Cell Communication and Signaling

REVIEW Open Access

The impact of epithelial-mesenchymal transition (EMT) induced by metabolic processes and intracellular signaling pathways on chemo-resistance, metastasis, and recurrence in solid tumors

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Abstract

The intricate cellular process, known as the epithelial-mesenchymal transition (EMT), significantly influences solid tumors development. Changes in cell shape, metabolism, and gene expression linked to EMT facilitate tumor cell invasion, metastasis, drug resistance, and recurrence. So, a better understanding of the intricate processes underlying EMT and its role in tumor growth may lead to the development of novel therapeutic approaches for the treatment of solid tumors. This review article focuses on the signals that promote EMT and metabolism, the intracellular signaling pathways leading to EMT, and the network of interactions between EMT and cancer cell metabolism. Furthermore, the functions of EMT in treatment resistance, recurrence, and metastasis of solid cancers are covered. Lastly, treatment approaches that focus on intracellular signaling networks and metabolic alterations brought on by EMT will be discussed.

Keywords EMT, Solid tumors, Metabolic profile, Chemotherapy resistance, Metastasis, Tumor recurrence

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Introduction

The EMT is a pleiotropic and adaptable change in cellular phenotype that occurs when epithelial cells take on mesenchymal traits [1]. EMT occurs in epithelial cells when they lose their junctions and apical-basal polarity, reorganize their cytoskeleton, modify the signaling pathways linked to cell shape, and alter gene expression. These modifications cause individual cells to become more motile, resulting in the emergence of an invading phenotype (Fig. 1) [2, 3]. The EMT International Association (TEMTIA) established standards and definitions of EMT in 2020 as part of efforts to unify the concept of EMT, prompted by the growing number of publications over the previous several years and the absence of a precise definition of EMT. According to recent research, EMT is often incomplete, resulting in cells that exhibit both mesenchymal and epithelial characteristics (partial EMT). For instance, studies have demonstrated that contrary to previous beliefs, the transition from epithelial to mesenchymal phenotypes is not a binary switch. These intermediate stages are also more capable of altering circulation, colonizing new sites, and producing metastases.

Furthermore, they can display a range of flexibility and metastatic potential [4]. Tumor-associated macrophages (TAMs) and fibroblasts within the stroma of tumors activate juxtacrine and paracrine signaling channels to induce EMT in cancer cells surrounding them [5–7]. As a result of EMT and the quasi-mesenchymal state, patients exhibit increased resistance to chemotherapy and immunotherapy [8]. In this line, EMT in breast cancer is associated with the expression of Snail (SNAI1), Twist-related protein 1 (TWIST1), and human epidermal growth factor receptor 2 (HER2) [9]. There are also connections between ZEB1-mediated switching from E-cadherin to N-cadherin during EMT and the progression of pancreatic cancer and metastasis [10]. The expression of Slug (SNAI2) and ZEB2 is elevated in the EMT state, correlating with poor prognosis in colorectal cancer [11]. Additionally, a correlation between EMT and solid tumors has been established through various lines of evidence [12]. So, our review aims to explore the metabolic processes and signaling pathways involved in drug resistance, metastasis, and recurrence of solid tumors from the perspective of EMT.

Intracellular signaling pathways leading to EMT

It can be argued that the main signaling pathway in the EMT of solid tumors is the TGF-β signaling pathway. TGF-β/ TGF-βR axis causes phosphorylation of Smad2 and Smad3. Smad2/3 associates with Smad4 to enhance the expression of target genes within the nucleus [14] (Fig. 2). Remarkably TGF-β also has another pathway

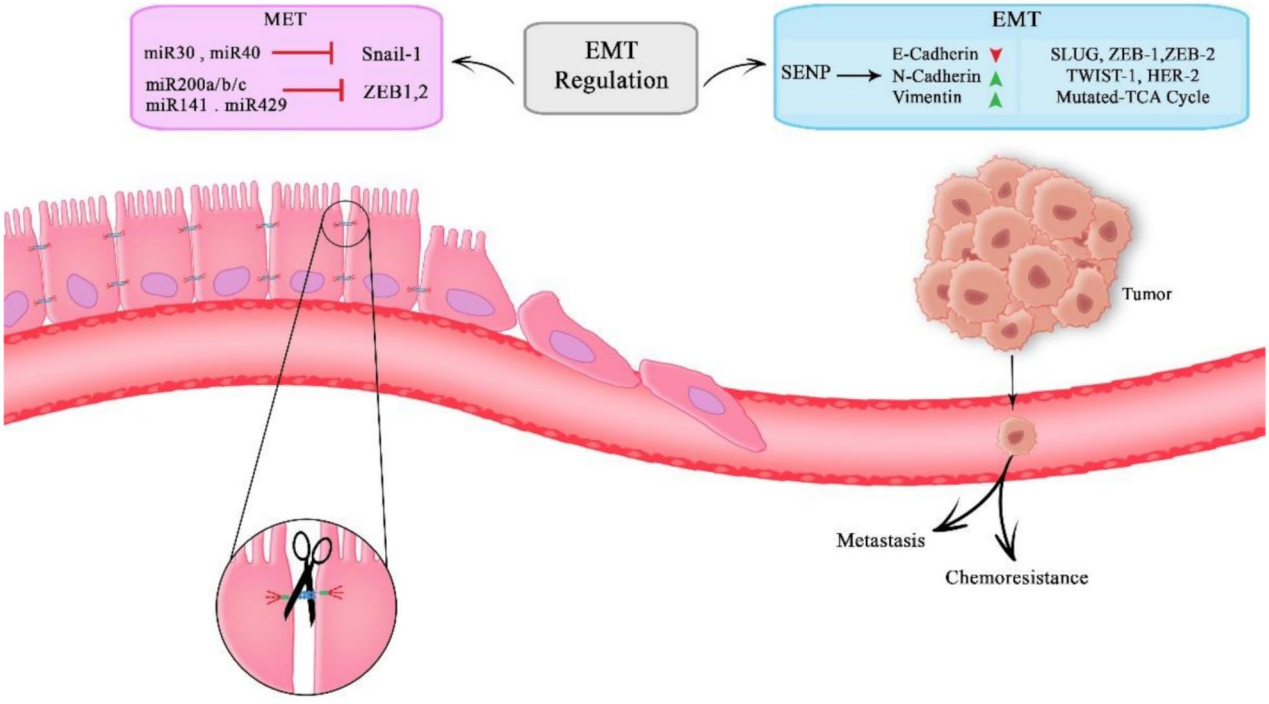

Fig. 1 The factors affecting EMT/mesenchymal to epithelial transition (MET) regulation. Certain microRNAs (miRs), such as miR-30, 34, which inhibit Snail-1, and miR-200a/b/c, miR-141, 429, which inhibit ZEB1, 2, are implicated in the control of EMT/MET. These two procedures tip the odds in MET's favor. Conversely, SENP (sentrin-specific proteases) participates in the EMT side by raising levels of Vimentin and N-cadherin and lowering those of E-cadherin. Furthermore, this diagram depicts the EMT process—the transition of blood vessel epithelial cells into mesenchymal form. Tumor cells can spread to other body parts during this phase, increasing vascular variability [13]

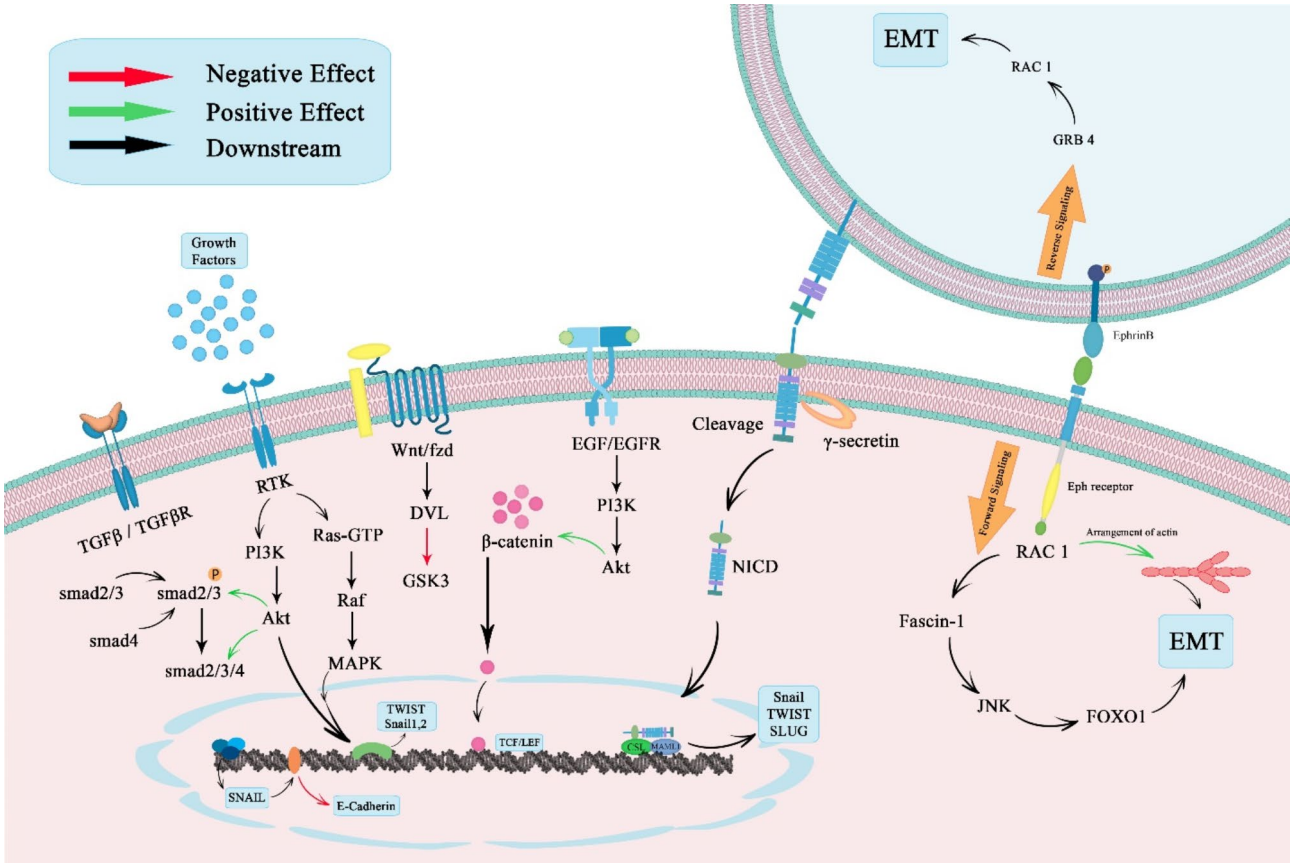

Fig. 2 Intracellular signaling pathways leading to EMT

that contrasts with this pathway. The shcA/Grb2/Sos complex, which results from the activation of shcA in the TGF-βRI, actives the Ras/c-Raf/MEK/ERK, and ERK also phosphorylates Smad2/3, causing Smad2/3 ubiquitination and destruction in the proteasome [15]. The role of the TGF-β/ TGF-βR axis in EMT is the expression of the zinc finger protein Snail superfamily. These groups of proteins are the transcription factors that negatively control E-cadherin gene transcription and prevent the β-catenin/E-cadherin complex from localization in the plasma membrane. This phenomenon reduces cellular adhesion [16–18].

