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Epithelial-mesenchymal transition in cancer metastasis: Molecular mechanisms, microenvironmental regulation, and therapeutic targeting

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ABSTRACT

Epithelial-mesenchymal transition is a crucial driver of cancer metastasis, enabling cancer cells to acquire invasive and migratory characteristics. This review synthesizes the molecular mechanisms underlying EMT, focusing on the transcription factors Snail, ZEB, and Twist, as well as the signaling pathways TGF-β/Smad and PI3K/Akt that regulate phenotypic plasticity. Components of the tumor microenvironment, including cytokines, hypoxia, and cancer-associated fibroblasts, synergistically activate EMT through dynamic interactions with oncogenic signaling pathways. The heterogeneity of EMT across different cancer types, such as hormone-mediated regulation in breast cancer and the involvement of non-coding RNAs in gastric malignancies, highlights its context-dependent role. Emerging therapies targeting EMT include small-molecule inhibitors, natural compounds, and herbal formulations, which aim to reverse EMT markers such as E-cadherin loss and vimentin upregulation, thereby sensitizing cancers to chemotherapy. Combinatorial approaches that integrate EMT suppression with conventional treatments show promise in overcoming drug resistance. However, challenges remain in clinical translation due to the plasticity of EMT and the adaptability of cancers. Future efforts should prioritize biomarker-driven strategies, and multi-omics approaches to refine the therapeutic targeting of EMT in metastatic cancers.

Introduction

Cancer metastasis is a critical factor in determining adverse clinical outcomes in oncology, responsible for approximately 90% of cancer-related mortality. This deadly process involves the spread of neoplastic cells from primary cancers to distant organs, where secondary cancers are formed. Understanding the molecular mechanisms underlying metastatic dissemination is essential for enhancing prognostic stratification and developing innovative therapies.

Epithelial-mesenchymal transition (EMT) is a conserved developmental program that is co-opted by malignancies and has been mechanistically linked to the acquisition of motile and invasive phenotypes in cancer cells. The activation of EMT is orchestrated through hierarchical signaling networks, with the TGF-β pathway serving as a master regulator. These pathways exhibit extensive crosstalk, collectively modulating downstream effectors that govern proliferation, extracellular matrix (ECM) remodeling, and the formation of metastatic niches. Notably, EMT is reciprocally regulated by the dynamics of the tumor microenvironment (TME): cancer-associated fibroblasts (CAFs) secrete matrix metalloproteinases (MMPs) to degrade basement membranes. At the same time, immune-derived exosomes deliver EMT-inducing cytokines such as IL-6 and TGF-β. These bidirectional interactions facilitate cytoskeletal reorganization and the loss of epithelial polarity, thereby enabling transendothelial migration.

Recent pharmacological screenings have identified agents targeting EMT that demonstrate preclinical efficacy in suppressing metastatic dissemination. Small-molecule inhibitors that disrupt TGF-β/Smad signaling and natural compounds that stabilize E-cadherin expression have shown particular promise in murine models. These advances not only elucidate the context-dependent regulation of EMT but also reveal druggable targets for personalized therapeutic regimens.

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In conclusion, EMT serves as a crucial mechanism that connects primary tumorigenesis to metastatic competence. Future research should focus on single-cell resolution mapping of EMT trajectories and the development of biomarker-guided strategies to combat therapy-refractory metastases.

Biological basis of EMT in metastatic progression

EMT refers to the transformation of epithelial cells into mesenchymal cells through a series of biological processes. This transformation is characterized by alterations in cell morphology and a weakening of intercellular junctions, ultimately enhancing cell migration and invasive capacity. EMT plays a crucial role in both physiological and pathological processes, including embryonic development, tissue repair, and cancer metastasis.

There are three types of EMT based on the distinct biological contexts in which they occur. Type I EMT is associated with the formation of embryonic blastocysts, where the primitive epiblast undergoes EMT to produce primary mesenchymal cells. These cells can be reinduced to form secondary epithelial cells through mesenchymal-epithelial transition (MET), which may then further differentiate into various types of epithelial tissues. Subsequently, these cells can undergo another round of EMT to produce connective tissue cells, such as chondrocytes, osteoblasts, and muscle cells.[1,2] Type II EMT is primarily associated with wound healing, tissue regeneration, and the development of organ fibrosis. It typically produces fibroblasts and other related cells that facilitate tissue reconstruction following trauma and inflammatory injury. This type of EMT responds to inflammation over an extended period, and the response ceases when inflammation subsides. Otherwise, it will continue to express itself, ultimately leading to the destruction of its organs.[1] Type III EMT is primarily associated with the invasion and migration of cancer cells. EMT is a dynamic process in which not all cancer cells transition from a fully epithelial to a mesenchymal state during metastasis; some cells undergo complete transformation, while others remain in a transitional stage. Additionally, some cells can revert from a mesenchymal state to an epithelial state, where mesenchymal-like cells acquire apical-basal polarity, reorganize their cytoskeleton, and enhance intercellular adhesion, ultimately becoming epithelioid cells. The activation of EMT equips cancer cells with the ability to migrate, invade, and undergo endocytosis and exocytosis. After cancer cells metastasize to distant organs, their mesenchymal characteristics are restored to a more epithelial identity through MET, allowing them to regain proliferative capacity and establish secondary growth in distant sites, which facilitates cancer progression. Therefore, elucidating the mechanisms of EMT in cancer cells and developing drugs to inhibit this process is crucial for addressing cancer progression.[3]

The EMT is a dynamic and reversible process of transdifferentiation characterized by the loss of initial epithelial cell morphology features, such as tight intercellular junctions and basal-apical polarity. A gradual transition to mesenchymal cell characteristics, including the development of peg-like changes in cell morphology, follows this loss of epithelial polarity. During this process, actin stress fibers acquire a posterior-to-anterior polarity. At the same time, cell adhesion is reduced, and motility is enhanced, providing the basis for migration and invasion into surrounding tissues.[2,4] Currently, many scientists believe that EMT may not be complete in all cells; instead, cells may exist in a mixed epithelial/mesenchymal (E/M) state, exhibiting characteristics of both epithelial and mesenchymal phenotypes.[5] This ability of cells to acquire mixed E/M traits is referred to as epithelial-mesenchymal plasticity (EMP). In this process, different cells typically express varying levels of epithelial and mesenchymal markers, displaying distinct phenotypic, transcriptional, and epigenetic characteristics. Various subpopulations of cells exist in different states, with some being mixtures of E and M cells, while others are single cells in intermediate E/M states.[6] A growing body of research has demonstrated that cancer cells retaining both epithelial and mesenchymal features are more responsive to environmental signals during metastasis and can better adapt to various stresses in the microenvironment.[7,8]

Single-cell sequencing and lineage tracing currently represent the primary methodologies for investigating EMT heterogeneity. In colorectal cancer, Wang et al. analyzed the spatiotemporal distribution of the immune microenvironment during EMT and identified extensive reprogramming of immune cells at the invasive front.[9] Building on this, Yu et al. demonstrated that distinct partial EMT (pEMT) states in colorectal liver metastasis (CRLM) and colorectal peritoneal metastasis (CRPM) are orchestrated by specific niche components within the tumor microenvironment.[10] The plasticity of EMT exhibits a cancer-type-specific dependency on contextual cues from the tumor microenvironment, including biomechanical constraints, metabolic reprogramming, and inflammatory signaling. For example, the high invasiveness of triple-negative breast cancer depends on EMT-associated M2-polarized macrophages and cancer-associated fibroblasts; EMT heterogeneity in hepatocellular carcinoma is modulated by fibroblast subsets within the tumor stroma; and hypoxia has been identified as a critical driver of EMT in epithelial ovarian cancer.[11–14] Collectively, these insights provide a rationale for targeting EMT-associated processes. Accordingly, docetaxel has been investigated and validated as a promising therapeutic agent in esophageal squamous cell carcinoma. It is this epithelial-mesenchymal plasticity that enables cancer cells to oscillate between EMT and MET, leading to increased invasiveness, drug resistance, and immune evasion.[15,16] However, the regulation of EMP in cancers remains insufficiently understood and requires further investigation (Fig. 1).

