# Epigenetic regulation of mRNA mediates the phenotypic plasticity of cancer cells during metastasis and therapeutic resistance (Review)

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**Abstract.** Plasticity, the ability of cancer cells to transition between differentiation states without genomic alterations, has been recognized as a major source of intratumoral heterogeneity. It has a crucial role in cancer metastasis and treatment resistance. Thus, targeting plasticity holds tremendous promise. However, the molecular mechanisms of plasticity in cancer cells remain poorly understood. Several studies found that mRNA, which acts as a bridge linking the genetic information of DNA and protein, has an important role in translating genotypes into phenotypes. The present review provided an overview of the regulation of cancer cell plasticity occurring via changes in the transcription and editing of mRNAs. The role of the transcriptional regulation of mRNA in cancer cell plasticity was discussed, including DNA-binding transcriptional factors, DNA methylation, histone modifications and enhancers. Furthermore, the role of mRNA editing in cancer cell plasticity was debated, including mRNA splicing and mRNA modification. In addition, the role of non-coding (nc)RNAs in cancer plasticity was expounded, including microRNAs, long intergenic ncRNAs and circular RNAs. Finally, different strategies for targeting cancer cell plasticity to overcome metastasis and therapeutic resistance in cancer were discussed.

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**Contents**



## 1. Background

Metastasis and therapeutic resistance often limit survival in cancer (1). These terminal states are facilitated by the evolution of cancer cells in primary and distal metastatic sites over extended periods. Cancer evolution is characterized by the dynamic development of various cellular subpopulations driven by progressive genetic and/or non-genetic changes (2). In response to microenvironmental cues and therapeutic selective pressures, cancer evolution [which follows the Darwinian theory (3) and/or Lamarckian theory (4)] produces tumor heterogeneity by altering the cellular phenotype. Intratumoral heterogeneity is responsible for cancer progression, metastasis and therapeutic failure (5,6). Even if the response to therapy is clinically complete, adaptive tumor evolution almost inevitably emerges and induces tumor recurrence and metastasis (Fig. 1), which are the primary obstacles to curing cancer.

Accumulated evidence indicates that individual cancer genomes have the capacity to generate multiple phenotypic states. Cancer cells exhibit cellular plasticity, meaning they can transition between differentiation states without genomic alterations (7). Epithelial-to-mesenchymal transition (EMT), which is an archetype of cancer cell plasticity, facilitates invasion, metastasis and chemoresistance in malignant epithelial cells via a gradual transition to the mesenchymal phenotype during tumorigenesis (8,9). That the phenotypic plasticity of cancer cells is unlocked has become a new hallmark of cancer (10). Numerous excellent reviews have analyzed the role of cell plasticity in tumor development (8,10). However, the molecular mechanisms of the phenomenon remain to be

fully elucidated. The phenotypic plasticity of cancer cells is generally underlain by changes in gene expression, which is a complex process that is regulated at numerous levels. According to the central dogma, genetic information flows from DNA to mRNA to protein (11). mRNA, which acts as a bridge between the genetic information of DNA and protein, has an important role in translating genotypes into phenotypes. Thus, the regulation of mRNA, which includes transcription, editing and translation, has a crucial role in mediating gene expression (Fig. 2) (12). The present review aimed to provide insight into the regulation of cancer plasticity via changes in the transcription and editing of mRNA. The role of mRNA translation in the regulation of cancer plasticity has been discussed in other excellent reviews (13,14) and was therefore not a focus of our review. Furthermore, relevant therapeutic strategies for cancer plasticity were also discussed.

## 2. Role of transcriptional regulation of mRNA in cancer cell plasticity

The regulation of gene expression has a key role in a wide variety of core biological processes ranging from organismal development and cell differentiation to cellular stress responses and tissue homeostasis. Much progress has been made in characterizing the molecular mechanisms of transcription, including the role of chromatin and its modifications (15). DNA-binding transcriptional factors (TFs), DNA methylation, histone modifications and enhancers, which are key regulators of transcription (Fig. 3A) (15,16), are involved in cancer cell plasticity.

*TFs*. TFs regulate gene expression and further control diverse cellular processes and cellular states (17). By regulating dedifferentiation, transdifferentiation and blocking differentiation, TFs mediate the plasticity of cancer cells (10).

Dedifferentiation refers to the process by which a specialized cell is converted to a less differentiated phenotype. In other cases, incompletely differentiated progenitor cells maintain a less differentiated phenotype by blocking differentiation. TF dysregulation is involved in these two modes of plasticity in various cancers. The TF Sox9, a marker of live progenitor cells and bile duct lining cells, is a downstream target of Yes-associated protein (YAP). Liu *et al* (18) reported that YAP activation in hepatocytes led to a transition from mature hepatocytes to live progenitor cells and then the formation of bile duct-lining cells. By regulating dedifferentiation, Sox9 has an important role in hepatocarcinogenesis (18). Furthermore, the TFs transcriptional enhanced associate domain 2 (TEAD2) and transcription factor E2-alpha (E2A) promote oncogenic dedifferentiation and proliferation in hepatocellular carcinoma (HCC). Mechanistically, TEAD2 and E2A repress acetyl-CoA synthesis to induce oncogenic dedifferentiation (19). Other examples include homeobox A5 (20) and SMAD4 (21) in colon cancer, Krüppel-like factor 5 in breast cancer (22) and microphthalmia-associated transcription factor in melanoma (23).

In addition, the TF forkhead box M1 (FoxM1) is highly expressed in breast cancers and is an adverse prognostic factor. Kopanja *et al* (24) found that FoxM1 associates with the retinoblastoma tumor suppressor (Rb) to repress its transcription. The loss of the FoxM1-Rb interaction enhances the mammary alveolar differentiation program by activating Akt signaling. Therefore, the repression of Rb transcription by FoxM1 is crucial for the plasticity of breast cancer cells, as it disrupts tumor differentiation (24). Furthermore, in pancreatic ductal adenocarcinoma (PDAC), the TF hepatocyte nuclear factor 1A (HNF1A) harbors susceptibility variants, whereas lysine-specific demethylase 6A (KDM6A) carries somatic mutations. Kalisz *et al* (25) show that HNF1A recruits KDM6A to genomic binding sites in pancreatic acinar cells and activates differentiated acinar cell programs to indirectly suppress oncogenic and EMT genes. As other examples, motor neuron and pancreas homeobox 1 blocks the differentiation of erythroid and megakaryocytic cells in acute myeloid leukemia (AML) (26), FOXC1 and myocyte enhancer factor 2D blocks the differentiation of hematopoietic cells in AML (27,28) and SOX10 blocks melanocyte differentiation in melanoma (29).

