Pancreatic cancer EMT-targeted therapy: Molecular mechanisms and clinical translation (Review)

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Abstract. Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, with a dismal 5-year survival rate of ~9%, primarily due to late diagnosis, aggressive metastasis and profound resistance to conventional therapies. Epithelial-mesenchymal transition (EMT) has been identified as a pivotal driver of these malignant phenotypes, facilitating early invasion, dissemination and treatment failure. The present review systematically elaborated on the multidimensional mechanisms underlying EMT in PDAC, emphasizing its operation as a spectrum of hybrid epithelial/mesenchymal states rather than a binary switch. Key molecular mechanisms include the activation of core transcription factors (such as Snail, ZEB, Twist), intricate crosstalk within the tumor microenvironment (such as transforming growth factor-β and hepatocyte growth factor signaling from stromal cells) and dynamic epigenetic reprogramming. Furthermore, EMT critically contributes to the acquisition of cancer stem cell properties and enhances the survival and colonization of circulating tumor cells. The present review also outlined emerging translational strategies targeting EMT-related pathways, highlighting agents such as STNM01 that have entered early-phase clinical trials. By synthesizing unprecedented insights into EMT's plastic spectrum states and subtype-specific regulatory networks, this work establishes a paradigm-shifting framework for advancing EMT-targeted therapies; offering transformative potential to overcome PDAC's historical therapeutic barriers and substantially improve patient survival outcomes. By synthesizing current insights from molecular pathways to therapeutic applications, the present review confirmed EMT as a promising therapeutic target and provides a strategic framework for advancing PDAC treatment, with the ultimate goal of improving clinical outcomes.

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Abbreviations: ADM, acinar-ductal metaplasia; CAFs, cancer-associated fibroblasts; CDH2, n-cadherin; CHST15, carbohydrate sulfotransferase 15; circRNAs, circular RNAs; CSC, cancer stem cell; CSCs, cancer stem cells; CTCs, circulating tumor cells; DKK3, Dickkopf-related protein 3; DNMTs, DNA methyltransferases; ECM, extracellular matrix; EGCG, epigallocatechin-3-gallate; EMT, epithelial-mesenchymal transition; EMT-TFs, EMT transcription factors; FAK, focal adhesion kinase; Gas6, growth arrest-specific protein 6; HDACs, histone deacetylases; HGF, hepatocyte growth factor; ICIs, immune checkpoint inhibitors; LIF, leukemia inhibitory factor; MET, mesenchymal-epithelial transition; MMPs, matrix metalloproteinases; myCAFs, myofibroblastic CAFs; PanINs, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; PDGF, platelet-derived growth factor; PSCs, pancreatic stellate cells; TCRV, triacetyl resveratrol; TGF-β, transforming growth factor-β; TME, tumor microenvironment

Key words: epithelial-mesenchymal transition, pancreatic ductal adenocarcinoma, molecular signaling pathways, targeted therapy, clinical translation

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1. Introduction

Pancreatic cancer stands among the leading causes of cancer-related mortality globally, with its incidence having

more than doubled over the past 25 years. Predominant in regions such as North America, Europe and Australia, pancreatic cancer accounts for over 90% of cases classified as pancreatic ductal adenocarcinomas, which exhibit an extremely poor prognosis; boasting an overall 5-year survival rate of merely ~9% (1). This dismal outcome is largely attributed to late-stage diagnosis and resistance to current therapies, underscoring the urgent need to unravel the underlying mechanisms driving disease progression.

A key biological process implicated in pancreatic cancer pathogenesis is the epithelial-mesenchymal transition (EMT), whereby epithelial cells lose characteristic features such as polarity and tight junctions, while acquiring mesenchymal traits including spindle-shaped morphology and enhanced migratory capacity. This dynamic shift occurs along a spectrum of intermediate states rather than as an abrupt switch and plays a pivotal role in embryonic development, fibrotic disorders and tumor progression (2). Functionally, EMT is categorized into three subtypes: Type 1, involved in embryogenesis and organ development without pathological consequences; Type 2, driven by inflammatory injury and contributing to tissue fibrosis; and Type 3, which occurs in neoplastic cells and directly facilitates cancer invasion and metastasis (3).

The aggressive biology of pancreatic cancer, characterized by early invasion, metastasis and chemoresistance, stems partly from such EMT-mediated processes, which contribute to its notoriously late diagnosis and dismal prognosis (4). Established risk factors (including smoking, obesity, diabetes and genetic mutations such as BRCA2) exert their pathogenic effects through pathways such as chronic inflammation and metabolic disorders, which in turn drive EMT activation (4). Notably, modifiable risk factors account for 65.6% of cases in patients aged ≤60 years, markedly higher than the 17.2% in older cohorts (5). This disparity highlights the potential of targeting EMT pathways regulated by these modifiable factors for early intervention, thereby providing a strategy to address the 'advanced-stage diagnosis' dilemma that plagues pancreatic cancer management.

The present review systematically elaborates on the molecular mechanisms governing EMT in pancreatic cancer, dissect targeted therapeutic strategies and discuss challenges in clinical translation. By synthesizing these insights, it aimed to provide a theoretical framework for the development of novel therapeutic regimens.

2. Multidimensional mechanisms of EMT driving the malignant phenotype of pancreatic cancer

EMT is a dynamic and reversible cellular process that plays a central role in driving the unique pathophysiology of pancreatic ductal adenocarcinoma (PDAC). Mutant Kirsten rat sarcoma virus oncogene homologue (KRAS), an oncogenic driver, serves as central driving force in pancreatic ductal adenocarcinoma. Its sustained signaling propels crucial malignant programs, including EMT, via downstream pathways such as MAPK and PI3K. Specifically, it upregulates transcription factors such as Snail and ZEB and synergizes with signals such as transforming growth factor-β (TGF-β) to suppress epithelial markers and promote a mesenchymal phenotype, thereby endowing cancer cells with invasive and metastatic capabilities (6). Unlike a number of other solid tumors, PDAC is characterized by an extremely dense desmoplastic reaction; a microenvironment rich in extracellular matrix (ECM) and stromal cells. This microenvironment not only acts as a physical barrier to tumor progression but also serves as a key signaling hub for inducing and maintaining EMT (7). In PDAC, EMT does not involve a simple binary switch between epithelial and mesenchymal phenotypes; instead, it is a continuous process encompassing multiple stable intermediate states (that is, partial EMT or hybrid E/M states), in which cells co-express both epithelial and mesenchymal markers. This phenotypic plasticity is critical to the malignant behavior of PDAC, endowing cancer cells with advantages in invasion, metastasis and tumor initiation (8). These effects are triggered by TME-derived signals [such as TGF-β and hepatocyte growth factor (HGF)], which activate a regulatory cascade involving EMT transcription factors (EMT-TFs) such as Snail and ZEB1: On one hand, enhancing cytoskeletal remodeling and matrix degradation to promote invasion and metastasis; on the other hand, activating stem cell signaling pathways (such as Notch and Wnt) and upregulating drug resistance-related molecules [such as ATP-Binding Cassette Subfamily G Member 2 (ABCG2)] to confer stemness and treatment resistance. Collectively, these processes systematically drive the malignant progression of PDAC (9,10). At the molecular level, TGF-β in the TME activates transcription factors of the Snail and ZEB families via Sma and MAD homologs (SMAD)-dependent and non-SMAD pathways [such as phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK)], while HGF induces the expression of factors such as Slug via extracellular signal-regulated kinase (ERK) signaling mediated by the c-mesenchymal-epithelial transition (MET) receptor. These core EMT-TFs [Snail, Slug, Zinc finger E-box-binding homeobox 1 (ZEB1/2), Twist] synergistically suppress epithelial markers (such as E-cadherin and Claudins) and activate mesenchymal molecules (such as Vimentin and N-cadherin), driving plastic phenotypic transitions in cells (2,11). By remodeling cell identity, these transcription factors enable PDAC cells to detach from the original ductal structure, invade the dense stroma, enter the circulatory system and form lethal metastatic lesions in distant organs (12,13).

Core programs of EMT-regulated invasion and metastasis. The most lethal feature of PDAC is the early onset of invasion and metastasis; even at the pre-cancerous pancreatic intraepithelial neoplasia (PanIN) stage, TME-derived signals such as TGF-β and HGF can induce EMT. EMT drives cells to detach from ductal structures, degrade the dense stroma and enter the circulatory system, initiating the metastatic cascade and serving as the core engine of this multi-step process (14). In this process, EMT not only reshapes the cellular phenotype in response to TME signals but also endows cells with migratory and invasive capabilities, laying the foundation for the early metastasis of PDAC (14). Ultimately, EMT provides PDAC cells (originally adherent to ductal structures) with a complete toolkit to break free from constraints and cross the dense stromal barrier unique to PDAC.

Disruption of cell adhesion and acquisition of motility. A classic hallmark of EMT is the downregulation or loss of function of E-cadherin, a core component of adherens junctions

between epithelial cells that maintains junction stability through binding to p120. The loss of E-cadherin disrupts intercellular junctions in pancreatic ductal epithelial cells, relieves inhibition of Rho family GTPases and enables cells to acquire individualistic characteristics and detach from the primary tumor, representing the critical first step in initiating metastasis (15). In PDAC, EMT-TFs (particularly SNAIL1 and ZEB1) activated by TME factors such as TGF-β can directly bind to the promoter of the CDH1 gene (which encodes E-cadherin). By recruiting epigenetic modification complexes [such as histone deacetylases (HDACs) and DNA methyltransferases (DNMTs)], these TFs strongly and stably repress CDH1 transcription (16,17). This breakage of the adhesion chain allows cancer cells to escape from the primary tumor mass, creating a prerequisite for invasion (18). Concurrently, EMT is often accompanied by cadherin switching: While inhibiting CDH1 expression, EMT-TFs upregulate N-cadherin (CDH2) expression, thereby achieving functional substitution between the two cadherins. This switch is not a simple replacement of expression patterns but rather remodels cell adhesion properties; shifting from E-cadherin-mediated homophilic adhesion between epithelial cells to N-cadherin-mediated heterophilic adhesion with stromal cells [such as cancer-associated fibroblasts (CAFs)] and activating the α-ctenin/vinculin-FAK/Src signaling pathway to enhance directed adhesion strength. laying the molecular foundation for subsequent interactions with stromal cells (19). In the PDAC TME, CAFs highly express N-cadherin, which forms mechanically active heterotypic adhesions with residual E-cadherin on the surface of EMT-experienced cancer cells. Through α-catenin/vinculin-mediated force transmission, this interaction activates the focal adhesion kinase (FAK)/Src signaling pathway to enhance directed migration. Meanwhile, this stable interaction provides mechanical support and survival signals for cancer cells to traverse the dense stroma, helping them adapt to TME stress (20).

Alongside changes in cell adhesion patterns, EMT drives cytoskeletal remodeling to meet migratory demands via a TGF-β-mediated alternative splicing regulatory network: alternative splicing variants of genes such as ARHGEF11 and CTTN activate Rho family GTPase signaling, prompting the reorganization of actin from a cortical network (which maintains polarity) into stress fibers that traverse the cell. This structural transition provides the mechanical basis for directed cell movement (21). These stress fibers anchor to the ECM via integrin-mediated focal adhesions and myosin contraction generates an intracellular tension gradient. This gradient, in coordination with traction forces transmitted by integrin-focal adhesions, enables cells to overcome the resistance of the dense stroma. The precise regulation of polarized reorganization of the actin cytoskeleton and dynamic balance of focal adhesions ultimately achieves morphological adaptation to the mesenchymal-like migration mode (22). Among Rho family GTPases (key molecules regulating cell functions), RhoA and Rac1 show opposite activity changes during EMT: Rac1 activity increases markedly, while RhoA activity decreases. These two enzymes regulate the contractility and stiffness of the actin cortex (a structure maintaining cell shape) with the cell cycle; in the interphase (when cells do not divide), they reduce cortical tension to adapt to shape changes caused by the environment; in mitosis (when cells divide), they enhance cortical mechanical strength to support cell shape adjustment. This regulation enables the mechanical transition of the cytoskeleton to accurately match EMT-related phenotypes (23,24).

Degradation of extracellular matrix and creation of invasive pathways. Another pathological challenge of PDAC is its abnormally dense fibrotic stroma, primarily composed of type I, III and IV collagen, fibronectin and hyaluronan. This stroma is synergistically deposited by tissue-resident macrophages of embryonic origin, activated pancreatic stellate cells (PSCs) and CAFs, driven by TGF-β and matrix stiffness via FAK signaling, forming a robust physical barrier (8,25,26). To breach this barrier for invasion and intravasation, cancer cells must actively degrade ECM components. Notably, the ECM in PDAC exhibits a paradoxical role: Although it is produced via synergistic deposition by pancreatic stellate cells (PSCs), cancer-associated fibroblasts CAFs and other cells, induced by tumor stimuli in the tumor microenvironment (such as TGF-β signaling, matrix stiffness), it forms a physical barrier that hinders the initial spread of tumors. Therefore, cancer cells need to overcome this barrier through EMT: EMT-related transcription factors (such as Snail, ZEB1) recruit co-activators with histone acetyltransferase activity (such as CBP/p300), thereby activating the expression of proteolytic enzymes such as matrix metalloproteinases (MMPs). These enzymes can specifically degrade ECM components such as collagen, creating pathways for cancer cell invasion (26). The MMP family plays a central role in this process: via MMP-14-mediated cascade activation (such as activating MMP-2 and MMP-9), combined with spatiotemporally specific degradation regulated by integrin/FAK signaling, MMPs act as key effectors for breaking through the dense stromal barrier (27). MMP-14 is particularly critical: it anchors to the cell membrane via its transmembrane domain and palmitoylation of Cys574 in its cytoplasmic tail further stabilizes membrane localization. Trafficking mediated by the LLY573 motif targets MMP-14 precisely to invadopodia; meanwhile, its homodimerization enhances collagenase activity, efficiently cleaving type I collagen. In coordination with the spatiotemporal degradation pattern regulated by FAK-p130cas signaling, MMP-14 creates invasive channels for cells (28).

More importantly, in the complex TME of PDAC, the EMT program establishes a destructive synergistic relationship between cancer cells and stromal cells: EMT-experienced cancer cells secrete TGF-β and platelet-derived growth factor (PDGF), which activate the transformation of PSCs into CAFs via the Smad pathway and MAPK/ERK signaling, respectively. Activated CAFs, in turn, become the primary source of matrix-degrading enzymes through high MMP expression (29,30). This bidirectional crosstalk forms a malignant positive feedback loop: EMT cells induce a CAF-mediated fibrotic TME via secretion of TGF-β, while excessive TGF-β secreted by CAFs in this microenvironment further reinforces the EMT phenotype via the SMAD pathway and non-SMAD signals (such as MAPK/ERK). Simultaneously, mechanical tension generated by ECM remodeling amplifies invasion signals via integrin/FAK signaling, paving the way for collective invasion of tumor cells (31). Thus, EMT endows cancer cells with autonomous motility and autophagy-regulated matrix

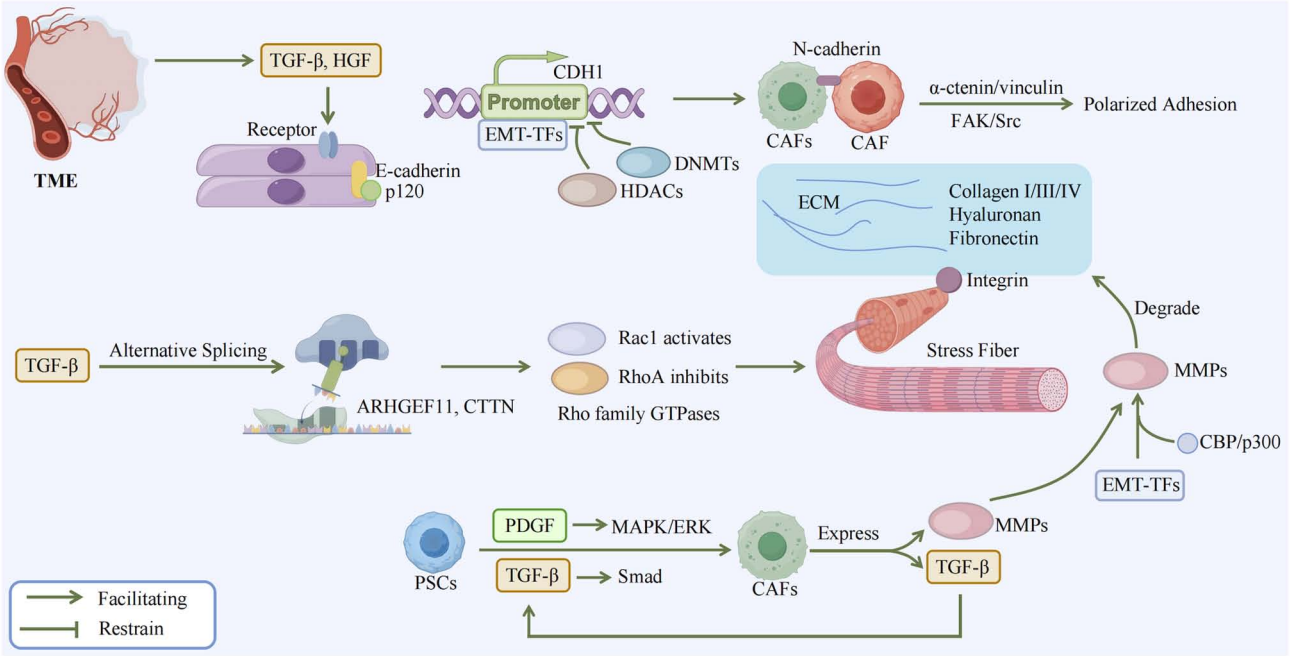

Figure 1. Mechanism of TME-induced EMT and the CAF-cancer cell feedback loop in PDAC progression. During the PanIN stage, signals derived from the TME, such as TGF-β and HGF, activate the EMT program via their cognate receptors. As a core component of epithelial adherens junctions, E-cadherin maintains junctional stability by binding to p120 catenin. The core executors of EMT-TFs bind to the promoter region of the CDH1 gene and recruit epigenetic modification complexes (such as HDACs, DNMTs) to suppress the expression of the epithelial marker E-cadherin, while simultaneously upregulating the mesenchymal marker N-cadherin. This 'cadherin switching' liberates cancer cells from their original cell-cell connections, allowing them to anchor to the stroma via heterotypic adhesion with CAFs and enhances directed migration by activating the α-catenin/vinculin-FAK/Src signaling pathway. Concurrently, TGF-β signaling modulates the activity of Rho GTPases (such as activating Rac1, inhibiting RhoA) by mediating the alternative splicing of genes such as ARHGEF11and CTTN. This drives cytoskeletal remodeling and stress fiber formation. The intracellular tension gradient generated by myosin contraction, coordinated with traction forces transmitted via integrin-mediated focal adhesions, helps cells overcome stromal resistance, thereby powering cell migration. To pave the way for invasion, EMT-transformed cancer cells secrete factors such as TGF-β and PDGF, which induce the transformation of PSCs into CAFs via the SMAD pathway and MAPK/ERK signaling, respectively. Activated CAFs not only highly express matrix metalloproteinases, becoming a major source of matrix-degrading enzymes, but also secrete excess TGF-β. This excess TGF-β further reinforces the EMT phenotype in cancer cells through both SMAD and non-SMAD pathways (such as MAPK/ERK). Simultaneously, mechanical tension generated by ECM remodeling amplifies invasion signals via integrin/FAK signaling, ultimately forming a malignant positive-feedback loop that drives progressive invasion. TME, tumor microenvironment; EMT, epithelial-mesenchymal transition; CAF, cancer-associated fibroblast; PDAC, pancreatic ductal adenocarcinoma; PanIN, precancerous pancreatic intraepithelial neoplasia; TGF-β, transforming growth factor-β; HGF, hepatocyte growth factor; EMT-TFs, EMT-EMT transcription factors; HDACs, histone deacetylases; DNMTs, DNA methyltransferases; FAK, focal adhesion kinase; PDGF, platelet-derived growth factor; PSCs, pancreatic stellate cells.

degradation capabilities. Through synergistic interactions with CAFs (via TGF-β/SMAD and MAPK/ERK signaling), EMT drives PDAC progression from in situ carcinoma to invasive cancer. Additionally, via autophagy-dependent exosome release and immune evasion (to avoid immune surveillance), EMT ultimately promotes efficient metastasis to distant organs such as the liver (32).

