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REVIEW

Harnessing function of EMT in cancer drug resistance: a metastasis regulator determines chemotherapy response

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Abstract
Epithelial-mesenchymal transition (EMT) is a complicated molecular process that governs cellular shape and function changes throughout tissue development and embryogenesis. In addition, EMT contributes to the development and spread of tumors. Expanding and degrading the surrounding microenvironment, cells undergoing EMT move away from the main location. On the basis of the expression of fibroblast-specific protein-1 (FSP1), fibroblast growth factor (FGF), collagen, and smooth muscle actin (-SMA), the mesenchymal phenotype exhibited in fibroblasts is crucial for promoting EMT. While EMT is not entirely reliant on its regulators like ZEB1/2, Twist, and Snail proteins, investigation of upstream signaling (like EGF, TGF-β, Wnt) is required to get a more thorough understanding of tumor EMT. Throughout numerous cancers, connections between tumor epithelial and fibroblast cells that influence tumor growth have been found. The significance of cellular cross-talk stems from the fact that these events affect therapeutic response and disease prognosis. This study examines how classical EMT signals emanating from various cancer cells interfere to tumor metastasis, treatment resistance, and tumor recurrence.

Keywords Mesenchymal-to-epithelial transition (MET) · Targeting therapy · Non-coding RNAs · Signaling pathways · Multidrug-resistance (MDR)

1 Introduction

Overcoming treatment resistance is now one of oncology's most significant issues since it is a recurring issue for the care of cancer patients. As metastasis is the primary cause of cancer-related mortality in human malignancies, it is crucial to vanquish therapeutic resistance by utilizing novel targeted-therapy tactics. Patients with resistance often also have an increase in metastases. Treatment resistance encompasses the rejection of medicines such as chemo, radiation, immunological, and targeted therapies in addition to the conventionally ingrained innate and acquired tumor therapy resistance [1, 2]. There are some important molecular mechanisms by which cancer cells can become resistant to chemotherapy, including alteration in influx transporters, overexpression of anti-apoptotic proteins, and overexpression of multidrug-resistance (MDR) efflux transporters that lead to increased drug efflux [3]. The molecular processes behind therapeutic resistance have, however, only recently been fully understood. EMT has come to be recognized as a significant factor in therapeutic resistance [4]. EMT is an utterly conserved cellular process that transforms immobile and polarized epithelial cells into mesenchymal, mobile cells [5]. During the EMT program, epithelial cells lose their apicobasal polarity and their cell–cell contacts. In addition, their actin cytoskeleton is reorganized, and all of these alterations enable them to invade the extracellular matrix as a single cell. EMT has a role in tumor progression, metastasis, and resistance to conventional treatments and inhibitors of small-molecule targeted [6, 7]. Significant research involving tumor cell lines show how EMT contributes to resistance brought on by radiotherapy or chemotherapy [8, 9]. Moreover, the epigenetic factors such as miRNAs have been considered as regulators of EMT in cancer invasion and metastasis [10, 11]. Yet there is not enough *in vivo* data

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accessible, mostly because there are not enough adequate *in vivo* models and there are not enough human samples to evaluate for thorough investigations. Nonetheless, it is crucial to emphasize that transitional epithelial and mesenchymal (E/M) phenotypes coexist in carcinomas. As a result, several subpopulations are discovered, boosting the tumor's adaptability. Pharmacogenomic techniques have an effect on this important element, even if the impact of these transitional E/M states on resistance to anticancer treatment medicines is not entirely known. Moreover, current oncology research has shown a crucial connection between EMT and the tumor microenvironment, emphasizing the necessity for customized cancer therapy for specific cancer patients [12, 13]. This topic would not be further examined in light of the excellent recent publications on the significance of the tumor microenvironment and EMT in multidrug resistance [14]. In-depth discussion of the molecular mechanisms by which EMT creates treatment resistance and the role of the microenvironment in this process in various malignancies will be covered in this review. Future views on bioinformatic and pharmacological techniques to overcome therapy resistance and the significance of non-coding RNAs in the regulation of EMT will also be reviewed.

2 EMT basics and role in metastasis of cancers

The biological process EMT is associated with both fibrosis and cancer [15]. It is crucial for developmental biology and wound healing. It is a biological process that is reversible and connected to epithelial cells' disruption of cellular orientation and adhesive interactions mediated by cadherins. These cells change into mesenchymal ones and then acquire the capacity for migration and invasion [16]. Receptor tyrosine kinases, Wnt/β-catenin, transforming growth factor-beta (TGF-β), Hedgehog (Hh), bone morphogenetic protein, and Notch are only a few of the signaling pathways that are involved in mediating EMT [17] (Fig. 1). The action of EMT and transcription factors (EMT-TFs) like Zinc finger E-box-binding homeobox 1/2 (ZEB1/2), Twist, SNAI1, and SNAI2 is to inhibit the expression of target genes, such as E-cadherin. Signaling pathways in turn mediate EMT-TFs like these. A crucial stage in EMT is thought to be the loss of E-cadherin [18]. EMT may cause cells to metastasize from primary tumor sites in the setting of malignancy, which has been linked to a poorer prognosis (Fig. 2).

Among the initial stages in the metastatic process thought to be the invasion of cells into the extracellular matrix, EMT has long been associated with cells that can migrate and infiltrate matrix, and this association has been utilized to characterize the function of EMT in metastasis [19]. A few of the numerous processes at work include the activation of MMP-2 and MMP-9, which breaks down the basement

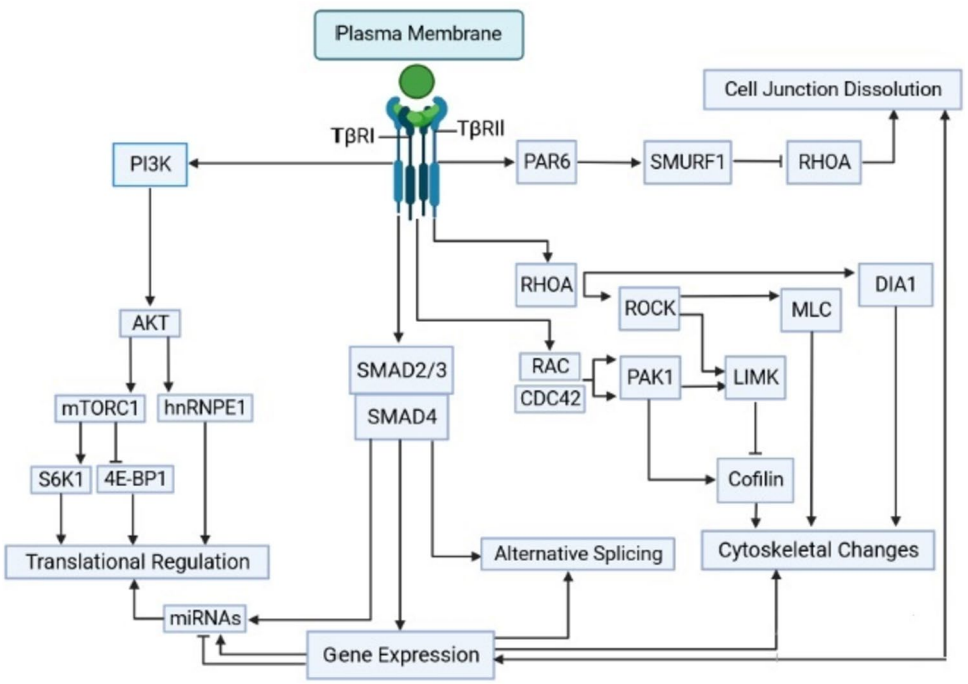

Fig. 1 Crosstalk between epithelial-mesenchymal transition and various signaling pathways

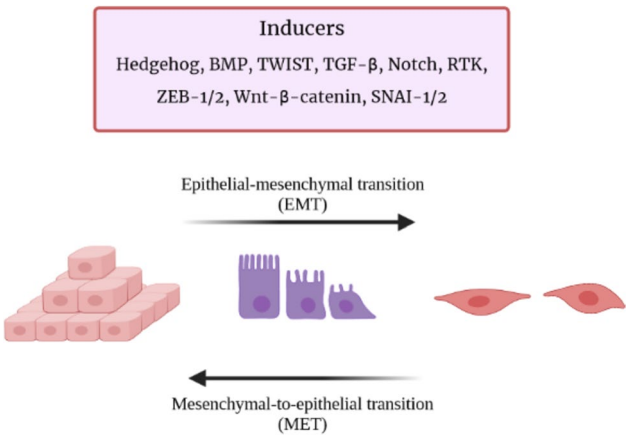

Fig. 2 Epithelial-mesenchymal transition and related signaling and transcription factors

membrane [20], cytoskeletal remodeling, changes in the expression of molecules involved in cell adhesion, and persistent autocrine growth factor signaling to prevent apoptosis and/or anoikis [21]. The initiation of EMT is necessary for primary tumor cells to migrate to the lungs. However, once these cells have disseminated, they must subsequently undergo a reversal of the EMT process and adopt epithelial traits in order to effectively establish visible metastatic growths, according to studies using mouse models of skin and breast cancer [22, 23]. In a number of carcinomas, experimental EMT activation dramatically increases the capacity of these cells to form filopodium-like extensions that permit EMT-activated cells to proliferate after exiting the bloodstream and ultimately empower them to initiate metastatic growth [24].