Transdifferentiation is a common phenomenon in solid tumor cells and it is defined as changes in the morphology and phenotype of a differentiated cell to those of another tissue type (10). EMT is a quintessence of transdifferentiation, providing migratory and invasive properties to cancer cells during tumor progression. The core group of EMT-associated TFs includes members of the SNAIL family (SNAIL and SLUG), the TWIST family (TWIST1 and TWIST2) and zinc finger E-box-binding homeobox (ZEB) factors (8). Xie *et al* (30) found that inhibitor of NF-κB kinase subunit epsilon (IKBKE) has an oncogenic role in breast cancer, with frequent amplification or activation of IKBKE observed in breast cancer cases. IKBKE controls the stability of SNAIL to induce EMT and metastasis in breast cancer (30). Yang *et al* (31) revealed that TWIST has an essential role in the metastasis of breast cancer. In highly metastatic breast cancer cells, TWIST suppression specifically inhibits metastasis from the mammary glands to the lungs by suppressing EMT. Similar to SNAIL and TWIST, ZEB1 can also induce EMT, promoting the stemness, invasion and metastasis of pancreatic cancer (32). In addition, transdifferentiation may occur independently of EMT. Chan *et al* (33) investigated the molecular mechanisms of lineage plasticity in prostate cancer and its relationship with resistance to anti-androgen therapy. They revealed that STAT upregulation occurs in the mixed luminal-basal phenotype, which is the beginning of plasticity in an epithelial population and is responsible for antiandrogen resistance in prostate cancer (33). In addition, lung adenosquamous cell carcinoma harbors strong plasticity and carries a poor prognosis. Tang *et al* (34) revealed that the dynamic dysregulation of the counteracting lineage-specific TFs, including NK2 homeobox 1, forkhead box A2 (FOXA2), tumor protein p63 and SOX2, finely tunes lineage transition via transdifferentiation. As other examples, TNF receptor-related factor 3 inactivation promotes the development of intrahepatic cholangiocarcinoma by NF-κB-inducing kinase-mediated hepatocyte transdifferentiation (35), and caudal-type homeobox 1 promotes gastric cancer by inducing intestinal metaplasia (36).

*DNA methylation*. DNA methylation is a heritable covalent modification of cytosine nucleotides in CpG dinucleotides during cell division. It defines cell types and lineages by controlling gene expression and genome stability (37). DNA

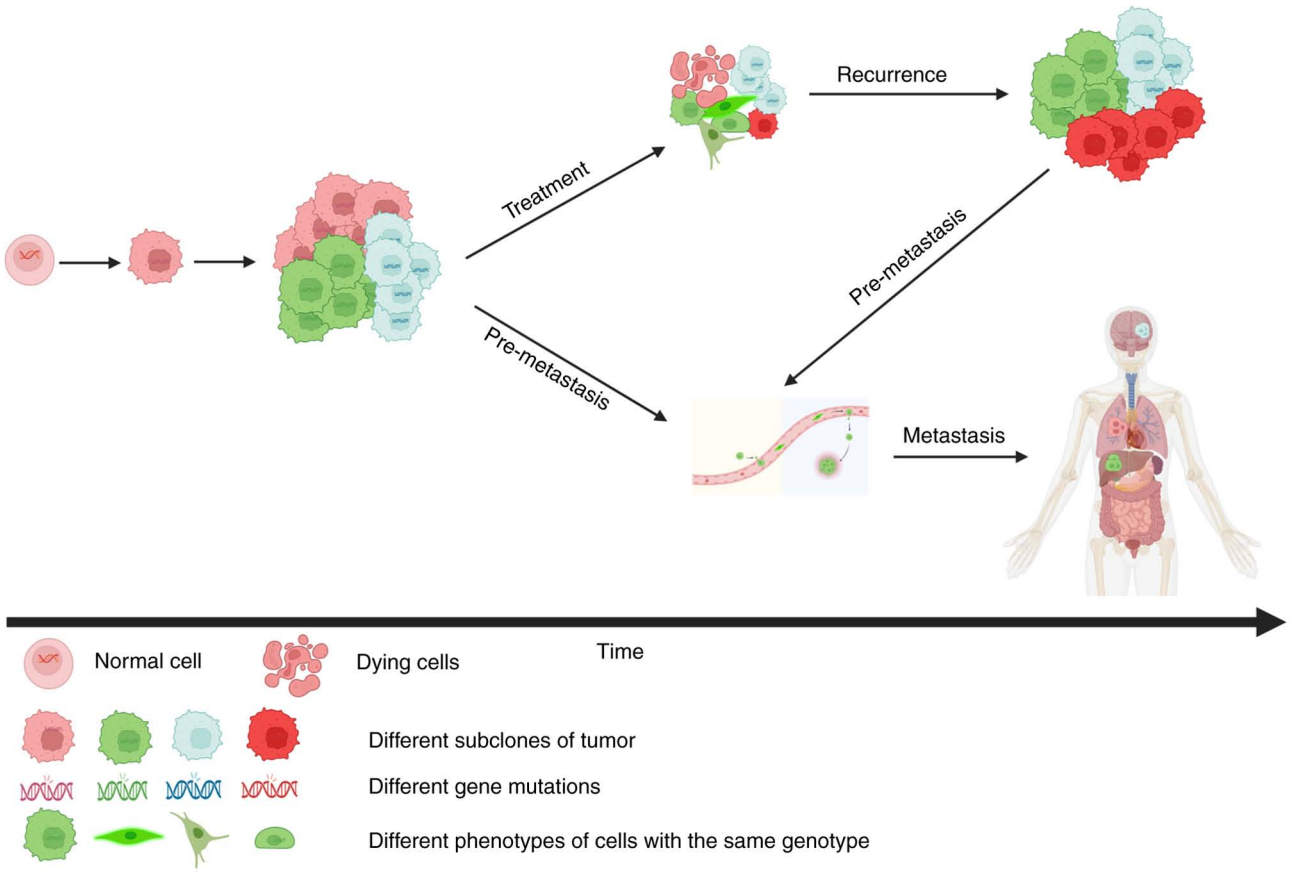


Figure 1. Cancer cell plasticity almost inevitably emerges and induces tumor recurrence and metastasis during tumor evolution. The image was created with BioRender.com.