At the end of the last century, researchers discovered that most non-invasive cancer cells with epithelial-like morphology express E-cadherin. In contrast, invasive cells with fibroblast-like morphology lose E-cadherin expression.[17] The absence of E-cadherin can disrupt intercellular junctions and promote intracellular signaling cascades that lead to the invasion and metastasis of cancer cells. Onder et al. demonstrated that E-cadherin is a crucial marker in EMT.[18] E-cadherin is located in the proximal fragment of the promoter within two key E-boxes.[19] This finding provided a foundational basis for the later identification of the promoter that regulates E-cadherin and EMT. Equally important to E-cadherin is N-cadherin.[20] The two are often referred to as the "calcium adhesion switch" in the context of EMT. Epithelial-mesenchymal metaplasia is frequently accompanied by a decrease in E-cadherin

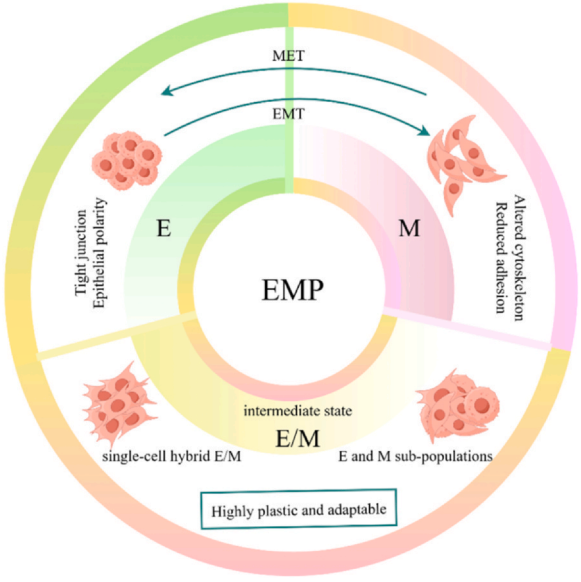


Fig. 1. During metastasis, cancer cells have epithelial-mesenchymal plasticity, meaning different cells exist in different states, which include E to M transition, EMT, and M to E transition, MET, as well as transitional states, hybrid E/M, which are further categorized into single-cells in the E/M intermediate state mixtures and E- and M-cells in the mixtures. The transition state tends to be more migratory.

expression and an increase in N-cadherin expression.[21,22] However, subsequent studies have shown that this change in cadherin expression is not always correlated with EMT.[23] Other markers indicate the occurrence of EMT in various cancers, including classical markers such as epithelial markers (ZO-1 and Occludin) and mesenchymal markers (Vimentin, an intermediate filament protein, and Fibronectin, a key component of the extracellular matrix).[24] Additionally, non-classical markers have been identified, such as Caveolin-1, may be a more suitable marker for EMT in breast cancer.[25]

Overall, EMT is characterized by a decreased expression of epithelial markers, an upregulation of mesenchymal markers, and modifications of histone proteins, as well as key EMT transcription factors, including Snail1, Snail2, Twist, and ZEB.[26] In 2020, the EMT International Association defined EMT status identification as based on changes in cellular characteristics and multiple markers rather than being limited to a single marker.[3] Therefore, when defining the occurrence of EMT in a cell, we should not only focus on morphological changes but also consider alterations in multiple markers to demonstrate the occurrence of EMT from various perspectives comprehensively.

Transcriptional networks associated with EMT in cancer

EMT, a critical pathobiological process in oncogenesis, orchestrates the invasion of malignant cells and their metastatic dissemination. Recent studies have demonstrated that understanding these molecular mechanisms is essential for uncovering the fundamental characteristics of cancer metastasis and for developing novel therapeutic strategies.

Key regulatory molecules in the EMT process

Transcription factors in EMT regulation

The Snail family of zinc finger transcription factors, which includes Snail (Snail1), Slug (Snail2), and Smuc (Snail3), exerts transcriptional repression through conserved structural motifs.[27] Mechanistically, Snail has been shown to bind to the 5′-CACCTG-3′ E-box motif located within the C-terminal domain of E-cadherin,[28] as well as to the SNAG sequence near histone deacetylase (HDAC)-interacting promoters.[29] Notably, Snail cooperatively recruits components of the Polycomb repressive complex 2 (PRC2), specifically Suz12 and Ezh2, to epigenetically silence the E-cadherin promoter in a PRC2-dependent manner.[30] Structurally distinct, Snail2 contains an additional C2H2 zinc-finger domain (ZF); functional analyses have revealed that ZF1/ZF2 mediate promoter repression in Snail, while ZF3/ZF4 are essential for Snail2's transcriptional activity.[31] Furthermore, Snail2 directly targets the occludin promoter to disrupt epithelial junctions.[32] Intriguingly, clinical correlation studies in breast cancer models have failed to establish a significant association between Snail expression and the transcriptional downregulation of E-cadherin, suggesting context-dependent compensatory mechanisms.[33] Beyond Snail1 and Snail2, the EMT transcriptional landscape exhibits significant cancer-type specificity. The research identified ZEB1 as a chromatin-level repressor of E-cadherin in breast carcinoma, directly occupying its promoter region *in vivo*.[33]

As a member of the ZEB family, which includes ZEB2, encoded by ZFHX1A and ZFHX1B,[34] ZEB1 orchestrates repression through multiple mechanisms. For instance, it engages directly with E-boxes (E-box1/E-box2), as validated in NMuMG cells,[35] recruits co-repressors,[36] and collaborates with chromatin remodeling factors.[37] Remarkably, ZEB1 dynamically modulates transcriptional complexes by interacting with PCAF/p300, converting these co-activators into repressive effectors.[34] This functional duality—context-dependent activation and repression via E-box binding—extends across EMT transcription factors. The bHLH factor Twist has emerged as a crucial regulator of EMT. In prostate cancer models, Twist1 was shown to bind to an intronic E-box (+2627 bp) in N-cadherin, with β1 integrin signaling promoting its nuclear accumulation.[38] Studies in breast cancer further revealed that Twist/SET8 mediates the epigenetic coordination of E-cadherin and N-cadherin through H4K20 monomethylation.[38] Functional validation through Twist knockdown demonstrated the upregulation of E-cadherin alongside the suppression of Fibronectin and α-SMA, while ectopic expression in LNCaP cells recapitulated EMT protein networks.[39]

