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Regulation of epithelial-mesenchymal transition by tumor microenvironmental signals and its implication in cancer therapeutics

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Abstract

Epithelial–mesenchymal transition (EMT) has been implicated in various aspects of tumor development, including tumor invasion and metastasis, cancer stemness, and therapy resistance. Diverse stroma cell types along with biochemical and biophysical factors in the tumor microenvironment impinge on the EMT program to impact tumor progression. Here we provide an in-depth review of various tumor microenvironmental signals that regulate EMT in cancer. We discuss the molecular mechanisms underlying the role of EMT in therapy resistance and highlight new therapeutic approaches targeting the tumor microenvironment to impact EMT and tumor progression.

Keywords

Epithelial-Mesenchymal Transition (EMT); Invasion and metastasis; Extracellular matrix (ECM); Hypoxia; Tumor stroma

1. Introduction

During tumor development, the dynamic interactions between tumor cells and their cellular and extracellular tissue microenvironment foster malignant progression and metastasis. Epithelial–mesenchymal transition (EMT) is a cellular process in which cells lose their epithelial characteristics (E-cadherin) and acquire mesenchymal features (N-cadherin, vimentin). EMT has been shown to promote the tumor initiation ability, linking EMT to cancer stem cells (CSCs) as well as playing integral roles in tumor invasion and metastasis [1–3].

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Conflicts of interest

The authors declare no conflict of interest.

Studies in mouse tumor models and human circulating tumor cells show that EMT is not a binary process during metastasis. In human breast cancer patients, circulating tumor cells (CTCs) present diverse EMT statuses and many CTCs express both epithelial and mesenchymal markers [4]. The intermediate EMT cells, named as hybrid-EMT or partial-EMT, exhibit both mesenchymal and epithelial properties. More recent studies described multiple intermediate EMT states in mouse and human tumor samples by single cell RNA-seq [5–8]. Tumor cells in various partial-EMT states contributes to tumor heterogeneity and cancer stem cell properties [9]. Using a skin tumor model, Tsai et al. show that induction of EMT promotes skin tumor invasion and dissemination; while reversion of EMT is essential for the regrowth of distant metastases [10]. Several in vivo lineage tracing studies have been performed in mouse breast tumor models to determine the role of EMT plasticity in tumor metastasis. Fisher et al. initially performed Fsp1 (fibroblast specific protein 1) and Vimentin promoter-driven Cre-mediated lineage tracing in the MMTV-PyMT breast tumor model and did not observe a requirement of EMT in generating lung metastasis [11]. Later, Li et al. used an elegant dual lineage-tracing system to demonstrate that transient activation of N-cadherin, which marks a partial EMT state, but not activation of vimentin, is required for tumor metastasis in the MMTV-PyMT breast tumor mouse model[12]. EMT marker specificity and lineage tracer sensitivity might contribute to this discrepancy. Bornes et al. reported that Fsp1, the same mesenchymal marker used in Fischer et al. study, was unable to trace most of the mesenchymal cells during tumor metastasis in the PyMT mouse model [13]. More recently, Luond et al. showed that partial EMT, not full EMT, contributes to lung metastasis in the MMTV-PyMT breast cancer mouse model. However, full EMT exhibited higher resistance to chemotherapy and facilitated tumor survival under stress [14]. Activation of partial EMT promoted collective migration and led to higher cell plasticity and metastasis capacity; in contrast, full EMT was difficult to reverse at distant organs, leading to reduced metastasis[14,15]. Therefore, epithelial-mesenchymal plasticity plays a critical role in tumor progression, metastasis, and therapy resistance[9].

The EMT program is orchestrated by a core group of EMT-inducing transcription factors (EMT-TFs), including the SNAIL family SNAI1[16, 17] and SNAI2[18], the ZEB family ZEB1 [19]and ZEB2[20], and the TWIST family TWIST1/2 [21–23]. The SNAIL and ZEB family transcription factors directly repress E-cadherin expression by binding E-boxes at its promoter region, thereby leading to EMT. TWIST1 induces invadopodia-mediated matrix degradation to facilitate tumor invasion and metastasis[21,24]. EMT-TFs recruit epigenetic regulators to regulate their target genes expression. For example, SNAI1 recruits HDAC1 and EZH2 to repress E-cadherin expression. ZEB1 recruits HDAC1 or DNMT1 to repress target gene expression[25]. Of note, the EMT-TFs regulate the transcription of each other and cooperate to orchestrate EMT progression[5,26]. For example, TWIST1 binds to the SNAI2 promoter and induces its transcription [27]. Many EMT-TFs are regulated by miRNAs. miR-200 family members and miR-205 repress ZEB1/2 expression to reverse EMT and suppress migration and invasion in various cancer types[28–30]. Reciprocally, ZEB1 was shown to directly repress the miR-200 family members to promote EMT and stemness acquisition, suggesting a negative feedback loop between miR-200 and ZEB[31,32]. Similarly, the EMT/MET switch could also be toggled by SNAIL/miR-34 circuit regulation[33].

The EMT/MET switches are controlled by both biochemical and biophysical factors in the tumor microenvironment to impact tumor development, progression, and treatment responses. The tumor microenvironment is largely composed of immune cells, stromal cells, blood vessels, and extracellular matrix, though the relative proportion of these components may vary in individual tumors. This review explores these environmental factors regulating EMT to reveal potential therapeutic targets and to predict treatment responses.

2. Regulation of EMT by the tumor microenvironment

2.1. Extracellular matrix in EMT regulation

Extracellular matrix (ECM) is a critical component of the tumor microenvironment that contributes to tumorigenesis and progression. Many ECM proteins, such as collagen I, hyaluronic acid (HA) and fibronectin, have been implicated in promoting EMT. Increasing ECM protein deposition and remodeling drive malignant progression partly via EMT. In addition to direct binding of ECM proteins to tumor cells to activate the downstream biochemical signaling, matrix stiffening during tumor progression exerts increased mechanical forces on tumor cells, which induces EMT and increases the risk of cancer development and progression.

2.1.1. ECM molecules in EMT regulation—The extracellular matrix molecules, including collagens, fibronectin and hyaluronan, all contribute to EMT activation (Fig. 1). Type IV collagen, a major component of the basement membranes, is essential for the maintenance of the epithelial properties of epithelial cells. Disruption of collagen IV deposition could upregulate TGFβ, a major inducer of EMT [34–36]. Collagen I induces EMT in lung cancer cells by activating PI3K/ERK signaling, which in turn stimulates the autocrine secretion of TGF-β3 to induce EMT[37]. Collagen I also binds to the collagen I receptor DDR2 to promote SNAI1 nuclear accumulation and increases SNAI1 protein level by inhibiting SNAI1 ubiquitylation. In turn, SNAI1 further upregulates Membrane type I-matrix metalloproteinase (MT1-MMP) and collagen I to sustain the EMT phenotype and facilitate tumor cell invasion [38]. Fibronectin is a marker of cells that have undergone EMT. During EMT, fibronectin assembly is increased, and fibronectin fibril formation is induced by TGF- β1. Fibronectin fibrils serve as an integration point for mechanical signals and TGF- β1 signaling to induce EMT. High levels of fibronectin have been detected in the stroma of breast tumors [39]. Fibronectin activates FAK and leads to recruitment of Src through binding to integrins. Cooperation between fibronectin and TGFβ is required to activate Src and ERK/MAPK to induce EMT[40]. HA is another important ECM molecule that is overproduced in many types of human tumors. HA is a key ligand of CD44, a cell surface glycoprotein that plays a critical role in cell migration, invasion, and cancer stem cell properties. The binding of HA to CD44 elicits high-affinity interaction between CD44 and the TGFβ receptor I, which increases downstream SMAD2/SMAD3 activation to induce EMT[41]. HA/CD44 interaction was also reported to cause CD44 to translocate into the nucleus and promote de novo transcription of lysyl oxidase (LOX), leading to TWIST1-dependent induction of EMT[42]. Taken together, ECM proteins, when dysregulated in cancer, directly affect EMT.

2.1.2. ECM remodeling in EMT regulation—Growing evidence suggests that increased ECM remodeling and deposition also drive malignant progression (Fig. 1). Matrix metalloproteinases (MMPs)-mediated ECM protein remodeling and LOX-mediated ECM protein crosslinking both play crucial roles in the EMT process. MMPs in the tumor environments are reported to participate in EMT induction. MMP-2 was found to degrade a wide variety of ECM proteins including fibronectin, collagen IV and collagen V [43–45] . High expression of MMP-3, a stromal enzyme upregulated in many breast tumors, induced expression of an alternatively spliced form of Rac1 and caused an increase in cellular reactive oxygen species. The reactive oxygen species could stimulate SNAI1 expression to facilitate cancer progression[46]. Lysyl oxidase (LOX) is an extracellular copper-dependent enzyme that promotes crosslinking of collagens or elastin to increase ECM tensile strength[47,48]. LOXL2 and LOXL3 are two members of the LOX gene family which can interact with and stabilize SNAI1 to downregulate E-cadherin expression, leading to an induction of EMT. Knockdown of LOXL2 in SNAI1-expressing metastatic carcinoma cells decreased tumor growth and reduced expression of mesenchymal markers and invasion, providing a direct link between LOXL2 and SNAI1 in tumor progression[49]. LOX can also bind and transactivate the SNAI2 promoter, and LOX/SNAI2 axis mediates TIMP4 (TIMP: tissue inhibitors of matrix metalloproteinases that can regulate the proteolytic activity of MMPs) secretion, then facilitating EMT progression[50]. Hypoxia induced the expression of LOX and LOXL2 via HIF1, which then repress E-cadherin to induce EMT [51]. From these studies, it is evident that ECM reorganization directly regulates EMT to impact tumor progression.

