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Review

Significance of Malic Enzyme 1 in Cancer: A Review

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Abstract: Malic enzyme 1 (ME1) plays a key role in promoting malignant phenotypes in various types of cancer. ME1 promotes epithelial–mesenchymal transition (EMT) and enhances stemness via glutaminolysis, energy metabolism reprogramming from oxidative phosphorylation to glycolysis. As a result, ME1 promotes the malignant phenotypes of cancer cells and poor patient prognosis. In particular, ME1 expression is promoted in hypoxic environments associated with hypoxia-inducible factor (HIF1) α. ME1 is overexpressed in budding cells at the cancer invasive front, promoting cancer invasion and metastasis. ME1 also generates nicotinamide adenine dinucleotide (NADPH), which, together with glucose-6-phosphate dehydrogenase (G6PD) and isocitrate dehydrogenase (IDH1), expands the NADPH pool, maintaining the redox balance in cancer cells, suppressing cell death by neutralizing mitochondrial reactive oxygen species (ROS), and promoting stemness. This review summarizes the latest research insights into the mechanisms by which ME1 contributes to cancer progression. Because ME1 is involved in various aspects of cancer and promotes many of its malignant phenotypes, it is expected that ME1 will become a novel drug target in the near future.

Keywords: malic enzyme 1; cancer stem cells; energy metabolism; epithelial–mesenchymal transition; hypoxia

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1. Introduction

ME1, also known as cytosolic NADP+-dependent malic enzyme and malate dehydrogenase, is a multifunctional protein that links glycolysis and the tricarboxylic acid cycle (TCA cycle) by directly converting the malate produced in the TCA cycle to pyruvate [1]. ME1 is involved in glycolysis, the TCA cycle, nicotinamide adenine dinucleotide phosphate (NADPH) production, glutamine metabolism, and lipogenesis, specifically through the decarboxylation of malate to form pyruvate and ultimately NADPH [2].

NADPH produced by ME1 plays important roles in other biological processes, including antioxidant stress and detoxification pathways, as well as the generation of reactive oxygen species (ROS). ME1, isocitrate dehydrogenase 1 (IDH1), and two enzymes of the pentose phosphate pathway (PPP), glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD), are involved in maintaining an adequate pool of NADPH [3–5].

ME1 was among the first insulin-regulated genes to be identified in liver and adipose tissue and is transcriptionally regulated by thyroxine [6,7]. ME1 activity is reciprocally and dynamically regulated by post-translational modifications such as K^{337} acetylation, which

enhances its activity, and S^{336} phosphorylation, which inhibits it. These modifications affect the NADPH/NADP ratio and fatty acid synthesis [8].

Although ME1 is overexpressed in various cancers, its role in cancer tumorigenesis and progression remains to be fully elucidated.

2. Discovery of ME1

In the 1950s, it was thought that in addition to the pentose phosphate pathway (PPP), another enzyme that decarboxylates malate to produce NADPH was required to supply NADPH to the high fatty acid synthesis activity observed in the liver and adipose tissue. Ochoa et al. identified an activity that decarboxylates malate to produce pyruvate in an $NADP^+$-dependent manner, and named it $NADP^+$-malic enzyme (ME1) [9]. Subsequently, ME2 and ME3, which exist in mitochondria and are dependent on NAD+ and NADP+, respectively, were identified [10]. ME1 is mainly present in the cytoplasm and catalyzes the following reaction [11].

3. Regulation of ME1 Expression

The regulation of ME1 expression in cancer is linked to p53 and KRAS mutations. Wild-type p53 suppresses ME1 expression, making ME1 overexpression common in cancers with p53 mutations [12]. Human spot 14 protein modulates p53 target genes through direct interactions with the thyroid receptor or other p53 coactivators such as Zac1, and also regulates ME1 promoter activity [13].

KRAS mutations also upregulate ME1 expression in hepatocellular carcinoma (HCC) [14], non-small-cell lung cancer (NSCLC) [15], and colorectal cancer (CRC) [16].

As an oxidative stress-related gene, ME1 is also regulated by the Kelch-like ECH-associated protein 1 (Keap1), the nuclear factor erythroid 2-related factor 2 (NRF2) oxidative stress response pathway [17], and BTB and CNC homology 1 (Bach-1), a mediator of oxidative stress responses [18].

Other regulators of ME1 expression include the canonical Wnt signaling pathway in breast cancer [19], dietary factors such as a high-fat diet in intestinal and hepatic tissues [20], and signaling through peroxisome proliferator-activated receptor (PPAR)/early growth response protein 4 (EGR4) [21].

Epigenetic regulation also plays a role in controlling ME1 expression. For instance, RNA m5C methyltransferase NSUN2 mediates 5-methyl cytosine (m5C) methylation, stabilizing ME1 and promoting metabolic reprogramming and cell cycle progression [22]. Deacetylase sirtuin 2 (SIRT2) mediates the deacetylation of phosphoglycerate mutase 5 (PGAM5), activating ME1, leading to ME1 dephosphorylation, which subsequently drives lipid accumulation and proliferation in HCC cells [23].