These EMT-TFs function within a tightly interconnected regulatory network. Research from Cameron P. Bracken's laboratory demonstrated that ZEB1 and ZEB2 engage in a positive feedback loop, reciprocally inducing each other's expression.[40] Following the discovery that Snail activates ZEB1 expression, it was further observed that the tumor promoter TPA induces the co-recruitment of Snail and EGR1 to the ZEB1 promoter.[41] In amniotes, Esmeralda Casas et al. identified a Twist1-binding site on the Snail2 promoter, where their cooperative binding enhances the EMT program.[42] Conversely, a repressive interaction has been reported in ovarian cancer, where Snail1 recruits HDAC co-repressors to the proximal E-box of the Snail2 promoter, thereby negatively regulating its expression.[43] Similarly, Snail1 binds to the Twist1 promoter to repress its transcription in breast cancer, with their spatiotemporal coordination critically governing EMT progression. However, this regulatory mechanism appears to be cancer-type specific, as Snail1 stabilizes the Twist protein without inducing its mRNA in lung cancer, indicating a post-translational mode of regulation. These two factors exhibit a codependent relationship, further supported by Twist's ability to bind the ZEB1 promoter and modulate its expression.[44] Novel transcriptional regulators are increasingly implicated in EMT plasticity. Zpo1 suppresses β-catenin driven transcription of E-cadherin,[45] whereas FOXA1/2 counteracts Snail1-mediated repression to reactivate epithelial programs.[46] In addition, there are transcription factors such as OVOL1/2, FOXC1/2, KLF4, KLF8, SOX4, SOX9, HMGI(Y), RUNX1/2, AP-1, and FOSL1; however, the regulatory relationships among them have not been clearly elucidated in current studies (Fig. 2).[47–55]

Non-coding RNAs in EMT regulation

Non-coding RNAs (ncRNAs) play a critical role in regulating EMT. Based on transcript length, ncRNAs are broadly classified into small non-coding RNAs and long non-coding RNAs (lncRNAs). Among these, microRNAs and lncRNAs have emerged as key modulators of EMT-related molecular networks.[56]

Multiple miRNAs engage in reciprocal regulatory interactions with EMT-TFs. A well-characterized double-negative feedback loop exists between the miR-200 family and ZEB1/ZEB2, which helps maintain epithelial homeostasis and can be disrupted by TGF-β to initiate EMT.[40] Similarly, miR-1199–5p forms a reciprocal inhibitory circuit with ZEB1 to regulate EMT dynamics.[57] Additional miRNAs directly target EMT-TFs: the miR-200 and miR-1 families bind the 3′-UTR of Snail2, while the miR-203 and miR-34 families interact with Snail1 to fine-tune EMT.[58–60] In colon cancer, miR-145 expression inversely correlates with Twist1 levels and contributes to EMT regulation,[61] whereas miR-138 targets Twist2 to modulate EMT in colorectal cancer.[62] In hepatocellular carcinoma, circ_0067835 promotes Twist2-driven EMT by sequestering miR-1236–3p.[63] Beyond direct TF interactions, miRNAs also suppress key EMT-related signaling pathways. For example, miR-122 attenuates EMT in lung cancer by inhibiting both the Wnt/β-catenin and PI3K/Akt pathways.[64] Meanwhile, lncRNAs primarily influence EMT by sponging miRNAs or modulating signaling cascades.

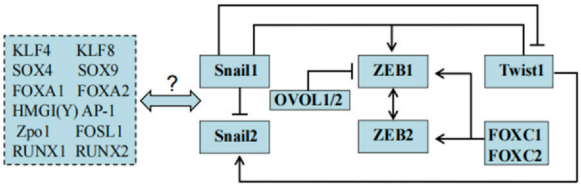


Fig. 2. EMT-TFs exhibit mutual dependence and form a regulatory network. The regulatory relationships shown on the right have been clearly defined, whereas the interactions among the transcription factors enclosed in the left box require further investigation and refinement.

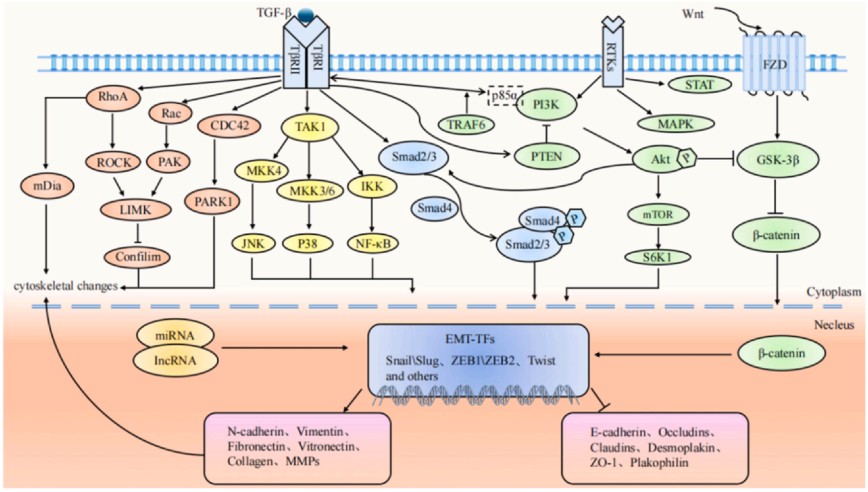


Fig. 3. EMT involves multiple signaling pathways to regulate the downstream expression of related genes by inducing EMT-TFs.

lncRNA AC010457.1 has been reported to drive EMT through activation of the PI3K/Akt pathway,[65] and AFAP1-AS1 promotes EMT in osteosarcoma via the RhoC/ROCK1/p38MAPK/Twist1 axis.[66] In gastric cancer, lncRNA MIR200CHG facilitates EMT by binding to and stabilizing miR-200c.[67]

Due to their high specificity, tissue-restricted expression patterns, and detectable presence in bodily fluids, ncRNAs represent promising biomarkers and therapeutic targets in oncology. An increasing number of clinical agents developed from ncRNA research have entered clinical trials, underscoring their potential to overcome therapy resistance and enhance cancer treatment.

Signaling pathways in EMT regulation

The TGF-β signaling pathway has been established as a principal regulator of EMT, orchestrating phenotypic plasticity through ligand-dependent activation of downstream transcriptional effectors.[68] Concurrently, the Wnt and Notch signaling pathways modulate EMT progression through distinct mechanisms facilitating intercellular communication and enhancing migratory competence, respectively. These pathways engage in dynamic crosstalk to amplify oncogenic signaling cascades in neoplastic cells.

