Journal of Translational Medicine

REVIEW

Open Access

Epithelial-mesenchymal transition orchestrates tumor microenvironment: current perceptions and challenges

Yuqi Xie[1], Xuan Wang[1,2], Wenquan Wang[1,2], Ning Pu[1,2] and Liang Liu[1,2*]

Abstract

The epithelial-mesenchymal transition (EMT) is a critical process in cancer progression, facilitating tumor cells to develop invasive traits and augmenting their migratory capabilities. EMT is primed by tumor microenvironment (TME)-derived signals, whereupon cancer cells undergoing EMT in turn remodel the TME, thereby modulating tumor progression and therapeutic response. This review discusses the mechanisms by which EMT coordinates TME dynamics, including secretion of soluble factors, direct cell contact, release of exosomes and enzymes, as well as metabolic reprogramming. Recent evidence also indicates that cells undergoing EMT may differentiate into cancer-associated fibroblasts, thereby establishing themselves as functional constituents of the TME. Elucidating the relationship between EMT and the TME offers novel perspectives for therapeutic strategies to enhance cancer treatment efficacy. Although EMT-directed therapies present significant therapeutic potential, the current lack of effective targeting approaches—attributable to EMT complexity and its microenvironmental context dependency—underscores the necessity for mechanistic investigations and translational clinical validation.

Keywords Epithelial-mesenchymal transition (EMT), Tumor microenvironment (TME), Tumor progression, Plasticity

Introduction

The epithelial-mesenchymal transition (EMT) is a reversible process operative in physiological and pathological contexts, marked by progressive loss of epithelial traits (e.g., cell–cell adhesion, apical-basal polarity) and concomitant adoption of mesenchymal phenotypes [1–3]. Although EMT plays pivotal roles in embryonic development and wound healing, its pathological activation drives carcinoma aggressiveness through augmented cellular motility and invasiveness [4, 5]. Accumulating evidence links EMT with cancer stem cells (CSCs) generation, thereby implicating this process in tumorigenesis [6–9]. Notably, EMT confers therapeutic resistance and facilitates immune escape mechanisms in malignant cells [8–11].

The EMT process does not occur spontaneously but is initiated by various signals from the surrounding tumor microenvironment (TME), a heterocellular ecosystem comprising immune cells, fibroblasts, endothelial cells and adipocytes all embedded within the extracellular matrix (ECM) [12]. TME-derived signals orchestrate epigenetic reprogramming of core EMT transcription factors (EMT-TFs), including SNAIL, TWIST, and ZEB family members. These master regulators execute EMT programming through transcriptional suppression of epithelial markers (e.g., E-cadherin-encoding CDH1) and coordinated induction of mesenchymal effectors (e.g., vimentin, fibronectin, N-cadherin) [13]. Extensive research over recent decades has established the TME

*Correspondence:
Liang Liu
liu.liang@zs-hospital.sh.cn
[1] Department of Pancreatic Surgery, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai 200032, People's Republic of China
[2] Cancer Center, Zhongshan Hospital, Fudan University, Shanghai 200032, China

as a key driver of cancer progression via bidirectional tumor-stroma crosstalk. However, the TME is not always a driving force behind malignancy. During early tumorigenesis, immune populations predominantly exhibit tumor-suppressive activity. Yet, malignant cells rapidly acquire immune-evasion capacities through intrinsic reprogramming and TME remodeling, fostering pro-tumorigenic niches [14]. This tumor-educated microenvironment—featuring immunosuppressive immune landscapes, activated stromal networks, and remodeled ECM architecture—collectively establishes a tumor-promoting milieu. This reciprocal co-evolution between tumor cells and their microenvironment underscores the remarkable adaptive plasticity of neoplastic ecosystems.

Substantial research efforts have elucidated EMT initiation mechanisms. Current paradigms position TME as inducers, EMT-TFs as regulators, and mesenchymal-associated proteins as terminal effectors in EMT execution. Emerging studies reveal EMT functions not merely as a TME-responsive program but rather as an active microenvironmental remodeler. This reciprocal relationship involves TME-mediated EMT induction followed by EMT-driven TME reconstitution. This review analyzes how EMT activation reprograms the TME landscape, ultimately influencing tumor progression trajectories and modulating responses to conventional therapeutics.

Multifaceted signaling: EMT-driven command of surrounding cells

Soluble secreted factors

EMT-reprogrammed tumor cells acquire enhanced paracrine signaling capacity, enabling intercellular communication within the TME via secreted mediators. This regulatory axis comprises three principal components: (i) chemokines, (ii) immunosuppressive ligands, and (iii) angiogenic factors, collectively driving stromal reprogramming and tumor evolution (Fig. 1).

Chemokines

The EMT master transcriptional factor SNAIL, first characterized for its E-cadherin-repressive function in EMT initiation [15], exhibits broader transcriptional regulatory capacities. Emerging studies demonstrate SNAIL's dual regulatory role: activating mesenchymal gene programs while enhancing tumor proliferation and upregulating CXCL1/CXCL2 to recruit myeloid-derived suppressor cells (MDSCs) into ovarian cancer TME [16]. Additionally, SNAIL directly binds to the E-box of IL-8 (also known as CXCL8), promoting its expression [17]. These chemokines, which share receptors on neutrophils, play

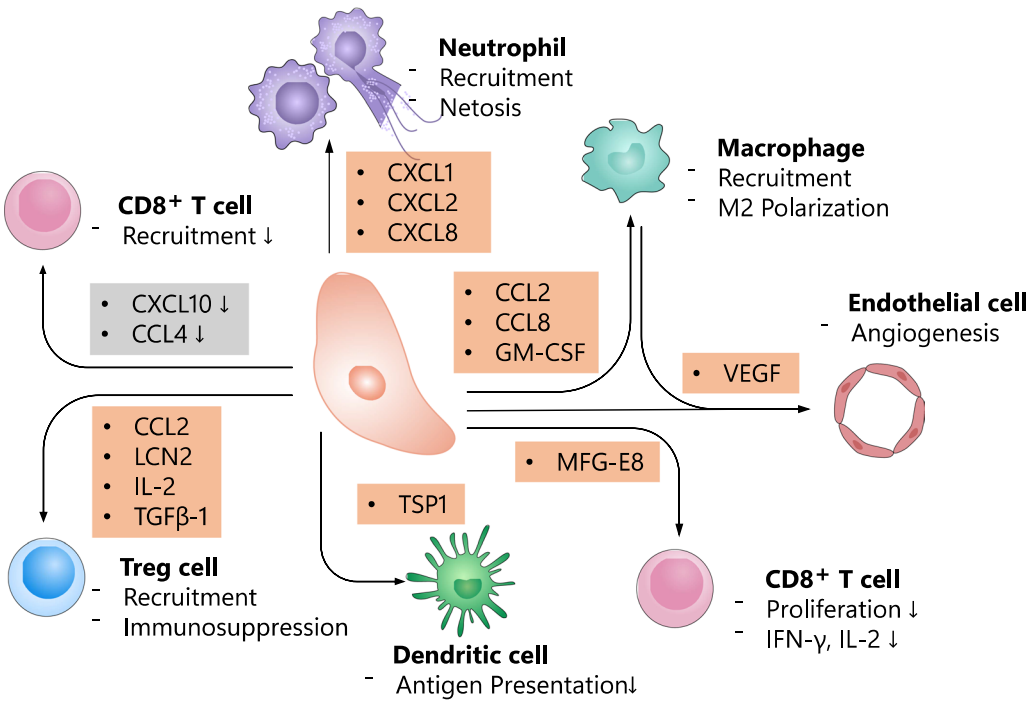

Fig. 1 EMT-induced paracrine secretion. EMT reprograms tumor cell secretomes, releasing soluble mediators that can influence the neighboring cells. The key impact of this paracrine signaling is on immune cells, affecting their recruitment, function, and phenotypic changes

crucial roles in mediating neutrophil chemotaxis and NETosis, a neutrophil-specific form of death linked to tumor metastasis in numerous oncology studies [18, 19].

Other key regulators of EMT, such as ZEB1 and TWIST1, are often expressed at the invasive front of tumors, steering cancer cells toward a pro-invasive, mesenchymal phenotype. This region also attracts macrophages (Mϕ), and the interplay between EMT and Mϕ chemoattractants may clarify this spatial relationship. Seminal work by Low-Marchelli et al. established TWIST1 as a direct inducer of CCL2 via gain/loss-of-function studies in mammary epithelium [20]. In cervical cancer, ZEB1 was shown to bind the CCL8 promoter and activate its transcription, thereby recruiting Mϕ through CCR2/NF-κB signaling [21]. Beyond these established chemotactic signals for Mϕ migration [22], EMT-dependent cytokines also direct Mϕ polarization towards pro-tumorigenic phenotypes. Su et al. observed that conditioned medium (CM) from mesenchymal-like breast cancer cell lines contains more tumor-promoting cytokines compared to their epithelial-like counterparts, a pattern replicated in MCF-7 cells undergoing EMT by treatment of transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α), or prolonged mammosphere culture [23]. Notably, GM-CSF, IL-8, CCL2, the GRO family of cytokines (GROα, GROβ, and GROγ) were significantly elevated in the CM of mesenchymal-like cells, consistent with findings in other cancer types as NF-kB target genes. However, only GM-CSF prominently induced cytokine production associated with tumor-associated macrophage (TAM), highlighting its essential role in their activation. The other cytokines may contribute to different functions: CCL2 aids in monocyte recruitment, GROs facilitate neutrophil recruitment, and IL-8 supports angiogenesis. This suggests that the outcomes of EMT are complex, with various soluble factors working together to create a conducive environment for tumor progression. Similar to ZEB1 and TWIST1, SNAIL can also activate TAM-related target genes involved in their recruitment and polarization. Hsu et al. demonstrated that the acetylation status of SNAIL dictates its role as either an activator or repressor [24]. Their ChIP experiments showed that acetylated SNAIL binds to the promoters of activated target genes, while non-acetylated SNAIL binds to those of repressed genes within the same cells. Remarkably, acetylated SNAIL retains its ability to drive EMT by inducing ZEB1 expression, which directly represses E-cadherin, illustrating the complementary functions of these transcription factors.

Since EMT-TFs typically exert transcriptional repression on their target genes, it is not surprising that the EMT process is often associated with the downregulation of certain cytokines. In hepatocellular carcinoma (HCC), SNAIL-mediated CXCL10 suppression diminishes $CD8^+$ T cell infiltration, resulting in immunosuppression and resistance to anti-PD1 therapy [25]. Similarly, in melanoma, ZEB1 binds to the promoters of CXCL10 and CCL4, leading to decreased secretion of these cytokines, which may impair $CD8^+$ T cell recruitment. Consistent with this mechanism, knockdown of ZEB1 potentiates immune checkpoint blockade (ICB) efficacy in preclinical models [26].

Immunosuppressive ligands

Mesenchymal-state tumor cells secrete soluble effectors that can directly impair T cell function. A parallel screening using CRISPR whole-genome knockdowns identified milk fat globule-EGF factor 8 (MFGE8) as a key immunosuppressive factor secreted by mesenchymal cancer cells, impairing $CD8^+$ T cell proliferation and interferon-γ (IFN-γ)/TNF-α production [27]. This mechanism aligns with previous findings in esophageal cancer, where MFGE8 expression was linked to T cell exclusion [28]. Notably, MFGE8 itself induces TWIST/SNAIL expression in melanoma cells, establishing a self-reinforcing EMT-immunosuppression loop [29].

Beyond direct immune cell inhibition, mesenchymal cells favor immunosuppressive Treg generation. SNAIL-expressing cells compromises dendritic cell (DC) functionality via thrombospondin-1 (TSP1) secretion and meanwhile induces $CD4^+Foxp3^+$ regulatory T cells (Tregs) [30]. Similarly, in cholangiocarcinoma (CCA), aPKC-ι/SNAIL-induced CCA cells with EMT-like features generate immunosuppressive $CD4^+CD25^-$ Tregs through the action of regulatory-inducible cytokines, including TGF-β1 and IL-2 [31]. Targeting SNAIL may reduce Tregs and increase the presence of tumor-specific tumor-infiltrating lymphocytes (TILs), presenting a potential strategy to enhance the effectiveness of immunotherapy [30].

Angiogenesis factors

The vasculature plays a crucial role in the TME, providing essential oxygen and nutrients and enabling hematogenous metastasis. SNAIL family member, SLUG, promotes ovarian cancer angiogenesis primarily through vascular endothelial growth factor (VEGF)-mediated endothelial cell survival and proliferation [32]. A similar phenomenon occurs in breast cancer, where ZEB1 upregulates VEGF expression and stimulates angiogenesis through paracrine mechanisms [33]. Additionally, a study on the antitumor drug Thalidomide in non-small cell lung cancer (NSCLC) identified a novel FGD5-AS1/miR-454-3p/ZEB1-VEGF axis, confirming that EMT-TF not only drive the EMT process but also facilitate the release of VEGF to promote angiogenesis [34].

Tumor cells undergoing EMT produce increased levels of VEGF to promote angiogenesis and may also exert pro-angiogenic effects via a non-cell autonomous mechanism. CM from primary ovarian tumor cells with a mesenchymal phenotype can induce the differentiation of monocytes into a pro-angiogenic $CD14^+/KDR^+$ population, creating a TME conducive to angiogenesis and metastasis [35]. Additionally, experiments involving Mϕ depletion and CCL2 rescue in mammary tumor cells indicate that CCL2-dependent Mϕ recruitment is essential for TWIST1's ability to promote angiogenesis in vivo [20].