Crucially, the signaling pathways PI3K/PDK1/AKT and Ras-GTP/Raf/MEK/ERK/MAPK are activated by the interaction of receptor tyrosine kinases (RTKs) with various growth factors, leading to the expression of EMT factors like Twist and SNAI1/2 [19]. Interestingly studies have shown that the ERK/MAPK pathway needs to be combined with other signaling pathways such as notch, Wnt, and NF-κB to induce EMT more effectively [20]. On the other hand, the RTK signaling pathway causes the expression of TGF-βRI and strength EMT indirectly [21]. Moreover, AKT, as a key factor in the RTK pathway, causes efficient translocation of Smad3 into the nucleus. In addition, in cervical carcinoma, Akt facilitates the phosphorylation of Smad2/3 by tuberous sclerosis protein (TSCH) at the TGF-βRI N-terminal. Interestingly, phosphorylated USP4 by AKT enhances the stability of TGF-β receptor type I (TGF-βRI) by preventing its ubiquitination, which is crucial for the activation of downstream TGF-β signaling pathways. This stabilization facilitates processes such as cell migration and invasion in cancer contexts, particularly in esophageal squamous cell carcinoma [21]. Along with the Wnt pathway, studies have reported that the Pi3k/Akt signaling pathway mediated by EGFR can activate β-catenin [22]. As well as, according to Yan et al. protein arginine methyltransferase 5 (PRMT5) as an important physiologic factor, has been increased in several cancers and causes upregulation of the PI3K/Akt signaling pathway in colorectal cancer [23]. To that end, Liu et al. have reported that silencing of EGFR reduces β-catenin [24].

According to several studies, when the notch receptor binds to its ligand, the notch intracellular domain (NICD), is transported to the nucleus and bonds to CSL/MAML1 after cleavage by γ-secretase and upregulates some target gene transcription such as Snail, Twist, and Slug and downregulates E-cadherin gene transcription [25]. Interestingly, the γ-secretase inhibitor, like LY-411,575, N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine

t-butyl ester (DAPT) has been used in colorectal, adenocarcinoma, blood, and breast cancers [26] but according to a study which has been done on mice, when γ-secretase, is inhibited, the number of jagged1, which is the Notch1 target in EMT, increases, leading to breast cancer metastasis to the bone [27].

Also, recent studies have reported that the ephrin-B (EphB) signaling pathway has a dual (reverse and forward) effect on EMT [28]. Likewise, the reverse signaling activates RAC1 by activating GRB4 and the forward signaling activates RAC1 directly [29]. Interestingly, Fascin-1 initiates EMT probably by rearrangement of the actin cytoskeleton. Accordingly, J. Pu et al. indicated that the liver cancer hypoxia causes upregulation of the AKT/RAC1 axis and RAC1 activates Fascin-1 [30]. Denticleless E3 ubiquitin protein ligase homolog (DTL), as an oncogenic gene factor, is used in the prognosis of several cancers. In a study by S. Liu et al., it has been proven that DTL has increased in cervical adenocarcinoma cancer. Importantly, DTL induces RAC1/JNK/FOXO1 axis and leads to EMT induction. In this study, JNK inhibition prevents EMT initiation completely and reduces the expression of FOXO1 to some extent [31].

Metabolism reprograming in Cancer Cell

Cancer cells can adapt their metabolic activities to efficiently utilize surrounding nutrients through various pathways, including glycolysis, mitochondrial respiration, fatty acid metabolism, and glutamine metabolism [32]. This process is known as metabolism reprogramming in cancer cells.

Abnormal glucose metabolism is a fundamental and prevalent metabolic characteristic of cancer cells. Since glucose is a primary fuel in eukaryotes, it not only helps with producing energy but also metabolites for a variety of anabolic pathways [33]. Glucose transporters facilitate cellular glucose absorption. Then it is converted to pyruvate in the cytosol by glycolysis, which also produces a slight amount of ATP [34]. For a long time, the Warburg effect was thought to be the most common metabolic phenotype in cancer cells. The glycolysis-derived pyruvate is mostly transported into the mitochondrial matrix, where it is converted to acetyl coenzyme A (acetyl CoA) by the pyruvate dehydrogenase (PDH) complex in normal (quiescent) cells. Acetyl CoA is subsequently directed to the tricarboxylic acid cycle (TCA cycle), followed by oxidative phosphorylation (OXPHOS) for high-efficiency ATP production. A single molecule of glucose can yield up to 38 ATP molecules when fully oxidized, including the 2 ATP generated during glycolysis. However, even in aerobic conditions, most cancer cells primarily obtain their energy through a high rate of glycolysis rather than mitochondrial oxidative phosphorylation. This phenomenon, known as the Warburg effect or aerobic glycolysis, occurs in the cytosol [35, 36]. The Warburg effect enables proliferating cells to meet three key needs of rapidly dividing cells: rapid ATP production, biomass synthesis, and stable levels of reactive oxygen species (ROS) [37]. So, the altered metabolism of most, if not all, cancer cells is a universal characteristic. Glycolysis is not the only cancer cells' energy source. Due to modifications in cellular metabolism, cancer cells generate intermediate biosynthetic precursors for proteins, lipids, and nucleic acids [38]. These changes also give cancer cells a lot of advantages in terms of survival and proliferation.

Even though the Warburg effect is a typical occurrence in cancer, the role of mitochondria in cancer cells cannot be overlooked, particularly in terms of drug resistance and metastasis [39]. Increased glycolytic activity in primary tumor cells compared to normal cells does not necessairily imply that mitochondrial activity must be reduced. OXPHOS contributes 36 to 99% of ATP synthesis among 31 cancer cell lines, according to a meta-analysis of 31 cancer cell lines [40]. Enhanced mitochondrial biogenesis or function has been found to accelerate cancer progression and EMT by promoting oxidative phosphorylation [41]. So, the role of mitochondria in cancer biology is critical and cannot be overlooked. Mitochondria are not only involved in energy production but also play significant roles in regulating metabolic pathways that influence tumor growth and survival. Recent studies have highlighted the impact of single nucleotide polymorphisms (SNPs) on mitochondrial function and cancer risk. For instance, a study found that cancer risk of SNPs preferentially targets oncogenes and tumor-suppressor genes, suggesting that these genetic variations can alter mitochondrial gene expression and contribute to cancer progression [42]. Moreover, alterations in mitochondrial metabolism have been linked to various malignancies, emphasizing the need for further investigation into how mitochondrial dysfunction can lead to therapeutic resistance. In particular, SNPs associated with metabolic pathways have been shown to affect the biochemical landscape of tumors, influencing their response to treatment. This connection between mitochondrial function and SNPs underlines the importance of understanding genetic factors in cancer metabolism and highlights potential avenues for targeted therapies [43].

As validated by clinical investigation of human invasive breast tumors, the transcription co-activator PGC-1α is overexpressed in invasive cancer cells and increases mitochondrial biogenesis and OXPHOS throughout their transit to metastatic locations [44]. Without affecting cell proliferation or primary tumor growth, PGC-1α silencing in cancer cells significantly reduced their ability to invade and decreased the frequency of metastasis. Notably, PGC-1α-induced metabolic conversion toward OXPHOS is synergistically coupled to a functional EMT program,

and while PGC-1α-induced pathways are not necessary for cancer cells to acquire a mesenchymal phenotype, both pathways agree and correlate with the achievement of invasive and metastatic properties [44].

Activated EMT as a result of metabolic switch

The role of glycolysis in EMT promotion

Increased glycolysis has been shown to enhance EMT in cancer cells [45]. Several glycolytic enzymes are associated with invadopodia structures and plasma membrane (PM) protrusions, which play crucial roles in extracellular matrix (ECM) degradation and metastasis [46]. Moreover, ATP produced through glycolysis serves as a primary energy source for cell survival during metastatic spread [44]. Numerous studies have established a close relationship between mitochondrial function regulation, glycolytic alterations, and TGF-induced EMT. In breast cancer cells, the development of EMT correlates with the expression of glucose transporters, lactate dehydrogenase (LDH), monocarboxylate transporters (MCTs), and glycogen phosphorylase isoforms—all essential components for sustaining enhanced aerobic glycolysis [47]. Additionally, in gastric cancer, EMT and aerobic glycolysis are linked to the emergence of a malignant and chemoresistant phenotype [48].

Glucose transporters 1 and 3 (GLUT1 and GLUT3) facilitate glucose entry into cells independently of insulin. These transporters are often overexpressed in cancer cells to enhance glucose uptake, with high levels of GLUT1 and GLUT3 typically associated with poor prognosis [49]. Hexokinases phosphorylate glucose to form glucose-6-phosphate, marking the first step in most glucose metabolic pathways, including glycolysis. The primary isoform overexpressed in malignancies is hexokinase 2 (HK2) [50]. Phosphoglucose isomerase (PGI) is an enzyme that transforms glucose-6 phosphate to fructose-6 phosphate. Surprisingly, cancer cells can release this protein and use it as a cytokine (autocrine motility factor; AMF) that can promote EMT in an NF-κB-dependent way via ZEB1/2, encouraging migration, invasion, and spread [51].

Elevated expression of matrix metalloproteinase 2 (MMP2), known to be overexpressed in various cancers and associated with invasiveness, has been related to elevated expression of GLUT1 [52]. In laryngeal cancer, the expression of GLUT1 has been linked to the expression of EMT markers such as Vimentin and N-cadherin. Additionally, GLUT3 is overexpressed in mesenchymal cells of non-small cell lung cancer (NSCLC) demonstrating that GLUT3 plays a crucial role in EMT (28). Some evidence suggests that the overexpression of HK2 may enhance EMT under hypoxic conditions [53]. For instance, during a study by Hanhee Jo et al. [53], under hypoxic conditions, the expression of HK2 increased continuously as oxygen levels decreased. This was accompanied by the upregulation of EMT markers like Snail/Slug and N-cadherin in hepatocellular carcinoma (HCC) [53]. In a lactate-dependent way, upregulation of HK2, which is engaged in the first rate-limiting stage of glycolysis, can boost glycolysis and improve metastasis of pancreatic cell line PANC-1 [54]. Downregulation of HK2 consistently resulted in reduced glycolysis and suppression of EMT. A different hexokinase isoform (HK3) has recently been linked to EMT in colorectal tumors [55]. Silencing of AMF/PGI resulted in increased MET of human lung fibrosarcoma cells and breast cancer cells with reduced malignancy. Acquisition of malignancy might be completed in part by up-regulation of AMF/PGI and waiver of malignancy might also be controlled by down-regulation of AMF/PGI [56].

ALDOA (aldolase A) is commonly overexpressed in malignancies and is linked to a bad prognosis [57, 58]. A study on HCC found that high expression of ALDOA was associated with poorer overall survival (OS) and relapse-free survival (RFS) in HCC patients. Multivariate analysis confirmed ALDOA expression as an independent factor for unfavorable OS in HCC [57]. Moreover, research on lung adenocarcinoma demonstrated that ALDOA mRNA and protein expression were higher in tumor tissues compared to normal tissues. High expression of ALDOA was significantly correlated with advanced tumor stage and predicted poor overall survival prognosis [58]. ALDOA is a glycolytic enzyme that catalyzes the conversion of fructose-1,6-bisphosphate to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate [59]. Enolase 1 (ENO1) is a protein that catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate (PEP) and is commonly overexpressed in malignancies [60]. The expression of mesenchymal markers was reduced in squamous lung cancer lines when ALDOA was downregulated [61]. Its overexpression in colon cancer is linked to a worse prognosis and contributes to EMT [57]. Other studies have found that silencing ALDOA enhanced E-cadherin (an epithelial marker) and decreased N-cadherin (a mesenchymal marker) in pancreatic cancer patients [62]. All of this suggests that ALDOA is important for cancer growth and metastasis and that ALDOA could be a promising and effective cancer therapy target. ENO1 is central to a protein-protein interaction network that promotes tumor growth and metastasis, according to a proteomic investigation in gastric cancer cells (230). ENO1 expression is upregulated in lung adenocarcinomas, and its knockdown suppresses EMT. By inactivating the PI3K/AKT signaling pathway, attenuation of ENO1 would decrease the production of mesenchymal cell markers such as Vimentin, Snail, and N-Cadherin, reversing the EMT phenotype of cancer cells [58].

