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Role of LDH in tumor glycolysis: Regulation of LDHA by small molecules for cancer therapeutics

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ABSTRACT

Lactate dehydrogenase (LDH) is one of the crucial enzymes in aerobic glycolysis, catalyzing the last step of glycolysis, *i.e.* the conversion of pyruvate to lactate. Most cancer cells are characterized by an enhanced rate of tumor glycolysis to ensure the energy demand of fast-growing cancer cells leading to increased lactate production. Excess lactate creates extracellular acidosis which facilitates invasion, angiogenesis, and metastasis and affects the immune response. Lactate shuttle and lactate symbiosis is established in cancer cells, which may further increase the poor prognosis. Several genetic and phenotypic studies established the potential role of lactate dehydrogenase A (LDHA) or LDH5, the one homo-tetramer of subunit A, in cancer development and metastasis. The LDHA is considered a viable target for drug design and discovery. Several small molecules have been discovered to date exhibiting significant LDHA inhibitory activities and anticancer activities, therefore the starvation of cancer cells by targeting tumor glycolysis through LDHA inhibition with improved selectivity can generate alternative anticancer therapeutics. This review provides an overview of the role of LDHA in metabolic reprogramming and its association with proto-oncogenes and oncogenes. This review also aims to deliver an update on significant LDHA inhibitors with anticancer properties and future direction in this area.

1. Introduction

Cancer is a complex and multi-step process including cell proliferation, invasion, angiogenesis, cell death resistance, and immune evasion, mainly caused by genomic instability [1–3]. Bioenergetics of cancer cells are largely different from normal cells and their reliance on aerobic glycolysis increases research interest in the area of tumor glycolysis and the development of new glycolytic inhibitors [4,5]. Most cancer cells follow reprogrammed glycolytic phenotype uncoupled with oxidative phosphorylation, which was first hypothesized by Otto Warburg in 1927, known as the "Warburg effect" (Fig. 1). He hypothesized that cancer cells preferentially consume glucose which is then catabolized into lactate through pyruvate whereas in normal cells it is catabolized into CO_2 and energy which is essential for cellular functioning [6,7]. Since then, cancer cell metabolism has attracted significant attention for the identification of potential targets and drug-like candidates to target cell metabolism [6,8,9]. Cancer cells are highly characterized by an enhanced rate of tumor glycolysis to ensure the high energy demand and essential metabolites for fast-growing cancer cells. An elevated rate of tumor glycolysis confirms the avidity of high consumption of glucose leads to excess production of lactate and less adenosine triphosphate (ATP) production in cytosol [10,11]. Besides, in normal cells, glycolysis is composed of ten successive steps, and the end product of glycolysis "pyruvate" is then entered into mitochondria for energy production through the TCA cycle (Fig. 1). If pyruvate does not enter into the TCA cycle, it produces less energy as per glucose molecules through

Abbreviations: LDHA/B, lactate dehydrogenase **A/B**; ERRB2, human epidermal growth factor receptor 2 (HER2)/erythroblastic oncogene B; CPTII, carnitine palmitoyltransferase II; PDAC, pancreatic-ductal-adenocarcinoma; KLF4, Kruppel-like factor 4; ErbB2, epidermal growth factor receptor 2; HSF1, Heat-shock factor 1; FOXM1, Forkhead box protein M1; K118su, lysine 118 succinylation; SIRT5, Sirtuin 5; NSCLC, non-small cell lung cancer; GPR81, G-protein-coupled receptor; NFAT, nuclear factor of activated T cells; TEM, transmission electron microscopy; ITGC, intestinal-type gastric cancer; GBM, human glioblastoma; NPC, nasopharyngeal carcinoma; CDK1, Cyclin-dependent kinase1; BMSCs, Bone marrow stromal cells; PPIs, protein-protein interactions; NHI, *N*-hydroxyindoles; OSCC, Oral Squamous Cell Carcinoma; LSCC, laryngeal squamous cell carcinoma.

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reprogrammed glycolysis [9,12]. The catalytical role of LDH under hypoxic conditions is to regenerate NAD^+ molecules which is essential to maintain glycolysis for continuous ATP production [13,14]. Lactate formation under hypoxic conditions attained by high glycolytic activity, resulting lactate is then converted into pyruvate by lactate dehydrogenase B (LDHB) for further metabolic processes. In cancer cells, the enhanced rate of tumor glycolysis is controlled by overexpressed transporters, enzymes including LDH, and cofactors. The pyruvate is reduced to lactate which is catalyzed by LDHA closely associated with hypoxia-inducible factor 1 (HIF-1) [15–17], coupled with oxidation of NADH to NAD^+ essential for the maintenance of high glycolytic flux [18,19]. Restoration of NAD^+ in cancer cells is not only beneficial to pyruvate reduction to lactate together with H^+ production but also facilitates lactate secretion to the microenvironment *via* monocarboxylate transporters (MCT) leading to decreased pH in the extracellular environment [20]. This biochemical phenomenon plays an important role in oncogenesis by enhancing the activity of pro-invasion factors and inducing invasion, immunosuppression, angiogenesis, and metastasis resulting in poor prognosis in cancers [21–24]. As well, NAD^+ serves as a cofactor in various redox reactions related to cell metabolism and acts as a substrate for different signaling enzymes including sirtuins, PARPs, and cADPRSs where degradation and cleavage of NAD^+ occur into ADP ribose and nicotinamide (NAM) [25]. Lactate formed in cancer cells through tumor glycolysis, is then transported outside the cells, and is further consumed by cancer cells for energy production mediated by oxidative mitochondrial metabolism and for amino acid formation [26]. Therefore, cancer cells established lactate shuttle by taking the advantage of overexpression of two MCT isoforms *i.e.* MCT1 and MCT4 widely expressed in cancer cells. Both MCT1 and MCT4 are bidirectional proton-linked transporters, however, MCT4 preferred lactate export and MCT1 preferred lactate import [27,28]. Wide literature suggests that LDH plays a significant role in cancer progression, survival, invasion angiogenesis, and metastasis *via* tumor glycolysis, and lactate shuttle and is considered a viable target for drug development (Fig. 2).

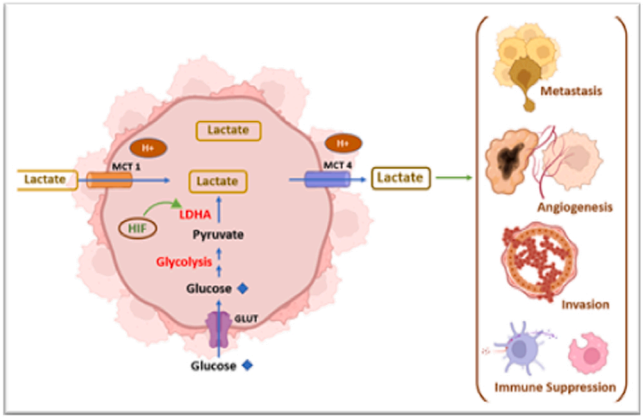

Fig. 2. Lactate; end product of glycolysis, its transportation through MCT and its involvement in metastasis, angiogenesis, invasion and in immune suppression.