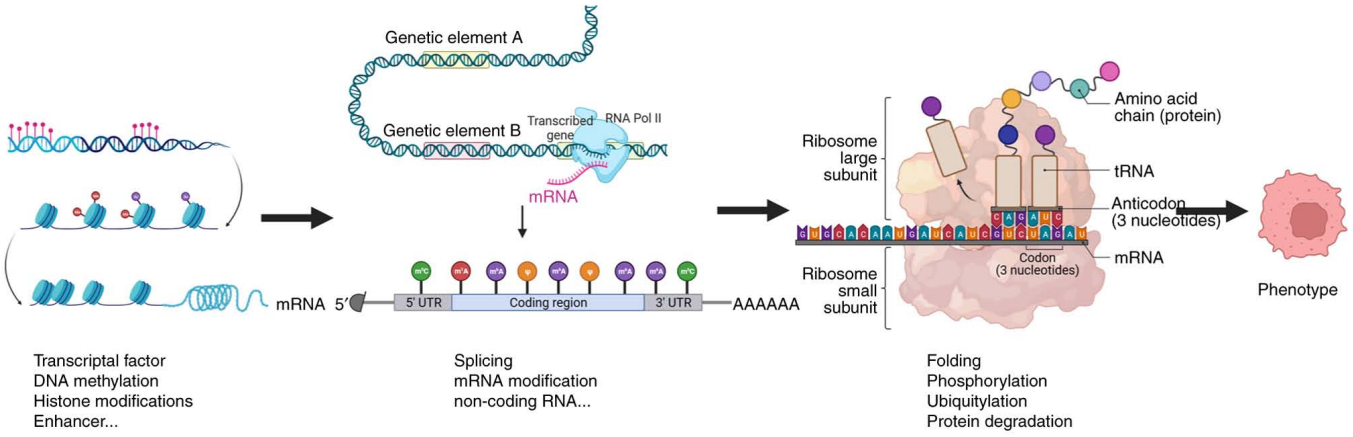


Figure 2. Flowchart of transformation from genotype to phenotype. In this flow, the regulation of mRNA, which includes transcription, editing and translation, has a crucial role in mediating gene expression. The image was created at BioRender.com. Pol, polymerase; Me, methyl; Ac, acetyl.

methylation is catalyzed by DNA methyltransferases (DNMTs), which introduce toxic 3-methylcytosine moieties into DNA. *De novo* DNA methylation is mainly catalyzed by DNMT3A and DNMT3B, which contain a highly conserved DNMT domain and two chromatin reader domains, in addition to alpha-thalassemia mental retardation X-linked DNMT3-DNMT3L and proline-tryptophan-tryptophan-proline (38). DNMT3L, which interacts with and stimulates the activity of DNMT3A and DNMT3B in the germline, catalytically inactivates DNMT (38). After *de novo* DNA methylation, only symmetrical CpG methylation is maintained during DNA replication. This is dependent on the methylation of the daughter DNA strand by DNMT1, representing the mechanism for maintaining DNA methylation during the cell proliferation process (38,39). Furthermore, ten-eleven translocation (TET) methylcytosine dioxygenases, oxidizing 5-methylcytosine to 5-hydroxymethylcytosine, 5-formylcytosine and 5-carboxylcytosine, demethylate active DNA.

A large number of studies have found abnormal DNA methylation in various cancers, including lung cancer (40), glioblastoma (41) and breast cancer (42). This aberrant DNA methylation in cancer cells enhances cellular plasticity and promotes adaptability and resistance to treatments (43). Davalos *et al* (44) reported that DNA methylation changes accompany the metastasis of melanoma, and nuclear receptor subfamily 2 group F, member 2 isoform (NR2F2-Iso2) is a transfer-driven factor involved in epigenetic regulation. Neural crest cells (NCCs) differentiate into melanocytes upon the inhibition of NR2F2-Iso2 expression via DNA methylation, whereas NR2F2-Iso2 is increasingly hypomethylated and re-expressed in metastatic melanoma. Therefore, it was indicated that DNA methylation changes allow transformed melanocytes to acquire NCC- and EMT-like features by controlling NR2F2 activity (44). In addition, Mancini *et al* (45) revealed that the deregulation of DNMTs and several microRNAs (miRNAs) has a relevant role in EMT of prostate cancer cells. By targeting DNMT3A, miR-429 modulates the expression of EMT factors, particularly ZEB1 (45). Liu *et al* (46) demonstrated that miR-135a, in conjunction with SET and MYND domain-containing 4 (SMYD4), co-activates Nanog expression, inducing the conversion of non-cancer stem cells (CSCs) into CSCs. By targeting DNMT1, miR-135a lowers the methylation level of the CG5 site in the *Nanog* promoter. SMYD4 binds to the unmethylated Nanog promoter to activate Nanog expression in Nanog-negative tumor cells. These findings indicate that the combination of miR-135a-DNMT1 with SMYD4 modulates the switch of non-CSCs to CSCs by regulating DNA methylation of the *Nanog* promoter (46). Morinishi *et al* (47) demonstrated that TET2 loss-of-function mutations facilitate the reversible switching from differentiated to stem-like states in AML cells by disturbing DNA methylation. This leads to increasing numbers of stem-like cells in AML cell populations. Consequently, AML associated with TET2 loss-of-function mutations is more likely to recur and develop resistance to drugs (47).

*Histone modification*. In eukaryotes, chromatin is composed of repeating units called nucleosomes. Each nucleosome consists of an octamer of histone proteins and the surrounding DNA fragments (48). The histone octamer forms a spherical core particle, consisting of an H3-H4 tetramer and two H2A-H2B dimers, with their N-terminal tails extending outward from the core particle (49). Over 10 post-translational modifications (PTMs) have been identified on various amino acid residues of the core histones. These modifications include acetylation of lysines, methylation of arginines and lysines, ubiquitination, phosphorylation and sumoylation (50) (Fig. 3B). These PTMs may occur in the N-terminal tail as well as in the core domain. Furthermore, PTMs result in an altered conformational state of chromatin, consequently regulating gene expression (49).

Mounting evidence has demonstrated that abnormal PTMs represent a common and pivotal event in a wide range of cancers. Furthermore, these aberrant PTMs lead to deregulation of gene expression, further shaping cancer pathogenesis, particularly cancer plasticity (51,52). In prostate and lung adenocarcinomas, cancer cell plasticity and neuroendocrine (NE) differentiation are major causes of resistance to targeted therapy. He *et al* (53) reported that the fate determinant Numb has an important role in mitochondrial autophagy mediated by Parkin by interacting with Parkin. Numb facilitates Parkin-mediated mitophagy, significantly contributing to mitochondrial quality control. Loss of the Numb-Parkin pathway significantly increases lactic acid production, further leading to increased histone acetylation and transcription of neuroendocrine-associated genes (53). Furthermore, epithelial plasticity describes the reversible regulation of cellular epithelial and mesenchymal characteristics, and it is associated with tumor metastasis and chemotherapy resistance. Yuan *et al* (54) discovered two histone-modifying enzymes, namely the nuclear SET domain 2 and KDM2A, involved in the writing and erasing of H3K36me2 that act reciprocally to regulate epithelial-mesenchymal identity, tumor differentiation and metastasis. Mechanistically, alteration of histone H3 lysine 36 dimethylation reprograms enhancers associated with the master regulator of the epithelial-mesenchymal state (54). Histone acetylation, which has key roles in gene regulation, is highly sensitive to the production and availability of acetyl-CoA. Carrer *et al* (55) found that in pancreatic acinar cells with Kras mutations, histone H4 acetylation increases before the appearance of precancerous lesions. They observed that acetyl-CoA levels are elevated in KRAS-mutant acinar cells to support acinar-to-ductal metaplasia. In PDAC cells, growth factors promote histone acetylation, resulting in cell proliferation and tumor growth. Thus, KRAS-driven metabolic alterations promote acinar plasticity and tumor development by inducing histone acetylation (55). Furthermore, histone methylation is involved in the regulation of cancer plasticity. Liau *et al* (56) demonstrated that glioblastoma stem cells (GSCs) can reversibly transition into a slow-cycling persistent state under the influence of targeted kinase inhibitors. This transition is involved in the widespread redistribution of repressive histone methylation. The upregulation and dependency of persistent GSCs are linked to the histone demethylases KDM6A and KDM6B. The presence of slow-cycling cells in primary glioblastomas before treatment, due to high Notch activity and histone demethylase expression, may contribute to recurrence (56).