MicroRNAs (miRNAs) further contribute to ME1 regulation. Examples include miR-30a [16], miR-30c-5p [24], miR-612 [25], and miR-885-5p [26], which target ME1 and influence its expression in various cancer contexts.

4. ME1 and Malignancy

ME1 is overexpressed in many cancers, contributing to poorer prognosis and more aggressive tumor behavior. In HCC, ME1 is highly expressed in intermediate cell subtypes [27], and its overexpression is associated with lower overall and progression-free survival rates compared with HCC with normal ME1 levels [14]. ME1 is also a poor prognostic factor for lipid metabolism in HCC [28,29], in which its overexpression can lead to epithelial–mesenchymal transition (EMT) [14] and anticancer drug resistance [30] in HCC. Finally, ME1 is key in the transformation from nonalcoholic steatohepatitis (NASH) to HCC [31].

In gastric cancer, ME1 promotes cell proliferation and metastasis [32], and its overexpression in CRC is associated with cancer progression [33], while it promotes colon carcinogenesis in $Apc^{Min/+}$ mice [34].

In breast cancer, ME1 overexpression correlates with proliferation, lymph node metastasis, vascular invasion, and poor prognosis. This is because of enhanced survival rate, motility, EMT, and reduced ROS levels [35]. ME1 is particularly associated with the malignant phenotypes of basal-like breast cancer [36]. ME1 expression is also significantly correlated with speedy/RINGO cell cycle regulator family member C (SPDYC), which influences the tumor immune microenvironment and lipid metabolism [37].

In NSCLC, ME1 is more strongly expressed in squamous cell carcinoma (SCC) than in adenocarcinoma and is correlated with smoking and poor prognosis [15,38].

In oral SCC (OSCC), ME1 is overexpressed in 48% of cases and correlates with tumor factors such as T stage, N stage, clinical stage, and histological grade. ME1 overexpression is also associated with poor prognosis [39] and increased malignancy, particularly invasiveness driven by EMT at the invasive front [39,40]. ME1 promotes cancer progression by altering metabolism and stemness, which then increases tumor growth and invasion [39,40].

ME1 is overexpressed in laryngeal SCC [41] and promotes the motility and invasiveness of nasopharyngeal carcinoma cells [42]. In non-solid tumors, ME1 overexpression leads to reduced ROS levels and drug resistance [43], which contribute to poor prognosis.

In acute myelocytic leukemia, melanoma, and papillary renal cell carcinoma, ME1 overexpression is similarly correlated with poor prognosis [44,45].

5. ME1 and Benign Diseases

ME1 is involved in several benign diseases, including metabolic syndrome and diabetes [46]. ME1 may induce hyperinsulinemia, hyperglycemia, inflammation, and oxidative stress in patients with obesity and type 2 diabetes and is a risk factor for the development of malignant tumors in these diseases [46,47]. Abnormal tubular lipid metabolism in diabetes is a risk factor for diabetic nephropathy, and ME1 is a risk factor for altered lipid metabolism [48,49]. ME1 is involved in the PPAR signaling pathway and is associated with hypertension risk [50]. ME1 also promotes cellular senescence in inflammatory diseases [51]. ME1 is also hypomethylated in endometriosis, making it a useful disease marker [49].

6. ME1 and Malignant Phenotypes

ME1 is involved in various malignant phenotypes. It enhances proliferation, cell motility, invasion, colony formation in soft agar, glucose consumption, lactate production, NADPH, and EMT [12,14–16,25,32,34,36,42–56]. Conversely, ME1 reduces senescence, ROS, and apoptosis [12,14,32,42,52,56]. ME1 also promotes cancer cell proliferation under hypoxic conditions [36]. Animal studies have demonstrated tumor growth in mouse models [16] and increased adenocarcinomas and adenomas in $APC^{MIN/+}$- and ME1-overexpressing mice [8,34].

In gastrointestinal cancer, the ME1 phenotype is characterized by important adipogenic components and paracrine communication between tumors and adjacent non-tumor tissues. This interaction induces lipid and mucin production, which support tumor growth [34,46]. Rather than acting as an independent cancer promoter, ME1 works in conjunction with lipid metabolism, cell proliferation, cell motility promotion, ROS generation related to EMT, NADP recycling enzymes, and redox networks. ME1 is thought to contribute significantly to ROS buffering via NADPH-dependent recycling in the glutathione and thioredoxin pathways [46].

7. EMT

EMT involves dynamic changes in cell organization, transitioning from epithelial to mesenchymal phenotypes, which leads to functional changes in cell migration and invasion [57]. EMT is characterized by decreased expression of epithelial cell–cell adhesion molecules such as E-cadherin (ECD) and claudin 4 and increased expression of mesenchymal intermediate fiber vimentin. EMT is involved in disease progression and is associated with poor prognosis in head-and-neck SCC [58], while ME1-induced EMT is prominent in OSCC [39].

