



# Epithelial-mesenchymal plasticity—engaging stemness in an interplay of phenotypes

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**Abstract:** Cancer is a genetic disease which results in a functional imbalance between tumour-repressive and oncogenic signals. The WHO highlights the burden of this indomitable disease, listing it as the second leading cause of death globally. The major cause of cancer-related death is rarely the effect of the primary tumour itself, but rather, the devastating spread of cancer cells in metastases. Epithelial-mesenchymal plasticity (EMP)—termed as the ability of cells to maintain its plasticity and transit between epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET) states—plays a fundamental role in cancer metastasis. These cell transitions allow them migrate from the primary tumour and invade the secondary site. EMP is associated with migration, invasion, colonisation, self-renewal and drug resistance. This review briefly elucidates the mechanism of EMP and the association between cancer stem cells (CSCs) and circulating tumour cells (CTCs), biomarkers and signalling pathways involved in EMP as well as drug resistance and therapeutic targeting.

**Keywords:** Cancer stem cells (CSCs); stemness; epithelial-mesenchymal plasticity (EMP); epithelial-mesenchymal transition (EMT); mesenchymal-epithelial transition (MET); metastasis

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## Introduction

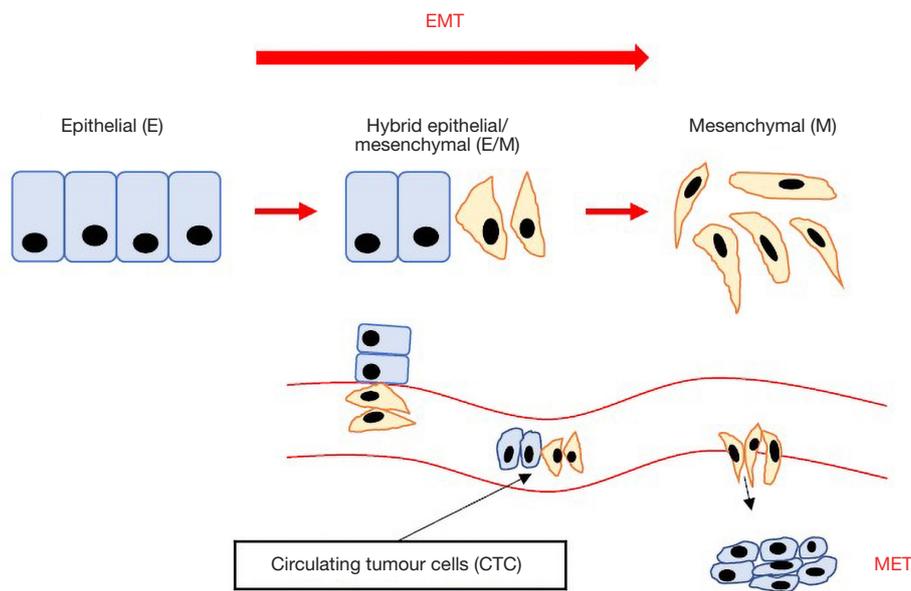
Cancer is a genetic disease that arises due to somatic mutations which results in a functional imbalance between tumour repressive and oncogenic signals (1). According to the World Health Organization (WHO), cancer is the second leading cause of death globally. The major cause of cancer-related death is rarely the effect of the primary tumour itself, but rather, the devastating spread of cancer cells in metastases (2).

Epithelial-mesenchymal plasticity (EMP) plays a fundamental role in cancer metastasis. EMP is termed as the ability of cells in maintaining its plasticity and transit between epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET) states (3). These

cell transitions allow them migrate from primary tumour and invade at the secondary site (4). EMP is associated with migration, invasion, colonisation, self-renewable and drug resistance (4-6). Although much research has delved into the process of carcinogenesis leading to metastasis, the crux of EMP mechanisms and its microenvironment remains poorly understood. This review briefly elucidates the mechanism of EMP, the association of cancer stem cells (CSCs) and circulation tumour cells, biomarkers and signalling pathways involved in EMP as well as drug resistance and therapeutic targeting.