1.1. LDH isoforms and their tissue distribution

LDH is a redox enzyme with a molecular weight of 134 kDa, consists of four peptide chains exist in two forms; LDH A (M) predominately found in skeletal muscle and liver, and LDHB (H) found in heart muscles, brain, spleen, kidney, and erythrocytes. LDHA and LDHB chains are both encoded by separate genes *ldha* and *ldhb* respectively (Fig. 3) [29,30]. LDH exists in five different isoforms *i.e.* LDHA1–5 (LDH1, LDH2, LDH3, LDH4, and LDH5) by various possible combinations of LDHA and LDHB subunits and is majorly expressed in the cytosol. Among these, only two LDH1 and LDH5 are homo-tetramers, LDH1 is comprised of four subunits of LDHB (LDH1; B4 or H4) and LDH5 is composed of four subunits of LDHA (LDH5; A4 or M4), (Fig. 3). Except for these, the other three enzymes LDH2, LDH3, and LDH4 are hetero-tetramers. Moreover, the sixth isoform LDHC (LDHX or LDHC4) is majorly found in human testis and sperm thus implicated in male fertility. LDH catalyzes the redox reaction, where the forward reduction reaction (conversion of pyruvate to lactate) is catalyzed by LDHA and LDHB catalyzes the backward oxidation reaction (conversion of lactate to pyruvate) [30,31].

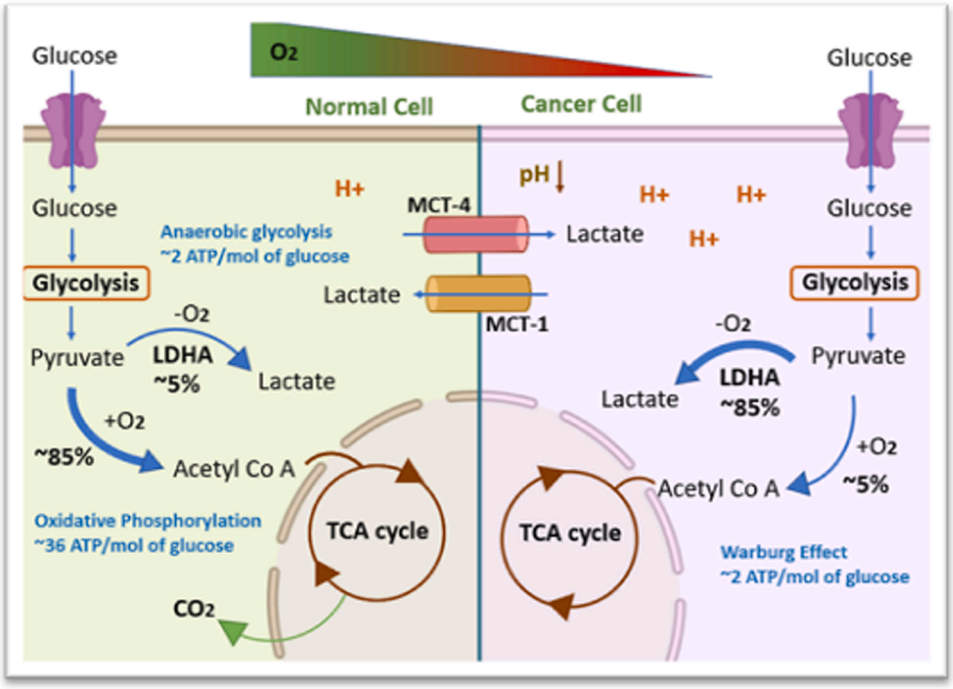

Fig. 1. Glycolysis- energetic difference of normal cell *vs* cancer cell.

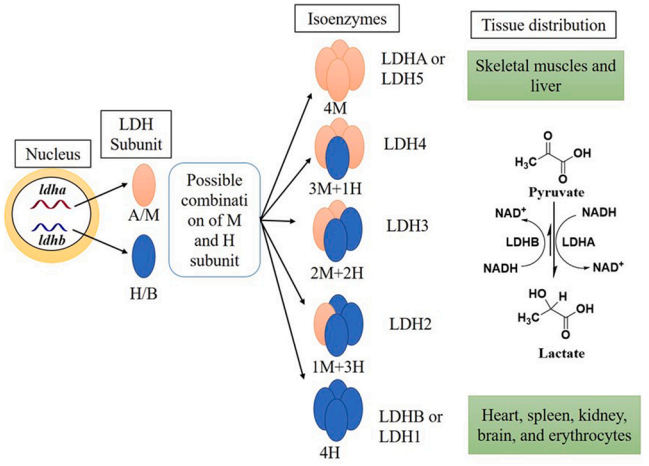

Fig. 3. Tumor glycolysis and LDH isoforms: (A) Homotetramers-LDH1 (red) and LDH5 (blue); (B) heterotetramers. LDH2, LDH3, LDH4; The LDH2 enzyme is compiled of one subunit of LDHM and three subunits of LDHH, the LDH3 is composed of two subunits of LDHM and two subunits of LDHH, and the LDH4 is made up of three subunits of LDHM and one subunit of LDHH.

1.2. LDHA linked with transcription factors, and cancer

Genetically, LDHA is closely associated with various human metabolic cancer including pancreatic [32], laryngeal squamous cell carcinoma (LSCC) [33], head and neck [34], renal [35], gastric [36], prostate cancer [37], breast [38], hepatocellular [39], Oral Squamous Cell Carcinoma (OSCC) [40], and cervical cancer [41,42]. Extensive literature data confirmed that the LDHA inhibition showed a reduction in tumor proliferation in various cancers such as head and neck, pancreatic, cervical ad prostate cancer, and others [32,34,37,41,42]. Inhibition of LDHA reduces the migration of cancer cells, invasion, angiogenesis, and cancer metastasis. Moreover, LDHA inhibition increases sensitivity to chemotherapy and radiotherapy in resistant cancer cells [43–46]. The tamoxifen resistance was closely linked with a reduced level of ATP production and elevated rate of tumor glycolysis resulting in induced autophagy to ensure the energy requirement in breast cancer [45]. Further, genetic and pharmacological inhibition of LDHA showed a reduction in pro-survival autophagy mediated by restoration of apoptosis and epithelial-to-mesenchymal transition (EMT) in tamoxifen-induced resistant breast cancer cell lines, this might offer to develop a new strategy to treat tamoxifen resistance by targeting LDHA in breast cancer [47]. The triple-negative breast cancer (TNBC), where hormone receptors (such as endrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER2)/erythroblastic oncogene B (ERRB2)) are absent, showed an abundance release of lactic acid, under all normoxic, hypoxic, and hyperoxic conditions leading to sustains acidosis which promotes metastatic invasion and malignant aggressiveness. However, LDHA silencing alone was not effective to interrupt lactic acid production [38]. Overexpression of LDHA and immunoexpression of carnitine palmitoyltransferase II (CPTII) are significantly linked with therapy resistance in prostate cancer which might be a predictive marker in prostate cancer [37]. Overexpression of LDHA in OSCC was found to be linked with EMT progression which can be targeted by LDHA inhibition. Oxamate, an LDHA inhibitor significantly reduces tumor glycolysis, cell proliferation, angiogenesis, migration, invasion, and metastasis in OSCC cells, which confirms the close association of LDHA with EMT [40]. LDHA is a crucial checkpoint in hypoxic conditions and is a powerful driving force for proliferation, growth, metastasis, and chemoresistance in the pancreatic-ductal-adenocarcinoma (PDAC). LDHA inhibitors in combination with gemcitabine showed a synergistic effect in the hypoxic condition in LPC006 cancer cell lines which showed that LDHA can be a viable target in PDAC and can be an innovative tool for treatment in hypoxic cancer [32]. Moreover, LDHA inhibition by any means (small molecules, noncoding RNA (siRNA, shRNA)) would be a preferred target in drug design and discovery to increase sensitivity for cancer resistance by chemotherapy and radiotherapy.