Phosphofructokinase 1 (PFK1) is a glycolytic enzyme that catalyzes the conversion of fructose 6-phosphate to fructose 1,6-bisphosphate; it acts oppositely to fructose-1,6-bisphosphatase 1 (FBP1). Enhanced PFK1 expression supports glycolytic flow and is typically activated by HIF-1 as part of a broader transcriptional response [63]. FBP1 is an enzyme that regulates gluconeogenesis by hydrolyzing fructose 1,6-bisphosphate to fructose 6-phosphate and inorganic phosphate. In two luminal breast cancer cell lines, Snail was discovered to directly suppress the expression of FBP1, resulting in increased glycolytic flow, reduced oxygen consumption, and increased ROS generation. FBP1 reduction results in improved breast cancer stem cell (BCSC)-like properties for Snail-mediated EMT by maintaining ATP production and boosting glycolytic intermediates for biosynthesis [44].

In a human hepatocarcinoma cell line, enhanced hepatocyte growth factor (HGF) signaling was linked to increased PFK1 activity and EMT. When resources are low in cancer cells, glycolysis is no longer the "preferred" pathway and glycolytic flux is shifted to the pentose phosphate pathway (PPP), where phosphofructokinase platelet (PFKP), a key isoform of PFK1, is inhibited [64]. As a result, its metastatic potential rises. The Snail, a major EMT-associated transcription factor (EMT-TF), has been identified as a PFK repressor [65]. The downregulation of Snail can be suppressed by inhibiting either PFKFB-3 or glyceraldehyde-3-phosphate dehydrogenase (GAPDH) [44].

In breast cancer cell lines, under conditions of limited nutrients, PPP will be promoted by Snail which generates NADPH, a reducing equivalent, and precursors for the synthesis of fatty acids, amino acids, and nucleotides [66]. In this approach, cancer cells that have been "stressed" can survive food deprivation [66]. FBP1 downregulation has been linked to a poor prognosis in gastric cancer and aggressive glioblastomas, highlighting the significance of this discovery [67]. De novo DNA methylation of FBP1's promoter appears to be the cause of its suppression [68].

The last step of glycolysis, pyruvate kinase (PK), catalyzes the transfer of a phosphoryl group from PEP to ADP, producing pyruvate and ATP in the process. Pyruvate kinase M2 (PKM2), a splice variant of PK that catalyzes the last irreversible metabolic conversion of PEP to pyruvate, is the final rate-limiting enzyme of glycolysis that has been extensively explored [69]. PKM2 has been demonstrated to be involved in EMT in human colorectal cancer cells and is expressed in prenatal tissues and malignancies [70]. PKM2 translocation, in particular, can cause EMT by causing nuclear translocation and subsequent transcriptional inhibition of the E-cadherin gene (*CDH1*) [71]. Specifically, PKM2 translocates in the nucleus during EMT where it represses E-cadherin transcription by interacting with TGFβ-induced factor homeobox 2 (TGIF2) [64]. This activity of PKM2 is non-canonical in that it does not directly connect to the enzyme's classic purpose (catalysis of glycolysis), but it does demonstrate that metabolism-related enzymes can gain alternate activities (the group of proteins moonlighting) in cancer cells that may be crucial in cancer cell fate. Of fact, there are other examples where PKM2 expression is increased in malignancies and favors the glycolytic route [72]. It is interesting to note that nuclear PKM2 can activate β-catenin, which raises MYC activity and causes increased PKM2, LDHA, and GLUT1 expression. This creates a positive feedback loop that fortifies the link between glycolysis and EMT [73]. Activated kinases phosphorylate PKM2 at tyrosine, conferring oncogenic activity to PKM2 in breast cancer cells by promoting YAP nuclear translocation. YAP silencing blocks the EMT process and reverses chemotherapy resistance by suspending oncogenic kinase-induced BCSC characteristics [74].

Another important glycolytic enzyme, PDK1, stimulates NF-κB signaling in gastric cancer to induce EMT. It does this by inactivating PDH, which prevents pyruvate from being converted into acetyl-CoA to fuel the TCA cycle. PDH is a crucial link between these two metabolic processes, diverting glucose flux from glycolysis to OXPHOS [44]. Downregulation of PDK1 in ovarian cancer reduces cisplatin resistance and EMT, which is a frequent EMT-linked characteristic [65]. PDK1 suppression can cause mitochondrial activation, which in turn suppresses HIF-1 signaling and angiogenesis—two important processes involved in tumor metastasis. This demonstrates the catastrophic role that PDK1 plays in the progression of tumors [46]. Furthermore, the glycolytic activity and BCSC characteristics are dependent on the long non-coding RNA H19, which is strongly linked to PDK1 expression. H19 silencing inhibits PDK1 expression in hypoxia, glycolysis, and the ability to self-renew. Importantly, aspirin can significantly reduce BCSC characteristics by inhibiting both H19 and PDK1, thereby providing new insights on how to stop the EMT process [66, 75]. The stimulation of glycolytic metabolism by PDK1 is required for the establishment of liver metastases [76]. In addition, PDK1 is necessary to induce EMT. Inhibition of PDK1 significantly suppresses lung-specific metastatic potential by downregulating mesenchymal markers. Exogenous PDK1 expression permits PDK1-deficient breast cancer cells to reclaim mesenchymal characteristics [77].

Surprisingly, another PDK isozyme, PDK4, has the exact opposite effect on EMT. PDK4 is a phosphorylation-dependent inhibitor of the pyruvate dehydrogenase complex found in the mitochondrial matrix [78]. As a result, it inhibits the conversion of pyruvate to

acetyl-CoA, lowering the flux of metabolites into the TCA, inhibiting aerobic respiration, and favoring glycolysis and fat metabolism. In human colon cancer cells, PDK4 has been shown to play an oncogenic role [79]. TGF-β induced EMT in lung cancer is partially blocked by PDK4 overexpression. Inhibition of PDK4 is enough to cause EMT and confer resistance to erlotinib [80]. This finding is similar to the anti-metastasis effect of pyruvate carboxylase suppression, which catalyzes the carboxylation of pyruvate to oxaloacetate to replenish the TCA cycle in breast cancer [81]. These findings imply that EMT-affected lung and breast cancer cells may still require glucose diversion to the TCA cycle. This divergence could be due to the need for TCA activity to supply citrate to enhance the cellular acetyl-CoA pool [76].

Lastly, LDHA can improve EMT by upregulating ZEB2, which is responsible for converting pyruvate into lactate, the final product of glycolysis. Increased E-cadherin expression and decreased focal adhesion kinase (FAK), MMP2, and Vascular Endothelial Growth Factor (VEGF) expression were seen after LDHA knockdown, all of which are important changes in EMT [46]. Furthermore, lactate produced by cancer cells can induce EMT by decreasing extracellular pH and activating dormant extracellular TGF-β [64]. In the meantime, the cellular release of lactate raises intracellular pH, which stimulates Wnt signaling and may lead to EMT [82]. In conclusion, glucose transporters, most glycolytic enzymes (except for PDK4), and lactate buildup together promote EMT in different cancer types. Finally, overexpression of LDH causes bladder cancer cells to migrate and invade more readily [44]. Furthermore, in colon cancer, GAPDH silencing suppresses EMT by inhibiting Snail [66].

A metabolite profiling approach used in pancreatic ductal adenocarcinoma (PDAC) cells also supports the role of glycolysis for EMT. This profile revealed three distinct subpopulations with distinct phenotypes [83]. Curiously, the clone with the highest concentration of glycolytic-related metabolites has a mesenchymal phenotype. The results reaffirmed the role that glycolysis plays in cancer progression since mesenchymal features are positively linked with cancer aggressiveness and disease progression. Furthermore, exposing PDAC cells to known EMT inducers TNF-α and TGF-β stimulates glucose absorption and lactate secretion without changing OXPHOS metabolism [46]. Additionally, glycolysis has been connected to CSC, a characteristic that has similar molecular pathways to EMT [44].

The role of lipid metabolism in EMT promotion

Lipogenesis is frequently elevated in cancer cells [84] and this is why lipogenesis has been considered as a cancer therapeutic target. The importance of lipogenesis genes in EMT, however, remains unclear. The carboxylation of acetyl-CoA to malonyl-CoA is catalyzed by acetyl-CoA carboxylase (ACC). There are two ACC isoforms: ACC1, which is present in the cytoplasm and controls de novo lipogenesis, and ACC2, which is found at the mitochondrion membrane and controls fatty acid oxidation. Overexpression of ACC1 has been observed in tumors such as breast [85] and liver [86] in mice, and suppressing ACC1 has been found to prevent lung tumor growth in animals [87]. Except for a recent publication on breast cancer cells that revealed an alternate non-canonical role for ACC1 in EMT, there are fewer studies on the involvement of ACC1 in EMT. It was observed that leptin and TGF can reduce ACC1 function and promote EMT by phosphorylating ACC1 at Ser79 via AMPK [88]. It was proposed that this impact is mediated via acetyl-CoA buildup caused by ACC1 inhibition, as well as increased acetylation of SMAD2, which mediates TGF-β-induced EMT. As a result, even while ACC1 expression has been reported to be elevated in various malignancies, such as breast cancer, it does not appear that silencing ACC1 would be a useful treatment strategy because it can enhance metastatic potential through supporting EMT.

The primary role of fatty acid synthase (FASN) is to synthesize palmitate from acetyl-CoA and malonyl-CoA. A fusion of the FASN gene with the estrogen receptor α (ER-α) gene has been identified in several malignancies, which may have significant implications for estrogen signaling [89]. FASN overexpression has been seen in different tumors [90–92]. Increased expression of FASN in cisplatin-resistant non-small cell lung cancer cells is known to promote EMT through TGF signaling [92]. While other studies have suggested that FASN may play a significant role in EMT, they have not elucidated the underlying mechanisms. (261). Stearoyl-CoA desaturase-1 (SCD-1) is an endoplasmic reticulum-anchored enzyme that catalyzes the generation of monounsaturated fatty acids (oleate and palmitoleate from stearoyl-CoA and palmitoyl-CoA, respectively). In malignancies such as lung adenocarcinoma, SCD-1 is overexpressed, and its higher expression is associated with a negative prognosis [93]. Silencing SCD-1 in breast cancer cells resulted in reduced nuclear localization of β-catenin, a crucial mediator of EMT, and inhibited EMT-like activity [94]. ATP citrate lyase (ACLY) changes citrate from mitochondria into acetyl-CoA and oxaloacetate, which is required for lipogenesis. ACLY is commonly overexpressed in malignancies [95, 96], and it has been demonstrated to promote EMT phenotypes in colon cancer cells, partially via β-catenin signaling [97]. ACLY inhibition has been shown to prevent EMT generated by ambient fine particulate matter (PM 2.5) and alter EMT phenotype in a lung cancer cell line [98, 99]. Isoforms 1, 3, and 4 of Acyl-CoA Synthetase Long-Chain Family Member (ACSL) are responsible for converting fatty

acids into fatty acyl-CoA and are commonly found to be overexpressed in cancer cells [100]. ACSL1 uses oleate and linoleate, ACSL3 uses myristate, palmitate, arachidonate, and eicosapentaenoic, while ACSL4 utilizes arachidonate [101]. The activation of fatty acids by ACSL is required for both the production and β-oxidation of cellular lipids. Overexpression of ACSL1 and ACSL4 in colon cancer cells is linked to EMT characteristics [102]. The process is unknown, but according to one research, this gives cancer cells a metabolic advantage by making them more energy-efficient and enhancing the expression of SNAI2 and N-cadherin [103]. Finally, EMT is influenced by the metabolism of various lipids, particularly glycosphingolipids. Lactosyl ceramide is converted by GM3 synthase into GM3, a basic ganglioside that induces EMT by interacting with TGF receptors [104]. ZEB1 has been demonstrated to enhance the expression of the GM3 synthase gene in human lung cancer cells by binding to its promoter and inhibiting the microRNA-mediated GM3 synthase repression [105]. Further research is needed to determine the significance of this modulation of glycosphingolipid metabolism in EMT in different cancer types. The principal lipid metabolism routes that interact with the EMT process are summarized in Fig. 3.

