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Role of ENO1 and its targeted therapy in tumors

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Abstract
ENO1, also called 2-phospho-D-glycerate hydrolase in cellular glycolysis, is an enzyme that converts 2-phosphoglycerate to phosphoenolpyruvate and plays an important role in the Warburg effect. In various tumors, ENO1 overexpression correlates with poor prognosis. ENO1 is a multifunctional oncoprotein that, when located on the cell surface, acts as a "moonlighting protein" to promote tumor invasion and metastasis. When located intracellularly, ENO1 facilitates glycolysis to dysregulate cellular energy and sustain tumor proliferation. Additionally, it promotes tumor progression by activating oncogenic signaling pathways. ENO1 is a tumor biomarker and represents a promising target for tumor therapy. This review summarizes recent advances from 2020 to 2024 in understanding the relationship between ENO1 and tumors and explores the latest targeted therapeutic strategies involving ENO1.

Introduction

In normoxic conditions, glucose is fully metabolized into carbon dioxide and water by the tricarboxylic acid cycle and oxidative phosphorylation, creating large amounts of ATP. However, even under well-oxygenated conditions, tumor cells generate energy by aerobic glycolysis rather than oxidative phosphorylation, a phenomenon known as the Warburg effect [1]. Several studies have investigated the role of glycolysis-related genes in cancer development and progression, which has led to the development of promising targeted drugs. These genes include enolase (*ENO*), M2-type pyruvate kinase (*PKM2*), glucose transporters (*GLUTs*), and lactate dehydrogenase A (*LDHA*).

As one of the important enzymes catalyzing glycolysis, the primary function of enolase is to convert 2-phosphoglycerate (2-PG) into phosphoenolpyruvate (PEP) [2]. The three highly conserved isoforms of enolase in mammals are α-enolase (ENO1), β-enolase (ENO3), and γ-enolase (ENO2). Among them, ENO1 accounts for 90% of the glycolytic pathway's cytosolic enolase activity [3]. Furthermore, *ENO1* overexpression is associated with poor prognosis in many types of cancer [4]. ENO2, predominantly localized in the cytoplasm of neurons and neuroendocrine cells, has been identified as a serum marker for tumors of neuronal lineage, such as glioblastoma (GBM) and medulloblastoma [5, 6]. Recent studies, however, have revealed that ENO2 is not only highly expressed in neurological tumors but also plays a critical role in the progression of other malignancies, including lung adenocarcinoma (LUAD) and breast cancer. A multiomic analysis demonstrated that 3D tumor spheroid growth implies the overexpression of ENO2 and another glycolytic enzyme, ALDOC, concomitant with the enhanced consumption of glucose and fructose and the enhanced production of lactate, in lung and breast cancer cell lines in different nutrient environmental conditions [7]. ENO3 is predominantly expressed in muscle tissue, with studies indicating that 86% of rhabdomyosarcomas test positive

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for ENO3 [8]. Furthermore, recent research has shown that ENO3 expression is upregulated in colorectal cancer (CRC), where it promotes cell proliferation and migration by facilitating glycolysis [9]. Conversely, in hepatocellular carcinoma (HCC), ENO3 inhibits the proliferation, migration, invasion, tumor growth, and lung metastasis of HCC cells by suppressing the epithelial-mesenchymal transition (EMT) process and the Wnt/β-catenin pathway [10].

Apart from its function as a glycolytic enzyme, ENO1 has multiple biological functions as a moonlighting protein, depending on its localization. In the cytoplasm, ENO1 catalyzes glycolysis and promotes a variety of pro-tumorigenic effects, including tumorigenesis, cell proliferation, invasion, migration, and chemoresistance [11–14]. ENO1 also regulates multiple intracellular protumor signaling pathways. By acting as a plasminogen receptor on the cell surface, it enhances migration and invasion of tumor cells by promoting extracellular matrix (ECM) degradation [15]. ENO1 can also be secreted extracellularly and interact with other immune cells, such as tumor-associated macrophages, to promote tumor progression [16].

Given the aerobic glycolytic properties of tumor cells and the functional alterations of ENO1, treatments targeting ENO1 may be effective against cancer. Therefore, exploring the relationship between ENO1 function and tumor progression in cancer therapy is crucial. This article summarizes the functions and roles of ENO1 in cancer progression from 2020 to 2024, as well as reported ENO1-targeted drugs. This paper aims to provide insights and aid in targeting ENO1 in cancer therapy.

Clinical relevance of ENO1

ENO1 is overexpressed in various cancers and is associated with malignant progression of tumors, poor prognosis, pathological stage of tumors, immune cell infiltration, and tumor purity [4]. In GBM, elevated *ENO1* expression is associated with shorter patient survival and higher glioma tumor grade, suggesting a poor prognosis [17, 18]. ENO1 is also associated with low T-cell, B-cell, and natural killer cell infiltration, high immunosuppressive cell infiltration, and promotes microglia M2 polarization and malignant progression of GBM [19]. In CRC, elevated ENO1 expression predicts poor prognosis and correlates with CRC stage; high ENO1 levels predict poor survival and serve as a biomarker for radiation response [13, 20]. In HCC, high *ENO1* expression predicts poor prognosis, shorter survival [21], and correlates with tumor differentiation grade and tumor lymph node metastasis (TNM) stage [22]. As one of the hypoxia prognostic model genes, a high hypoxia score indicates a poor prognosis in HCC [23]. In bladder cancer, aberrant ENO1 overexpression correlates with clinicopathological features, poorer survival, poor prognosis, and has independent prognostic value in tumor progression [24–27]. A high expression of *ENO1* in pancreatic cancer is associated with a shorter survival time [28]. Pancreatic ductal adenocarcinoma with high *ENO1* expression has a poor prognosis; a high expression of ENO1 is strongly correlated with histological differentiation and tumor invasion; high ENO1 autoantibodies (aAb) in patients predict poor prognosis and are associated with reduced survival [29–32]. Moreover, to construct a prognostic model, *ENO1* was selected, and the high-risk group had a worse prognosis [33]. In melanoma, ENO1 overexpression in melanoma cells correlates with unfavorable prognostic factors, such as Clark levels, mitotic activity, Breslow thickness, and ulcers. It also correlates with increased tumor infiltration thickness and poorer long-term prognosis in patients with skin melanoma [34]. In breast cancer, elevated *ENO1* expression predicts poorer recurrence-free survival and overall survival, particularly in the aggressive triple-negative breast cancer (TNBC). ENO1 can also serve as a prognostic marker for breast cancer radiotherapy efficacy [35–37]. However, ENO1 is positively correlated with various anti-tumor infiltrating immune cells, such as NK cells, M1 macrophages, helper T cells, $CD8^+$ T cells and B cells in patients with stage I/II breast cancer. In early-stage breast cancer, higher ENO1 expression correlates with a better prognosis [38]. *ENO1* was highly expressed in malignant lobular tumors of the breast and correlated with hypoxia [39]. In lung cancer, ENO1 in sputum can be used as a biomarker for early detection of lung cancer [40]. Moreover, *ENO1* is strongly associated with poor prognosis in LUAD and sarcoma [41–43]. In osteosarcoma, a biomarker for immunodiagnosis and osteosarcoma progression can be determined by ENO1, which triggers an autoimmune response [44]. ENO1 autoantibody levels in patient sera are higher than in healthy individuals; predictive modeling of autoantibodies can help in the early detection of osteosarcoma, serving as a promising and powerful tool in clinical practice [45]. Analysis of gene expression profiling databases of multiple myeloma patients revealed a negative correlation between overall survival and*ENO1* expression [46]. In esophageal squamous cell carcinoma (ESCC), ENO1 is abnormally elevated in all cancer cytoplasm, significantly increasing with tumor stage progression and transition from Barrett's esophagus to esophageal adenocarcinoma [47], and the expression level of ENO1 is positively correlated with the clinicopathological TNM stage [48]. High expression of *ENO1* in prostate cancer is significantly associated with shorter patient survival [49]. *ENO1* is upregulated in the hair of female cervical cancer patients, according to metabolomic analysis [50]. In acute myeloid leukemia, high *ENO1* expression predicts poor overall survival [51] (Table 1).

Table 1 Summary of tumor clinical correlation and biological function of ENO1

Cancer type	Clinical correlation	Biological functions	References
Glioblastoma	Overall survival, poor prognosis, tumor stage, disease progression, immune suppression	Chemoresistance, stemness, autophagy	[17–19], [55], [112]
Colorectal cancer	Poor prognosis, tumor stage, overall survival, radiation marker	Tumorigenesis, cell proliferation, cell invasion, migration, EMT process, metastasis, chemoresistance	[11–14], [20], [53, 54], [63], [116]
Liver cancer		Tumorigenesis, chemoresistance	[62], [105]
Hepatocellular carcinoma	Poor prognosis, overall survival, tumor stage, lymph node metastasis	Cell proliferation, metastasis, ferroptosis	[21–23], [85], [99], [59]
Hepatopancreatobiliary cancers		Cell proliferation	[86]
Cholangiocarcinoma		Cell proliferation	[87]
Bladder cancer	Poor prognosis, overall survival, pathological features	Cell proliferation, invasion	[24–27]
Gastric cancer		Cell proliferation, invasion, migration, inhibiting apoptosis, stemness	[58], [66, 67], [114]
Pancreatic cancer	Overall survival	Tumorigenesis, cell proliferation, invasion, migration, EMT process, inhibiting apoptosis, chemoresistance autophagy	[28], [30], [61], [64, 65],
Pancreatic ductal adenocarcinoma	Poor prognosis, invasion, immune suppression	Cell migration, invasion, inhibiting apoptosis	[29–33], [61]
Melanoma	Poor prognosis	Cell proliferation, migration, invasion, metastasis	[34], [79, 80], [101]
Breast cancer	Poor prognosis, overall survival, hypoxia	Tumorigenesis, cell proliferation, metastasis, inhibiting apoptosis, radiotherapy resistance, cell cycle	[35–39], [52], [76],
Triple-negative breast cancer	Radiation marker, overall survival	Cell proliferation, migration, invasion, EMT process, chemoresistance, inhibiting apoptosis, cell cycle,	[35–37], [77], [98], [103, 104],
Ovarian cancer		Cell proliferation, metastasis	[83, 84]
Cervical cancer		Cell proliferation	[88]
Endometrial carcinoma		Cell proliferation, migration, invasion	[89]
Lung cancer	Poor prognosis	Cell proliferation, migration, metastasis, chemoresistance, stemness	[40], [68–70], [113]
Lung Adenocarcinoma	Poor prognosis	Tumorigenesis, cell cycle	[41, 42], [60], [72, 73]
Non-small cell lung cancer		Cell proliferation, invasion	[74], [97]
Small cell lung cancer		Chemoresistance	[106]
Sarcomas	Poor prognosis		[43]
Osteosarcoma	Disease progression, immune diagnosis		[44, 45]
Multiple myeloma	Overall survival	Cell migration, viability	[46], [100]
Esophageal squamous cell carcinoma	Tumor stage	Cell migration, invasion, EMT process, metastasis	[47, 48], [102]
Prostate cancer	Overall survival	Cell proliferation, invasion, angiogenesis	[49], [56], [78], [114]
Clear cell renal cell carcinoma		Cell proliferation, migration	[81]
Leukemia	Overall survival	Cell proliferation	[51], [82]
Head and neck squamous cell carcinoma		Cell proliferation, migration, invasion	[91]
Oral squamous cell carcinoma		Cell proliferation, migration, invasion, EMT process, chemoresistance, cell cycle	[16], [93, 94], [107]

Role of ENO1 in tumorigenesis and progression

Role of ENO1 in tumorigenesis

ENO1 can promote tumorigenesis by activating cellular signaling pathways and increasing cellular glycolysis. In breast cancer, ENO1 promotes glucose uptake through the PI3K/AKT pathway, thereby enhancing tumorigenesis [52]. In CRC, upregulation of ENO1 enhances cellular aerobic glycolysis, which subsequently promotes tumorigenesis [11]. In LUAD, ENO1 mRNA is methylated by m^6A at A359, enhancing its translation. The m^6A -dependent increase in ENO1 promotes glycolysis and tumorigenesis in LUAD [60]. In pancreatic cancer, ENO1 knockdown reduces cellular glycolysis and activates oxidative phosphorylation and lipid metabolism pathways by altering the expression of *UAP1*, *ALDOC*, *G6PD*,

and other related metabolic genes, thereby suppressing tumorigenesis [61]. In HCC, ENO1 binds to yes-associated protein 1 (YAP1) mRNA, promoting its translation, which activates arachidonic acid metabolism and prostaglandin E2 accumulation. A significant increase in ENO1/YAP1 activation in clinical samples of hepatocellular carcinoma suggests that ENO1 may play a role in cancer development via its regulation of arachidonic acid metabolism [62] (Fig. 1).