Following EMT-mediated invasion through the dense stroma, cancer cells further acquire the ability to intravasate into the vascular system. This process is facilitated by EMT-induced upregulation of MMPs (such as MMP-14) that degrade vascular basement membrane components, as well as enhanced interactions with endothelial cells via N-cadherin-mediated adhesion (20,28). EMT thus acts as a key driver linking tumor detachment, stromal invasion and vascular entry, laying the foundation for subsequent metastatic dissemination.

EMT is the core engine driving PDAC invasion and metastasis. TGF-β-induced E-cadherin suppression (via SNAIL1/ZEB1) and N-cadherin upregulation enable adhesion switching, conferring migratory capacity. Concurrently, EMT activates MMP-14 to degrade collagen and pave invasion routes. Crucially, EMT and CAFs form a TGF-β-driven positive feedback loop: EMT cells activate CAFs, which secrete TGF-β to reinforce EMT, collectively breaching the dense stroma and enabling metastasis (Fig. 1).

Role of EMT/MET plasticity in circulating tumor cell colonization. After intravasation, EMT continues to regulate the survival and metastatic potential of circulating tumor cells (CTCs) during circulation and mediates successful colonization at distant organs via mesenchymal-epithelial transition (MET) reversal.

After PDAC cells invade the vascular system, they disseminate in the blood or lymphatic fluid as CTCs, the essential carriers of distant metastasis. The pre-metastatic precursor cell properties enriched in CTCs have been confirmed in PDAC studies (33,34). The harsh environment of the circulatory system requires CTCs to resist blood shear stress, activate the YAP1 pathway via platelets to resist anoikis and evade immune surveillance with the help of neutrophil extracellular traps (33). EMT enhances the survival and metastatic capacity of CTCs by downregulating epithelial markers (such as EpCAM), upregulating mesenchymal phenotypes (such as

Vimentin) and activating the JNK signaling pathway, making it a key mechanism for CTCs to adapt to the circulatory environment (33,35).

Studies have found that CTCs in the peripheral blood of PDAC patients often exhibit varying degrees of EMT characteristics and their phenotypic heterogeneity is associated with TGFβ/Smad pathway activation and Snail-mediated downregulation of epithelial markers (36,37). Although cells that have fully undergone EMT exhibit enhanced motility via the RhoA/ROCK pathway: Activation of this pathway regulates actin filament contraction and focal adhesion dynamic assembly, thereby driving cytoskeletal reorganization to promote migration, while their single-cell state makes them more vulnerable to damage from blood shear stress and attack by natural killer (NK) cells (37,38). In recent years, the 'partial' EMT or 'hybrid' EMT state has been confirmed to be the phenotype with the highest metastatic efficiency: such cells acquire mesenchymal properties via Twist1/MAPK pathway activation to resist apoptosis, while retaining E-cadherin-mediated cell junctions; their plasticity is maintained by the Notch-Jagged1 signaling pathway, which sustains intercellular fate consistency through lateral induction (38).

Cells in this state achieve dual functions through unique phenotypic plasticity: On the one hand, they acquire mesenchymal characteristics (such as enhanced motility and anti-apoptotic potential) via EMT, enabling them to detach from the primary tumor and survive in the circulation (39); on the other hand, the retained E-cadherin mediates intercellular junctions, providing a structural basis for the formation of CTC clusters, which have markedly higher metastatic potential and circulatory survival rate than single CTCs (40,41).

CTC clusters enhance metastatic efficiency through synergistic mechanisms: Their aggregate structure, together with protective microthrombi formed by platelets, reduces direct damage to internal cells from fluid shear stress; meanwhile, by expressing molecules such as PD-L1 and CD47, CTC clusters inhibit T-cell function via the PD-1/PD-L1 signaling axis and block phagocytosis through the interaction between CD47 and macrophage SIRPα, thereby reducing the probability of elimination by immune surveillance (42); simultaneously, intercellular signal communication within CTC clusters (such as E-cadherin-mediated adhesion and Notch-Jagged1 signaling maintaining phenotypic plasticity) and interactions with platelets (such as TGF-β released by platelets activating Smad pathway to sustain mesenchymal properties and ADP promoting TGF-β release via platelet P2Y12 receptor) further enhance their survival capacity, making them more likely to be retained and colonized in distal capillaries (43,44).

Resisting anoikis is critical for CTC survival and EMT endows this capacity by activating pathways such as PI3K/Akt and MEK/ERK. For example, TWIST1 can upregulate Akt phosphorylation to inhibit the apoptotic program triggered by matrix detachment, while Snail enhances cell survival by regulating the expression of the anti-apoptotic protein Bcl-2 (45,46). Additionally, mesenchymal phenotype-related receptors (such as integrins) can bind to platelets or soluble matrix proteins (such as PDGF and VEGF) in the circulation, forming a protective microenvironment that further reduces the risk of apoptosis and lays the foundation for metastasis (47,48).

The final step of the metastatic cascade, and the key to the formation of metastatic lesions, is the successful colonization of CTCs in distant organs. To proliferate in the new microenvironment and form macroscopically visible secondary tumors, disseminated cancer cells must undergo MET, the reverse process of EMT. This process restores epithelial cell polarity and intercellular adhesion capacity, enabling cells to integrate into new tissues and proliferate in an orderly manner (49,50). This phenotypic plasticity depends not only on the dynamic regulation of transcription factors (such as Snail and Twist) but also on epigenetic reprogramming (such as histone modification and DNA methylation) and the regulation of mRNA stability by RNA-binding proteins (51,52). For example, lncRNA H19 maintains the balance of cell plasticity during EMT/MET switching by sponging miR-200b/c and let-7b (49).

The core of phenotypic plasticity lies in the dynamic adaptation to the pressure of the metastatic microenvironment: sustained TGF-β signals in the primary tumor induce an EMT-mediated mesenchymal phenotype (that is, a phenotype with low E-cadherin expression and high vimentin expression) in CTCs, enabling them to resist shear stress and immune attack in the circulation; when CTCs reach the metastatic site, epithelial differentiation signals (such as BMPs) in the microenvironment can activate the SMAD pathway, triggering MET to rebuild epithelial structures and support colonization and proliferation (53,54). This bidirectional switching mechanism allows cancer cells to resist shear stress and immune attack in the circulation with a mesenchymal phenotype and rebuild epithelial structures via MET to support proliferation during colonization. Histological analysis of PDAC liver metastases confirms that metastatic tumor cells transmit the CD44v6/C1QBP complex via exosomes, remodeling the hepatic fibrotic microenvironment and maintaining an epithelial-like differentiated state, providing direct evidence for the occurrence of MET (55). In summary, from driving invasion of the primary tumor, to endowing treatment resistance and stem cell phenotypes and finally to ensuring the circulatory survival of CTCs and their eventual distant colonization, EMT and its reverse process MET together form a core axis the entire metastatic process of PDAC. This remarkable cellular plasticity allows PDAC cells to flexibly adapt to various environmental pressures, making it one of the fundamental reasons for the difficulty in radical treatment-and thus an extremely attractive therapeutic target (Fig. 2).

Mechanisms of the EMT-stemness-therapy resistance axis. Beyond driving the entire metastatic cascade (detachment, invasion, intravasation, circulation and colonization), EMT also plays a pivotal role in mediating therapy resistance in PDAC; this mechanism is closely linked to EMT-induced stemness acquisition and phenotypic plasticity, independent of metastatic localization.

PDAC exhibits extreme resistance to current chemotherapy (such as gemcitabine and oxaliplatin) and radiotherapy, which contributes to its high mortality. Accumulating evidence indicates that extracellular vesicles derived from CAFs transmit molecules such as miR-146a (which activates Snail) and circFARP1 [which activates the LIF/signal transducer and activator of transcription 3 (STAT3) axis], mediating a mutually reinforcing vicious cycle among the EMT program, acquisition of

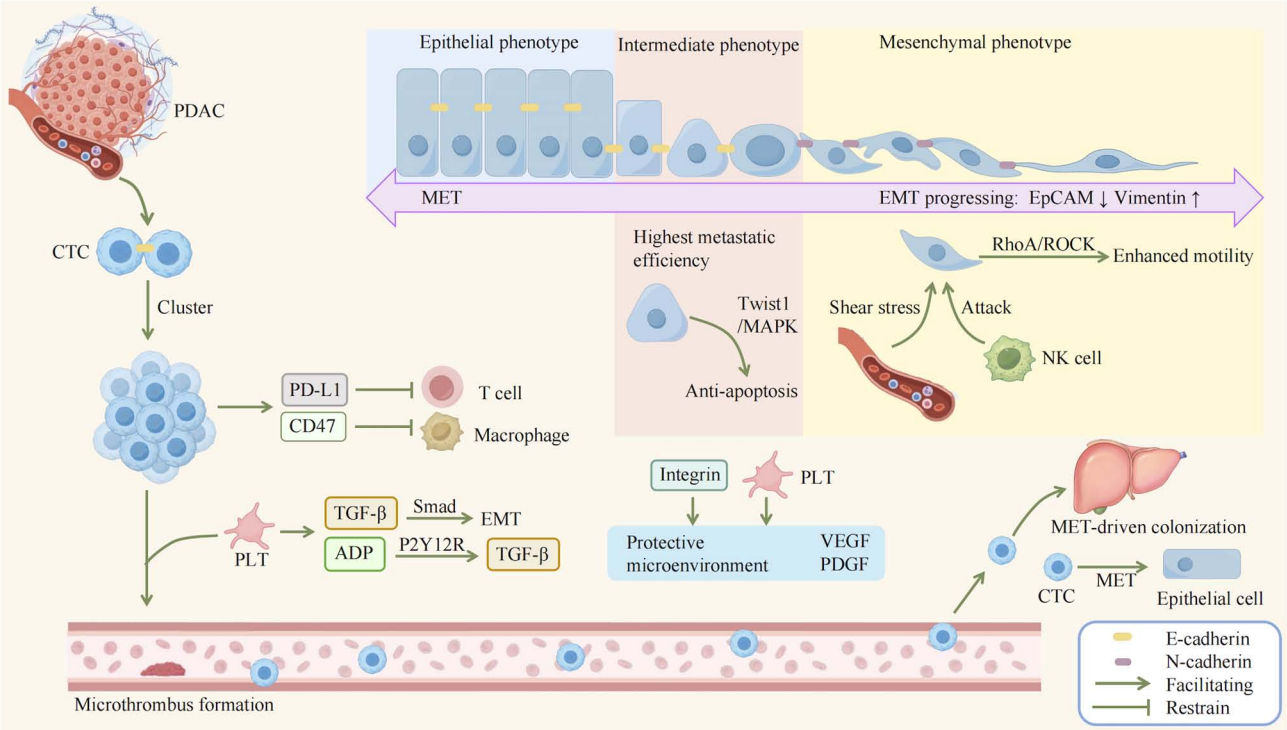

Figure 2. Mechanisms of circulating tumor cell survival and metastasis in PDAC. After detaching from the primary tumor and entering the bloodstream as CTCs, PDAC cells exhibit distinct metastatic behaviors: cells undergoing complete EMT, despite gaining enhanced motility via the RhoA/ROCK pathway, are vulnerable as single cells to shear stress and NK cell-mediated attacks. In contrast, the 'partial/mixed EMT' phenotype demonstrates the highest metastatic efficiency, acquiring anti-apoptotic capabilities through the Twist1/MAPK pathway. CTCs retaining E-cadherin can form clusters, which markedly enhance circulatory survival and metastatic potential via multidimensional cooperative mechanisms. These aggregates, shielded by platelet-rich microthrombi, reduce direct shear stress damage and facilitate immune evasion through PD-L1 expression (suppressing T cells) and CD47 expression (blocking macrophage phagocytosis). Interactions with platelets, such as TGF-β release activating SMAD signaling and ADP-P2Y12 receptor engagement promoting further TGF-β secretion, augment survival, while adhesion via integrins to platelets or soluble matrix proteins (such as PDGF and VEGF) creates a protective microenvironment that minimizes apoptosis. The final critical step in the metastatic cascade, successful colonization at distant organs, hinges on MET, which reestablishes epithelial polarity and intercellular adhesion capabilities. PDAC, pancreatic ductal adenocarcinoma; CTCs, circulating tumor cells; EMT, epithelial-mesenchymal transition; MAPK, mitogen-activated protein kinase; PD-L1, programmed cell death ligand 1; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; MET, mesenchymal-epithelial transition.

CSC properties and treatment resistance, collectively forming the biological basis for PDAC treatment failure (33,56,57).

The EMT program endows cancer cells with stem-like properties. Cancer stem cells (CSCs) are subpopulation of tumor cells with self-renewal capacity and multi-lineage differentiation potential. They maintain stemness by activating signaling pathways such as WNT/β-Catenin, Notch and TGF-β and serve as core drivers of tumor initiation, recurrence and metastasis (58,59). In PDAC, cell subpopulations expressing $CD44^+/CD24^+/EpCAM^+$, $CD133^+$, or high aldehyde dehydrogenase 1 (ALDH1) activity have been confirmed to be enriched in CSCs. Among these markers, CD133 expression is regulated by hypoxia-inducible factor 1α (HIF-1α), CD44 maintains stemness via the WNT/β-Catenin pathway and high ALDH1 activity is associated with the antioxidant phenotype and drug resistance of CSCs (60,61). A breakthrough finding is that in PDAC cells, TGF-β induces EMT via the Smad pathway, activating transcription factors such as Snail and ZEB1 and enabling differentiated non-stem cancer cells to acquire CSC characteristics; conversely, knockout of these EMT-TFs markedly impairs the self-renewal capacity and *in vivo* tumorigenicity of CSCs by inhibiting stemness-maintaining pathways such as WNT/β-Catenin (58,62).

Among EMT-TFs, ZEB1 plays a core integrative role: the bidirectional negative feedback loop formed between ZEB1 and the miR-200 family not only drives EMT phenotypic switching but also maintains cell stemness by stabilizing the expression of the stem cell factor Sox2; meanwhile, the direct interaction between ZEB1 and YAP1 can respond to TGF-β signals to activate downstream target genes, thereby coordinately regulating stem cell pluripotency (63). The key mechanism lies in the transcriptional inhibition of stemness-suppressing microRNAs (such as the miR-200 family) by ZEB1/2; in turn, the miR-200 family forms a mutually inhibitory feedback loop by targeting the 3' untranslated region (3'UTR) of ZEB1/2 and further indirectly regulates CSC properties by modulating these EMT-TFs (64). Specifically, the miR-200 family and ZEB1/2 form a mutually inhibitory negative feedback loop; ZEB1/2 transcriptionally inhibit miR-200 expression, while miR-200 inhibits ZEB1/2 function by targeting their 3'UTR; simultaneously, miR-200 can directly target and inhibit the stemness factor BMI1, thereby regulating CSC properties (65). Thus, high ZEB1 expression in PDAC enhances the activated phenotype of stromal myofibroblasts, activates KRAS and its downstream PI3K/AKT pathway in cancer cells via paracrine signals, disrupts the balance of the tumor microenvironment, accelerates the progression of PDAC from pre-cancerous

lesions to malignant tumors and markedly enhances its *in vivo* tumor-initiating capacity (66).