TGF-β/Smad signaling pathway

This section delineates the canonical TGF-β/Smad2/3 axis as a paradigm for EMT regulation. TGF-β superfamily ligands transduce signals through transmembrane serine-threonine kinase receptors. Ligand-bound receptor complexes phosphorylate Smad2/3, enabling heterotrimerization with Smad4, nuclear translocation, and cooperative binding with sequence-specific transcription factors, thereby epigenetically reprogramming EMT-associated gene networks. ZEB2 has been shown to preferentially interact with Smad3 over Smad2, thereby enhancing the efficiency of transcriptional repression.[69] ZEB1 synergizes with p300 to form pro-EMT transcriptional hubs, while ZEB2 recruits CtBP to transform Smad complexes into repressive scaffolds.[70] In renal epithelial cells, TGF-β modulates ZEB1/2-driven EMT through miR-200-mediated attenuation of Smad signaling.[71] BMP-7 antagonizes TGF-β-induced expression of Twist and N-cadherin in cholangiocarcinoma, highlighting the contextual antagonism within the TGF-β superfamily.[72] Smad2 resulted in the upregulation of Snail1 expression in cutaneous EMT models, with TGF-β stimulation exacerbating this effect.[73] Functional validation confirmed that TGF-β drives Snail promoter activation via Smad2/3/4, while inhibition of the PI3K/Akt signaling pathway reduced α-SMA expression, illustrating the crosstalk between these pathways.[74]

Other related signaling pathways

Non-canonical TGF-β signaling activates Rho-GTPases (RhoA, Rac1, and CDC42), which have been identified as critical mediators of TGF-β receptor-driven cytoskeletal remodeling.[75] RhoA has been implicated in TGF-β-mediated activation of the PI3K-Akt pathway while simultaneously orchestrating p160ROCK-dependent actin stress fiber polymerization.[76] Rac1, CDC42H, and other members of the Rho-GTPase family induce cytoskeletal remodeling through the formation of lamellipodia and filopodia. They converge with EMT-associated transcription factors and the PI3K, MAPK, and NF-κB signaling pathways via multi-layered crosstalk.[77,78] Tumor necrosis factor receptor–-associated factor 6 (TRAF6) catalyzes the polyubiquitination of the PI3K regulatory subunit p85α, thereby promoting the assembly of the TGF-β type I receptor (TβRI)–p85α complex and leading to the activation of PI3K and Akt. Simultaneously, the PI3K/Akt pathway is activated through complementary signaling mechanisms.[79] Phosphorylated Akt enhances the transcriptional activity of Smads, and Smads can bind to mTOR, a downstream effector of PI3K, forming a regulatory network.[80] TGF-β downregulates PTEN expression, abolishing its inhibitory effect on the PI3K/Akt pathway and thereby indirectly amplifying the PI3K-induced EMT signal.[81] The downstream effector of PI3K/Akt signaling, mTOR, coordinates cytoskeletal reorganization and enhances migratory capacity by upregulating Snail1 expression through S6 kinase 1-mediated transcriptional control.[82] Akt-mediated phosphorylation of GSK3 disrupts β-catenin sequestration, facilitating its nuclear translocation, where it functions as a master transcriptional regulator of EMT through integration with the Wnt pathway.[83] Notch signaling is recruited to the lysyl oxidase (LOX) promoter via HIF-1α-dependent mechanisms, enhancing LOX-mediated stabilization of Snail1, while the Notch intracellular domain (ICN) directly transactivates Snail1 expression through promoter binding.[84]

In conclusion, EMT represents a complex biological process governed by intricate molecular mechanisms (Fig. 3). This process is not only crucial for driving cancer cell plasticity but also establishes the pathobiological foundation for the dissemination and metastatic growth of neoplasms. As the molecular underpinnings of EMT continue to be clarified, future research is expected to facilitate the rational design of metastasis-targeted therapeutic strategies, ultimately enhancing clinical prognostication in oncology.

Cancer microenvironmental orchestration of EMT

EMT is intricately linked to dynamic alterations within the TME, where CAFs and immunosuppressive cell populations orchestrate EMT through paracrine cytokine and exosome signaling, thereby

accelerating metastatic progression. The TME comprises a heterogeneous network of immune cells, CAFs, endothelial cells, and an ECM scaffold. Proteolytic enzymes, including MMPs secreted by neoplastic cells, remodel stromal architecture, facilitating EMT induction in neoplastic cells and amplifying their invasive phenotype. The ECM serves as a biomechanical scaffold that maintains tissue architecture and activates mechanotransduction pathways by engaging surface receptors on cancer cells, thereby inducing the transcriptional program of EMT.[85] Fibronectin and laminin, key constituents of the ECM, activate Rho-GTPase and PI3K/Akt pathways via integrin receptor ligation, thereby enhancing cancer cell migratory competence. CAFs, defined as mesenchymal stromal cells lacking vascular, epithelial, or inflammatory markers, constitute the predominant ECM-producing population through their dual roles in modulating wound healing and forming inflammatory niches.[86] In oral squamous cell carcinoma, CAF-derived small extracellular vesicles (sEVs) are enriched with surface αLOX (lysyl oxidase homolog). sEV-αLOX initiates collagen crosslinking through integrin α2β1 binding while simultaneously activating YAP, a Hippo pathway effector, to reprogram EMT transcriptionally.[87]

Additionally, cytokines within the TME exert significant regulatory control over EMT across various malignancies. IL-1β, as a pleiotropic inflammatory mediator, orchestrates PI3K/Rho-GTPase signaling to facilitate β-catenin nuclear translocation, thereby activating EMT-associated transcription factors and driving cytoskeletal reorganization.[88] Mechanistically, IL-1β-dependent ZEB1 activation in head and neck squamous cell carcinoma directly engages E-box motifs within the E-cadherin promoter to epigenetically suppress its transcription.[89] IL-6 exerts pleiotropic effects across various malignancies, including head and neck, breast, and gastric carcinomas, where STAT3 activation via the JAK-STAT3 axis triggers EMT transcriptional reprogramming.[90] Notably, IL-6 derived from pancreatic stellate cells engages in autocrine and paracrine signaling in pancreatic ductal adenocarcinoma, linking JAK-mediated STAT3 phosphorylation to NRF2-driven redox adaptation during EMT progression.[91] Counter-regulatory mechanisms are present, as demonstrated by IL-32α mediated suppression of IL-6/STAT3 signaling, which effectively inhibits EMT and metastatic dissemination in pancreatic models.[92] TNF-α synergizes with TGF-β to enhance Smad-dependent EMT transcriptional networks in colorectal and pulmonary adenocarcinomas.[93] Cytokine crosstalk is pathologically significant, exemplified by the co-signaling of IL-1β and IL-6, which drives metastatic niche formation through the convergence of the NF-κB and STAT3 pathways in colorectal carcinogenesis.[94]