Role of ENO1 in tumor growth, anti-apoptosis, and tumor cell proliferation

Numerous studies have demonstrated that ENO1 enhances glycolysis and proliferation, while suppressing apoptosis in various tumors. ENOblock, a specific inhibitor of ENO1, significantly decreased *F. nucleatum*-induced cell proliferation in CRC. In a CRC xenograft mouse model, ENOblock treatment significantly diminished the tumor growth of *F. nucleatum*-cultured tumor cells [53]. Furthermore, knockdown of ENO1 hindered the proliferative capacity of CRC cells [14]. Another study revealed that decreased levels of ubiquitinated degradation of ENO1 promoted ERK phosphorylation and glycolytic activity in CRC cells. Inhibition of ENO1 reduces cellular proliferation [12]. Post-translational modifications of ENO1 are crucial in fundamental biological processes and are closely associated with tumor progression. Lysine crotonylation at K420 on ENO1 promotes CRC cell growth by enhancing ENO1 activity and regulating the expression of tumor-related genes [63]. In pancreatic cancer, the knockdown of ENO1 inhibited pancreatic cancer cell proliferation and colon-forming ability, and ENO1-KO significantly reduced tumor growth in a mouse model [28, 64]. Hyperlipidemia enhances tumor growth and increases the expression level of ENO1 in a subcutaneous xenograft mouse model [65]. ENO1 knockdown hinders the proliferative capacity of pancreatic ductal adenocarcinoma cells [61], and hypoxia

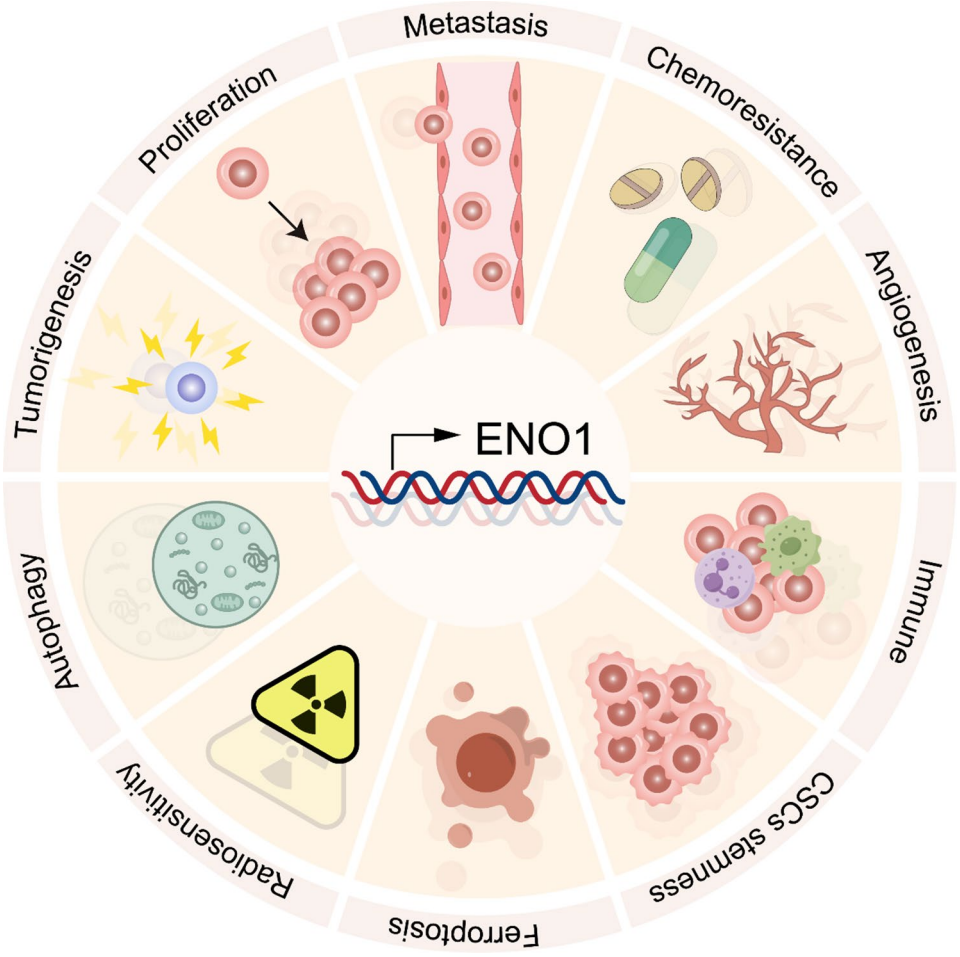

Fig. 1. ENO1 exerts significant pro-tumor effects in a variety of tumor types, including (1)promoting tumorigenesis [52], (2)enhancing tumor cell proliferation [53], (3)inducing EMT, promoting invasion, migration and metastasis [14, 54], (4)promoting chemoresistance [55], (5)stimulating angiogenesis [56], (6)shaping the immune microenvironment [38], (7)augmenting cancer stem cells stemness [57, 58], (8)inducing ferroptosis [59], (9)promoting resistance to radiotherapy [35], and (10)modulating cellular autophagy [30].

induces elevated ENO1 expression, which enhances ERK phosphorylation and suppresses apoptosis, leading to cell survival [31]. In gastric cancer, ubiquitination and degradation of ENO1 diminished AKT1 binding and subsequently inactivated AKT1, resulting in cell proliferation [66]. In gastric cancer, ENO1 binds to the mRNAs of vascular endothelial growth factor A (*VEGFA*), myeloid cell leukemia-1 (*MCL1*), SRY-box transcription factor 9 (*SOX9*) and G-protein-coupled receptor class C group 5 member A (*GPRC5A*), thereby stabilizing their expression and promoting gastric cancer cell growth. Additionally, ENO1 interacts with several small-molecule kinases (e.g., CD44, PKM2, NEAT1, and LINC00511) or other long-chain non-coding RNAs (lncRNAs) to regulate their expression and affect cell apoptosis and proliferation [67]. Elevated ENO1 activity regulates the PI3K/AKT pathway and promotes lung cancer cell proliferation [68, 69]. Elevated ENO1 activity regulates the flux of the oxidized pentose phosphate pathway and the glycolytic pathway in human lung cancer, thereby promoting tumor growth [70]. In LUAD, regulation of the expression of the glycolysis-related gene ENO1 suppresses tumor activity [71], and inhibition of ENO1 expression suppresses the proliferation of LUAD cells [72], and downregulation of ENO1 expression reduces the activation of AKT1 phosphorylation, which subsequently inactivates cell cycle signaling and inhibits cell proliferation [73]. In non-small cell lung cancer (NSCLC), decreased levels of ENO1 phosphorylation lead to reduced phosphorylation of PI3K and AKT, thereby further inhibiting cell proliferation and tumor progression [74]. In breast cancer, promoting m^6A methylation of ENO1 RNA can influence the glycolytic activity of breast cancer cells [75], and ENO1 contributes to breast cancer growth by promoting efficient glycolysis [76]. In TNBC, targeted depletion of ENO1 prevents TNBC cell colony formation, proliferation, and organoid tumor growth, and increases cell death [36]. ENO1 involvement in TNBC cell apoptosis and proliferation has been observed [37, 77]. In prostate cancer, targeting cell surface ENO1 reduces the growth of subcutaneous xenografts [56]. Increased transcription of *ENO1* promotes glycolysis in castration-resistant prostate cancer, subsequently promoting tumor growth [78]. In skin melanoma, activation of AKT-mTOR signaling promotes the expression of ENO1, thereby enhancing the growth and proliferation of melanoma cells [79]. Overexpression of ENO1 promotes proliferation of skin melanoma cells [80]. In clear cell renal cell carcinoma, upregulation of ENO1 expression promotes tumor cell proliferation and xenograft growth [81]. ENO1 upregulates levels of tumor cell glycolysis in leukemia, promoting cell proliferation and enhancing colony formation of hematopoietic stem and progenitor cells [82]. In ovarian cancer, stabilization of ENO1 mRNA in an m^6A -dependent manner by ENO1 promotes tumor growth and glycolysis [83], and the activation of ENO1 dimers increases glycolytic flux, accelerating tumor growth [84]. Activation of ENO1 promotes proliferation of hepatocellular carcinoma [85]. In HCC, exosomal ENO1 promotes HCC cell growth by upregulating integrin α6β4 expression and activating the FAK/Src-p38MAPK pathway [22]. In hepatopancreatobiliary cancer patient-derived organoids, ENO1 promotes their growth through the AKT/PI3K pathway [86]. In cholangiocarcinoma, ENO1 promotes aerobic glycolysis for tumor proliferation [87]. In bladder cancer, analysis of epithelial cells suggests ENO1's involvement in promoting bladder cancer progression through metabolism, cell cycle, and some pro-tumor pathways [27]. In cervical cancer, increased transcription of *ENO1* induces tumor cell glycolysis and promotes cancer progression [88]. In endometrial cancer, upregulation of ENO1 expression promotes cell proliferation [89]. The RNA deconjugating enzyme DHX33 promotes cancer cell proliferation by regulating several key genes involved in the Warburg effect such as ENO1 [90]. In head and neck squamous carcinoma (HNSCC), ENO1 regulates glycolysis, which is involved in the proliferation of HNSCC cells [91], and inhibition of ENO1 degradation promotes glycolysis and reduces ROS production in tumor cells [92]. In oral squamous cell carcinoma (OSCC), ubiquitination and degradation of ENO1 inhibit OSCC cell cycle transition, proliferation, and glycolysis, thereby triggering tumor suppressor functions [93]. Moreover, in OSCC, ENO1 levels are higher than those in other oral malignant diseases such as oral lichen planus [94].

Role of ENO1 in tumor cell invasion, migration and metastasis

EMT is an important biological mechanism in primary tumor metastasis. During EMT, epithelial cells undergo a transformation characterized by the downregulation of epithelial markers (such as E-cadherin) and the upregulation of mesenchymal markers (such as N-cadherin and Vimentin). This transformation can enhance tumor metastasis by promoting migration and invasion [95, 96]. In CRC, upregulation of ENO1 expression promotes CRC cells invasion, while knockdown of ENO1 inhibits the cellular EMT process and the migration ability of CRC cells [14, 54]. Additionally, blocking ENO1 partially inhibits invasion and metastasis of CRC [13]. Moreover, lysine crotonylation at the ENO1 K420 site enhances ENO1 activity, thereby promoting migration and invasion of CRC cells [63]. Reduced ubiquitination-mediated degradation of ENO1 promotes ERK phosphorylation and glycolytic activity in CRC cells. ENO1 inhibition reduces cell migration [12]. Lung cancer cell migration is promoted by ENO1 through the regulation of the PI3K/AKT pathway [69]. ENO1 promotes lung cancer cells

EMT process and contributes to lung tumor metastasis in a tail vein injection model [68]. AL355338 regulates the interaction between ENO1 and EGFR, thereby activating EGFR-AKT signaling and modulating invasiveness in NSCLC [97]. Breast cancer metastasis is fueled by ENO1 through the enhancement of cellular glycolysis [76]. In TNBC, elevated ENO1 expression activates glycolysis in TNBC cells, thereby promoting TNBC cell migration, invasion, and EMT [98]. ENO1 is instrumental in activating the EMT pathway in various tumor cells [37]. Additionally, ENO1 interacts with several small molecule kinases (e.g., LINC00511, PKM2, NEAT1, and CD44) or other lncRNAs, thereby regulating their expression and influencing cell migration [67]. In melanoma, overexpression of ENO1 promotes melanoma cell invasiveness and correlates with aggressive clinical behavior. Furthermore, it induces tumor cell invasion, migration, and elevated levels of MMP-9 and MMP-13 [34, 80]. ENO1 promotes HCC metastasis [85], while degradation of ENO1 inhibits its metastasis by promoting glycolytic reprogramming via the AKT/mTOR pathway [99]. Exosomal ENO1 promotes HCC metastasis through activation of the FAK/Src-p38MAPK pathway and the upregulation of integrin α6β4 expression [22]. Knockdown of ENO1 in pancreatic cancer cells inhibits migration, invasion, and EMT [64]. Knockdown of ENO1 inhibits cell invasion and migration in pancreatic ductal adenocarcinoma cells [61]. Hypoxia increases ENO1 expression in pancreatic ductal adenocarcinoma, thereby promoting tumor cell migration and invasion [31]. Upregulation of ENO1 expression promotes clear cell renal cell carcinoma cells migration [81]. In multiple myeloma, extracellular ENO1 enhances tumor cell glycolytic activity, the expression of glycolysis-related genes, pro-carcinogenic activity, cell migration, cell viability, and secretion of VEGF and TGF-β via HIF-1α [100]. In ovarian cancer, ENO1 stabilizes its mRNA in an m^6A manner to promote tumor metastasis [83]. ENO1 promotes migration and invasion of endometrial cancer cells [89]. In uveal melanoma with BAP1 inactivating mutation, inhibition of hypoxia- and ECM-related pathways, including the ENO1 gene, in vivo, suppresses cancer liver metastasis in BAP1 mutants [101]. ENO1 promotes bladder cancer cell invasion [24]. Furthermore, a study of epithelial cells revealed that ENO1 may promote bladder cancer progression through cell cycle, metabolism, and other oncogenic pathways [27]. In ESCC, ENO1 promotes tumor EMT, migration, invasion, and metastasis [102]. ENO1 secreted by OSCC cells promotes macrophage IL-6 secretion via toll-like receptor 4 (TLR4). In turn, secreted IL-6 inversely promotes OSCC invasion, migration, and EMT [16]. ENO1 regulates glycolysis, which is involved in HNSCC cell migration and invasion [91].

Role of ENO1 in chemoresistance

Chemotherapy is widely employed in cancer treatment; however, the resistance of tumor cells to chemotherapeutic agents markedly diminishes the clinical efficacy of this approach. Several studies have indicated that overexpression of ENO1 can contribute to antitumor resistance by accelerating glycolytic energy metabolism or by activating drug-resistant cell pathways (Fig. 2).

