despite these findings, a comprehensive systematic review delineating the precise role and mechanisms of LDHA in urinary system tumors remains conspicuously absent. Hence, the principal aim of this study is to meticulously elucidate the multifaceted functions of LDHA, thereby offering researchers a fresh and insightful vantage point.

In the realm of prostate cancer research, it is readily apparent that LDHA predominantly governs tumor proliferation, metastasis, drug resistance, metabolism, and the development of androgen independence. A noteworthy observation in our research is the interaction of KDM4B and KDM4C with LDHA in prostate cancer, showcasing distinct roles in CRPC and metastatic prostate cancer via diverse signaling pathways. This highlights the potential for the KDM4 family to have a broad impact on prostate cancer, prompting further exploration into the regulatory functions of additional KDM4 family

members in drug resistance and metabolism within the context of prostate cancer.

In a parallel fashion, the overexpression of LDHA has also been observed in bladder cancer. However, research in this area remains somewhat limited compared to that in prostate cancer. Existing studies predominantly center on aspects such as proliferation, metabolism, and drug resistance in bladder cancer. We have noticed that there are relatively few studies on the role of LDHA in distant metastasis and lymph node metastasis of bladder cancer, which indicates that LDHA may not exert a significant impact on the occurrence of distant metastasis and lymph node metastasis in bladder cancer, potentially attributable to the primary role of metabolism in early and intermediate stages of the disease.

While research on LDHA in RCC has provided valuable insights that can be broadly categorized into three key areas: investigating LDHA as a potential biomarker for RCC, elucidating the regulatory role of LDHA in the metabolic processes of RCC, and exploring the intricate interactions between LDHA and upstream/downstream proteins in the context of this disease. The investigation and research into LDHA as a biomarker in RCC have been thorough and all-encompassing. Researchers began by examining a wide range of biomarkers for RCC, and then proceeded to focus on LDH and D-lactate dehydrogenase before uncovering LDHA. This discovery has led to a more detailed examination of different pathological subtypes of kidney cancer.

When discussing LDHA's role in tumor cell metabolism and the Warburg effect, we cannot overlook other crucial factors involved in tumorigenesis and progression, such as angiogenesis and its connection to oxygen supply in tumor cells [57]. LDHA significantly influences glycolysis in tumor cells, and concurrently, angiogenesis in the tumor microenvironment provides abundant oxygen supply to these cells. This, in fact, presents a pivotal target for tumor-targeted therapy, leading researchers to discover numerous molecules that can predict the efficacy of anti-angiogenic therapies [58]. Moreover, LDHA may exhibit a parallel relationship with other biomarkers used in urological tumors. Numerous studies have demonstrated that LDHA is highly expressed in various tumor cells and can serve as a predictive marker for patient metastasis, recurrence, and prognosis, in conjunction with various other diagnostic indicators, such as urinary cytology for bladder cancer and prostate biopsy [59]. This approach not only enhances the accuracy of biomarkers but also increases their reliability, potentially becoming one of the essential clinical applications in urology in the future.

Lastly, as a potential auxiliary diagnostic method for urological tumors, LDHA, as one of the diagnostic indicators, exhibits a stronger prognostic guiding role. Studies have shown that LDH can serve as an important predictor of prognosis for patients with tumor thrombus [60]. Additionally, the detection of LDHA in serum or urine offers advantages such as non-invasiveness, affordability, and simplicity. When combined with imaging and symptomatic methods, it can better guide patient treatment and prognosis [61].

In conclusion, LDHA exerts diverse regulatory functions in the proliferation, metastasis, metabolism, and drug resistance of prostate cancer, bladder cancer, and renal cell carcinoma. It actively participates in various signaling pathways to elicit specific effects in these malignancies.

#### Author contributions

(I) Conception and design: Yifan Xu (II) Administrative support: Yifan Xu (VI) Manuscript writing: Zhiyuan Zhuo, Yu Wang (VII) Final approval of manuscript: All authors.

#### Funding

Not applicable.

