LDHA: The Obstacle to T cell responses against tumor

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Immunotherapy has become a successful therapeutic strategy in certain solid tumors and hematological malignancies. However, this efficacy of immunotherapy is impeded by limited success rates. Cellular metabolic reprogramming determines the functionality and viability in both cancer cells and immune cells. Extensive research has unraveled that the limited success of immunotherapy is related to immune evasive metabolic reprogramming in tumor cells and immune cells. As an enzyme that catalyzes the final step of glycolysis, lactate dehydrogenase A (LDHA) has become a major focus of research. Here, we have addressed the structure, localization, and biological features of LDHA. Furthermore, we have discussed the various aspects of epigenetic regulation of LDHA expression, such as histone modification, DNA methylation, N6-methyladenosine (m6A) RNA methylation, and transcriptional control by noncoding RNA. With a focus on the extrinsic (tumor cells) and intrinsic (T cells) functions of LDHA in T-cell responses against tumors, in this article, we have reviewed the current status of LDHA inhibitors and their combination with T cell-mediated immunotherapies and postulated different strategies for future therapeutic regimens.

KEYWORDS
LDHA, lactate, T cell responses, tumor, metabolic reprogramming

Introduction

Nowadays, a tumor still represents a grave life threat to humanity and has become the leading cause of mortality. The conventional regimens for tumors still rest on surgery, radiotherapy, and chemotherapy, whereas the curative efficiency and efficacy have not been satisfactory (1). Hopefully, immunotherapy, as a new generation of tumor therapy, aims to challenge or mobilize the immune system to control and destroy tumor cells (2).
T cells are a category of crucial components of the immune system, with activated T cells mediating the engagement of the immune system in the elimination of malignant tumor cells. Over the past decades, T cell-mediated immunotherapies, such as immune checkpoint blockade (ICB) therapy and adoptive T-cell therapy (ACT), have gained considerable therapeutic successes in a certain range of solid tumors and hematological malignancies, which promise the dawn for a complete remission of tumors (3). Unfortunately, this immunotherapeutic efficacy is frequently hindered in many other solid tumors. In addition, a wealth of studies have revealed that the immunotherapeutic inefficiency is implicated with cellular metabolic reprogramming of tumor cells and T cells (4).

Cellular metabolic reprogramming determines the functionality and viability of both cancer cells and T cells (5). Metabolic reprogramming, particularly glucose catabolism, is a hallmark of tumors (6). Tumor cells represent a transition in glucose utilization from mitochondrial oxidative phosphorylation to glycolysis, even in the presence of oxygen, to form lactate and ATP, a process known as aerobic glycolysis or the “Warburg effect” (7). This metabolic rewiring commonly results in a nutrient-depleted, acidic, and hypoxic immunosuppressive tumor microenvironment (TME). With respect to T cells, metabolic reprogramming is related to their activation and differentiation. Generally, naive T cells have a low glycolytic level and mainly rely on mitochondrial oxidation of fatty acids (FAO) for energy during the quiescence state. On activation, effector T cells switch to aerobic glycolysis or simultaneously upregulate oxidative phosphorylation to meet the energy and anabolic demands while inhibiting FAO (8). Thus, aerobic glycolysis exerts profound impacts on T cell-mediated antitumor immunity in the TME, as illustrated in the increased glycolytic metabolism in melanoma cells, which explicates the resistance to ACT and ICB (9, 10).

One of the key enzymes involved in glycolysis is lactate dehydrogenase A (LDHA), the catalyst of the conversion of pyruvate to lactate with the oxidation of nicotinamide adenine dinucleotide dehydrogenase (NADH) to NAD+ (11). Current knowledge has established that LDHA is involved in tumor initiation, development, progression, invasion, metastasis, angiogenesis, and immune escape (12). Additionally, LDHA functions as a biomarker for tumor diagnosis and prognosis (11, 12). Accordingly, LDHA has become an attractive target for possible pharmacological approaches in cancer therapy. In this review, we illustrated the LDHA structure, location, and biological features as well as the epigenetic mechanisms of LDHA expression. With a focus on the extrinsic (tumor cells) and intrinsic (T cells) effects of LDHA on T-cell responses against tumors, we reviewed the prevailing studies on LDHA-targeted therapies in order to address the prospect of LDHA inhibitors combined with T cell-mediated immunotherapy as a therapeutic strategy.