2.1.3. ECM-exerted mechanical force in EMT regulation—Tumor cells and stromal cells also respond to ECM stiffening-induced mechanical signals during tumor progression. Matrix rigidities can be sensed and transmitted across the plasma membrane by various mechanosensors, several of which are implicated in EMT regulation. Integrins are the best studied mechanosensors and play a critical role in driving EMT and invasion[52–54]. Blockade of integrin signaling via integrin-blocking antibodies completely abolished stiffness-induced EMT in breast cancer cells [55]. Many αV integrins, especially αVβ6, αVβ3 and αVβ5, are expressed at low levels in healthy epithelial tissues, but are upregulated during EMT [56,57]. Disruption of β1 integrin induced αVβ3 integrin switching and promoted TGFβ activation in E-cadherin-positive triple-negative breast cancer (TNBC) cells via a TGFβ-miR-200-ZEB signaling network to induce EMT and enhance dissemination[58]. DDR2 regulates the activation state of collagen-binding integrins α1β1 and α2β1, thus strengthening cell-ECM interactions and maintaining the mesenchymal phenotype in tumor cells [59,60]. ECM regulates MT1-MMP localization via β1 or αVβ3- integrins [61]. Colocalization and cooperation between β1-integrin and MT1-MMP1 plays an important role in EMT and early cancer dissemination by upregulating the Wnt signaling[62]. Integrin-linked kinase (ILK), as a mechanotransducer, is crucial for TGF-β1-induced EMT via the TWIST1-integrin β1-FAK/ILK pathway[63–65]. ECM stiffening is also reported to activate the mechanosensor Piezo1, which activates TGFβ signaling by recruiting Rab5c, thus promoting EMT and tumor progression[66,67]. TRPV4, a mechano-sensitive ion channel regulating calcium influx, promoted EMT and cell migration in breast cancer cells [68,69].

Several EMT transcription factors are regulated by mechanical forces exerted by ECM in the tumor microenvironment (Fig. 1). Increasing matrix stiffness in the tumor stroma activates TWIST1, a key mechano-responder to drive EMT and invasion at matrix stiffness. Mechanistically, high matrix stiffness releases the TWIST1 protein from binding to its cytoplasmic anchor protein G3BP2. TWIST1 then translocates into the nucleus to drive the transcriptional program of EMT and tumor invasion[55,70,71]. Upstream of TWIST1, high matrix stiffness activates ERK/RSK and leads to ligand independent EPHA2 S897 phosphorylation. EPHA2 then binds to and activates Lyn to phosphorylate TWIST1 and prevents its association with G3BP2, thus leading to TWIST1 nuclear translocation to promote EMT and invasion[55,72]. SNAI1 protein stability is regulated by matrix stiffness via DDR2. DDR2 activation led to activation of ERK, which directly phosphorylates SNAI1 to promote SNAI1 nuclear accumulation and reduces SNAI1 protein ubiquitylation, thus facilitating tumor cells to undergo EMT and invade through collagen I-rich extracellular matrices [38]. In summary, critical ECM molecules and mechanical forces exerted by tumor ECM can impinge on EMT transcription factors to regulate EMT.

2.2. Stromal and immune cells in EMT regulation

In the tumor microenvironment, stromal and immune cells secrete various cytokines and chemokines, which act in a paracrine fashion on nearby carcinoma cells. Some of these paracrine signals, often acting in combination, are potent inducers of EMT in carcinoma cells to promote tumor progression and metastasis.

2.2.1. Cancer-associated fibroblasts—Cancer-associated fibroblasts (CAFs) are a major component of the tumor stroma and play a critical role in facilitating crosstalk between cancer cells and the tumor microenvironment. Numerous studies revealed that CAFs could secret TGFβ[73], HGF[74], FGF[75], SDF-1 [76], IL-6[77], IL-32[78], CCL5[79], CXCL12 [80], MMP-2[81], and MMP-9 [82] to enable the EMT process in various cancer cells[83,84] (Fig. 2). In breast cancer and bladder cancer cells, TGFβ1 secreted by CAFs activated the canonical SMAD-mediated and SMAD-independent pathways, both of which play important roles during EMT induction [73,85,86]. For the canonical SMAD pathway, activated SMAD3/4 upregulated the expression of EMT-TFs, including SNAI1/2, TWIST1/2 and ZEB1/ZEB2 [87–89]. In the SMAD-independent non-canonical pathway, TGFβ activates MAPK/ERK, PI3K/AKT and Rho GTPase to aid EMT initiation[34]. Additionally, IL-6 secreted by CAFs induced EMT via STAT3 in ovarian, bladder, gastric and hepatocellular carcinoma cancer cell lines [77,90–92]. Mesenchymal stem cell (MSC)-derived CAFs or radiation-activated CAFs were shown to secrete enhanced levels of CXCL12, which bound to CXCR4 in tumor cells and stimulated EMT and metastasis in pancreatic and prostate cancer cells respectively [93, 94]. Li et al. suggested the CXCL12/CXCR4 axis activated the p38 kinase pathway to facilitate CAFs-mediated EMT[94]. Moreover, activated CAFs secreted MMP-2 and MMP-9 to remodel ECM, thereby facilitating EMT in prostate cancer cells [82]. In hepatocellular carcinoma cells, CAFs secreted HGF to stimulate the c-MET/FRA1/HEY1 axis and contributed to tumor invasion and metastasis both in vitro and in vivo [74]. More recently, several studies reported the existence of different subtypes of CAFs with distinct functions in the TME [95,96]. In particular, Öhlund et al. demonstrated two subtypes of CAFs, myofibroblastic

CAFs (myCAFs) and inflammatory CAFs (iCAFs), in the PDAC microenvironment [95]. myCAFs exhibited high levels of α-SMA and were found in close proximity to tumor cells[95]. In contrast, iCAFs showed lower α-SMA levels but highly expressed IL-6 and were located farther from tumor regions[95]. Co-culture with iCAFs, but not myCAFs, significantly upregulated ZEB1 and Vimentin expression and induced partial EMT in colon tumor organoids[97]. Taken together, CAFs in the tumor microenvironment secret various molecules to impact EMT and metastasis.

2.2.2. Cancer-associated adipocytes—Obesity, featuring the expansion of white adipose tissue. has been associated with malignant cancer progression. Adipose tissue consists of adipocytes, adipose mesenchymal stem/stromal cells (ASCs), endothelial cells, and immune cells [98]. Coculturing cancer cells with adipocytes or ASCs were shown to stimulate EMT in cancer cells by secreting IL-6 and activating IL-6/STAT3 pathway [99–101]. IL-6[100], Leptin [102–104], ETP[105], FABP4[106], TGF-β1[107,108], CCL5[109,110] and CXCL12[111] secreted by ASCs or adipocytes were reported to promote EMT in various cancer cell lines(Fig. 2). Leptin binds to leptin receptor (OB-R) and contributes to the EMT process by activating multiple pathways, including PI3K/AKT which phosphorylates GSK3β to increase β-catenin nuclear translocation, STAT3 which recruits G9a to regulate the miR-200c/ZEB1 feedback loop, and ERK which represses E-cadherin and increases vimentin expression[112–115]. FABP4 is shown to activate AKT/G3K3β/SNAI1 pathway, thereby facilitating EMT in cervical squamous cell carcinoma (CSCC) cells[116]. In the PyMT breast tumor mouse model, ETP augments EMT and metastasis by activating the TGF- β signaling pathway[105].

2.2.3. T Lymphocytes—T lymphocytes, such as $CD4^+$ T cells and $CD8^+$ T cells, play an important role in immune responses to tumors [117]. Numerous studies show that $CD4^+$ T cell or $CD8^+$ T cell infiltration inhibited tumor growth and correlated with a better prognosis [118–122]. However, some reports suggest they also promote tumor metastasis by inducing EMT in certain cancer cell lines. In breast cancer, $CD8^+$ T cells were reported to induce EMT and confer cancer cells with stemness characteristics, although the underlying mechanism is unclear[123]. In pancreatic ductal adenocarcinoma (PDAC) cells, Goebel et al. reported that $CD4^+$ T-effector cells stimulated EMT by secreting TNFα and IL-6. Co-culture with T-effector cells significantly upregulated ZEB1 in tumor cells, suggesting that T-effector cells-induced EMT might depend on ZEB1 [124]. More recently, Salazar et al. showed that $CD4^+$ Th9 and $CD4^+$ Th17 cells secreted IL-9 or IL-17, respectively and enabled lung cancer cells to undergo EMT both in vitro and in vivo[125]. In a xenograft mice model of lung cancer, co-injection of tumor cells with Th9 or Th17 cells significantly increased EMT and metastasis, while Th9 and Th17 blocking antibodies inhibited EMT and tumor progression[125]. Regulatory T cells (Tregs) are a subset of $CD4^+$ T cells mainly responsible for self-tolerance and homeostasis maintenance of T cells. Several studies revealed that Tregs could stimulate EMT in lung epithelial cells, hepatocellular carcinoma and melanoma cells [126–128]. In the Oh et al. study, melanoma cells co-injected with Tregs exhibited increased EMT and metastasis in vivo. TGFβ secreted by Tregs contributed to EMT in hepatocellular carcinoma and melanoma cells[128](Fig. 2). Therefore, in addition to

their critical roles in tumor immunity, T lymphocytes could impact EMT in tumor cells via cytokine production.

2.2.4. Macrophages—Macrophages in the tumor microenvironment are known as tumor-associated macrophages (TAMs)[129,130]. TAMs infiltration correlated with higher EMT and poor clinical outcomes in various cancers, including breast cancer, hepatocellular carcinoma, gastric cancer, colorectal cancer and lung cancer [131–138]. Macrophages in tumors are often divided into M1 and M2 macrophages. M1 macrophages secrete numerous pro-inflammatory cytokines and are considered to be anti-tumorigenic. In contrast, M2 macrophages mainly produce anti-inflammatory cytokines and exhibit pro-tumorigenic properties. Yeung et al. reports that M2 macrophages predominantly promoted EMT and metastasis in an orthotopic liver tumor mouse model[135]. Additionally, high M2 macrophages infiltration is positively associated with tumor aggressiveness and poor prognosis in bladder cancer and clear cell renal cell carcinoma(ccRCC) patients [139,140]. TAMs secrete numerous cytokines or chemokines to induce EMT in cancer cells, including TGFβ, TNFα, IL-6, IL-8, IL-10, G-SCF, CXCL13, CCL18, CCL22 and other factors [132–135,140,141–145](Fig. 2). In lung and colon carcinomas, macrophages could secrete TNFα, which synergizes with TGFβ to stimulate EMT [142,146]. Similarly, M2 macrophages also induced EMT by releasing TGFβ, resulting in β-catenin and SMAD2 activation in non-small cell lung cancer(NSCLC) cells and lung epithelial cells[141,147]. Additionally, IL-6 secreted by macrophages induced EMT by various mechanisms. In the Che et al. study, COX2 was upregulated by IL-6, which induced PEG2 and β-catenin nuclear translocation, thereby promoting EMT in lung cancer cells [148].