It should be mentioned that new research shows how important minerals and fat-soluble vitamins—especially vitamin D—are in controlling the metabolism of cancer cells, particularly when dysregulated metabolic pathways are linked to cancer development. The active form of vitamin D, 1,25-dihydroxyvitamin D (calcitriol), is essential for regulating the metabolism of cancer cells. It affects how energy is used and controls metabolic processes frequently changed in cancer cells. According to research, calcitriol can influence pathways linked to energy sensing and nutrition metabolism by controlling tumor suppressors and oncogenes, hence targeting metabolic abnormalities. As a transcription factor, calcitriol binds to the vitamin D receptor (VDR) to control genes related to apoptosis, differentiation, and cell division. It has been demonstrated to cause metabolic reprogramming in cancer cells by downregulating oncogenes essential for tumor metabolism, such as c-Myc and HIF1α [106, 107]. Its potential as an anticancer drug is influenced by this modulation, which may result in decreased proliferation of cancer cells and increased apoptosis.

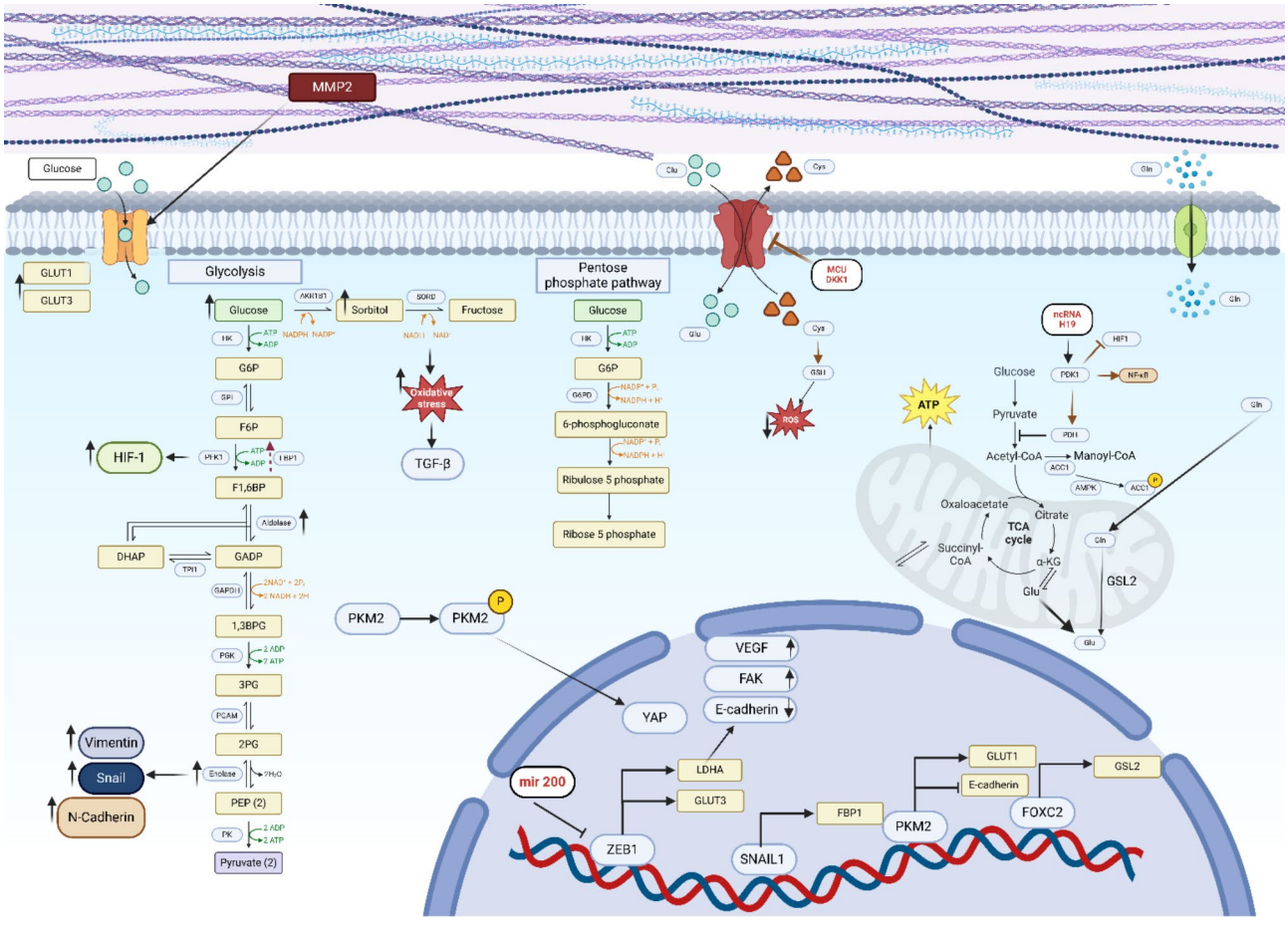

Fig. 3 The principal routes of carbohydrates, lipids, and amino-acids metabolism interacting with the EMT process

Moreover, vitamin D has immunomodulatory qualities that may affect tumor microenvironments. It further connects vitamin D levels with cancer outcomes by regulating immune responses that may either stimulate or hinder tumor development [108].

Additionally essential to cellular processes that might affect cancer metabolism are minerals like calcium and magnesium. Calcium levels have an impact on both apoptosis and cell division. As a result, cancer cells frequently exhibit disruption of calcium homeostasis. However, magnesium is essential for more than 300 enzymatic processes, such as those that repair DNA and provide energy for cells. Because low magnesium levels impede cellular activities, they have been associated with an increased risk of cancer [109].

The role of amino acid metabolism in EMT promotion

The regulation of cellular homeostasis requires amino acid metabolism. In cancer cells, the need for nitrogen in biosynthetic processes is elevated, amino acids are consumed more quickly, and there is a significant demand for non-essential amino acids [110]. It's also remarkable that glutamine is the second most-required nutrient in most cancer cells, after glucose [111]. Scientists emphasize the amino acids glutamine, asparagine, and cystine, which have been linked to EMT in cancer [112, 113]. Many cancer cells absorb a lot of glutamines, which is the most common amino acid in serum. It also acts as a fundamental source of α-ketoglutarate in glutamine-dependent cancer cells, which is utilized in the TCA cycle via a process known as glutaminolysis [114]. The hydrolysis of glutamine to glutamate and ammonia is catalyzed by glutaminases 1 and 2 (cytosolic GLS1, mitochondrial GLS2). TGFβ and Wnt can stimulate GLS1 and induce EMT in a Snail-dependent manner, whereas inhibiting GLS1 suppresses EMT [115]. GLS2 is principally expressed in the brain, liver, and pancreas, and is indirectly related to EMT in breast cancer and hepatocellular carcinoma cells, in comparison to GLS1, which is universally produced [115, 116]. These findings suggest that precise regulation of glutaminolysis in different regions of cancer cells, indicated by the GLS1/GLS2 ratio, could help maintain EMT, and targeting this could be a potential approach for suppressing EMT. GLS2 levels are linked to GLS1 levels in breast cancer cells, indicating that the downregulation of GLS2 is a consequence of EMT, rather than the cause [117]. While silencing forkhead box protein C2 (FOXC2) increased GLS2 levels, it did not affect GLS1 levels, leading to the suppression of EMT [116]. Asparagine, a non-essential amino acid in humans, has been linked to EMT and the metastatic potential of cancer cells. Increased intake of asparagine through the diet or increased activity of asparagine synthetase led to higher rates of metastasis, while reduced asparagine intake through the diet, decreased asparagine synthetase function, or treatment with L-asparaginase altered metastatic potential without affecting primary tumor growth [118]. In the case of glutamine deficiency in the tumor microenvironment, asparagine can become an important amino acid to promote protein synthesis and cell proliferation [119]. The asparagine content of proteins that are elevated during EMT is 20% greater than the normal condition [118]. As a result, it seems sensible to believe that decreased asparagine availability would limit EMT, particularly at the translational stage. However, it's unknown how asparagine affects the transcription of EMT genes like TWIST and N-cadherin [120]. To discover all of the potential mechanisms of asparagine's impact on EMT, further research is required. Cystines are produced when two cysteine molecules are oxidized and connected by a disulfide bond. It is the most commonly circulating form of cysteine that cells can absorb. Tumor cells can get "addicted" to cysteine [121] and this requirement could be linked to EMT [122]. Upregulation of the EMT inhibitor miR-200c in cystine-addicted breast cancer cells made them less sensitive to cystine deficiency [122]. Targeting glutaminolysis, particularly through the precise regulation of the GLS1/GLS2 ratio in different regions of cancer cells, emerges as a potential approach for suppressing EMT. These findings suggest that maintaining this ratio could help regulate EMT progression. For instance, GLS2, principally expressed in specific tissues like the brain, liver, and pancreas, is indirectly associated with EMT in breast cancer and HCC. In contrast, GLS1, universally produced, plays a distinct role [117]. Such insights underscore the potential therapeutic significance of targeting glutaminolysis to modulate EMT. This suggests that cysteine may play a significant role in EMT, but it remains uncertain how cysteine influences EMT. The interaction of amino-acid metabolism and the EMT process is summarized in Fig. 3.

The role of TCA (tricarboxylic acid) cycle in EMT promotion

The importance of mitochondria in the development of cancer was previously underestimated; however, extensive evidence now confirms their critical role in carcinogenesis. Mitochondrial alterations are necessary for the distinctive metabolic rewiring observed in cancer cells, and they also participate in various other cellular processes throughout cancer initiation and progression [123, 124]. It is noteworthy that conflicting studies have categorized the metabolic characteristics of invasive cancer cells undergoing EMT as either reliant on glycolysis or heavily dependent on OXPHOS, not only across different tumor types but also within specific cancer types [44, 125, 126]. EMT is frequently observed in tumors with mutations affecting enzymes of the TCA cycle, such

as fumarate hydratase (FH), Succinate dehydrogenase (SDH), and Isocitrate Dehydrogenases (IDH) [47, 127].