ENO1 expression was significantly elevated in five types of 5-FU-resistant CRC cells. Transfection of HCT-116/5-FU and SW620/5-FU cells with ENO1-shRNA resulted in decreased viability of 5-FU-resistant tumor cells, reduced proliferative and colony-forming abilities, and diminished migration ability and EMT levels. The impact of ENO1 on EMT progression was inhibited by the glycolysis inhibitor 2-DG, suggesting that ENO1's regulation of tumor proliferation, migration, and drug resistance may be linked to energy metabolism [14]. In TNBC, ENO1 knockdown by siRNA or 2-DG treatment in ANRIL-overexpressing TNBC cells demonstrated that ENO1 siRNA or 2-DG reversed adriamycin/doxorubicin (ADR) resistance in lncRNA ANRIL upregulated TNBC cells, indicating that ENO1 enhances ADR resistance by promoting glucose metabolism [104]. In liver cancer, scRNA-seq analysis identified ENO1 among five key energy metabolism-related genes in hepatocellular carcinoma. Drug sensitivity analyses showed that patients with lower scores in these genes were more responsive to metabolism-related chemotherapeutic agents and immune checkpoint inhibitors, such as methotrexate, metformin, and AICAR [105]. The methylation of the ENO1 R9/372 locus increased activity, and heightened ENO1 activity modulates the flux of the pentose phosphate pathway (PPP) and glycolysis in human lung cancer, contributing to cisplatin resistance [70]. This underscores the significant potential of ENO1 in regulating glucose energy metabolism in tumor cells. However, the mechanism by which ENO1-mediated enhancement of glycolysis promotes chemoresistance in tumor cells requires further investigation.

ENO1 not only promotes tumor drug resistance by regulating tumor cell metabolism but also activates associated cell signaling pathways to confer chemotherapy resistance. In GBM, temozolomide (TMZ)-resistant tumor cells secrete exosomes containing lnc-TALC. Lnc-TALC in these exosomes binds to ENO1 in microglia, which subsequently activates the p38 MAPK signaling pathway. p38 MAPK then interacts with the transcription factor MEF2C, enhancing its transcriptional activity and promoting C5a transcription. Elevated C5a in microglia is released into the tumor microenvironment and binds to C5aR on TMZ-sensitive tumor cells, facilitating TMZ-induced DNA damage repair and resulting

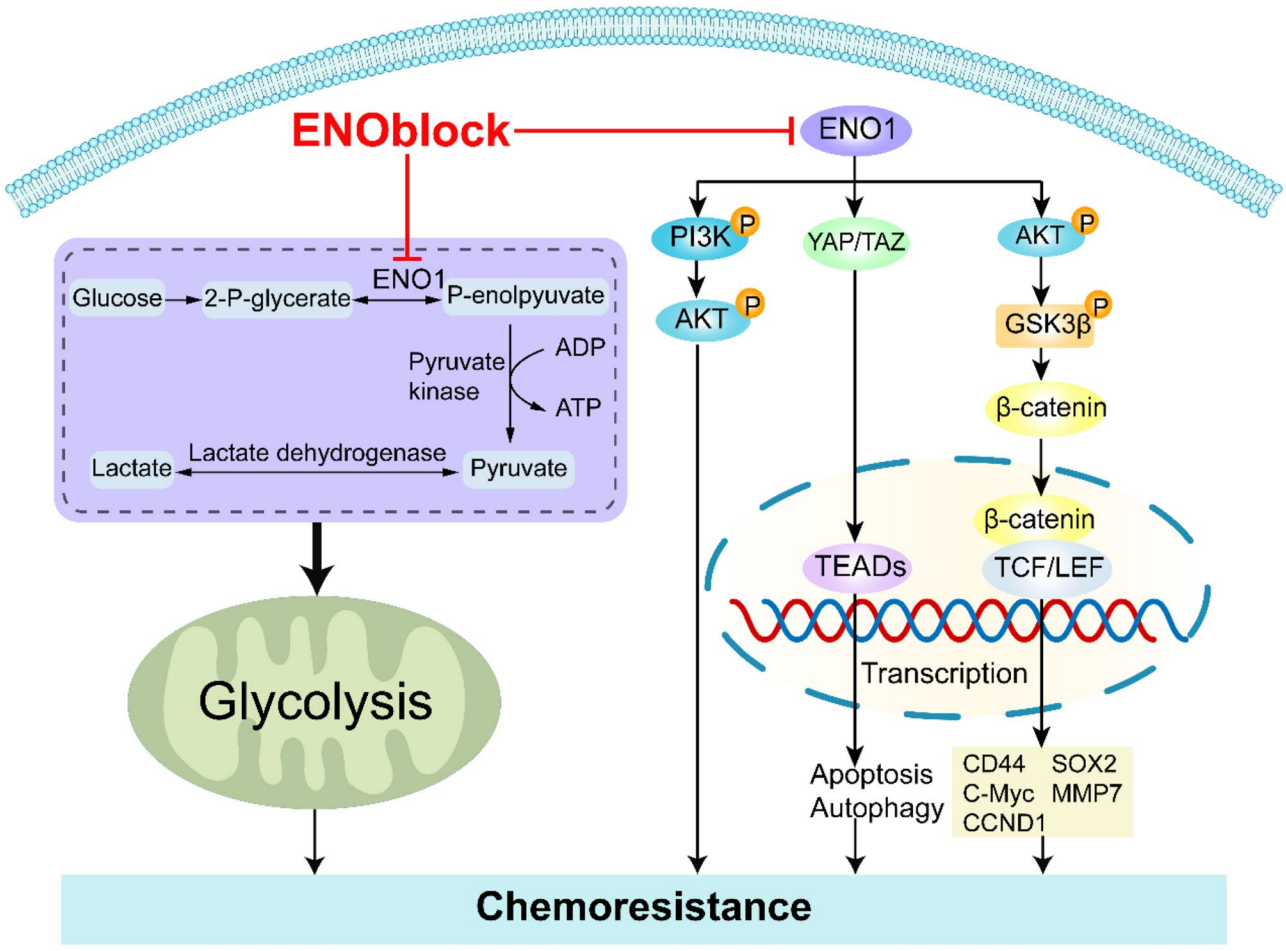

Fig. 2. ENO1 promotes chemoresistance in tumors by promoting glycolysis [14] and activating the PI3K/AKT [106], YAP1 [30], and Wnt/β-catenin signaling pathways [107]. ENOblock, an inhibitor of ENO1, blocks this chemoresistant effect by inhibiting ENO1 [58, 106].

in chemoresistance [55]. ENO1 is overexpressed in pancreatic cancer cells, and ENO1 knockdown enhances the cytotoxicity of gemcitabine while reducing YAP1 expression, a key downstream effector of the Hippo pathway. YAP1 promotes autophagy, thereby protecting pancreatic cancer cells from gemcitabine-induced apoptosis. This suggests that ENO1 overexpression increases gemcitabine resistance by upregulating YAP1, which promotes tumor growth and progression [30]. In OSCC, ENO1 activates the AKT/GSK3β axis within the Wnt signaling pathway, leading to increased β-catenin expression. This β-catenin binds to the transcription factors TCF/LEF in the nucleus and promotes the expression of CD44, C-Myc, and CCND1, which in turn enhances cisplatin resistance in OSCC cells [107].

Given the role of ENO1 in tumor chemotherapy resistance, targeting ENO1 represents a promising strategy to counteract chemotherapy resistance that develops during tumor progression. For instance, ENOblock, a well-known ENO1 inhibitor, has been shown to inhibit glycolysis and stemness in gastric cancer cells, thereby increasing their sensitivity to cisplatin [58]. In CRC, ENOblock significantly enhanced the tumor suppression effects of oxaliplatin and 5-FU in CRC cells inoculated with *Fusobacterium nucleatum*. Animal studies demonstrated that ENOblock treatment markedly improved tumor suppression efficacy in hormonally induced mice treated with oxaliplatin [53]. In small cell lung cancer (SCLC), ENO1 is highly expressed in chemoresistant cells and regulates chemoresistance through activation of the PI3K/AKT pathway. Treatment with ENOblock effectively reversed this ENO1-mediated chem22oresistance, highlighting its potential as a valuable therapeutic agent for ENO1-mediated chemoresistance and tumor treatment [106].

Role of ENO1 in angiogenesis

Tumor angiogenesis provides essential oxygen and nutrients to rapidly proliferating tumor cells and is a hallmark of tumor progression.

In prostate cancer, targeting ENO1 with ENO1 mAb HuL227 reduced angiogenesis in a PC-3 subcutaneous

xenograft model. In vitro, ENO1 mAb HuL227 inhibited VEGF-A-mediated angiogenesis in HUVEC cells, and this inhibition was ENO1-dependent and possibly related to fibrinolysis. However, the mechanism through which ENO1 upregulates VEGF-A and promotes angiogenesis requires further investigation [56].

ENO1 also plays an important role in angiogenesis in other diseases beyond cancer. ENO1 expression was elevated in hypoxic human pulmonary artery endothelial cells and in lung tissues of chronic obstructive pulmonary disease-associated pulmonary hypertension and hypoxic pulmonary hypertension mouse models. Elevated ENO1 promotes the angiogenesis by activating the PI3K/AKT/mTOR signaling pathway and inducing mitochondrial dysfunction [108]. ENO1-driven glycolysis promotes pathologic angiogenesis in small bowel vascular malformation [109]. In non-tumor diseases, ENO1 can promote angiogenesis by activating the PI3K/AKT/mTOR signaling pathway or by promoting glycolysis, raising the thought of whether ENO1 utilizes the similar mechanism to promote angiogenesis in the tumor environment.

Role of ENO1 in the tumor immune microenvironment

ENO1 correlates with the infiltration of several immune cells in tumor microenvironment and can act on immune cells to promote several tumor progression [24]. *ENO1* was associated with depletion of $CD8^+$T cells through large amounts of RNA-seq and scRNA-seq [27]. In prostate cancer, targeting cell surface ENO1 reduces monocyte recruitment in subcutaneous xenografts [56]. In glioblastoma, ENO1 is associated with low levels of NK cells, T cells and B cells, and in addition, ENO1 promotes M2 polarization of microglia [19]. ENO1 positively correlates with $CD4^+$ T cell infiltration in colon adenocarcinoma [110]. OSCC cells produce IL-8 in response to ENO1, which activates STAT3 signaling and inhibits Jurkat T cell proliferation [111]. OSCC-secreted ENO1 promotes macrophage IL-6 secretion via TLR4 [16]. In pancreatic cancer, knockdown of ENO1 in the mouse pancreatic cancer cell line PAN02 by CRISPR/CAS9 reduced the number of Treg cells in the tumor microenvironment and up-regulated the expression of *STAT1*, *TNF-α*, and granzyme B, and down-regulated the expression of typical anti-inflammatory and pro-apoptotic cytokines, including IL-10, ARG-1, TGF-β, IL-13, and BCL-2 [28]. In breast cancer, ENO1 expression is high and positively correlates with a variety of anti-tumor infiltrating immune cells in stage I/II patients, such as M1 macrophages, NK-cells, B-cells, helper T-cells, and $CD8^+$T-cells [38].

Role of ENO1 in promoting stemness in cancer stem cells

ENO1 has been shown to be positively associated with cancer stem cell (CSC) stemness and plays a key role in tumor invasion, migration, and chemoresistance, as indicated by recent studies. Expression of ENO1 was upregulated in a subset of stem cell-like glioblastomas. mRNA expression of ENO1 positively correlated with stemness markers, such as CD133/PROM1 and SOX2, in tumors of GBM patients [112]. In gastric cancer, ENO1 enhances the stemness of stem cells by increasing cellular glycolytic activity, which includes self-renewal ability, cell migration, invasion, chemotherapy resistance, and even tumorigenicity of gastric cancer cells. ENO1 is an important biomarker associated with the stemness of gastric cancer cells [57, 58]. In lung cancer stem cells, ENO1 activates AMPK/mTOR signaling, which increases self-renewal, growth, and invasion [113]. ENO1 is specifically expressed on the invasive surface of highly invasive and pro-metastatic cancer stem cell subpopulations in gastric and prostate cancers. Inhibition of ENO1 surface localization impairs invasive pseudopod biogenesis, protein hydrolysis, and CSC invasiveness [114].

Role of ENO1 in cellular ferroptosis

Cell death induced by excessive lipid peroxidation, known as ferroptosis, is associated with the development of various tumor types and their response to therapy. Impaired ferroptosis triggers inflammation-related immunosuppression in the tumor microenvironment, thus favoring tumor growth [115]. In HCC, CNOT6 is recruited by ENO1 to accelerate the mRNA decay of iron-regulated protein 1 by binding to RNA. This process suppresses mitochondrial ferritin 1 expression and subsequently inhibits mitochondrial iron-induced ferroptosis [59]. The silencing of ENO1 inhibits glycolysis and proliferation by inactivating AKT/STAT3 pathway, while promoting ferroptosis in CRC cells [116].

Role of ENO1 in radiosensitivity

Cancer treatment primarily involves surgery, radiotherapy, chemotherapy, and the rapidly evolving immunotherapy [117]. Although surgery is the preferred approach, radiotherapy continues to hold a relevant and significant role in cancer treatment. For example, many patients with advanced rectal or sigmoid colon cancer require both radiotherapy and initial surgical treatment [118].