Beyond inflammatory cytokines, growth factor signaling, particularly insulin-like growth factor-I (IGF-I) and its functional interplay with TGF-β homologs, has emerged as a critical modulator of EMT within the oncogenic secretome. Hyperactivation of IGF-IR in MCF-10A mammary epithelial cells induces a phenotypic switch from luminal-restricted growth to basal-like invasiveness, accompanied by an inversion of the cadherin profile (a shift from E-cadherin to N-cadherin).[95] Prostate adenocarcinoma models demonstrate that IGF-I mediates the transcriptional de-repression of ZEB1, establishing a feedforward loop that sustains EMT.[96] The convergence of the IGF-I/TGF-β1 axis in breast carcinogenesis activates PI3K-MAPK cross-talk, which enhances the phosphorylation of Smad2/3. Notably, dual kinase inhibition effectively disrupts this EMT-promoting circuitry.[97] The intracellular domain of the immunoglobulin superfamily member IGSF9 scaffolds GSK-3β/β-catenin complexes, facilitating Wnt-independent nuclear accumulation of β-catenin and subsequent LEF/TCF mediated transcriptional activation of EMT.[98] Tumor-associated macrophages (TAMs) further contribute to EMT through the secretion of paracrine effectors. In hepatocellular carcinoma, TAM-derived CCL18 engages PITPNM3 receptors, activating NF-κB-driven transcriptional networks that lead to cadherin switching and the acquisition of a mesenchymal phenotype.[99]

Hypoxia has been mechanistically linked to the induction of EMT in neoplastic cells. Notably, Lester et al. demonstrated that exposure to hypoxia triggers phenotypic switching to EMT in human breast cancer models, accompanied by hypoxia-driven overexpression of the urokinase plasminogen activator receptor (uPAR) across various malignancies. This overexpression has been shown to modulate EMT-related transcription factors by activating downstream signaling cascades, including the PI3K/Akt pathway.[100] In hepatocellular carcinoma models, hypoxic stress has been shown to promote EMT activation through HIF-1α-mediated transcriptional upregulation of Snail1, a master regulator of EMT dynamics.[101] Furthermore, hypoxic microenvironments have been demonstrated to enhance EV secretion within melanoma niches, with EV cargo containing proteins and microRNAs that modulate EMT and orchestrate mesenchymal transition programs.[102]

Accumulating evidence highlights the TME as a crucial factor influencing malignant phenotypic plasticity and metastatic capability through the dynamic regulation of EMT pathways. Future research on EMT-mediated cancer progression is anticipated to reveal more intricate mechanistic layers of metastasis, potentially guiding the development of innovative therapeutic strategies that target the microenvironmental drivers of cellular plasticity.

Characteristics of EMT in different cancer types

EMT represents a crucial biological program that drives cancer progression across various malignancies. This process endows neoplastic cells with increased invasive and metastatic potential, promoting their survival and clonal expansion within the TME. Emerging evidence highlights cancer-type-specific EMT mechanisms, revealing unique molecular signatures and regulatory networks that enhance our understanding of metastatic dissemination.

Breast cancer

Breast carcinoma, the most prevalent malignancy among women worldwide, is increasingly affecting younger populations. A cohort study focusing on early-stage breast cancer in Asian populations revealed that younger patients experience poorer survival outcomes compared to their middle-aged counterparts, with TME dynamics contributing to this disparity.[103] Recent advancements in EMT research have expanded beyond traditional pathway interactions to include hormonal signaling and microenvironmental reprogramming. Estrogen receptor (ER) isoforms have opposing effects: ERα preserves epithelial integrity and inhibits mesenchymal transformation, while ERβ promotes EMT-mediated metastatic potential. Bouris et al. demonstrated that the depletion of ERα in MCF-7 cells induces cadherin switching (downregulation of E-cadherin and upregulation of vimentin and fibronectin), activates EMT transcription factors (ZEB1 and Snail2), and triggers spindle-shaped morphological changes through the activation of the EGFR-ERK pathway, collectively enhancing invasiveness.[104] In a study, the inhibition of ERβ in highly invasive ERβ-positive breast cancer cells, specifically MDA-MB-231, was found to impact EMT markers through the EGFR/IGF-IR and JAK/STAT signaling pathways. This inhibition also resulted in a reduction in cell proliferation, migration, and invasion.[105] Triple Negative Breast Cancer (TNBC) is a subtype of breast cancer that lacks ER, progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2). Its prognosis is poor compared to other breast cancer subtypes, primarily due to its aggressive nature. TNBC has been shown to affect EMT-related markers such as E-cadherin and Vimentin.[106] Furthermore, microRNAs in breast cancer cells are closely associated with EMT; for instance, miR-340 inhibits EMT in human breast cancer cells by targeting ZEB1.[107]

Lung cancer

Non-Small Cell Lung Cancer (NSCLC) progression is critically influenced by the dynamics of EMT. The TGF-β pathway has been identified as a primary driver of EMT. At the same time, novel regulators, such as the Rho-GTPase family member RhoJ, have been shown to

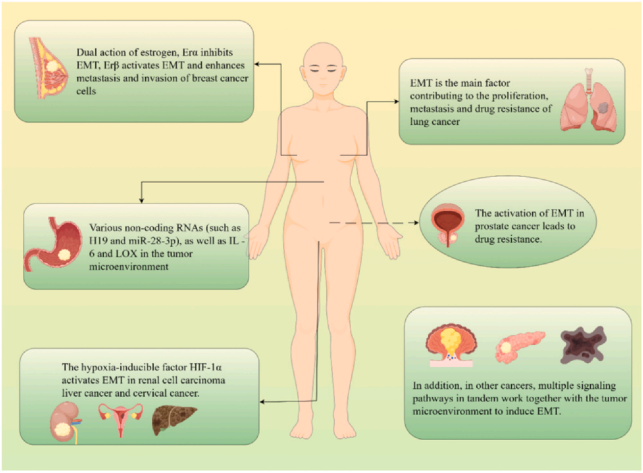


Fig. 4. EMT exhibits unique features and mechanisms in different types of cancers.

exhibit prognostic significance. Nozaki et al. reported that the downregulation of RhoJ in aggressive NSCLC correlates with EMT suppression through TGF-β/Smad inhibition, revealing its role in restraining metastasis.[108] Environmental cofactors, such as PM2.5 particulate matter, exacerbate EMT by activating the TGF-β/Smad pathway.[109] Beyond canonical pathways, the downregulation of Twist2 in NSCLC has been shown to reverse the expression of mesenchymal markers, including N-cadherin, vimentin, and Snail2. Additionally, FGF21-mediated inhibition of the AMPK/mTOR pathway promotes the suppression of Twist2 and induces EMT.[110] It is important to note that EMT is closely associated with drug resistance in lung cancer, which significantly impacts patient prognosis. Recent studies have reported that CLDN1, which is highly expressed in NSCLC and serves as a specific intracellular marker, upregulates the expression of IL-6 and TGF-β1, thereby inducing EMT and reducing susceptibility to doxorubicin.[111] Furthermore, earlier research has demonstrated that miR-451a mediates EMT in lung adenocarcinoma cells, contributing to the suppression of doxorubicin resistance in lung cancer cells.[112]