Fumarate is converted to malate by FH. Leiomyomatosis, kidney cancer, and pheochromocytomas are caused by FH loss of function mutations [128]. Fumarate accumulation in renal cancer cells resulting from these mutations can lead to EMT. SDH, a component of the respiratory chain that converts succinate to fumarate, is another TCA cycle enzyme linked to EMT [129]. Paragangliomas, gastric stroma tumors, and pulmonary chondromas have SDH loss of function mutations [130]. Metastatic pheochromocytomas and paragangliomas, characterized by reduced SDH expression resulting from SDHB (Succinate Dehydrogenase Complex Iron-Sulfur Subunit B) mutations, exhibit an EMT signature and increased protein expression of SNAI 1/2. This suggests that EMT induction may occur in these tumors [131]. Notably, breast cancer cell lines undergoing EMT display decreased SDH expression, whereas hepatocellular carcinoma cell lines with reduced SDH expression show elevated expression of EMT markers. This implies a potential association between EMT and SDH, which requires further investigation to elucidate the underlying molecular mechanisms [44]. It's possible that the accumulation of succinate caused by SDH mutations can similarly promote EMT with fumarate [132]. The depletion of SDHB in chromaffin cells triggers the activation of EMT-TFs, leading to the epigenetic suppression of keratin-19 [47, 133, 134]. The association between insufficient SDHB levels and EMT has also been confirmed in colorectal cancer, where the silencing of SDHB enhances cell migration and invasion through a pathway mediated by TGF-β/Snail [135]. This relationship has also been observed in ovarian cancer. Additionally, succinate dehydrogenase 5 (SDH5) contributes to lung cancer metastasis by regulating the glycogen synthase kinase 3β (GSK3β)-β-Catenin signaling pathway [47].

Isocitrate dehydrogenase (IDH) catalyzes the conversion of isocitrate to α-ketoglutarate. Humans have three isoforms: IDH1 and IDH2, which are $NADP^+$ dependent and unrelated to IDH3. IDH1 and IDH2 catalyze reversible processes, but IDH3 catalyzes non-reversible reactions that are sensitive to allosteric modifiers. IDH1 and IDH2 mutations have been found in malignancies, particularly gliomas [136]. Mutations in IDH1 and IDH2 cause the enzymes to generate 2-hydroxyglutarate rather than α-ketoglutarate. Accumulation of 2-hydroxyglutarate, which has been demonstrated to induce EMT and is dependent on overexpression of ZEB1 and downregulation of the miR-200 family, results in an EMT phenotype like that of cells lacking FH and SDH [137]. Cells from colorectal cancer and breast malignancies have both demonstrated this trait [44]. Finally, another TCA cycle enzyme linked to EMT is citrate synthase (CS), which catalyzes the TCA cycle's first committed step. Silencing CS causes EMT-like morphological and molecular alterations in human cervical cancer cells and increases metastasis in vivo [138]. Recent research indicates that CS levels are elevated in various tumor types, including ovarian malignancies, and that silencing CS inhibits tumor cell motility and invasion in vitro. Consequently, the role of CS in tumor progression is still not fully understood and may vary depending on the tissue type [139].

Signaling pathways enhancing EMT

Cellular metabolism is crucial for a cell's ability to respond to changes in both its internal and external environment. It regulates a wide range of molecular and biochemical activities [140]. EMT can be triggered by a variety of microenvironmental signals, which can potentially reprogram metabolism. The renewed interest in cancer cell metabolism has generated questions concerning the interaction between metabolism reprogramming and EMT, and it's difficult to decide which one is dominating [47, 141].

Cancer cells fine-tune their metabolic circuits during EMT, in particular, to meet the increasing bioenergetic demands of facing numerous hurdles along with cellular transit [142]. EMT-associated transcription factors (EMT-TFs) can overtly influence metabolic rewiring. In mesenchymal cells, higher levels of AKR1B1 (Aldo-keto-reductase-1 B1) contribute to EMT and stemness, according to an EMT-focused transcriptome analysis [64]. Cells use the polyol pathway, a two-step metabolic process mediated by sorbitol dehydrogenase (SORD) and AKR1B1, to convert excess glucose to fructose. A significant link between glucose metabolism and EMT has been suggested by the observation that excess glucose promotes EMT through autocrine TGF-β activation, while PP-deficient cells are resistant to glucose-induced EMT [143]. Furthermore, TGF-β is an EMT-inducing signal that exerts a dual impact. TGF-β is commonly used to promote EMT in a variety of cancer types that may help with metabolism by promoting glycolysis [144]. Therefore, a necessary component of the EMT phenotypic shift in cancer cells is metabolic reprogramming. Metabolic reprogramming, according to the metabostemness theory, is the first stage in EMT and stemness acquisition.

Conjectural association of EMT and metabolic reprogramming during stemness acquisition

Oxidative phosphorylation (OXPHOS) is required by differentiated epithelial cancer cells. These cells can increase their glycolytic activity to acquire stemness and become hybrid E/M-like cancer stem cells (CSCs; $OXPHOS^{high}$/$glycolysis^{high}$, proliferative) after undergoing EMT. The hybrid E/M-like CSCs can either decrease their OXPHOS activity and lose stemness to transition

into mesenchymal-like CSCs (glycolysis^{high}, quiescent) or decrease their glycolytic activity and lose stemness to transition into differentiated mesenchymal cancer cells (OXPHOS^{high}) [145]. It is important to mention that the high OXPHOS label does not necessarily reflect the level of activity of fatty acid oxidation, as this can vary among different types of differentiated cancer cells [47]. Quiescent mesenchymal-like CSCs with high glycolysis levels can either enhance their OXPHOS activity and transform into hybrid E/M-like cancer stem cells or transition from glycolysis to OXPHOS and differentiate into mesenchymal cancer cells. These cells can later undergo dedifferentiation and regenerate into mesenchymal-like cancer stem cells [146].

The trade-off between metabolic reprogramming and EMT in Cancer Stem cells

In CSC biology, metabolic reprogramming is crucial. CSCs and non-stem cancer cells share metabolic pathways in general [147]. The presence of glucose in the microenvironment promotes the growth of stem-like cancer cells in tumors, whereas glucose deprivation causes stem-like cancer cells to rapidly deplete. These effects are linked to CSCs' improved glucose metabolism pathway [148]. Non-stem cancer cells have lower glucose uptake, lactate generation, glycolytic enzyme expression, and ATP content than CSCs. Depending on the cancer type, CSCs may have enhanced glycolysis or OXPHOS [138]. The environment and cellular signaling pathway fine-tun the metabolic phenotype of CSCs between glycolysis and OXPHOS. During OXPHOS suppression, the CSC metabolic phenotype can transition to glycolysis [149]. The hybrid glycolysis/OXPHOS phenotype causes cancer cells to improve metabolic plasticity, allowing them to respond better to environmental stimuli and contributing to metastasis and treatment resistance [150]. In this regard, the Snail factor plays an important role. Several genes, including aldolase and glucose phosphate isomerase, involved in the metabolism of glucose, are regulated by Snail. Snail has recently been demonstrated to enhance glucose metabolism in basal-like breast cancer by promoting epigenetic silencing of FBP1. Snail also inhibits OXPHOS by inhibiting both cytochrome C oxidase and mitochondrial respiratory complex I activity [66]. Snail also reroutes glucose metabolism to the pentose phosphate pathway by inhibiting PFKP, a glycolysis rate-limiting enzyme [151]. Another EMT-TF, ZEB1, is involved in metabolic plasticity in pancreatic tumor cells, allowing cells to switch between an OXPHOS or glycolytic profile, depending on the situation [152]. The activation of 1-integrin, FAK, and the PI3K/AKT/mTOR pathways, as well as the suppression of the p53 pathway, cause this energy metabolic reprogramming [153]. The activation of PI3K has been shown to directly regulate glycolysis by mobilizing aldolase from actin. Additionally, the inactivation of the tumor suppressor p53, known for its role in promoting stemness traits, has been demonstrated to activate phosphoglycerate mutase, a key enzyme in glycolysis, while also reducing electron transport activity [154].

In pancreatic tumors, it has been shown to stimulate glycolysis by inhibiting glutaminolysis [139]. Metabolic reprogramming, on the other hand, may result in EMT and stemness. Folmes et al. showed in 2011 that the expression of glycolytic genes comes before the expression of pluripotency genes, implying that a glycolytic switch could cause cell dedifferentiation in mouse embryonic fibroblasts [155]. Data from ovarian tumors support the causal involvement of glycolysis reprogramming in EMT. Siu et al. discovered that the IL6-dependent increase in HK2, which is the rate-limiting initial step of glycolysis, results in the expression of stem markers (Nanog, Oct4, Klf4, Sox9, and CD117), as well as heightened invasiveness, following the activation of the FAK-ERK-MMP9 signaling pathway [138].

LDHA increases the transcription of genes involved in the EMT process by increasing H3K27 acetylation, which catalyzes the subsequent stage of glycolysis [156]. E-cadherin, an epithelial marker, is down-regulated in papillary thyroid cancer, whereas EMT-TFs, mesenchymal markers, and TGF-R1 are up-regulated [157]. Elevated lactate levels in the surrounding microenvironment have also been shown to trigger EMT in breast malignancies, and treating breast cancer cells with lactate leads to the expression of genes associated with stemness [158]. In addition, adding lactate and a high concentration of glucose to the culture medium results in the activation of genes associated with stemness including Nanog, Oct4, and Sox2 [64].

The roles of EMT in solid tumor metastasis, drug resistance, and recurrence

EMT and tumor metastasis

Due to the intricate diversity of molecular control systems, EMT is essential for a wide range of physiological functions at various stages of growth across different organs and tissues. Broadly speaking, EMT facilitates a shared characteristic known as "cellular plasticity," which refers to the ability of cells to alter their phenotype and function in response to specific stimuli [126]. Furthermore, cells are only partially exposed to EMT, reflecting the nature of cellular plasticity. EMT processes can also be reversible. Each of these steps is necessary for normal development. Oncogenic pathways exploit the initial flexibility of cells to transform them into tumor cells in a completely new pathological context. We now have evidence that the reversal processes known as MET and partial EMT are crucial for invasion and metastasis [159].

Instead of fully transforming into mesenchymal cells, as happens with full EMT during embryogenesis, tumor cells often adopt an epithelial/mesenchymal hybrid phenotype, which manifests as the simultaneous expression of mesenchymal and epithelial markers [160]. Interestingly, certain tumor cell groups retain elevated levels of E-cadherin expression, which is crucial for preserving the epithelial phenotype but does not hinder the formation of a partial epithelial/mesenchymal phenotype or its invasive and migratory potential [161].

Whether metastasis begins through the EMT pathway has been a topic of debate in experimental research using transgenic in vivo models of breast and pancreatic cancer. Nevertheless, there are issues with Fisher et al.'s experimental model [162] was later found to study EMT, including the erroneous selection of Fspl and Vim genes as mesenchymal markers (low expression in EMT-sensitive breast cancer cells) [163]. Multiple independent research studies have demonstrated the significant role of the cochlea in controlling EMT and metastasis in breast cancer [164]. Conclusions about the non-involvement of EMT in pancreatic cancer metastasis based on the importance of cochlear expression and torsion in EMT have also been investigated [160]. In addition, ZEB1 failure in the same transgenic model is associated with loss of cell flexibility (stabilization of epithelial phenotype by tumor cells), as well as decreased invasive and metastatic abilities [165].

The mesenchymal/epithelial hybrid phenotype's underlying molecular processes are not well understood and are sometimes challenging to explain using the accepted theory of transcriptional repression or activation of the respective "epithelial" and "mesenchymal" genes. E-cadherin malfunction can happen sometimes. The *CDH1* gene is associated with abnormal tumor microenvironment signals [166], and this disorder is not necessarily associated with decreased adhesion but is often associated with increased and activating its construct, which in some cases is important for metastasis [167].