In human OSCC cells, suppression of lactate fermentation by knockdown of ME1 and lactate dehydrogenase A or inhibition of pyruvate dehydrogenase (PDH) kinase reduces lactate secretion, increases extracellular pH, and suppresses the EMT phenotype [40]. In contrast, suppressing oxidative phosphorylation by knocking down PDH increases lactate secretion, decreases extracellular pH, and promotes the EMT phenotype [40]. Alterations in extracellular pH are strongly correlated with EMT [59]. Thus, EMT is linked to energy metabolism through glycolysis.

In HCC, silencing ME1 inhibits cell migration and invasiveness by inducing ECD expression and reducing N-cadherin and vimentin expression via an ROS-dependent pathway [11]. Thus, ME1 induces EMT in part by increasing SNAIL expression and suppressing ECD expression [42].

8. Budding

Budding at the invasive front of a tumor is correlated with malignant properties in many cancers. Tumor budding refers to the formation of small, undifferentiated cancer cell clusters consisting of up to five cancer cells or a single cancer cell at the invasion front [60]. This phenomenon is linked to the malignant properties of CRC and is used as a prognostic marker [61,62]. In oral cancer, tumor budding is also correlated with lymph node metastasis and worse disease-free and overall survival, making it an important prognostic marker [63–65].

Cancer cells exhibiting budding acquire metastatic potential by adopting EMT phenotypes such as reduced cell adhesion and enhanced stemness [66]. However, the EMT during budding is considered partial and incomplete [67]. The Warburg effect and hypoxic environment play important roles in the acquisition of EMT characteristics in budding cancer cells. Budding is correlated with glycolysis promotion via increased expression of glucose transporter type 1 (GLUT1), which promotes glucose uptake [68]. Fructose-1,6-bisphosphatase, which promotes oxidative phosphorylation (OXPHOS), is suppressed by EMT-induced Snail. Consequently, the energy metabolic pathway is reprogrammed toward glycolysis during the EMT process [69]. Hypoxia in the tumor microenvironment (TME) of advanced cancer promotes tumor budding in CRC [70].

Furthermore, chemical hypoxia induced by $CoCl_2$ treatment increases ME1 expression, enhances hypoxia-inducible factor (HIF)-1α expression, and promotes the EMT phenotype in OSCC cells [40]. Hypoxia also activates Yes-associated protein (YAP), which is reversed by ME1 knockdown. These findings suggest that in a hypoxic TME, cancer cells at the invasive front may reprogram their energy metabolism via ME1 overexpression, resulting in increased lactate secretion, decreased extracellular pH, and YAP activation. These changes facilitate EMT and subsequent tumor budding [40].

9. TME Acidification and Budding

As mentioned above, the Warburg effect, caused by the reprogramming of the energy metabolism of cancer cells, leads to acidification of the TME due to increased lactate secretion. A decrease in extracellular pH strongly correlates with EMT and promotes cancer

cell proliferation, migration, invasion, and metastasis in acidic environments through the pH-sensing G protein-coupled receptors (GPCRs) GPR4, GPR65 (T-cell death-associated gene 8 protein, TDAG8), GPR68 (ovarian cancer G-protein coupled receptor 1, OGR1), and GPR132 (G2 accumulation protein, G2A) [59]. Low pH in the cancer TME promotes the infiltration of myeloid-derived suppressor cells, regulatory T cells, and tumor-associated macrophages; induces programmed death ligand 1 (PD-L1) expression in cancer cells; and inhibits T-cell antitumor immunity [59,71]. Additionally, it enhances cancer cell resistance to anticancer drugs [59].

In OSCC, ME1 expression leads to a shift in energy metabolism from OXPHOS to glycolysis, resulting in decreased oxygen consumption and increased lactate production, which in turn promote tumor formation and growth [36,39]. Furthermore, knockdown of monocarboxylate transporter 1 (MCT1), a transporter responsible for lactate secretion, increases extracellular pH [40]. These changes in energy metabolism are closely related to extracellular pH. Along with ME1-mediated reprogramming of energy metabolism [40], extracellular carbonic anhydrase and monocarboxylate transporters play key roles in decreasing the extracellular pH under hypoxic conditions, further promoting cancer cell invasion, metastasis, and stemness [71].

Thus, a hypoxic environment, promotion of the Warburg effect, decreased extracellular pH, and EMT may be involved in tumor budding and the acquisition of a malignant phenotype. Moreover, tumor budding is significantly correlated with ME1 expression, with ME1 levels increasing with cancer progression. Therefore, tumor budding and ME1 expression may be useful markers of OSCC malignancy [40].

10. Energy Metabolism in Cancer Cells

In the presence of oxygen, most human cells convert lactate into carbon dioxide and usable energy through OXPHOS, which is localized in the mitochondria [72,73]. In contrast, Otto Warburg discovered the Warburg effect, in which tumors rapidly ferment glucose to lactate, even under oxygen-rich conditions [74,75] This process, unlike OXPHOS, relies on glycolysis, which produces less adenosine triphosphate (ATP) from glucose than OXPHOS [76]. However, glycolysis is more energy-efficient on a per minute basis, producing roughly twice as much energy as OXPHOS despite yielding less ATP per glucose molecule [77].