The structure, cellular localization, and biological features of LDHA

LDHA is a protein with 332 amino acids, which is encoded by LDHA genes with eight exons located on chromosome 11p15.1 (13). As well acknowledged, LDHA is a constituent subunit (M) of LDH in combination with LDHB subunit (H) to form five active LDH isoenzymes (Figure 1A), i.e., LDH-1 (4H), LDH-2 (3H1M), LDH-3 (2H2M), LDH-4 (1H3M), and LDH-5 (4M) (13). Of note, LDH1 and LDH5 are commonly known as LDHB and LDHA, respectively. LDHA is favored in low-oxygen tissues and is more effective in catalyzing pyruvate to lactate; conversely, LDHB prefers to exist in tissues with a potent aerobic metabolism and preferentially converts pyruvate to acetyl coenzyme A for entry into the tricarboxylic acid cycle (TAC) (14). As validated in a number of studies, the LDHA expression is upregulated in cancer cells (12, 15) in contrast to the approximately intact expression levels of LDHB in normal and carcinomatous tissues (12).

The structure of LDHA subunit has been unfolded (Figure 1B). Its N-terminus possesses a haphazard region formed by 20 amino acids to interact with the C-terminus of an adjacent subunit, a critical clue to the formation of LDH (16, 17). The residues 99-110 form the conformation of a flexible “active site loop,” which is often referred to as the substrate specificity loop and contributes to the LDHA catalysis (18). The well-preserved Arg105 in this loop is responsible for the trapping of adhered pyruvate (19, 20) via contact with nucleotides and substrates for stabilization (21). In addition, the residues 20-162 and 248-266 constitute the larger Rossmann domain, which is characteristic of three parallel β-strands enclosing two α-helices, i.e., the cofactor-binding site (22). At this site, NADH cofactors chiefly bind to four residues (Asp168, Arg171, and Thr246 and the catalytic His195) located in a groove of the central β-sheet (22–25). These residues are significantly involved in the catalytic activity of LDHA owing to the assembly of the geometry of the catalytic sites (22). The residues 163–247 and 267–331 comprise the mixed α/β substrate-binding domain. The substrates, such as pyruvate, interact with three residues (Arg171 and Thr246 along with Ala236) (19). The active site loop, the cofactor-binding site, and the substrate-binding site compose a certain spatial conformation and jointly contribute to the catalysis of LDHA. Consequently, these sites will become the ideal venue for the performance of the inhibitors.

The efforts revealed that the catalytic reaction followed an ordered event. First, NADH binds to the cofactor-binding site with His195. Thereafter, the substrate pyruvate interacts with the substrate-binding site and Arg105. Finally, the active site loop is enclosed to form a desolvated ternary complex, thereby facilitating the hydride transfer (19, 26). Notably, His195...
functions as a proton donor that could transfer a hydride ion from the nicotinamide ring of NADH to the carbonyl C-atom of the pyruvate, ultimately triggering a reaction to complete the oxidation of NADH to NAD\(^+\) and the release of NAD\(^+\) and lactate (27, 28).

LDHA is located also in the cytoplasm, mitochondrial matrix, and nucleus (12, 29, 30). In the liver, LDHA is mostly present in the mitochondrial matrix, whereas it is mainly localized in the cytoplasm of cancer cells (31, 32). However, regardless of its presence in the mitochondria or cytoplasm,
LDHA is mainly implicated in glycolysis (12, 29). In the nucleus, LDHA is likely involved in DNA duplication and transcription via its function as a single-stranded DNA-binding protein (SSB) (30). Another report described that nuclear LDHA induced the production of α-hydroxybutyrate and disruptor of telomeric silencing 1-like (DOT1L)-mediated histone H3K79 hypermethylation in a noncanonical manner of enzyme activity (33). These findings illuminate the avenue to elucidate the novel role of LDHA in the body.

The epigenetic regulation of the LDHA expression

With the discovery of LDHA, the mechanisms underlying its expression have been extensively mined. The details of regulatory mechanisms, such as transcription factors and posttranslational modification regulations, have been summarized (34, 35). In the section below, we focused on the LDHA expression profiles from the perspective of epigenetic modifications, such as histone modification, DNA methylation, N6-methyladenosine (m6A) RNA methylation, and noncoding RNA (Figure 2).

Histone modification

Histones are the basic structural proteins of eukaryotic chromosomes. The N-terminal amino tail of core histone can undergo posttranslational modifications, including methylation, acetylation, phosphorylation, glycosylation, and ubiquitination, which affect gene transcription (36).