3 An overview of EMT and drug resistance

Drug resistance is a well-known notion that has been investigated in a number of illness models. Drug resistance occurs when diseases stop responding to medicinal therapy. Acquired and *de novo* medication resistance have both been described [25]. Initially, "traditional" medicines like chemotherapy may be used to treat many malignancies, but as the biochemical and tumor microenvironment changes over time, cancer cells can sometimes develop resistance to these therapies. Many processes, including but not limited to metabolism, drug efflux, cell death inhibition, DNA damage repair, target alterations, and EMT, may contribute to this resistance [26]. Drug resistance in several malignancies, including pancreatic [27], lung [28], breast cancers [29], and bladder [30] has been observed to be related with EMT. The link between EMT and drug resistance in cancer was initially proposed for the first time in the 1990s [31]. Cancer drugs have been shown to be produced when a wide range of cellular signaling pathways, such as Wnt, Notch, TGF, and Hh [32, 33], which are known to cause EMT, are activated. While some of the precise processes are starting to become clear, the process is complicated due to the broad spectrum of medications, tissue types, and signaling pathways involved, as shown in Table 1.

Additional mechanisms that trigger EMT have been directly connected to cancer treatment resistance. It has been

Table 1 Mechanisms of drug resistance through crosstalk between EMT and signaling pathways and transcription factors

Signaling pathways/TFs	Drugs	Mechanism of drug resistance	Related malignancies	References
Hh	Anti-EGFR- tyrosine kinase inhibitors	Activation through EGFR-WT, EPHB3, Hh-STAT3, and EGFR-MT	Colorectal cancer and non-small lung cancer	[32, 34]
TGF-β	Doxorubicin, TβRI kinase inhibitor SB431542	Upregulation of PDK4 and TGF-β	Colorectal and colon cancer, triple-negative breast cancer	[35, 36]
Notch	Gemcitabine	Up-regulation of Notch signaling pathway	Pancreatic cancer	[37]
Wnt	Trastuzumab	Transactivation of EGFR through Wnt/β-catenin pathway	Breast cancer (HER2-over expressing)	[38]
TWIST	Taxol, anthracyclines	Up-regulated TWIST, P-glycoprotein expression activation mediated by twist	Bladder cancer, nasopharyngeal carcinoma	[39, 40]
ZEB2	Carboplatin, 5-fluorouracil (5-FU), and Oxaliplatin (OX)	Up-regulation of IL-1β that increases ZEB1, loss of FBXW7	Colorectal and colon cancers	[40, 41]
SNAI1/SNAI2	Multidrug	Up-regulation and activation of ABC transporters	Breast cancer	[30]
ZEB1	Temozolomide (TMZ)	Activation of CD133, OLIG2, MGMT and ROBO1	Glioblastoma	[42]

shown that Wnt contributes to therapy resistance in gastric cancer, Type-1 epithelial ovarian cancer, and HER2-overexpressing breast cancer [38, 43]. The activation of Wnt/β-catenin transactivating EGFR by Wnt3 overexpression in HER2-overexpressing breast cancer cells is thought to cause a partial EMT, which exploring its concept is crucial for gaining insights into trastuzumab resistance within these cells [38]. It has been shown that the Dapper1 Antagonist of Catenin1 (DACT1) adversely controls Wnt signaling and controls cisplatin resistance through controlling autophagy in EOCs. Full-length DACT1-carrying lentiviruses boosted autophagy and improved cisplatin sensitivity in EOC cells after transfection [44]. Overexpression of NANOGP8 in gastric cancer results in resistance to anti-oxaliplatin (L OHP). It enhances Wnt signaling, upregulates markers of EMT, and boosts nucleus accumulation of β-catenin [43]. Moreover, drug resistance in non-small cell lung cancer that is resistant to EGFR-tyrosine kinase inhibitors [32], and in colorectal cancer that is resistant to cetuximab [34] has been associated to Hh pathway activation. Lastly, treatment resistance in pancreatic cancer has been linked to the Notch pathway. In gemcitabine-resistant cells, Notch-2 and Jagged-1 (Notch-2 ligand) are both increased, and Notch knockdown partially reversed the EMT characteristics [37].

4 EMT-TFs and cancer drug resistance

As shown in Table 1, several investigations in a range of tissue types have discovered EMT transcription factors, including TWIST, ZEB1/2, and SNAIL1/2 can directly impart treatment resistance in malignancies [45, 46]. Drug resistance may be conferred simply by upregulating these transcription factors [47]. Enhanced levels of EMT transcription factors are linked to chemotherapy resistance and decreased survival in glioblastoma cells as well, where ZEB1 is abundantly expressed and connected to a variety of downstream targets (MGMT c-MYB, and ROBO1) via a ZEB1-miR200 feedback loop [42]. In CRC, it has been shown that the FBXW7-ZEB2 axis regulates a variety of crucial EMT-related traits as well as treatment resistance. The loss of FBXW7 as a tumor suppressor resulted in the EMT phenotype that ZEB2 knockdown was able to reverse [41]. Similar to this, TWIST overexpression or upregulation in cancer cells has been linked to chemoresistance; mechanistically, this is accomplished in bladder cancer via increasing P-Glycoprotein [40].

Numerous studies have demonstrated that several EMT-TFs, including snail proteins (SNAI1 and SNAI2), TWIST, and FOXC2, result in the overexpression of ABC transporters. Elevated transcription of these transporters imparts resistance to treatments, primarily due to their overexpression in malignant cells, potentially leading to the efflux of cytotoxic drugs [30]. Both morphological and phenotypic EMT hallmarks were seen in cell lines with cisplatin-resistant phenotype, and gene expression profiling discovered many EMT-TFs, like snail proteins that were later shown to be important participants in drug resistance [48]. EMT pathways have been shown to function in a broad range of cell lines and tissues, including breast, colon, gastric, ovarian, glioblastoma cells, and with a number of different medicines, indicating a serious problem.

4.1 EMT and basic helix–loop–helix (bHLH) transcription factors

Major regulators of differentiation and lineage specification are (bHLH) transcription factors. Inhibitor of differentiation (ID) proteins, E47 and E12, TWIST-1 and -2, are among those that play critical roles in the advancement of EMT [18, 49]. As well as SNAIL, the expression of TWIST upregulates mesenchymal gene expression while downregulating epithelial gene expression [50] (Fig. 3). Independent of SNAIL and most likely via the connection with other proteins, TWIST1 inhibits the production of E-cadherin and promotes the expression of N-cadherin in cancer cells [51]. In order to mediate H4K20 monomethylation, TWIST engages the methyltransferase SET8, which in humans is known as SETD8. H4K20 is a histone mark associated with the repression and activation of E-cadherin and N-cadherin promoters, respectively [51]. The PRC1 component B lymphoma Mo-MLV insertion region 1 homolog (BMI1), which is expressed in head and neck cancer cells, is activated by TWIST1. Then, at E-box sequences, BMI1 and TWIST1 collaborate to restrict the transcription of the cell cycle inhibitor p16 and E-cadherin [52]. PRC2 that can trimethylate H3K27 at the promoters of the E-cadherin and CDKN2A genes is recruited as part of this cooperation. TWIST expression is activated throughout development and cancer by different signaling pathways [17]. The hypoxia-inducible factor 1 (HIF1) as another transcription factor, in particular, promotes EMT, and tumor cell spreads by inducing TWIST expression when there is hypoxia68. Moreover, mechanical stress triggers the production of Twist in the epithelia of Drosophila melanogaster in a way that depends on β-catenin [53]. The makeup of TWIST's dimers has a significant impact on its actions. Using E12 or E47, TWIST1 and TWIST2 may create homodimers or heterodimers that control transcription and E-box DNA binding. Hence, ID proteins incapable of DNA binding connect with E12 or E47, and TWISTs, consequently hinder TWIST activity. As a consequence, TGF- 's suppression of ID gene expression causes TWIST (or other bHLH proteins) to be derepressed, which raises its activity in EMT [54]. Similar to SNAIL, phosphorylation controls TWIST1's stability. MAPKs