Vimentin, a type III intermediate filament protein, is commonly recognized as a marker for EMT. During EMT, the upregulation of vimentin expression leads to the cytoskeleton rearrangement, enhancing the cell's motility [36]. Recent research has also illuminated its functions outside the cell [37]. Soluble extracellular vimentin has been shown to mimic the action of VEGF as a pro-angiogenic factor [38]. Furthermore, soluble vimentin can influence inflammation and immune responses by interacting with pattern recognition receptors like Dectin-1 and the NLRP3 inflammasome, affecting immune signaling pathways [39, 40]. Conversely, extracellular vimentin may inhibit adaptive immune responses by blocking DCs' secretion of pro-inflammatory cytokines [41]. These findings highlight the diverse roles of soluble vimentin beyond its traditional structural functions within the cytoskeleton. While current research primarily focuses on vimentin as an intracellular marker for EMT, the functional significance of extracellular vimentin in this context warrants further investigation.

Cell–cell junctions

Immune checkpoints serve as essential regulators of the immune system, modulated by ligand-receptor interactions to prevent autoimmune diseases and excessive inflammation. However, tumors exploit these checkpoints to achieve immune escape. As tumor cells transform into a mesenchymal phenotype, their cell surface characteristics undergo significant changes, leading to the transmission of distinct signals to neighboring cells (Fig. 2).

PD-L1, CD47 and B7-H3

A strong correlation between EMT status and immune checkpoint expression has been observed across various cancers. Definition of EMT status vary among studies, typically relying on classical epithelial/mesenchymal markers and EMT-TFs as phenotypic indicators.

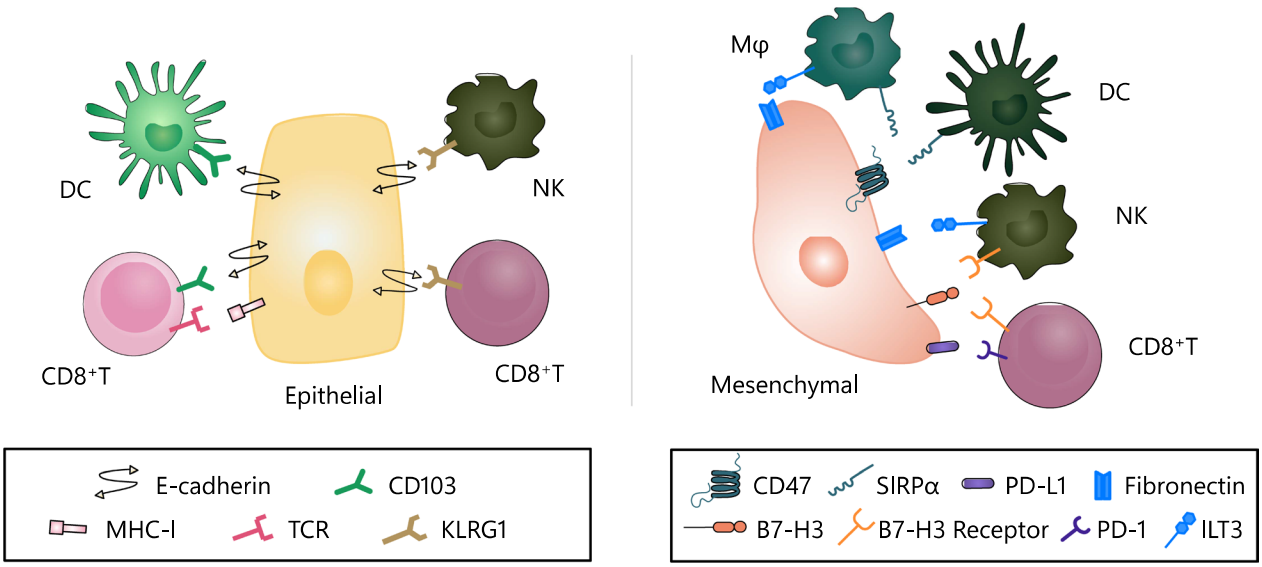

Fig. 2 Tumor cells in E/M states exhibit distinct surface markers. Epithelial-state tumor cells express higher levels of E-cadherin and Major Histocompatibility Complex (MHC), which can serve as antigens to activate DCs and $CD8^+$ T cells. In contrast, when tumor cells transition to a mesenchymal state, they downregulate these two molecules, effectively evading immune detection. On the other hand, E-cadherin can also bind to KLRG1 on the surface of natural killer (NK) cells and $CD8^+$ T cells, reducing the proliferation and cytotoxic capabilities of these immune cells. Mesenchymal cells upregulate several immunosuppressive ligands on their surface, including CD47, programmed death ligand 1 (PD-L1), and B7-H3. CD47 interacts with signal regulatory protein α (SIRPα) to deliver a "don't eat me" signal, weakening the phagocytic function of Mϕ and DCs. PD-L1, famous as a clinical immune checkpoint, binds to programmed death protein 1 (PD-1) to inhibit immune responses. B7-H3 also exerts broad immunosuppressive effects by affecting $CD8^+$ T cell proliferation, cytokine secretion, and NK cell cytotoxicity. Fibronectin, a classic mesenchymal cell marker, interacts with ILT3 on myeloid cells and NK cells thereby weakening their immune response

Bioinformatics studies utilizing transcriptomic data have shown that high EMT scores, characterized by multiple mesenchymal markers, positively correlate with PD-L1 expression in breast cancer, HCC, oral squamous cell carcinoma and pan-cancer groups [42–45].

Immunofluorescence staining of patient tissues provides a clear demonstration of this association at protein level. In head and neck squamous cell carcinoma (HNSCC) (n = 50), PD-L1 expression significantly correlates with EMT status, indicated by high vimentin and low E-cadherin levels [46]. Similarly, in extrahepatic CCA (n = 117), PD-L1 expression is correlated with elevated ZEB1, N-cadherin, and vimentin, along with reduced E-cadherin [47]. Kim et al. further reinforced this relationship in a larger cohort of pulmonary adenocarcinoma (pADC) cases (n = 409) [48]. Comparable findings have also been reported in breast cancer and esophageal squamous cell carcinoma [11, 49].

Three mechanistic frameworks may explain the correlation between EMT and PD-L1 expression: (i) common upstream activation (ii) EMT-driven PD-L1 upregulation, (iii) PD-L1-mediated EMT induction.

Signaling molecules from the TME interact with receptors on tumor cells, activating intracellular pathways that initiate the EMT process. Many of these pathways are also crucial for PD-L1 upregulation across various cancers. For instance, epidermal growth factor receptor (EGFR) triggers EMT through the MEK–ERK signaling pathway [1]. Additionally, EGF activates the JAK2–signal transducer and activator of STAT3 pathway, promoting EMT in multiple cancers. In NSCLC, triple negative breast cancer (TNBC) and HNSCC, EGFR signaling also enhances PD-L1 expression [50]. The overlapping pathways suggest that EMT and PD-L1 expression can be induced by a common stimulus. Therapeutic targeting of these nodes may dually suppress EMT and PD-L1. For example, mTORC1/2 inhibition concomitantly attenuates EMT and PD-L1, potentiating anti-tumor immunity in NSCLC [51].

Studies across malignancies have established a clear causal relationship between EMT-TFs and PD-L1, suggesting a direct regulatory connection rather than merely two branches of the same pathway. In diffuse large B cell lymphoma, ZEB1 not only upregulates PD-L1 but also induces $CD8^+$ T cell apoptosis via the PD-1/PD-L1 signaling [52]. In gastric cancer, ZEB1 upregulates PD-L1 expression, inhibiting T cell proliferation and suppressing IL-2 secretion [53]. Similarly, in colorectal cancer (CRC), ZEB1 positively regulates PD-L1, while biochanin A can downregulate PD-L1 by inhibiting ZEB1 expression [54]. Moreover, silencing ZEB1 via RNA interference has been shown to reduce both mRNA and protein levels of PD-L1 in esophageal squamous cell lines [49]. The regulatory influence of ZEB1 on PD-L1 likely stems from ZEB1 binding sites located in the promoter region of PD-L1, with mutation of these sites abolishing ZEB1's regulatory effect [55].

MicroRNAs (miRNAs) regulate target genes post-transcriptionally by promoting mRNA degradation or inhibiting translation, which leads to reduced protein levels. The miR-200 family, consisting of five members (miR-200a, 200b, 429, 200c, and 141), directly targets ZEB1 for inhibition, while ZEB1 can bind to the miR-200 motif to suppress its transcription [56]. This interaction creates a double-negative feedback loop that mutually regulates ZEB1 and miR-200, influencing the EMT process. In breast cancer, ZEB1's effect on PD-L1 was found to be antagonized by miR-200, which not only silenced ZEB1 but also reduced PD-L1 expression—an effect not observed with other EMT-TFs like SNAIL, TWIST, or SLUG [57]. In NSCLC, ectopic miR-200b/a/429 expression in highly metastatic cancer cells increased numbers of proliferating and granzyme B^+ $CD8^+$T cells and a decrease the exhausted $CD8^+$ T cells ($PD1^+$/$TIM3^+$), ultimately suppressing metastases [42]. Additionally, in hepatitis B, miR-200c overexpression counteracts HBV-mediated PD-L1 expression by directly targeting the 3′-UTR of CD274 (which encodes PD-L1), thereby reversing antiviral $CD8^+$ T cell depletion [58].

Beyond PD-L1, multiple immune checkpoints are associated with a more mesenchymal tumor phenotype. Overexpression of SNAIL1 or ZEB1 in epithelial-type breast cancer cells induces EMT with concomitant CD47 upregulation. Conversely, targeting SNAIL1 or ZEB1 with siRNA in mesenchymal-type breast cancer cells reverts EMT and downregulates CD47 [59]. Mechanistically, SNAIL1 and ZEB1 enhance CD47 expression by binding directly to E-box in the CD47 promoter, allowing cancer cells to evade Mϕ phagocytosis. A study in pancreatic cancer identified a miRNA that dually inhibit EMT and CD47 expression. This dual inhibition reprograms TME immune landscapes, increasing the proportion of DCs, $CD8^+$ T cells, and natural killer T cells (NKT) in the tumor and enhancing anti-tumor immunity [60].

PD-L1 itself reinforces EMT progression via tumor cell-intrinsic signaling. In renal cell carcinoma (RCC), PD-L1 can induce EMT and enhance RCC cell stemness through upregulating SREBP-1c [61]. In glioblastoma multiforme (GBM), PD-L1 contributes to the malignancy and aggressiveness of GBM cells by binding to Ras and activating the downstream ERK/EMT signaling pathway [62]. Similarly, in nasopharyngeal cancer, PD-L1 prominently activates the EMT process in a PI3K/AKT-dependent manner [63]. In human esophageal cancer cells, increased PD-L1 expression is associated with the

promotion of the EMT phenotype [64]. Moreover, downregulation of PD-L1 in breast cancer cells resulted in signs of EMT reversal, suggesting a bi-directional crosstalk between EMT and PD-L1 expression [43]. PD-L1 has also been reported to promote EMT by downregulating E-cadherin and upregulating SLUG and TWIST in skin epithelial cells [65].

Shrestha et al. developed a reversible EMT model using a HCC cell line and discovered that TGF-β1-induced EMT resulted in the upregulation of PD-L1 and B7-H3. Importantly, reversing EMT led to decreased expression of both PD-L1 and B7-H3, while knockdown of B7-H3 facilitated the reversal of TGF-β1-driven EMT [66]. B7-H3, also known as CD276, is an immunomodulatory protein from the B7 family of immune checkpoint molecules. It has been shown to suppress $CD8^+$ T cell activation, proliferation, and cytokine production, diminish NK cell-mediated tumor cell lysis, and increase the infiltration of Tregs [67–69].

Given the relationship between EMT and immune checkpoints, targeting key nodes in the EMT process may offer promising therapeutic strategies, either alone or in combination with ICB for enhanced efficacy.

E-cadherin

E-cadherin is a glycoprotein critical for cell–cell adhesion, acting as a molecular glue that maintains tissue integrity. E-cadherin loss represents an EMT hallmark, facilitating cellular movement and enhancing the invasive and metastatic capabilities of cancer cells [1]. This phenomenon, characterized by the concurrent upregulation of N-cadherin and downregulation of E-cadherin, is known as cadherin switching.

Beyond structural roles, E-cadherin engages immune cell receptors to modulate antitumor responses. For instance, E-cadherin can bind to KLRG1, an inhibitory receptor found on NK cells and various T cells, including $CD8^+$ T cells, $CD4^+$ T cells, and Tregs [70–73]. E-cadherin-KLRG1 interactions suppress the proliferation and cytotoxic capabilities of $CD8^+$ T cells and NK cells. Importantly, this effect can be reversed by using antibodies that inhibit the KLRG1-E-cadherin interaction [74–76].

E-cadherin can also bind to the αE(CD103)β7 heterodimer, which is expressed on immune cells such as T lymphocytes, mediating immune cell retention in epithelial tissues to potentiate immunosurveillance. Within TME, this adhesive interaction supports localized immune activation and effector function execution against malignant cells. Studies demonstrate interactions between αE(CD103)β7 and E-cadherin on tumor cells enhance cytotoxic T lymphocyte (CTLs)-mediated lysis in lung cancer and pancreatic cancer [77, 78]. Additionally, CD103 serves as a marker for a specific subset of DCs that play critical roles in immune defense, such as inducing Tregs to maintain tolerance and presenting antigens to $CD8^+$ T cells [79, 80].