1.3. LDHA linked with transcription factors

Genetically, the LDHA is closely associated with several transcription factors including c-myc, HIF-1, Heat-shock factor 1 (HSF1), Forkhead box protein M1 (FOXM1) and Kruppel-like factor 4 (KLF4) [48]. The c-myc oncogene plays an essential role in several cancers for example in pancreatic cancer [32,49–51]. Expression of LDHA was found positively correlated with c-myc, therefore, downregulation or knockdown of c-myc can inhibit tumor glycolysis through LDHA inhibition in pancreatic cancer [52]. Moreover, HIF protein is heterodimeric in nature consisting of two subunits α and β. Subunits α such as HIF-1α, HIF-2α, HIF-3α is an oxygen-sensitive, and the β subunit is expressed constitutively. Among these, HIF-1α plays a crucial role in the regulation of glycolysis; specifically, HIF-1α activates the expression of LDHA and promoted growth and migration in pancreatic cancer cells (Fig. 4) [53]. Recently, it has been shown that knockdown of HIFAL expression notably reduces the occupancy of HIF-1α at the promoter region of LDHA in a hypoxic condition which confirms the role of LDHA closely linked with HIF-1α [54]. HIFAL is necessary to maintain and enhance the HIF-1α-mediated transactivation and glycolysis [53]. In pancreatic cancer cells, transcription factor Krüppel-like factor 4 (KLF4), a tumor suppressor was negatively correlated with LDHA. Overexpression of LDHA was associated with under expression of KLF4 which indicated the stage of the disease. Therefore, compulsory expression of KLF4 declined the expression of LDHA, although knockdown of KLF4 expression by small interfering RNA (siRNA) showed a reverse effect [55]. Moreover, a zinc-finger transcription factor KLF4 regulates the LDHA expression *via* its binding at the promoter region of LDHA [55]. Further, knockdown of LDHA or inhibition of LDHA by oxamate showed a reduction in cell proliferation and cell growth, induces G2/M cell cycle arrest, and activated mitochondrial apoptosis mediated by JNK signaling pathway in pathogenesis in cervical cancer [56]. The direct link of the LDHA gene with HIF-1α and p53 further establishes their close association in TNBC. Overexpression of epidermal growth factor receptor 2 (ErbB2) has been found in breast cancer through Heat-shock factor 1 (HSF1) mediated by elevation of LDHA thus ErbB2 overexpression is closely related to HSF1/LDHA axis. HSF1/LDHA axis showed a significant role in tumor glycolysis contributing to elevated migration and invasion and promoting metastatic potential mediated by ErbB2 in breast cancer cells [57,58]. Forkhead box protein M1 (FOXM1) a member of the Forkhead transcriptional superfamily has been reported to regulate the expression of LDHA. In pancreatic cancer, the expression level of FOXM1 was found positively correlated expression level of LDHA (Fig. 4). In addition, FOXM1 facilitates its transcription in gastric cancer through the binding of FOXM1 in the promoter region of LDHA [59,60]. The decipher miRNAs for example miR-210–3p can regulate aerobic glycolysis mediated by modulating the downstream of HIF-1α and p53 in TNBC. The GPD1L and CYGB play a functional role in cancer, thus miR-210–3p can maintain the HIF-1α stabilization by targeting GPD1L and targeted CYGB to display suppression of p53 [61]. The tumor suppressor p53 plays a key role in cellular metabolism *via* LDHA regulation. Endogenous LDH-A endorses survival of cancer cells irrespective of p53 status which was confirmed by the fact that RNA interference (RNAi) showed a reduction in LDHA promotes cell death in p53-null, p53 wild-type, and mutant human cancer cell lines. Moreover, LDHA silencing, or inhibition mediated by either RNAi, or inhibition by small-molecule showed an increment in NADH: NAD^+ in cancer cells which were p53-dependent. This offers that LDHA suppression can kill cancer cells selectively (Fig. 4) [49]. In addition, LDHA suppression induced by wt-p53, inhibited tumor growth, survival, and invasion in breast cancer mediated by reduction in aerobic glycolysis which suggests

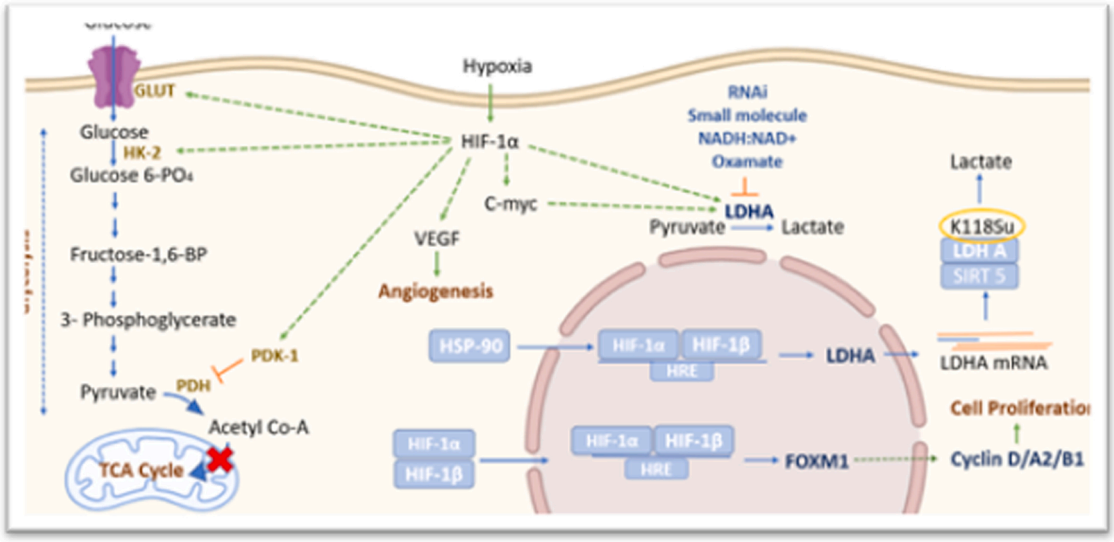

Fig. 4. LDHA closely associated with the HIF linked with glycolytic enzymes such as GLUT, HK, PDH and oncogenes including c-myc, VEGF, FOXM1, SIRT5, Cyclin D/A2/B1.

that p53 plays a key role in the progression and development of breast cancer [62]. The lysine 118 succinylation (K118su) of LDHA, serves as a Sirtuin 5 (SIRT5) substrate (Fig. 4) and increases migration and invasion significantly in prostate cancer cells and in overexpressed LDHA in patients. This suggests the key role of SIRT5 and LDHA-K118su in prostate cancer (PC) cells therefore reduction of both SIRT5 and LDHA-K118su can be considered as a potential strategy in castration-resistant PCa [63].