Histone methylation is a modification primarily in arginine and lysine, which is a reversible process regulated by histone methyltransferase (lysine methyltransferase, arginine methyltransferase) and histone demethylase to jointly affect the expression of target genes (36). Jumonji domain-containing protein 2A (JMJD2A) is a histone demethylase. In patients with nasopharyngeal carcinoma (NPC), the JMJD2A level was reported to be positively correlated with the LDHA expression (37), further demonstrating the JMJD2A-regulated LDHA expression at the level of transcription by the combination with the LDHA promoter region (37). Histone acetylation is also a modification dynamically regulated by histone acetyltransferase and histone deacetylase (HDAC), which plays a pivotal role in nucleosomal assembly, structural maintenance of chromatin, and gene transcription (36). Furthermore, histone deacetylase sirtuin 6 (SIRT6) negatively regulates the main glycolytic genes including LDHA (38). In nasal polyp fibroblasts, the decreased expression of SIRT6 resulted in the upregulation of LDH (39).

With respect to the effects of other histone modifications on the LDHA expression, further work is needed.

DNA methylation

DNA methylation is a process in which the DNA methyltransferase (DNMT) utilizing S-adenosylmethionine
study revealed that the writer METTL3 enhanced the expression including methyltransferases (writers), demethylases (erasers), and of LDHA (49). Mechanistically, the coding sequence (CDS) of methylation-binding proteins (readers) (48). To date, only one untranslated region (5′-UTR) or 3′-UTR. Then, METTL3 induced the LDHA transcription via the stabilization of the mRNA of hypoxia-inducible factor (HIF)-1α, further enhancing the YTH domain-containing family protein 1 (YTHDF1)-mediated translation of LDHA (49). However, more efforts are needed to elucidate the regulatory effect of the m6A modification of LDHA.

**Noncoding RNA**

Noncoding RNA refers to RNA that can be transcribed but cannot encode protein, including microRNAs (miRNAs), circular RNAs (circRNAs), and long noncoding RNAs (lncRNAs). Among them, miRNAs with a length of approximately 20–22 nucleotides function as crucial regulators of the gene expression by binding to the 3′-UTR of the target mRNA to inhibit the translation or promote the mRNA degradation (50). Until now, emerging evidence has confirmed the roles for miRNAs in the regulation of LDHA. In colorectal cancer, several miRNAs, such as miR-34a/c, miR-369-3p, miR-374a, and miR-4524a/b, directly bound the 3′-UTR of the mRNA of LDHA to inhibit the LDHA expression (51). Interestingly, there is a point mutation in the 3′-UTR of LDHA (rs18407893 at 11p15.4) in HCT116 colon and BxPC3 pancreatic cancer cells as well as four of 30 samples Aspire of colorectal cancer tissues. This mutation eliminated the binding of miR-374a (51). In addition, miR-200c, miR-449a, miR-30d-5p, miR1271, miR-142-3p, and miR-383 also directly regulated LDHA in different tumors (52–57). Indeed, miR-200c in bladder cancer and miR-449a in non-small-cell lung cancer cell lines were downregulated, enhancing the LDHA level (52, 53). Moreover, several miRNAs (including miR-92-1) indirectly govern the LDHA expression by stabilizing the HIF-1α (58, 59).

**circRNAs**

circRNAs are another kind of noncoding RNA and are also involved in the regulation of the LDHA expression. A study unveiled that circSLC25A16 interacted with miR-488-3p/HIF-1α to activate LDHA by promoting its transcription in non-small-cell lung cancer (60). Likewise, circ-CNST/miR-578 and circATRNL1/miR-409-3P regulated LDHA in osteosarcoma (61, 62). In pancreatic ductal adenocarcinoma (PDAC), circSLIT2 functioned as a miRNA sponge to target the miR-510-5p/c-Myc axis to activate the transcription by binding to the promoter region of LDHA (63). In addition, circPDCD11 enhanced the LDHA expression by sponging miR-432-5p in triple-negative breast cancer (64). In brief, circRNAs functioned as a miRNA sponge to promote the LDHA expression.

Long noncoding RNAs (lncRNAs) are an important subset of noncoding RNAs, which are the key regulators of gene expression. Recent research authenticated that LINCO1207 interacted with miR-1301-3p, the immediate upstream of LDHA (65). In gastric cancer, lncRNA-HAGLR sponged miR-338-3p while LDHA was the direct target of miR-338-3p (66). Additionally, a recent study demonstrated that lncRNA-NEAT1 sponged miR-410-3p to downregulate its expression, thereby inhibiting LDHA in intestinal epithelial cells (IECs) (67).