OXPHOS activity is linked to mitochondrial volume; however, ME1 knockdown increases mitochondrial area while reducing lactate production [39], which in turn promotes the Warburg effect. Cancer cells use ME1-generated pyruvate for lactate fermentation [78,79]. Reducing the glutamine concentration in the culture medium suppresses OSCC cell proliferation, while increasing the glutamine concentration enhances their proliferative ability, even in the absence of glucose. ME1 knockdown prevents glutamine-induced proliferation [39]. This suggests that OSCC cells utilize ME1 to induce glutaminolysis for energy production. A similar dependence on glutamine has also been observed in CRC cells [80].

11. Glutamine Metabolism and Redox

In normal human cells, glutamine is converted to α-ketoglutarate, which enters the TCA cycle and is used to generate ATP and produce nucleic acids, lipids, and other amino acids [81,82]. Cancer cells often metabolize glutamine to generate intermediates (e.g., lipids, nucleic acids, and amino acids) needed for the synthesis of these biological components [80].

ME1 knockdown suppresses cell proliferation, particularly under low-glucose and low-glutamine conditions. This effect is accompanied by upregulation of G6PD, a rate-limiting enzyme in the PPP, along with pyruvate kinase (PK) M and acetyl-coenzyme A carboxylase-α (ACC), and a decrease in glutamate dehydrogenase 1 (GLUD1) expres-

sion [39,42]. In contrast, ME1 enhances the levels of 6PDG, an enzyme involved in the second PPP reaction [55], thereby promoting tumorigenicity [83]. Thus, ME1 is involved in NADPH production and the conversion of malate to pyruvate, activating both glycolysis and the PPP through a positive-feedback mechanism [39].

The reprogramming of energy metabolism from OXPHOS to aerobic glycolysis suppresses mitochondrial ROS production [84,85]. In OSCC cells, ME1 knockdown increases the NADP/NADPH ratio and decreases the glutathione/glutathione SH (GSH/GSSG) ratio, suggesting that ME1 helps maintain the reducing environment in cancer cells [39]. ME1 depletion also reduces the cells' tolerance to low-glucose conditions [42] and enhances radiation-induced growth inhibition [56], primarily due to increased ROS levels.

In HCC cells, the transcriptional activation of ME1 by NRF2 helps cells exposed to strong ROS to adapt and survive [86]. In lung SCC, ME1 overexpression strengthens the glycolytic phenotype and increases the dependence on glutaminolysis compared with lung adenocarcinomas [87]. Additionally, the GSH/GSSG ratio is elevated in lung SCC, possibly due to increased NADPH production by ME1 [84].

In gefitinib-resistant NSCLC cell lines, ME1-induced NADPH elevation suppresses apoptosis [88], suggesting that increased NADPH causes drug resistance [86]. ME1 is strongly and consistently associated with NADPH-dependent reductases in NSCLC, highlighting the role of ME1 and G6PD in regulating the redox state and inducing drug resistance by altering NADPH levels [46,89].

NADP/NADPH-dependent reductases, such as prostaglandin reductase 1 (PTGR1) and thioredoxin reductase 1 (TXNRD1), detoxify or activate xenobiotics, metabolize intermediates of endogenous biochemical pathways, regenerate endogenous antioxidants, and mediate the overall redox state of cells. These enzymes contribute to anti-apoptotic survival, EMT, and metastasis, further emphasizing the role of ME1 in promoting cancer progression and resistance.

12. ME1 and Stemness

As mentioned earlier, ME1 is strongly associated with EMT, which is accompanied by enhanced stemness in cancer cells [90,91]. Stemness in turn is closely associated with metastatic potential [92,93]. ME1 is involved in several cancers, including gastric cancer [24,30], breast cancer [94], CRC [94], HCC [14,30], bladder cancer [25], and OSCC [39,40]. Therapeutic resistance is a hallmark of cancer stemness [95–97]. ME1 overexpression induces radioresistance in head-and-neck SCC and NSCLC [15,56] and has also been reported in acute myelocytic leukemia [43,98], NSCLC [89], HCC [30], and prostate cancer [99]. These findings suggest that ME1 plays a critical role in promoting cancer cell stemness.

The relationship between ME1 and stem cell-related genes is also significant. In $APC^{MIN/+}$ mice, ME1 overexpression enhances colon carcinogenesis, with increased expression of Wnt/Sp5, indicating that ME1 activates the β-catenin/Wnt signaling pathway [34]. In cytogenetically normal acute myeloid leukemia, ME1 activates the interleukin (IL)-6/Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) pathway, which correlates with poor prognosis [44]. Additionally, ME1-driven glutaminolysis is associated with KRAS mutations [100], which are a metabolic phenotype associated with cancer stem cells (CSCs) and are emerging as a potential therapeutic target [101,102].

ME1 upregulates the activation of YAP and tafazzin (TAZ) through the PPAR signaling pathway in association with glutaminolysis [21]. This activation enhances stemness [100,103]. YAP is activated by ME1-mediated metabolic reprogramming [104]. YAP/TAZ interacts with Snail/Slug to regulate stem cell function and the mesenchymal phenotype expression [105]. YAP is also activated in OSCC, but is abolished by ME1 [40]. YAP activation is a key factor

in promoting the EMT phenotype and cancer progression in OSCC [39]. Additionally, G6PD enhances stemness via the Krüppel-like factor 5 (KLF5) pathway [106].