*Enhancers*. Enhancers are non-coding cis-regulatory elements bound by TFs, cofactors, mediators and RNA polymerase (Pol) II that have a central role in precisely regulating spatiotemporal transcription (Fig. 3C), thereby participating in development and other biological processes in eukaryote organisms (57). As a special cluster of the enhancer family, super-enhancers are more strongly enriched in TFs, cofactors, mediators, RNA Pol-II and histone H3 lysine 27 acetylation (H3K27ac) than typical enhancers (58). Various TFs bind to enhancers and recruit chromatin-remodeling enzymes, leading to chromatin opening and the typical pattern of histone modifications on adjacent nucleosomes, including H3K27ac and histone H3 lysine 4 methylation. Furthermore, via active transcription, certain enhancers generate non-coding enhancer RNA, which is widely used to indicate enhancer activity and target gene induction. Numerous studies confirmed that enhancers have critical roles in cancer development, therapeutic resistance and cancer cell plasticity (59,60).

Bi *et al* (61) showed that endocrine therapy resistance is related to enhanced phenotypic plasticity, which is indicated

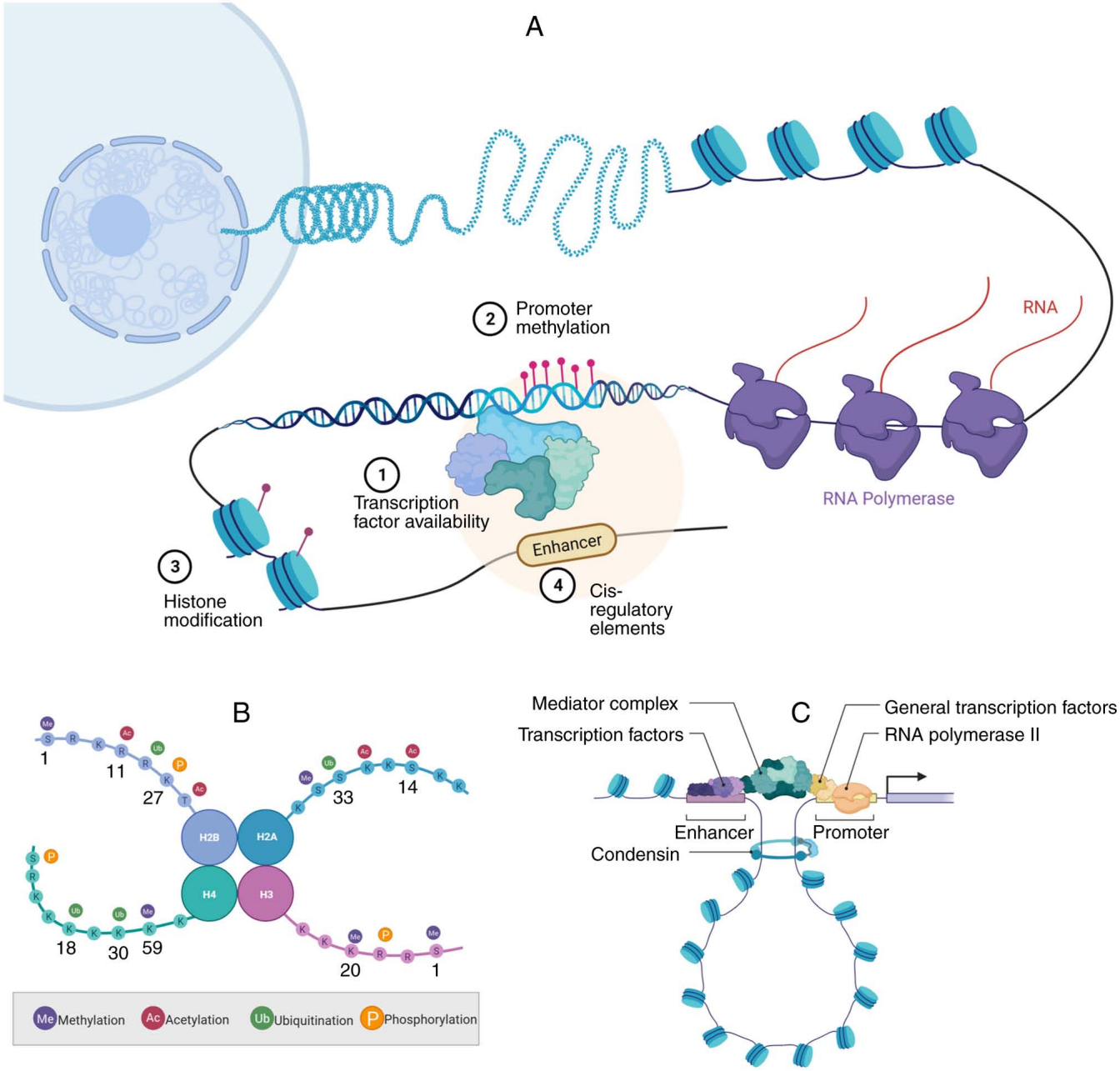


Figure 3. During mRNA transcription, DNA-binding TFs, DNA methylation, histone modifications and enhancers have crucial regulatory roles. (A) DNA-binding TFs, DNA methylation, histone modification and enhancers regulate mRNA transcription. (B) More than 10 different covalent histone modifications have been found on different amino acid residues of core histones. (C) Enhancers are non-coding cis-regulatory elements bound by TF cofactors, mediators and RNA polymerase II that have central roles in precisely regulating spatiotemporal transcription. The image was created at BioRender.com. TF, transcriptional factor.

by a general downregulation of luminal-epithelial differentiation markers and upregulation of basal-mesenchymal invasive markers. Mechanistically, they reveal that the different interactions between estrogen receptor α and other oncogenic TFs, such as GATA binding protein 3 and AP1, driving global enhancer gain/loss reprogramming that profoundly influences the transcriptional program in breast cancer. Thus, their study demonstrated that differential high-order assemblies of TFs on enhancers triggered genome-wide enhancer reprogramming, resulting in cancer cell plasticity and therapeutic resistance (61). Similarly, enhancers participate in cancer metastasis by regulating cancer cell plasticity. Han *et al* (62) illustrate that high expression of quaking (QKI) is related to short overall survival and metastasis in HCC. The Yin-Yang 1-p65-p300 complex activates QKI expression via inducing the formation of DNA loops. Aberrant QKI expression results in the occurrence of EMT and metastasis in HCC.