Reciprocally, tumor cells could secrete cytokines to recruit macrophages and induce M2 polarization of macrophages, reinforcing tumor progression and metastasis. Several studies uncovered the feedback loop between macrophages infiltration and tumor cells. In colon cancer cells, TAMs secreted IL-6 to stimulate EMT. Meanwhile, IL-6 activated the JAK2/STAT3/FoxA1 signaling in colon cancer cells, which led to high levels of CCL12 secretion in cancer cells to recruit more macrophages [149]. Similarly, Su et al. revealed that macrophages secreted CCL18 to activate NF-κB, thus enabling breast cancer cells to undergo EMT [132].

2.2.5. Myeloid-derived suppressor cells (MDSCs)—MDSCs are a population of heterogeneous immature myeloid cells that accumulate in the tumor microenvironment and have been shown to facilitate tumor progression by repressing anti-tumor immune responses and promoting angiogenesis [150,151]. MDSCs are generally divided into two subsets, polymorphonuclear/granulocytic MDSCs (PMN-MDSCs/G-MDSCs), which account for 70%–80% of MDSCs, and monocytic MDSCs (MO-MDSCs) [150,151]. MDSCs are shown to stimulate EMT in various cancer cell types [152–156](Fig. 2). MDSCs stimulated EMT by secreting TGFβ, VEGF, IL-6, IL-10 and IL-28 in melanoma, breast cancer and lung cancer [154,156–160]. Peng et al. reports that IL-6 and Nitric Oxide (NO) produced by MDSCs led to STAT3 and NOTCH activation, respectively, conveying stemness and EMT properties to breast cancer cells[157]. Li et al. reported that co-culture of nasopharyngeal carcinoma cells with MDSCs activated the COX2/β-catenin/TCF4 pathway via TGFβ

and NO secretion to provoke EMT[154]. In human NSCLC xenograft models, MDSCs stimulated EMT and metastasis via CCL11/CCR3[161]. Interestingly, primary melanoma cells recruited MDSCs via CXCL5. Consequently, recruited MDSCs promoted EMT and cancer cell dissemination via TGFβ, EGF and HGF[152]. Similarly, breast cancer cells were reported to attract MDSCs via CCL3 production. Reciprocally, infiltrated MDSCs promoted EMT and metastasis by activating the PI3K-Akt-mTOR pathway in cancer cells, suggesting a positive feedback loop between MDSCs recruitment and tumor progression[162]. In summary, tumor cells could secrete GM-SF, IL-6, CXCL5 or CCL3 to promote MDSCs recruitment and maturation. Reciprocally, infiltrated MDSCs stimulate EMT by secreting TGF-β, EGF, HGF, IL-6(target STAT3), IL-10, IL-28(target IFN-λ), NO (target NOTCH), NOS2 or CCL11(target AKT and ERK) (Fig. 2). The crosstalk between cancer cells and their surrounding stromal cells plays a critical role in EMT regulation, thereby impacting tumor progression and metastasis.

2.3. Hypoxia in EMT regulation

Tumor hypoxia is strongly associated with tumor progression, metastasis, and poor clinical outcomes. Hypoxia inducible factors (HIF), including HIF-1α and HIF-2α, are the main mediators of hypoxia responses. HIF target genes are involved in glycolysis, apoptosis, cell proliferation, angiogenesis and metastasis[163,164]. Hypoxia plays a major role in EMT regulation during tumor progression (Fig. 3).

2.3.1. Hypoxia promotes EMT via upregulating EMT transcription factors—

Hypoxia is shown to upregulate SNAI1/SNAI2 directly or indirectly in various cell types [165] via multiple mechanisms. Several studies revealed that HIF-1α or HIF-2α could directly regulate SNAI1 and SNAI2 transcriptionally[166–169] [179–182. In human hepatocellular carcinoma and pancreatic cancer cells, HIF-1α binds to SNAI1 at the –541 hypoxia-response element (HRE) site and promotes SNAI1 transcription to induce EMT[167–169]. Zhang et al. also reported that HIF-1α could directly induce SNAI2 transcription to promote EMT through direct binding to the HRE sequence located in its proximal promoter in HNSCC cells [170]. Hypoxia is also shown to indirectly regulate SNAI1 expression via uPAR or USP47[171,172] to mediate hypoxia-induced EMT in breast cancer cells. Upregulation of uPAR during hypoxia activates the downstream PI3K-AKT signaling, thereby stimulating SNAI1 expression and EMT [171]. Ubiquitin-specific protease 47 (USP47), a deubiquitinating enzyme, promotes SNAI1 protein stabilization through deubiquitylation. Choi et al. reported that HIF-1α indirectly enhances USP47 expression via SOX9 during hypoxia-induced EMT in colorectal cancer cells[172]. Hypoxia is also found to stimulates SNAI1 expression via the Notch pathway. Inhibition of Notch signaling abrogated hypoxia-induced SNAI1 upregulation and EMT in breast cancer cells and ovarian cancer cells [173,174]. ROS produced during hypoxia was shown to promote SNAI1 nuclear translocation via GSK-3β inactivation and stimulated EMT in various cancer cell lines [175]. Regulation of SNAI2 by hypoxia was reported via HIF-1α repressing miR-30c, leading to increased SNAI2 expression and EMT[176] in human renal cell carcinomas.

Hypoxia is also shown to stimulate TWIST1/TWIST2 expression in various cancer cells. HIF-1α directly upregulated TWIST1 expression by binding to the HRE sequence in the proximal TWIST1 promoter in hypopharyngeal cancer, breast cancer and lung cancer cell lines [177]. Similarly, HIF-2α directly induced TWIST1 transcription in cervix carcinoma, prostate cancer and colon cancer cell lines [178]. Prognostic analysis show that co-expression of either two factors among HIF-1α/TWIST1/SNAI1 correlates with poor recurrence-free survival in NSCLC patients[179].

Both ZEB1 and ZEB2 are also frequently upregulated by hypoxia in different cancer cell lines. In colorectal cancer cells, Zhang et al. reported that HIF-1α could directly induce ZEB1 expression by binding to the HRE sequence in the ZEB1 proximal promoter [180]. ZEB1 inhibition could significantly abrogate hypoxia-induced EMT and metastasis [180]. Similarly, hypoxia-induced ZEB1 upregulation led to cell migration and invasion in glioblastoma multiforme (GBM) cells [181, 182]. Indirect regulation of ZEB1 by hypoxia are also observed in multiple studies. In breast cancer cells, hypoxia repressed DICER expression epigenetically to reduce the miR- 16 − 200 level, promoting ZEB1 expression and subsequent EMT [183]. Su et al. reported that increased MEF2D expression in response to hypoxia directly regulated ZEB1 transcription through acetylation of ZEB1 promoter, leading to EMT in colorectal cancer cells[184]. LncRNA was also shown to regulate ZEB1 expression during hypoxia. LncRNA-BX111887 was highly upregulated during hypoxia and recruited YB1 to the ZEB1 promoter, enabling cells to undergo EMT in pancreatic cancer cells[185]. Zhang et al. found that LncRNA-HOTTIP acted as a sponge of miR-101 to stimulate ZEB1 mediated EMT in glioma cells[186]. Interestingly, hypoxia also promoted ZEB2–natural antisense transcript expression to increase ZEB2 translation efficiency[187].

These studies provide strong evidence that hypoxia regulates key EMT transcription factors, such as SNAI1/2, TWIST1/2 and ZEB1/2, to induce EMT in human cancer.

2.3.2. Hypoxia induces EMT via several signaling pathways including TGFβ, EGFR, Notch and Hedgehog pathway—The TGFβ pathway can be activated by hypoxia in various cancer cell lines. In gastric cancer cells, Matsuoka et al. showed that hypoxia upregulated TGFβ1 and TGFβR to stimulate the autocrine TGFβ/TGFβR signaling, resulting in EMT in diffuse-type gastric cancer cells[188]. Similarly, in lung epithelial cells, hypoxia was shown to stimulate EMT via TGF-β1 production, which is dependent on ROS production and HIF-α accumulation[189]. Additionally, HIF-1α directly regulates transcription of TGFβ1 and TGFβ3 through binding to the HREs in their promoters, thereby leading to TGFβ-induced EMT[190,191]. Several papers also suggest indirect regulation of the TGFβ signaling by hypoxia, as the hypoxia-stimulated unfolded-protein response boosted TGFβ expression in gastric cancer cells[192]. Similarly, Nagpal et al. found that miR-191 upregulation by HIF-1α/HIF-2α could increase TGFβ2 levels directly or indirectly through repressing HuR in breast cancer cells [193].

Hypoxia stimulates Notch signaling by increasing both Notch receptor and ligand levels in various cancer cell lines. Upon ligand binding, the active Notch intracellular domain (NICD) could directly upregulate SNAI1/2 transcription to promote EMT [173,194,195]. In ovarian cancer cells, Sahlgren et al. found that hypoxia increased the expression levels of

the Notch ligand DLL1 and NICD, thereby leading to SNAI1-mediated EMT[173]. NICD directly activates SNAI1 transcription through binding to the CSL motif in proximal to its promoter[173]. Notch receptor Notch3 and ligand DLL1, JAG1 and JAG2 levels were shown to be upregulated by hypoxia to facilitate EMT in breast cancer cells[174,196,197]. Du et al. found that hypoxia could indirectly increase expression of the Notch receptor Notch1 and the Notch ligand Jagged1 through suppressing miR-34a to promote EMT[198].