Major histocompatibility complex (MHC)/human leukocyte antigen (HLA)

EMT downregulates surface MHC class I/HLA molecules in breast cancer, impairing antigen presentation to T cells. This molecular camouflage enables immune evasion from CTL-mediated killing [81, 82]. Similarly, in NSCLC cells with mesenchymal phenotypes, a decline in immunoproteasome components has been noted. These components are essential for generating peptides that bind onto HLA molecules, a prerequisite for efficient antigen presentation [83, 84]. Collectively, these defects in antigen presentation machinery drive immunotherapy resistance by evading T cell recognition [85].

Fibronectin

Fibronectin is also a classic marker associated with the mesenchymal cell state [13] and serves as a physiological ligand for immunoglobulin-like transcript 3 (ILT3; also known as LILRB4) [86]. ILT3, highly expressed on tumor-associated myeloid cells, promotes their suppressive phenotype [87]. Fibronectin-ILT3 engagement drives myeloid cell suppression, reversible by anti-ILT3 blockade. Furthermore, ex vivo treatment of human tumor explants with anti-ILT3 antibodies reprogrammed tumor-associated myeloid cells into a stimulatory phenotype [88]. Activated NK cells paradoxically upregulate ILT3, sensitizing them to fibronectin-mediated inhibition [89]. Fibronectin-ILT3 binding quenches NK cell activation pathways while transmitting inhibitory signals, suppressing cytotoxic function.

Extracellular vesicles

Extracellular vesicles (EVs) represent lipid-bilayer nanoparticles secreted by donor cells, transporting proteins, nucleic acids, and lipids. Through recipient cell internalization, these vesicles facilitate paracrine-like effects, and serves as important mediators of intercellular communication [90]. Among the various cargo, miRNAs are the most stable components of EVs, and there is evidence suggesting they may be selectively loaded into these vesicles [91, 92]. Cancer cells undergoing EMT promote an immunosuppressive environment via miRNA-rich exosome delivery to surrounding cells.

SNAIL-expressing human HNSCC cells release exosomes containing miR-21, which are then internalized by $CD14^+$ monocytes, driving M2-like polarization of TAMs [93]. Further studies have shown that these SNAIL-driven, miR-21-rich exosomes inhibit

NLRP3 inflammasome activity in Mϕ, resulting in a poorer response to chemotherapy in HNSCC patients [94]. Another miRNA implicated in M2 polarization of TAMs is miR-106b, also found in exosomes from EMT cells. Yang et al. demonstrated that CRC cells secret more exosomes during EMT, which promote Mϕ polarization via miR-106b transfer [95]. These EMT-derived exosomes activate Mϕ, facilitating the intravasation of tumor cells and enhancing the generation of circulating tumor cells (CTCs) through a feedback loop, thereby supporting liver and lung metastasis in CRC.

Also in CRC, Bhome et al. identified reduced miR-200 family members (miR-200a/b/c/141) in mesenchymal CRC cells and their EVs versus epithelial states [96]. MiR-200 acts as a counterbalance to ZEB1 in tumor cells. Delivered to fibroblasts via exosomes, miR-200 reduces stromal ZEB1 levels and decreases sensitivity to TGF-β-mediated myofibroblastic differentiation. Conversely, lower levels of miR-200 allow fibroblasts to differentiate more freely in response to TGF-β signaling. This regulatory axis underlies CAF accumulation in mesenchymal CRC subtypes.

Beyond miRNAs, EV cargo incorporates metabolic intermediates and biosynthesis products reflecting cellular state changes [97]. There remains significant potential for exploration regarding the various substances released into the TME via EVs during EMT. Systematic characterization of EMT-EV cargo may reveal novel mechanisms governing tumor-stroma communication.

Metabolic changes: EMT-enhanced tumor cell survival at the expense of immune function

Metabolites exert pivotal roles in the TME, serving as fuel for energy production, building blocks for synthesis, or waste products that can disrupt normal cellular processes. Striking metabolic divergence exists between normal and malignant cells, given that tumors must simultaneously sustain proliferation while acquiring invasive capabilities under nutrient-deprived conditions. This phenomenon is illustrated by the Warburg effect, where tumors exhibit enhanced aerobic glycolysis, converting sugars into lactic acid even in the presence of oxygen, at levels far exceeding normal tissues [98]. Mesenchymal cells may also have distinct metabolic requirements compared to epithelial cells, particularly due to their enhanced motility [99]. Therefore, the phenotypic changes associated with EMT are often accompanied by metabolic reprogramming to meet heightened energy demands.

Shaul et al. analyzed the expression of metabolic genes in cancer cells expressing mesenchymal markers using publicly available data from nearly 1000 cancer cell lines, and identified 44 metabolic genes that exhibited generally high expression, termed the Mesenchymal Metabolic Signature (MMS) [100]. Furthermore, these genes were also found to be upregulated in human mammary epithelial cells upon induction of EMT by TWIST1 expression. These findings establish that mesenchymal cells adopt a distinct metabolic pattern compared to their epithelial counterparts (Fig. 3).

Glucose metabolism

The crosstalk between intracellular metabolic reprogramming and extracellular microenvironment manifests through substrate consumption and byproduct release. Specifically, EMT-mediated metabolic changes exacerbate enhanced glycolysis, directly reducing glucose availability while increasing lactate levels in the TME.

Glucose transporter 1 and 3 (GLUT1 and GLUT3) facilitate glucose uptake independently of insulin. Malignant cells frequently overexpress GLUT1/GLUT3, a biomarker associated with adverse clinical outcomes [101, 102]. In laryngeal cancer cells, a correlation has been observed between GLUT1 expression and the EMT markers vimentin and N-cadherin [103]. In NSCLC mesenchymal cells, ZEB1 orchestrates GLUT3 upregulation, highlighting its non-redundant role in EMT progression [104].

Besides glucose transporters, a variety of glycolytic enzymes are closely associated with the EMT process. The loss of fructose 1,6-biphosphatase (FBP1) in basal-like breast cancer, mediated by SNAIL, enhances glycolysis, leading to elevated glucose uptake, macromolecule biosynthesis, the formation of tetrameric pyruvate kinase M2 (PKM2), and sustained ATP production under hypoxic conditions [105]. Ectopic ZEB1 directly increases the transcriptional expression of key glycolytic enzymes, including hexokinase 2 (HK2), phosphofructokinase (PFKP), and PKM2, which are crucial for regulating glycolytic rates, thereby promoting the Warburg effect [106, 107].

The metabolic dysregulation of tumor cells imposes nutrient competition on infiltrating immune cells, impairing their normal physiological functions. Tumor cells preferentially utilize aerobic glycolysis to break down glucose for ATP production, resulting in decreased glucose availability and increased lactate levels in the TME. The glucose-deficient, lactate-rich environment adversely affects T-cell function and antitumor immunity, while also promoting Mϕ polarization toward the M2 phenotype [108].

Lactate, a prominent byproduct of aerobic glycolysis, is prevalent in the TME and significantly impacts both cancer cells and immune cells [109]. Elevated lactate concentrations and decreased pH reprograms immune cell phenotypes, fostering immunosuppression via multiple

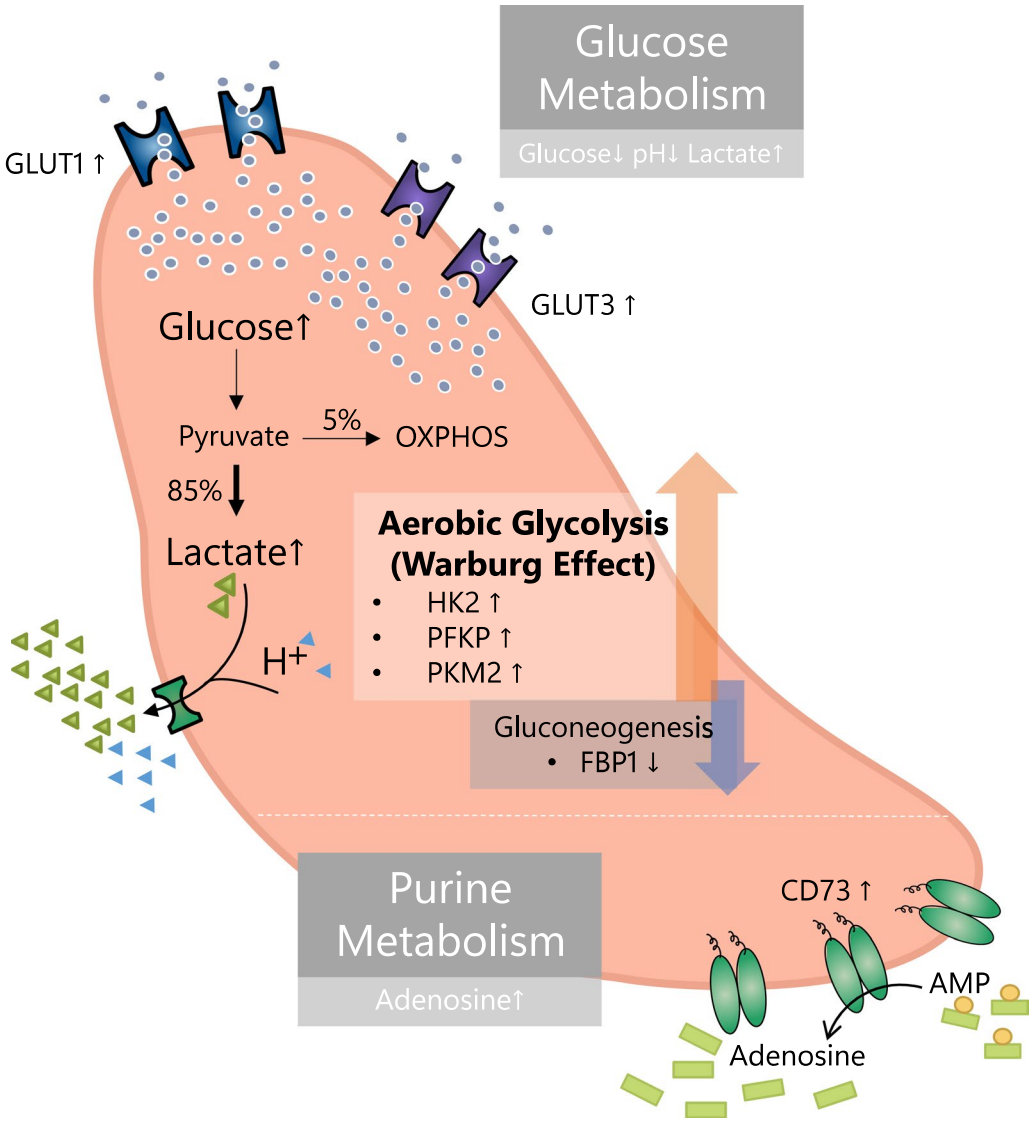

Fig. 3 EMT-Associated Metabolic Rewiring Shapes Immunosuppressive Niches. To meet increased energy demands, mesenchymal cells upregulate two glucose transporters, aggressively depleting glucose from the environment and creating a glucose-deficient state. Changes in the expression of metabolic enzymes and reduced gluconeogenesis further enhance glycolysis. The upregulation of glycolysis-related enzymes accelerates aerobic glycolysis, leading to the production of large amounts of lactate and H^+, which are released into TME. Additionally, mesenchymal cells exhibit a significant increase in CD73 expression, an enzyme that converts AMP into adenosine. This leads to the accumulation of adenosine, a known immunosuppressant, within TME

mechanisms. Lactate enhances the expression of collagen family genes in prostate cancer cells and signals Mϕ to reduce inflammasome activation and pro-inflammatory cytokine production [110]. Additionally, the lactate-induced pH reduction in the TME leads to decreased production of IFN-γ and IL-2 by CTLs [111], as well as inducing their apoptosis [112]. In breast cancer, both increased lactate levels and enhanced GM-CSF production are necessary for activating Mϕ to adopt an anti-inflammatory phenotype [23]. Critically, acidification by lactate—rather than HCl—induces M2-like TAM polarization, underscoring that lactate, rather than a simple pH drop, is responsible for these effects on Mϕ [23, 106].

Purine metabolism

EMT-associated metabolic reprogramming extends to extracellular adenosine metabolism—a potent immunosuppressive axis. The ectonucleotidase CD73 (NT5E) catalyzes AMP-to-adenosine conversion at

tumor cell surfaces, driving immunosuppressive adenosine accumulation in the TME [113].

Hasmim et al. found that SNAIL1 expression in the epithelial-like TNBC cell line MDA-MB-468 results in CD73 upregulation by direct binding to E-box motif in the CD73 promoter. This SNAIL1-dependent increase in CD73 leads to elevated levels of extracellular adenosine, which impairs NK cell cytotoxicity and proliferation by binding to A2a receptors expressed on NK cells. This mechanism contributes to the enhanced immunosuppressive properties of TNBC [114].