1.4. Lactate, cancer and immune cells

Cancer cells displayed aerobic glycolysis as a biomarker of showing to secrete lactate which inhibited Mϕs, regulatory T cells, and dendritic cells and represent an important role in tumor evasion and progression and consecutively suppressed immune responses [64]. Lactate can restrain metabolic phenotype. LDHA inhibitor oxamate showed a reduction in lactate production in cervical tumor cell spheroids to promote the secretion of IL-1β, IL-10, IL-6, and overexpression of HIF-1α expression [64]. Lactate accumulation activates a G-protein-coupled receptor (GPR81) for lactate through an autocrine mechanism and controls immune evasion [65]. Moreover, the paracrine activation of GPR81 through lactate accumulation also controls the immune evasion of stromal dendritic cells. Overexpression of GPR81 in breast cancer plays an autocrine role to stimulate tumor growth by lactate secretion in tumor cells [66]. Monotherapy of oxamate and pembrolizumab alone showed a potential effect in non-small cell lung cancer (NSCLC), however combination therapy of oxamate with pembrolizumab showed better efficacy. Infiltration of activated CD8 + T cells increases by treatment of oxamate and enhances the therapeutic potential of pembrolizumab [67]. Lactate accumulation inhibited immune T cells and NK cells in melanomas mediated by LDHA. Tumors with low lactate production showed enhanced infiltration with interferon-γ (IFN-γ) which are T and NK cells in immunocompetent C57BL/6 mice. Pathophysiological lactate level prevented the overexpression of nuclear factor of activated T cells (NFAT) present in T and NK cells leading to reducing IFN-γ production. This study confirms that lactate play important role in tumor immune escape by inhibiting T and NK cell function and survival [68].

1.5. LDHA regulation/ inhibition

LDHA composed of 332 amino acids exists in a bilobal structure having two domains *i.e.,* a larger Rossmann domain for cofactor NADH and a smaller one for substrate pyruvate [69]. Substrate pyruvate and cofactor NADH when bound with LDHA, activated site present in the extended groove between two domains. Consequently, amino acid Arg 105 present in activated site grasp pyruvate where hydride transfer occurs from nicotinamide ring of NADH to oxygen atom of carbonyl carbon of pyruvate [70]. Cytosolic LDHA plays an essential role in glycolysis whereas LDHA located in the nucleus functions as a DNA--binding protein *i.e.* SSB involved in DNA duplication and transcription [48]. Further, isolated mitochondria in incubation with lactate and in pyruvate individually when treated with oxamate showed a decline in respiration. Moreover, LDHB was found localized in mitochondria *via* transmission electron microscopy (TEM) analysis. This showed a close association of lactate metabolism with mitochondria specifically in fermenting mammalian cells [71]. Knockdown of LDHA by siRNA in intestinal-type gastric cancer (ITGC) cell lines showed a positive effect in invasion and migration through upregulation of ZEB2. The close relation of LDHA with ZEB2 showed that co-expression of these two showed a synergetic ability to predict survival [72]. A glycolytic inhibitor 2-deoxyglucose has the potential to block the oncogenic LDHA activities in human glioblastoma (GBM). Blocking of LDHA expression leads to a reduction in glycolysis, reduced cell growth, and increased cell invasion and apoptosis (Fig. 5) [73]. The overexpression of LDHA has been confirmed in gastric cancer, and oxamate was found to reduce lactate production. It inhibited cell proliferation in presence of glucose in a dose-dependent manner. Oxamate showed pro-apoptotic effect which might be due to the high expression of Bax, activated caspase-3, and by reduced Bcl-2 expression [74]. In addition, inhibition of LDHA can enhance the efficacy of anti-PD-1 treatment which can be observed in LDH-A deficient melanoma tumors mice to increase an anti-tumor immune response. A high level of infiltration of NK cells and $CD8^+$ cytotoxic T cells in LDH-A deficient tumors were observed which leads to overexpression of IFN-γ. This showed that the anti-PD-1 treatment enhanced mitochondrial activity and exhibited reactive oxygen species (ROS) levels. This proves that the anti-PD-1 therapeutics efficacy can be improved by LDHA knockdown or LDHA inhibition (Fig. 5) [75]. Ample literature data reveals that the LDHA is found overexpressed in several metabolic cancers. The elevated level of expression and the crucial role of LDHA in various cancers have been well established. Thus regulation/knockdown/inhibition of LDHA by any means such as ncRNA, peptide, and or small molecules can generate new medical tools in cancer therapeutics. LDHA inhibition can improve the efficacy of anti-PD-1 therapy.

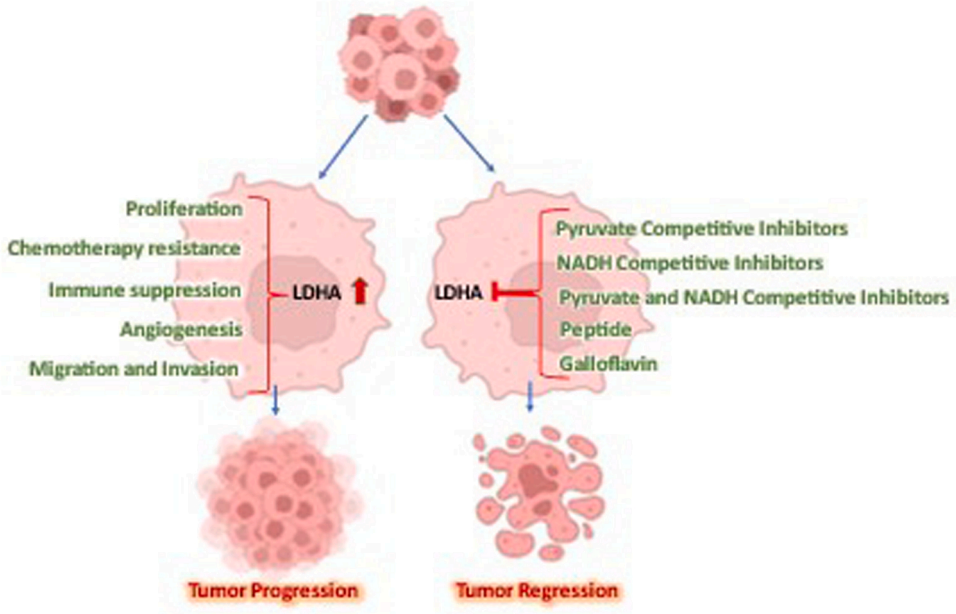

Fig. 5. Main implications of LDHA in tumor progression *vs* tumor regression.

Since the establishment of the crucial role of LDH in cancer growth, survival, invasion, angiogenesis, metastasis, and drug resistance many studies have been performed to develop potent and selective LDH inhibitors. Small molecules are known for their wide spectrum of biological activities including anti-inflammatory [76–78], antidiabetic [79], antimalarial [80], antibacterial [81] and anticancer [82–85]. Many small molecules as anticancer agents targeting potential LDHA inhibitors have been discovered, some are selective, and some are nonselective. Indeed, some molecules entered the preclinical trial, and a few entered the clinical trial, but no LDHA inhibitors are approved for clinics. This section provides potential LDHA inhibitors discovered so far.

1.6. LDHA inhibitors

LDHA inhibitors discovered so far have been classified into different classes depending on the mode of action such as substrate (pyruvate) competitive inhibitors, cofactor (NADH) competitive inhibitors, dual (substrate and cofactor) competitive inhibitors, (Fig. 5) and others where the mode of action is unknown. This section provides substrate or cofactor or both competitive potential LDH inhibitors discovered so far.