## 3. Role of mRNA editing in cancer cell plasticity

All precursor mRNAs (pre-mRNAs) of protein-coding genes undergo a basal level of RNA processing, including splicing and polyadenylation. Furthermore, the majority of human genes have the ability of alternative splicing and selective polyadenylation sites, leading to the expression of multiple mRNAs (63). In addition to mRNA processing, mRNA also

undergoes another editing mode, namely chemical modification (64). This mRNA editing has an important role in translating genotype to phenotype. Therefore, mRNA editing is also involved in cancer cell plasticity.

*mRNA splicing*. In eukaryotic cells, the splicing of pre-mRNAs is a complex and essential step in the flow of information from DNA to protein (65). Over the past 40 years, research has described the splicing process, including the detailed characterization of splicing reactions, the definition and identification of spliceosomes, biochemical analysis of splicing complexes and the understanding of their regulation (65). The process generates alternatively spliced mRNAs that produce distinct protein variants, which are involved in maintaining cellular homeostasis and regulating cell differentiation and development (66). Dysregulated RNA splicing is a molecular feature in almost all tumor types. Tumors have up to 30% more alternative splicing events than normal tissues (67). Recent studies illustrated that cancer-associated splicing isoforms have critical roles in various aspects of the biological behavior of cancer cells, such as increasing cell proliferation, enhancing migration and metastatic potential, and inducing resistance to therapy (68). In particular, emerging evidence indicates that cancer-associated splicing isoforms promote a permissive environment for increasing tumor heterogeneity and cellular plasticity (69).

Alternative splicing is widely recognized as a key mechanism for regulating gene expression. Mutations or expression changes in the components of the splicing machinery or splicing factors have a crucial role in the plasticity of cancer cells. Owing to cellular plasticity, NE differentiation is becoming more prevalent in metastatic castration-resistant prostate cancer (mCRPC). By analyzing prostate cancer cell lines, mCRPC specimens and LuCaP patient-derived xenograft models, Labrecque *et al* (70) detected alternative splicing of RE1-silencing transcription factor (REST) to REST4 and reduced REST activity in mCRPC with NE features. In CRPC cell lines, serine/arginine repetitive matrix protein 3 (SRRM3) induces alternative splicing of REST to REST4 and exacerbates the expression of REST-repressed genes. mCRPC with NE features is characterized either by REST attenuation and achaete-scute complex-like 1 activity or the progressive activation of neuronal transcription factor programs. Therefore, as the principal REST splicing factor, SRRM3 is expressed in early NE differentiation. Furthermore, it provides a framework to molecularly classify diverse NE phenotypes in mCRPC (70). In breast cancer, Li *et al* (71) found that QKI and RNA-binding protein fox-1 homolog 1 coordinately regulate the splicing and function of the actin-binding protein filamin B (FLNB), thereby regulating EMT in cancer cells. The skipping of FLNB exon 30 is strongly associated with EMT gene signatures in basal-like breast cancer. Furthermore, the skipping of FLNB exon 30 releases the FOXC1 transcription factor to induce EMT. This finding identified a specific dysregulation of splicing, which regulates cancer cell plasticity in breast cancer (71). In addition, Xu *et al* (72) reported the role of alternative splicing in eliciting phenotypic plasticity, which is involved in EMT, in colon cancer. Researchers found that the differential expression of downstream factors of the EMT master regulator ZEB1, such as epithelial splicing regulatory protein 1 and other RNA-binding proteins, alters the selective splicing patterns of a wide range of targets, including CD44 and NUMB. This resulted in the generation of specific isoforms associated with increasing invasiveness and metastasis in colon cancer (72).

*mRNA modification*. RNA epitranscriptomics is a burgeoning field focused on the study of RNA modifications. Originally, eukaryotic RNA modifications were primarily identified in transfer RNA and ribosomal RNA. Over the past decade, they have been identified and characterized in mRNA and various non-coding RNAs (ncRNAs). Recently, the significance of mRNA modifications has gained prominence, as their potential to exert direct functional effects on gene expression has been recognized (73,74). Increasing evidence suggests that mRNA modification pathways are also dysregulated in human cancers (64).

Internal modifications of mRNA include $N^6$-methyladenosine ($m^6A$), 5-methylcytosine, $N^1$-methyladenosine and internal 7-methylguanosine ($m^7G$) (74). The most characteristic RNA modification is the methylation of adenosine at the 6th position, resulting in $m^6A$ (75). It is involved in multiple aspects of RNA metabolism, such as RNA stability, translation, splicing, transport and localization, which have been discovered to affect various aspects of tumors (76). Tao *et al* (77) found that the $m^6A$ levels of RNA were reduced in glioblastoma cells and glioma tissues. AlkB homolog 5, an eraser of RNA. $m^6A$ enhances the progression of EMT in glioblastoma cells by decreasing RNA $m^6A$ methylation (77). Lin *et al* (78) illustrated that $m^6A$ modification of mRNAs increased during EMT, representing an important step in cancer cell metastasis. Downregulation of $m^6A$ induced by the deletion of methyltransferase-like 3 (METTL3) impairs migration, invasion and EMT in cancer cells. $m^6A$ sequencing and functional studies confirmed that the key transcription factor of EMT SNAIL, involved in EMT, is subject to $m^6A$ regulation. Researchers further demonstrated that YTH N6-methyladenosine RNA-binding protein 1 mediates the $m^6A$-induced translation of snail mRNA, thereby highlighting the critical roles of $m^6A$ in the regulation of EMT in cancer cells (78). In addition, certain studies indicated that METTL3-mediated $m^6A$ modification is critical for EMT in gastric cancer (79) and lung cancer (80). Meanwhile, Xia *et al* (81) verified that the expression of the $m^7G$ methyltransferase WD repeat domain 4 (WDR4) was high in HCC. WDR4 promotes metastasis and sorafenib resistance through EMT. Mechanistically, WDR4 enhances cyclin B1 (CCNB1) translation by promoting the binding of eukaryotic translation initiation factor 2A to CCNB1 mRNA to increase the progression and metastasis of HCC (81). Except for $m^6A$ and $m^7G$, the other mRNA modifications, which include 5-methylcytosine and $N^1$-methyladenosine, regulate the plasticity of cancer cells, have rarely been reported and further research is needed.