The Hedgehog (Hh) signaling also plays important roles in hypoxia-mediated EMT [199–201]. Activated GLI1 was shown to be responsible for upregulation of EMT-TFs, such as SNAI1/2 and TWIST1[202]. In particular, SNAI1 and TWIST1 were shown to be direct targets of GLI1 in hepatocellular carcinoma cells[203,204]. A study in mice shows that hypoxia could activate Hh signaling through HIF-1α mediated Shh upregulation[205]. Similarly, increased transcription of Shh, SMO and GLI1 level or GLI1 nuclear translocation by HIF-1α are also reported to facilitate EMT in various cancer cell lines[200,206]. Interestingly, in cholangiocarcinoma cells, HIF-1α-mediated Shh activation not only provoked EMT, but also increased cancer stemness[206]. Treatment with an Shh inhibitor, cyclopamine, attenuated Shh activation with substantial abrogation of EMT and stemness[206]. HIF-1α also triggered ligand-independent Hh signaling in pancreatic cancer cells, where hypoxia activated GLI1 directly and GLI1 depletion was sufficient to abrogate hypoxia-mediated EMT [201]. Moreover, Liu et al. found that HIF-1α regulated non-canonical Hh through ROS production, which facilitated GLI1-dependent EMT and invasion in hepatocellular carcinomas[207].

Hypoxia also activates EGFR signaling to facilitate EMT. Hypoxia promotes EMT by upregulating EGFR expression in many cancer types, including HNSCC, glioma, gastric cancer, breast cancer and lung cancer [206–210]. Recent studies suggest that HIF-1α directly regulates EGFR transcription through binding to the HRE sequence in EGFR intron 18 in breast cancer cells[211]. Moreover, EGFR translation efficiency was upregulated by hypoxia, whereby HIF-2α boosted EGFR protein synthesis and drove autonomous proliferation in glioma cells[209]. Additionally, EGF is shown to be upregulated by hypoxia to facilitate malignant progression in various cancer types[210,212]. In hepatocellular carcinoma cells, HIF-2α induced TGF-α and promoted EGFR activation under hypoxia [213,214].

In summary, hypoxia in the tumor microenvironment could impinge on a number of EMT-inducing signaling pathways to promote tumor invasion and metastasis.

3. EMT in cancer therapy resistance

3.1. EMT in chemoresistance

Increasing evidence shows that EMT plays a key role in chemoresistance in various human cancer types. Residual breast cancers often displayed a mesenchymal phenotype after chemotherapy in various human cancers[215]. The mesenchymal state induced by EMT confers drug resistance to many types of therapeutic agents. In Cyclophosphamide (CTX)-treated tumor-bearing mice, more than 60% of the surviving tumor cells presented a mesenchymal phenotype, indicating that mesenchymal tumor cells are more resistant

to chemotherapy[216]. Doxorubicin could activate the TGF-β signaling and EMT to promote breast cancer stem-like properties and drug resistance[217]. Chemotherapy in combination with TGF-β signaling inhibitors increased therapeutic efficacy and reduced chemoresistance[218]. Inhibition of ZEB1 has been shown to reverse EMT and chemoresistance in docetaxel-resistant human lung adenocarcinoma cell lines[219].

The EMT program confers therapy resistance via several mechanisms. Overexpression of EMT transcription factors is reported to increase the expression of ABC transporters, as expression of ABC transporters in breast cancer cells showed 10-fold more resistance to doxorubicin treatment compared with the control cells[220]. Activation of EMT also strongly induced expression of the AXL receptor tyrosine kinase in breast cancer cells[221]. Expression of the AXL receptor tyrosine kinase in carcinoma cells confers resistance to EGFR inhibitors on EGFR-mutant non-small-cell lung carcinoma (NSCLC) cells[222], thus Axl inhibition restored sensitivity to the EGFR inhibitor Erlotinib [223].

The EMT program has been shown to inhibit apoptosis to promote therapy resistance. EMT activation diminishes E−cadherin-mediated clustering of the TRAIL receptors DR4 and DR5, thereby making carcinoma cells resistant to TRAIL-induced apoptosis[224]. SNAI1 confers resistance against multiple apoptosis-inducing stimuli, in part by promoting AKT activation, upregulating the expression of the pro-survival protein Bcl-XL and delaying cell-cycle progression[225]. SNAI1 was also shown to confer chemoresistance by reducing the expression of p53 in carcinoma cells through interactions between SNAI1 and p53, thus allowing SNAG domain-associated HDAC1 to deacetylate p53[226]. SNAI2 blocks p53-mediated transcriptional induction of Encoding Bcl-2-binding Component 3 (BBC3) expression by directly repressing the BBC3 promoter region. Multiple lung adenocarcinoma cell lines acquire cisplatin resistance through AKT/NF-κB/Slug-mediated BBC3 reduction [227,228].

Cancer stem cells (CSCs) are a subpopulation of neoplastic cells with stem-cell properties. EMT has been shown to be a critical regulator for the induction and maintenance of CSC properties[229]. CSCs are less sensitive to various chemotherapeutic drugs, including doxorubicin, cisplatin, paclitaxel, temozolomide, and methotrexate[59–64] and contribute to tumor recurrence after drug treatment. Given the critical role of EMT in cancer therapy resistance, understanding the signaling pathways induced by EMT will provide additional drug targets to sensitize cancer cells to chemotherapy.

3.2. EMT in immunotherapy resistance

Numerous studies suggest that EMT is highly associated with an immunosuppressive microenvironment. For example, EMT is correlated with high expression levels of immune checkpoint proteins, including PD-L1, PD-L2, PD-1, TIM-3, B7-H3, BTLA, and CTLA-4, in NSCLC cells [230]. Similarly, the expression levels of CTLA-4/PD-1/PD-L1/TIM-3/LAG-3 were highly associated with MMP-13/TWIST1 in ESCC patients[231]. Additionally, higher Tregs infiltration, M2 macrophage polarization and lower CD8 + T cells were reported to correlate with EMT in ovarian cancer, prostate cancer and NSCLCs[230,232,233]. Interestingly, Hugo et al. found that upregulation of EMT-related gene sets correlated with resistance to anti-PD-1 therapy in melanoma patients[234].

EMT transcription factors contribute to immunotherapy resistance via multiple mechanisms. In melanoma cells, SNAI1-induced EMT was shown to promote Tregs infiltration and impair dendritic cells by secreting TSP1[235]. Akalay et al. found that SNAI1-induced mesenchymal breast cancer cells exhibited resistance to CTL-mediated lysis via autophagy activation[236]. In an aPKCι-induced EMT model, SNAI1 was upregulated by aPKCι/Sp1 to drive EMT, resulting in the induction of immunosuppressive Tregs partially via IL-2 and TGFβ production [237]. Additionally, Taki et al. demonstrated that high SNAI1 expressing tumors secreted high level of CXCL1 and CXCL2 chemokines via NF-κB activation, leading to MDSCs recruitment and $CD8^+$ infiltrating lymphocytes repression[238]. In breast cancer cells, cell surface expression of PD-L1 was shown to be stimulated by SNAI1 via post-translational upregulation of CMTM6 and CMTM7, leading to immune evasion [239]. CD47 is a macrophage immune checkpoint protein that suppresses macrophage phagocytic activity[240]. Overexpression of SNAI1 or ZEB1 increased CD47 expression in breast cancer cells, which significantly protected tumor cells from macrophage attack[241]. SNAI1 and ZEB1 were shown to directly bind to two E-boxes in the CD47 promoter[241]. In the transgenic MMTV-PyMT mouse model of breast adenocarcinoma, SNAI1-high mesenchymal tumor cells exhibited increased Tregs infiltration and M2 macrophage polarization compared to SNAI1-low epithelial tumors. Interestingly, mesenchymal tumor cells that showed high resistance to anti-CTLA4 treatment also conferred epithelial tumor cells resistance to immune attack[242]. Furthermore, SNAI1-high quasi-mesenchymal cells secreted high levels of CD73, CSF1 and SPP1, resulting in M2 polarization of TAMs and T cell suppression. Mechanistically, SNAI1 ChIP-seq data showed that SNAI1 was able to bind to 89 immunomodulatory genes[243].

Similarly, ZEB1 also plays an important role in immunosuppression by regulating PD-L1. In breast cancer cells and NSCLC cells, ZEB1 upregulated PD-L1 expression via repressing miR-200[244,245]. Chen et al. showed that miR-200 directly repressed PD-L1 transcription by binding to miR-200 family seed sequences on its 3'UTR. Therefore, ZEB1/miR-200 axis promotes PD-L1 upregulation to facilitate $CD8^+$ T cell exhaustion [244]. Recently, Guo et al. showed that ZEB1 directly induced PD-L1 and CD47 expression, both of which contain the ZEB1 binding E-box[246]. Thus, EMT in cancer cells leads to an immunosuppressive tumor microenvironment through various mechanisms, including T cell exhaustion and immune cell repression, that decreases the effectiveness of tumor immunotherapies.

4. Targeting EMT-inducing signals in the tumor microenvironment for cancer therapy

4.1. Targeting the extracellular matrix

Most of the currently available therapies targeting EMT are aimed at blocking upstream inducers of EMT. Several studies demonstrated that the extracellular matrix, many regulators of ECM stiffness, various mechanosensors, and mechanotransducers are all targetable. Numerous inhibitors against CD44, DDR, LOX/LOX2, integrins, and FAK have been developed and some have shown anticancer activities in preclinical studies (Table 1).

Increased collagen crosslinking increases matrix stiffness and promotes EMT. Using recombinant collagenases to remove collagen from tumor ECM has emerged as a potential therapeutic approach, as depleting extracellular collagen could normalize the tumor microenvironment and increase the drug delivery efficiency[272,273]. LOX-mediated collagen crosslinking is a major contributor to ECM stiffening that promotes EMT and breast tumor progression. CCT365623, a LOX inhibitor with great therapeutic promise[262], suppressed breast cancer growth and metastasis in mice[274]. LOXL2 is correlated with ECM formation and induction of EMT. Treatment with a small molecule inhibitor of LOXL2((2-Chloropyridin-4-yl) methanamine hydrochloride) reversed LOXL2-induced EMT and significantly decreased the invasive ability of cervical cancer cells[261].