2. Substrate (pyruvate) competitive inhibitor

Oxamate (**1**) (Fig. 6) is an analog of pyruvate or isosteric of pyruvate showed significant LDH inhibitory activity in competition with substrate pyruvate. Oxamate binds with LDH at the site of pyruvate and forms an inactive complex and showed inhibitory activity [86]. Oxamate showed a reduction in LDH levels in tumors in mice [87]. Moreover, **1** (Fig. 6) alone and/or in combination with pembrolizumab significantly reduces tumor growth in non-small cell lung cancer (NSCLC). Its treatment enhances the infiltration of activated CD8 + T cells and might improve the therapeutic potential of pembrolizumab by enhancing the CD8 + T cells [88]. Further, in a dose and time-dependent manner, LDHA inhibition *via* **1** suppressed the cell proliferation in nasopharyngeal carcinoma (NPC), downregulates the Cyclin-dependent kinase1 (CDK1)/cyclin B1 pathway, and induces G2/M cell cycle and apoptosis mediated by an increment of mitochondrial ROS generation [89]. Another class of small molecules based on central core azole has been developed having hydroxyl and carboxyl groups in close proximity. For example,

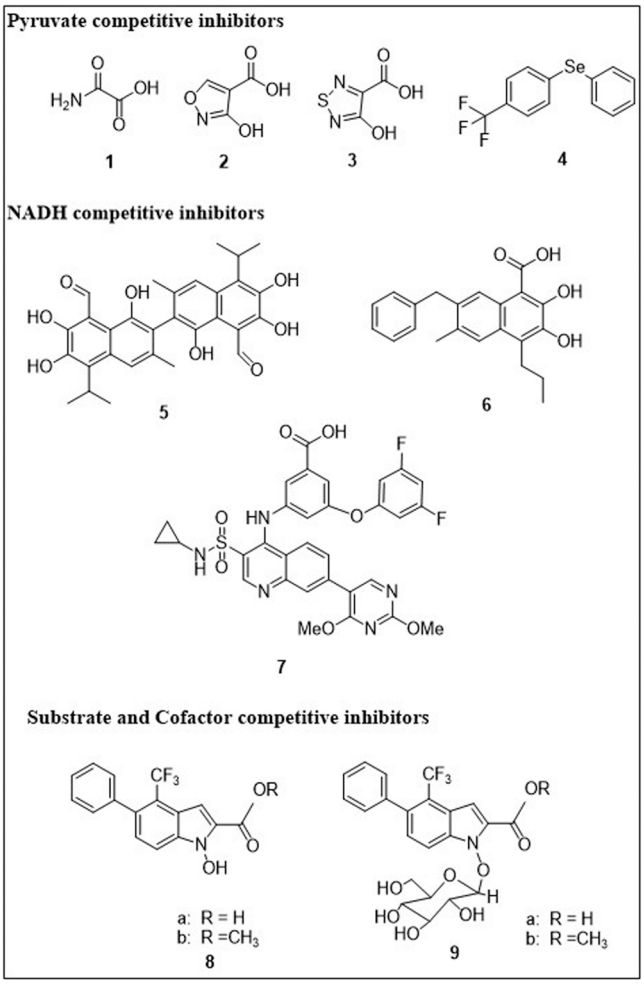

Fig. 6. Potential LDHA inhibitors; substrate (pyruvate) competitive, cofactor (NADH) competitive and substrate and cofactor competitive inhibitors.

3-hydroxyisoxazole-4-carboxylic acid (**2**) and 4-hydroxy-1,2,5-thiadiazole-3-carboxylic acid (**3**) was found to inhibit LDHA in competition with pyruvate. However, these molecules were designed for antimalarial activity against *Plasmodium falciparum* LDH (*pf*LDH) [90]. A selenobenzene-based pyruvate competitive LDHA inhibitor has been designed to exhibit promising LDHA inhibitory activities. *In silico* and biochemical assays confirm that these compounds showed strong LDHA inhibitory activities. The most potent compound 1-(phenylseleno)− 4-(trifluoromethyl)benzene (PSTMB, **4**) of this series showed an IC_{50} value of 145.2 nM which was found to be much lower than the IC_{50} value of oxamate (IC_{50} = 130.6 μM). It also inhibited anticancer activities in several cancer cell lines including NCI-H460, MCF-7, Hep3B, A375, HT29, and LLC. In HT29 human colon cancer cells. Moreover, it showed potential *h*LDHA inhibitory activities in both normoxic and hypoxic conditions and reduces lactate production [91].

3. Cofactor (NADH) competitive inhibitors

3.1. Gossypol

A polyphenolic compound Gossypol (**5**), (Fig. 3) isolated from cottonseed in the form of a racemic mixture, and its (+) and (−) enantiomers exist due to the restricted rotation through the binaphthyl bond. The (R)-(-) isomer of **5** showed non-selective LDH inhibitory activities in competition with cofactor NADH. Indeed, the (R)-(-) form of **1** is more active than (S)-(-) form [92]. It exhibited *h*LDHA inhibitory activity by showing Ki values of 1.9 μM and 1.4 μM for *h*LDHB. Although it exhibited a broad range of potential biological activities, has limitations for drug development due to its toxicity which might be due to the presence of aldehydic functional group [93]. *In vitro* studies of gossypol acetic acid on different isoforms, LDH reveals a nonselective manner. The gossypol acetic acid showed an IC_{50} value in the range of 16 and 42 μM against different LDH isoforms in presence of 0.27 mM pyruvate and 0.15 mM NADH for oxidation of pyruvate. In the reverse reaction, IC_{50} values were found at 125 μM in presence of 3.3 mM lactic acid and 1.8 mM $NAD+$. However, it showed LDH inhibitory activities in competition with NADH [94]. It also showed antifertility activity mediated by inhibitory activity against mitochondrial LDH-C_4 which is commonly found in sperm and testes [95]. An elevated level of LDHA due to radiation-induced pulmonary fibrosis was found reduced through treatment of gossypol mediated by LDHA inhibition through TGF-β activation [96]. It was found effective to prevent pulmonary fibrosis induced by bleomycin, this suggests that LDHA could be a viable target for the development of therapeutics for pulmonary fibrosis [96]. Among the 2,3-dihydroxy-1-naphtoic acid-based series, a new compound FX11 (**6**, [3-dihydroxy-6-methyl-7-(phenylmethyl)− 4-propyl naphthalene-1-carboxylic acid]) (Fig. 6) structurally related to gossypol, exhibited significant inhibitory activity against LDHA with Ki value 0.05 μM and showed mild selectivity exhibiting Ki value of 0.05 μM against *h*LDHB. Treatment of **6** showed a reduction in ATP levels and induces cell death and oxidative stress. In combination with FK866 an NAD^+ synthesis inhibitor, **6** induces lymphoma regression. Moreover, it showed potential activity but was proven as non-drug-like molecules due to the presence of the catechol group which is highly reactive and creates toxicity [97,98].