Gastric cancer

Phenotypic alterations characteristic of EMT have been extensively documented in gastric carcinoma cells. This pathophysiological process not only induces the disintegration of intercellular junctions but is also associated with transcriptomic reprogramming, thereby conferring enhanced metastatic potential to neoplastic cells. These phenomena have been mechanistically linked to elevated concentrations of TGF-β and other pro-inflammatory mediators within the TME. Notably, CAFs in gastric neoplasms demonstrate a robust secretory capacity for IL-6 and LOX. Empirical evidence confirms that IL-6 activates the JAK2/STAT3 axis to potentiate EMT progression, while RhoJ modulates cytoskeletal dynamics and has been shown to co-opt IL-6/STAT3 signaling to facilitate both cancer invasion and chemoresistance in gastric malignancies.[113,114] Concurrently, LOX has been validated to orchestrate EMT predominantly via TGF-β/Smad pathway activation, with emerging evidence revealing IGF-mediated synergistic modulation of EMT through crosstalk with TGF-β signaling.[115] Beyond TGF-β signaling, the PI3K/Akt cascade emerges as a critical regulator of EMT in gastric carcinogenesis, with multiple oncoproteins, including FBXO11, CRISPLD1, WIPF1, and ARHGAP9, demonstrated to coordinate EMT through dysregulation of the PI3K/Akt/mTOR axis.[116,117] Non-coding RNA species have garnered significant research attention in the pathobiology of gastric cancer. Long non-coding RNAs, such as MIR4435–2HG and H19, drive EMT via activation of the Wnt/β-catenin pathway,[118,119] while the lncRNA AC010457.1 and miR-140–5p exert analogous EMT-promoting effects through stimulation of the PI3K/Akt pathway.[120] Notably, certain microRNAs exhibit cancer suppressive functions, as exemplified by miR-28–3p-mediated inhibition of both cancer progression and Hedgehog signaling-dependent EMT through modulation of ARF6.[121]

Other types of cancer

In malignancies such as colorectal adenocarcinoma, pancreatic ductal adenocarcinoma, and hepatocellular carcinoma, EMT has been established as a crucial mechanism underlying the dissemination of neoplasms. This process involves multiple signaling pathways that synergistically interact with components of the TME to drive the progression of EMT. In renal cell carcinoma, loss-of-function mutations in the VHL gene, a tumor suppressor, result in impaired negative regulation of hypoxia-inducible factor-1α (HIF-1α). As a result, VHL-deficient RCC4 cells exhibit sustained overexpression of HIF-1α, which transcriptionally activates Snail1 and ZEB2, suppressing E-cadherin expression and thereby initiating EMT.[122] Cervical squamous cell carcinoma exhibits a complex regulation of EMT involving the Notch1-mediated activation of the PI3K pathway, IL-6-driven phosphorylation of STAT3, and hypoxia-induced overexpression of LOX.[123] Notably, Cui et al. showed that miR-155 enhances cisplatin sensitivity during EGF-triggered EMT in cervical carcinoma models.[124] Of particular interest, metastatic melanoma exhibits non-canonical EMT-like reprogramming, where oncogenic B-RAF mutations co-opt PI3K/Akt and NF-κB signaling pathways to promote the acquisition of mesenchymal-associated markers and pro-metastatic phenotypes, despite lacking an epithelial origin.[125] In prostate adenocarcinoma, therapeutic challenges arising from aggressive metastasis and chemoresistance have been mechanistically linked to dynamic EMT-MET plasticity.[126,127] Across these malignancies, EMT is associated with increased cancer aggressiveness, treatment resistance, and metastatic dissemination, suggesting that EMT-associated hallmarks are evolutionarily conserved in solid cancer.

In conclusion, EMT represents a pan-cancer phenomenon characterized by context-dependent mechanistic diversity (Fig. 4). These cancer-type-specific regulatory networks dictate not only malignant progression but also reveal novel therapeutic vulnerabilities, thereby informing the discovery of diagnostic biomarkers, precision treatment paradigms, and prognostic stratification frameworks.

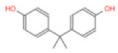
EMT targeted therapy in cancers

EMT represents a crucial pathobiological mechanism that orchestrates tumorigenesis and metastatic dissemination. Recent advances in understanding the molecular mechanisms that regulate EMT have revealed novel therapeutic opportunities across various malignancies.[128] These regulatory molecules can be categorized into EMT-inducing agents and EMT-suppressing compounds, with their therapeutic potential being progressively defined based on specific cancer types.

EMT activators and applications

Pro-inflammatory cytokines, such as TGF-β, EGF, and IL-6, enhance EMT through the activation of complex signaling networks. Notably, the H. pylori-derived Tipα oncoprotein has been shown to drive gastric carcinoma EMT via stimulation of the IL-6/STAT3 axis.[129] These secreted mediators, along with metabolically generated reactive oxygen species (ROS), collectively create a pro-EMT TME. Additionally, xenobiotic compounds exert EMT-promoting effects through the reprogramming of the microenvironment and the modulation of core pathways. For instance, cobalt chloride ($CoCl_2$) induces EMT in both MCF-7 and MDA-MB-231 breast cancer models, as well as in hepatocellular carcinoma systems.[130] Of particular concern, nicotine, a principal constituent of tobacco, was shown by Du et al. to downregulate miR-99b and miR-192 in NSCLC, thereby derepressing FGFR3 and RB1

Table 1
EMT-related activator in cancer cells.

Category	Activator	Molecular mechanisms related to EMT	EMT activate/inhibit	Chemical structures	Cancer types
Biological Factors	Tipα	IL-6/STAT3	activate	N/A	GC
Synthetic compounds	$CoCl_2$	HIF-α/Snail; MMP2; MMP9	activate		BRCA; HCC
	Nicotine	miR-99b/FGFR3; miR-192/RB1	activate		LC
	Plasticizer-phthalate	β-catenin/Akt/GSK3	activate		HMECs
	BPA	Slug	activate		BRCA
	Bap	p21	activate		LC
	Cd	TGF-β	activate	Cd	BRCA
	SWCNT	Slug	activate	N/A	LC

targets, which facilitates pulmonary EMT.[131] Phthalate esters mediate the overexpression of HDAC6 via the ER/EGFR/PKA/AP-2α signaling pathway, culminating in the nuclear translocation of β-catenin through Akt/GSK-3β-dependent transcriptional regulation.[132] Environmental carcinogens, including bisphenol A (BPA), benzo(a)pyrene (Bap), and cadmium (Cd), demonstrate the induction of pan-cancer EMT in mammary, pulmonary, vascular, and gastrointestinal malignancies.[133,134] Furthermore, chronic exposure to single-walled carbon nanotubes (SWCNTs) has been correlated with Snail2-mediated EMT activation in pulmonary neoplasms.[135] Despite the transient cancer-suppressive effects of specific EMT activators, chronic administration may paradoxically lead to chemoresistance and disease recurrence (Table 1).

EMT inhibitors and applications

Contrastingly, EMT inhibitors represent a novel therapeutic paradigm for reducing neoplastic invasiveness. Current investigational agents include small-molecule compounds, monoclonal antibodies, and phytochemical derivatives that target key EMT regulators, such as transcription factors and signaling mediators. Clinically validated inhibitors with demonstrated anti-metastatic efficacy are systematically cataloged; for instance, the N-cadherin antagonist ADH-1 has shown potent anti-neoplastic effects in gynecologic malignancies.[136] Mechanistic studies have revealed that the small-molecule compound CYD19 disrupts CBP/p300-mediated Snail acetylation through direct binding, thereby inhibiting Snail-driven EMT in carcinoma models.[137] The repurposed antiplatelet agent ticagrelor suppresses glioma EMT through dual inhibition of the PI3K-Akt/NF-κB signaling pathway and downregulation of GTSE1, effectively reducing cancer proliferation and invasive capacity.[138] The selective estrogen receptor modulator tamoxifen (TAM) reverses EMT in mammary and cervical carcinomas by epigenetically modulating miR-200 promoters and reprogramming EMT markers.[139] Innovative applications of nanotechnology demonstrate that Hypnea valentiae-functionalized gold nanoparticles reduce vimentin expression in glioma EMT cascades, significantly impairing cancer progression[140] (Table 2).