EMT-mediated resistance to chemo- and radiotherapy. The close association between EMT and CSCs is a key reason for the broad-spectrum resistance of tumors to treatment. EMT can induce cells to acquire CSC-like properties by activating stem cell-related signaling pathways [such as Notch and Hedgehog (Hh)] and downregulating epithelial markers (such as E-cadherin) while upregulating mesenchymal markers (such as Id-1, α-SMA), which specifically includes temporary entry into a dormant state (cell cycle arrest). Most chemotherapeutic drugs, such as gemcitabine, primarily target rapidly proliferating cells, allowing these dormant cells to evade drug attack and become the source of recurrence after treatment (67). Secondly, the EMT program can enhance cell survival signals by activating pro-survival signaling pathways such as PI3K/AKT and increase the apoptotic threshold by upregulating anti-apoptotic molecules (such as Bcl-xL) and inhibiting pro-apoptotic factors (such as BOK), making cells more likely to survive DNA damage induced by drugs or radiation (68).

In pancreatic cancer, EMT is a key mechanism mediating resistance to chemotherapy and radiotherapy and it affects the response of tumor cells to treatment through a multi-dimensional regulatory network. EMT-TFs such as ZEB1 play a central role: High ZEB1 expression is closely associated with gemcitabine resistance and ZEB1 can maintain the EMT phenotype and reduce drug sensitivity by inhibiting the miR-200 family to form a negative feedback loop; conversely, ZEB1 knockdown can markedly reverse this process (69,70). Additionally, EMT-induced metabolic reprogramming provides an energy basis for drug resistance: PDAC cells with ZEB1 deficiency cannot compensatorily enhance glycolysis when oxidative phosphorylation is inhibited, making them sensitive to metabolic stress; by contrast, EMT-activated cells maintain energy supply by upregulating glucose transporters [such as Glucose Transporter 3 (GLUT3)] and the Warburg effect, thereby tolerating metabolic stress induced by chemotherapeutic drugs (69). In terms of radioresistance, EMT achieves resistance by enhancing DNA damage repair capacity: ZEB1 can directly bind to the Ataxia Telangiectasia Mutated Protein (ATM) promoter and form a complex with p300/PCAF to promote ATM expression; meanwhile, ZEB1 stabilizes CHK1 by sequestering the deubiquitinase USP7, accelerating DNA damage repair to reduce radiation-induced cell death (69); furthermore, radiotherapy itself can upregulate EMT-TFs such as ZEB1 and Snail by activating pathways such as TGF-β and NF-κB, further exacerbating resistance (71). The involvement of the TME is another important aspect: Cytokines such as TGF-β and IL-6 secreted by CAFs can induce EMT, promoting resistance of PDAC cells to chemotherapeutic drugs; targeting paracrine signals between CAFs and tumor cells can partially reverse this resistance (69,71). Notably, while EMT is not necessary for metastasis, it clearly induces chemotherapy resistance in pancreatic cancer, this property provides a theoretical basis for EMT-targeted therapeutic strategies (72). Meanwhile, EMT is closely associated with the CSC phenotype: EMT-TFs can maintain the stemness of CSCs, making them less sensitive to radiotherapy and chemotherapy and forming a drug-resistant cell population (73).

The EMT-stemness-therapy resistance axis is central to PDAC malignancy. TGF-β-driven ZEB1 suppresses miR-200 and activates WNT/β-Catenin, conferring stemness (such as $CD44^{+}/CD133^{+}$) and cell-cycle arrest to evade chemotherapy (such as gemcitabine) and immune targeting. Concurrently, ZEB1 enhances DNA repair (ATM/CHK1) and metabolic reprogramming (Warburg effect) for broad resistance. Critically, therapeutic targeting faces major limitations: EMT-related molecules (such as ZEB1) have essential physiological roles in normal tissues, risking off-target toxicity; and discrepancies between preclinical models and human responses hinder clinical translation, necessitating more precise intervention strategies (Fig. 3).

3. Dynamic regulatory network of EMT: Transcriptional, signaling and epigenetic hierarchies

EMT is not an isolated event but is driven by an extraordinarily complex, multi-level and highly integrated molecular regulatory network (2). In the context of pancreatic cancer, dysregulation of this network is the core of tumor malignant progression. It begins with the perception of extracellular signals, which are transmitted through classical signal transduction pathways and ultimately converge on a small group of core transcription factors (EMT-TFs). The mesenchymal cell state is then consolidated and maintained through epigenetic remodeling. Meanwhile, dynamic changes in the TME and adaptive reprogramming of cellular metabolism provide continuous momentum and material basis for this process (74). Below, the key components of this complex network and their specific mechanisms of action in pancreatic cancer are introduced.

Core EMT transcription factor hubs: mechanisms, synergy and feedback loops of Snail/ZEB/Twist families. EMT-TFs are the core hubs of the regulatory network. After integrating upstream signals (such as pathways mediated by TGF-β and IL-6), they act as terminal effectors to directly execute gene expression switching, binding to the promoters of target genes to inhibit epithelial programs (such as the CDH1 gene encoding E-cadherin) and activate mesenchymal programs (75). In pancreatic cancer, the Snail, ZEB and Twist families are key executors of this process, playing indispensable roles.

EMT-TFs [Snail, ZEB, Twist and Paired Related Homeobox (PRRX) families] rely on conserved domains (zinc finger, bHLH and homeodomain) for DNA binding and transcriptional regulation. Their core commonality is regulating EMT via E-box binding, suppressing epithelial markers (such as CDH1) and activating mesenchymal genes, alongside forming miRNA negative feedback loops. Functionally divergent due to domain differences: Snail recruits co-repressors via SNAG domain, ZEB interacts with YAP/AP-1, Twist requires dimerization and PRRX synergizes with Twist to enhance invasiveness (76,77). Downstream, they form a bipolar target network: CDH1 is directly repressed by Snail/ZEB/Twist (a key EMT-initiating event), while mesenchymal targets (VIM, CDH2, MMP9) and fibroblast-related genes (activated by PRRX1-TWIST1) collectively drive PDAC progression (78,79).

Mechanisms of action of Snail, ZEB1/2 and Twist families. As a core EMT transcription factor, Snail1 drives the malignant

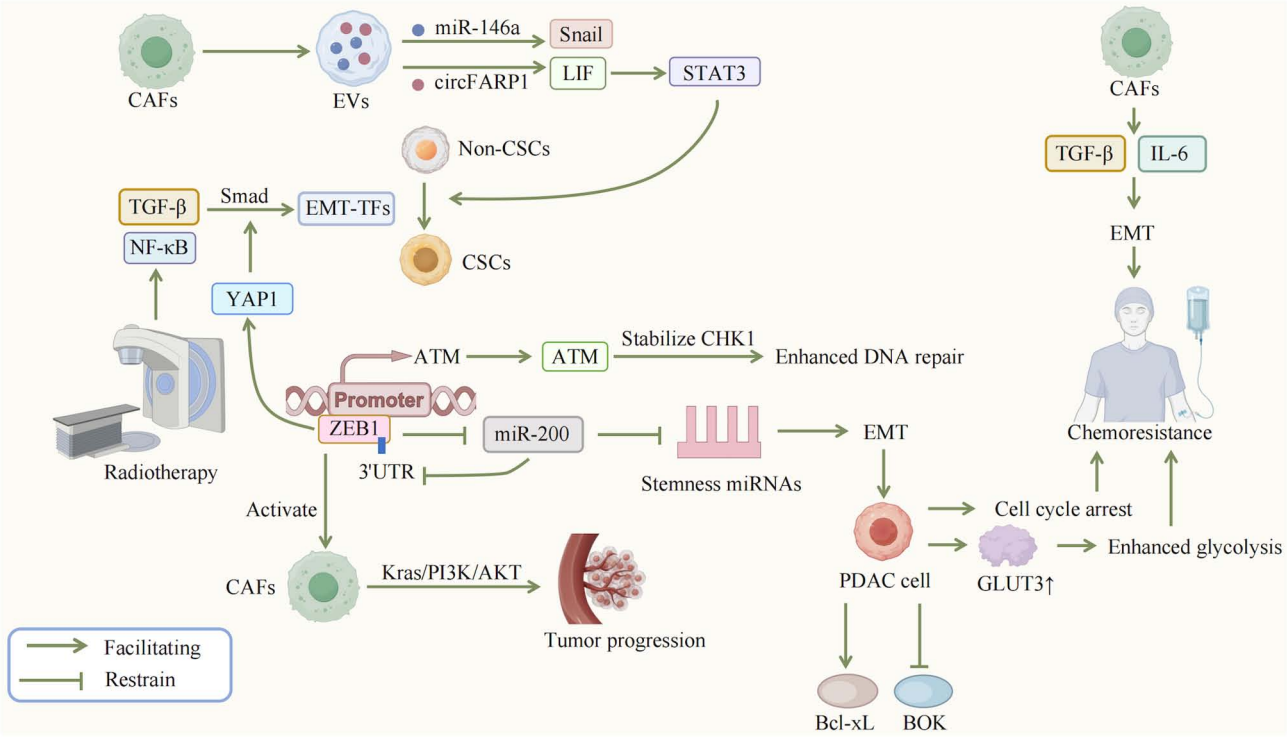

Figure 3. Therapeutic resistance mechanisms in PDAC. The extreme resistance of PDAC to chemotherapy and radiotherapy stems from its unique EMT-stemness-therapy resistance axis. The initiation of this vicious cycle critically depends on EVs secreted by CAFs. These EVs deliver molecules such as miR-146a (activating Snail) and circFARP1 (activating the LIF/STAT3 axis), which collaboratively induce the EMT program and the acquisition of CSC traits. TGF-β signaling further reinforces EMT via the Smad pathway and activates EMT-TFs such as ZEB1 and Snail, enabling differentiated non-stem-like cancer cells to gain CSC properties. Among these, ZEB1 directly interacts with YAP1 in response to TGF-β signaling, coregulating stem cell pluripotency, while ZEB1/2 maintains the EMT phenotype and reduces drug sensitivity by transcriptionally inhibiting the miR-200 family (microRNAs that themselves form a mutual inhibitory feedback by targeting the 3'UTRs of ZEB1/2). The EMT program also enhances cell survival signals by activating pathways such as PI3K/AKT and increases the apoptotic threshold through upregulation of the anti-apoptotic molecule Bcl-xL and suppression of the pro-apoptotic factor BOK, allowing cells to improved survive DNA damage induced by drugs or radiation. Simultaneously, EMT promotes CSC-like characteristics, including a transient entry into a dormant, cell cycle-arrested state, helping cells evade proliferation-targeting drugs. Metabolically, EMT-activated cells sustain energy supply by upregulating glucose transporter GLUT3 and enhancing the Warburg effect, thereby tolerating metabolic stress induced by chemotherapy. Additionally, ZEB1 directly binds to the ATM promoter to increase ATM expression and stabilizes CHK1, accelerating DNA damage repair and reducing radiation-induced cell death. Radiotherapy itself can further upregulate EMT-TFs such as ZEB1 and Snail by activating pathways such as TGF-β and NF-κB, forming a positive feedback loop that exacerbates therapy resistance. In summary, this multidimensional mechanism, encompassing EV-mediated signaling initiation, EMT-stemness coupling, survival signal enhancement, metabolic reprogramming and DNA repair activation, collectively underlies PDAC treatment failure. PDAC, pancreatic ductal adenocarcinoma; EMT, epithelial-mesenchymal transition; EVs CAFs, cancer-associated fibroblasts; CSC, cancer stem cell; TGF-β, transforming growth factor-β; EMT-TFs, EMT-transcription factors; LIF, leukemia inhibitory factor; STAT3, signal transducer and activator of transcription 3; ZEB1, Zinc Finger E-Box Binding Homeobox 1; YAP1, Yes-Associated Protein 1; GLUT3, glucose transporter 3; ATM, ataxia-telangiectasia mutated.

progression of pancreatic cancer through a multi-level regulatory network; its abnormal function is closely associated with the acquisition of the EMT phenotype and enhanced invasive/metastatic capacity. At the signaling pathway level, the TGF-β1-Smad2/3 pathway upregulates Snail1 via Numb-PRRL activation and synergizes with Notch1 to enhance the EMT phenotype, characterized by downregulation of E-cadherin and upregulation of N-cadherin and Vimentin (80). The WNT/β-catenin pathway forms a positive feedback loop with Snail1:STMN2 activates the WNT/β-catenin pathway (promoting β-catenin nuclear translocation to bind TCF transcription complex) to upregulate Snail1 expression, while the nuclear β-catenin/TCF complex in turn transactivates STMN2 gene expression; their mutual promotion collectively reinforces EMT and proliferation (81). At the metabolic level, RHOF enhances glycolysis via the c-Myc-PKM2 axis and lactic acid induces lactylation and nuclear translocation of Snail1 to drive EMT (82); epigenetically, miR-34a directly targets Snail1 mRNA to inhibit its expression, weakening the invasive capacity of cancer cells (83).

The protein stability of Snail1 is dynamically regulated by the ubiquitin-proteasome system: F-box/LRR-repeat protein 7 inhibits EMT by ubiquitinating and degrading Snail1 (84), while TGF-β-induced ubiquitin-specific peptidase 27X (USP27X) stabilizes Snail1 via deubiquitination, enhancing its pro-EMT and chemoresistant functions (85). Further studies have shown that 17 E3 ubiquitin ligases (such as FBXL14 and βTrCP1, which mediate Snail1 degradation via ubiquitination) and 23 deubiquitinating enzymes (such as USP47 and DUB3, which stabilize Snail1 via deubiquitination) together form a regulatory network for Snail1 protein stability; in addition, proteins such as COP9 signalosome subunit 2 (CSN2, not β-casein) can indirectly maintain Snail1 stability by inhibiting the activity of E3 ubiquitin ligases (86).

Phosphorylation regulation exhibits spatiotemporal specificity: Glycogen synthase kinase 3 beta (GSK3β) phosphorylates the Ser-rich domain (SRD) in the nucleus to promote Snail1 nuclear export and synergizes with CK1ε in the cytoplasm to phosphorylate Snail1 and form a degradation

motif; by contrast, kinases such as ATM and ERK2 phosphorylate specific sites in the nucleus, which can recruit Heat shock protein 90 to stabilize Snail1, reflecting the effect of subcellular localization on function (86). Modifications such as acetylation (for instance, CBP-mediated acetylation of Snail1 at Lys146/187, which enhances its transcriptional activation function and inhibits degradation) and glycosylation (such as O-GlcNAc modification at Ser112, which blocks GSK3β-mediated phosphorylation and degradation) further regulate Snail1's transcriptional activity and stability; its N-terminal intrinsically disordered region enables it to flexibly bind various regulatory factors (such as E3 ligases, deubiquitinating enzymes), making it a hub for integrating EMT signals (86).

During the occurrence and development of pancreatic cancer, Snail1 acts as a core driver in the progression of precursor lesions. Inhibition of Snail1 via gene knockout or drugs (such as GN25) can effectively delay the occurrence and development of pancreatic intraepithelial neoplasia (PanINs) and reduce acinar-ductal metaplasia (ADM) after pancreatic injury, suggesting its significant potential for early intervention in pancreatic cancer (87). From the perspective of downstream effects of signal transduction, the execution of the EMT phenotype mediated by Snail1 depends on the classical BMP signaling pathway, which regulates the expression of downstream target genes through synergy with SMAD4, ultimately achieving EMT-related invasive and metastatic phenotypes (88). At the clinical level, the metastasis suppressor Raf kinase inhibitor protein (RKIP) is markedly negatively correlated with Snail1 expression: high RKIP expression is often associated with a favorable prognosis in pancreatic cancer patients, while high Snail1 expression predicts disease progression and poor outcomes, this association provides an important molecular marker for prognosis evaluation of pancreatic cancer (39).

The ZEB family, especially ZEB1, serves as a core driver of EMT and stem cell properties in pancreatic cancer. It participates in multiple key links of tumor malignant progression through a complex regulatory network and its abnormal activation is driven by the synergy of multi-level upstream signals, non-coding (nc)RNA networks, inflammatory pathways and cell plasticity regulation. In the early stage of tumorigenesis, ZEB1 is a key driver of the progression of pancreatic precursor lesions: in the KRAS and p53 mutant pancreatic cancer model (KPC) mouse model (carrying KRAS and p53 mutations), deletion of ZEB1 can markedly reduce the number and grade of ADM and PanINs; in the KRAS mutant pancreatic cancer model (KC) model (carrying KRAS mutation but no p53 mutation), deletion of ZEB1 more markedly inhibits the formation of KRAS-driven early lesions, highlighting its importance in the initiation stage of pancreatic cancer (63). In terms of regulatory mechanisms: at the epigenetic level, enhancer of zeste homolog 2 (EZH2) inhibits miR-139-5p via lysine 27 trimethylation on histone H3 (H3K27me3), thereby relieving the targeted inhibition of ZEB1/2 by miR-139-5p (89); in the inflammatory microenvironment, macrophage migration inhibitory factor (MIF) downregulates miR-200b to enhance ZEB1/2 expression (90), while NF-κB directly binds to the ZEB1 promoter to promote its transcription (91). In signaling pathways, vasohibin 2 (VASH2) activates the Hh pathway to upregulate ZEB1/2 (92),TGF-β-induced EMT is dependent on ZEB1; ZEB1 deletion renders PDAC cells unable to undergo phenotypic switching in response to TGF-β stimulation, as 91% of TGF-β-regulated genes require ZEB1 involvement (63). ZEB1 forms a negative feedback loop with the miR-200 family: ZEB1 deletion leads to high miR-200c expression, which in turn inhibits stem cell markers such as Sox2 and markedly reduces sphere formation capacity and tumor-initiating potential (63).