## EMP

The ability of tumour cells to undergo EMT and the reverse



**Figure 1** The dynamic mechanism of EMT in cancer metastasis, highlighting the epithelial (E), hybrid (E/M), and mesenchymal (M) states of neoplastic cells. The fluidity of phenotypic change eases the transformation into CTCs in the blood or lymphatic circulation, which eventually invade a secondary distant site and reform epithelial cells via MET. CTCs, circulating tumour cells; EMT, epithelial-mesenchymal transition; MET, mesenchymal-epithelial transition.

differentiation process MET is termed as EMP. EMP is the dynamic flux within the spectrum of phenotypic states that invasive carcinoma cells may reside (4). EMT is significant during embryogenesis, wound healing, fibrosis and cancer metastasis as the cells transit between epithelial and mesenchymal states in a highly plastic and dynamic manner which can help in the understanding of human disease and tumour progression (7). EMT is associated with several traits, which are decreased cell-cell adhesion; alterations of cytoskeleton, tight junctions and hemidesmosomes; loss in apical-basal polarity and gain of front-rear polarity; promote migration and invasion of cells by degrading and remodelling extracellular matrix, and ultimately, colonise at the secondary site (8,9). Moreover, EMT is associated with drug resistance, evasion of the immune system and the ability to generate CSCs (4,8). Several microenvironment conditions may induce EMT, such as the activation of EMT transcription factors which include ZEB, Snail, and Twist; matrix stiffness and hypoxia (8,10). EMT transcription factors contribute to tumour progression by inducing resistance to apoptosis and maintaining stem-like properties demonstrated in recurrent tumours (10).

However, during EMT progression, cells can exhibit

a hybrid epithelial/mesenchymal (E/M) phenotype, of which the cells will co-express epithelial and mesenchymal markers (11-13) (Figure 1). It has been shown that cells exhibiting this mix of phenotypes will allow them to migrate collectively during mammary gland formation, trachea development and wound healing (12,14). In addition, collective cells would also be seen in migration as CTC clusters in the bloodstream of breast, lung and prostate cancer patients (15-18). CTC clusters that co-express epithelial and mesenchymal markers can enter and exit the bloodstream more efficiently, posing a higher metastatic risk in cancer cells (11,19). Stemness is also associated with cells that adopt the hybrid E/M state (11). As the clusters reach the distant target site, they will undergo MET which allows them to regain cell-cell adhesion and exhibit an epithelial phenotype, and thus colonise secondary site forming a secondary tumour. MET is found to be an essential driver in the later stages of metastasis.

In summary, the most striking difference between these three cell states is that EMT is crucial for the transformation of a benign tumour to an invasive carcinoma; cells in the hybrid E/M state are more aggressive and responsible for the migration of clusters in bloodstream; whereas MET is

crucial for the colonisation at distant sites.

### CSCs and circulating tumour cells (CTCs)

EMP induces tumour cells to develop stem cell characteristics, which promote cells to invade surrounding tissues and contribute to resistance against therapeutics. These cells are inherently termed 'cancer stem cells'. CSCs are a group of cells that are capable of self-renewal, initiate tumour generation, and undergo heterogeneous differentiation (20).

EMP also plays a critical role in disseminating tumour cells into the haemodynamic circulation, which is known as CTCs (9,21). CTCs are known as individual cells that dissolve from the primary tumour and enter the circulation during the tumour outgrowth (22). In addition, EMT facilitates the entry of CTCs into blood circulation by activation of the transforming growth factor-beta (TGF- $\beta$ ) pathway. CTCs are able to survive in circulation due to the presence of more mesenchymal-shifted cells in the clusters (21).

CSCs express specific cell-surface markers, namely CD24, CD44, CD133, CD200, epithelial cell adhesion molecule (EpCAM), ATP-binding cassette B5 (ABCB5) and THY1. The most significant property of CSCs is that it downregulates and upregulates the expression of CD24 and CD44 glycoproteins respectively. However, specific cancer types express unique cell surface markers and their level of expression depends on their phenotype and properties (9,23). For example, breast carcinoma cells express CD44<sup>high</sup>/CD24<sup>low</sup>, lung carcinoma has an elevated expression of CD44 and CD133, prostate carcinoma cells express EpCAM<sup>low</sup>/CD24<sup>low</sup>, while colon carcinoma cells express CD133<sup>high</sup>/CD26<sup>low</sup> (9).

### EMT biomarkers

In the course of EMT, the alteration of cellular phenotypes leads to the advent of specific biomarkers. Identification of biomarkers is clinically important in tumour diagnosis as the tumour biomarkers can be utilised in cancer patient therapy and enhance prognostic value (24). E-cadherin is a plasma membrane protein expressed by epithelial cells, which is responsible for maintaining cell adhesion as well as tight junction proteins (ZO-1).