## 4. Role of ncRNAs in cancer plasticity

NcRNAs, which are not translated into proteins, constitute >90% of RNAs encoded in the human genome. According to their length, shape and location, ncRNAs may be divided into

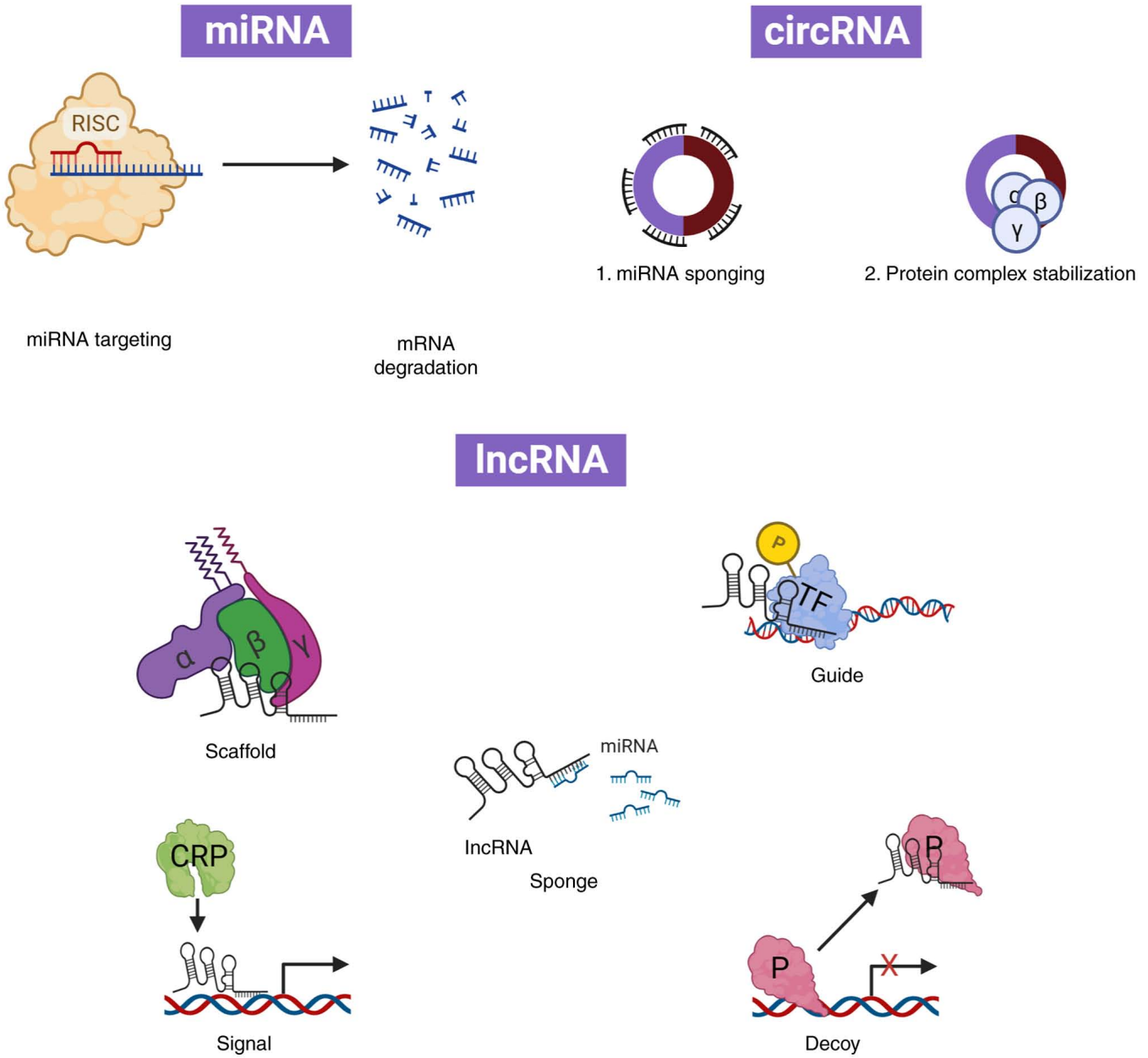


Figure 4. Different non-coding RNAs perform their functions via different molecular mechanisms. The image was created at BioRender.com. miRNA, microRNA; circRNA, circular RNA; lncRNA, long non-coding RNA; TF, transcriptional factor; CRP, C-reactive protein; RISC, RNA-induced silencing complex.

different classes, such as miRNA, long nc (lnc)RNA, circular (circ)RNA and piwiRNA (82). Growing evidence has facilitated our understanding of the mechanisms by which ncRNAs perform multiple vital functions in regulating the expression of genes and communicate with each other. These ncRNAs perform their function by different molecular mechanisms (Fig. 4). MiRNAs bind to complementary sequences in the 3'-UTR of mRNAs, resulting in their cleavage or translational repression. Compared with miRNAs, lncRNAs exert their functions via different regulatory models, including scaffolds, sponges, guides, signals and decoys. Concerning circRNAs, they perform their functions by sponging with miRNAs or proteins, thereby translating peptides (83-85). The dysregulation of ncRNAs has crucial roles in the initiation and progression of various cancers (82). The discovery of ncRNAs added a new dimension to understanding the malignant behavior of cancer, including proliferation, invasion, metastasis and cancer cell plasticity (86). In regulating cancer cell plasticity, the roles of ncRNAs are mainly reflected in the regulation of CSCs and EMT.

*miRNA*. Concerning miRNAs, Li *et al* (87) discovered that miR-148/152 family members are downregulated in gastric CSCs. Integrin α5 is a target gene of miR-148/152 family members. Their study demonstrated that miR-148/152 family members inhibit a gastric CSC-like state by targeting integrin α5 (87). In addition, Xu *et al* (88) found that the miR-119a-5p-SWI-SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4 axis has a role in promoting oral squamous cell carcinoma cell invasion and metastasis through EMT regulation (88).

*LncRNA*. lncRNAs are also involved in regulating CSCs and EMT in cancer. X inactive-specific transcript (XIST) is an lncRNA that initiates X-chromosome inactivation during early embryonic development, and its abnormal expression is a common feature in breast cancer. Ma *et al* (89) discovered that XIST is a key regulatory factor in breast cancer stem cells, which exhibit an aldehyde dehydrogenase-positive ($ALDH^+$) epithelial- and $CD24^{lo}CD44^{hi}$ mesenchymal-like phenotype. Furthermore, they demonstrated that XIST, acting as a nuclear sponge for let-7a-2-3p, activates $ALDH^+$ breast cancer cells to produce IL-6. This, in turn, promotes CSC self-renewal via STAT3 activation and the expression of key CSC factors. Therefore, this study concluded that XIST controls paracrine IL-6 pro-inflammatory signaling to promote CSC self-renewal in breast cancer (89). In addition, Fan *et al* (90) reported that the lncRNA LITATS1 acts as an epithelial gatekeeper in normal epithelial cells and can inhibit the EMT of breast cancer and non-small cell lung cancer (NSCLC) cells. Furthermore, they revealed that LITATS1 enhances the polyubiquitination and proteasomal degradation of TGF-β1 type receptor (TβR1) and interacts with TβR1 and the E3 ligase SMAD-specific E3 ubiquitin ligase 2 (SMURF2), keeping SMURF2 in the cytoplasm. This study highlighted the function of LITATS1 in epithelial integrity maintenance via TGF-β-SMAD signaling (90).