Functionally, ZEB1 endows pancreatic cancer with a malignant phenotype by maintaining cell plasticity: ZEB1 deletion fixes cells in the epithelial phenotype, losing the ability to switch between epithelial and mesenchymal phenotypes and resulting in the inability of the invasive front to undergo dedifferentiation. Metabolically, ZEB1 deletion markedly reduces oxidative phosphorylation and glycolytic reserves, rendering cells unable to adapt to changes in TME energy demands. Unlike Snail and Twist, ZEB1 is necessary for metastasis in the KPC model, ZEB1 deletion almost completely abolishes lung colonization capacity, while Snail deletion has no such effect, reflecting the non-redundancy of EMT-TFs. Clinically, high ZEB1 expression is associated with the 'quasi-mesenchymal' subtype of pancreatic cancer, while ZEB1 deletion enriches features of the 'classical' subtype (which has an improved prognosis) (63). The malignant function of ZEB1 can be counter regulated by SCAND1, which forms a complex with myeloid zinc finger 1 (MZF1) to inhibit ZEB1/2 expression (93). By regulating precursor lesion progression, cell plasticity, stem cell properties and metabolic adaptation, ZEB1 serves as a core node of EMT in pancreatic cancer and its unique role provides a specific target for targeted therapy.

The Twist family (Twist1 and Twist2), as core members of basic helix-loop-helix (bHLH) transcription factors, play key roles in EMT of pancreatic cancer through multi-dimensional regulation. Their functions are not only related to cell plasticity in embryonic development but also involved in malignant progression driven by the tumor microenvironment (94,95). Twist1 and Twist2 both bind to the promoters of epithelial marker genes such as E-cadherin to inhibit their expression, while upregulating mesenchymal markers such as Vimentin and N-cadherin, promoting the transformation of epithelial cells to an invasive phenotype (95). In terms of regulatory mechanisms, the Twist family is precisely regulated by tumor microenvironment signals: Hypoxia activates Twist1 transcription by stabilizing HIF-1α and this pathway is associated with lymph node metastasis and poor prognosis of pancreatic cancer (95,96); TGF-β upregulates SOX5 via a Smad-dependent pathway to enhance Twist1 expression and also synergizes with RAS signals via STAT3 and ETS1/2 to strengthen its expression (94,95); Aurora kinase A (AURKA) phosphorylates Twist1 at sites S123, T148 and S184 to inhibit its ubiquitination-mediated degradation and enhance its activity; meanwhile, Twist1 maintains AURKA protein levels by inhibiting its ubiquitination degradation and the two form a positive feedback loop to amplify the EMT effect (97). In downstream effects, Twist1 promotes invasion and cisplatin resistance by inducing MMP2 and GDF15 (98) and interacts with Ring1B and EZH2 to downregulate tumor suppressor genes and enhance proliferation (96). Twist2 is regulated by HIF-2α, specifically binds to the E-cadherin promoter to inhibit

its expression and is negatively correlated with E-cadherin expression (99). Additionally, arginine deprivation (that is, reducing extracellular arginine levels via arginine deiminase or other means to inhibit arginine-dependent pancreatic cancer cells from acquiring this essential amino acid) can downregulate Twist expression, thereby inhibiting EMT (100) and miR-539 directly targets Twist1 mRNA to inhibit its translation (101). In metastasis biology, Twist1-mediated EMT endows pancreatic cancer cells with the migratory ability to detach from the primary tumor, while colonization of metastatic lesions depends on the downregulation of Twist1 and activation of MET. This dynamic switching reflects the spatiotemporal specificity of the Twist family in different stages of metastasis (95).

Interactions and feedback loops among transcription factors. As the core EMT initiator, Snail1's stability is regulated by TGF-β-activated deubiquitinase USP27X; TGF-β upregulates USP27X, which then stabilizes Snail1 via deubiquitination. Notably, Snail1 positively feeds back on TGF-β (directly promoting TGF-β transcription or indirectly enhancing its signaling), forming a 'TGF-β-USP27X-Snail1' loop that continuously strengthens E-cadherin inhibition and mesenchymal phenotype acquisition to sustain tumor progression (85). ZEB1/2 inhibits the epithelial splicing regulatory proteins ESRP1/2, promoting the expression of the fibroblast growth factor receptor-3 IIIc subtype; the latter activates the MEK-ERK-ETS1/2 pathway to feedback and maintain high expression of ZEB1/2, forming an independent self-sustaining loop. Meanwhile, ZEB1/2 is functionally complementary to Snail1 (rather than co-expressed), jointly mediating EMT plasticity (63). In some pancreatic cancer cells, Slug and Snail1 exhibit a synchronized regulatory pattern in their expression; specifically, both are often regulated by upstream regulatory factors (such as RAB11FIP1) to be simultaneously upregulated or downregulated; and these two factors can synergistically respond to TGF-β signals, thereby inducing the epithelial-mesenchymal transition (EMT) process (102).

Cross-regulation between the Twist family and other EMT transcription factors further amplifies network effects: in a hypoxic environment, HIF-1α can simultaneously induce the expression of Twist1 and Snail1; among them, Twist1 enhances chromatin modification by binding to Ring1B and EZH2, synergizing with Snail1 to strengthen the transcriptional inhibition of E-cadherin (96); ZEB1 and Twist1 exhibit functional differentiation: ZEB1 mainly regulates the phenotypic plasticity and metastatic colonization capacity of tumor cells, while Twist1 focuses more on driving invasive capacity and chemotherapy resistance (63,72). A key feedback loop also includes the mutual stabilization between Twist1 and AURKA: AURKA phosphorylates Twist1 to inhibit its ubiquitination and degradation, while Twist1 in turn prevents AURKA degradation, forming a positive feedback loop that amplifies the EMT effect (102). Additionally, the miR-200 family acts as a core negative regulator that can simultaneously target ZEB1/2 and Twist1; the tumor suppressor Par-4 constructs a 'Par-4-miR-200c-ZEB1/Twist1' negative feedback loop by upregulating miR-200c, limiting excessive EMT activation (103). The synergy of this network is also reflected in the commonality of upstream regulation:arginine deprivation can synchronously downregulate the expression of the Snail, Slug and Twist families (98); overexpression of Dual-specificity tyrosine-phosphorylation-regulated kinase 2 indirectly affects the Snail/Slug-mediated EMT process by promoting the ubiquitination and degradation of Twist (104). These findings further confirm the close associations of various transcription factors within the network.

The regulatory roles of Snail, ZEB and Twist families, core EMT-TF hubs, in pancreatic cancer (PC) are analyzed in depth, with multi-dimensional mechanisms clearly elaborated. For Snail1, its activity is modulated by TGF-β/WNT signaling pathways, metabolic lactylation and post-translational modifications including ubiquitination and phosphorylation. ZEB1 exhibits non-redundant functions, particularly in metastasis (a unique trait validated in KPC models) and PC subtype switching. The Twist family, dependent on hypoxia/HIF-1α signaling, regulates cell invasion and exhibits spatiotemporal specificity in MET during metastasis.

Critical findings cover crosstalk between EMT-TFs, such as the TGF-β-USP27X-Snail1 positive feedback loop and functional differentiation between ZEB1 and Twist1. Negative regulatory networks, mediated by miR-200 and Par-4, are also highlighted. Clinically, the associations of these TFs with PanIN progression, prognostic evaluation (such as RKIP-Snail1 correlation) and therapeutic potential (such as GN25, arginine deprivation) provide practical value. This comprehensive network analysis enhances understanding of PC EMT plasticity and lays a theoretical foundation for developing targeted therapies (Fig. 4).

Tumor microenvironment-signal integration: Spatiotemporal regulation of TGF-β/Wnt/Notch/Hh pathways

TGF-β pathway: Dual roles, signal crosstalk and CAF-tumor cell feedback. The TGF-β signaling pathway exerts dual effects in EMT of PDAC The switch of its function from early tumor suppression to late metastasis promotion depends on multi-level regulation. In PDAC cells with retained SMAD4, TGF-β activates the SMAD2/3-SMAD4 complex to regulate transcription factors such as Snail and Twist; meanwhile, it maintains the activity of super-enhancers of genes such as SNAI1 and SOX9 with the help of the epigenetic regulator PHF13, ensuring the continuous expression of EMT-related genes (105,106); deletion of SMAD4 disrupts this regulation, converting SOX4 from a pro-tumor factor to a pro-apoptotic molecule, highlighting the decisive effect of SMAD4 on pathway function (105,107). Activation of the TGF-β pathway is regulated by a 'promotion-inhibition' dynamic balance: circEIF3I (CircBase ID: hsa_circ_0011385) promotes pathway activation by enhancing the binding of SMAD3 to TGFβRI (108). Under TGF-β1 stimulation, Numb-PRRL not only activates the SMAD2/3-Snail pathway downstream of the TGF-β signaling pathway to enhance EMT but also forms a cross-activation loop with Notch1 to synergistically strengthen the EMT-promoting effect of this pathway. Notably, Notch inhibitors (such as RO4929097) can block this cross-activation loop, thereby reversing the enhancing effect of Numb-PRRL on the SMAD2/3-Snail pathway (80). Conversely, abnormal expression of TGF-β receptors (TGFβRI/II) disrupts the balance, weakening tumor suppressor function and amplifying pro-metastatic signals (109).

Signal crosstalk further expands the pro-cancer effects of TGF-β: Numb-PRRL simultaneously participates in the

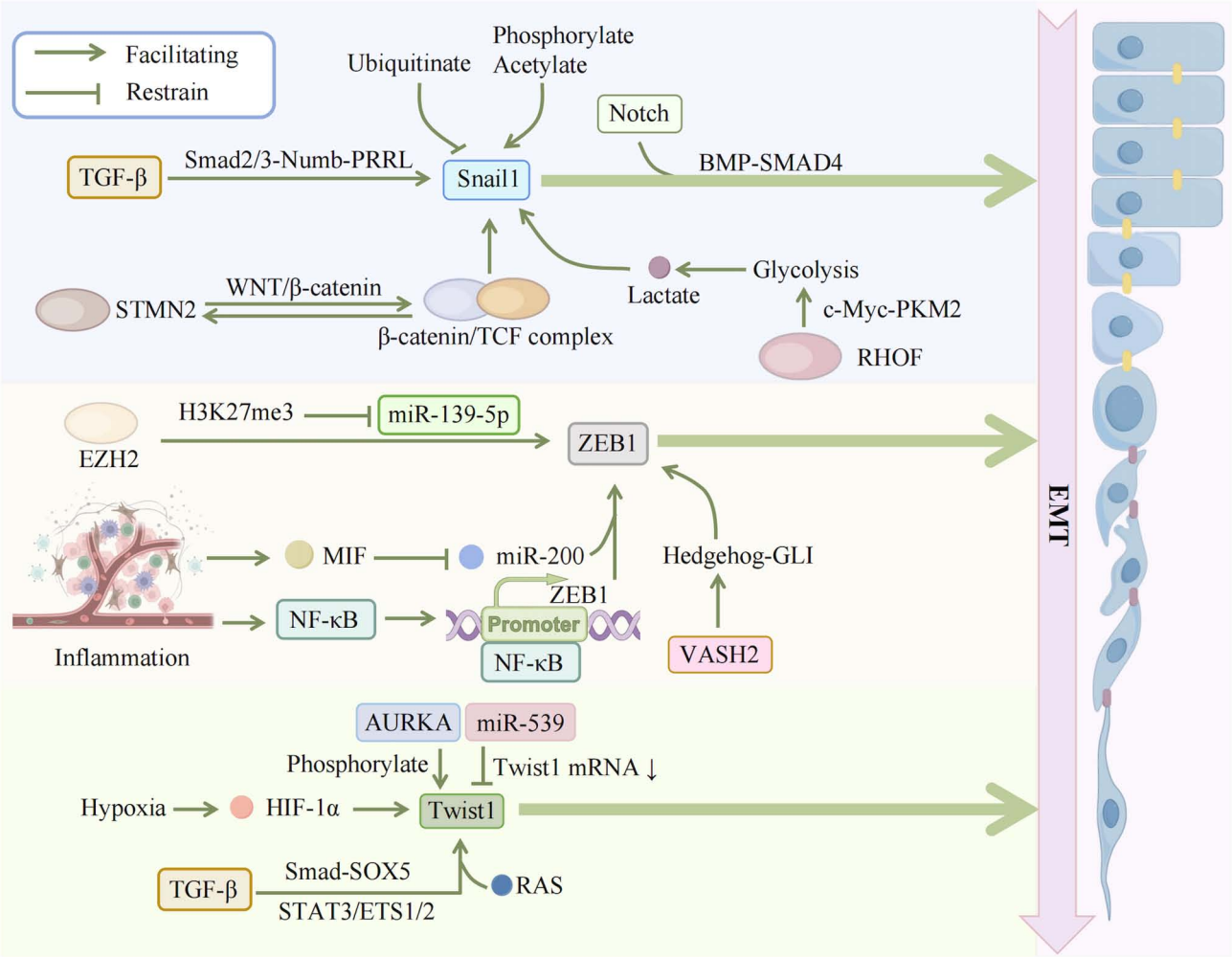

Figure 4. EMT regulatory network: Multi-layer control of transcription factors. TGF-β1 upregulates Snail1 via the Smad2/3-Numb-PRRL pathway and synergizes with Notch1 signaling to enhance EMT. The WNT/β-catenin pathway forms a positive feedback loop with Snail1: STMN2 activates the WNT pathway to upregulate Snail1 and nuclear β-catenin/TCF complexes transactivate STMN2. RHOF enhances glycolysis through the c-Myc-PKM2 axis and the resulting lactate induces Snail1 lactylation and nuclear translocation. Snail1 stability is controlled by ubiquitin-mediated degradation, while its transcriptional activity is enhanced by phosphorylation and acetylation. EZH2 suppresses miR-139-5p via H3K27me3 modification, relieving its targeted inhibition of ZEB1/2. In the inflammatory microenvironment, MIF downregulates miR-200b and NF-κB directly binds to the ZEB1 promoter to enhance its expression, while VASH2 upregulates ZEB1/2 by activating the Hh pathway; moreover, TGF-β-induced EMT requires ZEB1 participation. Upstream hypoxia stabilizes HIF-1α to activate Twist1 transcription; TGF-β upregulates Twist1 through the SMAD-SOX5 pathway and synergizes with STAT3/ETS1/2 and RAS signaling; AURKA phosphorylates Twist1 to inhibit its ubiquitin-mediated degradation, while miR-539 targets Twist1 mRNA to inhibit its translation. EMT, epithelial-mesenchymal transition; TGF-β, transforming growth factor-β; STMN2, stathmin 2; TCF, T Cell Factor; RHOF, Ras Homolog Family Member F; c-Myc, cellular Myc; PKM2, pyruvate kinase M2; EZH2, enhancer of Zeste Homolog 2; miR, microRNA; ZEB1, Zinc Finger E-Box Binding Homeobox 1; MIF, macrophage migration inhibitory factor; NF-κB, nuclear factor-kappa B; HIF-1α, hypoxia-inducible factor 1 alpha; SMAD, Sma- and Mad-related Protein; SOX5, SRY-Box transcription factor 5; RAS, rat sarcoma viral oncogene homolog; AURKA, aurora kinase A.

activation of the EGFR-ERK/MAPK pathway induced by EGF, enabling TGF-β and growth factor signals to synergistically enhance tumor migration and invasion (80); moreover, TGF-β maintains the expression of cancer stem cell markers such as CD24 and CXCR4 by regulating Snail and SLUG and silencing these transcription factors can reduce the sphere formation ability of PDAC cells (107). In the tumor microenvironment, TGF-β activates CAFs via the TGF-β1/Smad pathway; thrombospondin 2 and MMP11 secreted by CAFs activate the MAPK and PI3K/AKT pathways, respectively, forming a 'tumor cell-CAF' positive feedback loop that exacerbates stromal fibrosis (110-112).

Phase Ib/II clinical trial data show that the combination of the TGFβRI inhibitor vactosertib and gemcitabine can reduce extracellular matrix components by inhibiting the TGF-β/Smad2 pathway, thereby enhancing the penetration of the chemotherapeutic drug (113); the combination of TGF-β inhibitors and PD-1/PD-L1 blockers can reverse T-cell exclusion and restore anti-tumor immunity (114,115). However, treatment response needs to be combined with patient molecular subtypes (such as SMAD4 status may affect efficacy), suggesting that multi-target combination is required to achieve comprehensive regulation of EMT, CSC and the microenvironment (105-107).

The Wnt/β-catenin pathway: Link to PDAC stemness. In the EMT process of PDAC, the Wnt/β-catenin pathway is a core upstream driver. Its dysregulation connects intracellular regulation of cancer cells, paracrine signals of cancer-associated fibroblasts CAFs and molecular subtype

characteristics of PDAC, forming a multi-dimensional regulatory network (116-119). In cancer cells: FAM83A disrupts the β-catenin degradation complex by binding to β-catenin and BLK phosphorylation can strengthen this effect to promote β-catenin nuclear translocation by inhibiting the β-catenin cytoplasmic destruction complex; serine/threonine/tyrosine kinase 1 (STYK1) sequesters GSK3β into multivesicular bodies, maintaining pathway activity to support EMT (116,117). Among ncRNAs circRREB1 promotes WNT7B transcription and glycolysis adaptation to EMT by binding to the RRM domain of YAP1; circPHF14 stabilizes WNT7A mRNA to induce EMT transcription factors; exosomal miR-146a and lncRNA H19 derived from CAFs further potentiate Wnt/β-catenin pathway activity (118,120,121). Pathway activation shows significant subtype specificity (119): The squamous subtype is enriched with TP53/KDM6A mutations, highly expresses TP63ΔN and has hypermethylation of endodermal genes, thereby relieving the inhibition of pathways by these endodermal genes; the pancreatic progenitor subtype highly expresses developmental factors such as PDX1 and transforming growth factor beta receptor 2 (TGFBR2) mutations weaken TGF-β pathway inhibition and also enhance the interaction between ECM and β-catenin through mucins; the ADEX subtype relies on oncogenic KRAS to synergize with Wnt ligands to drive EMT (119). At the metabolic level: Frizzled5 binds to cholesterol to maintain Wnt/β-catenin pathway activation (more common in the squamous subtype); methyltransferase-like 3 mediates m6A modification of APC mRNA, which further recruits YTHDF proteins to promote APC mRNA degradation; this degradation reduces APC protein expression, thereby relieving APC's inhibitory effect on the Wnt/β-catenin pathway, activating downstream effectors including β-catenin, Cyclin D1, c-Myc and PKM2 and ultimately enhancing aerobic glycolysis (to support energy supply) and abnormal cell proliferation to drive tumor growth; a regulatory cascade that is more significant in the pancreatic progenitor subtype (122,123). In CAFs, myofibroblastic cancer-associated fibroblasts (myCAFs) secrete Wnt2 to create the immune microenvironment required for EMT; the squamous subtype additionally features a 'TP63ΔN-CAF-ECM-Wnt' positive feedback loop, whereby TP63ΔN induces CAF activation, these activated CAFs remodel the ECM; the altered ECM then activates Wnt signaling and this Wnt activation in turn reinforces the loop to strengthen the pathway (118,119).