3.2. Quinoline 3-sulfonamides

Quinoline 3-sulfonamides-based compounds were found to show significant LDHA inhibitory activity in competition with cofactor NADH with notable selectivity over LDHB. Lead optimization gave potential compounds **7** (Fig. 6) to exhibit significant activity as well as selectivity. Compound **7** (3-((3-(N-cyclopropylsulfamoyl)− 7-(2,4-dimethoxypyrimidin-5-yl)quinolin-4-yl)amino)− 5-(3,5-difluorophenoxy)benzoic acid) showed inhibitory potency against LDHA with an IC_{50} value of 0.0026 μM and an IC_{50} value of 0.043 μM against LDHB. It showed a reduction in the rate of lactate production in various cancer cell lines including breast and hepatocellular carcinomas [99]. Along with this, compound **7** showed an inhibitory effect on lactate production in hepatocellular carcinoma cells exhibiting an IC_{50} value of 0.4 μM. Conclusively, the cell-permeable quinoline 3-sulfonamides-based molecule showed potent and reversible LDHA inhibitory activity with significant selectivity and further showed a reduction in the rate of glucose consumption and simultaneously lactate reduction. These compounds were found competitive to cofactor NADH and non-competitive to substrate pyruvate. The most potent compound **7** of this series showed inhibitory activity against *h*LDHA with an IC_{50} value of 2.6 nM and showed significant selectivity over *h*LDHB exhibiting an IC_{50} value of 43 nM. More interestingly, it was found inactive over a wide range of approximately 32 enzymes, ion channels, and receptors even at high concentrations. It showed a rapid reduction of lactate production exhibiting EC_{50} values of 588 and 400 nM in HepG2 and Snu398 hepatocellular cells respectively. Moreover, mitochondrial oxygen consumption rate was found to increase with EC_{50} values of 900 and 500 nM in HepG2 cells and Snu398, respectively also reducing extracellular acidification in both cancer cell lines. Although these compounds showed significant potency as well as selectivity for LDHA, the pharmacokinetic properties of these compounds are not allowed for *in vivo* use [99].

4. Substrate and cofactor competitive inhibitors

A unique class of compounds based on central scaffold *N*-hydroxyindoles (NHI) **8a** and **8b** (Fig. 6) showed a potent *h*LDHA inhibitory effect with good selectivity against *h*LDHA over *h*LDHB. This class of compounds bears a hydroxyl group on the N atom of 1 position and a carboxyl group at 2nd position in close proximity can mimic the substrate pyruvate. Compound **8a** exhibited inhibitory activity in competition with substrate pyruvate (Ki = 4.7 μM) as well as in competition with NADH (Ki = 8.9 μM). Methyl ester derivative (**8b**) showed lower activity than **8a** in competition with NADH exhibiting a Ki value of 5.1 μM [100]. Interestingly, under both normoxic and hypoxic conditions, both derivatives **8a** and **8b** showed a significant synergistic cytotoxic effect in combination with gemcitabine, however, showed stronger synergistic cytotoxic effects in hypoxic conditions than in normoxic conditions. Further, in combination with gemcitabine, compounds **8a** and **8b** exhibited an inhibitory effect in spheroid growth, cell migration, and invasion in pancreatic cancer cells [32]. To further improve efficacy and cellular potency, on modification of compounds **8a** and **8b** by glucose at hydroxyl group at position 1 resulted in compounds **8a** and **8b** showing lower inhibitory activity with Ki values of 19.5 and 37.8 μM against *h*LDHA in competition with NADH. Interestingly, this gluco-conjugate **9a** and **9b** (Fig. 6) showed notable *h*LDHA inhibitory activities with increments in cellular uptake and showed higher efficacy compared to parent compounds [101].

5. Others small *h*LDHA inhibitors

Galloflavin (**10**) (Fig. 7) is a non-competitive potential inhibitor that binds to free enzymes without competition of substrate and cofactor and showed good LDHA inhibitory activity and good cell permeability [102]. It is a flavone-like compound synthesized by gallic acid that showed notable LDH inhibitory activities exhibiting Ki values of 5.46 μM against *h*LDHA and 56.0 μM for *h*LDHB [102]. It showed a competitive inhibitory effect with NADH and showed inhibition of aerobic glycolysis and decreases cell viability in various cancer cell lines such as breast, colon, liver cancers, Burkitt lymphoma, and endometrial cancer cell [103]. It showed a reduction in the growth of cancer cells with a similar effect in MCF-7 cells and in MDA-MB-231 and MCF-Tam cells where high LDH level and high glucose uptake was observed [104]. It showed a reduction in glycolysis and ATP production leads to inhibition of cancer cell proliferation and induces apoptosis [104]. It

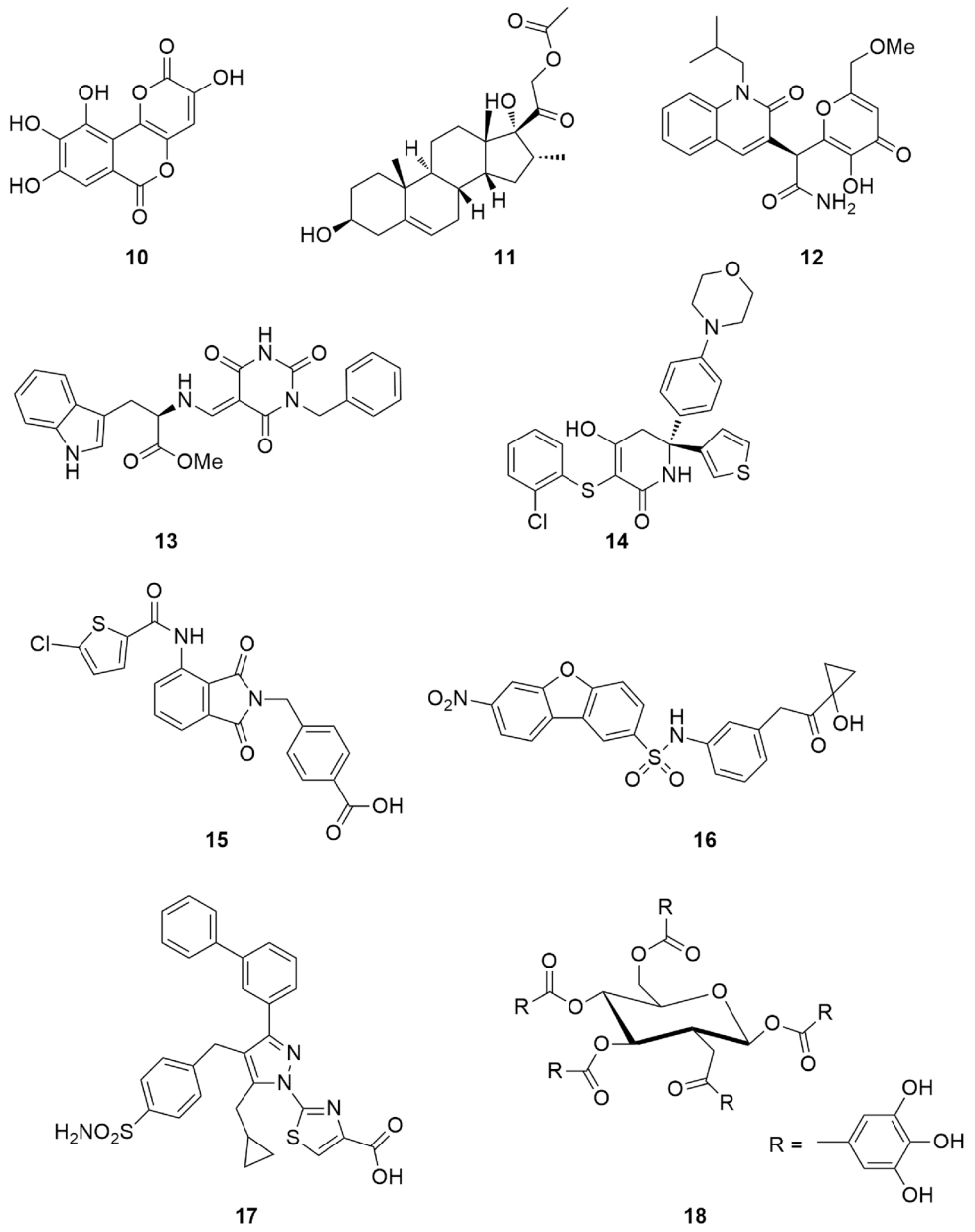

Fig. 7. Structure of LDHA inhibitors.

inhibited tumor glycolysis and induced cell death in PLC/PRF/5 hepatocellular carcinoma cell lines and was found nontoxic on human lymphoblasts and lymphocytes [102,104]. Moreover, in combination with metformin, it showed significant anticancer cells in PDAC cells [105]. Virtual screening of ZINC database and *in vitro* biochemical evaluation against LDHA resulted in compound **11** (Fig. 7) depicting good inhibitory activity exhibiting an IC_{50} value of 0.36 μM against LDHA. It also showed a reduction in growth with EC_{50} values of 5.5 and 3.0 μM in A549 and NCI-H1975 of lung cancer cells, respectively [106].