As mentioned, when EMT is in progress, cells will lose their adhesion and polarity characteristics. Thus, there will be reduced expression of E-cadherin, and vimentin filaments will be produced (24,25). Loss of E-cadherin is

said to be the hallmark of EMT (26). Mesenchymal markers such as N-cadherin, Snail, Slug, Twist, fibronectin and ZEB1 levels increase accordingly during the EMT process (27-29). An upregulation of N-cadherin expression with concomitant downregulation of E-cadherin contributes to the loss of cell-cell adhesion (30). Snail and Slug are Zinc-finger transcriptional factors which bind to the E-box of proximal E-cadherin promoter CDH1, and ultimately suppress E-cadherin transcription resulting in the disruption of cellular tight junctions (31-33).

Cytokeratin, a cytoplasmic intermediate filament protein, is the main structural element that make up the cytoskeleton in epithelial cells. It functions to maintain structural rigidity and multipurpose scaffolds. Recent studies show that cytokeratin 19 (KRT19) and CK19 is upregulated in breast cancer and lung cancer respectively (34,35). Not only that, overexpressed CK19 can be seen in most of the epithelial malignancies, such as cervical, colorectal and thyroid carcinomas. Keratin content increases when epithelial cells undergo EMT and transform into cancer cells (35).

Interestingly, extracellular vesicles also play a critical role in transitioning to mesenchymal-like cells. They help in migration between disseminated tumour cells and other cells in the tumour microenvironment by cell-cell interaction. Extracellular vesicle contents change with phenotypic alterations. Recently, many studies have shown that extracellular vesicles are associated with metastasis (24). For example, in an N-SMase2-knockout transplanted breast cancer model, the reduction in extracellular vesicles attenuated tumour metastasis (36). The reasons that highlight extracellular vesicles as ideal biomarkers for cancer prognosis and surveillance are their non-invasive sampling, high stability and sensitivity, ability to represent parent cells, and tumour-specific RNA molecules are transported in biological fluids throughout the body (24).

### Regulation of EMP by microRNAs

miRNAs are small, non-encoding RNAs that regulate gene expression by binding to mRNA, leading to translational silencing and subsequently repress protein production (37,38). Several studies have shown that miRNA expression in serum extracellular vesicles may be useful as biomarkers for various cancers such as non-small-cell lung carcinoma (NSCLS), liver metastasis, chronic lymphocytic leukaemia, colorectal cancer, pancreatic cancer and tongue squamous cell carcinoma (SCC) (39-43). For instance, a low expression of miR-146a-5p is associated with higher recurrence

rates in NSCLS patients compared to subjects expressing high levels (39). Other markers include miR-21, which is associated with oesophageal cancer recurrence and distant metastasis, miR-638 is correlated with liver metastasis and colorectal cancer, and miR-125b is implicated in advanced melanoma (24).

Many studies have illustrated that the modulation of miRNA expression not only contributes to tumorigenesis, metastasis, and multi-drug resistance, but also tumour response to treatment in various cancers (44-46). miRNAs target a multitude of signalling pathways and transcription factors, causing the aberrant mechanisms such as dysregulation of protein translation. A recent study showed that overexpression of miR-21 promotes invasion and migration, and decreases apoptotic effects induced by cisplatin in lung adenocarcinoma and gastric cancer cells respectively (40,47). Overexpression of miR-223 and miR-221 are shown to correlate with resistance towards Gemcitabine and 5-fluorouracil in pancreatic and oesophageal cancers respectively (48,49). Conversely, the inhibition of miR-223 reversed the EMT phenotype (49) while knockdown of miR-221 seemed to result in increased apoptosis, restored chemosensitivity and inactivation of the Wnt pathway (48).

### Signalling pathways involved in EMT stimulation

EMT is induced through the activation of several signalling pathways; the three most common being TGF- $\beta$  signalling, Wnt- $\beta$ -catenin pathway and Notch. Most of the time, these pathways and transcription factors will eventually lead to E-cadherin regulation by binding to the E-box of its DNA sequences (50,51).

The Wnt pathway is activated when Wnt ligands bind to seven-transmembrane receptor Frizzled (FZD) and low-density lipoprotein receptor-related protein (LRP), which subsequently accumulate and stabilise  $\beta$ -catenin, and then translocate into the nucleus and regulate gene expression (52,53).  $\beta$ -catenin is a co-activator of the TCF/LEF family that regulates Wnt target gene expression levels. Beta-catenin pathway-related genes that regulate its stability may be mutated and stimulate incessant  $\beta$ -catenin activity, for example in adenomatous polyposis coli (APC). Glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) and casein kinase I $\alpha$  (CKI $\alpha$ ) upregulate levels of  $\beta$ -catenin in the nucleus, subsequently activating Wnt target genes (54,55). Abnormal activation of Wnt signalling is shown to induce EMT (56,57).