Treatment needs to be adapted to subtypes: Fisetin inhibits β-catenin nuclear accumulation (suitable for the pancreatic progenitor subtype); riluzole directly blocks the Wnt-β-catenin pathway (targeting metabolism-related EMT in the squamous subtype); inhibiting CAF-derived Wnt2 can enhance the efficacy of anti-PD-1 in the immunogenic subtype; the squamous subtype can be combined with epigenetic drugs and Wnt inhibitors to restore endodermal gene expression (118,119,124,125).

Notch and Hh pathways: regulatory roles in the pancreatic cancer microenvironment. In the pancreatic cancer microenvironment, the Notch and Hh pathways regulate EMT through dynamic interactions with stromal cells, serving as key upstream signals driving tumor invasion and treatment resistance. In pancreatic cancer, the Notch pathway is activated by membrane-bound ligands (such as DLL, Jagged families) from adjacent cells. Upon ligand binding, the Notch receptor is cleaved, releasing its intracellular domain (NICD) into the nucleus to form a complex with transcription factors such as CSL and drive target gene expression. The Hh pathway is initiated by secreted ligands [such as Sonic Hedgehog (SHH)] binding to the PTCH receptor, which relieves its inhibition of SMO and ultimately leads to the activation of GLI family transcription factors. Together, these pathways co-regulate the EMT process (126).

EGFR/ERBB2 signals synergize with the Notch/Hh pathway to drive EMT in myCAFs induced by TGF-β (107). Specifically, TGF-β induces myCAFs to secrete autocrine amphiregulin (AREG), activating EGFR/ERBB2 heterodimer signals; IL-6 secreted by these $CD90^-$ myCAFs ($CD90^-$) can upregulate the expression of Snail and Twist in cancer cells via the STAT3 pathway; meanwhile, EGFR/ERBB2 signals enhance the γ-secretase activity of the Notch pathway to promote NICD nuclear translocation, forming a 'TGF-β-AREG-EGFR/Notch' cascade effect (107); Hh-highly active myCAFs remodel collagen structure via the PTCH-SMO-GLI1 axis, forming functional complementarity of 'structural remodeling-soluble factor regulation' with EGFR□myCAFs, reflecting the selective activation of pathways by CAF subtypes (107,118).

At the molecular level the long non-coding (lnc)RNA TRPM2-AS binds to miR-31-5p/miR-146a-5p via a ceRNA mechanism, relieving their inhibition of NUMB, thereby releasing the inhibition of Notch1 ubiquitination and degradation and maintaining continuous activation of the Notch pathway (107); meanwhile, GLI1 downstream of Hh can form an intranuclear complex with EGFR phosphorylation products, synergistically binding to the ZEB1 promoter; Notch-activated cMYC, which acts as an evolutionarily conserved proto-oncogenic transcription factor, strengthens EGFR signals by upregulating AREG transcription, constructing a multi-pathway positive feedback loop (107,127).

Clinical translation studies have shown that the combination of EGFR/ERBB2 inhibitors and Notch inhibitors (such as DAPT) can markedly reduce the expression of EMT markers induced by myCAFs and reverse CAF-mediated gemcitabine resistance in PDAC organoid models (107). This strategy avoids the problem of CAF subtype switching caused by the single use of Hh inhibitors (such as vismodegib) (118). in addition, dietary phytochemicals (such as curcumin) can indirectly inhibit the synergistic activation of EGFR/Notch by downregulating SP1, providing a supplement for combination therapy (107,128). These findings further support the multi-target therapeutic value of the pathway crosstalk-CAFs-EMT axis.

The paradigm of CAF-secreted TGF-β inducing EMT has been challenged by single-cell spatial transcriptomics; novel inflammatory CAFs (iCAFs) independently activate EMT via the IL-1β/JAK/STAT axis and this subpopulation markedly expands in the microenvironment after chemotherapy. More paradoxically, while stroma-depleting therapies targeting CAFs enhance drug delivery, they may accelerate tumor spread (the 'FA paradox'); although combining with CXCR4 inhibitors inhibits metastasis in KPC mice, differences in human stromal density may weaken efficacy. These findings require a re-evaluation of the clinical translation path of stroma targeting (Fig. 5).

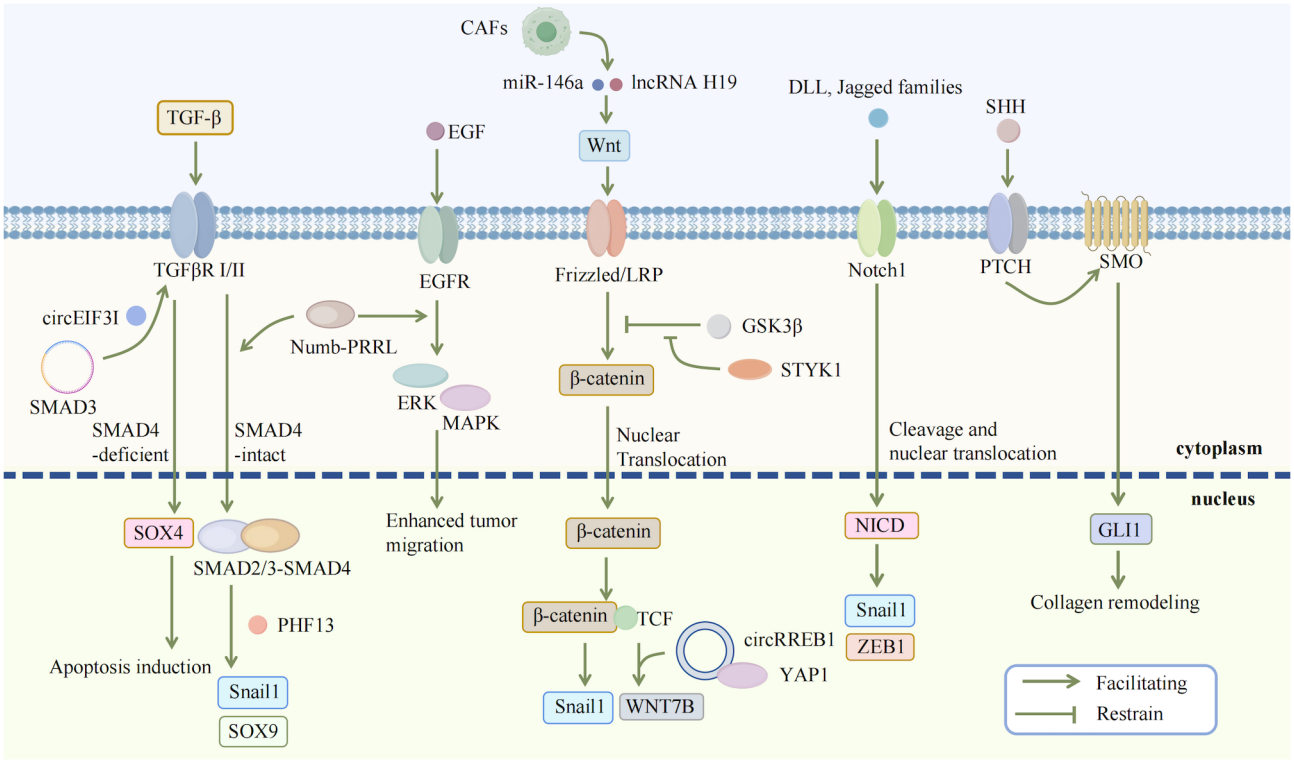

Figure 5. The dual role of signaling and pathway crosstalk in pancreatic cancer EMT. The role of the TGF-β pathway in EMT of pancreatic cancer is context-dependent. In the presence of SMAD4, TGF-β not only activates the SMAD2/3-SMAD4 complex to regulate key transcription factors such as Snail and Twist but also, with the assistance of PHF13, maintains the super-enhancer activity of SNAI1 and SOX9, ensuring sustained expression of EMT genes. Conversely, SMAD4 loss switches SOX4 from an oncogenic to a pro-apoptotic function. CircEIF3I enhances pathway activation by strengthening the interaction between SMAD3 and TGFβRI. Under TGF-β1 stimulation, Numb-PRRL activates the SMAD2/3-Snail pathway and forms a cross-activation loop with Notch1, synergistically promoting EMT. TGF-β also exhibits crosstalk with the EGF-EGFR-ERK/MAPK pathway to collectively enhance cancer cell migration and invasion. Intracellularly, FAM83A binds to β-catenin to disrupt the degradation complex, an effect potentiated by BLK phosphorylation, jointly promoting β-catenin nuclear translocation and Snail transcription; STYK1 maintains pathway activity by sequestering GSK3β into multivesicular bodies. Non-coding RNAs contribute to this regulation, such as circRREB1 binds to YAP1 to promote WNT7B transcription and glycolysis. Furthermore, the Notch signaling pathway, activated by membrane-bound ligands (such as DLL and Jagged) from neighboring cells, and the Hh pathway, initiated by secreted ligands (such as SHH) binding to the PTCH receptor, also participate in the fine-tuned regulation of EMT. EMT, epithelial-mesenchymal transition; TGF-β, transforming growth factor-β; SMAD4, Sma- and Mad-related Protein 4; PHF13, PHD Finger Protein 13; SOX, SRY-Box Transcription Factor; TGFβRI, Transforming Growth Factor-beta Receptor I; EGF, Epidermal Growth Factor; EGFR, Epidermal Growth Factor Receptor; ERK, Extracellular Signal-Regulated Kinase; MAPK, Mitogen-Activated Protein Kinase; FAM83A, Family With Sequence Similarity 83 Member A; BLK, B Lymphoid Tyrosine Kinase; STYK1, Serine/Threonine/Tyrosine Kinase 1; GSK3β, Glycogen Synthase Kinase 3 Beta; YAP1, Yes-Associated Protein 1; DLL, Delta-like ProteinHh, Hedgehog; SHH, Sonic Hedgehog; PTCH, Patched.

Epigenetic programming: epigenetic memory for stabilizing EMT states. DNA methylation plays a core role in the EMT of PDAC by regulating the tumor microenvironment, epigenetic landscape and signaling pathway networks. In the tumor microenvironment, PDAC cells with organ-specific metastatic potential can induce genomic DNA methylation changes in CAFs, for example, hypermethylation of metabolic genes NQO1 and ALDH1a3 leads to downregulation of their mRNA expression. This metabolic reprogramming provides a metabolic basis for CAFs to support the EMT process and the heterogeneity of CAFs further affects the transmission of EMT-related signals through epigenetic regulation (129,130).

Subtype-specific differences in the epigenetic landscape are another key aspect of EMT regulation: In the basal subtype of PDAC, key EMT pathways such as TGF-β are abnormally activated due to epigenetic modifications and the methylation imbalance of pathway genes enhances signal activity, directly triggering the transition of epithelial cells to a mesenchymal phenotype; the classical subtype indirectly affects the EMT process by regulating the methylation status of pancreatic development-related transcription factors (131). At the molecular mechanism level, high expression of DNA methyltransferase 1 (DNMT1) is a core driving factor: It targets and silences the promoters of EMT suppressors such as Krüppel-like factor 4, thereby relieving the inhibition that these suppressors originally exert on EMT transcription factors such as Snail and Twist (132,133). Meanwhile, DNMT1 forms a negative feedback regulatory axis with miR-148a, whereby DNMT1 overexpression in pancreatic cancer drives hypermethylation of the miR-148a promoter to suppress miR-148a expression, while miR-148a directly targets the 3'UTR of DNMT1 mRNA to inhibit its own upstream regulator. Disruption of this inhibitory loop (that is, the loss of miR-148a-mediated restraint on DNMT1) exacerbates the methylation-dependent silencing of EMT-related genes, thereby further promoting EMT (134).

At the signaling pathway level, abnormal methylation of DNA methylation-driven genes (such as GPRC5A) can activate the PI3K-AKT pathway; methylation silencing of

HIP1R enhances the migration and invasion ability of tumor cells via this pathway and this process has crosstalk with downstream signals of KRAS specifically, during pancreatic acinar-ductal metaplasia (ADM), a pre-neoplastic lesion of pancreatic cancer. This crosstalk between KRAS downstream pathways is achieved through the coordinated activation of the PI3K pathway (which regulates cell proliferation and survival) and the Rho/Rac/Cdc42 GTPase pathway (which modulates cytoskeletal remodeling and morphological transformation) (130,135,136). Notably, the DNA methylation 'memory' formed during pancreatic acinar-ductal metaplasia can continuously affect PI3K and Rho GTPase signals even in the absence of KRAS mutations, providing an epigenetic basis for the continuous activation of EMT (108). In addition, changes in global DNA methylation levels also participate in cytoskeletal reorganization by affecting the β-sheet structure of proteins, ultimately supporting EMT-mediated tumor invasion and metastasis (137).

Histone modifications play a core role in the EMT of pancreatic cancer by constructing a multi-level epigenetic regulatory network, with mechanisms involving the synergy and crosstalk of multiple modification types such as methylation, acetylation and ubiquitination. At the level of histone methylation, the protein arginine methyltransferase (PRMT) family exhibits significant functions; PRMT1 activates the Wnt pathway by binding to the β-catenin promoter, or enhances the transcriptional activity of Gli1 via methylation to induce the expression of EMT-related genes (such as ZEB1) (138,139); PRMT5 upregulates β-catenin via the EGFR/AKT/β-catenin axis, promoting the migration and invasion of pancreatic cancer cells (140). Among lysine methyltransferases (KMTs) loss of SETD2 accelerates KRAS-driven acinar-ductal metaplasia and EMT by continuously activating AKT and downregulating α-catenin (141); KMT5A upregulates stem cell and EMT-related genes by inducing ROR1 expression (142), KMT5C indirectly inhibits EMT by regulating epithelial transcription factors such as FOXA1 (143). The functional differentiation of histone demethylases (KDMs) is also critical: KDM2B activates the Hippo signal by inhibiting MOB1, or inhibits epithelial markers (such as CDH1) by regulating H1A ubiquitination, promoting migration and invasion (144,145). KDM3A is activated by HIF1α under hypoxic conditions, initiating EMT by upregulating DCLK1 (146). KDM4B directly activates ZEB1 transcription in response to TGF-β-induced EMT (147). KDM5A is regulated by NOX4 under hypoxic conditions, promoting invasion and metastasis by activating SNAIL1 (148). Loss of KDM6A enhances the mesenchymal phenotype by activating the activin A-p38 pathway (149).

The dynamic balance of histone acetylation is another important node in EMT regulation. p300/CBP activates GATA6 expression via H3K27ac, which directly or indirectly inhibits EMT (150,151). PCAF forms a complex with p300, activating miR200c transcription by acetylating ZEB1 and downregulation of the miR200 family is key to maintaining the mesenchymal phenotype (152). Among histone deacetylases (HDACs): HDAC1 and HDAC2 form a Snail/HDAC1/HDAC2 inhibitory complex to downregulate E-cadherin, enhancing tumor invasiveness (153,154); SIRT1 regulates the Wnt pathway by deacetylating β-catenin, participating in the process of pancreatic acinar-ductal metaplasia (155).

Histone ubiquitination affects EMT by regulating chromatin structure and transcription factor activity. Ring1A/Ring1B of the PRC1 complex is recruited by Snail with the assistance of EZH2 to inhibit E-cadherin transcription (156). Overexpression of Bmi1 directly promotes EMT by downregulating E-cadherin (157). Among deubiquitinases: USP22 upregulates ZEB1 and Snail by activating FAK signals, reducing E-cadherin expression (158) and USP28 activates the Wnt/β-catenin pathway by stabilizing FOXM1, inducing the expression of EMT-related genes (159).

These mechanisms collectively constitute a complex network of histone modification regulating EMT. Microenvironmental factors such as hypoxia and inflammation further amplify regulatory effects by affecting the activity of modification enzymes (such as activation of KDM3A and KDM5A under hypoxia) (146,148). Such regulation is not only involved in tumor invasion and metastasis but also associated with chemotherapy resistance and stem cell properties, providing multi-dimensional targets for the development of EMT intervention strategies targeting epigenetic modifications.

NcRNAs regulatory networks: Modulators of signaling pathways. NcRNAs construct a complex regulatory system for pancreatic cancer EMT through multi-dimensional interaction networks with proteins, covering aspects such as direct regulation of core EMT factors, activation of key signaling pathways, remodeling of the metabolic microenvironment and regulation of immune-related EMT paracrine signals.