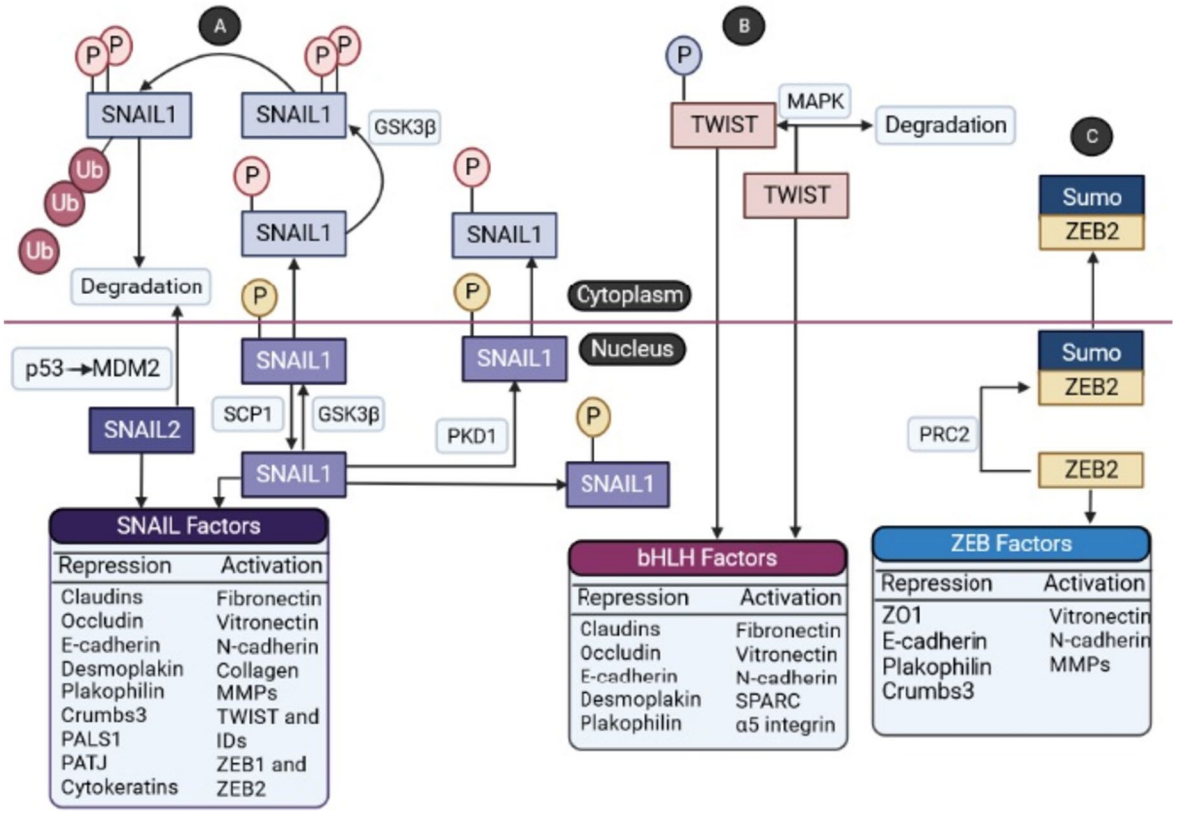

Fig. 3 Some most important transcription factors related to EMT

phosphorylate TWIST1 at Ser68, preventing its degradation mediated by ubiquitin and boosting its activity [55].

4.2 ZEB1/ZEB2

ZEB1 and ZEB2, the two vertebrate ZEB transcription factors, attach to regulatory gene sequences at E-boxes and have the capacity to either suppress or activate transcription [18]. ZEB1 inhibits expression of E-cadherin independently of C-terminal-binding protein by recruiting the Switch/sucrose nonfermentable (SWI/SNF) chromatin remodeling protein BRG1 in some cancer cells; however, ZEB-mediated transcriptional repression is frequently associated with the recruitment of a CTBP co-repressor [56]. ZEB1 may change from inhibiting transcription to promoting transcription by interacting with the transcriptional coactivators including p300/CBP-associated factor (PCAF) and p30074. Moreover, ZEB1 may activate Lys-specific demethylase 1 (LSD1), suggesting a potential connection between it and EMT75's histone demethylation. Consequently, similar to TWIST and SNAIL, ZEBs bind E-boxes and operate as transcriptional activators and repressors, promoting transcription of mesenchymal genes that characterize the EMT phenotype while suppressing certain epithelial junction and polarity genes [18] (Fig. 3).

When SNAIL expression is turned on, ZEB expression often follows and aligns with SNAIL1 directly targeting the ZEB1 gene. Furthermore, TWIST1 and SNAIL1 work together to trigger the expression of ZEB1 [57]. ZEB transcription is elevated in response to growth factors, such as Wnt and TGFβ proteins, that stimulate RAS-MAPK signaling. Activation of ETS1 mediated by MAPK signaling is involved in the activation of ZEB expression by TGF signaling [58]. Polycomb repressive complex 2 (PRC2) sumoylates ZEB2 in the post-translational level inhibits it from associating with CTBP and enhances its cytoplasmic location, which weakens inhibition of gene expression mediated by ZEB2 [59].

4.3 Slug and snail

SNAIL1 (SNAIL), SNAIL2 (SLUG), and SNAIL3 are the three vertebrate snail proteins that induce the EMT program throughout fibrosis, development, and tumor progression. SNAIL proteins have carboxy-terminal zinc-finger domains by which attaching to E-box DNA sequences and inhibit the expression of epithelial genes [18, 50, 60] (Fig. 3). SNAIL1 activation at the E-cadherin promoter provides a clear illustration of how SNAIL suppresses gene expression [61]. When E-box sequences within the proximal binding site of

the E-cadherin gene promoter region are engaged, SNAIL1 triggers the activation of PRC2. This complex encompasses corepressor SIN3A, histone deacetylases 1, 2, and/or 3, Lys-specific demethylase 1, as well as the methyltransferases enhancer of zeste homolog 2 (EZH2), G9a, and repressors, leading to a cascade of regulatory events [62]. Repressive chromatin is marked by H3K9 and H3K27 methylation, whereas active chromatin is identified by H3K4 methylation and H3K9 acetylation. In many promoters in embryonic stem cells, repressive and active markers coexist in "bivalent domains," as shown in the promoter of E-cadherin [63]. This poised condition for the promoter allows for achieving prompt activation while preserving inhibition in the absence of differentiation cues. The E-cadherin promoter's bivalent control may help explain why EMT is reversible. In addition to activating genes involved in the mesenchymal phenotype, SNAIL1 represses genes related to the epithelium. Bivalent domains, characterized by the presence of repressive H3K9 trimethylation alongside activating H3K18 acetylation, may potentially have a role in enabling the production of the mesodermal transcription factor goosecoid in response to the TGF-related factor Nodal55.

Many signaling pathways work together to start and advance EMT, and they often trigger SNAIL1 transcription. Contingent upon the physiological setting, the Wnt family proteins, TGFs, Notch, and other types of growth factors that work via RTKs all trigger SNAIL1 expression [18]. To regulate gene expression, SNAIL1 and SNAIL2 work in concert with other transcription regulators. Moreover, it helps the SMAD3-SMAD4 complex induce TGF-β Signaling pathways-initiated post-translational changes and also regulates the location, degradation, and consequently SNAIL1 activation [18]. Its transcriptional activity is activated by the phosphorylation of SNAIL1 at two Ser-rich regions by GSK3. The nuclear export of SNAIL1 is facilitated by the phosphorylation of Ser97 and Ser101 in the first motif, and the following phosphorylation of Ser112, Ser120, Ser108, and Ser116 in the second motif marks SNAIL1 for degradation mediated by ubiquitin [64]. Many signaling pathways enhance SNAIL1 activity by modulating GSK3β-mediated phosphorylation. GSK3 phosphorylation of SNAIL1 is inhibited by the PI3K/AKT and Wnt/β-catenin pathways, while GSK3-SNAIL1 connections are disrupted by Notch and NF-κB signaling, both of which enhance SNAIL1 stability and mediated suppression of the expression of occludin and E-cadherin [65]. Small C-terminal domain phosphatase 1 (SCP1), on the other hand, blocks GSK3's phosphorylation of SNAIL1, keeps it in the nucleus, and inhibits transcription [66]. In addition, phosphorylated Ser11 in SNAIL1 mediated by PKD1 promotes nuclear export, while phosphorylation of Ser246 in SNAIL1 via PAK1 activation or by large tumor suppressor 2 (LATS2) at Thr203 results in an increase in nuclear retention and encourages EMT. After its association with the ubiquitin ligase mouse double minute 2 (MDM2), p53 (as a critical tumor suppressor) recruits SNAIL2 for degradation, therefore inhibiting cancer invasion (Fig. 2) [67].