Scientific research has increasingly focused on pharmacologically active botanical constituents with EMT suppressive properties. Curcumin demonstrates multi-modal EMT inhibition across pulmonary, thyroid, and pancreatic malignancies by concertedly modulating the TGF-β/Smad, PI3K/Akt, and Hedgehog signaling pathways.[141] In

Table 2
EMT-related synthetic compounds inhibitor in cancer cells.

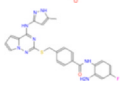
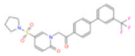
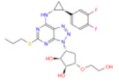
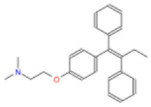
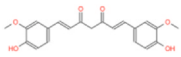
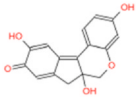
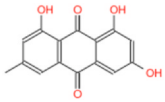
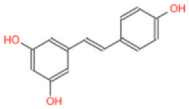
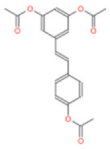
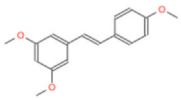
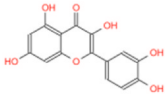
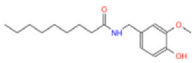
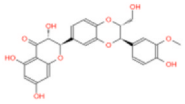
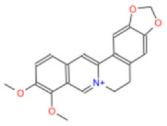
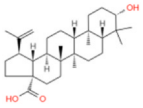
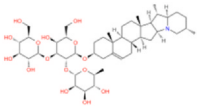
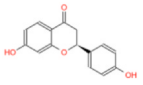
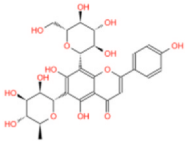
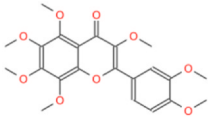
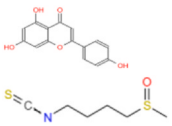
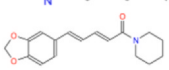
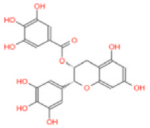
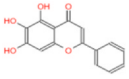
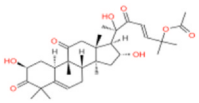
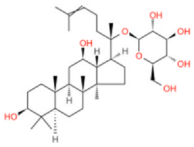
Inhibitor	Molecular mechanisms related to EMT	EMT activate/inhibit	Chemical structures	Cancer types
ADH-1	N-cadherin	inhibit		BRCA; CC
CYD19	Snail	inhibit		BRCA; CRC
ML210	Oxidation of membrane lipids	inhibit;Overcome GEM resistance	N/A	PC
TBOPP	DOCK1 Inhibitor (Twist)	inhibit;Overcome CDDP resistance		BRCA
Ticagrelor	PI3K-Akt/NF-κB	inhibit		GLM
TAM	miR-200	inhibit		BRCA; CC
Hypnea valentiae seaweed loaded gold nanoparticles	Vimentin	inhibit	N/A	LC

Table 3
EMT-related natural products inhibitor in cancer cells.

Inhibitor	Molecular mechanisms related to EMT	EMT activate/inhibit	Chemical structures	Cancer types
Curcumin	TGF-β/Smad; PI3K/Akt;Hedgehog; NF-κB;HDGF/β-catenin	inhibit; Overcome L-OHP resistance		LC; HCC; BRC; PC; HNSCC; TC; GLM
Brazilein	GSK-3β/β-catenin; PI3K/Akt; MMP-2	inhibit		BRCA
Emodin	TGF-β; ZEB1; Twist1; GSK-3β/β-catenin	inhibit		BRCA; OV; HNSCC
Resveratrol	TGF-β; PTEN/Akt	inhibit; Overcome Dox resistance		LC; CRC; BRCA; GLM
TCRV		inhibit		PC
3;5;4′-Trimethoxystilbene		inhibit		BRCA
Quercetin	Akt; STAT3; MMPs; TGF-β/Smad; EMT-TFs (Snail; Twist)	inhibit; Synergistic inhibition by 2-ME		CRC; LC; PRAD; GC; PC; OC
COE	HIF-1α/Twist1	inhibit	N/A	HCC
CAP	TGF-β/Smad4; AMPK/mTOR; Autophagy	inhibit		GC; RCC
Silibinin	TGF-β; Wnt/β-catenin;Autophagy	inhibit		BC; RCC
Berberine	TGF-β	inhibit		PC; BRCA
Betulinic acid	TGF-β	inhibit		GC; PC
α-solanine	PI3K/Akt; ERK	inhibit		PRAD
LQ	ER stress; PI3K/Akt	inhibit		PRAD; CRC
Isoviolanthin	TGF-β/Smad; PI3K/Akt	inhibit		HCC
AC	Wnt/β-catenin	inhibit	N/A	CRC; BRCA
HMF	Oxidative stress; Autophagy; TGF-β	inhibit		LC
HRC	PI3K/Akt/mTOR	inhibit	N/A	BRCA
Apigenin	NF-κB/Snail; IL-6	inhibit		CRC; HCC; BRCA

(*continued on next page*)

Table 3 (*continued*)

Inhibitor	Molecular mechanisms related to EMT	EMT activate/inhibit	Chemical structures	Cancer types
SFN	miR-200c/ZEB1	inhibit		BC
Piperine	TGF-β; STAT3/Snail	inhibit		HCC; LD; CRC
HJJ_3_5	E-cadherin; N-cadherin; Vimentin	inhibit	N/A	CRC
EGCG	TGF-β; Vimentin; MMP2	inhibit		LC; CC; OC
Black tea polyphenols	Vimentin; MMP3	inhibit	N/A	OC
Rubus idaeus L.	FAK/Snail; ERK1/2/MMP2/u-PA	inhibit	N/A	LC
Saponins of *patrinia villosa*	NF-κB	inhibit	N/A	CRC
Baicalein	PI3K/Akt; NF-κB	inhibit; Overcome GEF resistance		LC
CuB	PI3K/Akt/mTOR; TGF-β	inhibit; Overcome CDDP resistance		LC
Ginsenoside CK	PI3K/Akt	inhibit; Overcome L-OHP resistance		GC