#### Data availability

No datasets were generated or analysed during the current study.

## Declarations

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no competing interests.

Received: 12 June 2024 / Accepted: 22 August 2024
Published online: 30 August 2024

#### References

1. Bray F, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin. 2024;74(3):229–63.
2. Jokhadze N, Das A, Dizon DS. Global cancer statistics: a healthy population relies on population health. Cancer J Clin. 2024;74(3):224–6.
3. Xu K, et al. Glycolysis fuels phosphoinositide 3-kinase signaling to bolster T cell immunity. Volume 371. New York, N.Y.: Science; 2021. pp. 405–10. 6527.
4. Wang X-H, et al. Hypoxia-induced FOXO4/LDHA axis modulates gastric cancer cell glycolysis and progression. Clin Translational Med. 2021;11(1):e279.
5. Jiang Y, et al. KDM6B-mediated histone demethylation of LDHA promotes lung metastasis of osteosarcoma. Theranostics. 2021;11(8):3868–81.
6. Kraus AP, Neely CL. HUMAN ERYTHROCYTE LACTATE DEHYDROGENASE: 4 GENETICALLY DETERMINED VARIANTS. Sci (New York N Y). 1964;145(3632):595–7.
7. Blake NM, et al. Lactate dehydrogenase electrophoretic variant in a New Guinea Highland population. Volume 163. New York, N.Y.): Science; 1969. pp. 701–2. 3868.
8. Shim H, et al. c-Myc transactivation of LDH-A: implications for tumor metabolism and growth. Proc Natl Acad Sci USA. 1997;94(13):6658–63.
9. Miyajima H, et al. Molecular characterization of gene expression in human lactate dehydrogenase-A deficiency. Neurology. 1993;43(7):1414–9.
10. Fantin VR, St-Pierre J, Leder P. Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. Cancer Cell. 2006;9(6):425–34.