5 EMT and TGF-β

TGF-β signaling has been linked to a variety of tissues, including stem cells from colorectal, breast, and squamous cell carcinomas [68]. Nevertheless, the mechanisms by which it contributes to treatment resistance have been debated. Katsuno et al.'s study has illuminated the role of metabolism in colorectal cancer (CRC) by demonstrating that TGF-β governs 5-Fluorouracil resistance via the regulation of PDK4 [36]. TGF-β transcriptionally stimulates p21, stabilizes NRF2, and increases glutathione metabolism in squamous cell carcinoma, decreasing the efficacy of treatments [69]. In contrast, it was revealed that downregulating Smad4 increased sensitivity in colon cancer exhibiting resistance to doxorubicin (Dox), which had been indicated to be mediated by TGF-β [35]. TGF-β has been documented to play a crucial role in epirubicin resistance in triple-negative breast cancer by controlling EMT and cell death [68]. Resistance to anti-cancer medication has also been linked to long-term TGF-β treatment [36].

6 Non-coding RNAs (ncRNAs) modulating EMT

Many types of RNAs without the capacity to encode proteins have regulatory roles in various physiological processes and have been found by several researchers. Researchers have been able to detect the presence of short ncRNAs in a variety of sample sources due to the advancement of high-throughput RNA sequencing technology [70]. These methods are very effective and sensitive for analyzing different short non-coding RNAs [71]. These non-coding RNAs (ncRNAs), which also include miRNAs, lncRNAs, piRNAs, siRNAs, snRNAs, tiRNAs/trfs, and snoRNAs, have a crucial biological role in the transcriptional or post-transcriptional regulation of genes. To modify biological functions, they may interact with proteins, RNA, DNA, or other molecules. Non-coding RNAs (ncRNAs) have the ability to control a wide range of disorders, such as cancer, neurological, viral infection, and many others [72, 73]. It has been discovered that these non-coding RNAs control the EMT process and either encourage or hinder the spread of cancer cells. ncRNAs may be applied as potential diagnostic and prognostic biomarkers in a variety of malignancies if their regulatory functions in EMT and metastasis are better understood.

MicroRNAs, which have a length of 21–25 nucleotides, are categorized as small ncRNAs. The transcription of its target gene is controlled by miRNA, which may destabilize the target mRNAs or prevent their translation. They control a vast range of physiological processes. MiRNA function dysregulation leads to the emergence of a number of illnesses, including cancer. More than 50% of miRNAs are unregulated in human malignancies, according to recent research. Moreover, distinct predictive miRNA signatures for each kind of cancer exist and may be utilized to predict the prognosis of the illness [74]. Both positive and negative regulation of the EMT by miRNAs has been shown. MiRNAs that specifically target the epithelial markers may increase chemoresistance. For instance, miR-375 causes paclitaxel chemoresistance in lung cancer by specifically decreasing E-cadherin [75]. Furthermore, miR-514b-5p may lower E-cadherin expression to promote drug resistance. Interestingly, miR-514b-3p performs a different function in reversing the drug resistance caused by EMT, while being produced from the same RNA hairpin [76]. More research is needed to determine how the miR-514 precursor develops into the mature miR-514b-3p and miR-514b-5p, which play different functions. Moreover, the miR-106b 25 cluster increases doxorubicin resistance by suppressing EP300, an E-cadherin transcriptional activator [75].

Other lncRNAs have recently been linked to EMT and cancer cell metastasis through controlling EMT-TFs via a variety of ways. For example, the interaction between lncRNA antisense to ZEB1 (ZEB1-AS1) with MLL1 can employ it to the promoter area of ZEB1 leading to ZEB1overexpression, increasing EMT and promoting metastasis in cancer cells [77]. Also, in a xenograft mouse model of pancreatic cancer, direct interaction between lncRNA-BX111887 and transcriptional factor Y-box protein (YB1) attracts YB1 to the ZEB1 promoter area and then promotes the expression of ZEB1 through high rate of its transcription [78]. In addition, a group of lncRNAs that sequester miRNAs may post-transcriptionally control ZEB expression has been discovered.

Furthermore, it is discovered that a wide range of circRNAs regulate EMT by altering vital cytoskeleton and cell junctional elements. For instance, circ-AKT3 can sponge miR-296-3p to increase the expression of CDH1, which inhibits tumor cell dissemination *in vivo*, and invasion and migration of cancer cell lines [79]. Similar to this, circPTPRA controls E-cadherin and EMT in NSCLC by miR-96-5p sponging, allowing the production of RASSF8, which is the downstream tumor suppressor of miR-96-5p sequence. RASSF8 can interact with E-cadherin and maintain adhesion junctions [80]. Additionally, by acting as a sponge for miR-193a-5p, circAMOTL1L increases protocadherin-α (Pcdha) transcription. Pcdha belongs to the cadherin superfamily and mediates cell–cell adhesion. Therefore, it is indicated that loss of Pcdha in prostate cancer cells encourages cell invasion, EMT, and cell migration cell lines as well as tumor development in prostate cancer animal models [81]. Intriguingly, targeting circPTK2 with shRNA dramatically reduced tumor metastasis in a xenograft mice model of CRC. CircPTK2 may bind to Ser82, Ser55, and Ser38 locations of vimentin and promote EMT both in tumor cell lines and animal models [82]. Combining the expanding understanding of ncRNAs in EMT and metastasis with ongoing advancements in nucleotide alterations and *in vivo* delivery technologies may eventually make it possible to use this fresh information in therapeutic settings. Various ncRNAs and their association with EMT in different cancer metastasis and drug resistance are elaborately described in refs [83] and [84].

7 EMT and chemoresistance in various cancers

EMT was previously exclusively linked to the invasion and metastasis of cancer cells. Recent research has indicated that cancerous cells undergoing EMT exhibit increased anti-apoptotic activity, which considerably increases the resistance of tumors to therapy [85, 86]. Moreover, EMT-affected tumor cells may develop a resistance to apoptosis, which has a direct effect on the effectiveness of chemotherapy, radiotherapy, targeted treatment, and immunotherapy. As a possible method of treating tumors, reversing EMT or eliminating tumor cells with EMT defects has been suggested [86].

7.1 Brain tumors

The separation of tumor cells from the basement membrane is a component of EMT. Despite the absence of this essential tissue component in the central nervous system (CNS), other cancer types and CNS malignancies share crucial invasive processes [87]. Glioma mesenchymal characteristics may potentially be activated by the same triggers that cause EMT in other malignancies. EMT is a significant inducer of the stemness phenotype in cancer cells, in addition [88]. Glioblastoma mesenchymal subtypes (GBM) often display markers of neural stem cells and have an aggressive behavior [89]. *In vitro* and in the clinical context, expression of stem cell markers in glioma cells grants them high level of invasion potency and resistant to chemo- and radiation therapy [90]. Overall, a hypoxic microenvironment is thought to be a powerful EMT trigger in different epithelial cancer types [91]. The recruitment of circulating or resident myeloid cells, such as macrophages or microglia, into the tumor stroma in gliomas may be caused by inflammatory processes or a hypoxic TME or close-by normal tissues [91]. The resident or circulating myeloid cells discharge a variety of growth factors, such as EGF, TGF, PDGF, and FGF2, that

cause changes in the levels of EMT-TFs and in a variety of proteases that promote invasion potency into the surrounding normal brain [92]. Hence, in a hypoxic milieu, EMT may occur in glioma cells that are impacted by spectator myeloid cells and similar signaling factors.