**The extrinsic (tumor) and intrinsic (T cells) effects of LDHA on T-cell responses to tumors**

The effect of lactate dehydrogenase A in tumor on T-cell responses

Numerous studies have confirmed the elevated LDHA levels in several different cancer types and highly expressed LDHA-
mediated tumor immune escape by inhibiting immune killing and promoting immunosuppression (12, 68). In tumor cells, LDHA catalyzes the conversion of pyruvate to lactate, then excessive intracellular lactate is excreted from the cytoplasm by monocarboxylate transporters (MCTs) into the TME, thus resulting in an extracellular acidic microenvironment. Researchers have proposed that the LDHA-lactate-acidic microenvironment can establish a barrier for the T-cell response (Figure 3A). The T-cell response is dependent on antitumor effector cells including CD4+ and CD8+ cells, which orchestrate and perform the antigen-specific killing of cancer cells, respectively. CD4+ T cells comprise numerous subsets, such as T helper 1 (Th1) cells that possess a significant antitumor activity and regulatory T (Treg) cells that have an immunosuppressive role and protect tumor cells from other killer cells. CD8+ cells are critically important in direct killing of tumor cells via the induction of apoptosis and cytokine secretion [interferon (IFN)-γ, granzyme B].

LDHA in tumors negatively affects the immune cell infiltration (9, 69). In a mouse model of melanoma and pancreatic tumor with low or null LDHA, the infiltration and activation of CD8+ T cells and NK cells were enhanced, and these infiltration cells produced the increased IFN-γ and granzyme B (69, 70). Similar results have been found in breast tumors that the shRNA-mediated reduction of LDHA enhanced the infiltration of CD3+ and CD4+ T cells (71). Additionally, LDHA was negatively associated with the T-cell activation markers (granzyme K and CD25) in human melanoma (69). Moreover, the infiltration of Treg cells was attenuated (70). However, a study reported that renal cell carcinoma (RCC) with a high expression of LDHA showed significant multiplication of T cells (including CD3+, CD8+, and Foxp3+ T cells) and decreased effector molecules (granzyme B and perforin) in these tumor-infiltrating T cells (72), suggesting that RCCs are infiltrated by functionally inactive cytotoxic T cells. These findings indicate that the modulation by LDHA has more effect on the activity than on the population of T cells.

![Figure 3](https://example.com/figure3.png)

**Figure 3**
The extrinsic and intrinsic roles of lactate dehydrogenase A (LDHA) in T-cell responses to tumors. (A) In the tumor, LDHA catalyzed the conversion of pyruvate to lactate; then, intracellular excessive lactate was excreted from the cytoplasm by MCT into the TME, thus resulting in an extracellular acidic microenvironment with a low pH. The LDHA-lactate-acidic microenvironment established a barrier for T-cell response. MCT, monocarboxylate transporter; TME, tumor microenvironment. (B) In activated T cells, when naive T cells were activated with anti-CD3 and anti-CD28, the TCR signaling promoted the activation of PDHK1, suppressing the mitochondrial import of pyruvate. Meanwhile, the TCR induced the LDHA expression through PI3K/AKT signaling in activated T cells, then catalyzed lactate production. LDHA deficiency in CD4+ T cells impaired the cell activation and proliferation and the Th17 cell differentiation mediated by the defective termination of the AKT-regulated Foxo1-dependent gene expression program. In CD8+ T cells, LDHA deficiency resulted in defective cell expansion via impairment of AKT and Foxo1 phosphorylation. Moreover, the LDHA inhibition combined with IL-21 promoted the differentiation into TSCM. PDHK1, pyruvate dehydrogenase kinase 1; PI3K, phosphoinositide 3-kinase; TSCM, T memory stem cells.
The regulatory effect of LDHA on immune escape by infiltrating T cells is mainly dependent on the excessive lactate secretion from tumor cells to the TME, which might reach levels of up to 10–40 mM over 10 times greater than physiological lactate concentrations (73). High lactate levels could increase Treg cells through a lactate-based nuclear factor (NF)-κB activation and FoxP3 expression as well as drive Foxp3 metabolically reprogrammed T cells to allow Treg cells to work efficiently (74, 75). Furthermore, Treg cells actively absorbed lactate via MCT1 and promoted the expression of programmed death 1 by enhancing the nuclear factor of activated T cell (NFAT)-1 translocation into the nucleus (76). Moreover, lactate attenuated the differentiation of the antitumoral Th1 subset by triggering the SIRT1-mediated transcription factor T-bet deacetylation (77), while sodium lactate induced the Th1 differentiation (77). In acute myeloid leukemia (AML), lactate induced the exhaustion of CD8+ T cells by altering the lytic granule exocytosis and promoting a higher PD-1 expression (81, 82). Moreover, lactic acid blunted the proliferation, degranulation, motility, and expression of effector molecules (IFN-γ, granzyme, and perforin) (83–85). Mechanically, lactic acid impaired the TCR-triggered phosphorylation of p38 and c-Jun N-terminal kinase/c-Jun in Cytotoxic T lymphocytes, which is involved in IFN-γ production (84). Another study reported that lactic acid prevented the translation of IFN-γ by allowing GAPDH to bind to IFN-γ mRNA (77, 86). Therefore, the CTL function could be restored after treatment with lactate-free medium (83). The acidification of the TME also decreased the IFN-γ production by downregulating the NFAT in T and NK cells, triggering a tumor immune escape (69). Similarly, acidic conditions impaired the antitumor immunity by disturbing the calcineurin-mediated nuclear translocation of NFAT (87). The pH values within the TME mostly decrease between 6.0 and 7.0,