colorectal carcinoma models, it overcomes oxaliplatin resistance by suppressing the TGF-β/Smad2/3 axis and reversing EMT.[142] Mechanistic investigations further elucidate its NF-κB-mediated suppression of microenvironment-driven EMT in mammary, head and neck squamous cell and hepatic neoplasms.[143] Notably, curcumin disrupts the interactions between HDGF and β-catenin, thereby mitigating glioma invasiveness.[144] Phytochemical derivatives exhibit distinct mechanisms for targeting EMT. Brazilein, an extract from Caesalpinia sappan, modulates the GSK-3β/β-catenin and PI3K/Akt signaling pathways to downregulate MMP-2 in mammary EMT.[145] Emodin, a constituent of tiger nut, inhibits the TGF-β1/GSK-3β/β-catenin axis, thereby blocking the ZEB1/Twist1 mediated suppression of E-cadherin.[146] Resveratrol reprograms TGF-β-induced EMT through the activation of the PTEN/Akt pathway while also sensitizing various malignancies to doxorubicin.[147,148] Mechanistically, resveratrol exerts dual regulatory effects by upregulating PTEN, which suppresses the Akt pathway and enhances chemosensitivity to doxorubicin.[149] The compound's efficacy in inhibiting EMT demonstrates context-dependent pathway activation across different malignancy subtypes.[150] Structurally modified derivatives, including triacetyl resveratrol (TCRV) and 3,5,4′-trimethoxystilbene, exhibit enhanced EMT-suppressive potency in models of pancreatic and mammary carcinoma.[151] Quercetin orchestrates a multimodal blockade of EMT through the inhibition of core pathways, including the Akt/STAT3/TGF-β/Smad axes, downregulation of transcriptional regulators such as Snail and Twist, and remodeling of the ECM via the regulation of adhesion molecules.[152,153] The synergistic enhancement of its therapeutic index is achieved when combined with 2-methoxy estradiol (2-ME).[154] Botanical-derived agents exhibit a variety of mechanisms targeting EMT, including *Celastrus orbiculatus* Thunb. Extract (COE),[155] capsaicin (CAP),[156] silibinin,[157] berberine, betulinic acid,[158,159] Liquiritigenin (LQ), α-solanine,[160] Isoviolanthin (Dendrobium officinale extract),[161] Antrodia camphorate (AC),[162] HMF (Breynia fruticosa),[163] Hypericum roeperianum extract (HRC),[164] apigenin,[165] sulforaphane (SFN),[166] epigallocatechin gallate (EGCG),[167] Black tea polyphenols,[168] phytoconstituents from Rubus idaeus (Rubus idaeus L.),[169] saponins of Patrinia villosa,[170] piperine,[171,172] and the novel piperine derivative HJJ_3_5.[173] These phytochemicals collectively inhibit oncogenic EMT by interfering with molecular pathways, thereby establishing a botanical arsenal for interventions that suppress metastasis (Table 3).

Chinese herbal remedies, including Gancao Xiexin Decoction (GCXXD, derived from the Treatise on Typhoid Fever pharmacopeia and comprising six medicinal constituents),[174] Wensheng Zhuanggu Formula (WSZG, a postoperative adjuvant regimen for osseous metastases resulting from breast cancer),[175] and Xihuang Pill (XHP, which contains Bos taurus gallbladder calculus as the primary active component with established on therapeutic applications),[176] have been shown to inhibit the TGF-β/Smad signaling axis, thereby reducing EMT in cancer cells (Table 4).

These findings collectively establish EMT inhibitors as promising therapeutic modalities in oncology, particularly for intercepting metastasis during the progression of neoplasms.

EMT and cancer drug resistance

Despite the therapeutic potential of EMT targeting agents, significant translational challenges remain. First, the inherent spatiotemporal heterogeneity of EMT across various malignancies limits the broad applicability of EMT-directed therapies. Second, the modulation of EMT may trigger compensatory activation of parallel survival pathways, which could lead to the emergence of novel drug-resistant phenotypes. Therefore, the rational design of polypharmacological regimens that co-target EMT coregulators is expected to be effective in reducing metastatic progression and overcoming therapeutic resistance.

Notable preclinical evidence supports this paradigm. The GPX4 inhibitor ML210 synergistically reverses gemcitabine resistance in

Table 4
EMT-related Chinese medicine formula inhibitor in cancer cells.

Drug name	Molecular mechanisms related to EMT	EMT activate/ inhibit	Chemical structures	Cancer types
GCXXD	TGF-β/Smad	inhibit	N/A	GC
WSZG	TGF-β/Smad	inhibit	N/A	BRCA
XHP	TGF-β/Smad	inhibit	N/A	BRCA

pancreatic ductal adenocarcinoma by simultaneously blocking EMT in PDAC cells and enhancing ferroptosis.[177]

DOCK1 through TBOPP not only inhibits EMT in mammary carcinoma but also increases chemosensitivity to cisplatin by enhancing apoptosis mediated by cytoskeletal remodeling.[178]

Baicalein-mediated modulation of the NF-κB/PI3K/Akt axis induces MET in NSCLC, providing a biochemical rationale for platinum resensitization.[179]

Cucurbitacin B (CuB) orchestrates redox homeostasis to disrupt TGF-β1-driven EMT in NSCLC while simultaneously overcoming resistance to tyrosine kinase inhibitors through the reprogramming of the PI3K/Akt/mTOR signaling pathway.[180]

Ginsenoside CK's effects on suppressing EMT in gastric adenocarcinoma are associated with the enhancement of oxaliplatin response, mediated by the downregulation of drug efflux transporters through the PI3K/Akt signaling pathway.[181]

These collective findings underscore the transformative potential of EMT pharmacomodulation in precision oncology. Although current limitations necessitate rigorous mechanistic investigation, a systems-level dissection of EMT plasticity networks may catalyze paradigm-shifting therapeutic innovations.

Conclusion and discussion

While the molecular mechanisms underlying EMT have been systematically elucidated, the regulatory dynamics between pathways within this complex process require thorough delineation. Although numerous pharmacotherapeutics targeting EMT have entered preclinical development, therapeutic resistance associated with EMT modulation remains a significant translational bottleneck, exacerbated by suboptimal rational polypharmacology strategies. Consequently, the development of EMT-centric anticancer agents holds considerable translational potential in contemporary oncology.

Given the dual role of EMT in orchestrating metastatic dissemination and the evolution of chemoresistance, pharmacological modulation of EMT-associated signaling pathways may synergistically enhance the therapeutic index while reducing metastatic potential, a factor critically linked to oncological outcomes. Future research should prioritize the development of precision combinatorial regimens targeting EMT to address cancer heterogeneity and acquired resistance. These strategies should be integrated with conventional surgical interventions, immunooncology platforms, and radiotherapeutic approaches to establish a comprehensive multimodal therapeutic framework.

The systematic execution of biomarker-driven clinical trials will empirically validate these innovative paradigms and facilitate the implementation of cancer-type-specific therapeutic algorithms. Ultimately, ongoing exploration of the pleiotropic roles of EMT in neoplastic ecosystems will drive the development of mechanistically advanced antineoplastic agents.

Declarations

Not applicable.

CRediT authorship contribution statement

guo shuai: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Yinuo Liu:** Writing – review & editing, Writing – original draft, Software, Investigation, Data curation, Conceptualization. **Zhouye Ma:** Investigation. **Yue Chen:** Investigation. **Yuwei Cui:** Investigation. **Haifu Wan:** Investigation. **Xuzhao Wang:** Writing – review & editing, Conceptualization. **Xianjiang Kang:** Writing – review & editing, Conceptualization.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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Authors' other information

Not applicable.

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