Adenosine receptors are widely expressed across immune cells (CTLs, Mϕ, DCs), thereby exerting a broader immunosuppressive effect [115, 116]. Turcotte et al. revealed that human mammary cells undergoing EMT upregulate CD73 expression on their surface, promoting TME adenosine accumulation. This accumulation affects the number and function of infiltrating immune cells [116]. Their investigation focused on the impact of CD73 on trastuzumab therapy in HER2-positive breast cancer, where trastuzumab is an anti-ErbB2 monoclonal antibody that targets HER2 signaling and stimulates antitumor immunity. They observed decreased levels of NK, $CD4^+$, and $CD8^+$ T cells, along with increased Tregs and myeloid cells, contributing to resistance to trastuzumab. Co-blockade of CD73 and HER2 synergistically restored treatment sensitivity.

Gene Ontology (GO) enrichment analysis links CD73 to ECM remodeling pathways [117]. CD73 showed a positive correlation with several genes involved in ECM organization, including lysyl oxidase (LOX), lysyl hydroxylase 2 (PLOD2), cathepsin K (CTSK), integrin subunit alpha 11 (ITGA11), matrix metalloproteinase-13 (MMP-13). Investigating the effects of adenosine signaling on these genes could provide valuable insights into the relationships among EMT, CD73 expression and TME remodeling.

ECM dynamics: enzymatic contributions from EMT

The ECM is a three-dimensional network of macromolecules that provides structural and biochemical support to surrounding cells. Compared with normal epithelial cells, tumor cells and CAFs significantly contribute to the ECM by supplying a wealth of its components [118]. Additionally, they produce enzymes that remodel the ECM, such as LOX family and matrix metalloproteinases (MMPs). LOX catalyzes collagen crosslinking for ECM stiffening, whereas MMPs mediate proteolytic ECM degradation [119, 120]. Although their roles may seem contradictory, both enzymes drive tumor progression and metastatic competence (Figs. 4 and 5).

LOX

Collagen, as the predominant ECM component, dictates mechanical strength and biological properties of ECM. Analysis of transcriptome data from the TCGA database revealed a strong positive correlation between collagen-associated genes and EMT signatures in lung cancer, validated through immunohistochemical staining of patient specimens. Subsequent in vivo and in vitro experiments confirmed that lung cancer cells undergoing EMT are directly responsible for increased collagen levels in the ECM. The ZEB1/miR-200 axis specifically controls the expression of LOX and lysyl oxidase like 2 (LOXL2), independent of other EMT-TFs like SNAIL [121]. The LOX family facilitates the conversion of lysine residues in collagen—primarily type I collagen—and elastin precursors into highly reactive aldehydes, initiating cross-linking and stabilization of these proteins [122].

The stiffening of the ECM establishes a positive feedback loop between LOX and the EMT process. Mechanoreceptors, primarily integrins, transmit mechanical signals into the cell, activating downstream signaling pathways such as the focal adhesion kinase (FAK) and the Rho/Rho-associated protein kinase (ROCK) pathway and culminating in EMT-TF (SNAIL, TWIST, ZEB) activation [119].

Furthermore, LOX confers chemoresistance. A denser and stiffer ECM acts as a barrier, restricting the penetration of anticancer drugs into tumors [123]. Inhibiting LOX can reduce collagen cross-linking and fibronectin assembly, thereby enhancing the permeability of therapeutic drugs and their efficacy [124–126].

ECM rigidity impairs immune surveillance through both physical exclusion and functional suppression of infiltrating immune cells [127–131]. Stiff environments can prompt Mϕ to adopt a pro-inflammatory phenotype, impairing their phagocytic capabilities. In contrast, softer conditions encourage Mϕ to take on an anti-inflammatory and highly phagocytic phenotype [132, 133]. Emerging data established collagen deposition as a key immune evasion mechanism. In NSCLC, insufficient responses to ICB correlates with collagen deposition pathways. Preclinical models have shown that inhibiting collagen deposition can enhance the effectiveness of anti-PD-1 immunotherapy, suggesting a potential therapeutic strategy to improve immune responses in tumors [134].

MMPs

EMT initiation coincides with EMT-TF-driven MMP upregulation [135, 136]. MMP-2 and MMP-9, in particular, degrade collagen—primarily Type IV collagen—which provides structural support and rigidity to the ECM, creating pathways for tumor cell migration and

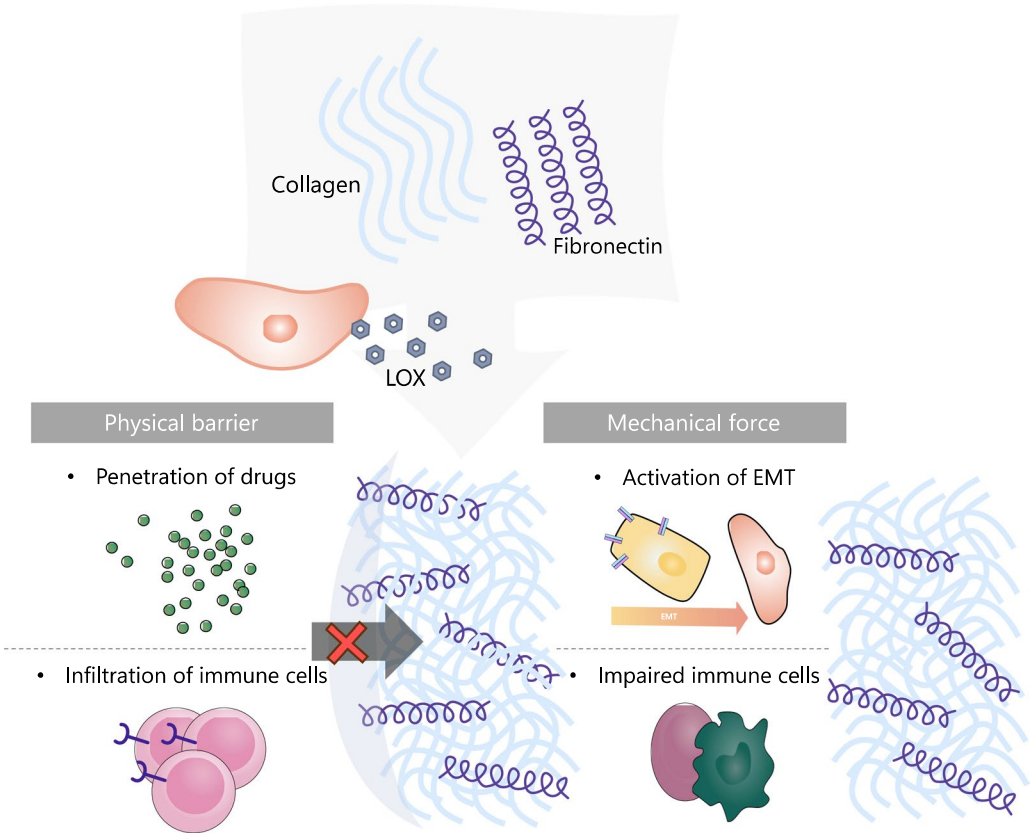

Fig. 4 LOX-Driven Biomechanical Remodeling in EMT. Mesenchymal cells upregulate LOX expression, which facilitates collagen cross-linking and fibronectin assembly. This leads to: (i) densified ECM impeding drug/immune cell infiltration; (ii) mechanotransduction via integrin/FAK/Rho pathways reinforcing EMT; (iii) stiffness-induced $CD8^{+}$T cell dysfunction and macrophage M2 polarization

invasion [137]. Additionally, MMP-mediated ECM degradation releases bioactive molecules, such as growth factors and cytokines that were previously sequestered within the ECM [137]. For example, MMP-9 can bind to CD44 and degrade fibronectin, resulting in the release of active TGF-β [120]. When the ECM is altered, these bioactive molecules are released into the extracellular space, where they can influence cellular behaviors and tissue processes. In pancreatic neuroendocrine tumors, MMP-9 can free VEGF from the matrix, thereby triggering angiogenesis and further promoting tumor growth and spread [138].

Metalloproteinases can also cleave signaling molecules and receptors within the TME. MMP-9 and MMP-2 can cleave the inactive latent form of TGF-β by generating various proteolytic fragments, thus initiating TGF-β downstream signaling [139]. Additionally, MMPs subvert IL-2 signaling via receptor cleavage—a key immunosuppressive mechanism. Shedding of IL-2Rα subunit by MMPs depletes surface receptors, attenuating T cell proliferation [140].

Apart from LOX, discoidin domain receptor 1 (DDR1) is another important collagen partner positively correlated with EMT in various cancers, including breast cancer [141–143], squamous cell carcinoma [144], HCC [145, 146], CRC [147], gastric cancer [148] and RCC [149]. This transmembrane receptor specifically binds to collagen, regulating cell adhesion and migratory. Its extracellular domain (ECD), which can be cleaved by MMPs, is critical for the arrangement of collagen fibers, thus affecting the structural organization of the ECM [150]. Inhibition of DDR1 phosphorylation by PRTH-101 reduces collagen-mediated cell attachment and prevents DDR1 shedding from the cell surface. This disruption affects the alignment of collagen fibers within the tumor ECM and promotes the infiltration of $CD8^{+}$ T cells into tumors, enhancing anti-tumor immune responses [151].

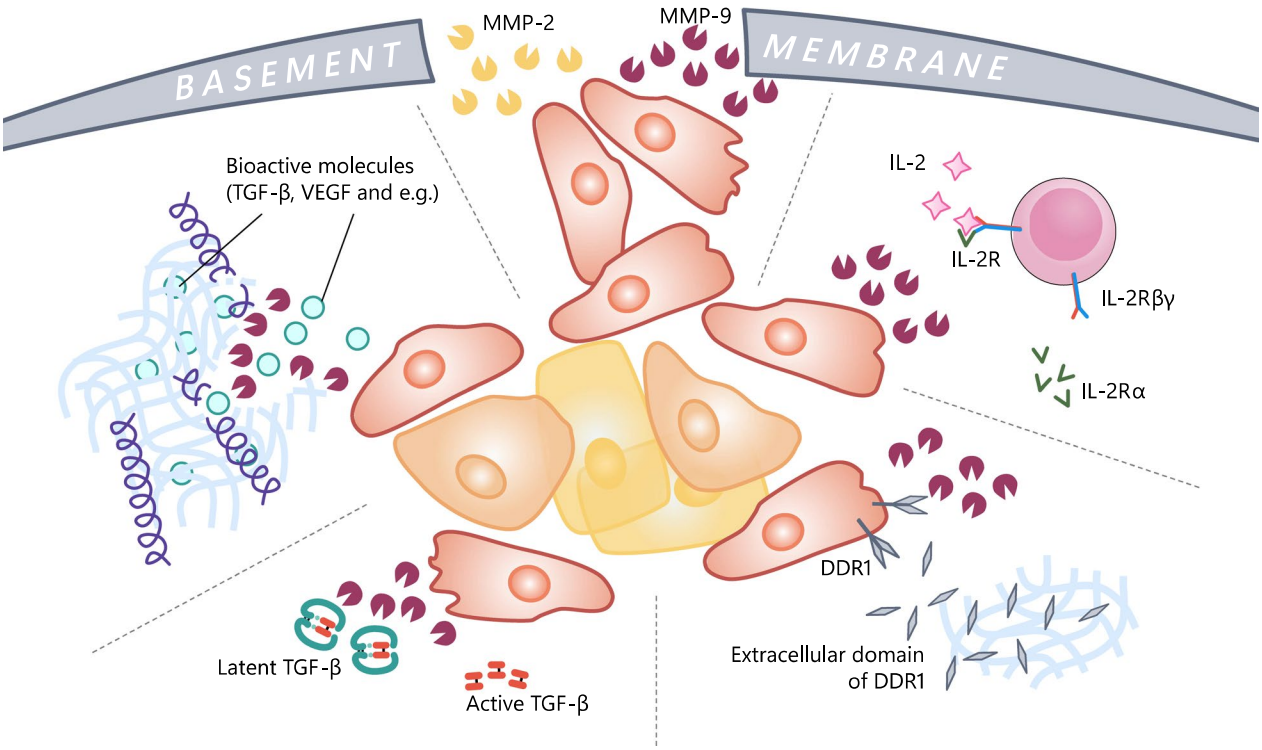

Fig. 5 MMPs as marker of EMT: multifaceted roles in TME. MMPs are classic markers of EMT and are known for their protein-cleaving and degrading capabilities in TME. EMT-associated MMPs execute triple oncogenic functions: (i) basement membrane proteolysis enabling invasion; (ii) latent TGF-β activation fueling progression; (iii) receptor editing (IL-2Rα shedding, collagen receptor ECD cleavage)

CAFs genesis: from tumor cells through the EMT process

The primary source of CAFs involves the phenotypic transformation of resident fibroblasts in response to signaling stimuli. Additionally, non-fibroblastic lineages, including epithelial cells undergoing EMT and endothelial cells via endothelial-mesenchymal transition (EndMT), may transdifferentiate into CAFs [147].

Recent advancements in molecular biology, particularly single-cell RNA sequencing (scRNA-seq), reveal distinct subtypes of CAFs. scRNA-seq in NSCLC stratifies CAFs into five subtypes, based on their collagen and ECM molecule expression, with one subpopulation showing high EMT and ECM-related gene expression [152]. Bartoschek et al. identified four CAF subpopulations in mammary tumors, each of which displays unique gene signatures with distinct functional roles. The dCAF subpopulation stands out due to its expression of stem cell-associated genes like Scrg1, Sox9, and Sox10, along with a strong presence of transgenic polyomavirus middle T antigen (PyMT) oncogenes not seen in other subsets [153]. The shared oncogenes with tumor cells suggests that dCAFs may originate from tumor cells undergoing EMT. Furthermore, the localization of dCAFs at the tumor-stroma boundary, marked by Scrg1, hints at their malignant origin and potential role in tumor progression.