It is well-established that TGF- $\beta$  signalling is one of the

major pathways that promote EMT through the activation of SMAD family (Smad 2 and Smad 3) proteins which will translocate to nucleus and act as a cofactor in transcription of target genes (58). Several mesenchymal markers such as Snail, Slug, Twist and ZEB1 are induced through Smad signalling, which will subsequently repress E-cadherin (59). Interestingly, the Wnt pathway can cross talk with TGF- $\beta$ /SMAD due to the removal of  $\beta$ -catenin from adherent junctions in a process that involves TGF- $\beta$ -dependent PTEN dissociation from  $\beta$ -catenin and Akt activation (60).

The Notch signalling pathway is activated when Notch, a transmembrane receptor binds to the transmembrane ligands, Delta and Jagged. Ligand binding causes cleavage in Notch to release Notch intra-cellular domain (NICD) which will then enter the nucleus and activate the Notch pathway (61-63). Studies have shown that Notch activity downregulates E-cadherin and upregulates Snail (64,65). A recent study has revealed an inhibitor of the Notch signalling pathway—Numb, which can essentially prevent cells from undergoing a full transition into the mesenchymal phenotype (66).

Further investigations are indispensable to unravel the complex signalling pathways that drive EMT. Blocking or inactivating specific pathways may prove useful to restrain EMT from occurring and eventually prevent tumorigenesis, invasion and migration of cancer cells.

### Drug resistance and therapeutic targeting in EMT

EMT is well-studied in that the process itself, in the presence of CSCs, not only show resistance to apoptotic stimuli, but also contribute to drug resistance (35,67-69). EMT-induced CSCs that are mediated by the FGFR signalling pathway activation are more resistant to drugs (70). Gene mutations, abnormal cell cycle regulation and DNA repair, and long-term drug administration induce multi-drug resistance (MDR) and cause tumour cells to exhibit EMT-associated phenotypic changes in cellular morphology and also enrich the CD44<sup>+</sup>/CD24<sup>-</sup> stem cell population (71-73). A breast cancer cell line, MDA-MB-231, and advanced hepatocellular carcinoma cells (HCCs) were shown to have resistance towards epirubicin and sorafenib respectively after long term exposure (71,74).

Evidence show that over-expression of GNA13 contributes to drug resistance in head and neck squamous cell carcinoma (HNSCC). To overcome this, inhibition of GNA13-induced signalling effectively alleviated

**Table 1** Targeted therapy in various cancers

| Cancer type                           | Targeted therapy                                      | Reference |
|---------------------------------------|-------------------------------------------------------|-----------|
| Oesophageal cancer                    | Knockdown of miR-221                                  | (48)      |
| Pancreatic cancer                     | Inhibition of miR-223                                 | (49)      |
| Patient-derived thyroid cancer        | Combine histone deacetylase with lenvatinib           | (70)      |
| Head and neck squamous cell carcinoma | Inhibition of GNA13-induced signalling                | (75)      |
| Breast cancer                         | Inhibition of 14,15-EET restore cisplatin sensitivity | (76)      |

drug resistance (75). Luo *et al.* (in 2018) reported that upregulation of 14,15-epoxyeicosatrienoic acid (14,15-EET) induces EMT in breast cancer cells and confer cisplatin resistance. In contrast, inhibition of 14,15-EET may restore cisplatin sensitivity (76). Lee *et al.* (in 2018) discovered that combining HNHA (histone deacetylase) and lenvatinib in treating patient-derived thyroid cancer cells has a significant effect by blocking the FGFR signalling pathway, and thus inhibit EMT (70). Some examples of tumour-specific targeted therapeutic regimens are itemised in *Table 1*.

## Conclusions

In summary, EMP has cemented its pivotal role in cancer progression. This review summarised the association between CSCs and EMT, signalling pathways that drive EMT, potential biomarkers of EMT, drug resistance and possible targeting therapeutic treatment in various cancers. Much effort has been made by researchers to obtain a more in-depth understanding of the mechanism of EMT and MET, as well as their association with CSCs. Future work could be focused on elucidating different biomarkers for early prognosis of cancer; silencing signalling pathways that drive EMT and possibly prevent cancer metastasis; and evoke further understanding of miRNAs as potential targeted therapy to overcome chemo-resistance in various cancers.

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## Footnote

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

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