Aiello et al. verified the potential for utilizing two forms of EMTs in tumor invasion: complete EMT, which is characterized by reduced E-cadherin transcription and increased vimentin transcription, and partial EMT, which is characterized by the retention of E-cadherin mRNAs and increased vimentin transcription. The research employed a mouse reporter line as an in vivo model of pancreatic cancer, which is mentioned in part EMT [168]. In addition, compared to complete EMT, it is characterized by decreased expression of the transcription factors Etv1, Prrx1, Zeb1, Twist1, SNAI1, SNAI2, and Zeb2. Furthermore, a significant proportion of the model rat tumors had incomplete EMT. It was also demonstrated that this kind of EMT dominated human colon and breast cancer cells. Tumor cells undergoing partial EMT lack E-cadherin surface labeling during immune-stimulus experiments. The authors demonstrated how surface protein and surface E-cadherin reperfusion to late endosomes are related to partial EMT pathways [168].

Various EMT programs are associated with distinct invasion mechanisms. Tumor cells utilize partial EMT to migrate as multicellular clusters while preserving intercellular contacts, but they can also migrate individually [169]. Conversely, complete invasion and migration of EMTs occur exclusively in the form of single cells. Numerous studies have substantiated the collective migration of tumor cell clusters undergoing partial EMT during invasion [170].

Tumor cells near the cluster's margins lack E-cadherin expression and exhibit a more mesenchymal phenotype, despite the majority of the cells that comprise these clusters expressing E-cadherin and maintaining intercellular connections. Therefore, "leading" cluster cells that have had their motility enhanced by EMT are linked to higher metalloproteinase synthesis, which degrades the extracellular matrix linked to E-cadherin re-expression and promotes active invasion of the whole cluster [167].

It is crucial to understand that metastasis is an inefficient process since only a tiny portion of the tumor cells in circulation are kept from growing and developing into new tumors [171]. Metastases are frequently the consequence of tumor cell cluster colonization, even though fewer clusters are circulating in tumor cells than there are single tumor cells. These clusters also result in many colonies of secondary tumor sites [172].

Tumor metastasis is a multistage process that includes colonization (proliferation of tumor cells at the location of the secondary tumor) in addition to invasion, migration, and extravasation (tumor cells penetrating through blood artery walls into the tissue). A different procedure that emphasizes the significance of cell plasticity for tumor growth is EMT. Epithelial cells that resemble original tumor cells in morphology—marked by the reexpression of epithelial markers and the inhibition of EMT factors—form metastases [173].

On the other hand, several processes promote the development of an epithelial phenotype. Growth differentiation factor 10 (GDF10), sometimes referred to as bone morphogenetic protein 3B (BMP-3B), raises the expression of E-cadherin and tumor susceptibility while suppressing vimentin expression as well as migration and invasion in aquamous cell carcinoma of the head an neck [174]. In response to cytotoxic treatment, cells undergo programmed cell death. A worse overall survival rate is linked to low GDF10 expression. It is noteworthy that the reduction of TGFBR3, a type III TGF-β receptor, is responsible for the production of GDF10 and is regulated by Smad-dependent activator signals. Furthermore, ERK

signaling induces the suppression of GDF10, in addition to the traditional TGF-β/EMT signaling [175].

In hepatocellular carcinoma cells, a specific form of connexin, Cx32 isoform, promotes MET [176]. Cx32 inhibits liver cancer and the spread of cancer cells in the liver, and its presence is decreased in biliary carcinoma cells compared to normal liver tissue [176]. One of the mechanisms of resistance to apoptosis and cytotoxic chemotherapy in tumor cells is the mesenchymal phenotype, and EMT is believed to contribute to this resistance. It is worth noting that in a publication by Yu et al. [176], a line derived from doxorubicin DNA-resistant liver cancer shows signs of EMT. Thus, the authors postulated that EMT brought on by chemotherapy would be associated with both increased vimentin expression and reduced expression of Cx32 and E-cadherin. In doxorubicin-resistant cells, overexpression of Cx32 results in MET along with re-expression of E-cadherin and reduced vimentin expression. It is important to note, nevertheless, that the scientists are only moderately certain that the possible correlation between phenotypes serves as the basis for Cx32's function in controlling tumor cells' susceptibility to chemotherapy and its use as a therapeutic target [176].

The transcription factor GRHL2, which stimulates the production of many epithelial adhesion molecules and inhibits the expression of EMT proteins like ZEB1, is another significant MET trigger [177]. Numerous tissue-specific processes control the mechanisms in which GRHL2 regulates the growth of tumors. In addition, this transcription factor can contribute to tumor progression [178, 179] or suppress tumor growth [180]. A comprehensive analysis of GRHL2 expression patterns in normal tissue samples and several cancer types revealed complicated patterns, with varying tumors expressing the protein at higher and lower levels. It is noteworthy that epithelial cells with stem cell properties that are actively dividing exhibit elevated levels of GRHL2. This observation has been validated in a study that examined the function of GRHL2 in pancreatic cancer, squamous cell carcinoma of the head and neck, and non-invasive forms of cancer [178, 179]. Furthermore, big tumor sizes, late clinical stages of colorectal cancer, and elevated proliferative activity are linked to higher GRHL2 expression. Although extremely uncommon, GRHL2-negative breast cancer is typically linked to lymph node metastases. In addition, overexpression in breast cancer cells promotes cell division and is linked to a low rate of disease-free survival [179]. Prostate cancer is similarly linked to the dual impact of GRHL2. The prevalence of GRHL2-negative tumors is a characteristic shared by gastric and renal cancers. In these types of cancer, GRHL2 functions as a tumor suppressor, inhibiting invasion and metastasis [181].

It is unclear how reprogramming factors affect the growth of tumors and how they contribute to MET induction. The production of induced pluripotent stem cells (iPSCs) from mouse fibroblasts was demonstrated to activate the epithelial program associated with induction of miR-205/miR-200, cochlear suppression 1, and TGF-β1/TGF-βR2 when cells are exposed to MET. This was achieved by inducing overexpression of reprogramming factors Oct3 / 4, Klf4, c-Myc, and Sox2 (OKMS) [181].

Experiments involving the reprogramming of tumor cells have contradictory effects on malignant progression. While reprogramming can result in a reduction of oncogenic traits and the suppression of metastasis associated with MET, the expression of reprogramming factors is also linked to certain outcomes [182, 183]. Given the dismal prognosis, further research and a deeper understanding of the molecular mechanisms linking cell potency and plasticity are essential to fully comprehend the induction of EMT by reprogramming factors. This understanding may enhance the potential of this approach as a promising anticancer treatment.

EMT and tumor recurrence

As previously mentioned, EMT and CSCs may be associated with drug resistance during cancer. Continuous efforts are being made to identify cancer cell populations that are enriched in CSCs. However, recurrence, metastasis, drug resistance, and malignant traits of tumor cells occur when CSCs retain their EMT feature following the cancer treatment [184, 185]. Efflux of anticancer drugs from CSCs is mediated by transporters expressed on their cells' membranes [186], and EMT regulates cellular processes such as migration, invasion, metastasis, alteration of the ECM, and apoptotic flux [187]. Drug resistance may be acquired through the alteration of gene and protein expression in CSCs. Studying the relationship between gene-expression profiles of tumor cells and clinical responses of patients has identified strong correlations between the expression of genes associated with EMT and resistance to treatment [188].

A large cohort of breast cancer patients was examined for their responses to chemotherapy. It was found that chemotherapy resistance was closely associated with genes typically expressed by the stromal cells by activation of the EMT program within carcinoma cells [189].

Another study showed that the presence of 76 EMT genes in different cell lines derived from patients with NSCLC was a strong predictor of clinical resistance to EGFR or PI3K inhibitors [190].

Therapeutic strategies can be developed by preventing the induction of EMT. TGF-β signaling is one of the best-identified pathways in EMT induction [191]. However, this cytokine has multiple effects on cancer cells, and therefore its inhibition requires caution. In other

words, The overexpression of SKI and SnoN, endogenous inhibitors of TGF-β signaling, is associated with the development of many types of human cancers, including melanoma and esophageal cancer [192].

As the other therapeutic goal to prevent EMT induction, targeting hepatocyte growth factor (HGF)-receptor signaling has attracted much attention. Frequent activation of this pathway, typically by the HGFR gene (c-MET) being mutated or amplified, is exhibited in many cancer types as a contributor to cancer pathogenesis [193]. Inhibition of HGFR helps antitumor activity and prevents the induction of EMT. Of note, crizotinib, for the treatment of NSCLC, and cabozantinib for the treatment of medullary thyroid cancer and renal cell carcinoma RCC are already approved by the FDA [194]. Mechanistically, crizotinib is a potent drug that disrupts the growth and survival of NSCLC, as well as other particular types of cancers by targeting multiple receptor tyrosine kinases (RTKs), including anaplastic lymphoma kinase (ALK), Recepteur d'Origine Nantais (RON), and the aforementioned c-Met) [195]. Specifically, ALK gene translocations can occur in some tumors, leading to the formation of abnormal fusion proteins. These proteins act like a permanently switched-on signal, driving uncontrolled cell division. Crizotinib effectively inhibits these fusion proteins by blocking their phosphorylation, as a critical step in their activation. This targeted inhibition mediated by crizotinib has been demonstrated in laboratory studies using cancer cell lines and in animal models harboring tumors with specific ALK fusion proteins or c-Met overexpression. These studies demonstrate crizotinib's ability to suppress tumor growth and promote apoptosis in these models [196]. Originally designed to target c-Met, Crizotinib emerged as a multi-targeted therapy with potent activity against both ALK and the related ROS1 receptor tyrosine kinase. This versatility expands its potential application in treating NSCLC and a variety of neoplasms driven by these specific molecular alterations [195]. C-Met has also been reported to be inhibited by cabozantinib, as an oral potent tyrosine kinase inhibitor that also blocks Vascular endothelial growth factor receptor 2 (VEGFR2), Tyrosine-protein kinase receptor UFO (AXL), tunica interna endothelial cell kinase 2 (TIE2), FMS-like tyrosine kinase 3 (FLT3), and rearranged during transfection (RET) signaling axes. A study utilizing the RIP-Tag2 transgenic mouse model, which mimics pancreatic neuroendocrine carcinoma, revealed key insights into treatment strategies for this cancer. This study demonstrated that cabozantinib could represent a more comprehensive therapeutic effect. It not only suppressed tumor growth but also significantly reduced both invasion and metastasis of the malignancy, while selective VEGF inhibitor reduced tumor growth, but unfortunately led to increased invasion of surrounding tissues [197, 198].

It has also been found that there are same effects on multiple prostate cancer cell lines treated with monoclonal antibodies against the ectodomain of N-cadherin, an important marker of EMT [199]. Other findings for kinase inhibitors showed that inhibitors target PKCα selectively eliminate human mammary epithelial cells (HMLEs) with an active EMT program [200].

EMT and drug resistance

Recent research has discovered a link between drug resistance and the EMT phenotype. Different forms of malignancies, such as head and neck squamous cell carcinoma and hepatocellular carcinoma, as well as cancer therapy with EGFR inhibitors like cetuximab and gefitinib, validated this resistance. EMT has also been demonstrated to have a role in giving drug resistance to cancer cells when they are exposed to conventional therapies such as taxol, vincristine, and oxaliplatin. Other studies have shown that EMT has been linked to gemcitabine-resistant in pancreatic cancer cells, oxaliplatin-resistant in colorectal cancer cells, and lapatinib-resistant in breast cancer [201].