Additionally, in a brain slice culture and using xenotransplantation orthotopic model, it has been demonstrated that Twist expression is increased in malignant gliomas and encourages invasion in glioma cell via the mesenchymal target gene Slug and the fibroblast activation protein, independent of the cadherin switch [93]. Moreover, Twist expression suppression significantly slows down the development and production of GBM stem cell spheres. According to Nagaishi et al. [94], they found that mesenchymal gliosarcomas express Twist in a distinctive way; EMT is a factor in the development of biphasic tumor gliosarcoma. Slug is also intimately linked to the expansion of malignant glioma migration and invasion [95]. As was already indicated, the notable transcription factors ZEB1 and ZEB2 are involved in mediating EMT in different cancers, like gliomas [96]. According to Wang et al. [96], individuals with GBM that included ZEB2 overexpression showed signs of recurrence with malignant transformation substantially sooner than patients with low levels of ZEB2. Nuclear factor B is activated by connective tissue growth factor, which makes glioma cells very invasive and starts the development of ZEB1, as well [97].

E-cadherin traps β-catenin in the cytoplasm in a variety of cancers, and β-catenin translocation into the nucleus after E-cadherin downregulation is directly associated with the development of the mesenchymal phenotype [98]. Despite the fact that the majority of GBMs do not exhibit E-cadherin expression, localization of β-catenin in the nucleus is mostly seen in the tumor's invasive front [99]. Additionally, considerably shorter patient survival periods are associated with GBMs that exhibit high amounts of Wnt/β-catenin [100, 101]. Twist1, ZEB1, Snail, and Slug are among the EMT activators that are expressed by GBM cells when the Wnt/β-catenin pathway is engaged [102]. Additionally, the Wnt/β-catenin receptor Frizzled4 is highly expressed, which encourages Snail expression and the development of a mesenchymal character in GBM [103]. Moreover, NOTCH has a substantial role in the formation of many different cell and tissue types [104]. In several epithelial malignancies, including those of the lung, breast, and pancreatic, NOTCH signaling is a major EMT inducer [105]. According to Fan and colleagues, the level of CD133-positive stem-like cells in GBMs decreases when NOTCH signaling is inhibited by secretase inhibitors. NOTCH is a key regulator of stemness phenotype in glioma cells in their TME in addition to Wnt/β-catenin [106]. PI3K/Akt pathway activation and NOTCH are also closely connected [107]. In addition, CD44s are the key inducers of EMT in colorectal and breast cancer. According to TCGA data, tumor invasion and resistance to treatments are both elevated in GBMs with transcriptional upregulation of EMT-inducing hallmark markers, such as Slug and CD44 [108]. Nevertheless, functional information on EMT mediated by CD44 in GBM has not been completely clarified [109]. Overall, as glioma cells undergo EMT, they gain the ability to start metastasis and invasion. The TME, in particular, a hypoxic environment or one in which recruited myeloid or mesenchymal stem cells produce proinflammatory chemicals, has a significant impact on this process. These conditions may promote the development of cancer stem cells and result in chemoresistance.

7.2 Urological tumors

The metastatic process in prostate cancer (PCa) is tightly controlled by the interplay of molecular pathways that influence the EMT mechanism. While significant effort has been dedicated to the identification of different molecular pathways that control metastasis in prostate cancer, all of them have one thing in common: EMT's crucial role as an inducer of metastasis and invasion. In actuality, the EMT state dictates the phenotype of cancerous prostate cells. These include both variables that induce EMT and those that inhibit PCa metastasis via modulating EMT. The regulation of EMT is a HOXD13 function in PCa, and the ultimate effect is given through interacting with several molecular pathways. PCa has been shown to proceed much faster both *in vitro* and *in vivo* when HOXD13 is lost. Bone metastatic lesions in PCa increase when depletion of HOXD13 develops. Up-regulation of BMP4 causes EMT in PCa, while HOXD13 works by inhibiting SMAD1 to prevent BMP4 from causing EMT in PCa [110]. Studies' specific findings about the molecular interactions controlling the EMT process are their main area of strength. Yet, it might be challenging to determine a gene's role in modulating EMT when a gene exhibits multiple roles in malignancies. A bad prognosis is provided by SHMT2 upregulation in bladder cancer [111]. Moreover, SHMT2 may encourage the proliferation and invasion of cancer cells [112]. As a result, SHMT2 function seems to be carcinogenic. In contrast to other research, however, decreased expression of SHMT2 in PCa encourages tumor cell invasion. PCa is prevented from progressing by SHMT2, and when it is deficient, EMT is stimulated, accelerating cancer invasion [113]. While research suggests that S100A14 may have a role in drug resistance and EMT induction in human malignancies [114], S100A14's role in PCa is based on boosting FAT1 expression, which causes Hippo signaling, which lowers PCa malignancy and inhibits EMT [114]. Consequently, a critical discussion of a gene's or protein's role in controlling EMT in PCa is necessary. A protein or gene may target more than one component that controls growth and invasion at once, and

EMT is not necessarily its only target. For example, in PCa, FSCN1 activates the YPA/TAZ axis, which improves glycolysis (metabolism) and encourages invasion through EMT [113]. EMT therefore participates crucially in controlling PCa metastasis and development [115]. The human tumors CXCR4 and CXCR7 exhibit overexpression, and they are powerful modulators of cancer growth [116]. In order to increase survival, angiogenesis, and growth, CXCL12 interacts with CXCR4 and activates signaling pathways such MEK/ERK, PI3K/Akt, JAK-STAT, and NF-κB [117]. The role of the atypical chemokine receptor CXCR7 in cancer is debatable [118]. The modulation of cancer growth involves CXCR4, CXCR7, and ultimately CXCL12 [119]. A recent experiment examines the role of CXCR4 and CXCR7 in PCa growth. When CXCL12 is upregulated as a consequence of CXCR4 inhibition, EMT is induced and proliferation is sped up. Moreover, CXCR7 suppression has comparable effects in slowing PCa development. Because of this, CXCR4 and CXCR7 help to promote PCa development and induction of EMT [120].

According to a recent investigation, acetylated KLF5 may boost CXCR4 expression, induce EMT, and maintain PCa cells as they acquire docetaxel resistance [121]. ISL1 is an oncogenic factor that promotes cancer development, metastasis, and angiogenesis [122]. Furthermore, ISL1 may make tumor cells resistant to cisplatin [123]. ISL1's EMT pathway-related action mechanism in PCa is crucial. In order to mediate EMT in PCa cells and impart enzalutamide resistance, ISL1 stimulates Akt phosphorylation [124]. According to intriguing research, activating the EMT process may cause PCa to relapse and acquire docetaxel resistance [125]. Castration resistance in PCa may also be caused by overexpression of the oncogenic FOX2 and development of EMT [126]. It has been demonstrated that the androgen receptor (AR) prompts the upregulation of Twist1 through ETV1, leads to increased EMT and enhanced migration of prostate cancer cells, and mediates castration resistance in PCa. Moreover, experimental studies indicated that TGF-β increases androgen receptor expression and that Twist1 and androgen receptor expression can be suppressed by TGF-β inhibitors [127]. Hypoxia is one of the factors that accelerates PCa development.

Chrysin exerts its anti-tumor effect by suppressing the SPHK/HIF-α1 axis to slow the evolution of PCa, and expression level increases during hypoxia to facilitate glycolysis, which is disturbed by docetaxel [128, 129]. Propofol lowers HIF-1 to decrease EMT in order to overcome docetaxel resistance in PCa cells since HIF-α1 expression levels rise during hypoxia [130]. The formation of radioresistance in tumor cells may be caused by EMT, despite the fact that research has mostly focused on the involvement of EMT in chemoresistance [129, 131]. Radio resistance develops in PCa as a result of SMC1A's induction of EMT [132]. Future research should take into account the molecular factors that contribute to EMT involvement in radioresistant PCa.