Recently, a growing number of studies have demonstrated that ENO1 contributes to radiation resistance. A proteomic analysis suggested that metabolic proteins regulating glycolysis, including ENO1, could serve as biomarkers of CRC radioresponsiveness [20]. TCGA gene analysis showed that ENO1 expression was significantly upregulated in CRC tissues [20]. In breast cancer, RNA-seq analysis of the BC cell line MDA-MB-231 (ionizing radiation-sensitive, IR-S) and its IR-R counterpart, performed using the GEO database, revealed that ENO1 was

the most highly expressed gene in IR-R BC cells [35]. The high expression of ENO1 in radiotherapy-resistant IR-R cells was verified at the gene and protein levels, respectively. This suggests that ENO1 can be used as a prognostic marker for the efficacy of radiotherapy in breast cancer. ENO1 reduces reactive oxygen species (ROS) production and apoptosis in vitro and in vivo by regulating mitochondrial homeostasis, which enhances therapeutic resistance to radiotherapy in breast cancer [35]. However, further research is required to elucidate the specific mechanism by which ENO1 drives tumor radiotherapy resistance.

Role of ENO1 in cellular autophagy

During autophagy, damaged organelles, pathogens, and aggregated proteins are translocated to the lysosome for degradation, maintaining cellular homeostasis [119]. Autophagy can keep tumor cells alive under stress during the tumor development stage and seems to play a significant role in tumor cell metastasis [120]. Silencing of *ENO1* inhibits pancreatic cancer cells autophagy [30]. Inhibition of glycolysis, which includes ENO1, leads to autophagy induction in a subset of stem cell-like GBM tumors [112].

Role of ENO1 in anti-tumor immunity

However, ENO1 is not always a promoter of tumor progression, and recent reports suggest that ENO1 has an important role in exerting anti-tumor immunity. Condition medium (CM) of such tumor cells (breast, prostate, and pancreatic) was collected, and genome-wide proteomic analysis was performed. An analysis of the proteomic profile of CM revealed that it enriched with ENO1 and had significant tumor suppressor effects [121, 122]. ENO1 inhibits tumor progression through cell adhesion receptors and interacts with the CSC marker CD44 [121–123].

According to Di Ge et al., ENO1 also plays a crucial role in antitumor immunity. By promoting ubiquitination and subsequent proteasomal degradation of programmed cell death ligand 1 (PD-L1) in lung cancer cells, ENO1 destabilizes and reduces PD-L1 expression. Moreover, ENO1 overexpression enhances antitumor immunity mediated by T-cells by sensitizing tumor cells to specific T-cell killing [124]. However, given the antitumor effects of ENO1, more studies are needed to clarify the specific antitumor mechanisms.

Specific mechanisms

ENO1 and PI3K/AKT/mTOR signaling pathway

The PI3K/AKT/mTOR signaling pathway is a highly conserved network in eukaryotic cells promoting cell survival, cycle progression and growth. The PI3K/AKT signaling pathway primarily drives glycolysis in cancer cells. ENO1 acts as a key activator of the PI3K/AKT signaling pathway. ENO1 promotes aerobic glycolysis, tumorigenesis, proliferation, invasion, migration, metastasis, and chemoresistance of tumor cells through the activation of the PI3K/AKT/mTOR pathway. In Xie et al.'s study, ENO1 promotes breast tumorigenesis through the activation of PI3K/AKT [52]. In hepatocellular carcinoma, circRPN2 binds to ENO1, accelerating its degradation, and inhibits HCC metastasis by reducing aerobic glycolysis via the AKT/mTOR pathway [99]. In pancreatic cancer, the knockdown of ENO1 inhibits the invasion, migration, and proliferation of pancreatic cancer cells via the PI3K/AKT pathway [64]. In gastric cancer, CCDC65 binds to ENO1, contributing to tumor pathogenesis through its structural domain (a.a. 130–484), and further promoting the ubiquitination of ENO1 through the recruitment of the E3 ubiquitin ligase FBXW7. And then ENO1 reduces its binding to and further inactivates AKT1, leading to a reduction in cell proliferation and the loss of EMT signaling [66]. Lactate promotes growth via the HIF1α/ENO1/PI3K/AKT pathway in patient-derived organoids of hepatopancreatobiliary carcinoma [86]. In lung cancer, B7-H3 (CD276) interacts directly with ENO1 in lung cancer cells and regulates the PI3K/AKT pathway through ENO1, thereby promoting the proliferation and migration of lung cancer cells [69]. In SCLC, fibroblast growth factor receptor-like 1 regulates chemotherapy resistance by interacting with ENO1 and modulating its downstream PI3K/AKT signaling pathway [106]. In NSCLC, reduced ENO1 phosphorylation results in reduced PI3K and AKT phosphorylation, which is associated with a decrease in cell proliferation and tumor progression [74] (Fig. 3).

ENO1 not only positively regulates the PI3K/AKT/mTOR signaling pathway, in turn the PI3K pathway, a key activator of the Warburg effect in tumor cells, also upregulates the expression of various key glycolytic genes, including *ENO1*, thereby mediating tumor progression. The PI3K signaling pathway affects the expression of glycolytic genes, including *ENO1*, in glioblastoma [17]. In clear cell renal cell carcinoma, the knockdown of PB1 activates AKT-mTOR signaling and increases the expression of key glycolytic enzymes, including ENO1, at both the gene and protein levels [81].

ENO1 and Wnt/β-catenin signaling pathway

Wnt signaling regulates essential developmental gene expression programs by increasing nuclear and cytoplasmic β-catenin. Abnormal activation of the Wnt/β-catenin signaling pathway promotes self-renewal of cancer stem cells, cell proliferation, and other oncogenic processes, thereby promoting tumor progression [126]. In OSCC, ENO1 drives cisplatin resistance through the AKT/GSK3β axis modulating Wnt signaling [107]. Moreover,

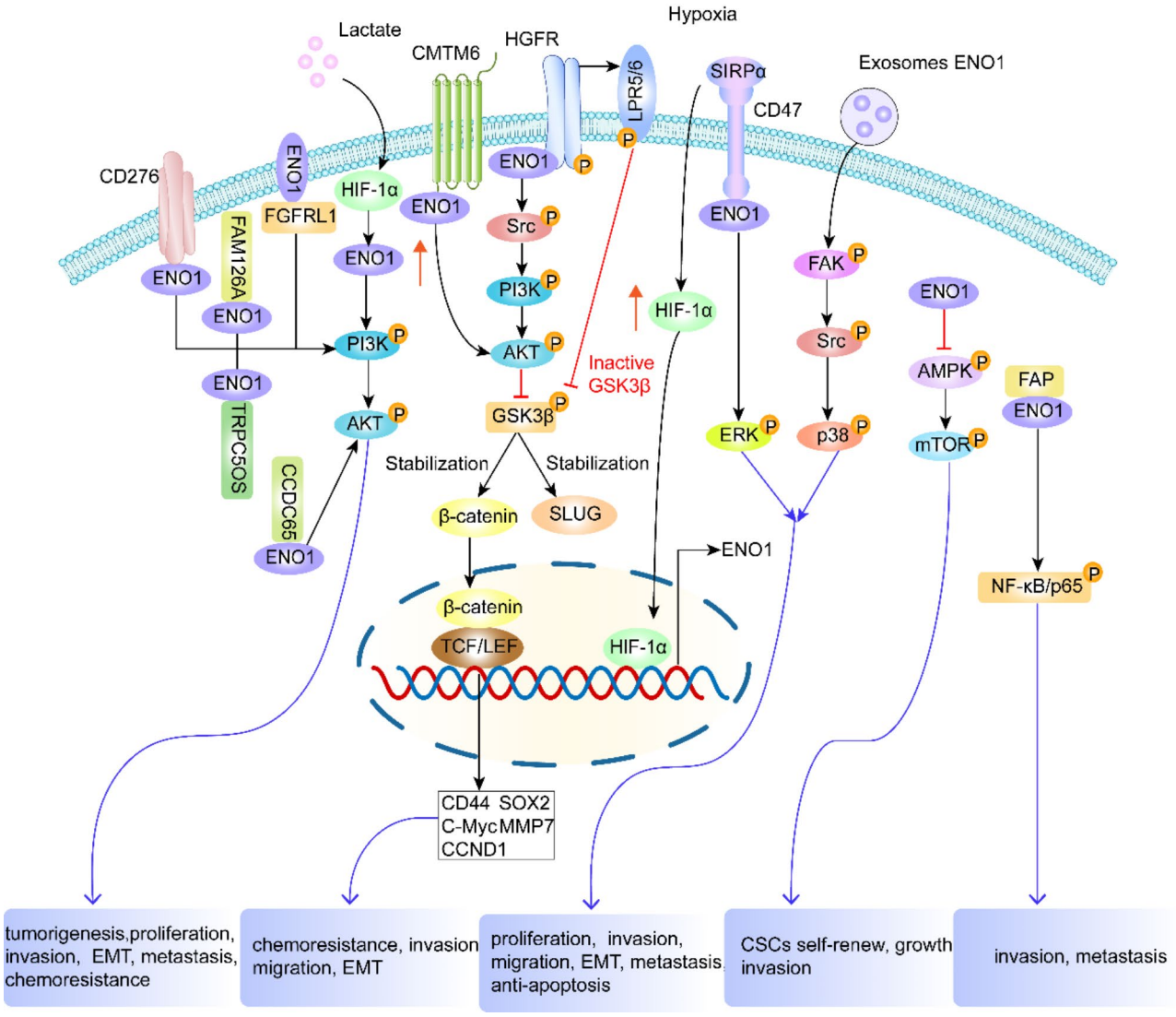

Fig. 3. ENO1 is stimulated by extracellular signals or binds to intracellular proteins and activates relevant oncogenic pathways in tumor cells, such as the PI3K/AKT signaling pathway [64], Wnt/β-catenin signaling pathway [107, 125], MAPK signaling pathway [12, 22, 31], AMPK signaling pathway [113], and NF-κB signaling pathway [13]. These pathways promote tumor cell proliferation, anti-apoptosis, invasion and metastasis, chemoresistance, and self-renewal, growth and invasion of cancer stem cells.

metformin and anti-ENO1 antibody may alleviate CSC resistance by blocking the Wnt/β-catenin pathway [125].

ENO1 and MAPK signaling pathway

The mitogen-activated protein kinase (MAPK) pathway transports extracellular signals from membranes to intracellular targets. It is implicated in various tumor biological functions, including tumor invasion, metastasis, cell proliferation, apoptosis, cell cycle progression, cellular metabolism, and ultimately cell death or survival [127]. In GBM, temozolomide-associated lnc-RNA binds to ENO1, leading to the phosphorylation of p38 MAPK in microglia. This promotes the release of C5a into the tumor microenvironment, enhancing the chemoresistance of GBM to TMZ [55]. In hepatocellular carcinoma, exosomal ENO1 increases the proliferation and metastasis of HCC cells by stimulating the production of integrin α6β4 and turning on the FAK/Src-p38MAPK pathway [22].

The RAF-MEK-ERK signaling cascade is a well-characterized MAPK pathway that participates in cell proliferation and survival [128]. In pancreatic ductal adenocarcinoma, hypoxia induces an increase in ENO1 expression, which in turn promotes ERK phosphorylation and inhibits tumor cell apoptosis, resulting in cell survival and invasion [31]. CD47 interacts with ENO1, and then promotes ERK phosphorylation and glycolytic activity in CRC cells, thus enhancing tumor cell growth and migration [12].

ENO1 and AMPK signaling pathway

AMP-activated protein kinase (AMPK) maintains energetic homeostasis by coordinating various cellular processes such as adipogenesis, glycolysis, the TCA cycle, cell cycle progression, and mitochondrial dynamics [129]. ENO1 enhances lung cancer stem cells self-renewal, growth, and invasion via the AMPK/mTOR pathway [113].

ENO1 and NF-κB signaling pathway

Activation of NF-κB may promote tumor cell proliferation, survival, angiogenesis, and invasion during tumorigenesis and progression [130]. In CRC, ENO1 binds to fibroblast activation protein α (FAP) and activates the ENO1-dependent NF-κB signaling pathway. FAP-mediated pro-tumor invasive and metastatic effects are partly mitigated by blocking ENO1 [13].

ENO1-targeted tumor therapy

Considering the significant role of ENO1 in tumors, therapeutic strategies targeting ENO1 have gained widespread attention. In recent years, ENO1 inhibitors and other targeted therapies, including specific antibody and DNA vaccine, have demonstrated remarkable efficacy in pharmacological studies and preclinical trials.

ENOblock

ENOblock, also known as AP-III-a4, functions as a non-enzymatic active site inhibitor by binding to enolase directly without the need for a substrate analog [131]. AP-III-a4 has been extensively utilized to elucidate the role of ENO1 in cancer development [35, 46, 53, 58]. ENOblock inhibits *F. nucleatum*-induced CRC cell proliferation, and it significantly reduces tumor growth of *F. nucleatum*-cultured tumor cells in a CRC xenograft mouse model [53]. ENOblock inhibits the proliferation of tumor cells and the growth of tumor spheres in vitro while enhancing the tumor cell sensitivity to chemotherapy drugs. For example, in gastric cancer, ENOblock increases the sensitivity of GC cells to cisplatin by inhibiting their stemness and levels of glycolysis [58]. In addition, ENOblock exhibits a synergistic anti-tumor effect when used in combination with radiotherapy. In breast cancer, ENO1 enhances radiation therapy resistance by modulating mitochondrial homeostasis in vitro and in vivo to reduce ROS production and inhibit apoptosis. In contrast, radiation therapy sensitivity is restored in breast cancer cells by ENOblock. This suggests that ENOblock can produce strong synergistic anti-tumor effects when used in combination with radiation therapy [35] (Fig. 4 and Table 2).