Several types of collagen molecules bind to and activate the discoidin domain receptors (DDRs). DDR1 and DDR2 are overexpressed in many cancer types. Inhibition of DDR1 with an ATP-competitive small-molecule kinase inhibitor (7rh) inhibited peritoneal metastasis in gastric carcinoma. Inhibition of DDR1 by 7rh also hindered tumor development in pancreatic ductal adenocarcinoma[251,253]. The small molecule allosteric inhibitor of DDR2 WRG-28 is shown to efficiently disrupt DDR2 receptor–collagen ligand interaction and DDR-mediated tumor progression in preclinical tumor models[252]. Dasatinib, another DDR2 inhibitor, shows promising results in preclinical models of DDR2-positive head and neck squamous cell carcinoma[275]. The extracellular domain of CD44 contains binding sites for various ECM molecules such as hyaluronan, collagen, and fibronectin. Activation of CD44 downstream signaling is involved in EMT-induced tumor progression. Several CD44 blocking antibodies and peptides have been developed to target CD44[276,277]. RO5429083, one of the CD44 antibodies, just entered a Phase 1 clinical trial (Clinicaltrials.gov identifier: NCT01358903).

Inhibition of the integrin function has been shown to lead to reduced metastatic burden in various animal tumor models. αVβ3 and αVβ5 expression is significantly upregulated during EMT. Cilengitide is an integrin αvβ3 and αvβ5 inhibitor that is well tolerated and demonstrated modest antitumor activity among recurrent GBM patients in a phase I study [263]. However, several recent clinical trials showed that selective integrin inhibitors did not reach expected efficacy[278]. Emerging studies therefore focused on targeting the integrin downstream signaling, especially focal adhesion kinase (FAK), an important cell signaling hub that is highly activated upon integrin activation. FAK inhibition is identified as a potential strategy to overcome chemotherapy resistance. FAK activation coupled with the WNT-β-catenin signaling sustained tumor growth by promoting cancer stem cell survival and platinum resistance[279]. Combing a small molecule inhibitor of FAK with carboplatin and paclitaxel for the treatment of platinum-resistant high-grade serous ovarian cancer is now entering a clinical trial [280, 281]. Defactinib (VS-6063) is a FAK inhibitor currently tested in patients with advanced solid tumors in multiple clinical trials (Clinicaltrials.gov identifier: NCT04620330; NCT02546531; NCT03287271)[278,282]. Integrin-linked kinase is another mechanotransducer and a critical regulator of intracellular integrin signaling. Preclinical studies show that QLT-0267, an ILK inhibitor, presented anticancer activities in colon cancer [63,283].

4.2. Targeting stromal and immune cells

4.2.1. Targeting cancer-associated fibroblasts—Therapeutically targeting CAF-stimulated EMT has shown promises in cancer treatment. Multiple drugs are shown to impair CAFs-stimulated EMT by interfering with the IL-6/IL-6R signaling, including siltuximab, tocilizumab, retinoic acid (RA), somatostatin analog SOM230 (pasireotide), nab-paclitaxel (nab-PTX), and cucurbitacin I (JSI-124)[284–289]. Siltuximab, an IL-6 neutralizing antibody, is shown to inhibit IL-6-mediated EMT in cholangiocarcinoma cells and exhibited anti-tumor efficacy in a xenograft model with co-injection of CAFs and lung cancer cells [284,290]. Clinically, Siltuximab treatment contributed to stable disease in more than 50% of patients with metastatic renal cell carcinoma[291]. Tocilizumab, an IL-6R inhibitor, blocked paracrine pro-EMT effects of CAFs on breast cancer cells in vitro and in vivo[285]. Interestingly, Billah et al. found that SOM230 specifically impaired IL-6 expression in CAFs through repressing eiF4E-Binding Protein-1 (4E-BP1)-mediated protein synthesis in pancreatic cancer[287]. Bae et al. demonstrates that an AXL inhibitor BGB324 could significantly suppress CAFs-induced EMT in gastric cancer cells, where AXL was activated by CAFs-secreted GAS6[292]. Targeting SDF-1 or the CXCL12/CXCR4 axis is also a promising therapeutic strategy. AMD3100, a CXCR4 antagonist, was shown to prevent CAFs-induced EMT in pancreatic and prostate cancer cells[93,94]. Specifically, AMD3100 treatment blocked the CXCL12/CXCR4 axis and suppressed p38 kinase, leading to reduced EMT, invasion and lung metastasis in pancreatic cancer cells[94]. Another CXCR4 antagonist BL-804, combined with pembrolizumab, showed benefit in metastatic PDAC patients [293]. Inhibitors targeting TGFβ signaling, such as SB431542 or pirfenidone, are also shown to abrogate CAFs-induced EMT in breast cancer cells [294]. PHA-665752, a c-Met kinase inhibitor, attenuated CAFs-stimulated migration, invasion and tumorigenesis in hepatocellular carcinoma [74](Table 2).

4.2.2. Targeting cancer-associated adipocytes—Several targeting strategies have also been developed to target cancer-associated adipocytes to inhibit EMT. Adiponectin, secreted from normal adipocytes and downregulated in cancer-associated adipocytes (CAAs), was shown to reverse EMT and impair migration and invasion in NSCLC cells[330]. Adiponectin analogue ADP335 was developed to mimic its function on tumor progression. In breast cancer or prostate cancer xenograft models, ADP335 treatment significantly repressed tumor progression by modulating AMPK, Akt, STAT3 and ERK1/2 signaling [295,296]. Targeting leptin is also showing promise in halting tumor progression. PEG-LPrA2, acting as a leptin receptor antagonist, significantly reduced tumor growth in breast cancer xenografts in mice by repressing ERK, AKT or VEGF upregulation [297,298]. Additionally, a FABP4 inhibitor BMS309403 was reported to efficiently inhibit adipocyte-mediated EMT and metastasis in cholangiocarcinoma[106]. Niclosamide treatment repressed adipocyte-induced EMT by inhibiting IL-6/STAT3 axis in breast cancer cells[299]. Depletion of ASCs by D-CAN, also effectively repressed obesity-mediated EMT and prostate tumor progression[111,300](Table 2).

4.2.3. Targeting lymphocytes—Targeting EMT induction in combinations with anti-PD-1/PD-L1 immunotherapies has shown improvement in the response to immuno-therapies in cancer patients. Multiple studies suggest that anti-TGFβ treatment could inhibit EMT

and synergize with immunotherapy to boost immune response and attenuate tumor progression[301,302]. In chemically induced squamous cell carcinomas, α-PD-1 therapy not only inhibited tumor growth, but also provoked immunosuppressive Tregs and activated TGFβ/pSMAD3 signaling in tumors, leading to EMT, while addition of anti-TGFβ treatment attenuated EMT and alleviated α-PD-1 resistance[301]. Thus, the anti-TGFβ/anti-PD-1 combination therapy significantly inhibited CCK168 tumors growth and promoted survival in mice[301]. Indeed, bifunctional molecules targeting both TGFβ and PD-L1 exhibited higher anti-tumor efficiency than anti-TGFβ or anti-PD1-L1 monotherapy. M7824, an anti-PD-L1/ TGFβ Trap fusion protein, was shown to revert EMT in vivo and in vitro in lung cancer models and to boost $CD8^+$ T cell and NK cell responses in various cancers, thereby leading to tumor regression and longer survival in mice [303–306]. The M7824 phase I trial showed promising antitumor efficacy in advanced solid tumor patients[307]. More recently, YM101, a new bifunctional antibody against TGFβ and PD-L1 was shown to inhibit EMT and revert immunosuppression in tumor-bearing mice [308]. In KRAS mutant lung cancer models, combination of a MEK inhibitor and anti-PD-L1 therapy inhibited tumor growth, but also led to therapy resistance by increasing $CD4^+$ Th17 infiltration[309]. $CD4^+$ Th17 is implicated in inducing EMT in tumor cells by secreting IL-17. Peng et al. demonstrated that anti-IL-17 in combination with a MEK inhibitor and an anti-PD-L1 antibody significantly reduced tumor metastasis and therapy resistance in tumor-bearing mice[309](Table 2).

4.2.4. Targeting macrophages—TAMs play critical roles in promoting EMT, invasion and metastasis. Numerous macrophages targeting therapies significantly impede tumor progression, including blocking macrophages recruitment, TAMs depletion and reprogramming macrophages polarization[130,331]. Several studies show that blocking the CCL2/CCR2 axis could repress macrophage recruitment. A CCL2 neutralization antibody significantly inhibited macrophage infiltration and tumor metastasis in tumor-bearing mice[131]. RDC018, a CCR2 antagonist, significantly inhibited hepatocellular carcinoma tumor growth and metastasis[310]. Depletion of TAMs could also be achieved through interfering with CSF-1/CSF-1R axis. RG7155, a monoclonal antibody targeting CSF-1 receptor (CSF-1R), could deplete M2 macrophages both in vitro and in vivo, reducing tumor burden in diffuse-type giant cell tumor (Dt-GCT) patients[313]. CSF-1R inhibitors BLZ945 and PLX3397 not only eliminated immunosuppressive M2-like cells, but also boosted T cell response, leading to tumor regression in glioma and pancreatic cancer models[311,312]. Reprogramming TAMs to anti-tumor macrophages has also been tested to induce tumor regression. Hagemann et al. demonstrated that NF- κB inhibition reprogramed M2 macrophages to M1 macrophages and repressed tumor growth by increasing IL-12-dependent NK activity[332]. BAY11–7082, a NF-κB inhibitor, was shown to repress TAMs-mediated EMT and stemness in bladder cancer cells by suppressing M2 polarization[139]. IPI-549, a specific PI3Kγ inhibitor, switched immunosuppressive TAMs to immunostimulatory macrophages by activating NF-κB and inhibiting PI3Kγ/mTOR-S6Kα-C/EBPβ, facilitating spontaneous breast carcinoma regression and reduced lung metastasis[315]. Additionally, the cannabinoid receptor-2 agonist, JWH-015 was shown to repress M2 macrophage-stimulated EMT in NSCLC cells and inhibit tumor growth in mice[316](Table 2).