11. Siciliano MJ, et al. A human trophoblastic isozyme (lactate dehydrogenase-Z) associated with choriocarcinoma. Cancer Res. 1980;40(2):283–7.
12. Lewis BC, et al. Tumor induction by the c-Myc target genes rcl and lactate dehydrogenase A. Cancer Res. 2000;60(21):6178–83.
13. Xian Z-Y, et al. Inhibition of LDHA suppresses tumor progression in prostate cancer. Tumour Biology: J Int Soc Oncodevelopmental Biology Med. 2015;36(10):8093–100.
14. Mane MM, et al. Lactate dehydrogenase A depletion alters MyC-CaP tumor metabolism, microenvironment, and CAR T cell therapy. Mol Therapy Oncolytics. 2020;18:382–95.
15. Hiew K, et al. Primary mutational landscape linked with pre-docetaxel lactate dehydrogenase levels predicts docetaxel response in metastatic castrate-resistant prostate cancer. Eur Urol Focus. 2019;5(5):831–41.
16. White NMA, et al. Quantitative proteomic analysis reveals potential diagnostic markers and pathways involved in pathogenesis of renal cell carcinoma. Oncotarget. 2014;5(2):506–18.
17. Song Y, et al. Data-independent acquisition-based quantitative proteomic analysis reveals potential biomarkers of kidney cancer. Proteomics Clin Appl. 2017;11:11–2.
18. Wang Y, et al. Prognostic value of D-lactate dehydrogenase in patients with clear cell renal cell carcinoma. Oncol Lett. 2018;16(1):866–74.
19. Chen J, et al. The novel role of LDHA/LDHB in the prognostic value and tumor-immune infiltration in clear cell renal cell carcinoma. PeerJ. 2023;11:e15749.
20. Girgis H, et al. Lactate dehydrogenase A is a potential prognostic marker in clear cell renal cell carcinoma. Mol Cancer. 2014;13:101.
21. Soltysova A, et al. Deregulation of energetic metabolism in the clear cell renal cell carcinoma: a multiple pathway analysis based on microarray profiling. Int J Oncol. 2015;47(1):287–95.
22. Singer K, et al. Warburg phenotype in renal cell carcinoma: high expression of glucose-transporter 1 (GLUT-1) correlates with low CD8(+) T-cell infiltration in the tumor. Int J Cancer. 2011;128(9):2085–95.
23. Wu H-F, et al. CENPE and LDHA were potential prognostic biomarkers of chromophobe renal cell carcinoma. Eur J Med Res. 2023;28(1):481.
24. Cascardo F et al. HO-1 modulates aerobic glycolysis through LDH in prostate cancer cells. Antioxidants (Basel, Switzerland). 2021;10(6).
25. Singh KB, et al. Reversal of the Warburg phenomenon in chemoprevention of prostate cancer by sulforaphane. Carcinogenesis. 2019;40(12):1545–56.
26. Cheng H, et al. PLCε promotes urinary bladder cancer cells proliferation through STAT3/LDHA pathway–mediated glycolysis. Oncol Rep. 2019;41(5):2844–54.
27. Wei Y, et al. Hypoxia-induced circular RNA has_circRNA_403658 promotes bladder cancer cell growth through activation of LDHA. Am J Translational Res. 2019;11(11):6838–49.
28. Li T, et al. Starvation induced autophagy promotes the progression of bladder cancer by LDHA mediated metabolic reprogramming. Cancer Cell Int. 2021;21(1):597.
29. Burns JE, et al. The Warburg effect as a therapeutic target for bladder cancers and intratumoral heterogeneity in associated molecular targets. Cancer Sci. 2021;112(9):3822–34.
30. Wang Z, et al. Extracellular matrix protein 1 (ECM1) is associated with carcinogenesis potential of human bladder cancer. OncoTargets Therapy. 2019;12:1423–32.
31. Yuan B, Zhou J. N6-methyladenosine (m6A) reader IGF2BP1 facilitates clear-cell renal cell carcinoma aerobic glycolysis. PeerJ. 2023;11:e14591.
32. Li J, et al. Circular RNA circVAMP3 promotes aerobic glycolysis and proliferation by regulating LDHA in renal cell carcinoma. Cell Death Dis. 2022;13(5):443.
33. Tang Y, et al. PBRM1 deficiency oncogenic addiction is associated with activated AKT-mTOR signalling and aerobic glycolysis in clear cell renal cell carcinoma cells. J Cell Mol Med. 2022;26(14):3837–49.
34. Ashrafian H, et al. Expression profiling in progressive stages of fumarate-hydratase deficiency: the contribution of metabolic changes to tumorigenesis. Cancer Res. 2010;70(22):9153–65.
35. Hao J, et al. Proteomic identification of the lactate dehydrogenase A in a radioresistant prostate cancer xenograft mouse model for improving radiotherapy. Oncotarget. 2016;7(45):74269–85.
36. Jiang X, et al. EIF4A3-induced circARHGAP29 promotes aerobic glycolysis in docetaxel-resistant prostate cancer through IGF2BP2/c-Myc/LDHA signaling. Cancer Res. 2022;82(5):831–45.