![Diagram](image-url)

**FIGURE 4**
The different strategies of the combination therapy with the lactate dehydrogenase A (LDHA) inhibitor and T-cell immunotherapy. ① Targeting the inhibition of LDHA in the tumor and regulating the tumor microenvironment to increase the T-cell antitumor response. ② Targeting LDHA in T cells to enhance the efficacy of the adoptive T-cell therapy. ③ Simultaneous treatment of tumor cells and T cells with LDHA inhibitors to enhance the antitumor efficacy.
but the lowest pH could reach 5.6 (88, 89). The reduced extracellular pH impaired almost all aspects of the CD8+ and CD4+ lymphocyte function: activation, cytotoxicity, chemotaxis, motility, and proliferation (89–91). Furthermore, lactate and decreased pH showed a synergistic effect on T cells by inducing apoptosis after 24 h and reducing the IFN-γ and IL-2 production (83). Numerous studies have proven that neutralization of the acidic TME with proton pump inhibitors or bicarbonate can restore T-cell function to improve antitumor responses to immunotherapy (91, 92).

In summary, the LDHA-lactate-acidic microenvironment establishes a barrier not only for T-cell numbers but also for T-cell responses. As the initiator, LDHA is a promising target for immunotherapy.

The effect of LDHA in T cells on T-cell responses

It is instructive to note that aerobic glycolysis is a hallmark of activated T cells, which indicates the intrinsic role of LDHA in T-cell responses (Figure 3B). When naïve T cells were activated with plate-bound anti-CD3 and anti-CD28, TCR signaling promoted the activation of pyruvate dehydrogenase kinase 1 (PDHK1), suppressing the mitochondrial import of pyruvate (93). Meanwhile, TCR induced the LDHA expression through the phosphoinositide 3-kinase (PI3K)/AKT signaling in activated T cells and then catalyzed the lactate production (94, 95). Indeed, LDHA induced the immature thymocyte antigen-1 (IMT-1) expression from the cytoplasm to the cell surface membrane during the thymocytic differentiation, the process of which is critical for the selection of thymocytes (96). However, LDHA deficiency in CD4+ T cells did not affect the thymic development of Treg cells or T-cell homeostasis (97). Furthermore, LDHA deficiency impaired the T-cell activation, proliferation, and migration and the Th17 cell differentiation partly mediated by the defective termination of the Akt-regulated Foxo1-dependent gene expression program (95). LDHA promoted IFN-γ expression by maintaining high levels of acetyl coenzyme A to enhance the histone acetylation and transcription of IFN-γ but not via a 3′-UTR-dependent mechanism of translation in vivo (97). In addition to CD4+ T cells, LDHA deficiency resulted in a defective CD8+ T cell expansion and differentiation by impairing the Akt and Foxo1 phosphorylation (94). Moreover, LDHA regulated the differentiation of CD8+ T-cell effectors into T memory stem cells (Tscm). LDHA inhibition combined with IL-21 in vitro promoted the formation of Tscm with increased antitumor activity in vivo after adoptive transfer (98).

Taken together, the above evidence indicates that targeting LDHA to modulate the effector functions of T cells in antitumor responses is an efficient strategy for immunotherapy.