Compound **12** (Fig. 7) based on tetrahydroquinolinyl-propanamide exhibited significant inhibitory activity against *h*LDHA in low micromolar range possessing an IC_{50} value of 0.33 μM. Moreover, it showed very good cellular potency demonstrating a reduction in tumor growth exhibiting an EC_{50} value of 3.35 μM and showed induced apoptosis in MG-63 cancer cells [107]. Further, trioxotetrahydropyrimidine-based compound **13** (Fig. 7) showed significant activity in the low micromolar range with an IC_{50} value of 0.96 against *h*LDHA. It showed inhibition of the growth of the A549 cancer cell line by 63.4 % and in NCI-H1975 of the lung cancer cell growth by 67.4 % [107]. A dihydropyrimidine derivative **14** (GNE-140) (Fig. 7), discovered by Genentech showed significant *h*LDHA inhibitory activity, however, showed in a low micromolar range with an IC_{50} value of 0.48 μM. Further inhibitory activity evaluation of compounds of this class showed inhibitory activity in the nanomolar range with low selectivity (IC_{50} value of 2–4 μM for *h*LDHB) displaying with limitation of high protein binding affinity and poor cell membrane permeability) The racemic mixture of **14** also showed potential LDHA inhibitory activity and R isomer was found 18-fold more active than the S enantiomer. Moreover, the R isomer displayed high bioavailability with 5 mg/kg in mice [108].

A biochemical high throughput screening program resulted in two phthalimide and dibenzofuran central scaffold-based novel classes of selective LDHA inhibitors [109]. The phthalimide derivative **15**, (4-((4-(5-chlorothiophene-2-carboxamido)− 1,3-dioxoisoindolin-2-yl) methyl)benzoic acid), (Fig. 7) showed selective LDHA inhibitory activity exhibiting an IC_{50} value of 308 nM. A dibenzofuran derivative **16** (*N*-(3-(2-(1-hydroxycyclopropyl)− 2-oxoethyl)phenyl)− 7-nitrodibenzo [*b*,*d*]furan-2-sulfonamide), (Fig. 7) slightly lower LDHA inhibitory activity possessing an IC_{50} value of 757 nM [109]. Both compounds **15** and

Table 1
Chemical name, inhibitory activities and mode of inhibition of most significant LDHA inhibitors.

Compounds no	Chemical name	Inhibitory activity ($^{\#}IC_{50}$ /$^{*}K_i$)		Mode of inhibition	Ref.
		LDHA	LDHB		
1	2-Amino-2-oxoacetic acid	130.6 μM$^{\#}$	–	Substrate competitive	[86, 87]
2	3-Hydroxyisoxazole-4-carboxylic acid	~50 μM$^{\#}$	–	inhibitor	[90]
3	4-Hydroxy-1,2,5-thiadiazole-3-carboxylic acid	~50 μM$^{\#}$	–		[90]
4	1-(Phenylseleno)– 4-(trifluoromethyl)benzene	0. 145 μM$^{\#}$	–		[90, 91]
5	1,1′,6,6′,7,7′-Hexahydroxy-3,3′-dimethyl-5,5′-di(propan-2-yl)[2,2′-binaphthalene]– 8,8′-dicarbaldehyde	1.9 μM*	1.4 μM*	Cofactor competitive	[92, [93]
6	3-Dihydroxy-6-methyl-7-(phenylmethyl)– 4-propyl naphthalene-1-carboxylic acid	0.05 μM*	0.05 μM*	inhibitor	[97, 98]
7	3-((3-(N-cyclopropylsulfamoyl)– 7-(2,4-dimethoxypyrimidin-5-yl)quinolin-4-yl)amino)– 5-(3,5-difluorophenoxy)benzoic acid	0.0026 μM*	0.043 μM*		[99]
8a	1-Hydroxy-5-phenyl-4-(trifluoromethyl)– 1 H-indole-2-carboxylic acid	4.7 μM*		Substrate competitive inhibitor	[100]
		8.9 μM*		Cofactor competitive inhibitor	
8b	Methyl 1-hydroxy-5-phenyl-4-(trifluoromethyl)– 1 H-indole-2-carboxylate	5.1 μM*		Cofactor	
9a	5-Phenyl-4-(trifluoromethyl)– 1-(((2 S,3 R,5 S,6 R)– 3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2 H-pyran-2-yl)oxy)– 1 H-indole-2-carboxylic acid	19.5 μM*		competitive inhibitor	[101]
9b	Methyl 5-phenyl-4-(trifluoromethyl)– 1-(((2 S,3 R,5 S,6 R)– 3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2 H-pyran-2-yl)oxy)– 1 H-indole-2-carboxylate	37.8 μM*			[101]
10	3,8,9,10-Tetrahydroxypyrano[3,2-*c*]isochromene-2,6-dione	5.46 μM*	56.0 μM*	Non-competitive	[102]
11	2-((3 S,8 R,9 S,10 R,13 S,14 R,16 R,17 R)– 3,17-dihydroxy-10,13,16-trimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1 H-cyclopenta[*a*]phenanthren-17-yl)– 2-oxoethyl acetate	0.36 μM$^{\#}$	–	inhibitor	[106]
12	(*S*)– 2-(3-hydroxy-6-(methoxymethyl)– 4-oxo-4 H-pyran-2-yl)– 2-(1-isobutyl-2-oxo-1,2-dihydroquinolin-3-yl)acetamide	0.33 μM$^{\#}$	0.33 μM$^{\#}$		[107]
13	(R,*E*)-Methyl 2-(((1-benzyl-2,4,6-trioxotetrahydropyrimidin-5(2 H)-ylidene)methyl)amino)– 3-(1 H-indol-3-yl)propanoate	0.96 μM$^{\#}$	–		[107]
14	(R)– 3-((2-chlorophenyl)thio)– 4-hydroxy-6-(4-morpholinophenyl)– 6-(thiophen-3-yl)– 5,6-dihydropyridin-2(1 H)-one	0.48 μM$^{\#}$	2–4 μM$^{\#}$		[108]
15	4-((4-(5-Chlorothiophene-2-carboxamido)– 1,3-dioxoisoindolin-2-yl)methyl)benzoic acid	308 nM$^{\#}$	–		[109]
16	N-(3-(2-(1-hydroxycyclopropyl)– 2-oxoethyl)phenyl)– 7-nitrodibenzo[*b*,*d*]furan-2-sulfonamide	757 nM$^{\#}$	–		[109]
17	2-(3-([1,1′-Biphenyl]–3-yl)– 5-(cyclopropylmethyl)– 4-(4-sulfamoylbenzyl)– 1 H-pyrazol-1-yl) thiazole-4-carboxylic acid	517 nM$^{\#}$	0.854 nM$^{\#}$		[109]