Interestingly, a mutant ME1 protein lacking enzymatic activity still promoted cell proliferation and colony formation in wild-type ME1-silenced cells, suggesting that ME1 may enhance stemness through 6PGD activation [55].

ME1 also contributes to the production of NADPH, which plays a role in maintaining stemness through redox maintenance [107]. ME1 is co-expressed with two other cytoplasmic NADPH-generating enzymes (G6PD and IDH1), along with other cytoplasmic enzymes that utilize NADPH as an electron donor, such as PTGR1 and NAD(P)H quinone dehydrogenase 1 (NQO1), and antioxidant stress-related proteins such as tripartite motif-containing 16 (TRIM16) [47]. These redox-related genes may play a role in promoting stemness. In OSCC, NQO1 expression is regulated by sponging microRNA-494, involving homeobox protein Hox-A11 antisense RNA (HOXA11-AS), a long non-coding RNA (lncRNA) belonging to the homeobox (HOX) gene cluster that promotes liver metastasis in CRC [108–110].

13. Hypoxia and HIF1α

As noted above, the relationship between ME1 and budding is critical for cancer invasive fronts that exhibit budding. This is significant because cancer cells at these invasive fronts infiltrate stromal tissues with low vascular density, making them susceptible to hypoxic conditions. Hypoxic cancers are more invasive and have a worse prognosis than non-hypoxic cancers [111]. Thus, hypoxia is closely related to the promotion of tumor budding phenotypes. In oral malignant melanoma, hypoxia occurs at the invasion front, accompanied by increased HIF1α expression [112]. Under hypoxic conditions, HIF1α is stabilized and activated, leading to the upregulation of key factors, including vascular endothelial growth factor (VEGF), which drives angiogenesis, matrix metallopeptidase 9 (MMP9), and MMP7, which enhance cancer invasion, and EMT-related genes [100,112–114]. Additionally, increased ROS also stabilizes HIF1α [115].

Simultaneous upregulation of HIF1α and ME1 is observed at the cancer front [40], with ME1 expression being induced by hypoxia [36,40]. HIF1α knockdown reduces ME1 expression [116], indicating that ME1 is a target gene of HIF1α and that its overexpression at the invasive front is part of the hypoxic response. Hypoxia also leads to mitochondrial dysfunction, reducing the mitochondrial membrane potential, inhibiting OXPHOS, and lowering oxidative stress [40]. Thus, a hypoxic environment reprograms energy metabolism, suppresses OXPHOS, and promotes glycolysis and lactate fermentation, thereby contributing to altered cancer phenotypes [117]. HIF1α activity further enhances glycolytic flux [118–120].

Hypoxia-induced HIF1α plays a critical role in anticancer drug resistance, partly through mitochondrial changes [121]. HIF1α promotes dynamin-related protein 1-dependent mitochondrial fission, facilitating the Warburg phenotype [122–125]. Divided mitochondria are observed in cells with reduced respiratory activity [126]. We previously demonstrated that HIF1α stabilization promotes reprogramming of energy metabolism and contributes to early resistance to gemcitabine treatment [127]. Under hypoxic conditions, ME1 is induced by HIF1α and participates in metabolic reprogramming [40].

Hypoxia also activates YAP via HIF1α-mediated upregulation of G protein-coupled receptor class C group 5 member A (GPRC5A) [128]. In turn, activated YAP stabilizes HIF1α and enhances its activity [129]. YAP plays a role in EMT induction and energy metabolism under hypoxic conditions [40]. Hypoxia also activates jagged canonical Notch ligand 2 (JAG2), which promotes cancer stemness and EMT through the NOTCH and AKT signaling pathways [130].

14. NADPH

NADPH is an electron donor required for reductive regeneration of antioxidant systems such as glutathione (GSH) and thioredoxin (Trx) [131]. ME1 produces NADPH during enzymatic reactions and therefore acts as a supplier of NADPH (Figure 1). In addition, G6PD and IDH1 act as NADPH suppliers (Figure 1). ME1, G6PD, and IDH1 all play important roles in metabolic pathways that are often altered in cancer cells to support their rapid growth and proliferation. In cancer cells, they are all upregulated or, like IDH1, activated by genetic mutations [132,133]. G6PD catalyzes the first reaction of the PPP and is the rate-limiting enzyme of this pathway. In the PPP, NADPH is further produced by 6-phosphogluconate dehydrogenase (6PDG). G6PD and PPP play a major role in NADPH production and contribute significantly to the NADPH pool [134]. MYC and PI3K/AKT signaling are involved in G6PD activation. ME1 and IDH1 provide alternative sources of NADPH. However, ME1 is the main supplier of NADPH in some tumors [32]. Gene expression of antioxidant pathways, including NADPH production pathways such as G6PD, 6PGD, IDH1, and ME1, is regulated by Nrf2 and is induced by increased oxidative stress [135,136]. Mutant IDH1 generates 2-hydroxyglutarate (2-HG) instead of α-ketoglutarate, increasing PPP flux [137]. Cancer cells are redundantly dependent on these pathways to meet the high demands of ROS detoxification and lipid synthesis. In CSCs, oxidative stress is a major impediment to their survival, which, together with the suppression of NADPH consumption [138], leads to increased activity of NADPH suppliers to prevent NADPH depletion [139]. A decrease in NADPH leads to fluctuations in redox balance, resulting in the accumulation of oxidative stress and cell death [106,140]. Thus, NADPH is essential for the survival of CSCs, and one of its suppliers, ME1, plays an important role in maintaining CSCs.