At the level of circular RNAs (circRNAs) circRTN4 maintains the protein stability of RAB11FIP1 by masking the ubiquitination site at Lys578 of RAB11FIP1, continuously activating downstream EMT genes (102). circEIF3I promotes the aggregation of TGFβ receptor I in early endosomes and the phosphorylation of SMAD3 by simultaneously binding to AP2A1 and SMAD3, driving the expression of invasion-related genes such as MMP2/9 (108). The newly identified circRREB1 promotes the nuclear localization of YAP1 by binding to the RRM domain of YAP1, activating WNT7B transcription and the Wnt/β-catenin pathway and upregulating EMT transcription factors such as Snail and Twist (120). These circRNAs form functional complexes with proteins through specific domains, precisely regulating key signal nodes of EMT.

lncRNAs exhibit bidirectional regulatory characteristics: in positive regulation, ZFAS1 maintains EMT activity through an AMPK-ZEB1 positive feedback loop under metabolic stress (160). FGD5-AS1, upregulated by the IL-6/STAT3 pathway, enhances the acetylation of STAT3 by bridging p300 and STAT3, activating the STAT3/NF-κB pathway and inducing M2 macrophage polarization, which reinforces EMT via paracrine TGF-β (161). LINC00842 binds to the inhibitory domain of PGC-1α in a high-glucose environment, maintaining its activity to support EMT-related fatty acid synthesis metabolism (162). In negative regulation, MTSS1-AS accelerates the degradation of MZF1 by promoting the interaction between MZF1 and STUB1, upregulating the EMT suppressor MTSS1 (163). KCNK15-AS1 activates PTEN by mediating REST degradation, inhibiting the expression of Vimentin driven by the PI3K/Akt pathway (164). The newly identified MEG3, as a tumor-suppressive lncRNA, upregulates

E-cadherin expression by sponging miR-421 and can also regulate SLFN5 expression by targeting miR-146b-5p, dualistically inhibiting the EMT process (165,166).

MicroRNAs (miRNAs) play a significant role in hypoxic adaptation regulation: miR-301a is transcriptionally activated by HIF-2α under hypoxic conditions, inhibiting the tumor-suppressive branch of the TGF-β pathway by targeting SMAD4, while downregulating PTEN and TP63 to enhance Akt activity and upregulate mesenchymal markers, respectively, forming a 'hypoxia-HIF-2α-miR-301a-EMT' regulatory axis (167). Exosomal miRNAs spread the EMT phenotype through intercellular communication; for example, the absence of exosomal miR-128-3p leads to overexpression of its target gene Bmi1, which not only promotes EMT but also enhances drug efflux capacity, being associated with gemcitabine resistance in pancreatic cancer (168).

The transfer (t)RNA-derived stress-induced RNAs (tiRNAs) RNA-Val-CAC-2 prevents the ubiquitination and degradation of FUBP1 by binding to the RRM domain of FUBP1; stabilized FUBP1 accumulates in the FUSE region of the c-Myc promoter, activating its transcription to drive the expression of EMT effector genes such as N-cadherin and Twist1 (169).

These mechanisms collectively reveal the molecular basis of ncRNAs regulating pancreatic cancer EMT through a cascade mode of 'protein stability regulation-signaling pathway activation-metabolic adaptation-phenotype spread.' Microenvironmental factors such as hypoxia and metabolic stress further amplify regulatory effects by selectively upregulating specific ncRNAs (such as ZFAS1, miR-301a under hypoxia). Such regulatory networks are not only involved in tumor invasion and metastasis but also closely associated with chemotherapy resistance, providing diverse targets for the development of EMT intervention strategies targeting ncRNAs.

4. Targeted therapeutic strategies for EMT: From basic research to clinical translation

Given the core role of EMT in PC invasion, metastasis, maintenance of stem cell properties and treatment resistance, direct targeting of EMT-related pathways has become a highly attractive therapeutic direction. This strategy aims to reverse the invasive phenotype of tumor cells, restore their sensitivity to conventional treatments and inhibit metastatic spread by interfering with upstream EMT-inducing signals, core transcriptional regulatory networks, or downstream effector molecules. Currently, numerous preclinical studies and several clinical trials are exploring multiple EMT-targeted strategies, covering small-molecule inhibitors, natural compounds, gene therapy and innovative combination therapeutic regimens.

Inhibiting upstream signaling pathways that drive EMT. The initiation and maintenance of EMT are driven by the continuous activation of multiple upstream signaling pathways, forming a complex regulatory network. Directly targeting the source of these signals represents a fundamental strategy to inhibit EMT and its associated malignant phenotypes in pancreatic cancer. Current research has focused on several key pathways, with the TGF-β pathway being one of the most intensively studied. The TGF-β signaling pathway is a potent inducer of EMT and its aberrant activation is closely linked to disease progression and poor prognosis (57). Clinical translation efforts are exploring combinations, such as TGFβRI inhibitor with nal-IRI/5-FU/LV chemotherapy, in phase Ib/II trials. Preclinical studies showed that this combination could inhibit tumor invasion and prolong survival in mouse models by inducing the tumor suppressor gene CCDC80 and blocking EMT (170). Repurposed drugs have also shown unexpected efficacy; the antifungal agent itraconazole suppresses the TGF-β/SMAD2/3 pathway to inhibit EMT, invasion and migration (171), while the NSAID indomethacin blocks TGF-β-mediated EMT by upregulating E-cadherin and downregulating N-cadherin and Snail (172). The regulatory network is highly complex, involving molecules such as Menin, which enhances TGF-β-mediated EMT by inhibiting C/EBPβ and autocrine TGF-β1, which can form a self-sustaining feed-forward loop via the ALK5-MEK-ERK signal, antagonizing the effects of exogenous TGF-β1 (173,174). Furthermore, super-enhancers can regulate TGFBR2 expression, offering an epigenetic target (175). Natural products provide additional resources; extracts from *Cynanchum paniculatum* inhibit EMT by suppressing the TGF-β1/Smad2/3 pathway (176) and baicalein disrupts the TGF-β/FTO/ZEB1 axis by downregulating the m6A demethylase FTO, reducing ZEB1 mRNA stability (177). However, the dual role of TGF-β as both a tumor suppressor and promoter necessitates careful consideration, as some agents such as calycosin can inhibit proliferation but paradoxically promote EMT by upregulating TGF-β1 (178). A multi-faceted intervention system has thus been established, encompassing TGFβRI inhibitors, approved drugs, natural compounds and combination therapies with chemotherapy to improve drug penetration and clinical translation potential.

Beyond TGF-β, the Wnt/β-catenin and Hh pathways are critical targets. The Wnt/β-catenin pathway is inhibited by various natural products: oridonin suppresses the pathway and reduces β-catenin levels to inhibit migration and EMT (179). *Trametes robiniophila* (Huaier) extract inhibits proliferation, migration and EMT by downregulating β-catenin (180) and high-dose vitamin C blocks invasion and metastasis by suppressing Wnt/β-catenin-mediated EMT (181). At the molecular level, restoring the expression of the Wnt antagonist DKK3 blocks hypoxia-induced nuclear translocation of β-catenin and reverses EMT, enhancing gemcitabine's effect (182). Silencing molecules such as LRRFIP1 enhances β-catenin phosphorylation and reduces its nuclear localization, while silencing GPX2 downregulates key Wnt pathway molecules, both effectively reversing the EMT phenotype (183,184). Similarly, CHRNB2 exerts anti-tumor effects by downregulating β-catenin pathway activity via a non-acetylcholine-dependent mechanism (185). Epigenetic regulation also plays a role, as TET1 catalyzes DNA hydroxymethylation in the SFRP2 promoter, activating this Wnt inhibitor and blocking both canonical and non-canonical Wnt signaling (186). The Hh pathway maintains cancer stem cell properties and promotes EMT by regulating transcription factors such as Gli. Curcumin exerts multi-target effects, reversing hypoxia-induced EMT by suppressing Hh pathway activation (downregulating SHH, SMO, GLI1) and inhibiting crosstalk between CAFs and tumor cells (107,128,187). The

resveratrol derivative triacetyl resveratrol (TCRV) inhibits EMT transcription factors such as Zeb1 by upregulating the miR-200 family and simultaneously inhibits the SHH pathway (188). Another natural product, α-mangostin, targets Hh pathway molecules (Gli1 and Smoothened) and core EMT-TFs (Snail and Slug); when encapsulated in PLGA nanoparticles, it effectively targets Shh pathway-related genes *in vivo*, reducing cancer stem cell markers and inhibiting tumorigenesis (189,190). *Sedum sarmentosum* Bunge extract also downregulates Hh pathway activity (191). A significant challenge is the compensatory activation of other pathways; for instance, Hh pathway inhibitors (SHhi) can improve drug delivery by enhancing vascular patency but may induce an FGF-driven EMT phenotype. This can be addressed by a dual inhibition strategy combining SHhi with FGFR inhibitors such as infigratinib, which reverses EMT while retaining improved vascular permeability (192).

Interventions targeting other key pathways, such as PI3K/Akt/mTOR and MAPK/ERK, further enrich the therapeutic arsenal. The PI3K/Akt/mTOR pathway is inhibited by agents such as the Aurora kinase A inhibitor alisertib, which reduces N-cadherin and upregulates E-cadherin to block EMT while inducing cell cycle arrest and autophagy (193). Natural products such as betulinic acid and irisin inhibit EMT and stemness by activating AMPK to suppress mTOR signaling (194,195) and plumbagin inhibits the PI3K/Akt/mTOR pathway while synergistically regulating p38 MAPK and AMPK activation (196). Inhibiting KIN17 downregulates this pathway, upregulating E-cadherin and reducing vimentin and N-cadherin (197), while arsenic trioxide reverses EMT and enhances chemosensitivity by inhibiting TIMP1-mediated PI3K/Akt/mTOR activation (198). The MAPK/ERK pathway is another key target. Curcumin inhibits IL-6-mediated ERK and NF-κB phosphorylation by suppressing PSC activation and IL-6 secretion under hypoxia, thereby disrupting tumor-stroma crosstalk (199). HNRNPA2B1 promotes EMT by activating the ERK/Snail axis (200), whereas miR-338-5p inhibits the EMT process by targeting EGFR and blocking EGF-induced MAPK/ERK signaling (201). The TAp73 protein inhibits basal and TGF-β-induced ERK activation in a SMAD4-dependent manner, upregulating E-cadherin and downregulating Snail to inhibit migration (202). Targeting receptor tyrosine kinases such as MET and AXL is also promising. The inhibitor NPS-1034 targets the MET/PI3K/AKT axis to suppress EMT and migration, shows synergistic effects with chemotherapy and exhibits immunomodulatory potential by inducing type I interferon and TNF (203). Similarly, a novel AXL/triple angiokinase inhibitor effectively suppresses AXL and lung metastasis, with its mechanism involving EMT inhibition (204). Furthermore, inhibiting the HGF/c-MET pathway not only directly inhibits tumor growth but also enhances cytotoxic T-cell infiltration by reducing TGF-β secretion, linking EMT inhibition to immune regulation (205).

In summary, a comprehensive intervention system targeting upstream signaling pathways of EMT has been established (Table I). This system includes diverse strategies: Blocking the TGF-β pathway with inhibitors and repurposed drugs, targeting the Wnt/β-catenin and Hh pathways with natural products, molecular interventions and combination therapies and inhibiting pathways such as PI3K/Akt/mTOR and HGF/c-MET with specific inhibitors that can synergize with chemotherapy. These multi-dimensional approaches, validated in preclinical studies, aim to reverse the invasive phenotype, restore treatment sensitivity and inhibit metastasis, providing a strong rationale for their clinical translation to address therapeutic resistance in pancreatic cancer.

Targeting core EMT regulators. In addition to blocking upstream signals, directly targeting the core molecules that execute the EMT program, specifically EMT-transcription factors (EMT-TFs) and the epigenetic mechanisms governing their expression, represents a more precise therapeutic strategy.

A primary approach involves inhibiting key EMT-TFs such as Snail, Slug, ZEB and Twist. This can be achieved through diverse mechanisms. For instance, miRNAs offer precise regulation: miR-34a directly targets Snail1 and Notch1 (83), miR-539 inhibits TWIST1 (101) and miR-200b-3p suppresses ZEB1 (204). Nutrient deprivation strategies, such as arginine deprivation, can simultaneously downregulate multiple EMT-TF families (Snail, Slug and Twist) while upregulating E-cadherin and inhibiting invasion (100). Natural products also exhibit multi-target effects; α-mangostin inhibits Snail and Slug (190), while the resveratrol derivative TCRV targets Snail, Slug and Zeb1 (188). Furthermore, the protein DACH1 can directly bind to SNAI1 to inhibit its transcriptional activity, thereby blocking EMT and promoting apoptosis (207). These strategies collectively reverse the EMT phenotype by upregulating epithelial markers and downregulating mesenchymal markers.

Beyond direct TF targeting, interventions against epigenetic and post-transcriptional mechanisms have emerged as powerful tools. ncRNAs function as critical regulators: lncRNA GAS5 acts as a ceRNA for miR-221 to upregulate SOCS3, reversing EMT and gemcitabine resistance (208), whereas LINC00958 promotes EMT by sponging miR-330-5p (209). Conversely, lncRNA GATA6-AS1 inhibits EMT by reducing SNAI1 mRNA stability in an m6A-dependent manner by inhibiting FTO (210). The m6A modification itself is a key regulatory layer; the 'eraser' FTO promotes EMT and can be targeted for intervention (212) and the 'demethylase' ALKBH5 exerts anti-tumor effects by demethylating mRNAs of iron metabolism regulators, indirectly leading to SNAI1 degradation (211). Histone modifications are another major target. HDAC inhibitors, such as a novel dual HDAC2/6 inhibitor and the pan-HDAC inhibitor LAQ824, can reverse TGF-β-induced EMT, induce apoptosis and enhance antigen presentation (212,213). Similarly, the histone methyltransferase inhibitor DZNep reshapes miRNA expression to block the TGF-β signaling pathway and associated EMT (214,215).

In summary, a two-dimensional intervention system has been established, encompassing the direct inhibition of EMT-TFs and the regulation of their epigenetic landscape (Table II). Preclinical studies confirm that these strategies can effectively reverse the EMT phenotype, weaken tumor stemness and invasive capacity and provide precise molecular targets for overcoming therapeutic resistance in pancreatic cancer.

Table I. Core strategies targeting EMT signaling pathways.

First author/s, year	Targeted pathway	Key target(s)	Reresentative intervention(s)	Mechanism and effects	Research model	(Refs.)
Hong *et al*, 2020	TGF-β Signaling Pathway	TGFβRI	Vactosertib	Blocks receptor kinase activity; inhibits SMAD2/3 phosphorylation and Snail/ZEB1 expression; reverses EMT.	Preclinical models, pancreatic tumor mouse models	(170)
Zhao *et al*, 2024		TGFβRI	Riboflavin (Vitamin B2)	Directly binds and inhibits TGFβRI, blocking TGF-β signaling and inhibiting EMT and metastasis.	*In vitro* and *in vivo* models	(206)
Chen *et al*, 2018		TGF-β/SMAD axis	Itraconazole	Suppresses the TGF-β/SMAD2/3 signaling pathway, inhibiting EMT, invasion and migration.	Pancreatic cancer cells, animal models	(171)
Sezer *et al*, 2022		TGF-β-mediated EMT	Indomethacin	Upregulates E-cadherin, downregulates N-cadherin and Snail, blocking TGF-β-induced EMT.	Pancreatic cancer cells models	(172)
Cheng *et al*, 2019		Menin/C/EBPβ axis	Menin inhibition (mechanism study)	Menin enhances TGF-β signal-mediated EMT by inhibiting C/EBPβ expression; exhibits prometastatic effects when C/EBPβ is absent.	Pancreatic cancer cells models	(173)
Cheng *et al*, 2019		TGF-β signaling feedback	-(Mechanism study)	Autocrine TGF-β1 forms a self-sustaining feed-forward loop via ALK5-MEK-ERK, antagonizing exogenous TGF-β1 effects.	Pancreatic cancer cells models	(173)
Zhu *et al*, 2020		TGFBR2 epigenetic regulation	-(Mechanism study)	Super-enhancers regulate TGFBR2 expression, affecting TGF-β signaling activity and pancreatic cancer progression.	Pancreatic cancer cells models	(175)
Cheng *et al*, 2024		TGF-β/Smad2/3 axis	*Cynanchum paniculatum* extract	Suppresses the TGF-β1/Smad2/3 signaling pathway, exerting EMT-inhibiting effects at non-cytotoxic doses.	*In vitro* cell models and *in vivo* animal models	(176)
Ungefroren *et al*, 2021		TGF-β/FTO/ZEB1 axis	Baicalein	Downregulates m6A demethylase FTO, enhancing m6A modification of ZEB1 mRNA and reducing its stability, disrupting EMT.	Pancreatic cancer cells models	(174)
Zhao *et al*, 2025	Wnt/β-catenin Signaling Pathway	β-catenin nuclear translocation	Oridonin	Inhibits Wnt/β-catenin pathway, reduces cytoplasmic and nuclear β-catenin levels, suppressing migration and EMT.	Pancreatic cancer cells models and *in vivo* animal models	(177)
Zhou *et al*, 2020		Wnt/β-catenin pathway	*Trametes robiniophila* (Huaier) extract	Suppresses Wnt/β-catenin pathway (downregulates β-catenin), inhibiting proliferation, migration, invasion and EMT.	Pancreatic cancer cells and animal models	(180)

Table I. Continued.