Su et al. identified a CAF subset defined by the surface markers CD10 and GPR77, which correlates with chemoresistance and poor survival in breast cancers and lung cancers [154]. This subset appears to overlap with the dCAF cluster, suggesting they may represent the same population [153]. Anti-GPR77 monoclonal antibodies effectively attenuate tumor formation and chemoresistance in patient-derived xenograft (PDX)-bearing mice, validating $CD10^{+}GPR77^{+}$ CAF subset as a therapeutic target.

In breast cancer, CD10 + GPR77 + CAF phenotype is found to be activated by TAM-derived CCL18, which can enrich CSCs and induce chemoresistance via IL-6 and IL-8 production [155]. Similarly, CCL18 from TAMs can upregulate ZEB1 in breast cancer cells, enhancing both EMT and the expression of IL-6 and IL-8 [156]. These data establish a potential link between EMT cells and CAFs, indicating that EMT cells may serve as precursors to CAFs.

In addition, recent findings indicate CD10 and GPR77 can serve as biomarkers for predicting chemoresistance in locally advanced gastric cancer and correlate with overall survival [157]. However, it's still unclear if a

$CD10^+GPR77^+$ CAF population exists specifically in gastric cancer. This highlights the need for further investigation to establish whether this CAF subtype is present in other cancers and to explore its potential EMT origins.

EMT inhibition: unmet challenge in cancer therapeutics

EMT has long been recognized as a promising target for therapeutic intervention, owing to its critical role in cancer progression and metastasis. Recent insights have further elucidated the substantial influence of EMT on the reconfiguration of the TME, thereby enhancing the appeal of this target in the development of novel therapeutic strategies. Current strategies for targeting EMT include: (i) inhibition of upstream signaling pathways (TGF-β, NF-κB, EGFR, c-MET, WNT, and Notch signaling), (ii) suppression of EMT-TFs, (iii) targeting mesenchymal characteristics (as summarized in previous reviews [158, 159]).

Inhibitors targeting pathways such as TGF-β, NF-κB, EGFR, c-MET, WNT, and Notch are currently the most advanced and closest to clinical application, with several approved drugs already on the market. However, these inhibitors do not specifically target EMT. For instance, EGFR, first discovered in 1977, undergoes dimerization upon ligand binding to its ECD, which activates intracellular tyrosine kinase activity. Downstream phosphocascades triggers a broad range of signaling pathways involved in cell proliferation, invasion, and metastasis [160, 161]. TGF-β signaling is not limited to tumor cells. TGF-β simultaneously shapes adaptive immunity via Treg expansion, $CD4^+$ T cell response, and effector T cell function [162]. Innate immunity is similarly modulated by TGF-β through NK cell, Mϕ, DCs, and granulocytes regulation [163, 164]. While EMT inhibition contributes to therapy efficacy, it is overly simplistic to attribute these effects solely to their inhibition of EMT. These inhibitors have broader effects on various cellular processes, which complicates drawing direct conclusions about their EMT-specific actions.

In previous reviews on EMT therapeutic strategies, histone deacetylase inhibitors (HDACi) have been classified as drugs targeting EMT-TFs, as they can induce the epigenetic reprogramming required to suppress EMT phenotypic changes [165]. However, much like pathway inhibitors, the effects of HDACi are not limited to the regulation of EMT in tumor cells. HDACi exert global chromatin modifications with systemic immunological consequences. Studies conducted in tumor-bearing animal models have demonstrated that HDACi can modify the immunosuppressive TME and enhance the TILs [166–169]. These effects are largely due to increased tumor antigen expression and presentation, DC activation, and the inhibition of T cell exhaustion, or these mechanisms altogether. In summary, no truly EMT-selective inhibitors exist to date. This may stem from our still incomplete understanding of the key mechanisms driving EMT. Thus, EMT-targeted drug development remains a challenging and ongoing endeavor.

Another major challenge in inhibiting EMT is the risk of side effects. EMT not only plays a pro-carcinogenic role but is also involved in normal physiological processes, such as wound healing [3, 13]. Inhibiting its physiological functions could lead to undesirable consequences. Moreover, attention must be given to the reverse process of EMT, known as mesenchymal-epithelial transition (MET) [170]. Although EMT promotes metastatic dissemination, metastatic colonization demands MET-mediated reversion to epithelial states [171]. This implies that inhibiting EMT at an inappropriate time could unintentionally promote MET in CTCs, thereby accelerating their colonization and growth at metastatic sites.

Concluding remarks

Evolving understanding of EMT, EMT-TFs and related proteins

Traditionally, EMT has been viewed as a response of tumor cells to environmental factors. It is now increasingly recognized that cells undergoing EMT actively influence and modify their surrounding environment. EMT establishes self-reinforcing signaling circuits through bidirectional tumor-stroma crosstalk. Mesenchymal-like breast cancer cells can activate Mϕ via GM-CSF, transforming them into TAM. In turn, CCL18 produced by TAMs can induce EMT in cancer cells. The interaction between deposited collagen and DDR1 on the cell membrane triggers downstream signaling pathway that facilitate EMT. Enzymes such as MMP-3 and MMP-7 contribute to the cleavage of E-cadherin, resulting in the release of soluble fragments that further induce EMT [172]. Moreover, the regulatory capacity of EMT-TFs extends beyond a few key target genes, leading to widespread reprogramming of gene expression. This reprogramming not only governs EMT but also influences other pathways, including aerobic glycolysis. EMT-related proteins also have functions that surpass their roles in the EMT process. For example, E-Cadherin, typically recognized for maintaining epithelial cell adhesion, also functions as a ligand for immune receptors. Vimentin, a crucial intermediate filament protein that supports cell structure and motility during EMT, has significant roles in its soluble form. These diverse roles of EMT-TFs and proteins highlight their involvement in a wider array of cellular processes beyond their classical functions in EMT. This evolving understanding of EMT, EMT-TFs

and related proteins opens the door for more targeted and effective therapeutic strategies.

Limitations of current research

Currently, most studies equate the upregulation of EMT-TFs with the occurrence of EMT itself. While EMT-TFs are indeed crucial initiators of the process, can the upregulation of a single EMT-TF recapitulate the pathophysiological EMT spectrum in vivo? The study by Gu et al. provides valuable insights into this issue, which employed a sustained activating mutant of the TGF-β receptor in mesenchymal-like carcinoma cells sharing the same genomic background, and then captured a broader range of molecular changes that occur during the natural EMT process in tumor metastasis, rather than focusing solely on the direct upregulation of EMT-TFs. The emergence of innovative methodologies will enhance our understanding of EMT and the TME, paving the way for the identification of novel treatment strategies.

Remodeling of distant environments

Tumor-secreted factors (soluble mediators, exosomes, ECM enzymes) prime distant organs for metastatic colonization. LOX secreted by breast cancer cells induces pre-metastatic niche formation through ECM stiffening [173], while LOX inhibition attenuates lung metastasis in murine breast cancer models [174]. Pancreatic cancer models recapitulate this LOX-metastasis axis, suggesting a pan-cancer mechanism [175]. EMT thus orchestrates both local and distant microenvironment, creating a conducive niche for tumor cells to form secondary sites. Gaining a deeper understanding of these mechanisms can inform strategies for preventing or targeting metastasis in cancer therapy.

Dynamic and complexity of EMT

Recent advances challenge the binary epithelial/mesenchymal paradigm, revealing EMT as a dynamic continuum characterized by partial transition and cellular plasticity [176]. EMT may not represent a fixed tumor state, but rather a continuum of cellular plasticity, where some cells exhibit more epithelial traits and others display more mesenchymal ones, with the extremes resembling classical EMT phenotypes [177]. Identifying and quantifying EMT remains challenging due to the lack of reliable biomarkers and the inherent complexity and fluidity of the process [178]. A deeper understanding of how EMT influences the TME, and strategies to target these interactions, will be critical for improving therapeutic outcomes.

Abbreviations

EMT	Epithelial-mesenchymal transition
CAF	Cancer-associated fibroblast
CCA	Cholangiocarcinoma
CM	Conditioned medium
CRC	Colorectal cancer
CSC	Cancer stem cell
CTC	Circulating tumor cell
CTL	Cytotoxic T lymphocyte
CTSK	Cathepsin K
DC	Dendritic cell
DDR1	Discoidin domain receptor 1
ECD	Extracellular domain
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
EMT-TF	EMT transcription factor
EndMT	Endothelial-mesenchymal transition
EV	Extracellular vesicle
FAK	Focal adhesion kinase
FBP1	Fructose 1,6-biphosphatase
GBM	Glioblastoma multiforme
GLUT1	Glucose transporter 1
GLUT3	Glucose transporter 3
GO	Gene Ontology
HCC	Hepatocellular carcinoma
HDACi	Histone deacetylase inhibitor
HK2	Hexokinase 2
HLA	Human leukocyte antigen
HNSCC	Head and neck squamous cell carcinoma
ICB	Immune checkpoint blockade
IFN-γ	Interferon-γ
ITGA11	Integrin subunit alpha 11
LOX	Lysyl oxidase
MDSC	Myeloid-derived suppressor cell
MET	Mesenchymal-epithelial transition
MFGE8	Milk fat globule-EGF factor 8
MHC	Major histocompatibility complex
miRNA	MicroRNA
MMP	Matrix metalloproteinase
MMP-13	Matrix metallopeptidase-13
MMS	Mesenchymal metabolic signature
Mφ	Macrophage
NK	Natural killer
NKT	Natural killer T cell
NSCLC	Non-small cell lung cancer
pADC	Pulmonary adenocarcinoma
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PDX	Patient-derived xenograft
PFKP	Phosphofructokinase
PKM2	Pyruvate Kinase M2
PLOD2	Lysyl Hydroxylase 2
PyMT	Polyomavirus Middle T antigen
RCC	Renal cell carcinoma
ROCK	Rho/Rho-associated protein kinase
scRNA-seq	Single-cell RNA sequencing
SIRPα	Signal regulatory protein α
TAM	Tumor-associated macrophage
TGF-β	Transforming growth factor-β
TIL	Tumor-infiltrating lymphocyte
TME	Tumor microenvironment
TNBC	Triple negative breast cancer
TNF-α	Tumor necrosis factor-α
Treg	Regulatory T cell
VEGF	Vascular endothelial growth factor

Acknowledgements

Not applicable.

Author contributions

YX drafted the manuscript and created the figures. XW, WW and NP assisted with literature collection and organizing key findings. LL revised the manuscript. All authors read and approved the final manuscript.

Funding
This work was supported by grants from National Natural Science Foundation of China (82473459, 82303443, 82273382, 82272929, 82103409, 82103417), Program of Shanghai Academic/Technology Research Leader (23XD1400600), Shanghai Science and Technology Commission Innovative Pharmaceutical Products Application Demonstration Project (24SF1900300), Shanghai Municipal Health Commission (20244Y0023, 201940019), Beijing Xisike Clinical Oncology Research Foundation (Y-2022METAZQN-0003, Y-Gilead2024-PT-0002, Y-HR2022MS-0251, Y-HR2022QN-0085), Shanghai "Rising Stars of Medical Talents" Youth Development Program, and Science and Technology Planning Project of Yunnan Province (202305AF150148). The funding agencies had no role in the study design, data collection and analyses, decision to publish, or preparation of the manuscript.