4.2.5. Targeting MDSCs—Similarly to TAMs, MDSCs were implicated to stimulate EMT and facilitate metastasis. Several approaches were developed to repress MDSC functions, including depleting MDSCs, inhibiting MDSC recruitment, repressing MDSC function and promoting MDSC differentiation [333,334]. CSF-1R, CCR5 and CXCR2 could be targeted to block MDSCs recruitment and revert the immunosuppressive tumor environment [323,322,324]. Blattner et al. demonstrated that the CCR5-Ig fusion protein treatment reduced MDSCs and Tregs infiltration, thereby impeding melanoma tumor progression[323]. Similarly, CSF-1R inhibitors, PLX647 and PLX5622, and CXCR2 inhibitor SX682 were also reported to block MDSCs recruitment, enhancing the response to T cell checkpoint immunotherapy[322,324]. Several compounds including the PDE5 inhibitor, the COX-2 inhibitor and triterpenoid CDDO-Me were reported to impair the immunosuppressive function of MDSCs [325–327]. For example, Sildenafil, a PDE5 inhibitor neutralized MDSC function, thereby facilitating $CD8^+$ T cell activation and inhibiting tumor growth[325]. Song et al. show that Ginsenoside Rg3 blocked MDSC-mediated EMT and stemness acquisition in breast cancer cells by repressing Notch and STAT3 activation, resulting in tumor suppression [335](Table 2). Given these studies, targeting both TAMs and MDSCs in the tumor microenvironment could be a feasible approach to block tumor cell EMT and metastasis.

4.3. Targeting hypoxia

Hypoxia-mediated tumor malignant transformation is mainly orchestrated by HIF-1α/HIF-2α proteins. Numerous inhibitors targeting HIF-1α/ HIF-2α were developed for potential cancer therapies, including 1) PX-478[336,337] that inhibits HIF-1α transcription, translation and de-ubiquitination; 2) digoxin[338,339] and topotecan[340,341] that inhibit HIF-1α/2α protein synthesis; 3) acriflavine[342] that blocks HIF-1α/2α dimerization with HIF-1β; 4) 2-methoxyestradiol (2ME2) that inhibits HIF-1α/2α nuclear accumulation[343]; 5) echinomycin (NSC-13502) [344–346] that inhibits HIF-1α binding to the HRE; 6) chetomin[347], bortezomib[348], YC-1[349], all of which inhibit HIF-1α/2α binding to its transactivator p300 (Table 3). PX-478 treatment efficiently suppressed tumor metastasis in HIF-1α-expressing lung cancer cells[350]. Clinically, PX-478 treatment contributed to improved radiotherapy or chemotherapy efficacy in combination with anti-cancer drugs[351]. Digoxin is shown to prevent hypoxia-mediated EMT by blocking the HIF-1α-ZEB1 axis, further repressing the migration and invasion capacity of GBM cells[182]. Moreover, Carmen et al. demonstrated that either digoxin or acriflavine significantly reduced lung metastasis in breast cancer xenografts in mice [352]. In glioma cells, echinomycin prevented hypoxia-induced EMT and invasion by repressing the HIF-1α/miR-210/TGF-β and HIF-1α/miR-210/NF-κB axis, respectively[353]. Similarly, YC-1 treatment reduced hypoxia-induced migration and invasion, leading to metastasis suppression in hepatocellular carcinoma and breast cancer xenografts in mice[354,355].

HIF-2α is a key oncogene in ccRCC, especially in VHL-deficient tumors, where stabilized HIF-2α drives tumor invasion and metastasis [366]. Thus, multiple inhibitors specifically targeting HIF-2α were designed to impair its oncogenic activity, such as THS-044[366], PT2385 (MK-3795)[362,363], PT2399[360,361] and belzutifan (MK-6482 or PT2977) [364](Table 3). These inhibitors significantly reduce HIF-2α target gene expression

by interrupting its heterodimerization with HIF-1β. PT2385 treatment was shown to inhibit HIF-2α-induced expression of VEGF-A, PAI-1 and cyclin D1, thereby leading to tumor regression of the VHL-deficient ccRCC xenograft model [362]. Furthermore, tumor regression in 34% VHL-deficient ccRCC patients was reported in a phase I clinical study of patients with locally advanced or metastatic ccRCC[363]. Rui et al. developed the second generation HIF-2α inhibitor, belzutifan, which significantly repressed HIF-2α target erythropoietin (EPO) expression and promoted tumor regression in ccRCC bearing mice[364]. Belzutifan showed promising anti-tumor activity in metastatic ccRCC patients[365]. Additionally, belzutifan, in combination with cabozantinib, demonstrated to be an effective treatment for patients with metastatic ccRCC (NCT03634540) and has recently been approved by FDA for VHL-related diseases, including ccRCC tumors[367]. Although the action of HIF inhibition on tumor cells is pleiotropic, EMT is likely to be one of the key effects that can be targeted to inhibit metastasis and chemoresistance.

5. Conclusion

In this review, we summarized various important microenviron-mental cues that impinge on the EMT program to impact tumor development, progression, and therapy response in human tumors, including ECM, hypoxia, stroma cells, and immune cells. Much has been learned from the past two decades of intensive research on EMT and the tumor microenvironment. First, the communication between the tumor microenvironment and the EMT program is not unidirectional. Instead, tumor cells that have undergone EMT can also modulate stromal cells, immune cells, and the ECM to generate a more tumor-prone tumor microenvironment to further facilitate tumor development and progression. Dissecting the bidirectional interactions between tumor cells and their microenvironment and their effects on EMT requires more innovative in vitro culture systems to better mimic the complex three-dimensional biochemical and biophysical tumor microenvironment. Second, the interaction between the tumor microenvironment and EMT is highly dynamic in time and space. As discussed above, the EMT program is a dynamic and transient program during tumor progression. While activation of the transient EMT program promotes tumor cell dissemination into distant organs, tumor cells undergo MET to regain growth at distant organs. Therefore, the same microenvironmental cues in primary tumors and distant organs may impact tumor progression differentially, which should be carefully considered in selecting targeted therapies. Third, extensive clinical and experimental data show a tight association between the mesenchymal state and resistance to various cancer therapeutics. Given many such therapies target cell proliferation, it is conceivable why the mesenchymal state with reduced proliferation is resistant to such therapeutics. However, EMT is also reported to provide resistance to numerous therapeutics, such as immunotherapies, that do not directly target cell proliferation. Elucidating how EMT provides resistance to various cancer therapeutics is critical for developing new approaches to overcome therapy resistance. Lastly, many therapeutic approaches that target tumor microenvironmental cues impact EMT and tumor progression, some of which showed promising clinical benefits in cancer patients. While EMT plays an important role in tumor metastasis, very few cancer therapeutics are designed for metastasis prevention. As our knowledge of EMT and metastasis continues to grow, it becomes evident that metastasis prevention will become

an effective approach for high-risk cancer survivors that are prone to developing metastatic recurrence. The EMT research could contribute significantly to the next generation of cancer therapeutics on metastasis prevention.

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Data Availability

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

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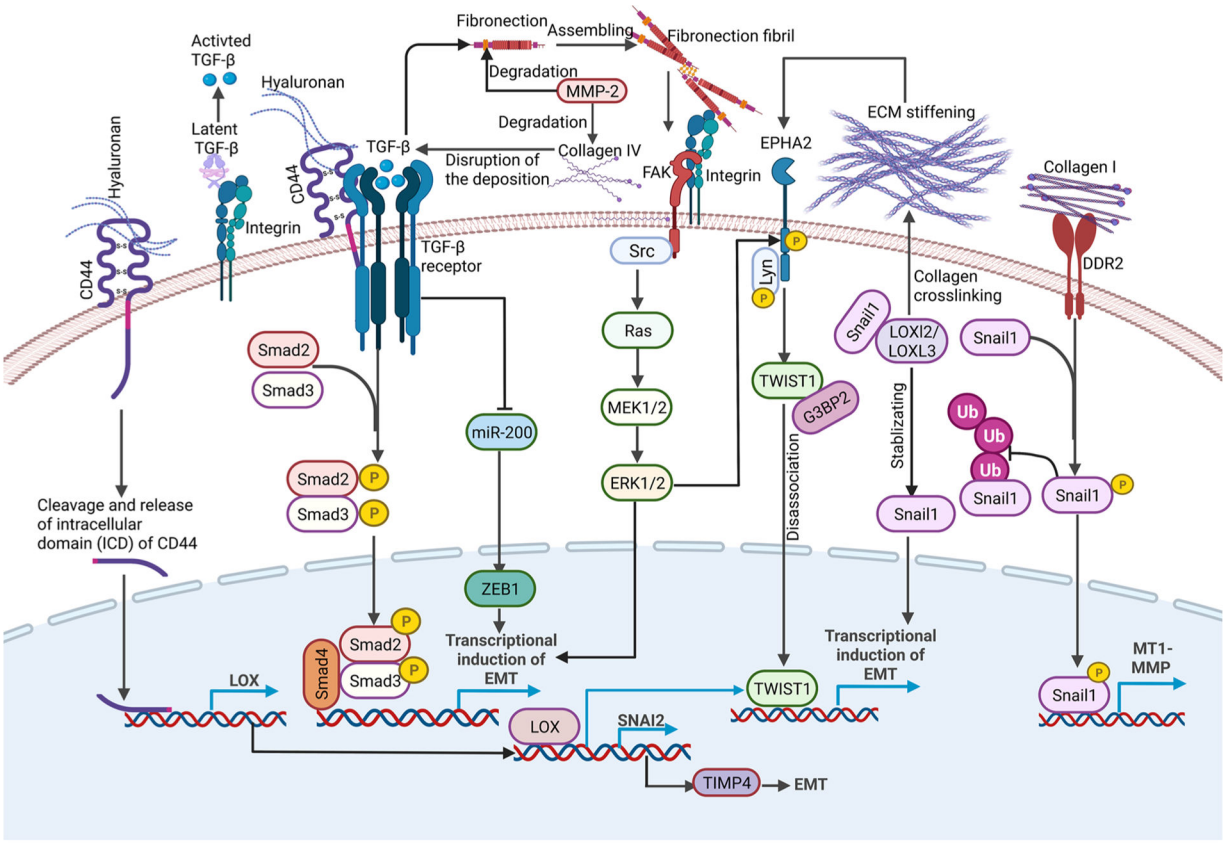

Fig. 1.

A summary of various extracellular matrix signals implicated in EMT regulation in the tumor microenvironment. Various ECM molecules, ECM remodeling proteins and physical forces exerted from ECM in the tumor microenvironment activate various biochemical and mechanical signaling pathways to regulate the EMT inducers and EMT transcription factors to drive EMT and tumor progression.