When considering therapeutic intervention, special attention should be paid to stem features acquired during the EMT process. In gemcitabine treatment resistance, activation of Notch signaling was linked to enhanced cell proliferation and survival [202]. In addition, resistance to drugs like paclitaxel has been linked to enhanced tumor cell migration and invasion [203]. Slug and Snail expression are also linked to chemotherapy resistance, as they reduce apoptosis while promoting stemness [204]. Twist causes EMT and promotes treatment resistance in breast cancer cells by reducing estrogen receptors and increasing Akt [205, 206]. In addition, the findings were related to breast cancer resistance to EGFR tyrosine kinase inhibitors such as gefitinib. In SK-Br-3, MDA-MB-261, and MDA-MB-468 breast cancer cells, gefitinib efficiently decreased EGFR activation [207]. Therapeutic resistance was found to be closely linked to enhanced expression of genes typically expressed by stromal cells in patients with breast cancer; EMT activation in the carcinoma cells may contribute to this transcriptional upregulation [189]. Clinical samples and cell lines derived from patients with non-small-cell lung carcinoma have been found to show a 76-gene EMT signature that predicts resistance to EGFR or PI3K inhibitors [190]. Non-small cell lung cancer is often treated with EGFR-TKIs such as erlotinib and gefitinib. EGFR-TKIs can bind to the ATP-binding sites of EGFRs, blocking their activity and causing cell apoptosis. EMT has been shown to cause cancer cells to become resistant to EGFR-TKIs [208]. Research has shown that EMT-TFs may be able to prevent EGFR-TKI-induced

apoptosis. Slug is thought to give gefitinib resistance in NSCLC patients by reducing Bim expression and increasing caspase-9 activity [209]. Notch-1 overexpression shields EGFR-mutant cells from gefitinib-induced apoptosis and is related to EMT in gefitinib-acquired resistance [210].

Hypoxia is another significant factor that promotes EMT and treatment resistance. HIF-1α activation in hypoxic conditions increased EMT and drug resistance in hepatocellular carcinoma through enhanced MDR1 expression [211]. Under hypoxia, inhibiting HIF-1α reversed the EMT phenotype and eliminated the drug-resistant phenotype in HCC, indicating that hypoxia/HIF-1α plays a role in EMT-driven drug resistance [208].

Sommers et al. discovered that EMT occurred in two adriamycin-resistant MCF-7 cell lines as well as a vinblastine-resistant ZR-75-B cell line [212]. Adriamycin-resistant MCF-7 cells had a large increase in vimentin expression and less development of desmosomes and tight junctions, both of which are typical EMT phenotypes [208]. Moreover, research revealed that TGFβ promoted EMT, which resulted in drug resistance. In animal models, doxorubicin has been shown to stimulate the expression of circulating TGF [213].

Further research is needed to describe and uncover the mechanisms of EMT in drug resistance. The understanding of the specific mechanisms that drive the expression of EMT features in cancer cells will likely aid in the development of more tailored therapeutic methods that could be used in conjunction with existing treatments.

Therapeutic perspectives to target EMT

Traditional cancer treatments like chemotherapy show encouraging results, but there are still problems like high rates of metastasis and drug resistance. Therefore, there is a pressing need to investigate and assess new therapeutics, notably in the area of EMT. Several techniques in this field target EMT, including inhibiting the upstream signaling pathway, going after the molecular triggers of EMT, the EMT effectors, and the glycosylation mechanisms that control EMT-transcriptional factors (EMT-TFs) [214]. Therefore, we'll briefly introduce a few of them. Targeting genes has proven to be difficult, especially when several transcription factors work together to control the transcription of important molecules involved in a variety of signaling pathways [215]. As a result, several inhibitors have been researched to specifically target EMT-TF regulators. In the context of breast cancer cells, the Zeb1 expression was observed to be downregulated by the cyclin-dependent kinase 4/6 inhibitor PD0332991 [216]. Furthermore, the miR-200 family of miRNAs can hinder the expression of ZEB1 and ZEB2, suggesting that this drug could be effective in targeting both the CSC to non-CSC transition and EMT-TFs [217]. As natural compounds, in vitro research has shown that Scutellariae Radix or Huangqin may have the potential to inhibit HCC cell metastasis by regulating the activities of matrix metalloproteinase-2 (MMP2), as well as forkhead box protein M1 (FOXM1), which induces EMT by binding directly to the Zeb2 promoter [218]. Baicalin, a flavonoid compound found in Huangqin, has recently been recognized for its anti-metastatic properties in various types of cancer. Baicalin inhibits the extracellular signal-regulated kinase (ERK) pathway, which reduces MMP activity and boosts tissue inhibitors of MMP-1 expression. This prevents HCC invasion and metastasis, according to a recent in vivo and in vitro study. The TGF-β/Smad, mitogen-activated protein kinase, and NF-kB pathways were all susceptible to the effects of baicalin [219]. Twist1 and Vimentin are downregulated in pancreatic cancer cells by sulforaphane, which reduces the stem-like characteristics of the cells [220]. Recently, it has also been revealed that the dietary polyphenol resveratrol can inhibit the main regulators of EMT, such as Zeb1, Snail, and Slug, while at the same time inhibiting tumor growth and invasion in a mouse model of pancreatic ductal adenocarcinoma [221]. Thymoquinone, the primary chemical constituent of Nigella sativa, promotes Twist1 promoter methylation, which inhibits migration and invasion while stimulating E-cadherin [222]. The brown seaweed polysaccharide, Fucoidan, has been found to hinder EMT in breast cancer cell lines like 4T1 and MDA-MB-231 by decreasing the expression of Twist1, SNAI1, and SNAI2 [223]. Similarly, the migration and metastasis of MDA MB 231 breast cancer cells have been restrained by Moscatilin which targets the Akt-Twist-dependent pathway [224]. Orchid Dendrobrium loddigesii's component, Moscatilin, specifically targets the Akt-Twist-dependent pathway to curb the migration and metastasis of human breast cancer MDAMB-231 cells [224]. Moreover, the suppression of EMT has been demonstrated through the utilization of various inhibitors, including proteasome inhibitors and NpI-0052, which reduce the expression of NF-κB and Snail [225]. Additionally, small-molecule drugs such as GN 25 and GN 29 hinder the interaction between p53 and Snail, while Co(III)-Ebox impedes the binding of Snail to the promoter of the E-cadherin gene [220]. Recent studies have shown that MRX34, a liposomal miR-34a mimic, is effective in treating advanced solid tumors, as evidenced by its success in phase I trials. It inhibits Snail and the Notch signaling pathway-mediated EMT in prostate cancer cells [226]. Recently, a drug called DAPT (*N*-[*N*-(3, 5-difluorophenacetyl)-l-alanyl]-*s*-phenylglycinet-butyl ester) that inhibits γ-secretase was found to suppress the growth of medulloblastoma and cause G0-G1 cell cycle arrest and apoptosis in a T-ALL animal model [227]. γ-secretase inhibitors are currently being tested in Phase

I clinical trials, indicating that targeting Notch signaling is a crucial aspect of cancer therapy. However, the major challenge with these inhibitors is to prevent unwanted toxicity, especially in the gastrointestinal tract. Furthermore, γ-secretase inhibitors may have adverse effects in vivo as proteases like γ-secretase are involved in various cellular functions [228]. In contrast, genistein and curcumin (non-toxic dietary agents) can inhibit Notch-1 activation in pancreatic cancer cells, leading to apoptotic cell death [229]. Other studies have shown that resveratrol, another non-toxic dietary agent, can induce apoptosis by inhibiting the Notch pathway through the inactivation of p53 and PI3K/Akt in T-ALL [230]. Bufalin also regulates the levels of marker proteins related to EMT and the extracellular matrix through the Hedgehog and PI3K/AKT/mTOR/HIF-1α axis, thereby preventing EMT in highly metastatic hepatoma cells [230]. Another study has shown that cinobufacini increases the expression of E-cadherin protein while reducing the expression of N-cadherin, vimentin, and EMT-related transcription factors through the c-Met/ERK signaling pathway [231]. Quercetin, a major polyphenol, and flavonoid commonly found in many fruits and vegetables, reduces migration ability in part by decreasing the production of Twist, N-cadherin, and vimentin [232]. Compounds such as LY2157299 (galunisertib) act as inhibitors of TGFβ and target the TGFβ pathway. They are currently undergoing phase II studies for the treatment of glioblastoma and hepatocellular carcinoma [233]. SB525334 and SU9516 are two medications that aim to block the process of EMT in lung cancer cells by targeting TGFβR1 (TGFβ receptor 1) and CDK2 (cyclin-dependent kinase 2) [234]. SB431542 is a TGFβR kinase inhibitor that can prevent TGFβ-induced EMT in pancreatic cancer cells. SD-093 and LY-580,276 function as competitive inhibitors for the ATP-binding site of TGFβRI kinase and can inhibit EMT and cancer cell migration in various cell types [235]. In recent times, there have been new and specific inhibitors of TGFβ, namely EW-705, EW-7195, and EW-7197, that have been proven to disrupt EMT in breast cancer cells treated with TGFβ [236]. These inhibitors have also been tested in vivo using the 4T1 orthotopic xenograft mouse model. A human anti-TGFβ antibody called fresolimumab has recently undergone phase I clinical trials on patients with melanoma or renal cell carcinoma. The trials have shown acceptable safety and toxicity, and the maximum dose of 15 mg/kg has been established for phase II clinical trials [214]. In vitro, the EGFR kinase inhibitor AG1478 has been found to block this activation [237]. Another EGFR tyrosine kinase inhibitor, Erlotinib, has been approved for treating advanced NSCLC patients [238]. The Src kinase inhibitor dasatinib can inhibit the growth and development of breast cancer cells that exhibit EMT characteristics [239]. Recent reports suggest that small-molecule inhibitors against mutant forms of IDH1 and IDH2 are feasible. An inhibitor against IDH2 R140Q has been shown to reduce both intracellular and extracellular levels of 2HG, suppress cell growth, and increase differentiation of primary human AML cells [240]. During the progression of cancer, fibroblasts that are associated with cancer (CAFs) change their metabolism to become more glycolytic. This is achieved through the extrusion of lactate, which is dependent on oxidative stress and HIF1 [240]. By inhibiting the metabolic circuitry between prostate cancer cells and CAFs with metabolism inhibitors like dichloroacetate (DCA) and 2-deoxyglucose (2-DG), cancer cell growth is significantly reduced [241]. In contrast, when exposed to hyperglycemic conditions, Snail is O-GlcNAcylated (OGT) to prevent GSK-3β phosphorylation, leading to the stabilization of Snail and the repression of E-cadherin. This results in cancer cells undergoing EMT-mediated migration. As a result, multiple OGT inhibitors have been developed, including 5-thioglucosamine (5SGlcNAc) and its per-O-acetylated analog Ac5S-GlcNAc. Ac-5SGlcNAc can transform into UDP-5SGlcNAc through the GlcNAc reclamation route, which causes a hindrance in O-GlcNAcylation by competing with UDP-GlcNAc. Various other inhibitors of OGT, for example, ST045849 and Alloxan, have demonstrated their effectiveness in impeding the movement and growth of mouse embryonic stem cells and retinal pericytes, respectively [242] (Table 1).