Availability of data and material
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 24 December 2024 Accepted: 25 March 2025
Published online: 02 April 2025

References

1. Dongre A, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. Nat Rev Mol Cell Biol. 2019;20(2):69–84.
2. Nieto MA, Huang RY, Jackson RA, Thiery JP. EMT: 2016. Cell. 2016;166(1):21–45.
3. Thiery JP, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. Cell. 2009;139(5):871–90.
4. Rhim AD, Mirek ET, Aiello NM, Maitra A, Bailey JM, McAllister F, et al. EMT and dissemination precede pancreatic tumor formation. Cell. 2012;148(1–2):349–61.
5. Krebs AM, Mitschke J, Lasierra Losada M, Schmalhofer O, Boerries M, Busch H, et al. The EMT-activator Zeb1 is a key factor for cell plasticity and promotes metastasis in pancreatic cancer. Nat Cell Biol. 2017;19(5):518–29.
6. Mani SA, Guo W, Liao MJ, Eaton EN, Ayyanan A, Zhou AY, et al. The epithelial-mesenchymal transition generates cells with properties of stem cells. Cell. 2008;133(4):704–15.
7. Reiman JM, Knutson KL, Radisky DC. Immune promotion of epithelial-mesenchymal transition and generation of breast cancer stem cells. Cancer Res. 2010;70(8):3005–8.
8. Singh A, Settleman J. EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer. Oncogene. 2010;29(34):4741–51.
9. Shibue T, Weinberg RA. EMT, CSCs, and drug resistance: the mechanistic link and clinical implications. Nat Rev Clin Oncol. 2017;14(10):611–29.
10. Terry S, Savagner P, Ortiz-Cuaran S, Mahjoubi L, Saintigny P, Thiery JP, et al. New insights into the role of EMT in tumor immune escape. Mol Oncol. 2017;11(7):824–46.
11. Dongre A, Rashidian M, Reinhardt F, Bagnato A, Keckesova Z, Ploegh HL, et al. Epithelial-to-mesenchymal transition contributes to immunosuppression in breast carcinomas. Cancer Res. 2017;77(15):3982–9.
12. de Visser KE, Joyce JA. The evolving tumor microenvironment: from cancer initiation to metastatic outgrowth. Cancer Cell. 2023;41(3):374–403.
13. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. J Clin Invest. 2009;119(6):1420–8.
14. Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat Med. 2018;24(5):541–50.
15. Cano A, Pérez-Moreno MA, Rodrigo I, Locascio A, Blanco MJ, del Barrio MG, et al. The transcription factor snail controls epithelial-mesenchymal transitions by repressing E-cadherin expression. Nat Cell Biol. 2000;2(2):76–83.
16. Taki M, Abiko K, Baba T, Hamanishi J, Yamaguchi K, Murakami R, et al. Snail promotes ovarian cancer progression by recruiting myeloid-derived suppressor cells via CXCR2 ligand upregulation. Nat Commun. 2018;9(1):1685.
17. Hwang WL, Yang MH, Tsai ML, Lan HY, Su SH, Chang SC, et al. SNAIL regulates interleukin-8 expression, stem cell-like activity, and tumorigenicity of human colorectal carcinoma cells. Gastroenterology. 2011;141(1):279–91, 91.e1–5.
18. Albrengues J, Shields MA, Ng D, Park CG, Ambrico A, Poindexter ME, et al. Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice. Science. 2018;361(6409):eaao4227.
19. Teijeira Á, Garasa S, Gato M, Alfaro C, Migueliz I, Cirella A, et al. CXCR1 and CXCR2 chemokine receptor agonists produced by tumors induce neutrophil extracellular traps that interfere with immune cytotoxicity. Immunity. 2020;52(5):856-71.e8.
20. Low-Marchelli JM, Ardi VC, Vizcarra EA, van Rooijen N, Quigley JP, Yang J. Twist1 induces CCL2 and recruits macrophages to promote angiogenesis. Cancer Res. 2013;73(2):662–71.
21. Chen XJ, Deng YR, Wang ZC, Wei WF, Zhou CF, Zhang YM, et al. Hypoxia-induced ZEB1 promotes cervical cancer progression via CCL8-dependent tumour-associated macrophage recruitment. Cell Death Dis. 2019;10(7):508.
22. Briukhovetska D, Dörr J, Endres S, Libby P, Dinarello CA, Kobold S. Interleukins in cancer: from biology to therapy. Nat Rev Cancer. 2021;21(8):481–99.
23. Su S, Liu Q, Chen J, Chen J, Chen F, He C, et al. A positive feedback loop between mesenchymal-like cancer cells and macrophages is essential to breast cancer metastasis. Cancer Cell. 2014;25(5):605–20.
24. Hsu DS, Wang HJ, Tai SK, Chou CH, Hsieh CH, Chiu PH, et al. Acetylation of snail modulates the cytokinome of cancer cells to enhance the recruitment of macrophages. Cancer Cell. 2014;26(4):534–48.
25. Huang XY, Zhang PF, Wei CY, Peng R, Lu JC, Gao C, et al. Circular RNA circMET drives immunosuppression and anti-PD1 therapy resistance in hepatocellular carcinoma via the miR-30-5p/snail/DPP4 axis. Mol Cancer. 2020;19(1):92.
26. Plaschka M, Benboubker V, Grimont M, Berthet J, Tonon L, Lopez J, et al. ZEB1 transcription factor promotes immune escape in melanoma. J Immunother Cancer. 2022;10(3): e003484.
27. Gu Y, Zhang Z, Camps MGM, Ossendorp F, Wijdeven RH, Ten Dijke P. Genome-wide CRISPR screens define determinants of epithelial-mesenchymal transition mediated immune evasion by pancreatic cancer cells. Sci Adv. 2023;9(28):eadf9915.
28. Kanemura T, Miyata H, Makino T, Tanaka K, Sugimura K, Hamada-Uematsu M, et al. Immunoregulatory influence of abundant MFG-E8 expression by esophageal cancer treated with chemotherapy. Cancer Sci. 2018;109(11):3393–402.
29. Jinushi M, Nakazaki Y, Carrasco DR, Draganov D, Souders N, Johnson M, et al. Milk fat globule EGF-8 promotes melanoma progression through coordinated Akt and twist signaling in the tumor microenvironment. Cancer Res. 2008;68(21):8889–98.
30. Kudo-Saito C, Shirako H, Takeuchi T, Kawakami Y. Cancer metastasis is accelerated through immunosuppression during Snail-induced EMT of cancer cells. Cancer Cell. 2009;15(3):195–206.
31. Qian Y, Yao W, Yang T, Yang Y, Liu Y, Shen Q, et al. aPKC-ι/P-Sp1/Snail signaling induces epithelial-mesenchymal transition and immunosuppression in cholangiocarcinoma. Hepatology. 2017;66(4):1165–82.
32. Gu A, Jie Y, Yao Q, Zhang Y, Mingyan E. Slug is associated with tumor metastasis and angiogenesis in ovarian cancer. Reprod Sci. 2017;24(2):291–9.

33. Liu L, Tong Q, Liu S, Cui J, Zhang Q, Sun W, et al. ZEB1 Upregulates VEGF Expression and Stimulates Angiogenesis in Breast Cancer. PLoS ONE. 2016;11(2): e0148774.
34. Xia Y, Wang WC, Shen WH, Xu K, Hu YY, Han GH, et al. Thalidomide suppresses angiogenesis and immune evasion via lncRNA FGD5-AS1/miR-454-3p/ZEB1 axis-mediated VEGFA expression and PD-1/PD-L1 checkpoint in NSCLC. Chem Biol Interact. 2021;349: 109652.
35. Collino F, Revelli A, Massobrio M, Katsaros D, Schmitt-Ney M, Camussi G, et al. Epithelial-mesenchymal transition of ovarian tumor cells induces an angiogenic monocyte cell population. Exp Cell Res. 2009;315(17):2982–94.
36. Tabatabaee A, Nafari B, Farhang A, Hariri A, Khosravi A, Zarrabi A, et al. Targeting vimentin: a multifaceted approach to combatting cancer metastasis and drug resistance. Cancer Metastasis Rev. 2024;43(1):363–77.
37. Arrindell J, Desnues B. Vimentin: from a cytoskeletal protein to a critical modulator of immune response and a target for infection. Front Immunol. 2023;14:1224352.
38. van Beijnum JR, Huijbers EJM, van Loon K, Blanas A, Akbari P, Roos A, et al. Extracellular vimentin mimics VEGF and is a target for anti-angiogenic immunotherapy. Nat Commun. 2022;13(1):2842.
39. Kim S, Cho W, Kim I, Lee SH, Oh GT, Park YM. Oxidized LDL induces vimentin secretion by macrophages and contributes to atherosclerotic inflammation. J Mol Med (Berl). 2020;98(7):973–83.
40. dos Santos G, Rogel MR, Baker MA, Troken JR, Urich D, Morales-Nebreda L, et al. Vimentin regulates activation of the NLRP3 inflammasome. Nat Commun. 2015;6:6574.
41. Yu MB, Guerra J, Firek A, Langridge WHR. Extracellular vimentin modulates human dendritic cell activation. Mol Immunol. 2018;104:37–46.
42. Chen L, Gibbons DL, Goswami S, Cortez MA, Ahn YH, Byers LA, et al. Metastasis is regulated via microRNA-200/ZEB1 axis control of tumour cell PD-L1 expression and intratumoral immunosuppression. Nat Commun. 2014;5:5241.
43. Alsuliman A, Colak D, Al-Harazi O, Fitwi H, Tulbah A, Al-Tweigeri T, et al. Bidirectional crosstalk between PD-L1 expression and epithelial to mesenchymal transition: significance in claudin-low breast cancer cells. Mol Cancer. 2015;14:149.
44. Mak MP, Tong P, Diao L, Cardnell RJ, Gibbons DL, William WN, et al. A Patient-Derived, Pan-Cancer EMT signature identifies global molecular alterations and immune target enrichment following epithelial-to-mesenchymal transition. Clin Cancer Res. 2016;22(3):609–20.
45. Wu T, Tang C, Tao R, Yong X, Jiang Q, Feng C. PD-L1-mediated immunosuppression in oral squamous cell carcinoma: relationship with macrophage infiltration and epithelial to mesenchymal transition markers. Front Immunol. 2021;12: 693881.
46. Ock CY, Kim S, Keam B, Kim M, Kim TM, Kim JH, et al. PD-L1 expression is associated with epithelial-mesenchymal transition in head and neck squamous cell carcinoma. Oncotarget. 2016;7(13):15901–14.
47. Ueno T, Tsuchikawa T, Hatanaka KC, Hatanaka Y, Mitsuhashi T, Nakanishi Y, et al. Prognostic impact of programmed cell death ligand 1 (PD-L1) expression and its association with epithelial-mesenchymal transition in extrahepatic cholangiocarcinoma. Oncotarget. 2018;9(28):20034–47.
48. Kim S, Koh J, Kim MY, Kwon D, Go H, Kim YA, et al. PD-L1 expression is associated with epithelial-to-mesenchymal transition in adenocarcinoma of the lung. Hum Pathol. 2016;58:7–14.
49. Tsutsumi S, Saeki H, Nakashima Y, Ito S, Oki E, Morita M, et al. Programmed death-ligand 1 expression at tumor invasive front is associated with epithelial-mesenchymal transition and poor prognosis in esophageal squamous cell carcinoma. Cancer Sci. 2017;108(6):1119–27.
50. Yamaguchi H, Hsu JM, Yang WH, Hung MC. Mechanisms regulating PD-L1 expression in cancers and associated opportunities for novel small-molecule therapeutics. Nat Rev Clin Oncol. 2022;19(5):287–305.
51. Zhang Q, Zhang Y, Chen Y, Qian J, Zhang X, Yu K. A novel mTORC1/2 inhibitor (MTI-31) inhibits tumor growth, epithelial-mesenchymal transition, metastases, and improves antitumor immunity in preclinical models of lung cancer. Clin Cancer Res. 2019;25(12):3630–42.
52. Zhao L, Liu Y, Zhang J, Liu Y, Qi Q. LncRNA SNHG14/miR-5590-3p/ZEB1 positive feedback loop promoted diffuse large B cell lymphoma progression and immune evasion through regulating PD-1/PD-L1 checkpoint. Cell Death Dis. 2019;10(10):731.
53. Liang Y, Liu Y, Zhang Q, Zhang H, Du J. Tumor-derived extracellular vesicles containing microRNA-1290 promote immune escape of cancer cells through the Grhl2/ZEB1/PD-L1 axis in gastric cancer. Transl Res. 2021;231:102–12.
54. Xu J, Yang X, Pan J, Fan H, Mei J, Hua D. Biochanin a suppresses tumor progression and PD-L1 expression via inhibiting ZEB1 expression in colorectal cancer. J Oncol. 2022;2022:3224373.
55. Speir ML, Zweig AS, Rosenbloom KR, Raney BJ, Paten B, Nejad P, et al. The UCSC genome browser database: 2016 update. Nucleic Acids Res. 2016;44(D1):D717–25.
56. Lamouille S, Subramanyam D, Blelloch R, Derynck R. Regulation of epithelial-mesenchymal and mesenchymal-epithelial transitions by microRNAs. Curr Opin Cell Biol. 2013;25(2):200–7.
57. Noman MZ, Janji B, Abdou A, Hasmim M, Terry S, Tan TZ, et al. The immune checkpoint ligand PD-L1 is upregulated in EMT-activated human breast cancer cells by a mechanism involving ZEB-1 and miR-200. Oncoimmunology. 2017;6(1): e1263412.
58. Sun C, Lan P, Han Q, Huang M, Zhang Z, Xu G, et al. Oncofetal gene SALL4 reactivation by hepatitis B virus counteracts miR-200c in PD-L1-induced T cell exhaustion. Nat Commun. 2018;9(1):1241.
59. Noman MZ, Van Moer K, Marani V, Gemmill RM, Tranchevent LC, Azuaje F, et al. CD47 is a direct target of SNAI1 and ZEB1 and its blockade activates the phagocytosis of breast cancer cells undergoing EMT. Oncoimmunology. 2018;7(4): e1345415.
60. Xi Q, Chen Y, Yang GZ, Zhang JY, Zhang LJ, Guo XD, et al. miR-128 Regulates Tumor Cell CD47 expression and promotes anti-tumor immunity in pancreatic cancer. Front Immunol. 2020;11:890.
61. Wang Y, Wang H, Zhao Q, Xia Y, Hu X, Guo J. PD-L1 induces epithelial-to-mesenchymal transition via activating SREBP-1c in renal cell carcinoma. Med Oncol. 2015;32(8):212.
62. Qiu XY, Hu DX, Chen WQ, Chen RQ, Qian SR, Li CY, et al. PD-L1 confers glioblastoma multiforme malignancy via Ras binding and Ras/Erk/EMT activation. Biochim Biophys Acta Mol Basis Dis. 2018;1864(5 Pt A):1754–69.
63. Fei Z, Deng Z, Zhou L, Li K, Xia X, Xie R. PD-L1 induces epithelial-mesenchymal transition in nasopharyngeal carcinoma cells through activation of the PI3K/AKT pathway. Oncol Res. 2019;27(7):801–7.
64. Chen L, Xiong Y, Li J, Zheng X, Zhou Q, Turner A, et al. PD-L1 expression promotes epithelial to mesenchymal transition in human esophageal cancer. Cell Physiol Biochem. 2017;42(6):2267–80.
65. Cao Y, Zhang L, Kamimura Y, Ritprajak P, Hashiguchi M, Hirose S, et al. B7–H1 overexpression regulates epithelial-mesenchymal transition and accelerates carcinogenesis in skin. Cancer Res. 2011;71(4):1235–43.
66. Shrestha R, Bridle KR, Crawford DHG, Jayachandran A. Immune checkpoint molecules are regulated by transforming growth factor (TGF)-β1-induced epithelial-to-mesenchymal transition in hepatocellular carcinoma. Int J Med Sci. 2021;18(12):2466–79.
67. Getu AA, Tigabu A, Zhou M, Lu J, Fodstad Ø, Tan M. New frontiers in immune checkpoint B7–H3 (CD276) research and drug development. Mol Cancer. 2023;22(1):43.
68. Zhao B, Li H, Xia Y, Wang Y, Wang Y, Shi Y, et al. Immune checkpoint of B7–H3 in cancer: from immunology to clinical immunotherapy. J Hematol Oncol. 2022;15(1):153.
69. Zhou WT, Jin WL. B7–H3/CD276: an emerging cancer immunotherapy. Front Immunol. 2021;12: 701006.
70. Butcher S, Arney KL, Cook GP. MAFA-L, an ITIM-containing receptor encoded by the human NK cell gene complex and expressed by basophils and NK cells. Eur J Immunol. 1998;28(11):3755–62.
71. Blaser C, Kaufmann M, Pircher H. Virus-activated CD8 T cells and lymphokine-activated NK cells express the mast cell function-associated antigen, an inhibitory C-type lectin. J Immunol. 1998;161(12):6451–4.
72. Beyersdorf N, Ding X, Tietze JK, Hanke T. Characterization of mouse CD4 T cell subsets defined by expression of KLRG1. Eur J Immunol. 2007;37(12):3445–54.
73. Borys SM, Bag AK, Brossay L, Adeegbe DO. The Yin and Yang of Targeting KLRG1(+) Tregs and Effector Cells. Front Immunol. 2022;13: 894508.
74. Rosshart S, Hofmann M, Schweier O, Pfaff AK, Yoshimoto K, Takeuchi T, et al. Interaction of KLRG1 with E-cadherin: new functional and structural insights. Eur J Immunol. 2008;38(12):3354–64.
75. Henson SM, Akbar AN. KLRG1–more than a marker for T cell senescence. Age (Dordr). 2009;31(4):285–91.