First author/s, year	Targeted pathway	Key target(s)	Reresentative intervention(s)	Mechanism and effects	Research model	(Refs.)
Kim *et al*, 2022		Wnt/β-catenin-mediated EMT	High-dose Vitamin C	Inhibits glycolysis and Wnt/β-catenin-mediated EMT, blocking cancer cell growth and metastasis.	Pancreatic cancer cells models	(181)
Guo *et al*, 2015		DKK3	DKK3 gene restoration	Antagonizes Wnt signaling, blocks hypoxia-induced β-catenin nuclear translocation, reverses EMT, enhances gemcitabine efficacy.	Pancreatic cancer Bxpc-3 cells models, clinical sample analysis and animal models	(182)
Douchi *et al*, 2015		β-catenin degradation complex	Silencing LRRFIP1	Enhances β-catenin phosphorylation and reduces its nuclear localization by targeting the degradation complex, reversing EMT phenotype.	Pancreatic cancer cells models, animal models	(183)
Li *et al*, 2020		Wnt pathway key molecules	Silencing GPX2	Downregulates key Wnt pathway molecules, inhibiting Wnt/β-catenin pathway and reversing EMT.	Pancreatic cancer cells models, clinical research	(184)
Qin *et al*, 2022		β-catenin pathway	CHRNB2	Downregulates β-catenin pathway activity via a non-acetylcholine-dependent mechanism, inhibiting migration and invasion; associated with EMT inhibition.	Pancreatic cancer cells models, clinical research	(185)
Wu *et al*, 2019		SFRP2 epigenetic activation	TET1	Catalyzes DNA hydroxymethylation in the SFRP2 promoter, initiating its transcriptional activation, inhibiting canonical/non-canonical Wnt pathways and blocking EMT.	Clinical sample analysis, cell and animal models	(186)
Cao *et al*, 2017	Hedgehog Signaling Pathway	SMO/Gli	Curcumin	Reverses hypoxia-induced EMT by downregulating SHH, SMO, GLI1 expression; also targets other pathways (EGFR/Notch, PSC activation).	Pancreatic cancer cells models	(187)
Ma *et al*, 2019		Hh pathway and EMT-TFs	α-Mangostin	Targets Hh pathway molecules (Gli1, Smoothened) and core EMT-TFs (Snail, Slug), weakening CSC properties and blocking EMT.	Pancreatic cancer cells models	(190)
Verma *et al*, 2016		Shh pathway-related genes	α-Mangostin-PLGA nanoparticles	Specifically targets Shh pathway-related genes in KPC mice, reducing CSC marker expression and inhibiting tumorigenesis and liver metastasis.	KPC transgenic mouse model, cell model	(189)

Table I. Continued.

First author/s, year	Targeted pathway	Key target(s)	Reresentative intervention(s)	Mechanism and effects	Research model	(Refs.)
Bai *et al*, 2016		Hh pathway	*Sedum sarmentosum* extract (SSBE)	Downregulates Hh pathway activity, inhibits cancer cell proliferation, weakens stem cell properties, blocks EMT.	Pancreatic cancer cells model, animal models	(191)
Chaudhuri *et al*, 2024		SHHi-induced FGF compensation	SHHi + FGFR inhibitor (such as Infigratinib)	SHHi improves drug delivery but induces FGF-driven EMT; combination reverses EMT while retaining improved vascular permeability.	Preclinical studies	(192)
Fu *et al*, 2019		Shh pathway and miR-200	Triacetyl resveratrol (TCRV)	Upregulates miR-200 family to inhibit Zeb1, inhibits Shh pathway activity reducing Cyclin D1 and Bcl-2, synergistically inhibiting EMT.	Pancreatic cancer cells model, animal model	(188)
Wang *et al*, 2015	Other key signaling pathways (PI3K/Akt/mTOR, MAPK/ERK, HGF/c-MET)	PI3K/Akt/mTOR	Alisertib (Aurora kinase A inhibitor)	Inhibits PI3K/Akt/mTOR pathway, reduces N-cadherin, upregulates E-cadherin, blocks EMT; induces G2/M arrest and autophagy.	Pancreatic cancer cells model	(193)
Sun *et al*, 2019		AMPK/mTOR	Betulinic acid	Activates AMPK, suppressing downstream mTOR signaling, inhibiting EMT and stem cell properties.	Pancreatic cancer cells model	(194)
Wang *et al*, 2015		PI3K/Akt/mTOR and p38 MAPK	Plumbagin	Inhibits PI3K/Akt/mTOR, synergistically regulates p38 MAPK and AMPK activation, upregulates E-cadherin, downregulates N-cadherin, blocks EMT, induces autophagy.	Pancreatic cancer cells model, animal model	(196)
Li *et al*, 2020		MAPK/ERK (IL-6 mediated)	Curcumin	Suppresses hypoxic PSC activation and IL-6 secretion, inhibiting IL-6-mediated ERK and NF-κB phosphorylation, interfering with tumor-stroma interactions and EMT.	Pancreatic cancer cells models	(199)
Sun *et al*, 2021		MAPK/ERK (EGF induced)	miR-338-5p	Directly targets EGFR, blocking EGF-induced MAPK/ERK pathway activation, inhibiting EMT and metastasis.	Pancreatic cancer cells models, clinical research	(201)
Luan *et al*, 2024		HGF/c-MET pathway	NPS-1034 (MET/AXL inhibitor)	Inhibits MET/PI3K/AKT axis-induced EMT, suppresses migration; synergizes with chemotherapy; shows immunomodulatory potential.	Pancreatic cancer cells models	(203)

Table I. Continued.

First author/s, year	Targeted pathway	Key target(s)	Reresentative intervention(s)	Mechanism and effects	Research model	(Refs.)
Mekapogu *et al*, 2023		HGF/c-MET pathway and Immunity	c-MET inhibitors/antibodies	Inhibiting HGF/c-MET directly inhibits tumor growth/metastasis and increases cytotoxic T-cell infiltration by reducing TGF-β secretion.	Animal models and cells models	(205)

EMT, epithelial-mesenchymal transition; ALK5, Activin Receptor-Like Kinase 5; AMPK, Adenosine Monophosphate-Activated Protein Kinase; AXL, AXL Receptor Tyrosine Kinase; β-catenin, Beta-Catenin; c-MET, Hepatocyte Growth Factor Receptor; CHRNB2, Cholinergic Receptor Nicotinic Beta 2 Subunit; CSC, Cancer Stem Cell; DKK3, Dickkopf-Related Protein 3; EGF, Epidermal Growth Factor; EGFR, Epidermal Growth Factor Receptor; EMT, Epithelial-Mesenchymal Transition; ERK, Extracellular Signal-Regulated Kinase; FGFR, Fibroblast Growth Factor Receptor; FTO, Fat Mass and Obesity-Associated Protein; Gli, Glioma-Associated Oncogene Homolog; GPX2, Glutathione Peroxidase 2; HGF, Hepatocyte Growth Factor; Hh, Hedgehog; IL-6, Interleukin 6; KPC, LSL-Kras G12D/+; LSL-Trp53 R172H/+; Pdx1-Cre; LRRFIP1, Leucine-Rich Repeat FIP Family Member 1; MAPK, Mitogen-Activated Protein Kinase; MEK, Mitogen-Activated Protein Kinase Kinase; miR, MicroRNA; MMP, Matrix Metalloproteinase; NF-κB, Nuclear Factor-Kappa B; PAX8, Paired Box 8; PI3K, Phosphatidylinositol 3-Kinase; PLGA, Poly(Lactic-Co-Glycolic Acid); p38 MAPK, p38 Mitogen-Activated Protein Kinase; PSC, Pancreatic Stellate Cell; SHH, Sonic Hedgehog; SHHi, Hedgehog Pathway Inhibitor; SFRP2, Secreted Frizzled-Related Protein 2; Snail, Snail Family Zinc Finger; Snail1, Snail Family Zinc Finger 1; Slug, Snail Family Zinc Finger 2; SMAD, Sma- and Mad-Related Protein; SMO, Smoothened; SOCS3, Suppressor of Cytokine Signaling 3; SNAI1, Snail Family Zinc Finger 1; TCRV, Triacetyl Resveratrol; TET1, Ten-Eleven Translocation 1; TGF-β, Transforming Growth Factor-β; TGFβRI, Transforming Growth Factor-Beta Receptor I; TGFBR2, Transforming Growth Factor-Beta Receptor II; TNF, Tumor Necrosis Factor; Wnt, Wingless-Type MMTV Integration Site Family; ZEB1, Zinc Finger E-Box Binding Homeobox 1.

Table II. Targeting core EMT regulators and microenvironment.

First author/s, year	Target category	Specific target/ molecule	Representative intervention(s)	Mechanism of action	Research model (cell/animal)	(Refs.)
Tang *et al*, 2017	Inhibiting EMT transcription factors (EMT-TFs)	Snail1/Notch1	miR-34a	Directly targets and inhibits Snail1 and Notch1 mRNA.	Pancreatic cancer cells	(83)
Yu *et al*, 2019		TWIST1	miR-539	Exerts tumor-suppressive function by targeting TWIST1 mRNA.	Pancreatic cancer cells	(101)
Gui *et al*, 2017		ZEB1	miR-200b-3p	Inhibits EMT by directly targeting ZEB1 mRNA.	Pancreatic cancer cells Animal model	(216)
Wang *et al*, 2020		Snail, Slug, Twist	Arginine deprivation	Downregulates multiple EMT-TF families (Snail, Slug, Twist), upregulates E-cadherin, inhibits MMP-1/9, weakens PI3K/Akt pathway.	Pancreatic cancer cells	(100)
Ma *et al*, 2019		Snail/Slug	α-Mangostin	Exerts multi-target effects by inhibiting Snail and Slug.	Pancreatic cancer cells	(190)
Fu *et al*, 2019		Snail, Slug, Zeb1	Triacetyl resveratrol	Inhibits multiple EMT-TFs (Snail, Slug, Zeb1) by upregulating the miR-200 family	Pancreatic cancer cells	(188)

Table II. Continued.

First author/s, year	Target category	Specific target/ molecule	Representative intervention(s)	Mechanism of action	Research model (cell/animal)	(Refs.)
Bu *et al*, 2016		SNAI1	DACH1 overexpression	Directly binds to SNAI1 to inhibit its transcriptional activity, upregulates E-cadherin and promotes apoptosis via Bcl-2 axis.	Pancreatic cancer cells	(207)
Garg *et al*, 2022		FTO	FTO inhibitors	Targeting the m6A 'eraser' FTO reverses EMT and inhibits tumor growth.	Pancreatic cancer cells	(217)
Kim *et al*, 2023		Snail (protein stability)	ERK3 inhibition (mechanism study)	Targeting ERK3 may inhibit Snail activity by preventing ERK3 from enhancing Snail stability (via inhibiting FBXO11 binding).	Clinical Sample Analysis, Cell Model	(218)
Liu *et al*, 2018	Epigenetic and post-transcriptional regulation	miR-221/ SOCS3	lncRNA GAS5	Acts as a ceRNA to 'sponge' miR-221, upregulating SOCS3 expression, thereby reversing EMT and gemcitabine resistance.	Pancreatic cancer cells, animal model	(208)
Chen *et al*, 2019		miR-330-5p/ PAX8	Silencing LINC00958	Silencing this lncRNA inhibits progression by sponging miR-330-5p to downregulate PAX8.	Pancreatic cancer cells, animal model	(209)
Zhou *et al*, 2023		FTO/SNAI1 mRNA stability	lncRNA GATA6-AS1	Reduces SNAI1 mRNA stability in an m6A-dependent manner by inhibiting the m6A demethylase FTO.	Animal model cells, model clinical research	(210)
Hu *et al*, 2018		NLRP3 promoter	lncRNA XLOC_ 000647	Downregulates adjacent gene NLRP3 by inhibiting its promoter activity, inhibiting EMT and invasion.	Pancreatic cancer cells, animal models, clinical research	(219)
Li *et al*, 2023		miR-140-3p/ TRAM2	circ-STK39	Acts as a ceRNA for miR-140-3p, relieving its inhibition of TRAM2 to promote EMT.	Pancreatic cancer cells, animal models, clinical research	(220)

Table II. Continued.

First author/s, year	Target category	Specific target/ molecule	Representative intervention(s)	Mechanism of action	Research model (cell/animal)	(Refs.)
Cao *et al*, 2024		miR-147b/ SOCS1	circTMEM59	Sponges miR-147b to upregulate SOCS1, exerting an inhibitory effect on EMT.	Pancreatic cancer cells, clinical research	(221)
Huang *et al*, 2021		ALKBH5/ FBXL5/SNAI1	ALKBH5 (mechanism study)	Demethylates mRNA of iron metabolism regulators (such as FBXL5), indirectly leading to SNAI1 degradation, inhibiting migration/ invasion.	Pancreatic cancer cells	(211)
Su *et al*, 2023		METTL3/ AREG mRNA stability	miR-33a-3p	Targets METTL3 to inhibit its-mediated m6A modification and stabilization of AREG mRNA, inhibiting invasion/ metastasis.	Pancreatic cancer cells. animal model	(222)
Schiedlauske *et al*, 2024		HDAC2/ HDAC6	Novel dual HDAC2/6 inhibitor	Upregulates E-cadherin, reverses TGF-β-induced EMT, induces apoptosis and cell cycle arrest.	Pancreatic cancer cells	(212)
Jia *et al*, 2025		Pan-HDAC/ MHC-I	Pan-HDAC inhibitor LAQ824	Inhibits HDAC activity, blocks EMT, induces apoptosis; enhances chromatin accessibility of MHC-I genes to promote antigen presentation.	Pancreatic cancer cells, animal model	(213)
Edderkaoui *et al*, 2018		GSK3B/ HDACs	Metavert (dual inhibitor)	Weakens EMT and inhibits tumorgrowth/ metastasis.	KPC mouse models, cells model	(223)
Mody *et al*, 2016 Mody *et al*, 2017		EZH2/miRNAs (miR-202, etc.)	3-deazaneplanocin A (DZNep)	Reshapes miRNA expression (such as miR-202 targets TGFBR1/2; miR-663a/miR-4787-5p target ligands), blocking TGF-β signaling and EMT.	Pancreatic cancer cells, animal model	(214, 215)

EMT, epithelial-mesenchymal transition; ALKBH5, AlkB Homolog 5; AXL, AXL Receptor Tyrosine Kinase; circRNA, Circular RNA; DKK3, Dickkopf-Related Protein 3; EZH2, Enhancer of Zeste Homolog 2; EMT-TFs, EMT Transcription Factors; FBXL5, F-Box And Leucine Rich Repeat Protein 5; FTO, Fat Mass and Obesity-Associated Protein; GSK3B, Glycogen Synthase Kinase 3 Beta; HDAC, Histone Deacetylase; KPC, LSL-Kras G12D/+; LSL-Trp53 R172H/+; Pdx1-Cre; lncRNA, Long Non-Coding RNA; MAPK, Mitogen-Activated Protein Kinase; METTL3, Methyltransferase-Like 3; miR, MicroRNA; MMP, Matrix Metalloproteinase; MHC-I, Major Histocompatibility Complex Class I; m6A, N6-Methyladenosine; NLRP3, NLR Family Pyrin Domain Containing 3; Notch1, Notch Receptor 1; PAX8, Paired Box 8; PI3K, Phosphatidylinositol 3-Kinase; Snail, Snail Family Zinc Finger; Snail1, Snail Family Zinc Finger 1; Slug, Snail Family Zinc Finger 2; SOCS1, Suppressor of Cytokine Signaling 1; SOCS3, Suppressor of Cytokine Signaling 3; SMAD, Sma- and Mad-Related Protein; SNAI1, Snail Family Zinc Finger 1; TGFBR1/2, Transforming Growth Factor-Beta Receptor 1/2; TRAM2, Translocation Associated Membrane Protein 2; TWIST1, Twist Family BHLH Transcription Factor 1; Twist, Twist Family BHLH Transcription Factor; ZEB1, Zinc Finger E-Box Binding Homeobox 1.

Disrupting the mesenchymal phenotype and TME crosstalk. EMT not only alters the characteristics of cancer cells themselves but also reshapes their interactions with the TME, particularly with CAFs and the ECM. Disrupting this crosstalk is therefore a critical strategy to inhibit metastasis.

Targeting tumor stroma and ECM: The dense fibrotic stroma of PC acts as a physical barrier to drug penetration and actively drives EMT and immune suppression through the secretion of various factors (224). Therapeutic strategies targeting stromal components have shown promising results. For instance, the oncolytic adenovirus HEmT-DCN/sLRP6 co-expresses decorin (to degrade ECM) and a Wnt decoy receptor (sLRP6), thereby improving drug penetration and directly inhibiting the Wnt/β-catenin pathway to block EMT (225). In clinical translation, RNA oligonucleotide STNM01, which targets carbohydrate sulfotransferase 15 (CHST15), has been shown in phase II trials to increase tumor-infiltrating T cells and improve patient survival (226). Additionally, inhibiting YAP expression can reduce connective tissue growth factor secretion, suppressing CAF activation and tumor-stroma interactions (227).

Blocking key tumor-stroma signaling molecules: Beyond the physical stroma, blocking key signaling molecules between tumor and stromal cells is equally important. Pharmacological inhibition of the Gas6/AXL axis, primarily produced by tumor-associated macrophages and CAFs, can partially reverse EMT and activate NK cells to inhibit metastasis (228). Similarly, a nanotechnology-delivered CXCL13 'trap' can counteract the dual effects of this chemokine, which recruits immunosuppressive regulatory B cells (Bregs) and directly stimulates EMT, thereby inhibiting tumor growth (229). Furthermore, targeted inhibition of the HGF/c-MET pathway has demonstrated stronger anti-metastatic activity than standard chemotherapy in animal models (230). These strategies highlight the potential of simultaneously reversing the EMT phenotype and activating anti-tumor immunity.

Combination strategies and clinical translation. Given the complexity of pancreatic cancer, combining EMT-targeted strategies with conventional therapies is essential to overcome resistance and achieve synergistic effects (Table III).