*CircRNA*. Regarding circRNAs, Xiong *et al* (91) reported that the expression of circulating Ras-specific GTPase-activating protein 1 (circRACGAP1) drives the development of NSCLC. CircRACGAP1 is highly expressed in NSCLC and is associated with the expression of the stemness marker Sox2. By depleting circRACGAP1, stemness, metastasis and EMT are repressed in NSCLC cells. Mechanistically, circRACGAP1 recruits the RNA-binding protein polypyrimidine tract-binding protein 1 to enhance the stability and expression of sirtuin-3 (SIRT3), leading to the deacetylation of replication timing regulatory factor 1 (RIF1) and activation of the Wnt-β-catenin pathway. Overexpression of circRACGAP1 counteracts the SIRT3 or PIF1 knockdown-mediated inhibition of stemness and metastasis in NSCLC cells. Consequently, this study uncovered that circRACGAP1 facilitates stemness and metastasis in NSCLC cells via the recruitment of polypyrimidine tract-binding protein 1 to promote SIRT3-mediated RIF1 deacetylation (91). CircRNAs also regulate EMT in cancer cells. Wang *et al* (92) demonstrated that circZFR sponges miR-375 to enhance the expression of gremlin 2 (GREM2), which is a target gene of miR-375. By increasing GREM2 expression, circZFR enhances the activation of the JNK pathway to promote EMT in pancreatic cancer cells, facilitating metastasis in pancreatic cancer (92). Various excellent reviews have specifically discussed the mechanisms by which ncRNAs regulate CSCs and EMT in cancer (93-96).

## 5. Targeting cancer plasticity

A greater understanding of cancer biology and the identification of oncogenic drive alterations have markedly altered the therapeutic landscape, particularly for NSCLC. However, a phenotypically static cancerous cell state being the driving force of oncogenesis was an early idea in cancer biology. With the advent of single-cell multiomics sequencing and sophisticated mathematical modeling, it was found that cancer cells are heterogeneous, dynamic entities that evolve over time and change in response to external cues, including therapy. In the course of cancer evolution, cancer cell plasticity has a critical role. Most studies on cancer cell plasticity are motivated by the goal of developing new therapeutic strategies to cure cancer. The two major contributors to cancer-related death are metastasis and therapeutic resistance, both of which are mediated by cancer cell plasticity. Therefore, cancer cell plasticity both provides therapeutic challenges and offers novel therapeutic targets that may be exploited to improve the survival of patients with cancer.

*Targeting cancer plasticity to combat cancer metastasis*. Most deaths in patients with cancer are attributable to metastatic disease opposed to the primary tumor. Cell plasticity refers to the dynamic non-heritable adaptive capacity of cells in response to various stressors associated with metastasis and changes in the tumor microenvironment (TME), is emerging as a crucial hallmark of metastasis (97). EMT, as a mode of cancer cell plasticity, is closely related to cancer metastasis. Furthermore, it was suggested that EMT was dispensable for metastasis in a mouse model of PDAC (98). During EMT, a number genetic, epigenomic, transcriptomic and proteomic factors are involved and interact with each other. These factors have the potential to be therapeutic targets.

Core EMT-associated TFs, including SLUG, SNAIL, TWIST and ZEB1, are involved in orchestrating the various manifestations of EMT. However, the precise role of each EMT-associated TF depends on the TME and certain EMT-associated TFs have complimentary and redundant roles. Furthermore, transcription is a nuclear event not readily accessible to drugs, and transcriptional factors have been widely considered undruggable (99). Based on these drawbacks, targeting EMT-associated TFs is potentially hazardous. Focusing on their interactions with crucial co-factors would be more advantageous. Certain clinical trials have investigated the therapeutic effects on different types of cancer. A phase II clinical trial examined the Wnt pathway inhibitor LGK974 in patients with advanced solid tumors. The results indicated good tolerability of LGK974, but no significant clinical benefit was observed (100). In addition, the hedgehog pathway inhibitor vismodegib was investigated in a phase II trial of patients with metastatic colorectal cancer, but the results were disappointing (101). In addition, clinical trials have investigated the effect of epigenetic regulators to inhibit EMT in cancer therapy. In a phase I/II clinical trial of the histone deacetylase inhibitor vorinostat in patients with metastatic breast cancer, the results illustrated that the combination of vorinostat and paclitaxel was well tolerated with promising activity in inhibiting EMT in patients (102). A phase I clinical trial investigated miRNA mimics, which are used to regulate EMT, in the treatment of cancer and obtained positive early outcomes. However, further clinical trials are needed to confirm whether epigenetic regulators can achieve good clinical outcomes in various cancers.

In addition, a variety of cues from the TME can induce EMT in cancer cells, such as growth factors and cytokines. For instance, the TGF receptor inhibitors galunisertib and erlotinib have been approved for use in various cancers (103,104).

The TGF-β pathway, the most common inducer of EMT, has been investigated as a potential therapeutic target for inhibiting EMT in cancer cells. The TGF-β receptor inhibitor galunisertib was investigated in a phase I/II clinical trial in patients with advanced HCC. The results demonstrated that galunisertib was well tolerated, but no clinical benefit was achieved (105). Table I presents a summary of drugs in various stages of clinical development that target EMT signaling to treat metastasis.

*Targeting cancer cell plasticity to overcome therapeutic resistance in cancer.* One of the current obstacles to curing cancer is the development of acquired resistance to therapy, which contributes to ~90% of cancer-related deaths (106). With our growing understanding of the adaptive mechanisms by which cancer evades therapies, the contribution of cancer cell plasticity to therapeutic resistance has gained greater and wider recognition in the field. It has been suggested that adaptation via cancer cell plasticity permits initial survival under treatment, enabling a small subset of cancer cells [clinically defined as minimal residual disease (MRD)] to acquire secondary resistance mutations, leading to disease progression (107). That is, drug-tolerant persister (DTP) cells originate from MRD cells present at the time of clinical remission following initial therapy. Thus, when the patient who completed therapy and achieved complete remission enters a convalescent phase of careful observation, strategies that counter the adaptive mechanisms should potentially be introduced.