16 inhibited *in vitro* lactate production in a dose-dependent manner of recombinant human LDHA. However, both **15** and **16** compounds were found inactive in the inhibition of lactate production in cells [109]. Further, a novel lead compound **17** (Fig. 7) from the pyrazole-based series was disclosed as an inhibitor of human LDHA exhibiting inhibitory activity in the low nM range against LDHA and LDHB with IC_{50} values of 0.517 and 0.854 μM, respectively. It exhibited lactate production in MiaPaCa2 pancreatic cancer and A673 sarcoma cells with an IC_{50} value of 32 nM and 27 nM, respectively. It showed an inhibitory effect with an IC_{50}s of 2.23 and 1.21 μM in the growth of MiaPaCa2 pancreatic cancer and A673 sarcoma cells. It was considered as a lead compound for further optimization based on the inhibitory effect of cellular lactate production in sub micromolar range and it also showed good aqueous solubility and microsomal stability. Based on these parameters further optimization can be accepted for *in vivo* efficacy studies [110]. The high-throughput screening of natural products resulted potential *h*LDHA inhibitors 1,2,3,4,6-Penta-O-galloylglucose (**18**) (Fig. 7) from the Chinese gallnut herb. Compound **18** showed *h*LDHA inhibitory activity in nM range and, also showed a reduction in the growth of TNBC cells, however, it was not found to hamper the lactate concentration [110,111]. Table 1.

6. Peptides as *h*LDHA inhibitors

Recently, peptide sequences cGmC9 have been reported by following rational and computer-based approaches, to show *h*LDHA inhibitory activity. It showed a strong affinity to a β-sheet region which play an important role in protein-protein interactions (PPIs) essential for *h*LDHA inhibitory activities. This cGmC9 was obtained by grafting peptide sequence into β-hairpin peptide a cyclic cell-penetrating scaffold. This grafted sequence showed *in vitro* LDH5 inhibitory activity in the low micromolar range and better than GNE-140 LDHA inhibitors [112].

7. Conclusion and future prospects

In all living beings, energy is required for everything a cell does including breaking down and building up molecules. Glucose is the main source of energy and metabolizes through glycolysis to generate the pyruvate considered as the energy hub for the cells. Pyruvate is then entered into mitochondrial for energy production through oxidative phosphorylation in normal cells. Besides, in cancer cells, pyruvate is preferably converted into lactate catalyzed by LDHA by consumption of NADH to NAD^+. The LDHA enzyme is highly overexpressed in almost all cancer cells as well as in stem cells too and is strongly correlated with cancer initiation, development, invasion, angiogenesis, and metastasis. Numerous preclinical studies have proven the therapeutic potential of LDHA as its inhibition determined significant anti-proliferative effects in several cancer cells including breast, prostate, and pancreatic cancer. However, selective, and effective inhibition of LDHA in cancer is quite challenging because of the narrow substrate-binding pocket of LDHA. Recently, it has been reported that an active form of vitamin D induced apoptosis, stimulated cell differentiation, showed an anti-proliferative effect. LDHA inhibition together with vitamin D enhanced the effectiveness in prostate cancer animal models [113]. The oxamate and pembrolizumab monotherapy showed a significant reduction in tumor growth in NSCLC humanized mouse model. However, the combination

therapy (oxamate and pembrolizumab) showed improvement in reduction in tumor growth. Oxamate treatment alone improved the infiltration of activated CD8 + T cells in humanized mice model which confirm the effective role of LDHA inhibitor oxamate and also confirm that the CD8 + T cells play important role in the effectiveness of oxamate [67]. In addition, oxamate induces both OXPHOS and osteoblast differentiation and was observed nontoxic in undifferentiated osteoprogenitors cells *in vitro*. Oxamate showed improvement in bone mineral density, cortical bone architecture, and bone biomechanical strength *in vivo* and also increases bone formation. This fact confirms that glycolytic inhibitors such as LDHA inhibitors might be helpful in bone diseases, related bone loss, and osteoporosis, and in improvement in Bone marrow stromal cells (BMSCs) [113]. In summary, LDHA inhibitors used as anti-glycolytic agents showed significant therapeutic potential in cancer, cancer stem cells and in bone diseases. Selective inhibition of LDHA is challenging, however recent studies evaluated new strategies to develop safe and novel candidates. LDHA exits at the bifurcation point from where pyruvate either enter into mitochondria or catalysed by LDHA to generate lactate. Selective inhibition of LDHA can block the energy requirement for cancer development, survival, invasion, angiogenesis, and metastasis. A flexible loop within the amino terminus of human tumor suppressor folliculin (FLCN) which is binding partner and noncompetitive inhibitor of LDHA regulates the LDHA active-site loop movement, regulate the enzyme activity followed by metabolic homeostasis in normal cells. Besides in cancer cells FLCN was found dissociated from LDHA, thus inactivation of FLCN or dissociation from LDHA caused the glycolytic shift in cancer cells. This study offers new paradigm in regulation of tumor glycolysis through FLCN mediated LDHA inhibition [114]. Small molecules capsaicin directly binds to PKM2 and LDHA mediated by covalent bond formation with cysteine amino acids and showed inhibition of PKM2 and LDHA and supresses the Warburg effect in inflammatory macrophages [115]. In addition, LDHA inhibition together with glycolate oxidase create effect on endogenous oxalate synthesis might be useful in primary hyperoxaluria treatment [116]. Therefore, LDHA inhibition not only counteracts the Warburg effect in cancer but could also be explored for other diseases too. For example, osteoporosis and bone loss may be reduced by LDHA suppression [117]. Many small molecules including natural and synthetic and peptides as *h*LDHA inhibitors have been discovered, few entered in pre-clinical trials and very few in the clinical trial, unfortunately none of them reached to clinics. LDH has a crucial position in the metabolic reprogramming of tumour cells, maintaining an altered glycolytic metabolism and allowing tumour cells to survive when glycolysis is their primary source of energy. Despite significant efforts, LDH inhibitors with significant selectivity and *in vivo* efficacy are yet to be discovered. The LDH enzyme's substrate-binding pocket hosts Asp-168, Arg-171, Thr-246, and Arg-106 at the active site, in addition to the catalytically important His-193. The active amino acid His-193 is found in the active site in humans and other animal species. The active site of LDHA is located quite deep inside the protein and its accessibility is very narrow. However, selective targeting of LDH is quite difficult but not impossible. Overall, the catalytic site is quite polar and rich in arginine amino acid which makes the catalytic site cationic. This would explain the structural requirement of LDHA inhibitors which bears anionic moiety. Despite the structural similarity of all LDH isozymes, each has unique kinetic properties due to differences in charged amino acids flanking the active site. There is an urgent need to fill the chemicals gap in order to develop new small molecules LDHA inhibitors with improved selectivity for the starvation of cancer cells. LDHA inhibitors alone or in combination with standard drugs or with another agents, such as Vitamin D, represent indeed a potential new medical tool for the development of new anticancer therapies with minimal side effects.

Author contributions

All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

Conflict of interest

This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue. The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript

Data availability

No data was used for the research described in the article.

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