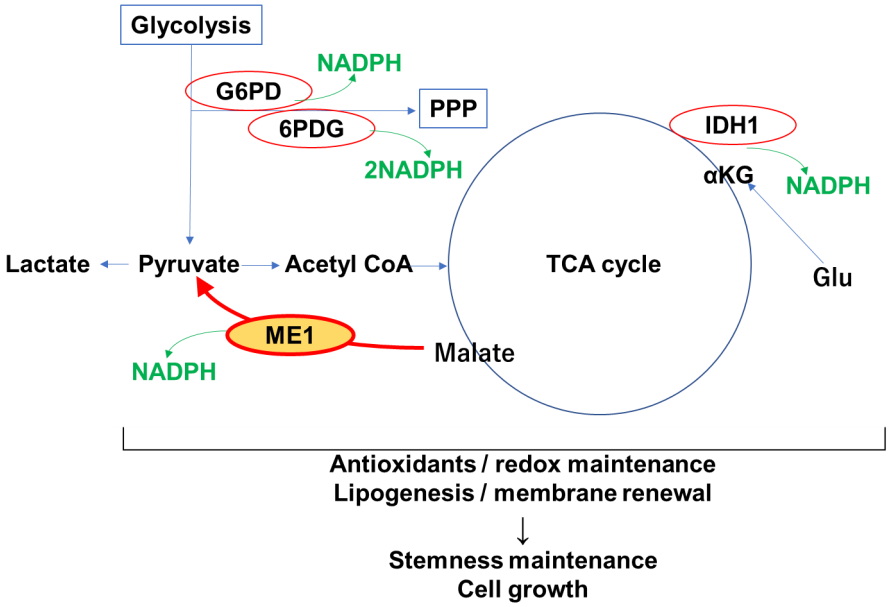

Figure 1. Role of ME1 in production of NADPH. NADPH is mainly produced by G6PDH and 6PDG in PPP, IDH1, and ME1, which maintain the NAPDH pool. NAPDH contributes to elimination of ROS, maintenance of redox balance, and lipogenesis, renewing membranes of cytoplasm and organelles. These roles of NADPH are essential for maintaining the stemness and proliferation of cancer cells. NADPH, nicotinamide adenine dinucleotide phosphate; ME1, malic enzyme 1; G6PD, glucose-6-phosphate dehydrogenase; 6PDG, 6-phosphogluconate dehydrogenase; IDH1, isocitrate dehydrogenase 1; αKG, α-ketoglutarate; Glu, glutamate; PPP, pentose phosphate pathway; ROS, reactive oxygen species.

15. Carcinogenesis

Increased lipid metabolism correlates with enhanced extracellular signal-regulated kinase 2 (ERK2) activity in human patients and plays an important role in the development of CRC. Ubiquitin-specific peptidase 19 (USP19) antagonizes ring finger protein 1 (RNF1)-mediated ME1 degradation by deubiquitination, thereby promoting lipid metabolism and NADPH production, and suppressing ROS, thereby promoting colorectal carcinogenesis [141]. Wnt-mediated transcriptional activation leads to upregulation of phosphoglycerate mutase family member 5 (PGAM5) and ME1, and dephosphorylation of S336 of ME1 by PGAM5 increases ME1 K337 acetylation mediated by acetyl-CoA acetyltransferase 1 (ACAT1), leading to ME1 dimerization and activation [8]. ME1 overexpression in $APC^{MIN/+}$ mice increases adenomas due to activation of the Wnt/β-catenin pathway and increases expression of KLF9 [34]. ME1 is also involved in hepatocarcinogenesis as one of five important prognostic genes (ME1, TP53I3, SOCS2, GADD45G, CYP7A1) associated with NASH-HCC progression [31]. In hexavalent chromium-induced lung cancer, epigenetically upregulated ME1 induces lung carcinogenesis [22]. Thus, ME1 promotes carcinogenesis by reprogramming NADPH production and metabolism.

16. ME1-Targeting Therapy

ME1 promotes the malignancy of various cancers by reprogramming energy metabolism, maintaining redox potential, enhancing stemness, and facilitating EMT. In particular, in low-glucose environments, cancer cells become dependent on ME1 for the supply of NADPH and pyruvate [52], ME1 has emerged as a novel molecular target for cancer therapy [142,143]. In synovial sarcoma, decreased ME1 levels promote ferroptosis by altering redox homeostasis [144].

miRNAs targeting ME1 have shown potential in suppressing cancer progression. For instance, miR30a suppresses colon carcinogenesis driven by KRAS mutations [16], while miR-885-5p suppresses gastric cancer metastasis and EMT in laryngeal SCC [26,145]. Similarly, miR-612 suppresses malignant phenotypes, including EMT, in bladder cancer [25].