37. Cakici C, et al. LDH-A inhibitor as a remedy to potentiate the anticancer effect of docetaxel in prostate cancer. J Cancer. 2024;15(3):590–602.
38. Wang Y-Y, Chen C. lncRNA-DANCR promotes taxol resistance of prostate cancer cells through modulating the miR-33b-5p-LDHA Axis. Dis Markers. 2022;2022:p9516774.
39. Liu X, et al. Overexpression of ABCC3 promotes cell proliferation, drug resistance, and aerobic glycolysis and is associated with poor prognosis in urinary bladder cancer patients. Tumour Biology: J Int Soc Oncodevelopmental Biology Med. 2016;37(6):8367–74.
40. Li M, et al. CDKN3 overcomes bladder cancer cisplatin resistance via LDHA-dependent glycolysis reprogramming. OncoTargets Therapy. 2022;15:299–311.
41. Chen G, et al. ARNT-dependent CCR8 reprogrammed LDH isoform expression correlates with poor clinical outcomes of prostate cancer. Mol Carcinog. 2020;59(8):897–907.
42. Xia K-G, et al. LncRNA NEAT1-associated aerobic glycolysis blunts tumor immunosurveillance by T cells in prostate cancer. Neoplasma. 2022;69(3):594–602.
43. Liang T, et al. FAM46B promotes apoptosis and inhibits glycolysis of prostate cancer through inhibition of the MYC-LDHA axis. OncoTargets Therapy. 2020;13:8771–82.
44. Lin C-Y, et al. Inhibition of KDM4C/c-Myc/LDHA signalling axis suppresses prostate cancer metastasis via interference of glycolytic metabolism. Clin Translational Med. 2022;12(3):e764.
45. Kwon OK, et al. LDHA desuccinylase sirtuin 5 as a novel cancer metastatic stimulator in aggressive prostate cancer. Proteom Bioinf. 2023;21(1):177–89. Genomics.
46. Wu M-J, et al. Targeting KDM4B that coactivates c-Myc-regulated metabolism to suppress tumor growth in castration-resistant prostate cancer. Theranostics. 2021;11(16):7779–96.
47. Xu L, et al. ATM deficiency promotes progression of CRPC by enhancing Warburg effect. Endocrine-related Cancer. 2019;26(1):59–71.
48. Guo J, et al. MiR-204-3p inhibited the proliferation of bladder cancer cells via modulating lactate dehydrogenase-mediated glycolysis. Front Oncol. 2019;9:1242.
49. Yuan D, et al. MiR-200c inhibits bladder cancer progression by targeting lactate dehydrogenase A. Oncotarget. 2017;8(40):67663–9.
50. Wang X, et al. Inhibition of LDHA deliver potential anticancer performance in renal cell carcinoma. Urol Int. 2017;99(2):237–44.
51. Liu R, et al. FKBP10 promotes clear cell renal cell carcinoma progression and regulates sensitivity to the HIF2α blockade by facilitating LDHA phosphorylation. Cell Death Dis. 2024;15(1):64.
52. Zhao J, et al. LDHA promotes tumor metastasis by facilitating epithelial–mesenchymal transition in renal cell carcinoma. Mol Med Rep. 2017;16(6):8335–44.
53. Shi L, et al. PCK1 regulates glycolysis and tumor progression in clear cell renal cell carcinoma through LDHA. OncoTargets Therapy. 2020;13:2613–27.
54. Muramatsu H, et al. Targeting lactate dehydrogenase–A promotes docetaxel–induced cytotoxicity predominantly in castration–resistant prostate cancer cells. Oncol Rep. 2019;42(1):224–30.
55. Lea MA, Guzman Y, Desbordes C. Inhibition of growth by combined treatment with inhibitors of lactate dehydrogenase and either phenformin or inhibitors of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3. Anticancer Res. 2016;36(4):1479–88.
56. Sourbier C, et al. Proteasome inhibition disrupts the metabolism of fumarate hydratase- deficient tumors by downregulating p62 and c-Myc. Sci Rep. 2019;9(1):18409.
57. Klagsbrun M, Knighton D, Folkman J. Tumor angiogenesis activity in cells grown in tissue culture. Cancer Res. 1976;36(1):110–4.
58. Martini M, et al. VEGF-121 plasma level as biomarker for response to anti-angiogenetic therapy in recurrent glioblastoma. BMC Cancer. 2018;18(1):553.
59. Pierconti F, et al. Methylation study of the Paris system for reporting urinary (TPS) categories. J Clin Pathol. 2021;74(2):102–5.
60. Zhu B, et al. Construction of the prognostic model in non-metastatic renal cancer patients with venous tumor thrombus. Translational Androl Urol. 2023;12(11):1645–57.
61. Pepe P, et al. Multiparametric MRI apparent diffusion coefficient (ADC) accuracy in diagnosing clinically significant prostate cancer. In vivo (Athens Greece). 2017;31(3):415–8.


## Publisher's note