Combining LDHA inhibitors with T cell-mediated immunotherapy

In the light of the important role of LDHA in oncology, selective LDHA inhibition can be deemed as a potentially safe target. To date, significant progress has been achieved in the discovery and development of selective small-molecule LDHA inhibitors. Recently, there are more researchers who reviewed the state of the LDHA inhibitors (99–103). Albeit the inhibitors with a promising antitumor activity both in vitro and in vivo have been revealed, none of them showed any real clinical benefit. Only one phase III clinical trial of gossypol combined with docetaxel and cisplatin scheme in advanced non-small-cell lung cancer with apurinic/apyrimidinic endonuclease 1 high expression was conducted by the Third Military Medical University (ClinicalTrials.gov Identifier: NCT01977209). The purpose of this study was to find out whether gossypol can improve the sensitivity of the cisplatin-based chemotherapy. However, no study results were posted for this study (Source of information: ClinicalTrials.gov). This is probably due to some reasons: one is that very few clinical applications associated with LDHA inhibition until the relationships between LDHA and aerobic glycolysis were recently discovered. Another reason is that a high serum LDHA is only considered as a robust biomarker of a poor prognosis (103). Meanwhile, the nature of the LDHA structure has not been understood for a long time (102). Moreover, the highly unspecific toxicity or the limited membrane permeability of inhibitors is also a limiting factor (100). Therefore, a progressive increase in the discovery of new LDHA inhibitors with improvement in selectivity, inhibitory activity, low toxicity, and delivery is hopefully accessible in the clinic soon.

Given the role of LDHA in T-cell responses, the combination of LDHA inhibition with T cell-mediated immunotherapy holds promise to patients with tumors. The combination of LDHA depletion with anti-human prostate-specific membrane antigen (hPSMA)-Chimeric antigen receptor T cell therapy could significantly retard tumor growth (104). Moreover, a recent study reported that the shRNA-mediated blockade of LDHA improved the efficacy of anti-PD-1 therapy by enhancing T-cell infiltration in melanoma (70). ML-05 is a novel potent LDHA inhibitor. In a mouse model of B16F10 melanoma, intratumoral injection of ML-05 significantly suppressed tumor growth and released an antitumor immune response of T-cell subsets (Th1 and GMZB+CD8 T cells) in the TME. Furthermore, ML-05 treatment combined with anti-PD-1 antibody or stimulator of interferon genes protein (STING) could enhance the antitumor activity in the B16F10 melanoma model (105). Unfortunately, the clinical success of treatment strategies that combine LDHA inhibitor with T cell-mediated immunotherapy is lacking.
Current challenges and future directions

Cellular metabolic reprogramming, such as aerobic glycolysis, is a marked feature of tumor cells and immune cells in the TME. As an enzyme that catalyzes the final step of glycolysis, LDHA is the focus of research. In this review, we recapitulated the LDHA structure, location, and biological features as well as the epigenetic mechanisms of the LDHA expression. However, the literature regarding how epigenetic modifications regulate LDHA expression is limited. Moreover, most of the data from the above studies were identified in tumor cells, while evidence in other cells such as immune cells is deficient.

Furthermore, we summarized the extrinsic (tumor cells) and intrinsic (T cells) effects of LDHA on T-cell responses to tumors. The LDHA-lactate-acidic microenvironment established a barrier not only for T-cell populations but also for T-cell responses. Moreover, some small-molecule LDHA inhibitors play a marked effect on tumor burden, metastases, and cell death. However, few studies have evaluated the response changes of immune cells in the context of LDHA inhibitors in tumor treatment.

In this review, we also summarized the current studies of the combination therapy with LDHA-targeted therapies and T cell-mediated immunotherapy. However, these studies are designed for animal tumor models, and few clinical trials are designed to assess the therapeutic efficacy of combined therapy. Thus, further studies to elucidate the clinical efficiency of the combined treatment will be appreciated. It is worth noting that in the clinical trial of LDHA inhibitors combined with T-cell immunotherapy, a variety of different strategies should be adopted to enhance the efficacy, such as targeting the inhibition of LDHA in tumors and regulating the TME to increase the T-cell antitumor response, targeting LDHA in T cells to enhance the efficacy of ACT, and simultaneous treatment of tumor cells and T cells with LDHA inhibitors to enhance the antitumor efficacy (Figure 4).

Author contributions

YT and SG drafted the original manuscripts. SG provided some constructive comments on the revision of the manuscripts. LZ and WZ reviewed and edited the manuscript. CZ guided on the structure of the manuscript. WZ provided the funding. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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