Lanthanides have also been identified as ME1 inactivators, suppressing cell proliferation, motility, and EMT in OSCC cells [39]. Lanthanide administration in mouse tumor models further demonstrated suppressed tumor growth and extended survival [39].

Efforts to develop small-molecule inhibitors targeting ME1 have also shown promise. AS1134900, a novel small-molecule inhibitor, binds to a unique allosteric site outside the ME1-active site to inhibit its activity [146].

In addition, attempts have been made to discover new ME1 inhibitors. Fragment-based virtual library design and virtual screening have identified a piperazine-1-pyrrolidine-2,5-dione scaffold-based malic enzyme inhibitor that targets the NADP-binding site of malic enzyme [147].

Using a fragment-based drug discovery approach using molecular dynamic simulations and molecular docking, about 90,000 interactions were tested for the type of interaction with the NAD(P)-binding site of ME1, the binding energy, and the orientation of the compound at the site, and combination 1f was finally selected as the best inhibitor [148].

There have also been attempts to design malic enzyme inhibitors based on the X-ray crystal structure of malic enzyme, studies of pH and allosteric regulators, and the structure and dynamics of malic enzyme suggested by molecular dynamic simulations [149].

However, despite the numerous attempts mentioned above, no drugs specifically targeting ME1 have been tested in clinical trials or in late-stage clinical trials as of 2025. All cancers that overexpress ME1 have the potential to benefit from ME1-targeted therapy, making ME1 highly adaptable to cancer. Future development of ME1 inhibitors is eagerly awaited.

17. Conclusions

ME1 promotes the reprogramming of energy metabolism from OXPHOS to glycolysis and lactate fermentation, resulting in TME alterations. This shift promotes the expression

of stemness-related genes, supports stemness-related metabolism, and promotes malignant phenotypes, including EMT (Figure 2). ME1 is strongly associated with poor prognosis and treatment resistance of various tumors, making it a novel therapeutic target.