Genes strongly control the EMT-related proteins in modifying bladder cancer (BC) development. In order to improve N-cadherin and vimentin levels while downregulate E-cadherin, YKL-40 promotes Slug, Snail, and Twist, as inducers of EMT in BC [133]. Many malignancies, including liver cancer and BC, have been linked to the etiology of type II diabetes mellitus (TIIDM) [134]. High glucose levels have also been linked to the etiology of diabetic problems such nephropathy and macrovascular proteins, as well as the ability to mediate EMT [135]. High glucose levels in BC increase YAP1 and TAZ expression, promoting tumor spread and inducing EMT, demonstrating the need for greater attention to be paid to the care and management of diabetic patients [136]. A lot of work has gone into understanding the variables that control EMT, but what is fascinating is that SOX2 and Nanog levels are promoted by EMT, which increases the stemness of BC cells [137]. Hence, inhibiting EMT may reduce BC cell stemness in addition to decreasing invasion. BC cells become less sensitive to chemotherapy when EMT is induced. By increasing E cadherin levels and lowering N-cadherin and vimentin levels, suppressing Notch signaling prevents EMT and increases BC's drug sensitivity [138]. Autophagy is one of the systems that breaks down macromolecules and organelles and maintains cellular homeostasis. Its activation may happen under hunger and stress situations. Moreover, too much autophagy might cause cell death [139]. Current research has examined the role of autophagy in BC, and it has been shown that 4-Methoxydalbergione reduces the growth of tumor cells by inhibiting autophagy [140]. In addition, autophagy inhibition increases the expression of PD-1 and boosts immunosuppression in tumor cells [141]. Yet, autophagy's protective role may help BC cells advance. Capsaicin increases Dhh/Ptch2/Zeb2 expression levels as a part of Hh signaling to cause EMT and mediate resistance to treatment with mitomycin C, gemcitabine, and doxorubicin in BC [142]. The complex signaling networks that exist in BC cells may contribute to BC's development of treatment resistance. SETDB1 is an H3K9 methyltransferase whose role in numerous physiological and pathological conditions has been well established [143]. It is involved, among other cellular mechanisms, in gene regulation at the epigenetic level, such as the regulation of cell proliferation, cell death, the antiviral response, the inactivation of the X chromosome, and inflammatory responses. Circ-PTK2 has an interaction with PABPC1 to improve SETDB1's stability at the mRNA level. This increases cancer spread and initiates gemcitabine resistance by inducing EMT [144].

Transmembrane metalloproteinases of the ADAM protein family have crucial roles in signal transmission, cellular connections, and proteolysis [145]. A member of the ADAM

family, ADAM12, has been investigated for its participation in tumor progression and its role in promoting the spread of cancer cells [146]. Gemcitabine resistance in BC is mediated by an increase in EGFR expression and stimulation of the EMT process by ADAM12 [147]. ADNP, whose overexpression induces Akt signaling and accelerates BC cell proliferation, is another crucial element in the development of the disease [148]. Notably, ADNP promotes cisplatin resistance in tumor cells by promoting TGF-mediated EMT and is also implicated in the invasion of BC cells [149]. Chemokines have an important function in the course of BC, and a high level of CXCL5 expression mediated by circDHTKD1 may lead to lymphatic metastasis [150]. To attract myeloid-derived suppressor cells and speed up BC development, KIF4A promotes CXCL5 expression [151]. Suppressing of CXCL5 down-regulates CD44 expression and reduces BC cell stemness and metastasis [152]. Mitomycin C resistance in BC is mediated by CXCL5, which elevates NF-κB levels and induces EMT [153]. These results suggest that EMT activation may make BC cells more aggressive and that when this happens, tumor cells are more likely to become resistant to treatment. Hence, EMT inhibition may increase cancer cells' receptivity to treatment.

There are a few research assessing the role of EMT in renal cancer that should be taken into consideration in the upcoming trials, despite the fact that the EMT mechanism in other urological malignancies, such as BC and PCa, has been well investigated. The first crucial element is the contribution of the EMT process to the accelerated advancement of kidney cancer. Although overexpression of SLC27A2 is a detrimental factor that inhibits EMT through a decrease in the expression to obstruct tumor cell development and metastasis, CDK3 can enhance EMT in the evolution of renal cancer [154]. SLC17A9, a separate factor from ALC27A2 that can also control the growth and metastasis of renal cancer, has a distinct method of action. SLC17A9 increases the expression of PTHLH to promote EMT during the invasion of renal carcinoma. As a result, SLC17A9 silencing may hinder EMT in renal carcinoma metastasis [155]. It has to be emphasized, nonetheless, that induction of EMT in renal cells does not always suggest that the risk of cancer metastasis is increased. For instance, research has indicated that the cancer stem cell marker, CD105, may trigger EMT but cannot promote metastasis [156]. To determine if there is a correlation between EMT and enhanced cancer invasion, investigations should assess EMT, cell transformation, and ultimate impact on the invasion of tumor cells. ZEB protein control of EMT was extensively covered in earlier sections. When ZEB2 is overexpressed in kidney carcinoma, EMT is stimulated, which accelerates the growth of tumor cells. Nevertheless, miR-124 and miR-203 work in concert to decrease ZEB2 and prevent kidney carcinoma cells from migrating and invading [157]. Hence, deregulation of molecular pathways may result in EMT modulation in renal cancer, just as it occurs in other urological cancers [158]. Importantly, the EMT process and chemoresistance in kidney cancer are related. Rock2 is upregulated when Nc886 expression levels rise in renal carcinoma due to its phosphorylation. Then, it is discovered that β-catenin nuclear transfer underlies EMT-induced chemoresistance in renal carcinoma [159]. Moreover, HP-1's EMT inhibition helps tumor cells become more sensitive to sunitinib [160]. The use of anticancer substances that control EMT in renal cancer is thus advantageous in reducing carcinogenesis [161].

7.3 Gastrointestinal tumors

The contribution of EMT in metastasis and drug resistance in different gastrointestinal tumors, including gastric cancer, esophageal cancer, hepatocellular carcinoma, colorectal cancer, pancreatic cancer, and cholangiocarcinoma, has been reported in recent studies. According to reports, TGF-β1 causes EMT in esophageal adenocarcinoma (EAC) by activating the SMAD4 pathway. BMP7 as a member of the TGF-β1 superfamily, blocks this signaling [162]. It was shown that TGF-β1 controls mitochondrial superoxide dismutase 2 (SOD2), an antioxidant enzyme, to change $CD44^{low}$ cells into $CD44^{high}$ cells using immortalized esophageal keratinocytes. NF-κB and ZEB2, but not ZEB1, were transcriptionally responsible for regulating SOD2 expression [163]. In addition, it is mentioned that TGF-β1-mediated EMT in the same cells needed p53 mutation together with high-level expression of ZEB1 and the loss of EGFR-dependent senescence program [164]. To investigate the reasons for resistance to chemotherapy and the poor prognosis after treatment in esophageal cancer, Liu et al. created esophageal cancer cells, which are resistant to paclitaxel (PTX). Their research showed that these cancer cells exhibited stem cell biomarkers and were susceptible to EMT had features of cancer cells that are stem cells. Their findings revealed that after taking chemotherapeutic medications continuously for a while, the EMT biomarkers expression and EMT-related proteins linked to stemness increased in esophageal cancer cells. This research suggested that a better approach to treating drug resistance in esophageal cancer may include concurrently attacking EMT and stemness [165].

The *Helicobacter pylori* cytotoxin-associated gene A (CagA) oncoprotein, which causes the *in vitro* "hummingbird" phenotype that resembles EMT, may play a role in the association between EMT and gastric cancer (GC) [166]. GC cells overexpressing CagA increased the transcription of mesenchymal and stem cell markers including CD44 [166]. Cancer cells with high levels of CagA shown a strong capacity for tumorigenesis *in vivo*. Overexpression of CD44 and upregulation of other mesenchymal markers were confirmed by immunohistochemical examination of samples

from people with *H. pylori* infection [167]. The runt domain transcription factor RUNX3 serves as a crucial TGF-pathway mediator in the stomach epithelium. Gastric epithelial cells lacking RUNX3 undergo EMT and produce a fraction that expresses Lgr5 (the gastric stem cell marker), which is tumorigenic stem cell-like. Gastric epithelial cells were more susceptible to TGF-induced EMT as a consequence of the suppression of RUNX3 and p53, and the resulting induction of Lgr5 was made more potent by an aberrantly active Wnt pathway [168]. In gastric cancer, Cao et al. studied the possibility that FHL3 leads to EMT and drug resistance by upregulating slug and activating TGF-β/Smad-independent pathways [169]. Their findings suggested that lower overall survival and greater TNM stage are invariably associated with increased FHL3 expression. Oxaliplatin (OHP) resistance might result from excessive FHL3 expression. Although FHL3 knockdown significantly sensitized chemotherapy *in vivo* and *in vitro*, it only mildly decreased cell proliferation. Moreover, although down-regulating FHL3 lowered E-cadherin, as the epithelial marker, it raised Slug, Snail, Twist1, and Vimentin (as the mesenchymal markers) [170]. It has also been shown via cell and animal studies that downregulating FHL3 may reduce cancer cell metastasis. For the purpose of studying the process, inhibition of FHL3 declined the levels of the TGF-β/PI3K/Akt/GSK3b-(Ring Finger Protein 146) RNF146/ubiquitin pathway and the MAPK/ ERK pathway. The ubiquitin complex (Slug/GSK3b/RNF146) and Slug were competitively bound by FHL3, which prevented Slug from being ubiquitinated. Multidrug Resistance Gene 1 (MDR1) is more prevalent in mesenchymal phenotypic cells, and FHL3 knockdown reverses MDR1 in these cells [169].