76. Schwartzkopff S, Gründemann C, Schweier O, Rosshart S, Karjalainen KE, Becker KF, et al. Tumor-associated E-cadherin mutations affect binding to the killer cell lectin-like receptor G1 in humans. J Immunol. 2007;179(2):1022–9.
77. Franciszkiewicz K, Le Floc'h A, Jalil A, Vigant F, Robert T, Vergnon I, et al. Intratumoral induction of CD103 triggers tumor-specific CTL function and CCR5-dependent T-cell retention. Cancer Res. 2009;69(15):6249–55.
78. French JJ, Cresswell J, Wong WK, Seymour K, Charnley RM, Kirby JA. T cell adhesion and cytolysis of pancreatic cancer cells: A role for E-cadherin in immunotherapy? Br J Cancer. 2002;87(9):1034–41.
79. Fu C, Jiang A. Dendritic cells and CD8 T cell immunity in tumor microenvironment. Front Immunol. 2018;9:3059.
80. Salmon H, Idoyaga J, Rahman A, Leboeuf M, Remark R, Jordan S, et al. Expansion and activation of CD103(+) dendritic cell progenitors at the tumor site enhances tumor responses to therapeutic PD-L1 and BRAF inhibition. Immunity. 2016;44(4):924–38.
81. Pishesha N, Harmand TJ, Ploegh HL. A guide to antigen processing and presentation. Nat Rev Immunol. 2022;22(12):751–64.
82. Blum JS, Wearsch PA, Cresswell P. Pathways of antigen processing. Annu Rev Immunol. 2013;31:443–73.
83. Tripathi SC, Peters HL, Taguchi A, Katayama H, Wang H, Momin A, et al. Immunoproteasome deficiency is a feature of non-small cell lung cancer with a mesenchymal phenotype and is associated with a poor outcome. Proc Natl Acad Sci USA. 2016;113(11):E1555–64.
84. Shi S, Ou X, Liu C, Wen H, Jiang K. Immunoproteasome acted as immunotherapy 'coffee companion' in advanced carcinoma therapy. Front Immunol. 2024;15:1464267.
85. Rouanne M, Adam J, Radulescu C, Letourneur D, Bredel D, Mouraud S, et al. BCG therapy downregulates HLA-I on malignant cells to subvert antitumor immune responses in bladder cancer. J Clin Invest. 2022;132(12):1.
86. Xiang Z, Yin X, Wei L, Peng M, Zhu Q, Lu X, et al. LILRB4 Checkpoint for Immunotherapy: structure, mechanism and disease Targets. Biomolecules. 2024;14(2):187.
87. Cella M, Döhring C, Samaridis J, Dessing M, Brockhaus M, Lanzavecchia A, et al. A novel inhibitory receptor (ILT3) expressed on monocytes, macrophages, and dendritic cells involved in antigen processing. J Exp Med. 1997;185(10):1743–51.
88. Paavola KJ, Roda JM, Lin VY, Chen P, O'Hollaren KP, Ventura R, et al. The fibronectin-ILT3 interaction functions as a stromal checkpoint that suppresses myeloid cells. Cancer Immunol Res. 2021;9(11):1283–97.
89. Itagaki F, Nakatsuka K, Sakai H, Endo S, Su MT, Takai T. Fibronectin on target cells attenuates natural cytotoxicity of NK cells via myeloid immune checkpoint ILT3/LILRB4/gp49B. Int Immunol. 2023;35(7):339–48.
90. Maas SLN, Breakefield XO, Weaver AM. Extracellular vesicles: unique intercellular delivery vehicles. Trends Cell Biol. 2017;27(3):172–88.
91. Bhome R, Del Vecchio F, Lee GH, Bullock MD, Primrose JN, Sayan AE, et al. Exosomal microRNAs (exomiRs): Small molecules with a big role in cancer. Cancer Lett. 2018;420:228–35.
92. Janas T, Janas MM, Sapoń K, Janas T. Mechanisms of RNA loading into exosomes. FEBS Lett. 2015;589(13):1391–8.
93. Hsieh CH, Tai SK, Yang MH. Snail-overexpressing Cancer Cells Promote M2-Like Polarization of Tumor-Associated Macrophages by Delivering MiR-21-Abundant Exosomes. Neoplasia. 2018;20(8):775–88.
94. Cheng HY, Hsieh CH, Lin PH, Chen YT, Hsu DS, Tai SK, et al. Snail-regulated exosomal microRNA-21 suppresses NLRP3 inflammasome activity to enhance cisplatin resistance. J Immunother Cancer. 2022;10(8):e004832.
95. Yang C, Dou R, Wei C, Liu K, Shi D, Zhang C, et al. Tumor-derived exosomal microRNA-106b-5p activates EMT-cancer cell and M2-subtype TAM interaction to facilitate CRC metastasis. Mol Ther. 2021;29(6):2088–107.
96. Bhome R, Emaduddin M, James V, House LM, Thirdborough SM, Mellone M, et al. Epithelial to mesenchymal transition influences fibroblast phenotype in colorectal cancer by altering miR-200 levels in extracellular vesicles. J Extracell Vesicles. 2022;11(5): e12226.
97. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020;367(6478):eaau6977.
98. DeBerardinis RJ, Chandel NS. We need to talk about the Warburg effect. Nat Metab. 2020;2(2):127–9.
99. Metabolic rewiring is required for epithelial-mesenchymal transition. Cancer Discov. 2014;4(11):Of20.
100. Shaul YD, Freinkman E, Comb WC, Cantor JR, Tam WL, Thiru P, et al. Dihydropyrimidine accumulation is required for the epithelial-mesenchymal transition. Cell. 2014;158(5):1094–109.
101. Krzeslak A, Wojcik-Krowiranda K, Forma E, Jozwiak P, Romanowicz H, Bienkiewicz A, et al. Expression of GLUT1 and GLUT3 glucose transporters in endometrial and breast cancers. Pathol Oncol Res. 2012;18(3):721–8.
102. Yu M, Yongzhi H, Chen S, Luo X, Lin Y, Zhou Y, et al. The prognostic value of GLUT1 in cancers: a systematic review and meta-analysis. Oncotarget. 2017;8(26):43356–67.
103. Zuo J, Wen J, Lei M, Wen M, Li S, Lv X, et al. Hypoxia promotes the invasion and metastasis of laryngeal cancer cells via EMT. Med Oncol. 2016;33(2):15.
104. Masin M, Vazquez J, Rossi S, Groeneveld S, Samson N, Schwalie PC, et al. GLUT3 is induced during epithelial-mesenchymal transition and promotes tumor cell proliferation in non-small cell lung cancer. Cancer Metab. 2014;2:11.
105. Dong C, Yuan T, Wu Y, Wang Y, Fan TW, Miriyala S, et al. Loss of FBP1 by Snail-mediated repression provides metabolic advantages in basal-like breast cancer. Cancer Cell. 2013;23(3):316–31.
106. Jiang H, Wei H, Wang H, Wang Z, Li J, Ou Y, et al. Zeb1-induced metabolic reprogramming of glycolysis is essential for macrophage polarization in breast cancer. Cell Death Dis. 2022;13(3):206.
107. Zhou Y, Lin F, Wan T, Chen A, Wang H, Jiang B, et al. ZEB1 enhances Warburg effect to facilitate tumorigenesis and metastasis of HCC by transcriptionally activating PFKM. Theranostics. 2021;11(12):5926–38.
108. Ajam-Hosseini M, Heydari R, Rasouli M, Akhoondi F, Asadi Hanjani N, Bekeschus S, et al. Lactic acid in macrophage polarization: a factor in carcinogenesis and a promising target for cancer therapy. Biochem Pharmacol. 2024;222: 116098.
109. Hirschhaeuser F, Sattler UG, Mueller-Klieser W. Lactate: a metabolic key player in cancer. Cancer Res. 2011;71(22):6921–5.
110. Ippolito L, Duatti A, Iozzo M, Comito G, Pardella E, Lorito N, et al. Lactate supports cell-autonomous ECM production to sustain metastatic behavior in prostate cancer. EMBO Rep. 2024;25(8):3506–31.
111. Mendler AN, Hu B, Prinz PU, Kreutz M, Gottfried E, Noessner E. Tumor lactic acidosis suppresses CTL function by inhibition of p38 and JNK/c-Jun activation. Int J Cancer. 2012;131(3):633–40.
112. Xia H, Wang W, Crespo J, Kryczek I, Li W, Wei S, et al. Suppression of FIP200 and autophagy by tumor-derived lactate promotes naïve T cell apoptosis and affects tumor immunity. Sci Immunol. 2017;2(17):eaan631.
113. Xia C, Yin S, To KKW, Fu L. CD39/CD73/A2AR pathway and cancer immunotherapy. Mol Cancer. 2023;22(1):44.
114. Hasmim M, Xiao M, Van Moer K, Kumar A, Oniga A, Mittelbronn M, et al. SNAI1-dependent upregulation of CD73 increases extracellular adenosine release to mediate immune suppression in TNBC. Front Immunol. 2022;13: 982821.
115. Vijayan D, Young A, Teng MWL, Smyth MJ. Targeting immunosuppressive adenosine in cancer. Nat Rev Cancer. 2017;17(12):765.
116. Vigano S, Alatzoglou D, Irving M, Ménétrier-Caux C, Caux C, Romero P, et al. Targeting adenosine in cancer immunotherapy to enhance T-Cell function. Front Immunol. 2019;10:925.
117. Turcotte M, Allard D, Mittal D, Bareche Y, Buisseret L, José V, et al. CD73 promotes resistance to HER2/ErbB2 antibody therapy. Cancer Res. 2017;77(20):5652–63.
118. Walker C, Mojares E, Del Río Hernández A. Role of Extracellular Matrix in Development and Cancer Progression. Int J Mol Sci. 2018;19(10):3028.
119. Barker HE, Cox TR, Erler JT. The rationale for targeting the LOX family in cancer. Nat Rev Cancer. 2012;12(8):540–52.
120. Jabłońska-Trypuć A, Matejczyk M, Rosochacki S. Matrix metalloproteinases (MMPs), the main extracellular matrix (ECM) enzymes in collagen degradation, as a target for anticancer drugs. J Enzyme Inhib Med Chem. 2016;31(sup1):177–83.
121. Peng DH, Ungewiss C, Tong P, Byers LA, Wang J, Canales JR, et al. ZEB1 induces LOXL2-mediated collagen stabilization and deposition in the extracellular matrix to drive lung cancer invasion and metastasis. Oncogene. 2017;36(14):1925–38.
122. Kagan HM, Li W. Lysyl oxidase: properties, specificity, and biological roles inside and outside of the cell. J Cell Biochem. 2003;88(4):660–72.