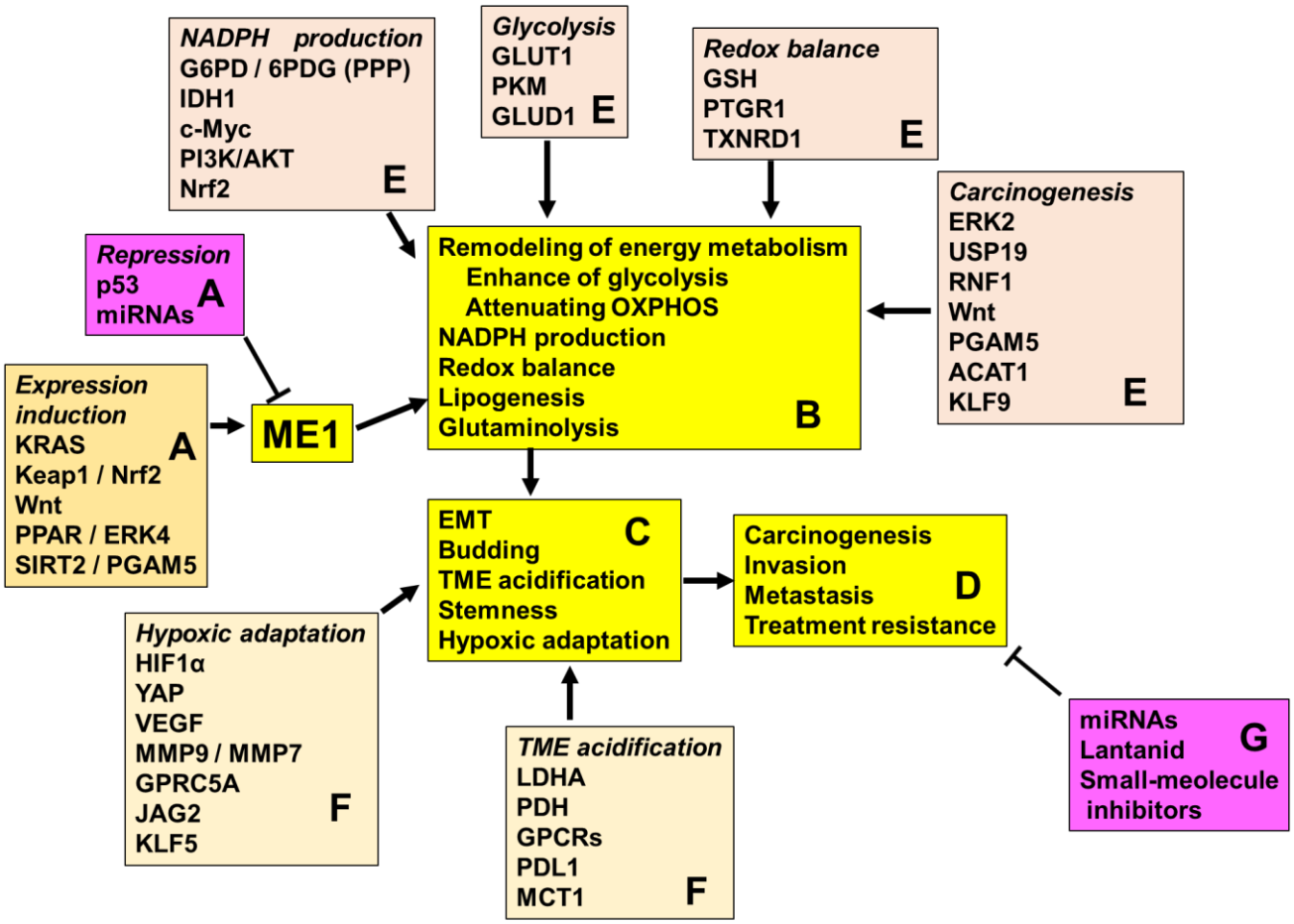

Figure 2. Roles of ME1 in cancer. A. Factors that affect ME1 expression. B. Biochemical changes caused by ME1 in cancer cells. C. Changes caused by ME1 in the phenotype of cancer cells. D. Changes caused by ME1 in the clinical dramatype of cancer cells. E. Factors that cooperate with the biochemical activity of ME1. F. Factors that act cooperatively on ME1-induced cancer cell phenotypes. G. Drugs targeting ME1. ME1, malic enzyme; EMT, epithelial–mesenchymal transition; NADPH, nicotinamide adenine dinucleotide phosphate; IDH1, isocitrate dehydrogenase 1; PPP, pentose phosphate pathway; G6PD, glucose-6-phosphate dehydrogenase; 6PGD, 6-phosphogluconate dehydrogenase; Keap1, Kelch-like ECH-associated protein 1; NRF2, nuclear factor erythroid 2-related factor 2; PPAR, peroxisome proliferator-activated receptor; EGR4, early growth response protein 4; SIRT2, sirtuin 2; PGAM5, phosphoglycerate mutase 5; miRNA, microRNA; PDH, pyruvate dehydrogenase; GLUT1, glucose transporter type 1; OXPHOS, oxidative phosphorylation; TME, tumor microenvironment; HIF, hypoxia-inducible factor; YAP, Yes-associated protein; PDL1, programmed death ligand 1; MCT1, monocarboxylate transporter 1; PK, pyruvate kinase; GLUD1, glutamate dehydrogenase 1; GSH, glutathione; PTGR1, prostaglandin reductase 1; TXNRD1, thioredoxin reductase 1; KLF5, Krüppel-like factor 5; VEGF, vascular endothelial growth factor; MMP, matrix metallopeptidase; GPRC5A, G protein-coupled receptor class C group 5 member A; JAG2, jagged canonical Notch ligand 2.

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Abbreviations

ME1, malic enzyme; EMT, epithelial–mesenchymal transition; TCA cycle, tricarboxylic acid cycle; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; IDH1, isocitrate dehydrogenase 1; PPP, pentose phosphate pathway; G6PD, glucose-6-phosphate dehydrogenase; 6PGD, 6-phosphogluconate dehydrogenase; HCC, hepatocellular carcinoma; NSCLC, non-small-cell lung cancer; CRC, colorectal cancer; Keap1, Kelch-like ECH-associated protein 1; NRF2, nuclear factor erythroid 2-related factor 2; Bach-1, BTB and CNC homology 1; PPAR, peroxisome proliferator-activated receptor; EGR4, early growth response protein 4; m5C, 5-methyl cytosine; SIRT2, sirtuin 2; PGAM5, phosphoglycerate mutase 5; miRNA, microRNA; NASH, nonalcoholic steatohepatitis; SPDYC, speedy/RINGO cell cycle regulator family member C; SCC, squamous cell carcinoma; OSCC, oral SCC; ECD, E-cadherin; PDH, pyruvate dehydrogenase; GLUT1, glucose transporter type 1; OXPHOS, oxidative phosphorylation; TME, tumor microenvironment; HIF, hypoxia-inducible factor; YAP, Yes-associated protein; PD-L1, programmed death ligand 1; MCT1, monocarboxylate transporter 1; ATP, adenosine triphosphate; PK, pyruvate kinase; ACC, acetyl-coenzyme A carboxylase-α; GLUD1, glutamate dehydrogenase 1; GSH, glutathione; GSSG, glutathione SH; PTGR1, prostaglandin reductase 1; TXNRD1, thioredoxin reductase 1; IL, interleukin; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; CSC, cancer stem cell; TAZ, tafazzin; KLF5, Krüppel-like factor 5; NQO1, NAD(P)H quinone dehydrogenase 1; TRIM16, tripartite motif-containing 16; HOXA11-AS, homeobox protein Hox-A11 antisense RNA; lncRNA, long non-coding RNA; VEGF, vascular endothelial growth factor; MMP, matrix metallopeptidase; GPRC5A, G protein-coupled receptor class C group 5 member A; JAG2, jagged canonical Notch ligand 2.

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