Specific antibody

The use of anti-ENO1 monoclonal antibodies is a promising targeted therapy. In GC and NSCLC, metformin combined with anti-ENO1 antibody can overcome CSC resistance by suppressing the Wnt/β-catenin pathway [125]. In addition to directly impacting tumor cells,

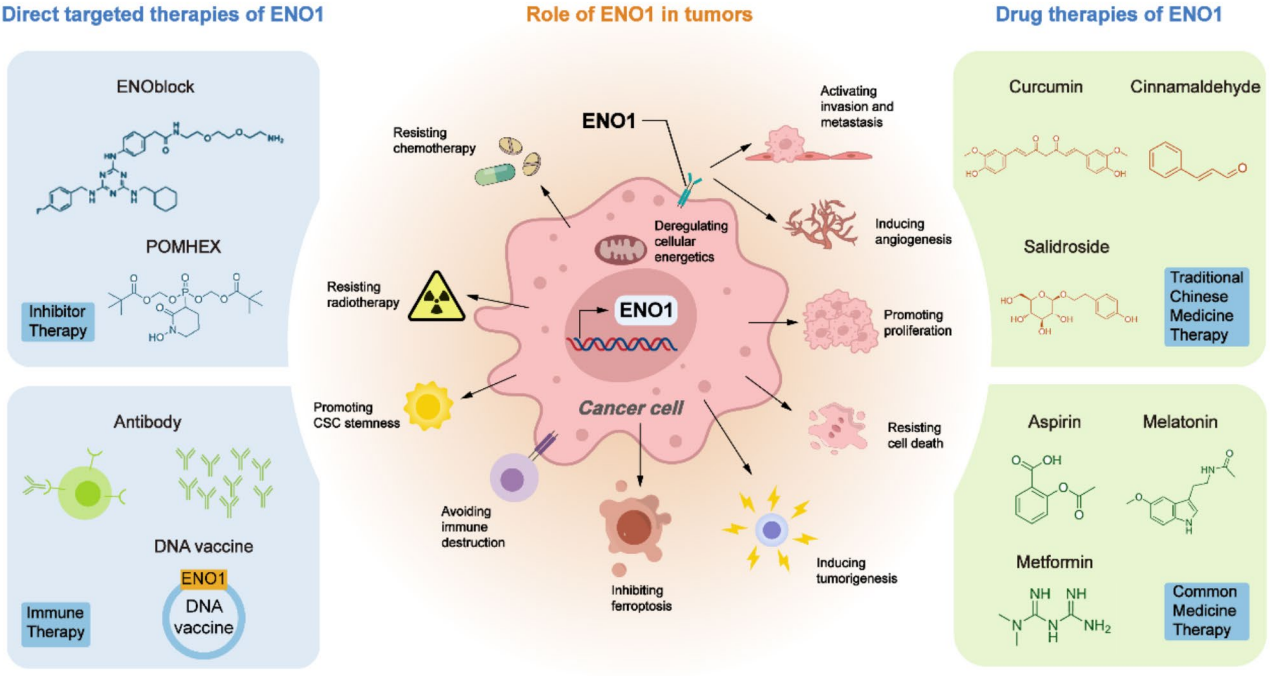

Fig. 4. Role of ENO1 in tumor progression and its treatment, including inhibitor therapy, immunotherapy, traditional Chinese medicine therapy, and common medicine therapy.

Table 2 Targeted therapeutic strategies of ENO1 in various tumors

Drug	Mechanisms of Action	Cancer Type	Biological Functions	References
AP-III-a4 (ENOblock)	Nonsubstrate analog inhibitor	Colorectal cancer	Cell proliferation, tumor growth	[53]
		Gastric cancer	Cell stemness, glycolysis, chemoresistance	[58]
		Breast cancer	Radiosensitivity	[35]
HuL227	Antibody	Prostate cancer	Tumor growth, monocyte recruitment, angiogenesis	[56]
Anti-ENO1 antibody	Antibody	Gastric cancer, non-small cell lung cancer	Chemoresistance	[125]
Ag85B-ENO146-82	DNA vaccine	Lewis lung cancer	Tumor growth, immune response	[132]
ENO1 DNA vaccine	DNA vaccine	Pancreatic cancer	Immune response, survival of tumor bearing mice	[133]
POMHEX	Substrate-competitive inhibitor	*ENO1*-deleted glioblastoma	Cell viability	[134]
Curcumin	Downregulation of ENO1 expression	Glioblastoma	Glycolysis, migration, invasion, apoptosis	[18]
	Downregulation of ENO1 expression	Triple-negative breast cancer	Glycolysis	[135]
Cinnamaldehyde	Downregulation of ENO1 expression	Melanoma	Tumor growth, apoptosis, glycolysis, cell cycle	[136, 137]
	Covalent conjugation	Hepatocellular carcinoma	Glycolysis, TCA cycle	[138]
ISL-NLs	Downregulation of ENO1 expression	Colorectal cancer	Glycolysis	[139]
Salidroside	Downregulation of ENO1 expression	Gastric cancer	Glycolysis, cell proliferation	[140]
Aspirin	Post-translational modifications	Hepatocellular carcinoma	Glycolysis, cell proliferation, tumorigenesis	[62], [141]
Macrosphelide A	Specific binding	Liver cancer, leukaemia, breast cancer	cell proliferation, apoptosis	[142]
Metformin	Promoting ubiquitination	Gastric cancer	cell proliferation, EMT	[66]
Melatonin	Downregulation of ENO1 expression	Bladder cancer	Glycolysis, tumorigenesis, chemoresistance	[143]
Triterpenoids		Colorectal cancer	Glycolysis, cell proliferation, apoptosis	[144]

ENO1 antibodies can inhibit tumor progression by modulating the tumor microenvironment. One effective and potentially beneficial approach to targeted therapy is the use of anti-ENO1 antibodies. In prostate cancer, the use of ENO1 mAb (HuL227) reduces subcutaneous xenograft growth, monocyte recruitment, and intratumoral angiogenesis by targeting cell surface ENO1 via a fibrinolytic-associated mechanism within the tumor microenvironmental ecosystems involved in prostate cancer progression and bone metastasis, which could provide a new immunotherapeutic approach for prostate cancer patients [56].

DNA vaccine

Therapeutic DNA cancer vaccines are now recognized as a very promising strategy to activate the immune system against cancer. Developing a therapeutic cancer vaccine, Ag85B-ENO146-82, according to the ENO1 tumor-associated antigen, which prevents the growth of lung cancer in vivo. Anti-tumor effects were shown in tumor-loaded immune-competent C57BL/6 mice treated with Ag85B-ENO146-82 for Lewis lung cancer (LLC). Ag85B-ENO146-82 therapy boosted tumor-specific IFN-γ and TNF-α released by $CD8^+$ T cells, generated dense infiltration of $CD4^+$ and $CD8^+$ T cells in tumors, and promoted M1 phenotypic polarization of macrophages. Analysis using flow cytometry revealed that $CD8^+$T effector memory cells and central memory cells were upregulated. qPCR and ELISA tests revealed that the expression of TNF-α and IFN-γ was upregulated, while the expression of IL1β, IL6, and IL10 was downregulated [132]. It highlights the potential of the ENO1 DNA vaccine as an innovative immunotherapy for Lewis lung carcinoma patients. Additionally, ENO1 DNA vaccine combined with chemotherapy has been shown to significantly enhance the therapeutic efficacy against tumors.

Recent studies have demonstrated favorable therapeutic effects of ENO1 DNA vaccine in combination with chemotherapy in the treatment of pancreatic cancer. As compared to mice vaccinated or treated with gemcitabine alone, mice treated with gemcitabine prior to ENO1 DNA vaccination developed $CD4^+$T cell antitumor activity and significantly impaired tumor progression [133]. This study supports the potential of combination therapy in cancer treatment.

POMHEX

Recently, HEX and its prodrug POMHEX, possessing high cellular and blood-brain barrier permeability, have been rapidly developed. The small molecule enolase inhibitor POMHEX selectively kills *ENO1*-deficient glioma cells at low nanomolar concentrations and

eradicates intracranial in situ *ENO1*-deficient tumors in mice at doses that are well tolerated by nonhuman primates, exhibiting a notable safety profile, indicating their potential for clinical applications [134].

Traditional Chinese medicine

Traditional Chinese medicine extract components also play a significant role in targeting ENO1 in tumors. In glioblastoma, the expression of ENO1 was significantly reduced in tumor cells treated with curcumin, and *ENO1* emerged as a potential target gene affected by curcumin for glioblastoma prognosis. Curcumin also inhibited migration and invasion while promoting apoptosis in GBM cells [18]. The development of electrical pulse (EP)-mediated turmeric-silver nanoparticle (TurNP) therapy in triple-negative breast cancer; high-throughput, label-free quantitative proteomics analysis reveals the downregulation of ENO1 expression by TurNP + EP treatment [135]. CAD-14, a cinnamaldehyde (CA) compound, inhibits the p38 pathway in melanoma and suppresses tumor growth by inhibiting ENO1 expression, which induces apoptosis [136]. Moreover, the covalent binding of CA to ENO1 alters ENO1 protein stability and impacts glycolytic activity. Additionally, a combination of dacarbazine (DTIC) and CA significantly inhibited melanoma cell growth both in vitro and vivo by enhancing S-phase cell cycle arrest. Since CA inhibits ENO1 covalently, it may offer benefits to patients who are resistant to antimelanoma treatment when combined with DTIC [137]. In hepatocellular carcinoma, CA covalently binds with ENO1, impacting both the stability and activity of ENO1 and altering the dynamic balance of glucose metabolism. Blockading ENO1-induced gluconeogenic reflux enhances the TCA cycle, ultimately resulting in lower blood glucose levels and increased mitochondrial efficiency [138]. In CRC, isoglycyrrhizin-loaded nanoliposomes (ISL-NLs) inhibit tumor progression by modulating ENO1 in glycolysis and suppressing lactate production via the AMPK/mTOR pathway [139].Salidroside suppresses tumor cell proliferation by inhibiting glycolysis through the suppression of ENO1 expression in gastric cancer cells [140]. Mechanistically, these traditional Chinese medicines inhibit the glycolysis of tumor cells by downregulating ENO1 expression, thereby inhibiting tumor cell proliferation, invasion, and migration. This highlights the potential of traditional Chinese medicine extracts in targeting ENO1 for cancer treatment; however, the mechanisms by which they downregulate ENO1 expression require further investigation.

Others

Aspirin decreases the activity of ENO1 by modulating its lysine 2-hydroxyisobutyrylation (Khib) level, thereby attenuating both glycolysis and proliferation of hepatocellular carcinoma cells [141]. Additionally, aspirin delays tumorigenesis of hepatocellular carcinoma via ENO1/YAP [62]. Macrosphelide A inhibits the proliferation of cells and induces apoptosis in hepatocellular carcinoma, leukemia, and breast cancer by targeting key glycolytic enzymes, including ENO1 [142]. In gastric cancer, metformin significantly inhibits cell proliferation mediated by the ENO1-AKT1 complex and EMT signaling, ultimately suppressing the malignant phenotype of gastric cancer cells [66]. In bladder cancer, melatonin inhibits tumorigenesis as well as enhances the resistance of bladder cancer cells to gemcitabine through PPARγ/ENO1-mediated glycolysis [143]. Triterpenoids promote the proliferation and inhibit the apoptosis of CRC cells by targeting ENO1 along with other key targets involved in glycolytic and glutaminolytic pathways [144].

Given that ENO1 plays a significant role in the development of various tumors, it would be beneficial to address potential clinical drugs targeting ENO1. ENO1 inhibitors, including ENOblock and POMHEX, have been developed. However, all ENO1 inhibitors remain in the preclinical research stage and have not yet entered clinical treatment. Immunotherapies targeting ENO1, including monoclonal antibodies and DNA vaccines, have also been developed. Beyond specific ENO1 inhibitors, antibodies and vaccines, several potential drugs may indirectly target ENO1. Some traditional Chinese medicines, such as curcumin, cinnamaldehyde, and salidroside, have been found to reduce ENO1 expression in tumors, exerting anti-tumor effects, though the mechanisms require further investigation. Additionally, common drugs such as aspirin, metformin, and melatonin have also been shown to reduce ENO1 expression in tumors, but available data are limited and further research is needed.

ENO1 inhibitors have demonstrated promising results in preclinical studies. More complex combination therapies, such as the integration of DNA vaccines with chemotherapy, have shown potential. Nevertheless, certain challenges remain, such as suboptimal drug targeting. Given that ENO1 is widely expressed in various tissues and cells, future studies should prioritize optimizing drug targeting, reducing side effects, and exploring the combined application with other therapeutic approaches. In conclusion, ENO1-targeted therapeutic agents hold promise, but further research and optimization are required to fully realize their clinical potential.

Conclusion and future perspectives

In summary, ENO1 is associated with a poor prognosis and overexpressed in a variety of human malignant tumors, and can be used as a tumor biomarker. ENO1 exhibits a variety of biological functions in tumor progression, which include promotion of tumorigenesis, increase in glycolysis, stimulation of cell EMT, migration,

invasion, metastasis and proliferation, activation of oncogenesis-related signaling pathways, angiogenesis, and chemoresistance. Thus, ENO1 can be regarded as a crucial oncoprotein that facilitates and sustains tumor progression. In recent years, comprehensive studies of clinical and physiological functions have identified ENO1 as a key target for therapeutic development.