In cancerous cells that were resistant to regorafenib therapy, it has been discovered that HEY1, HES1, and Notch-1 were considerably elevated. It is reported that suppressing Notch-1 in resistant cells partly reversed resistance to regorafenib treatment *in vitro* studies [171]. Furthermore, because over-activation of Wnt/β-catenin signaling is a significant contributor to the formation of CRC, Wnt signaling is both a key route for CRC progression and one of the variables contributing to the evolution of EMT [172]. A number of secreted glycoproteins make up the Wnt/β-catenin pathway. Hence, EMT activity in CRC cells and tolerance to certain cisplatin-based medications may be promoted by aberrant stimulation of Wnt/β-catenin signaling [173]. To evaluate CRC cells with various degrees of resistance to oxaliplatin, Zhou et al. measured the levels of miR-506 in individuals with the disease. They discovered that upregulation of miR-506 decreased the Wnt/β-catenin pathway, reduced expression of MDR1 and P-gp, and increased oxaliplatin sensitivity in HCT116-OxR cells [173]. Consequently, the modulation of specific signaling pathways, like Notch, enables the potential reversion or elimination of cancerous cells that have already undergone EMT. This is a prominent concern in modern clinical practice [85]. In addition, Wang and colleagues discovered that colorectal cancer cells with high levels of Snail expression had significantly enhanced 5-Fluorouracil resistance. The direct binding of Snail to the promoter of ABCB1 can increase its expression [174]. Also, they discovered that cutting down the ABCB1 gene might drastically reduce resistance to 5-Fluorouracil induced by Snail in colorectal cancer cells, suggesting a possible mechanism for EMT and chemoresistance and offering a potential target for therapeutic therapy of this malignancy.

Transcriptomic research on human hepatocellular cancer tissue samples found that TGF-β signaling was active in a subset of HCC, known as Wnt-TGF-β subclass [170]. According to a sequential transcriptome study, TGF signaling was a late event that was accompanied by significant gene changes [175]. During EMT, TGF-β has been found to cause post-translational modifications in hepatocyte nuclear factor-4α (HNF-4α) that coincide with the early loss of the capacity of HNF-4α to bind to promoters of target genes through GSK-3β kinase [176]. By phosphorylating SMAD3's linker region at Ser213, which leads to the overexpression of TGF-target genes such Snail, MMP9, PAI1, and the receptor tyrosine kinase Axl [175].

The greatest barrier to treating hepatocellular cancer is medication resistance. The acid-sensing ion channel 1a (ASIC1a) plays crucial functions in the invasion and metastasis of cancer cells and in the development of therapeutic resistance [177]. ASIC1a levels and their connection to cell invasion, cell migration, and cell proliferation were examined by Zhang et al. HCC tissues overexpress ASIC1a and resistant HCC cells overexpress ASIC1a even more. Drug-resistant cells experienced EMT more often than parental cells. Via EMT, ASIC1a inactivation reduced cell invasion and migration and boosted chemosensitivity in cells. When ASIC1a was overexpressed, it produced drug resistance, activated EMT, and boosted cell invasion, migration, and proliferation. When ASIC1a was knocked down by shRNA, the EMT program would be reversed. By controlling the production of fibronectin, vimentin, and catenin through the AKT/GSK-3/Snail pathway activated by TGF/Smad signals, ASIC1a promoted cell motility and invasion via EMT. Drug resistance in HCC is mediated by ASIC1a via EMT through the AKT/GSK-3/Snail pathway [177].

7.4 Gynecological tumors

Gynecologic malignancies are caused by neoplastic cells that develop in the ovaries, vagina, cervix, uterus, vulva, and fallopian tubes growing uncontrollably. Studies have shown that gynecologic malignancies have comparable risk factors, including obesity, exposure to certain chemicals, smoking, age, HIV infection, and infection to human papillomavirus.

This is true even if these tumors have diverse signs and symptoms. Despite recent improvements in gynecologic cancer prevention, diagnosis, and treatment, many patients still die from metastasis and recurrence. Significant emphasis should be provided in order to recognize the molecular anomalies causing EMT and its underlying signaling to decrease cancer morbidity and mortality because numerous pieces of evidence indicate that the EMT process has a crucial role in metastatic relapse of cancer. Gynecological malignancies have increased cellular migration, metastasis, survival, recurrence, invasion, and treatment resistance, which may be caused by EMT [178]. Furthermore, chemo- and radiation resistance in cervical malignancies has been linked to its increased expression [179]. Patients with cervical squamous cell carcinoma who express Twist2 have a higher risk of developing metastatic disease [180]. The induction of the AKT and Wnt/β-catenin pathways as well as the maintenance of the cells' stem cell-like properties are caused by the expression of these transcription factors in cervical cancer cells [181]. Twist overexpression has been shown to be related with a worse patient survival rate in invasive endometrial carcinomas [182]. Twist1 overexpression decreases keratin-8 and E-cadherin expression while promoting N-cadherin transcription in ovarian cancer [183]. It has been reported that Twist2 decreases E-cadherin expression and is involved in EMT induction in vulvar cancer [184]. Twist expression in endometrial cancer cells can be induced by the upregulation of transcription factor KLF17. As a result, EMT was subsequently activated, cell invasion was enhanced, and drug resistance was developed. Twist and KLF17 both exhibit increased expression in endometrial cancer cells [185]. KLF4, a transcription factor related to KLF17, inhibits cell migration, cell invasion, and cell proliferation by modulating EMT induction mediated by TGF in ovarian cancer cells, acting as a tumor suppressor [186]. A proinflammatory cytokine called interleukin 6 (IL-6) causes EMT in cervical and ovarian malignancies [187]. Via the STAT3 pathway, IL-6 promotes EMT activation in cervical cancer [188]. Increased levels of EGF in ovarian cancer boost the release of IL-6, which, via the PI3K/Akt SHP-2/Ras, JAK/STAT3, and MAPK signaling pathways, promotes the cell mobility and cancer cells resistance to chemotherapy [189]. According to research, TFs including Twist, Snail, and FOXC2 overexpression in breast cancer boost the promoter activity of ABC transporters, suggesting that EMT triggers are some of the ABC transporter regulators. Hence, transcription factors related to EMT are suggested as emerging therapeutic strategies to address metastasis and the associated treatment resistance [30]. Significantly, breast cancer cells with intermediate E/M phenotypes are more capable of acquiring metastasis and treatment resistance than those with a fully mesenchymal condition [190]. The production of ITGB4 + in intermediate stages, which is controlled by Zeb1 via its suppression of Tap63 expression, a protein that promotes ITGB4 expression, is one of the molecular mechanisms hypothesized for this resistance in mesenchymal-like triple-negative breast cancer cells [191].

In both normal and transformed human mammary epithelial cells, stimulation of Twist up-regulation or inhibition of E-cadherin confers resistance to doxorubicin and paclitaxel. This is a noticeable example of EMT role and its related transcription factors in chemotherapy resistance. Yet, in basal-like breast cancer cells, Snail provides resistance to docetaxel and gemcitabine. Paclitaxel is only effective against breast cancer cells that have mesenchymal features. In fact, the EMT induction activates PERK-eIF2 and makes cells more vulnerable to substances that disrupt the function of the endoplasmic reticulum (ER) [192]. This illustrates a brand-new ER-stress sensitivity susceptibility of cancer cells during EMT. It is significant that the relationship between EMT and resistance to endocrine treatment in luminal breast cancer has been observed utilizing in xenograft models and in vitro studies. It is interesting to note that the production of estrogen receptor alpha gene (ESR1) fusion proteins in breast cancer cell lines accelerates the development of EMT without the use of estrogen by upregulating Snail and downregulating E-cadherin [193].