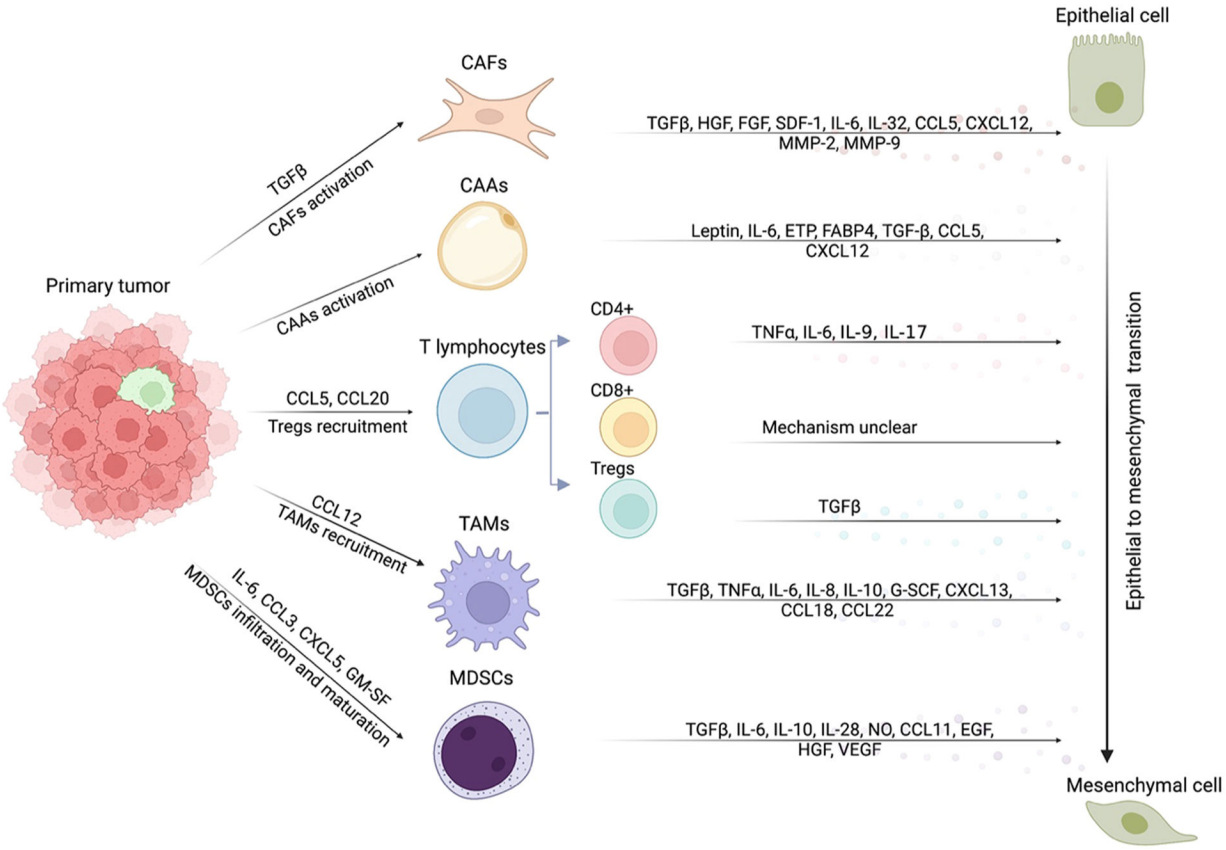

Fig. 2.

A summary of various secreted factors implicated in EMT induction by stromal cells and immune cells. CAFs, CAAs and immune cells including T lymphocytes, TAMs and MDSCs could promote EMT in cancer cells through the secretion of cytokines, chemokines and growth factors, such as TGFβ, IL-6, CXCL12, CCL18, FGF and HGF. Meanwhile, cancer cells secrete various factors to stimulate CAFs or CAAs formation and recruit more Tregs, TAMs or MDSCs. CAFs: cancer associated fibroblasts; CAAs: cancer associated adipocytes; TAMs: tumor associated macrophages; MDSCs: myeloid-derived suppressor cells.

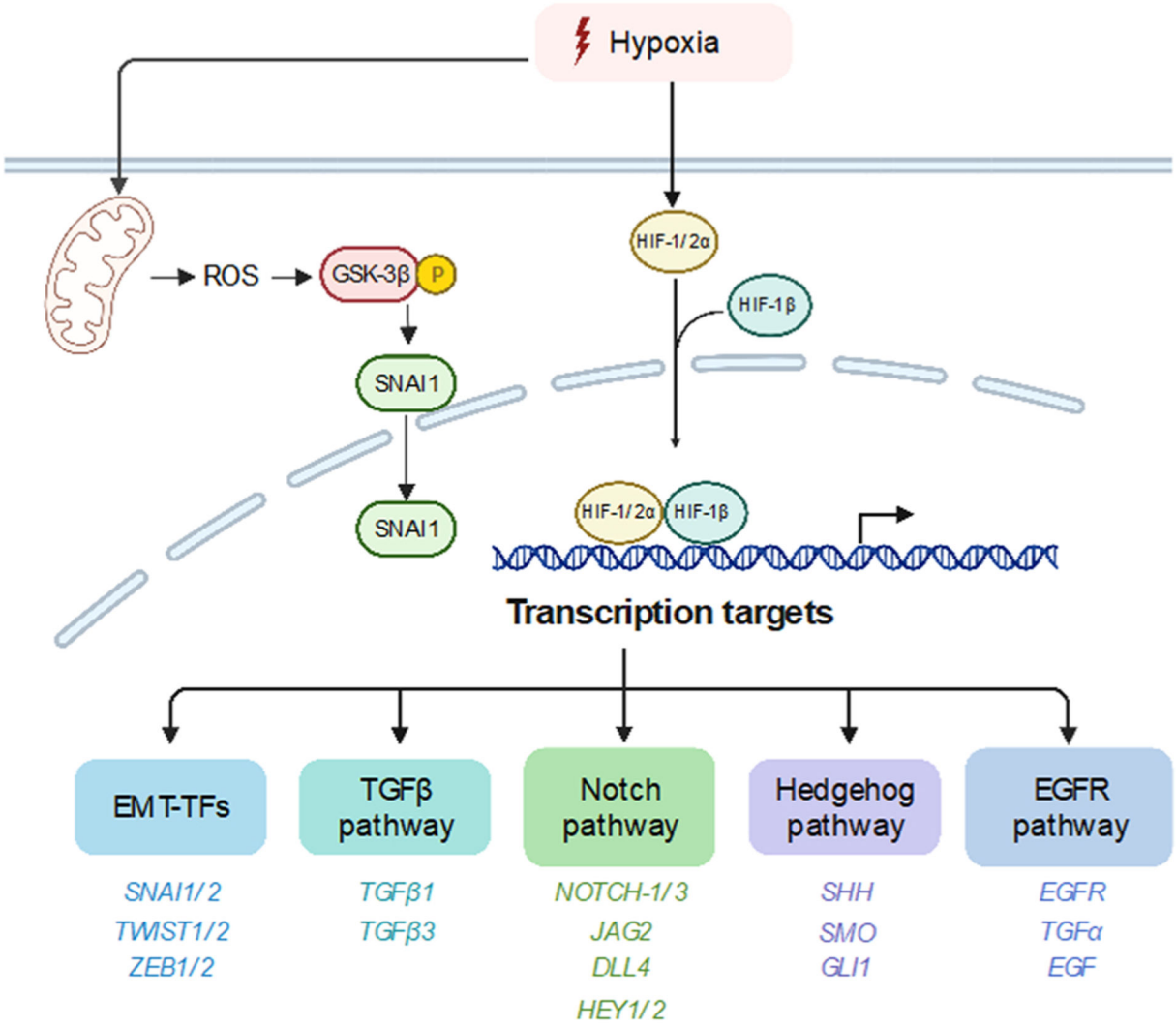

Fig. 3.

A schematic diagram summarizing mechanisms underlying hypoxia-mediated EMT. Hypoxia activates EMT by directly increasing EMT-TFs expression or stimulating various signaling pathways, including TGFβ, Notch, Hedgehog pathway and EGFR pathway. Direct transcription targets, like SNAI1, TGFβ, NOTCH1–1, SHH and EGFR are listed in diagram. Except for HIF-1/2α, ROS could also stimulate EMT by promoting SNAI1 nuclear translocation under hypoxia condition.

Table 1

Targeting extracellular matrix.