Localization of ENO1 on the cell membrane can promote tumor development and metastasis. Intracellularly, it can activate glycolytic energy metabolism or act as a regulator in several pathways such as hypoxia signaling, PI3K/AKT/mTOR, Wnt/β-catenin, MAPK, AMPK, and NF-κB. LncRNAs can also regulate the transcriptional and enzymatic activities of ENO1 in tumors. Moreover, ENO1 can be secreted by tumor cells into the tumor microenvironment, where it interacts with other cells, such as tumor-associated macrophages, promoting the release of cytokines or other mediators, which in turn promote the progression of tumors. Therefore, detailed studies of ENO1 transcription, translation, activity, translocation, and roles in cellular signaling pathways are essential to guide effective tumor therapies. The role of ENO1-regulated lactic acid in the tumor microenvironment and the soluble ENO1-mediated interaction between tumor cells and other cells deserve further investigationThe targeted nature of ENO1 renders it an attractive tumor biomarker as well as a therapeutic target. ENO1 is a very suitable cancer biomarker for both prognostic and diagnostic purposes due to its cell surface location. Because of its location in tumor cells, important metabolic roles, and capacity to accelerate the growth of tumors, it can be used to develop a very promising targeted therapeutic strategy to bring hope to cancer patients.

Abbreviations

GBM	Glioblastoma
CRC	Colorectal cancer
HCC	Hepatocellular carcinoma
TNM	Tumor lymph node metastasis
TNBC	Triple-negative breast cancer
LUAD	Lung adenocarcinoma
ESCC	Esophageal squamous cell carcinoma
YAP1	Yes-associated protein 1
NSCLC	Non-small cell lung cancer
HNSCC	Head and neck squamous carcinoma
OSCC	Oral squamous cell carcinoma
EMT	Epithelial-mesenchymal transition
TMZ	Temozolomide
SCLC	Small cell lung cancer
CSC	Cancer stem cell
CM	Condition medium
PD-L1	Programmed cell death ligand 1
MAPK	Mitogen-activated protein kinase
AMPK	AMP-Activated protein kinase

Author contributions

Y.L. wrote the main manuscript text. L.L. prepared Figs. 1 and 2; Table 1. B.L. edited and significantly revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data availability

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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References

1. Warburg O. On the origin of cancer cells. Science. 1956;123:309–14.
2. Díaz-Ramos À, Roig-Borrellas A, García-Melero A, López-Alemany R. α-Enolase, a multifunctional protein: its role on pathophysiological situations. J Biomed Biotechnol. 2012;2012:1–12.
3. Muller FL, Colla S, Aquilanti E, Manzo VE, Genovese G, Lee J, Eisenson D, Narurkar R, Deng P, Nezi L, et al. Passenger deletions generate therapeutic vulnerabilities in cancer. Nature. 2012;488:337–42.
4. Xu W, Yang W, Wu C, Ma X, Li H, Zheng J. Enolase 1 correlated with Cancer Progression and Immune-infiltrating in multiple Cancer types: a Pan-cancer Analysis. Front Oncol 2021, 10.
5. Cras P, Martin JJ, Gheuens J. Gamma-enolase and glial fibrillary acidic protein in nervous system tumors. An immunohistochemical study using specific monoclonal antibodies. Acta Neuropathol. 1988;75:377–84.
6. von Deimling A, Janzer R, Kleihues P, Wiestler OD. Patterns of differentiation in central neurocytoma. An immunohistochemical study of eleven biopsies. Acta Neuropathol. 1990;79:473–9.
7. De Vitis C, Battaglia AM, Pallocca M, Santamaria G, Mimmi MC, Sacco A, De Nicola F, Gaspari M, Salvati V, Ascenzi F et al. ALDOC- and ENO2- driven glucose metabolism sustains 3D tumor spheroids growth regardless of nutrient environmental conditions: a multi-omics analysis. J Experimental Clin Cancer Res 2023, 42.
8. Royds JA, Variend S, Timperley WR, Taylor CB. An investigation of beta enolase as a histological marker of rhabdomyosarcoma. J Clin Pathol. 1984;37:905–10.
9. Chen J, Zhang Z, Ni J, Sun J, Ju F, Wang Z, Wang L, Xue M. ENO3 promotes colorectal cancer progression by enhancing cell glycolysis. Med Oncol 2022, 39.
10. Cui H, Guo D, Zhang X, Zhu Y, Wang Z, Jin Y, Guo W, Zhang S. ENO3 inhibits growth and Metastasis of Hepatocellular Carcinoma via Wnt/β-Catenin signaling pathway. Front Cell Dev Biology 2021, 9.
11. Jing Z, Liu Q, He X, Jia Z, Xu Z, Yang B, Liu P. NCAPD3 enhances Warburg effect through c-myc and E2F1 and promotes the occurrence and progression of colorectal cancer. J Experimental Clin Cancer Res 2022, 41.
12. Hu T, Liu H, Liang Z, Wang F, Zhou C, Zheng X, Zhang Y, Song Y, Hu J, He X, et al. Tumor-intrinsic CD47 signal regulates glycolysis and promotes colorectal cancer cell growth and metastasis. Theranostics. 2020;10:4056–72.
13. Yuan Z, Hu H, Zhu Y, Zhang W, Fang Q, Qiao T, Ma T, Wang M, Huang R, Tang Q et al. Colorectal cancer cell intrinsic fibroblast activation protein alpha binds to Enolase1 and activates NF-κB pathway to promote metastasis. Cell Death Dis 2021, 12.
14. Gu J, Zhong K, Wang L, Ni H, Zhao Y, Wang X, Yao Y, Jiang L, Wang B, Zhu X. ENO1 contributes to 5-fluorouracil resistance in colorectal cancer cells via EMT pathway. Front Oncol 2022, 12.
15. Kumari S, Malla R. New Insight on the role of plasminogen receptor in Cancer Progression. Cancer Growth Metastasis 2015, 8.
16. Lin Y, Zhang W, Liu L, Li W, Li Y, Li B. ENO1 promotes OSCC Migration and Invasion by orchestrating IL-6 secretion from macrophages via a positive feedback Loop. Int J Mol Sci 2023, 24.

17. Udawant S, Litif C, Lopez A, Gunn B, Schuenzel E, Keniry M. PI3K pathway inhibition with NVP-BEZ235 hinders glycolytic metabolism in Glioblastoma Multiforme Cells. Cells 2021, 10.
18. Su X, Chen S, Lu H, Li H, Qin C. Study on the Inhibitory Effect of Curcumin on GBM and its potential mechanism. Drug Des Devel Ther. 2021;15:2769–81.
19. Liang X, Wang Z, Dai Z, Zhang H, Zhang J, Luo P, Liu Z, Liu Z, Yang K, Cheng Q, Zhang M. Glioblastoma glycolytic signature predicts unfavorable prognosis, immunological heterogeneity, and ENO1 promotes microglia M2 polarization and cancer cell malignancy. Cancer Gene Ther 2022.
20. Islam Khan MZ, Tam SY, Azam Z, Law HKW. Proteomic profiling of metabolic proteins as potential biomarkers of radioresponsiveness for colorectal cancer. J Proteom 2022, 262.
21. Cai C, Yang L, Zhou K. 8DEstablishment and validation of a hypoxia-related signature predicting prognosis in hepatocellular carcinoma. BMC Gastroenterol 2021, 21.
22. Jiang K, Dong C, Yin Z, Li R, Mao J, Wang C, Zhang J, Gao Z, Liang R, Wang Q, Wang L. Exosome-derived ENO1 regulates integrin α6β4 expression and promotes hepatocellular carcinoma growth and metastasis. Cell Death Dis 2020, 11.
23. Wang J, Jin Z, Wu G, Deng Z, Wang J, Xu B, Zhu H, Guo Y, Wen Z. Construction of a 3-mRNA hypoxia prognostic model to evaluate immune microenvironment in hepatocellular carcinoma. Medicine 2022, 101.
24. Huang Z, Yan Y, Wang T, Wang Z, Cai J, Cao X, Yang C, Zhang F, Wu G, Shen B. Identification of ENO1 as a prognostic biomarker and molecular target among ENOs in bladder cancer. J Translational Med 2022, 20.
25. Stroggilos R, Frantzi M, Zoidakis J, Mokou M, Moulavasilis N, Mavrogeorgis E, Melidi A, Makridakis M, Stravodimos K, Roubelakis MG et al. Gene expression monotonicity across bladder Cancer stages informs on the Molecular Pathogenesis and identifies a Prognostic eight-gene signature. Cancers 2022, 14.
26. Sun X, Xin S, Li W, Zhang Y, Ye L. Discovery of Notch Pathway-related genes for Predicting Prognosis and Tumor Microenvironment Status in bladder Cancer. Front Genet 2022, 13.
27. Su Z, You L, He Y, Chen J, Zhang G, Liu Z. Multi-omics reveals the role of ENO1 in bladder cancer and constructs an epithelial-related prognostic model to predict prognosis and efficacy. Sci Rep 2024, 14.
28. Huang CK, Lv L, Chen H, Sun Y, Ping Y. ENO1 promotes immunosuppression and tumor growth in pancreatic cancer. Clin Transl Oncol. 2023;25:2250–64.
29. Zubair H, Patel GK, Khan MA, Azim S, Zubair A, Singh S, Srivastava SK, Singh AP. Proteomic analysis of MYB-Regulated Secretome identifies functional pathways and biomarkers: potential pathobiological and clinical implications. J Proteome Res. 2020;19:794–804.
30. Ma H, Kong L, Liu L, Du Y, Zhu X, Wang J, Zhao W. ENO1 contributes to the gemcitabine resistance of pancreatic cancer through the YAP1 signaling pathway. Mol Carcinog 2024.
31. Sun H, Mo J, Cheng R, Li F, Li Y, Guo Y, Li Y, Zhang Y, Bai X, Wang Y, et al. ENO1 expression and Erk phosphorylation in PDAC and their effects on tumor cell apoptosis in a hypoxic microenvironment. Cancer Biology Med. 2022;19:1598–616.
32. Curcio C, Rosso T, Brugiapaglia S, Guadagnin G, Giordano D, Castellino B, Satolli MA, Spadi R, Campra D, Moro F, et al. Circulating autoantibodies to alpha-enolase (ENO1) and far upstream element-binding protein 1 (FUBP1) are negative prognostic factors for pancreatic cancer patient survival. Clin Experimental Med. 2023;23:5089–100.
33. Zhou L, Zhang W, Ni H, Liu J, Sun H, Liang Z, Wang R, Xue X, Chen K, Li W. A bioinformatics analysis and an experimental validation of the hypoxia-related prognostic model. J Gastrointest Oncol. 2023;14:1504–24.
34. Hippner M, Majkowski M, Biecek P, Szkudlarek T, Simiczyjew A, Pieniazek M, Nowak D, Miazek A, Donizy P. Alpha-enolase (ENO1) correlates with invasiveness of cutaneous Melanoma—An in Vitro and a clinical study. Diagnostics 2022, 12.
35. Ma J, Zhu J, Li J, Liu J, Kang X, Yu J. Enhanced E6AP-mediated ubiquitination of ENO1 via LINC00663 contributes to radiosensitivity of breast cancer by regulating mitochondrial homeostasis. Cancer Lett 2023, 560.
36. Vishnubalaji R, Alajez NM. Single-cell transcriptome analysis revealed heterogeneity and identified novel therapeutic targets for breast Cancer subtypes. Cells 2023, 12.
37. Chen X, Li Z, Liang M, Zhang Z, Zhu D, Lin B, Zhou R, Lu Y. Identification of DDIT4 as a potential prognostic marker associated with chemotherapeutic and immunotherapeutic response in triple-negative breast cancer. World J Surg Oncol 2023, 21.
38. Shi Y-Y, Chen X-L, Chen Q-X, Yang Y-Z, Zhou M, Ren Y-X, Tang L-Y, Ren Z-F. Association of Enolase-1 with prognosis and Immune infiltration in breast Cancer by clinical stage. J Inflamm Res. 2023;16:493–503.
39. Li X, Vail E, Maluf H, Chaum M, Leong M, Lownik J, Che M, Giuliano A, Cao D, Dadmanesh F. Gene expression profiling of Fibroepithelial lesions of the breast. Int J Mol Sci 2023, 24.
40. Li N, Holden VK, Deepak J, Todd NW, Jiang F. Autoantibodies against tumor-associated antigens in sputum as biomarkers for lung cancer. Translational Oncol 2021, 14.
41. Liu X-S, Zhou L-M, Yuan L-L, Gao Y, Kui X-Y, Liu X-Y, Pei Z-J. NPM1 is a prognostic biomarker involved in Immune Infiltration of Lung Adenocarcinoma and Associated with m6A modification and Glycolysis. Front Immunol 2021, 12.
42. Luo X, Xu JG, Wang Z, Wang X, Zhu Q, Zhao J, Bian L. Bioinformatics Identification of Key genes for the Development and Prognosis of Lung Adenocarcinoma. INQUIRY: J Health Care Organ Provis Financing 2022, 59.
43. Song Y, Yang K, Sun T, Tang R. Development and validation of prognostic markers in sarcomas base on a multi-omics analysis. BMC Med Genom 2021, 14.
44. Li J, Dai L, Huang M, Ma Y, Guo Z, Wang X, Li W, Zhang J-Y. Immunoseroproteomic profiling in autoantibody to ENO1 as potential biomarker in immunodiagnosis of osteosarcoma by serological proteome analysis (SERPA) approach. *OncoImmunology* 2021, 10.
45. Luo M, Wu S, Ma Y, Liang H, Luo Y, Gu W, Fan L, Hao Y, Li H, Xing L. Evaluating a Panel of Autoantibodies against Tumor-Associated Antigens in Human Osteosarcoma. Front Genet 2022, 13.
46. Ray A, Song Y, Du T, Chauhan D, Anderson KC. Preclinical validation of alpha-enolase (ENO1) as a novel immunometabolic target in multiple myeloma. Oncogene. 2020;39:2786–96.
47. Hoang AT, Vizio B, Chiusa L, Cimino A, Solerio D, Do NH, Pileci S, Camandona M, Bellone G. Impact of Tissue Enolase 1 protein overexpression in Esophageal Cancer Progression. Int J Med Sci. 2021;18:1406–14.
48. Liu W, Wang Q, Chang J, Bhetuwal A, Bhattarai N, Zhang F, Tang J. Serum proteomics unveil characteristic protein diagnostic biomarkers and signaling pathways in patients with esophageal squamous cell carcinoma. Clin Proteomics 2022, 19.
49. Zhang L, Wang B, Wang Z-S, Guo Y-L, Shen H, Shi J. Construction of Glycolytic Regulator Gene Signature to predict the prognosis and Tumor Immune cell infiltration levels for prostate Cancer. Comput Math Methods Med. 2022;2022:1–13.
50. Ran R, Zhong X, Yang Y, Tang X, Shi M, Jiang X, Lin A, Gan X, Yu T, Hu L et al. Metabolomic profiling identifies hair as a robust biological sample for identifying women with cervical cancer. Med Oncol 2023, 40.
51. Lincz LF, Theron DZ, Barry DL, Scorgie FE, Sillar J, Sefhore O, Enjeti AK, Skelding KA. High Expression of ENO1 and Low Levels of Circulating Anti-ENO1 Autoantibodies in Patients with Myelodysplastic Neoplasms and Acute Myeloid Leukaemia. *Cancers* 2024, 16.
52. Cui Y, Peng J, Zheng M, Ge H, Wu X, Xia Y, Huang Y, Wang S, Yin Y, Fu Z, Xie H. TRPC5OS induces tumorigenesis by increasing ENO1-mediated glucose uptake in breast cancer. Translational Oncol 2022, 22.
53. Hong J, Guo F, Lu S-Y, Shen C, Ma D, Zhang X, Xie Y, Yan T, Yu T, Sun T, et al. F. Nucleatum targets lncRNA ENO1-IT1 to promote glycolysis and oncogenesis in colorectal cancer. Gut. 2021;70:2123–37.
54. Xu L, Huan L, Guo T, Wu Y, Liu Y, Wang Q, Huang S, Xu Y, Liang L, He X. LncRNA SNHG11 facilitates tumor metastasis by interacting with and stabilizing HIF-1α. Oncogene. 2020;39:7005–18.
55. Li Z, Meng X, Wu P, Zha C, Han B, Li L, Sun N, Qi T, Qin J, Zhang Y, et al. Glioblastoma cell–derived lncRNA-Containing exosomes induce Microglia to produce complement C5, promoting Chemotherapy Resistance. Cancer Immunol Res. 2021;9:1383–99.
56. Chen M-L, Yuan T-T, Chuang C-F, Huang Y-T, Chung IC, Huang W-C. A novel Enolase-1 antibody targets multiple interacting players in the Tumor Microenvironment of Advanced prostate Cancer. Mol Cancer Ther. 2022;21:1337–47.
57. Tang C, Zhang H, Deng WS, Xiong LQ, Zhou LQ. Role of POU1F1 promoting the properties of stemness of gastric carcinoma through ENO1-mediated glycolysis reprogramming. Kaohsiung J Med Sci. 2023;39:904–15.
58. Yang T, Shu X, Zhang H-W, Sun L-X, Yu L, Liu J, Sun L-C, Yang Z-H, Ran Y-L. Enolase 1 regulates stem cell-like properties in gastric cancer cells by stimulating glycolysis. Cell Death Dis 2020, 11.
59. Zhang T, Sun L, Hao Y, Suo C, Shen S, Wei H, Ma W, Zhang P, Wang T, Gu X, et al. ENO1 suppresses cancer cell ferroptosis by degrading the mRNA of iron regulatory protein 1. Nat Cancer. 2021;3:75–89.