The wide range of metabolic pathways targeted by new clinical compounds in oncology reflects the significant advancements made in understanding tumor metabolism through basic and translational research over the past few decades. Several established targets, such as IDO1 (Indoleamine 2,3-dioxygenase 1) and IDH1, have multiple clinical compounds in advanced stages of development across various tumor types. Additionally, many early-phase studies are being initiated with first-in-class agents aimed at unexplored metabolic nodes, such as IACS-010759 and opaganib. Given the essential role of various metabolic pathways in maintaining normal cellular homeostasis, one major challenge in developing metabolic inhibitors for cancer treatment is achieving antitumor efficacy without adversely affecting non-cancerous cells [243]. For instance, the inhibition of glutamine metabolism by DON can be toxic to the gastrointestinal tract, which is rich in glutamine-consuming cells. However, the prodrug approach utilized for tumor-targeted delivery of DON, as demonstrated by sirpiglenastat, has proven effective in minimizing gastric toxicity. Furthermore, targeting neomorphic functions of mutant enzymes presents a unique opportunity to develop anticancer agents with a better therapeutic index, as seen with the selective inhibition of mIDH1

Table 1 Therapeutic perspectives for targeting EMT in cancer cells

Drug/Factor	Target	Description	Ref.
PD0332991	Zeb1	A cyclin-dependent kinase 4/6	[216]
miR-200	ZEB1 and ZEB2	Effective in targeting both the CSC to non-CSC transition and EMT-TFs	[217]
Scutellariae Radix or Huangqin	MMP2 and FOXM1	Induces EMT by binding directly to the Zeb2 promoter in HCC cells	[218]
Baicalin	1) Extracellular signal-regulated kinase (ERK) pathway 2) TGF-β/Smad, and NF-kB pathways	Reduces MMP activity and boosts tissue inhibitor of MMP-1 expression in HCC cells	[219]
Sulforaphane	Twist1 and vimentin	Reduces the stem-like characteristics of the cells	[220]
Resveratol	1) Zeb1, Snail, and Slug 2) p53 and PI3K/Akt in T-ALL	1) Inhibiting tumor growth and invasion in a mouse model of pancreatic ductal adenocarcinoma 2) Inhibiting the Notch pathway	[221]
Thymoquinone	Twist1	Promotes Twist1 promoter methylation, which inhibits migration and invasion while stimulating E-cadherin	[222]
Fucoidan	Twist1, Snail, and Slug	Hinder EMT in breast cancer cell lines like 4T1 and MDA-MB-231	[223]
Moscatilin	Akt-Twist-dependent pathways	1) Hinder EMT 2) Curb the migration and metastasis of human breast cancer MDAMB-231 cells	[224]
NpI-0052	NF-κB and Snail	Reduce the expression of NF-κB and Snail	[251]
GN 25 and GN 29	p53 and Snail	Hinder the interaction between p53 and Snail	[220]
Co(III)-Ebox	Snail and E-cadherin gene	Impedes the binding of Snail to the promoter of the E-cadherin gene	[220]
MRX34	Snail and the Notch signaling pathway-mediated EMT	A liposomal miR-34a mimic	[226]
DAPT	γ-secretase	Suppress the growth of medulloblastoma and cause G0-G1 cell cycle arrest and apoptosis in a T-ALL animal model	[227]
Genistein and curcumin	Notch-1	Inhibit Notch-1 activation in pancreatic cancer cells	[229]
Bufalin	Hedgehog and PI3K/AKT/mTOR/HIF-1α axis	Preventing EMT in highly metastatic hepatoma cells	[230]
Cinobufacini	E-cadherin, N-cadherin, vimentin, and EMT-related transcription factors	Effect the targets via c-Met/ERK signaling pathway	[230]
Quercetin	Twist, N-cadherin, and vimentin	Reduces migration ability	[232]
LY2157299 (galunisertib)	TGFβ	Undergoing phase II studies for the treatment of glioblastoma and hepatocellular carcinoma	[233]
SB525334 and SU9516	TGFβR1, and CDK2	Two medications that aim to block the process of EMT in lung cancer cells	[234]
SB431542	TGFβR kinase	Prevent TGFβ-induced EMT in pancreatic cancer cells	[235]
SD-093 and LY-580,276	TGFβRI kinase	Function as competitive inhibitors for the ATP-binding site of TGFβRI kinase	[236]
EW-705, EW-7195, and EW-7197	TGFβ	Disrupt EMT in breast cancer cells treated with TGFβ and 4T1 orthotopic xenograft mouse model	
Fresolimumab	TGFβ	Undergone phase I clinical trials on patients with melanoma or renal cell carcinoma	[214]
AG1478	EGFR kinase	-	[238]
Erlotinib	EGFR kinase	Approved for treating advanced NSCLC patients	[239]
Dasatinib	Src kinase	Inhibit the growth and development of breast cancer cells	[239]
R140Q	IDH2	Reduces both intracellular and extracellular levels of 2HG, suppress cell growth, and increase differentiation of primary human AML cells	[240]
Dichloroacetate (DCA) and 2-deoxyglucose (2-DG)	Metabolic circuitry between prostate cancer cells and CAFs	Metabolism inhibitors	[252]
5-thioglucosamine (5SGlcNAc), and Ac5SGlcNAc	OGT	Ability to transform into UDP-5SGlcNAc through the GlcNAc retrieval route, which causes a hindrance in O-GlcNAcylation by competing with UDP-GlcNAc	[253]

and mIDH2. A notable advantage of metabolic inhibitors is the ability to identify biomarkers in plasma that correspond to substrates and products of target enzymes. These biomarkers have played a crucial role in developing many metabolic inhibitors discussed in this article. For example, measurements of D2HG related to serum drug pharmacokinetics were instrumental in developing IDH1 inhibitors [244]. Additionally, tumor and plasma levels of S-adenosylmethionine (SAM), a product of the MAT2A-catalyzed reaction involving methionine and ATP, served as biomarkers for AG-270 target engagement in mouse xenografts [245] and a first-in-human trial, guiding dose selection for future studies [246]. Similarly, elevated urine lactate levels have been used as a biomarker in trials for IACS-010759 [247]. Imaging biomarkers utilizing nuclear medicine tracers have also been incorporated into clinical trials for telaglenastat. With remarkable technological advancements in bioanalysis and metabolic profiling, we anticipate that metabolic biomarkers will play an even more significant role in future developments. However, a challenge in developing metabolic inhibitors for oncology lies in identifying patients whose tumors are most likely to benefit from specific agents. A lack of understanding or incomplete knowledge of biomarkers for patient enrollment has been cited as a contributing factor to negative outcomes in clinical studies involving metabolic inhibitors, such as the ECHO-301 trial combining an IDO1 inhibitor with immunotherapy [248]. Conversely, several strategies have successfully identified patients likely to respond to other metabolic inhibitors. One approach involves utilizing genetic markers found in tumor cells when specific gene mutations are associated with the relevant metabolic target; this strategy was employed in trials for the IDH inhibitors ivosidenib and enasidenib [249]. The deletion of MTAP is being used for patient selection in AG-270 trials (ClinicalTrials.gov NCT03435250). For other metabolic inhibitors like telaglenastat, surrogate genetic biomarkers indicating tumor glutamine dependence (e.g., NRF2/KEAP1) are being utilized [250]. Another potential strategy for patient selection includes using imaging markers to assess tumor metabolic pathways and monitor early responses to therapy.

Certain inhibitors targeting metabolism have advanced further in clinical development than others due to several key factors. First, the identification of specific metabolic targets, such as IDH mutations in certain cancers, has provided a clear rationale for drug development, leading to successful therapies like ivosidenib and enasidenib. Second, a deeper understanding of the metabolic pathways involved in cancer progression has facilitated the design of inhibitors that effectively disrupt these processes while minimizing toxicity to normal cells. Additionally, preclinical success demonstrating the efficacy of these inhibitors in overcoming drug resistance mechanisms, such as those associated with EMT, has propelled them into clinical trials. The ability to target both tumor metabolism and the TME further enhances their therapeutic potential, making them more attractive candidates for advanced clinical stages. Finally, the competitive landscape and market demand for effective cancer therapies have driven investment and research into specific metabolic pathways, accelerating the development of certain inhibitors over others.

Conclusions and future directions

In conclusion, EMT is a complex process that plays a critical role in the progression of solid tumors. EMT is associated with changes in cell morphology, gene expression, and metabolism that promote tumor cell invasion, metastasis, drug resistance, and recurrence. The crosstalk network between EMT and cancer cell metabolism, the signals that enhance EMT and metabolism, and the intracellular signaling pathways leading to EMT have been discussed in this review. Additionally, the roles of EMT in solid tumor metastasis, drug resistance, and recurrence have been examined. Finally, therapeutic perspectives targeting EMT-induced metabolic changes and intracellular signaling pathways have been explored.

Future perspectives in this field include the development of more effective and specific therapeutic strategies that target EMT-induced changes in metabolism and signaling pathways. The identification of novel therapeutic targets and the development of combination therapies could improve treatment outcomes for patients with solid tumors. Furthermore, the use of biomarkers to predict EMT and its associated changes in metabolism could aid in the selection of appropriate therapeutic strategies. The integration of multi-omics data and machine learning approaches may also improve our understanding of the complex mechanisms underlying EMT and its role in solid tumor progression. Overall, continued research in this area has the potential to lead to significant advances in the treatment of solid tumors.

Abbreviations

EM	Epithelial-mesenchymal transition
TEMTIA	The EMT International Association
TWIST1	Twist-related protein 1
HER2	Human epidermal growth factor receptor 2
acetyl CoA	Acetyl coenzyme A
TCA cycle	Tricarboxylic acid cycle
OXPHOS	Oxidative phosphorylation
ROS	Reactive Oxygen Species
HIF-1α	Hypoxia-inducible factor-1α
STAT3	Signal transducer and activator of transcription-3
TGF-β	Tumor growth factor-β
Akt	Protein kinase B
SORD	Sorbitol dehydrogenase
EMT-TFs	EMT-associated transcription factors
AKR1B	Aldo-keto-reductase-1 B1
SNPs	Single nucleotide polymorphisms

ECM	Extracellular matrix
LDH	Lactate dehydrogenase
MCTs	Monocarboxylate transporters
GLUT1	Glucose transporters 1
NSCLC	Non-small cell lung cancer
ENO1	Enolase 1
PEP	Phosphoenolpyruvate
PFK1	Phosphofructokinase 1
PPP	Pentose phosphate pathway
PKM2	Pyruvate kinase M2
TGIF2	TGFβ-induced factor homeobox 2
MMP2	Matrix metalloproteinase-2
FOXM1	Forkhead box protein M1
ERK	Extracellular signal-regulated kinase
TGFβR1	TGFβ receptor 1
CDK2	Cyclin-dependent kinase 2

Acknowledgements
Not applicable.

Author contributions
Mahsa Liyaghat: Searched and wrote the manuscript text. Saeid Ferdousmakan: Conceived the hypothesis. Searched and wrote the manuscript text. Hanieh Mortazavi: Searched and wrote the manuscript text. Sheyda Yahyazadeh: Searched and wrote the manuscript text. Asrin Irani: Searched and wrote the manuscript text. Sara Banihashemi: Searched and wrote the manuscript text. Fatemeh Sadat Seyedi Asl: Searched and wrote the manuscript text. Abdullatif Akbari: Searched and wrote the manuscript text. Farnoosh Farzam: Searched and wrote the manuscript text. Created the figures. Contributed in the revision.Fatemeh Aziziyan: Searched and wrote the manuscript text. Maryam Bakhtiyari: Searched and wrote the manuscript text. Mohammad Javad Arghavani: Searched and wrote the manuscript text. Hamidreza Zalpoor: Conceived the hypothesis and designed the study. Searched and wrote the manuscript text. Created the figures. Edited the final version of the manuscript. Contributed to the revision. Supervised the study. Mohsen Nabi-Afjadi: Conceived the hypothesis and designed the study. Searched and wrote the manuscript text. Edited the final version of the manuscript. Contributed to the revision. Supervised the study. All authors read and approved the final manuscript.

Funding
No fund is applicable for this study.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 13 February 2024 / Accepted: 22 November 2024
Published online: 02 December 2024

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