7.5 Hematological tumors

It is interesting to note that mounting data suggests that transcription factors related to EMT are crucially involved in hematologic disorders. Hematopoietic and leukemic stem cells both exhibit high levels of Twist1 expression [194]. Hematopoiesis is associated with Twist1 expression. Twist1 promotes apoptosis resistance and cancer cell self-renewal ability in leukemia and solid tumors [52, 195]. By preventing apoptosis, the snail family also aids in the growth of lymphocytes [196]. These results have prompted research into the involvement of EMT-TFs in the development of hematological malignancies and their resistance to treatments. Drug resistance may also result from Twist1 expression. According to Nan et al., Twist1 expression was linked to mitoxantrone and daunorubicin resistance, which has a negative impact on prognosis. Nevertheless, the molecular and cytogenetic risk was unclear in this investigation [197]. As opposed to this, different research found that the aggressive types of AML associated with high levels of Twist1 had a stronger response to cytarabine therapy, resulting in a positive outcome [195]. These findings suggested that upregulation of Twist1 was linked to low cytogenetic and/or molecular risk, which might account for the favorable prognosis. However, further research is needed to understand how signaling pathways have an effective interaction with Twist1 in a low-risk AML subtype. Regardless of any additional resistance mechanisms, the amount of Twist1

expression in CD34 + CML cells served as both a prognostic indicator and a biomarker for early identification of tyrosine kinase inhibitor resistance in CML. Twist1 may be a crucial prognostic indicator for myeloid malignancies even if the relationship between it and Bcr-Abl translocation is unclear [198].

Mancera and coworkers discovered that the expression of Snail2 was increased and is necessary for the elevation of leukemogenesis in Bcr-Ablp^{190} transgenic mice [199]. Moreover, Snail2 expression made leukemia cells resistant to apoptosis, but Snail2 inhibition promoted cell death [200]. Since ERK1/2 stimulates the expression of Snail2, p53 up-regulated modulator of apoptosis (PUMA) is down-regulated, which results in chemoresistance to cytarabine and adriamycin [201]. Mancini et al. demonstrated in a CML cell line that Bcr-Ablp210 controlled Snail2 expression through ERK1/2, resulting in resistance to imatinib mesylate [202]. Leukemia development could be enhanced in Snail1-expressing mice, and Snail1 expression also encouraged resistance to apoptosis, leading in radiotherapy resistance [203]. Overall, the Snail family, notably Snail2, may regulate leukemia's capacity for self-renewal, resistance to treatment, and anti-apoptosis. As a result, Snail proteins family is a possible target for leukemia therapy. Moreover, ZEB2 was shown to be a crucial transcription factor for maintaining the stemness of leukemia cells, and its absence resulted in abnormal differentiation and reduced proliferation [204].

8 EMT-mediated tumor therapeutic resistance: therapeutic approaches

Reversing or suppressing EMT is a novel notion for therapeutic tumor sensitization because of the critical role EMT plays in tumor metastasis and tumor resistance. The process of mesenchymal-epithelial transition (MET) can be considered as the inverse of EMT. In contrast to the process of EMT, the process of MET involves the reversal of cellular phenotype from a mesenchymal state to an epithelial state. This transition is characterized by a shift towards a cellular phenotype that is more structured, less motile, and less invasive. As a result, tumor cells become more resistant to treatment by re-expressing epithelial markers and losing their mesenchymal properties [205]. A novel strategy for therapy resistance could be offered by the transformation of mesenchymal tumor cells into epithelioid phenotype. Targeting transcription factors related to EMT can be a strategy for treating cancers that have become resistant to therapy since MET may be caused by the diminished expression of EMT-TFS and EMT-TRAN [206]. Via the AKT/GSK-3/Snail signaling pathway, it has been discovered that ionizing radiation increases the radiotherapy resistance of hypopharyngeal cancer cells and promotes EMT. The EMT is reversed and the radiotherapy resistance of hypopharyngeal cancer cells is greatly reduced when Snail is silenced, but in oral squamous cell carcinoma, inhibiting Slug improves the cancer cells' susceptibility to radiation [207, 208]. These findings imply that Snail and Slug may represent viable targets for EMT-mediated radiation resistance treatment. With the E-cadherin promoter region, Twist may create a dimer or heterodimer, limiting its expression and accelerating the start of EMT [207]. Mice with reduced TWIST levels showed increased sensitivity to cisplatin treatment in cases of epithelial ovarian cancer when siTWIST-MSN-HA, a novel nanoparticle delivery system, inhibited the expression of Twist. This suggests that this technology could be applicable to malignancies characterized by Twist overexpression [209]. In addition to being necessary for EMT activation, ZEB1 is also essential for the emergence of chemotherapeutic resistance. It has been shown that inhibiting ZEB1 expression makes CRC cells more susceptible to chemotherapy, suggesting that inhibiting the expression of ZEB1 can help reverse chemotherapy resistance mediated by ZEB1[210].

By effectively suppressing EMT to some extent, inhibitors of several signaling pathways might reduce tumor resistance to therapy. As mentioned before, EMT is governed by the TGF-β/Smad signaling pathway. In gastric cancer and glioma cells, LV2109761 and LV364947 have been shown to impede EMT brought on by ionizing radiation, hence increasing tumor cells' irradiation sensitivity. Both LV2109761 and LV364947 are the TGF-receptor inhibitors [211, 212]. Moreover, regarding to the role of Wnt/β-catenin signaling pathway in EMT-mediated tumor therapy resistance, driamycin sensitivity in lymphoma patients may be considerably increased by WNT974 as a suppressor of the Wnt/β-catenin signaling pathway. Moreover, radiation sensitivity of cervical cancer cells has been markedly elevated by XAV939, which is a tankyrase inhibitor [213].

Numerous investigations have shown a connection between EMT and the control of certain ribosomal proteins in diverse cancer types. Inhibiting EMT and ultimately leading to chemoresistance, several ribosomal proteins have the capacity to control cell migration [214, 215]. Although the suppressing of RPL34, a ribosomal protein, is enough to diminish the EMT phenotype, inhibiting invasion and migration of esophageal cancer cells, the down-regulation of uL3, another ribosomal protein, is associated with promoted cell migration and EMT that in turn results in chemotherapy resistance [216]. Ribosomes are produced as a result of the translation of ribosomal protein-coding mRNAs (RP-mRNAs), although it is unclear how these processes are controlled in relation to other cellular processes. During the process of cell migration into their environment, the RP-mRNAs are localized in actin-rich cell protrusions. The localization of this protein is caused by the RNA-binding protein La-related protein 6 (LARP6). LARP6-mediated

Table 2 Clinical trials targeting EMT in various cancers

Clinical trial	Status	Cancer	Treatment approach
NCT02412462	Completed (Phase I)	Solid tumors	AB-16B5 (humanized monoclonal antibody) inhibits secreted form of clusterin (sCLU) (EMT inducer)
NCT00900328	Completed	Adenocarcinoma (AC) of the lung	Correlation of c-Met expression and EMT
NCT01070355	Completed (Phase II)	Colorectal cancer liver metastases	Targeted EMT by eicosapentaenoic acid (EPA)
NCT02204943	Completed	Bone metastatic castration-resistant prostate cancer	Treated with Radium-223 that decreases EMT markers
NCT00769483	Completed (Phase I/II)	Advanced pancreatic cancer	MK-0646 and gemcitabine ± erlotinib to target and decrease EMT markers
NCT01534585	Completed (Phase I/II)	Nasopharyngeal cancer	Icotinib hydrochloride combined with intensity-modulated radiotherapy to target EMT
NCT01468922	Completed (Phase I)	Advanced solid tumors	Pazopanib and ARQ 197 (Tivantinib) block (c-MET)

mRNA localization is necessary for cell migration, and this pathway is connected to cancer formation during EMT [217]. Table 2 summarized some of the clinical trials related to targeted EMT for cancer treatment.

9 Conclusion and remarks

Several mechanisms underlie the development of treatment resistance in tumor cells, and the processes behind therapeutic effectiveness and resistance vary greatly across people with various tumor types. Tumor treatment resistance is a result of heterogeneity and biological processes, like drug metabolism, DNA damage repair, autophagy, cell cycle arrest, drug efflux, and EMT. The treatment of tumor therapeutic resistance may also be influenced by the TME and other small-molecule substances in the blood. Future study should concentrate on the fundamental process in tumor cells that leads to their resistance to treatment since addressing only one of the processes mentioned above is inadequate to entirely reverse tumor cell treatment resistance. One of the most prevalent mechanisms causing cancer therapy resistance is EMT. The function of EMT and the cellular process through which it takes place have gained considerable understanding as research has progressed. In cancer patients, EMT and therapy resistance have all been clearly linked, according to a number of clinical investigations. Unfortunately, there are presently few therapeutic medications or healing methods that might improve the EMT process and, thus, the effectiveness of tumor treatments. Targeting certain sites can reverse EMT and increase tumor treatment sensitivity in cell and animal studies, but there are still significant hazards and challenges to long-term human success. As a consequence, a more thorough and in-depth investigation of the connection between EMT and tumor treatment resistance is required. To create a new strategy for the treatment of customized tumors in the future, fundamental experimentation, clinical research, and development must still be coordinated with translational medicine at their heart.

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