60. Ma L, Xue X, Zhang X, Yu K, Xu X, Tian X, Miao Y, Meng F, Liu X, Guo S et al. The essential roles of m6A RNA modification to stimulate ENO1-dependent glycolysis and tumorigenesis in lung adenocarcinoma. J Experimental Clin Cancer Res 2022, 41.
61. Song Q, Zhang K, Sun T, Xu C, Zhao W, Zhang Z. Knockout of ENO1 leads to metabolism reprogramming and tumor retardation in pancreatic cancer. Front Oncol 2023, 13.
62. Sun L, Suo C, Zhang T, Shen S, Gu X, Qiu S, Zhang P, Wei H, Ma W, Yan R, et al. ENO1 promotes liver carcinogenesis through YAP1-dependent arachidonic acid metabolism. Nat Chem Biol. 2023;19:1492–503.
63. Hou J-Y, Cao J, Gao L-J, Zhang F-P, Shen J, Zhou L, Shi J-Y, Feng Y-L, Yan Z, Wang D-P, Cao J-M. Upregulation of α enolase (ENO1) crotonylation in colorectal cancer and its promoting effect on cancer cell metastasis. Biochem Biophys Res Commun. 2021;578:77–83.
64. Li Y, Li Y, Luo J, Fu X, Liu P, Liu S, Pan Y. FAM126A interacted with ENO1 mediates proliferation and metastasis in pancreatic cancer via PI3K/AKT signaling pathway. Cell Death Discovery 2022, 8.
65. Qin L, Sun K, Shi L, Xu Y, Zhang R, Pan J. High-Fat mouse model to explore the relationship between abnormal lipid metabolism and enolase in pancreatic Cancer. Mediat Inflamm. 2023;2023:1–16.
66. Deng T, Shen P, Li A, Zhang Z, Yang H, Deng X, Peng X, Hu Z, Tang Z, Liu J, et al. CCDC65 as a new potential tumor suppressor induced by metformin inhibits activation of AKT1 via ubiquitination of ENO1 in gastric cancer. Theranostics. 2021;11:8112–28.
67. Wang N, Qiao H, Hao J, Deng C, Zhou N, Yang L, Zeng M, Guan Q. RNA-binding protein ENO1 promotes the tumor progression of gastric cancer by binding to and regulating gastric cancer-related genes. J Gastrointest Oncol. 2023;14:585–98.
68. Li H-J, Ke F-Y, Lin C-C, Lu M-Y, Kuo Y-H, Wang Y-P, Liang K-H, Lin S-C, Chang Y-H, Chen H-Y, et al. ENO1 promotes Lung Cancer Metastasis via HGFR and WNT signaling–driven epithelial-to-mesenchymal transition. Cancer Res. 2021;81:4094–109.
69. Wu X, Ding C, Liu Y, Dong K, Zhang H. B7-H3 promotes proliferation and migration of lung cancer cells by modulating PI3K/AKT pathway via ENO1 activity. Translational Cancer Res. 2024;13:833–46.
70. Sun M, Li L, Niu Y, Wang Y, Yan Q, Xie F, Qiao Y, Song J, Sun H, Li Z, et al. PRMT6 promotes tumorigenicity and cisplatin response of lung cancer through triggering 6PGD/ENO1 mediated cell metabolism. Acta Pharm Sinica B. 2023;13:157–73.
71. Zhang Y-H, Liu X-S, Gao Y, Yuan L-L, Huang Z-M, Zhang Y, Liu Z-Y, Yang Y, Liu X-Y, Ke C-B, Pei Z-J. SFXN1 as a potential diagnostic and prognostic biomarker of LUAD is associated with 18F-FDG metabolic parameters. Lung Cancer 2024, 188.
72. Xiao W, Geng W, Zhou M, Xu J, Wang S, Huang Q, Sun Y, Li Y, Yang G, Jin Y. POU6F1 cooperates with RORA to suppress the proliferation of lung adenocarcinoma by downregulating HIF1A signaling pathway. Cell Death Dis 2022, 13.
73. Zhang Z, Xu P, Hu Z, Fu Z, Deng T, Deng X, Peng L, Xie Y, Long L, Zheng D, et al. CCDC65, a Gene Knockout that leads to early death of mice, acts as a potentially novel tumor suppressor in Lung Adenocarcinoma. Int J Biol Sci. 2022;18:4171–86.
74. Feng T, Feng N, Zhu T, Li Q, Zhang Q, Wang Y, Gao M, Zhou B, Yu H, Zheng M, Qian B. A SNP-mediated lncRNA (LOC146880) and microRNA (miR-539-5p) interaction and its potential impact on the NSCLC risk. J Experimental Clin Cancer Res 2020, 39.
75. Ou B, Liu Y, Yang X, Xu X, Yan Y, Zhang J. C5aR1-positive neutrophils promote breast cancer glycolysis through WTAP-dependent m6A methylation of ENO1. Cell Death Dis 2021, 12.
76. Park MK, Zhang L, Min K-W, Cho J-H, Yeh C-C, Moon H, Hormaechea-Agulla D, Mun H, Ko S, Lee JW, et al. NEAT1 is essential for metabolic changes that promote breast cancer growth and metastasis. Cell Metabol. 2021;33:2380–e23972389.
77. Peng J, Pei S, Cui Y, Xia Y, Huang Y, Wu X, Zheng M, Weng M, Han X, Fu H et al. Comparative analysis of transient receptor potential channel 5 opposite strand–induced gene expression patterns and protein–protein interactions in triple–negative breast cancer. Oncol Lett 2022, 24.
78. Wu M-J, Chen C-J, Lin T-Y, Liu Y-Y, Tseng L-L, Cheng M-L, Chuu C-P, Tsai H-K, Kuo W-L, Kung H-J, Wang W-C. Targeting KDM4B that coactivates c-Myc-regulated metabolism to suppress tumor growth in castration-resistant prostate cancer. Theranostics. 2021;11:7779–96.
79. Lu J-J, Chen F-J, Li Y, Xu X, Peng C, Yu N, Su L-N, Tang L. DTL promotes melanoma progression through rewiring cell glucose metabolism. Annals Translational Med. 2022;10:68–68.
80. Zhang K, Tian R, Zhang W, Li Y, Zeng N, Liang Y, Tang S. α-Enolase inhibits apoptosis and promotes cell invasion and proliferation of skin cutaneous melanoma. Mol Biol Rep. 2022;49:8241–50.
81. Tang Y, Jin YH, Li HL, Xin H, Chen JD, Li XY, Pan YF. 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;26:3837–49.
82. Wang Y, Liu Y, Xu Y, Xing H, Tian Z, Tang K, Rao Q, Wang M, Wang J. AML1-ETO-Related Fusion Circular RNAs contribute to the proliferation of Leukemia cells. Int J Mol Sci 2022, 24.
83. Gan L, Zhao S, Gao Y, Qi Y, Su M, Wang A, Cai H. N6-methyladenosine methyltransferase KIAA1429 promoted ovarian cancer aerobic glycolysis and progression through enhancing ENO1 expression. Biol Direct 2023, 18.
84. Xie F, Zhang H, Zhu K, Jiang CS, Zhang X, Chang H, Qiao Y, Sun M, Wang J, Wang M et al. PRMT5 promotes ovarian cancer growth through enhancing Warburg effect by methylating ENO1. MedComm 2023, 4.
85. Xia P, Zhang H, Lu H, Xu K, Jiang X, Jiang Y, Gongye X, Chen Z, Liu J, Chen X, et al. METTL5 stabilizes c-Myc by facilitating USP5 translation to reprogram glucose metabolism and promote hepatocellular carcinoma progression. Cancer Commun. 2023;43:338–64.
86. Wang Z, Yu Y, Wu P, Ye Q, Guo Y, Zhang X, Xi L, Li Q, Jin Y, Zhou D et al. Lactate promotes the growth of patient-derived organoids from hepatopancreatobiliary cancers via ENO1/HIF1α pathway and does not affect their drug sensitivities. Cell Death Discovery 2022, 8.
87. Xu X, Chen Y, Shao S, Wang J, Shan J, Wang Y, Wang Y, Chang J, Zhou T, Chen R, et al. USP21 deubiquitinates and stabilizes HSP90 and ENO1 to promote aerobic glycolysis and proliferation in cholangiocarcinoma. Int J Biol Sci. 2024;20:1492–508.
88. Zhang Z, Peng J, Li B, Wang Z, Wang H, Wang Y, Hong L. HOXA1 promotes aerobic glycolysis and cancer progression in cervical cancer. Cell Signal 2023, 109.
89. Gong W, Ekmu B, Wang X, Lu Y, Wan L. AGR2-induced glucose metabolism facilitated the progression of endometrial carcinoma via enhancing the MUC1/HIF-1α pathway. Hum Cell. 2020;33:790–800.
90. Peng C, Hou ST, Deng CX, Zhang Y. Function of DHX33 in promoting Warburg effect via regulation of glycolytic genes. J Cell Physiol. 2020;236:981–96.
91. Luo J-T, Wang Y-f, Wang Y, Wang C-L, Liu R-Y, Zhang Z. A circular RNA, hsa_circ_0018180 (circPARD3), triggers glycolysis and promotes malignancy of Head and Neck squamous cell Carcinoma through the miR-5194/ENO1 Axis. Biochem Genet. 2022;61:316–35.
92. Nie Q, Cao H, Yang J, Liu T, Wang B. Long non-coding RNA NMRAL2P promotes glycolysis and reduces ROS in head and neck tumors by interacting with the ENO1 protein and promoting GPX2 transcription. PeerJ 2023, 11.
93. Zhang G, Zhao X, Liu W. NEDD4L inhibits glycolysis and proliferation of cancer cells in oral squamous cell carcinoma by inducing ENO1 ubiquitination and degradation. Cancer Biol Ther. 2022;23:243–53.
94. Liu J, Yang Q, Sun H, Wang X, Saiyin H, Zhang H. The circ-AMOTL1/ENO1 Axis implicated in the Tumorigenesis of OLP-Associated oral squamous cell carcinoma. Cancer Manage Res. 2020;12:7219–30.<\/p>
95. Mani SA, Guo W, Liao M-J, Eaton EN, Ayyanan A, Zhou AY, Brooks M, Reinhard F, Zhang CC, Shipitsin M, et al. The epithelial-mesenchymal transition generates cells with properties of Stem cells. Cell. 2008;133:704–15.
96. Sahai E, Toh B, Wang X, Keeble J, Sim WJ, Khoo K, Wong W-C, Kato M, Prevost-Blondel A, Thiery J-P, Abastado J-P. Mesenchymal transition and dissemination of Cancer cells is driven by myeloid-derived suppressor cells infiltrating the primary tumor. PLoS Biol 2011, 9.
97. Hua Q, Wang D, Zhao L, Hong Z, Ni K, Shi Y, Liu Z, Mi B. AL355338 acts as an oncogenic lncRNA by interacting with protein ENO1 to regulate EGFR/AKT pathway in NSCLC. Cancer Cell Int 2021, 21.
98. Lai Y-W, Hsu W-J, Lee W-Y, Chen C-H, Tsai Y-H, Dai J-Z, Yang C-C, Lin C-W. Prognostic value of a Glycolytic Signature and its regulation by Y-Box-binding protein 1 in Triple-negative breast Cancer. Cells 2021, 10.
99. Li J, Hu Z-Q, Yu S-Y, Mao L, Zhou Z-J, Wang P-C, Gong Y, Su S, Zhou J, Fan J, et al. CircRPN2 inhibits aerobic glycolysis and metastasis in Hepatocellular Carcinoma. Cancer Res. 2022;82:1055–69.
100. Chung IC, Huang W-C, Huang Y-T, Chen M-L, Tsai A-W, Wu P-Y, Yuan T-T. Unrevealed roles of extracellular enolase–1 (ENO1) in promoting glycolysis and pro–cancer activities in multiple myeloma via hypoxia–inducible factor 1α. Oncol Rep 2023, 50.