123. Netti PA, Berk DA, Swartz MA, Grodzinsky AJ, Jain RK. Role of extracellular matrix assembly in interstitial transport in solid tumors. Cancer Res. 2000;60(9):2497–503.
124. Le Calvé B, Griveau A, Vindrieux D, Maréchal R, Wiel C, Svrcek M, et al. Lysyl oxidase family activity promotes resistance of pancreatic ductal adenocarcinoma to chemotherapy by limiting the intratumoral anticancer drug distribution. Oncotarget. 2016;7(22):32100–12.
125. Miller BW, Morton JP, Pinese M, Saturno G, Jamieson NB, McGhee E, et al. Targeting the LOX/hypoxia axis reverses many of the features that make pancreatic cancer deadly: inhibition of LOX abrogates metastasis and enhances drug efficacy. EMBO Mol Med. 2015;7(8):1063–76.
126. Saatci O, Kaymak A, Raza U, Ersan PG, Akbulut O, Banister CE, et al. Targeting lysyl oxidase (LOX) overcomes chemotherapy resistance in triple negative breast cancer. Nat Commun. 2020;11(1):2416.
127. Kuczek DE, Larsen AMH, Thorseth ML, Carretta M, Kalvisa A, Siersbæk MS, et al. Collagen density regulates the activity of tumor-infiltrating T cells. J Immunother Cancer. 2019;7(1):68.
128. García-Mendoza MG, Inman DR, Ponik SM, Jeffery JJ, Sheerar DS, Van Doorn RR, et al. Neutrophils drive accelerated tumor progression in the collagen-dense mammary tumor microenvironment. Breast Cancer Res. 2016;18(1):49.
129. Rømer AMA, Thorseth ML, Madsen DH. Immune modulatory properties of collagen in cancer. Front Immunol. 2021;12: 791453.
130. Tharp KM, Kersten K, Maller O, Timblin GA, Stashko C, Canale FP, et al. Tumor-associated macrophages restrict CD8(+) T cell function through collagen deposition and metabolic reprogramming of the breast cancer microenvironment. Nat Cancer. 2024;5(7):1045–62.
131. Peng DH, Rodriguez BL, Diao L, Chen L, Wang J, Byers LA, et al. Collagen promotes anti-PD-1/PD-L1 resistance in cancer through LAIR1-dependent CD8(+) T cell exhaustion. Nat Commun. 2020;11(1):4520.
132. Mei F, Guo Y, Wang Y, Zhou Y, Heng BC, Xie M, et al. Matrix stiffness regulates macrophage polarisation via the Piezo1-YAP signalling axis. Cell Prolif. 2024;57(8): e13640.
133. Sridharan R, Cavanagh B, Cameron AR, Kelly DJ, O'Brien FJ. Material stiffness influences the polarization state, function and migration mode of macrophages. Acta Biomater. 2019;89:47–59.
134. Mei J, Cai Y, Xu R, Li Q, Chu J, Luo Z, et al. Conserved immuno-collagenic subtypes predict response to immune checkpoint blockade. Cancer Commun (Lond). 2024;44(5):554–75.
135. Miyoshi A, Kitajima Y, Sumi K, Sato K, Hagiwara A, Koga Y, et al. Snail and SIP1 increase cancer invasion by upregulating MMP family in hepatocellular carcinoma cells. Br J Cancer. 2004;90(6):1265–73.
136. Miyoshi A, Kitajima Y, Kido S, Shimonishi T, Matsuyama S, Kitahara K, et al. Snail accelerates cancer invasion by upregulating MMP expression and is associated with poor prognosis of hepatocellular carcinoma. Br J Cancer. 2005;92(2):252–8.
137. Winkler J, Abisoye-Ogunniyan A, Metcalf KJ, Werb Z. Concepts of extracellular matrix remodelling in tumour progression and metastasis. Nat Commun. 2020;11(1):5120.
138. Bergers G, Brekken R, McMahon G, Vu TH, Itoh T, Tamaki K, et al. Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. Nat Cell Biol. 2000;2(10):737–44.
139. Yu Q, Stamenkovic I. Cell surface-localized matrix metalloproteinase-9 proteolytically activates TGF-beta and promotes tumor invasion and angiogenesis. Genes Dev. 2000;14(2):163–76.
140. Yadav L, Puri N, Rastogi V, Satpute P, Ahmad R, Kaur G. Matrix metalloproteinases and cancer-roles in threat and therapy. Asian Pac J Cancer Prev. 2014;15(3):1085–91.
141. Takai K, Drain AP, Lawson DA, Littlepage LE, Karpuj M, Kessenbrock K, et al. Discoidin domain receptor 1 (DDR1) ablation promotes tissue fibrosis and hypoxia to induce aggressive basal-like breast cancers. Genes Dev. 2018;32(3–4):244–57.
142. Koh M, Woo Y, Valiathan RR, Jung HY, Park SY, Kim YN, et al. Discoidin domain receptor 1 is a novel transcriptional target of ZEB1 in breast epithelial cells undergoing H-Ras-induced epithelial to mesenchymal transition. Int J Cancer. 2015;136(6):E508–20.
143. Taube JH, Herschkowitz JI, Komurov K, Zhou AY, Gupta S, Yang J, et al. Core epithelial-to-mesenchymal transition interactome gene-expression signature is associated with claudin-low and metaplastic breast cancer subtypes. Proc Natl Acad Sci U S A. 2010;107(35):15449–54.
144. Hidalgo-Carcedo C, Hooper S, Chaudhry SI, Williamson P, Harrington K, Leitinger B, et al. Collective cell migration requires suppression of actomyosin at cell-cell contacts mediated by DDR1 and the cell polarity regulators Par3 and Par6. Nat Cell Biol. 2011;13(1):49–58.
145. Park HS, Kim KR, Lee HJ, Choi HN, Kim DK, Kim BT, et al. Overexpression of discoidin domain receptor 1 increases the migration and invasion of hepatocellular carcinoma cells in association with matrix metalloproteinase. Oncol Rep. 2007;18(6):1435–41.
146. Ezzoukhry Z, Henriet E, Piquet L, Boyé K, Bioulac-Sage P, Balabaud C, et al. TGF-β1 promotes linear invadosome formation in hepatocellular carcinoma cells, through DDR1 up-regulation and collagen I cross-linking. Eur J Cell Biol. 2016;95(11):503–12.
147. Hu Y, Liu J, Jiang B, Chen J, Fu Z, Bai F, et al. MiR-199a-5p loss up-regulated DDR1 aggravated colorectal cancer by activating epithelial-to-mesenchymal transition related signaling. Dig Dis Sci. 2014;59(9):2163–72.
148. Xie R, Wang X, Qi G, Wu Z, Wei R, Li P, et al. DDR1 enhances invasion and metastasis of gastric cancer via epithelial-mesenchymal transition. Tumour Biol. 2016;37(9):12049–59.
149. Song J, Chen X, Bai J, Liu Q, Li H, Xie J, et al. Discoidin domain receptor 1 (DDR1), a promising biomarker, induces epithelial to mesenchymal transition in renal cancer cells. Tumour Biol. 2016;37(8):11509–21.
150. Sun X, Wu B, Chiang HC, Deng H, Zhang X, Xiong W, et al. Tumour DDR1 promotes collagen fibre alignment to instigate immune exclusion. Nature. 2021;599(7886):673–8.
151. Liu J, Chiang HC, Xiong W, Laurent V, Griffiths SC, Dülfer J, et al. A highly selective humanized DDR1 mAb reverses immune exclusion by disrupting collagen fiber alignment in breast cancer. J Immunother Cancer. 2023;11(6):e006720.
152. Lambrechts D, Wauters E, Boeckx B, Aibar S, Nittner D, Burton O, et al. Phenotype molding of stromal cells in the lung tumor microenvironment. Nat Med. 2018;24(8):1277–89.
153. Bartoschek M, Oskolkov N, Bocci M, Lövrot J, Larsson C, Sommarin M, et al. Spatially and functionally distinct subclasses of breast cancer-associated fibroblasts revealed by single cell RNA sequencing. Nat Commun. 2018;9(1):5150.
154. Su S, Chen J, Yao H, Liu J, Yu S, Lao L, et al. CD10(+)GPR77(+) cancer-associated fibroblasts promote cancer formation and chemoresistance by sustaining cancer stemness. Cell. 2018;172(4):841-56.e16.
155. Zeng W, Xiong L, Wu W, Li S, Liu J, Yang L, et al. CCL18 signaling from tumor-associated macrophages activates fibroblasts to adopt a chemoresistance-inducing phenotype. Oncogene. 2023;42(3):224–37.
156. Long L, Hu Y, Long T, Lu X, Tuo Y, Li Y, et al. Tumor-associated macrophages induced spheroid formation by CCL18-ZEB1-M-CSF feedback loop to promote transcoelomic metastasis of ovarian cancer. J Immunother Cancer. 2021;9(12):e003973.
157. Niu N, Yao J, Bast RC, Sood AK, Liu J. IL-6 promotes drug resistance through formation of polyploid giant cancer cells and stromal fibroblast reprogramming. Oncogenesis. 2021;10(9):65.
158. Huang Y, Hong W, Wei X. The molecular mechanisms and therapeutic strategies of EMT in tumor progression and metastasis. J Hematol Oncol. 2022;15(1):129.
159. Jonckheere S, Adams J, De Groote D, Campbell K, Berx G, Goossens S. Epithelial-mesenchymal transition (EMT) as a therapeutic target. Cells Tissues Organs. 2022;211(2):157–82.
160. Olayioye MA, Neve RM, Lane HA, Hynes NE. The ErbB signaling network: receptor heterodimerization in development and cancer. Embo J. 2000;19(13):3159–67.
161. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004;304(5676):1497–500.
162. Travis MA, Sheppard D. TGF-β activation and function in immunity. Annu Rev Immunol. 2014;32:51–82.
163. Peng D, Fu M, Wang M, Wei Y, Wei X. Targeting TGF-β signal transduction for fibrosis and cancer therapy. Mol Cancer. 2022;21(1):104.
164. Sanjabi S, Oh SA, Li MO. Regulation of the immune response by TGF-β: from conception to autoimmunity and infection. Cold Spring Harb Perspect Biol. 2017;9(6):a022236.
165. Skrypek N, Goossens S, De Smedt E, Vandamme N, Berx G. Epithelial-to-mesenchymal transition: epigenetic reprogramming driving cellular plasticity. Trends Genet. 2017;33(12):943–59.

166. Topper MJ, Vaz M, Chiappinelli KB, DeStefano Shields CE, Niknafs N, Yen RC, et al. Epigenetic therapy ties MYC depletion to reversing immune evasion and treating lung cancer. Cell. 2017;171(6):1284-300.e21.
167. Luo N, Nixon MJ, Gonzalez-Ericsson PI, Sanchez V, Opalenik SR, Li H, et al. DNA methyltransferase inhibition upregulates MHC-I to potentiate cytotoxic T lymphocyte responses in breast cancer. Nat Commun. 2018;9(1):248.
168. Fukumoto T, Fatkhutdinov N, Zundell JA, Tcyganov EN, Nacarelli T, Karakashev S, et al. HDAC6 inhibition synergizes with anti-PD-L1 therapy in ARID1A-inactivated ovarian cancer. Cancer Res. 2019;79(21):5482–9.
169. Peng X, Li L, Chen J, Ren Y, Liu J, Yu Z, et al. Discovery of novel histone deacetylase 6 (HDAC6) inhibitors with enhanced antitumor immunity of anti-PD-L1 immunotherapy in melanoma. J Med Chem. 2022;65(3):2434–57.
170. Nieto MA. Epithelial plasticity: a common theme in embryonic and cancer cells. Science. 2013;342(6159):1234850.
171. Ocaña OH, Córcoles R, Fabra A, Moreno-Bueno G, Acloque H, Vega S, et al. Metastatic colonization requires the repression of the epithelial-mesenchymal transition inducer Prrx1. Cancer Cell. 2012;22(6):709–24.
172. Noë V, Fingleton B, Jacobs K, Crawford HC, Vermeulen S, Steelant W, et al. Release of an invasion promoter E-cadherin fragment by matrilysin and stromelysin-1. J Cell Sci. 2001;114(Pt 1):111–8.
173. Erler JT, Bennewith KL, Cox TR, Lang G, Bird D, Koong A, et al. Hypoxia-induced lysyl oxidase is a critical mediator of bone marrow cell recruitment to form the premetastatic niche. Cancer Cell. 2009;15(1):35–44.
174. Rachman-Tzemah C, Zaffryar-Eilot S, Grossman M, Ribero D, Timaner M, Mäki JM, et al. Blocking surgically induced Lysyl oxidase activity reduces the risk of lung metastases. Cell Rep. 2017;19(4):774–84.
175. Alonso-Nocelo M, Ruiz-Cañas L, Sancho P, Görgülü K, Alcalá S, Pedrero C, et al. Macrophages direct cancer cells through a LOXL2-mediated metastatic cascade in pancreatic ductal adenocarcinoma. Gut. 2023;72(2):345–59.
176. Brabletz S, Schuhwerk H, Brabletz T, Stemmler MP. Dynamic EMT: a multi-tool for tumor progression. Embo j. 2021;40(18): e108647.
177. Sample RA, Nogueira MF, Mitra RD, Puram SV. Epigenetic regulation of hybrid epithelial-mesenchymal cell states in cancer. Oncogene. 2023;42(29):2237–48.
178. Yang J, Antin P, Berx G, Blanpain C, Brabletz T, Bronner M, et al. Guidelines and definitions for research on epithelial-mesenchymal transition. Nat Rev Mol Cell Biol. 2020;21(6):341–52.

Publisher's Note