Sensitization to chemotherapy/radiotherapy: Reversing EMT can resensitize tumors to chemotherapy and radiotherapy. Nanotechnology platforms enable effective co-delivery; for instance, EGFR-targeted micelles co-delivering gemcitabine and miR-205 can inhibit the growth of resistant tumors and reduce EMT (231). Natural products also show promise in combination regimens. β-sitosterol and epigallocatechin-3-gallate (EGCG) both synergize with gemcitabine by inhibiting the AKT/GSK-3β pathway and regulating EMT-related phenotypic switching, respectively (232,233). The TGM2 inhibitor GK921 enhances cisplatin-induced apoptosis by inhibiting EMT (234), while hyperthermia can restore gemcitabine sensitivity in resistant cells by reversing EMT (235). In radiotherapy, the pan-VEGFR inhibitor cediranib can directly inhibit EMT and enhance radiosensitivity (236).

Combination with immunotherapy to remodel the immune microenvironment: Combining EMT inhibition with immunotherapy represents another promising direction. The pan-HDAC inhibitor LAQ824 not only blocks EMT but also upregulates MHC-I molecules to enhance antigen presentation and tumor immunogenicity (213). Inhibiting the HGF/c-MET pathway can reduce TGF-β secretion, thereby relieving immunosuppression and increasing cytotoxic T-cell infiltration in the TME (205). Furthermore, a bispecific nanobody targeting PD-L1 and CXCR4 can delay EMT and disrupt the immunosuppressive TME, promoting T cell infiltration (224). These approaches aim to transform 'cold' tumors into immunoresponsive ones, improving the efficacy of immune checkpoint inhibitors.

In summary, a multi-pronged therapeutic approach targeting EMT has emerged, ranging from disrupting the TME to designing rational combination therapies (Table III). The future challenge lies in the precise clinical translation of these strategies, leveraging biomarkers to identify patient populations most likely to benefit.

Challenges in clinical translation of EMT-targeted therapies. Despite promising preclinical data, EMT-targeted therapies for PDAC face substantial translational barriers. Reliable EMT-specific biomarkers are lacking; traditional markers fail to capture EMT heterogeneity, single-cell sequencing-identified hybrid E/M states are hard to translate into routine assays (237) and CA19-9 reflects tumor burden but not EMT activity (238,239). Systemic toxicity and off-target effects further narrow the therapeutic window; EMT pathways (such as TGF-β, Wnt) have critical physiological roles, leading to severe side effects such as cardiovascular toxicity that halts anti-TGF-β therapies clinically (240), while core EMT-TFs (such as Snail and Twist) are 'undruggable' and upstream inhibition disrupts basal physiology (241).

Tumor cells exhibit robust compensatory mechanisms: blocking one EMT pathway activates parallel signaling networks, with combined PI3K/Akt and MAPK inhibition more effective than monotherapy and EMT-TME crosstalk offsets targeted effects via CAF-derived pro-EMT signals (242). Additionally, preclinical models (such as KPC mice) differ from human PDAC in TME, immune context and pharmacokinetics (243), while patient-specific factors (genetic heterogeneity and comorbidities) are underrepresented, exacerbating the translational gap. Addressing these challenges requires integrated strategies for biomarker development, improved drug specificity, compensatory network disruption and model refinement.

5. Conclusions

EMT serves as an indispensable driver of PDAC malignant progression, being tightly linked to PDAC's most devastating clinical characteristics; early metastasis, chemoresistance and a dismal ~9% 5-year survival rate. As detailed in the present review, EMT exerts its pathological effects not through a simple epithelial-mesenchymal binary switch, but via a spectrum of stable intermediate (hybrid E/M) states that are well-adapted to PDAC's unique pathophysiology. Specifically, PDAC's extremely dense desmoplastic microenvironment (fibroproliferative reaction) acts both as a physical barrier and a key signaling hub: CAFs and PSCs secrete TGF-β and HGF to activate EMT-TFs, such as ZEB1 and Snail1). These TFs orchestrate a cascade of molecular events; they disrupt

Table III. Combination strategies and clinical translation.

First author/s, year	Therapeutic strategy	Target/ pathway	Representative intervention(s)	Mechanism of action	Research model (cell/animal)	(Refs.)
Li *et al*, 2019	Targeting tumor stroma and ECM	ECM barrier and Wnt pathway	Oncolytic adenovirus HEmT-DCN/sLRP6	Co-expresses decorin (degrades ECM) and sLRP6 (Wnt decoy); enhances drug penetration and blocks EMT.	Animal model, cells model	(225)
Fujisawa *et al*, 2022		CHST15	STMN01 (RNA oligonucleotide)	Targets carbohydrate sulfotransferase 15; increases tumor-infiltrating T cells and improves survival.	Clinical trial (patients with unresectable PDAC)	(226)
Jiang *et al*, 2018		YAP/CTGF	YAP inhibition	Reduces Connective Tissue Growth Factor (CTGF) secretion; inhibits CAF activation and tumor-stroma interactions.	Animal model, cells model	(227)
Ireland *et al* L, 2020	Blocking Tumor-Stroma Signals	Gas6/AXL axis	Pharmacological Gas6 inhibitor	Partially reverses EMT and activates NK cells to inhibit metastasis.	Animal model, cells model	(228)
Shen *et al*, 2022		CXCL13	CXCL13 'trap' (nanotechnology)	Blocks CXCL13-mediated Breg recruitment and direct EMT stimulation; inhibits tumor growth.	Animal model	(229)
Pothula *et al*, 2016		HGF/c-MET pathway	c-MET inhibitors	Inhibits tumor growth, metastasis and enhances anti-metastatic activity compared to gemcitabine.	Animal model, cells model	(230)
Mondal *et al*, 2017	Sensitization to Chemo-/ Radiotherapy	EGFR and miR-205	EGFR-targeted micelles (co-deliver Gemcitabine + miR-205)	Reverses EMT and inhibits growth of drug-resistant tumors.	Animal model, cells model	(231)
Cao *et al*, 2019		AKT/GSK-3β pathway	β-sitosterol + Gemcitabine	Inhibits EMT markers; synergistically enhances inhibition of growth, migration and invasion.	Animal model, cells model	(232)
Wei *et al*, 2019		Akt pathway	EGCG + Gemcitabine	Regulates EMT-related phenotypic switching (such as cadherin switching, ZEB1	Animal model, cells model	(233)

Table III. Continued.

First author/s, year	Therapeutic strategy	Target/ pathway	Representative intervention(s)	Mechanism of action	Research model (cell/animal)	(Refs.)
				downregulation).		
Li *et al*, 2024		TGM2	GK921 (TGM2 inhibitor) + Cisplatin	Inhibits TGM2-induced EMT; enhances cisplatin-induced apoptosis and cell cycle arrest.	Animal model, cells model	(234)
Jin *et al*, 2018		EMT reversal	Hyperthermia + Gemcitabine	Reverses EMT to restore sensitivity in gemcitabine-resistant cells.	Pancreatic cancer cells (such as PANC-1)	(235)
Momeny *et al*, 2020		VEGF receptors	Cediranib (pan-VEGFR inhibitor) + Radiotherapy	Directly inhibits EMT and enhances radiosensitivity.	Pancreatic cancer cells	(236)
Mondal *et al*, 2016		Glucocorticoid Receptor and Hsp90	GR-targeted liposomes (co-deliver drug + anti-Hsp90 gene)	Reverses EMT and induces drug sensitivity.	Animal model, cells model	(237)
Gui *et al*, 2017	Combination with Immunotherapy	HDAC/ MHC-I	LAQ824 (pan-HDAC inhibitor) + ICIs	Upregulates MHC-I molecules (enhances antigen presentation) while inhibiting EMT.	Animal model, cells model	(216)
Mekapogu *et al*, 2023		HGF/c-MET/TGF-β	c-MET inhibitors + ICIs	Reduces TGF-β secretion, relieving immune suppression and increasing cytotoxic T-cell infiltration.	Animal model, cells model	(205)
Li *et al*, 2024		PD-L1/ CXCR4	Bispecific nanobody (anti-PD-L1/CXCR4)	Delays EMT by inhibiting SDF-1/ CXCR4 pathway; disrupts TME and promotes T-cell infiltration.	Cells model	(224)

ECM, extracellular matrix; AKT, Protein Kinase B; AXL, AXL Receptor Tyrosine Kinase; Breg, Regulatory B Cells; CAF, Cancer-Associated Fibroblast; CHST15, Carbohydrate Sulfotransferase 15; Cisplatin, Cis-Diamminedichloroplatinum(II); CXCL13, C-X-C Motif Chemokine Ligand 13; CXCR4, C-X-C Motif Chemokine Receptor 4; EGCG, Epigallocatechin-3-Gallate; EGFR, Epidermal Growth Factor Receptor; EMT, Epithelial-Mesenchymal Transition; ECM, Extracellular Matrix; Gas6, Growth Arrest-Specific Protein 6; Gemcitabine, 2',2'-Difluorodeoxycytidine; GR, Glucocorticoid Receptor; GSK-3β, Glycogen Synthase Kinase 3 Beta; HGF, Hepatocyte Growth Factor; Hsp90, Heat Shock Protein 90; HDAC, Histone Deacetylase; ICIs, Immune Checkpoint Inhibitors; MHC-I, Major Histocompatibility Complex Class I; miR, MicroRNA; NK, Natural Killer; PD-L1, Programmed Cell Death Ligand 1; SDF-1, Stromal Cell-Derived Factor 1; TGF-β, Transforming Growth Factor-β; TGM2, Transglutaminase 2; TME, Tumor Microenvironment; VEGFR, Vascular Endothelial Growth Factor Receptor; Wnt, Wingless-Type MMTV Integration Site Family; YAP, Yes-Associated Protein; CTGF, Connective Tissue Growth Factor; c-MET, Hepatocyte Growth Factor Receptor.

epithelial adhesion by suppressing E-cadherin and switching to N-cadherin (enabling cancer cells to detach from ductal structures); upregulate MMP-14 and MMP-2 to degrade type I/III collagen (creating invasive channels through the extracellular matrix) and form a reciprocal 'EMT-stemness-therapy resistance' axis (via crosstalk between ZEB1 and YAP1 or miR-200/ZEB1 feedback loops) that sustains CD44+/CD133+ CSCs and helps evade gemcitabine or radiotherapy.

At the regulatory level, EMT is governed by a hierarchical, context-dependent network; upstream signals (TGF-β, Wnt and Notch) converge on core TFs, which are further stabilized by epigenetic modifications (DNMT1-mediated CDH1 silencing, HDAC1/2-driven E-cadherin suppression) and ncRNAs (circEIF3I promoting SMAD3 phosphorylation, lncRNA H19 sponging miR-200b). Importantly, translational studies confirm that targeting this network, whether using TGFβR1 inhibitors (vactosertib) to reverse EMT-driven metastasis, HDAC inhibitors (LAQ824) to restore MHC-I expression and overcome immune escape, or CAF-targeted agents (STNM01, a CHST15-targeting RNA oligonucleotide) to reduce stromal TGF-β, can suppress PDAC progression in preclinical models. However, these advances also highlight a core challenge: EMT's phenotypic plasticity allows tumor cells to compensate for single-target inhibition (for example, Snail1 silencing leads to Slug upregulation), emphasizing the need for combinatorial strategies that disrupt the entire EMT network rather than individual nodes. Collectively, these findings confirm EMT as a central therapeutic target for PDAC and provide a mechanism-based framework to guide the design of next-generation interventions.

Among the EMT-targeted strategies summarized, three approaches show the highest promise for inhibiting PDAC metastasis: Disrupting CAF-TME crosstalk (such as STNM01 targeting CHST15) addresses the root of EMT activation in the desmoplastic microenvironment; combined pathway inhibition (such as Hh + FGFR inhibitors and TGFβRI inhibitors + chemotherapy) overcomes compensatory signaling; and epigenetic modulation (such as pan-HDAC inhibitors) synergistically targets EMT and immunosuppression. Direct EMT-TF targeting is less feasible due to off-target risks.

Given EMT's early activation in PanIN lesions, early intervention relies on three practical directions: using EMT biomarkers (miR-200/ZEB1 ratio, Vimentin+/CD44v6+ CTCs) to stratify high-risk populations; repurposing low-toxicity agents (metformin, aspirin) to block risk factor-driven EMT; and inhibiting upstream signals (TGF-β and HGF) to halt EMT initiation before invasion. This strategy intercepts metastasis at its origin, complementing late-stage therapies.

6. Future perspectives

While mechanistic insights into PDAC-related EMT have advanced rapidly, translating these discoveries into clinical benefits remains limited by unresolved gaps; gaps that must be addressed to meet the rigor and innovation standards of top-tier oncology journals. Below is outlined priority research directions based on the unmet needs highlighted in the present review:

Define molecular signatures of EMT spectrum states for subtype-specific targeting. The present review emphasized that hybrid E/M states (rather than full EMT) confer the highest metastatic potential and chemoresistance in PDAC. However, the molecular markers that distinguish these states (such as specific EMT-TF, miRNA, or protein post-translational modification signatures) remain poorly defined. Current PDAC subtype classifications (classical compared with quasi-mesenchymal) also lack clear links to EMT trajectories; for example, high ZEB1 expression correlates with quasi-mesenchymal subtypes, but how this translates to therapeutic vulnerability is unclear. Future studies must use single-cell spatial multi-omics technologies (single-cell RNA sequencing combined with spatial proteomics) on patient-derived samples (primary tumors, CTCs, liver metastases) to map EMT phenotypic landscapes. This will enable identification of subtype-specific EMT drivers (such as Twist1 for classical PDAC, ZEB1 for quasi-mesenchymal PDAC) and development of companion diagnostics (such as circulating miR-200/ZEB1 ratio) to stratify patients for targeted therapy, avoiding the failure of unselected trials seen with earlier EMT inhibitors.

Dissect bidirectional TME-EMT crosstalk to overcome stromal compensation. PDAC's desmoplastic stroma is not just a passive barrier but an active driver of EMT: CAFs secrete AREG to activate EGFR/Notch signaling in tumor cells, while PSCs deposit hyaluronan to amplify mechanical tension-driven EMT. Yet, the field still lacks a clear understanding of CAF subtype-specific regulation of EMT (myCAFs compared with inflammatory CAFs) and how EMT reciprocally reshapes stromal function (for example, tumor-derived PDGF activating PSCs). Current strategies targeting the stroma (such as Hh inhibitors) often trigger compensatory EMT via FGF signaling, highlighting the need for co-targeting approaches. Future work should use exosome tracing and cell-cell communication modeling to dissect paracrine loops (such as CAF-derived miR-146a activating Snail1) and develop rational combinations; for example, pairing CAF subtype-specific inhibitors (CHST15 antisense oligonucleotides) with EMT blockers (TGFβR1 inhibitors) to disrupt the 'EMT-stroma' positive feedback loop without destabilizing beneficial stromal functions (such as immune cell recruitment).

Address translational bottlenecks in EMT-targeted therapy. Two critical barriers limit clinical translation, as highlighted in the present review: The absence of dynamic EMT monitoring tools and poor *in vivo* efficacy of EMT inhibitors. For biomarkers, while CTCs with hybrid E/M phenotypes correlate with poor prognosis, current CTC detection methods (based on EpCAM enrichment) miss mesenchymal CTCs with low EpCAM expression. Future efforts should validate EMT-specific CTC markers (such as Vimentin/CD44v6) or circulating extracellular vesicle (EV) cargo (circFARP1, miR-146a) as surrogate endpoints for therapy response. For drug delivery, EMT inhibitors (such as HDAC inhibitors, TGF-β antagonists) suffer from low tumor penetration and off-target toxicity; potential solutions include ECM-targeted nanoparticles (decorin-functionalized carriers that bind collagen) or CAF-homing liposomes to deliver EMT-TF siRNAs (such as ZEB1 siRNA) directly to the stroma-tumor interface. Additionally, clinical trials must incorporate molecular stratification (such as TGF-β pathway activity, ZEB1 expression) to enrich for responsive patients, as seen in the phase I/II trial of STNM01 (a CHST15 inhibitor) which improved survival only in PDAC patients with high CAF levels.

Leverage early EMT intervention to target modifiable risk factors. A less emphasized finding in the present review is that modifiable risk factors (smoking, obesity, diabetes)

account for 65.6% of PDAC cases in patients ≤60 years, yet how these factors drive EMT (such as chronic inflammation activating NF-κB/Snail1, hyperglycemia upregulating LINC00842/PGC-1α) remains understudied. Early PDAC lesions (PanIN) already exhibit EMT features, presenting a window for chemoprevention. Future research should explore repurposed agents targeting risk factor-driven EMT (such as metformin inhibiting mTOR/EMT in diabetic patients, aspirin blocking NF-κB/Snail1 in obese patients) in high-risk cohorts. Combining these agents with EMT monitoring tools (such as plasma EMT-related ncRNAs) could enable early intervention to halt PanIN progression to invasive PDAC, addressing the 'late diagnosis' dilemma that is the root cause of PDAC's poor prognosis.

Modifiable risk factors account for 65.6% of PDAC cases in patients ≤60 years, driving EMT via chronic inflammation or hyperglycemia. Early PanIN lesions already exhibit EMT features, offering a chemoprevention window. Future research should prioritize: i) Validating non-invasive EMT biomarkers for high-risk stratification; ii) evaluating repurposed agents (metformin, aspirin) in chemoprevention trials; iii) dissecting risk factor-EMT crosstalk to identify precise early targets. Combining these with dynamic EMT monitoring can halt PanIN progression to invasive PDAC, addressing late diagnosis.

In summary, advancing PDAC-EMT research requires a shift from 'broad EMT inhibition' to 'precision EMT modulation,' integrating insights into phenotypic heterogeneity, stromal crosstalk and early intervention. Only by addressing these gaps can EMT-targeted strategies fulfill their potential to transform PDAC from a lethal disease to a manageable one.

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GZ, YW, MW and SH were co-first authors, JW was correspnding author. JW, GZ, SH, MW, QW and YW designed the study. JW, GZ and SH wrote the paper. ZX and SL contributed to manuscript revision and academic quality control. Data authentication is not applicable. All authors reviewed and approved the final manuscript.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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