101. Li J, Cao D, Jiang L, Zheng Y, Shao S, Zhuang A, Xiang D. ITGB2-ICAM1 axis promotes liver metastasis in BAP1-mutated uveal melanoma with retained hypoxia and ECM signatures. Cell Oncol 2023.
102. Tian M, Zhu R, Ding F, Liu Z. Ubiquitin-specific peptidase 46 promotes tumor metastasis through stabilizing ENO1 in human esophageal squamous cell carcinoma. Exp Cell Res 2020, 395.
103. Vishnubalaji R, Alajez NM. Transcriptional landscape associated with TNBC resistance to neoadjuvant chemotherapy revealed by single-cell RNA-seq. Mol Therapy - Oncolytics. 2021;23:151–62.
104. Ma J, Zhao W, Zhang H, Chu Z, Liu H, Fang X, Tang D. Long non-coding RNA ANRIL promotes chemoresistance in triple-negative breast cancer via enhancing aerobic glycolysis. Life Sci 2022, 306.
105. Xu B, Peng Z, An Y, Yan G, Yao X, Guan L, Sun M. Identification of Energy metabolism-related gene signatures from scRNA-Seq Data to predict the prognosis of Liver Cancer patients. Front Cell Dev Biology 2022, 10.
106. Chen R, Li D, Zheng M, Chen B, Wei T, Wang Y, Li M, Huang W, Tong Q, Wang Q, et al. FGFRL1 affects chemoresistance of small-cell lung cancer by modulating the PI3K/Akt pathway via ENO1. J Cell Mol Med. 2020;24:2123–34.
107. Mohapatra P, Shriwas O, Mohanty S, Ghosh A, Smita S, Kaushik SR, Arya R, Rath R, Das Majumdar S, Muduly DK et al. CMTM6 drives cisplatin resistance by regulating wnt signaling through ENO-1/AKT/GSK3β axis. JCI Insight 2021.
108. Shi Y, Liu J, Zhang R, Zhang M, Cui H, Wang L, Cui Y, Wang W, Sun Y, Wang C. Targeting endothelial ENO1 (Alpha-Enolase) -PI3K-Akt-mTOR Axis alleviates hypoxic pulmonary hypertension. Hypertension. 2023;80:1035–47.
109. Zhang Q-W, Lin X-L, Dai Z-H, Zhao R, Hou Y-C, Liang Q, Zhang Y, Ge Z-Z. Hypoxia and low-glucose environments co-induced HGDILnc1 promote glycolysis and angiogenesis. Cell Death Discovery 2024, 10.
110. Martínez-Esquivias F, Gutiérrez-Angulo M, Becerra-Ruiz JS, Martinez-Perez LA, de la Cruz-Ahumada CJ, Guzmán-Flores JM, Kim BS. Bioinformatic analysis of the Effect of Silver nanoparticles on Colorectal Cancer Cell line. Biomed Res Int. 2022;2022:1–10.
111. Wang J, Man Q, Zhong N, Wang H, Zhang C, Li S, Bu L, Liu B. ENO1 binds to ApoC3 and impairs the proliferation of T cells via IL-8/STAT3 pathway in OSCC. Int J Mol Sci 2022, 23.
112. Martell E, Kuzmychova H, Senthil H, Kaul E, Chokshi CR, Venugopal C, Anderson CM, Singh SK, Sharif T. Compensatory cross-talk between autophagy and glycolysis regulates senescence and stemness in heterogeneous glioblastoma tumor subpopulations. Acta Neuropathol Commun 2023, 11.
113. Shu X, Cao K-Y, Liu H-Q, Yu L, Sun L-X, Yang Z-H, Wu C-A, Ran Y-L. Alpha-enolase (ENO1), identified as an antigen to monoclonal antibody 12C7, promotes the self-renewal and malignant phenotype of lung cancer stem cells by AMPK/mTOR pathway. Stem Cell Res Ther 2021, 12.
114. Huang S-S, Liao W-Y, Hsu C-C, Chan T-S, Liao T-Y, Yang P-M, Chen L-T, Sung S-Y, Tsai KK. A novel invadopodia-specific marker for Invasive and Pro-metastatic Cancer Stem cells. Front Oncol 2021, 11.
115. Chen X, Kang R, Kroemer G, Tang D. Broadening horizons: the role of ferroptosis in cancer. Nat Reviews Clin Oncol. 2021;18:280–96.
116. Liu Y, Hou Y, Zhang F, Wang X. ENO1 deletion potentiates ferroptosis and decreases glycolysis in colorectal cancer cells via AKT/STAT3 signaling. Experimental Therapeutic Med 2024, 27.
117. Huang R-X, Zhou P-K. DNA damage response signaling pathways and targets for radiotherapy sensitization in cancer. Signal Transduct Target Therapy 2020, 5.
118. Chen M, Chen L-z, Xu L, Zhang J-s, Song X. Neoadjuvant chemoradiation for locally advanced rectal cancer: a systematic review of the literature with network meta-analysis. Cancer Manage Res. 2019;11:741–58.
119. Mowers EE, Sharifi MN, Macleod KF. Functions of autophagy in the tumor microenvironment and cancer metastasis. FEBS J. 2018;285:1751–66.
120. Xu Y, Xia X, Pan H. Active autophagy in the tumor microenvironment: a novel mechanism for cancer metastasis. Oncol Lett. 2013;5:411–6.
121. Liu S, Sun X, Li K, Zha R, Feng Y, Sano T, Dong C, Liu Y, Aryal UK, Sudo A, et al. Generation of the tumor-suppressive secretome from tumor cells. Theranostics. 2021;11:8517–34.
122. Li K, Sun X, Zha R, Liu S, Feng Y, Sano T, Aryal UK, Sudo A, Li B-Y, Yokota H. Counterintuitive production of tumor-suppressive secretomes from Oct4- and c-Myc-overexpressing tumor cells and MSCs. Theranostics. 2022;12:3084–103.
123. Li K-X, Sun X, Li B-Y, Yokota H. Conversion of osteoclasts into Bone-Protective, tumor-suppressing cells. Cancers 2021, 13.
124. Zhang C, Zhang K, Gu J, Ge D. ENO1 promotes antitumor immunity by destabilizing PD-L1 in NSCLC. Cell Mol Immunol. 2021;18:2045–7.
125. Shu X, Zhang HW, Liu SY, Sun LX, Zhang T, Ran YL. Anti-ENO1 antibody combined with metformin against tumor resistance: a novel antibody-based platform. PeerJ 2024, 12.
126. Zhang Y, Wang X. Targeting the Wnt/β-catenin signaling pathway in cancer. J Hematol Oncol 2020, 13.
127. Bahar ME, Kim HJ, Kim DR. Targeting the RAS/RAF/MAPK pathway for cancer therapy: from mechanism to clinical studies. Signal Transduct Target Therapy 2023, 8.
128. Ullah R, Yin Q, Snell AH, Wan L. RAF-MEK-ERK pathway in cancer evolution and treatment. Sem Cancer Biol. 2022;85:123–54.
129. Hsu C-C, Peng D, Cai Z, Lin H-K. AMPK signaling and its targeting in cancer progression and treatment. Sem Cancer Biol. 2022;85:52–68.
130. Karin M. Nuclear factor-κB in cancer development and progression. Nature. 2006;441:431–6.
131. Jung D-W, Kim W-H, Park S-H, Lee J, Kim J, Su D, Ha H-H, Chang Y-T, Williams DR. A unique small molecule inhibitor of Enolase clarifies its role in fundamental biological processes. ACS Chem Biol. 2013;8:1271–82.
132. Liu F, Huang H, Yang X, Jiang S, Xu A, Yu Z, Li J, Yu M, Wang Y, Wang B. Ag85B-ENO146-82 therapeutic vaccines enhance anti-tumor immunity by inducing CD8 + T cells and remodeling tumor microenvironment. Int Immunopharmacol 2024, 130.
133. Mandili G, Curcio C, Bulfamante S, Follia L, Ferrero G, Mazza E, Principe M, Cordero F, Satolli MA, Spadi R et al. In pancreatic cancer, chemotherapy increases antitumor responses to tumor-associated antigens and potentiates DNA vaccination. J Immunother Cancer 2020, 8.
134. Lin Y-H, Satani N, Hammoudi N, Yan VC, Barekatain Y, Khadka S, Ackroyd JJ, Georgiou DK, Pham C-D, Arthur K, et al. An enolase inhibitor for the targeted treatment of ENO1-deleted cancers. Nat Metabolism. 2020;2:1413–26.
135. Mittal L, Camarillo IG, Varadarajan GS, Srinivasan H, Aryal UK, Sundararajan R. High-throughput, label-free quantitative proteomic studies of the Anticancer effects of Electrical pulses with Turmeric Silver nanoparticles: an in vitro Model Study. Sci Rep 2020, 10.
136. Jiang R, Shen F, Zhang M, Mulati S, Wang J, Tao Y, Zhang W. Evaluating the Anti-melanoma effects and Toxicity of Cinnamaldehyde Analogues. Molecules 2023, 28.
137. Zhang W, Gao J, Cheng C, Zhang M, Liu W, Ma X, Lei W, Hao E, Hou X, Hou Y, Bai G. Cinnamaldehyde enhances Antimelanoma Activity through Covalently binding ENO1 and exhibits a promoting effect with Dacarbazine. Cancers 2020, 12.
138. Zhang W, Gao J, Shen F, Ma X, Wang Z, Hou X, Hao E, Hou Y, Bai G. Cinnamaldehyde changes the dynamic balance of glucose metabolism by targeting ENO1. Life Sci 2020, 258.
139. Wang G, Yu Y, Wang Y-Z, Yin P-H, Xu K, Zhang H. The effects and mechanisms of isoliquiritigenin loaded nanoliposomes regulated AMPK/mTOR mediated glycolysis in colorectal cancer. Artif Cells Nanomed Biotechnol. 2020;48:1231–49.
140. Salidroside Induces Apoptosis. In human gastric Cancer cells via the downregulation of ENO1/PKM2/GLUT1 expression.
141. Yuan Y, Yuan H-f, Geng Y, Zhao L-n, Yun H-l, Wang Y-f, Yang G, Zhang X. -d: aspirin modulates 2-hydroxyisobutyrylation of ENO1K281 to attenuate the glycolysis and proliferation of hepatoma cells. Biochem Biophys Res Commun. 2021;560:172–8.
142. Song K, Rajasekaran N, Chelakkot C, Lee HS, Paek S-M, Yang H, Jia L, Park HG, Son WS, Kim Y-J et al. Macrosphelide A exhibits a specific Anti-cancer Effect by simultaneously inactivating ENO1, ALDOA, and FH. Pharmaceuticals 2021, 14.
143. Shen D, Deng Z, Liu W, Zhou F, Fang Y, Shan D, Wang G, Qian K, Yu M, Zhang Y et al. Melatonin inhibits bladder tumorigenesis by suppressing PPARγ/ENO1-mediated glycolysis. Cell Death Dis 2023, 14.
144. Wang G, Wang Y-Z, Yu Y, Wang J-J, Yin P-H, Xu K. Triterpenoids extracted from-Rhus chinensis MillAct Against Colorectal Cancer by inhibiting enzymes in Glycolysis and glutaminolysis: Network Analysis and experimental validation. Nutr Cancer. 2019;72:293–319.

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