Drug/inhibitor	Target	Effectiveness	Reference
Bivatuzumab	CD44	Bivatuzumab can direct against CD44v6, blocking CD44-HA interaction	[247,248]
RO5429083	CD44	A monoclonal CD44 antibody, block the interaction between CD44 and HA, which have been entered phase 1 clinical trial conducted among patients with CD44-expressing malignant tumors	[249]
Verbascoside	CD44	Verbascoside suppressed growth of glioblastoma cells by inhibiting CD44 dimerization, as well as suppress tumor stem cell formation	[250]
7rh	DDR1	Inhibition of DDR1 by 7rh reduces collagen-mediated tumorigenicity in pancreatic ductal adenocarcinoma	[251]
WRG-28	DDR2	By targeting DDR2, WRG-28 can efficiently prevent disrupt DDR2 receptor-collagen ligand interaction and DDR- mediated tumor progression in preclinical models	[252]
Imatinib, nilotinib and dasatinib	DDR1 and DDR2	These 3 compounds are potent inhibitors of both DDR1 and DDR2 by inhibiting collagen- induced discoidin domain receptor 1 and 2 activation	[253–255]
Fresolimumab	Collagen	An anti-TGF-β antibody, suppress TGF-β-regulated gene expression, decreases collagen synthesis, it is currently tested in a phase 1 clinical trial	[256,257]
Losartan	Collagen	Losartan inhibits collagen I production via TGF-β pathways and improves the distribution and efficacy of nanotherapeuticsin tumors	[258]
Simtuzumab	LOXL2	Simtuzumab (GS-6624) is a selective inhibitor of LOXL2, which suppress LOXL2 enzymatic activity and inhibits collagen crosslinking, it is currently tested in a phase II clinical trial to test the efficacy and safety of GS-6624 combined with gemcitabine as first-line treatment for metastatic pancreatic adenocarcinoma	[259,260]
(2-Chloropyridin-4-yl) methanamine hydrochloride	LOXL2	(2-Chloropyridin-4-yl) methanamine hydrochloride is a small molecule inhibitor of LOXL2, it suppresses transformation abilities by repressing LOX2 induced EMT in cervical cancer	[261]
CCT365623	LOX	CCT365623 is a pharmacological inhibitor of LOX, it disrupts TGFβ1/ HTRA1/ MATN2/EGFR signaling axis and reduces tumor progression.	[262]
Cilengitide	αvβ3 and αvβ5 integrin	Cilengitide is an inhibitor of αvβ3 and αvβ5 integrin, demonstrated modest antitumor activity among recurrent glioblastoma multiforme patients in a prior phase I study	[263]
Curcumin	αvβ3 integrin	Curcumin is a natural derivative of turmeric, it influences αvβ3 integrin expression and up-regulation of PDK4 in Erlotinib resistant SW480 colon cancer cells	[264]
Defactinib(VS-6063)	FAK	Defactinib is a FAK inhibitor which targets FAK catalytic activity, FAK is a key mediator of therapeutic resistance, it is a potential inhibitor to overcome adaptive resistance to chemotherapy, combinations with the other therapy drugs (such as Pembrolizumab; Paclitaxel and carboplatin; VS-6766) have been tested in the clinical trial phase I or II	[265–267]
IN10018	FAK	IN10018 is a highly selective oral inhibitor of FAK, it is currently tested in a phase Ib clinical trial to study of IN10018 in combination with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer	[268]
GSK2256098	FAK	GSK2256098 is an ATPcompetitive inhibitor that binds to the ATP-binding pocket of FAK, it is currently tested in a phase 1 clinical trial to study of GSK2256098 in patients with advanced solid tumors in the United Kingdom	[269,270]
BI853520	FAK	BI853520 is a highly selective ATP-competitive inhibitor of FAK, it is currently tested in a phase I clinical trial to study of BI853520 in patients with advanced or metastatic nonhematologic malignancies	[271]

Table 2

Targeting stromal cells and immune cells.

Inhibitor	Target cell	Target	Effectiveness	Reference
AMD3100	CAFs	CXCR4 specific inhibitor	Inhibit CAFs-induced EMT, migration and invasion	[94]
Siltuximab	CAFs	IL-6 blocking antibody	Inhibit tumor growth, showed anti-tumor activity in Phase I/II clinical study	[284,290,291]
Tocilizumab	CAFs	IL-6R blocking antibody	Inhibit CAFs-induced EMT, migration and invasion, repress tumor growth	[285]
Nab-paclitaxel	CAFs	Decrease IL-6 secretion	Inhibit CAFs-induced EMT and invasion	[288]
PHA-665752	CAFs	c-Met inhibitor	Inhibit CAFs-induced migration and invasion	[74]
SOM230 (pasireotide)	CAFs	Protein synthesis inhibitor	Inhibit CAFs-induced EMT, migration and invasion	[287]
BGB324	CAFs	AXL inhibitor	Inhibit CAFs-induced EMT and migration	[292]
SB431542,pirfenidone	CAFs	TGF-P1 inhibitor	Inhibit CAFs-induced EMT and migration	[294]
ADP335	CAAs	Adiponectin analog	Inhibit tumor growth	[295,296]
PEG-LPrA2	CAAs	Leptin peptide receptor antagonist	Inhibit tumor growth	[297,298]
BMS309403	CAAs	FABP4 inhibitor	Inhibit Adipocytes-mediated EMT, repress tumor metastasis	[106]
Niclosamide	CAAs	Potent STAT3 inhibitor	Inhibit Adipocytes-mediated EMT	[299]
D-CAN	CAAs	ASCs depletion	Inhibit obesity-associated EMT, improve chemotherapy outcome	[111,300]
α-TGFβ/α-PD-1	T lymphocytes	PD-1 and TGFβ blocking antibody	α-PD-1 boost T cell response, α-TGFβ block α-PD-1-stimulated EMT, TGFβ/α-PD-1 combination inhibit tumor growth and promote mice survival	[301]
SAR439459/α-PD-L1	T lymphocytes	TGFβ inhibitor /PD-1 blocking antibody	Promote anti-tumor immunity, induce tumor regression	[302]
M7824	T lymphocytes	PD-1 and TGFβ blocking antibody	Inhibit TGFβ-mediated EMT, block PD-L1, booster T cell response, inhibit tumor growth, metastasis, promote mice survival, show promising efficacy in clinical phase I	[303–307]
YM101	T lymphocytes	PD-L1 and TGFβ blocking antibody	Enhance anti-tumor immune response, inhibit EMT, invasion and tumor growth	[308]
AZD6244/Anti-PD-L1/ Anti-IL-17	T lymphocytes	MEK inhibitor, IL-17 and PD-L1 blocking antibody	Overcome Th17-mediated therapy resistance, reduce tumor growth and lung metastasis	[309]
RDC018	TAMs	CCR2 antagonist	Inhibit TAM infiltration, repress M2 polarization, stimulate CD8 +T cell response	[310]
BLZ945	TAMs	CSF-1R inhibitor	Repress M2 polarization, induce established tumor regression	[311]
PLX3397	TAMs	CSF1R inhibitor	Reduce tumor burden, inhibit metastasis, prolong metastasis-free survival	[312]
RG7155	TAMs	CSF-1R mAb	Reduces TAMs, increase T cell infiltration	[313]
CP-870,893	TAMs	CD40 agonist mAb	Reprogram TAMs, FGK45 combined with gemcitabine therapy inhibit PDA tumor in mice, showed anti-tumor activity in Phase I study	[314]
BAY11–7082	TAMs	NF-κB inhibitor	Reprogram TAMs, Inhibit TAMs-mediated EMT	[139]
IPI-549	TAMs	PI3Kγ inhibitor	Reprogram TAMs, inhibit tumor metastasis	[315]
JWH-015	TAMs	Cannabinoid receptor-2 agonist	Inhibit TAMs-mediated EMT	[316]

Inhibitor	Target cell	Target	Effectiveness	Reference
Gemcitabine	MDSCs	Thymidylate synthetase inhibitor	Induce MDSCs apoptosis, combined with IFN-β to inhibit tumor growth	[317]
5-fluorouracil (5FU)	MDSCs	Thymidylate synthetase inhibitor	Induce MDSCs apoptosis, inhibit tumor growth	[318]
Sunitinib	MDSCs	Receptor tyrosine kinase inhibitor	Induce MDSCs apoptosis	[319]
Paclitaxel	MDSCs	Microtubule stabilization	Reduce MDSCs	[320]
Peptide-Fc	MDSCs	S100 family protein binding	Reduce MDSCs, restore CD8 +Teff activity, reduce tumor burden and prolong mice survival	[321]
PLX647, PLX5622	MDSCs	CSF-1R inhibitor	Block MDSCs recruitment, combine with anti-PD-L1 and anti CTLA-4 inhibit tumor growth and prolong mice survival	[322]
CCR5-Ig	MDSCs	CCR5 ligand neutralizer	Block MDSC and Tregs trafficking, inhibit tumor progression and prolong mice survival	[323]
SX682	MDSCs	CXCR2 inhibitor	Block PMN-MDSC recruitment, combined with anti-PD-1 inhibit tumor growth and prolong mice survival	[324]
Sildenafil	MDSCs	PDE5 inhibitor	Repress MDSC function, enhance T cell therapy efficacy	[325]
Celecoxib	MDSCs	COX-2 inhibitor	Deplete MDSC, impair MDSC function, combined with DC immunotherapy to improve mice survival	[326]
CDDO-Me	MDSCs	Reduce ROS	Neutralize MDSC activity, inhibit tumor growth	[327]
TBCA	MDSCs	CK2 inhibitor	Improve myeloid cell differentiation, inhibit tumor growth	[328]
ATRA	MDSCs	CK2 inhibitor	Improve dendritic cell differentiation	[329]

Table 3

Targeting hypoxia.

Inhibitor	Target	Mechanism	Effectiveness	Reference
chetomin	HIF-1α,HIF-2α	Inhibit p300 binding to HIF-1α/2α	Induce tumor necrosis	[347]
YC-1	HIF-1α,HIF-2α	Decrease HIF-1α/2α protein, inhibit p300 binding via FIH	Inhibit hypoxia-mediated migration, invasion and tumor metastasis	[349]
Bortezomib	HIF-1α	Inhibit p300 binding via FIH	Induce tumor cell death	[348]
Echinomycin (NSC-13502)	HIF-1α	Inhibit HIF-1α/DNA interface	Inhibit hypoxia-mediated EMT, reduce metastasis in mice model, but show toxicity and limited efficacy in clinical phase II	[344–346]
PX-478	HIF-1α	Inhibit HIF-1α transcription, translation and deubiquitination	Inhibit tumor growth and metastasis	[350,351]
Acriflavine	HIF-1α,HIF-2α	Inhibit Dimerization with HIF-1β	Inhibit tumor growth and metastasis	[342]
Digoxin	HIF-1α,HIF-2α	Inhibit HIF-1α/2α protein synthesis	Inhibit hypoxia-mediated EMT, migration and invasion. Reduce metastasis in mice model, but phase II clinical trial showed no effects	[338,339,356]
EZN-2968	HIF-1α	Reduce HIF-1α mRNA level	Inhibit tumor growth. Clinal trail was premature closed	[357,358]
Topotecan	HIF-1α	Inhibit HIF-1α translation	Inhibit tumor growth and angiogenesis, show effective anti-tumor activity in clinical phase I/II/III	[340,341,359]
2-methoxyestradiol (2ME2)	HIF-1α,HIF-2α	Inhibit HIF nuclear accumulation by disrupt tubulin	Inhibit angiogenesis	[343]
PT2399	HIF-2α	blocks the heterodimerization of HIF-2α with HIF-1β	Inhibit tumor growth, induce tumor regression	[360,361]
PT2385	HIF-2α	blocks the heterodimerization of HIF-2α with HIF-1β	Induce tumor regression	[362,363]
Belzutifan (MK-6482, PT2977)	HIF-2α	blocks the heterodimerization of HIF-2α with HIF-1β	Induce tumor regression, safe and efficient in Phase I/II clinical trials	[364,365]