It is conceived that different strategies may target cancer cell plasticity to resolve the hurdle of DTP (Fig. 5). First, one potential strategy suppresses the progression of cancer cell plasticity by preventing its initiation and converting a drug-resistant population to a drug-sensitive population by leveraging cancer cell plasticity for therapeutic benefit. However, there is evidence that drug withdrawal or intermittent drug dosing may overcome DTP cells (108). However, it is difficult to prevent the initiation of cancer cell plasticity using this approach. Targeting the driving factors of cancer cell plasticity is a potential strategy. For instance, NSCLC PC9 cells express an activated mutant form of EGFR that drives cellular proliferation, which is critical for their survival. The cells are highly sensitive to EGFR inhibitor, resulting in growth arrest and loss of viability. However, a small population of PC9 cells treated with EGFR inhibitors may escape cell death during the course of treatment. After several days of EGFR inhibitor treatment, DTP cells start proliferating. However, neither acquired EGFR gene mutations or amplifications, nor expression of the receptor tyrosine kinase mesenchymal epithelial transition factor receptor, are observed in DTP PC9 cells. The phenomenon was reversible, as cells regained drug sensitivity upon discontinuation of treatment. The DTP state was driven by insulin-like growth factor-1 receptor tyrosine kinase signaling and the upregulation of histone demethylase KDM5A. Knockdown of KDM5A was sufficient to restore drug sensitivity (109). Similarly, Deng *et al* (110) revealed that JAK-STAT signaling pathway is a critical executive factor that drives the plasticity of the prostate cancer lineage and contributes to androgen receptor (AR)-targeted therapy resistance. Inhibition of JAK-STAT signaling may convert AR-targeted therapy-resistant cells to a sensitive phenotype by leveraging cell plasticity (110). Conversion of the drug-resistant phenotype is the other strategy for maintaining the sensitivity of cancer cells. IL-8, a pro-inflammatory cytokine, promotes tumor cell remodeling and results in the persistence of drug-tolerant cells. C-X-C chemokine receptor 1 antagonists have been revealed to reverse IL-8-induced cancer cell plasticity (111). In addition, reversible transition between EMT and mesenchymal-to-epithelial transition is a key aspect of cancer cell plasticity. SNAIL is a transcription factor related to EMT, and revering EMT by inhibiting SNAIL signaling is a promising strategy to reverse cancer cell plasticity. Qin *et al* (112) demonstrated that SNAIL was upregulated in osimertinib-resistant H1975 cells. Knockdown of SNAIL restored the sensitivity of osimertinib-resistant H1975 cells to the drug by reversing cancer cell plasticity (112). Similarly, EZH2, which is the central player in epigenetic gene silencing, is also involved in the regulation of EMT. Overexpression of EZH2 is related to the conversion of prostate adenocarcinoma to NE prostate cancer, which is resistant to enzalutamide. Inhibition of EZH2 reverses NE prostate cancer to prostate adenocarcinoma and restores the sensitivity to enzalutamide (113).

The second strategy involves targeting intermediate states of cancer plasticity in MRD. It may envisage the other strategy that diverts the fate of various DTP cells into a single permanently dormant state. Ideally, DTP cells should be maintained in a dormant state for a long period to allow them to be eradicated by taking advantage of their sensitivity to inhibitors or immune-mediated clearance of the homogeneous dormant cancer cell population (107). DTP cells are heterogeneous and not all DTP cells have the ability to contribute to cancer relapse. After chemotherapy, glioblastoma and osteosarcoma were demonstrated to relapse from a subset of cancer cells, namely CSCs overexpressing stem cell genes. Thus, DTP cells with stemness properties are the main causes of cancer recurrence. Targeting these CSCs is a potential strategy for various cancers. Of note, inhibition of crucial CSC regulators, including CSC markers, epigenetic modifiers and signaling pathways, sensitizes cancer cells to therapy (114). For instance, Wang *et al* (115) revealed that METTL3 induced $m^6A$ methylation of Frizzled 10 (FZD10) mRNA to activate FZD10 in liver CSCs. FZD10 promotes the self-renewal and tumorigenicity of liver CSCs by activating β-catenin and YAP1. Furthermore, the FZD10-β-catenin-c-Jun-MEK-ERK axis determines the response of hepatoma cells to lenvatinib, and targeting FZD10 or β-catenin restores sensitivity in lenvatinib in lenvatinib-resistant HCC (115).

When cancer cell plasticity results in cancer histological transformation, tumor cells exhibit different characteristics, necessitating new treatment strategies. After targeted therapy, histological transformation occurs in up to 10% of EGFR-mutant lung adenocarcinomas (116) and at least 20% of prostate adenocarcinomas, leading to acquired resistance to such treatment (117). When lung adenocarcinomas transform into SCLC, cancer cells become resistant to EGFR inhibitors. Transformed SCLC displays greater responsiveness to platinum-etoposide therapy, similar to primary SCLC.

Table I. Summary of drugs targeting epithelial to mesenchymal transition signaling to treat metastasis at various stages of clinical trials.

| Drug | Target | Primary tumor type | FDA approval | Identifier and status |
|---|---|---|---|---|
| Galunisertib (LY2157299) | TGF-βRI | Pancreatic cancer; colorectal cancer; breast cancer; prostate cancer | Phase 1 and 2 | NCT01373164 (completed); NCT02734160 (completed); NCT01722825 (complete); NCT05700656 (not yet recruiting); NCT02538471 (terminated); NCT03470350 (withdrawn); NCT02452008 (recruiting); NCT02672475 (active, not recruiting); NCT02154646 (completed) |
| Vactosertib (TEW-7197) | TGF-βRI | Colorectal cancer; gastric cancer; pancreatic cancer; non-small cell lung cancer; rectum cancer; acute myeloid leukemia; acute lymphoblastic leukemia; chronic myeloid leukemia; chronic lymphocytic leukemia; Hodgkin lymphoma; non-Hodgkin lymphoma; plasma cell myeloma | Phase 1 and 2 | NCT03844750 (recruiting); NCT03698825 (unknown); (completed) NCT03724851 (active, not recruiting); NCT04258072 (recruiting); NCT04656002 (not yet recruiting); NCT03732274 (unknown); NCT05400122 (recruiting); NCT02160106 |
| Resveratrol | TGF-β1 | Colorectal cancer; liver cancer | Phase 1 and 2 | NCT00920803 (completed); NCT02261844 (withdrawn) |
| AVID200 | TGF-β | Advanced and metastatic malignancies | Phase 1 | NCT03834662 (unknown) |
| Trabedersen | TGF-β2 mRNA | Pancreatic cancer; colorectal cancer; melanoma | Phase 1 | NCT00844064 (completed) |
| Regorafenib | RTK | Colorectal cancer; biliary tract carcinoma; pancreatic adenocarcinoma; gastrointestinal stromal tumors; sarcoma; esophageal cancer; stomach cancer | Phase 1-3 and approved | NA |
| NIS793 | TGF-β | Pancreatic cancer; colorectal cancer | Phase 1-3 | NCT04935359 (recruiting); NCT04390763 (active, not recruiting); NCT04952753 (recruiting); NCT05417386 (recruiting) |
| Fresolimumab | TGF-β | Breast cancer | Phase 2 | NCT01401062 (completed) |
| SAR439459 | TGF-β | Malignant solid neoplasm | Phase 1 | NCT04729725 (active, not recruiting) |
| Celecoxib | COX-2 | Colorectal cancer; breast cancer; prostate cancer; sarcoma; melanoma; thyroid cancer; pancreatic cancer; sarcoma; cholangiocarcinoma; renal cell cancer; esophageal cancer; nasopharyngeal cancer; gastric carcinoma; gastroesophageal junction carcinoma; thoracic sarcomas; thoracic cancers; small cell lung cancers; NSCLC; Ewing's sarcoma | Phase 1-3 and approved | NA |
| Panitumumab | EGFR | Colorectal cancer; rectal cancer; breast cancer; head and neck squamous cell carcinoma; esophageal squamous cell cancer; biliary cancer; cholangiocarcinoma; pancreatic cancer; gastric cancer; biliary tract cancer; gallbladder cancer | Phase 1-3 and approved | NA |

Table I. Continued.

| Drug | Target | Primary tumor type | FDA approval | Identifier and status |
|---|---|---|---|---|
| Ipatasertib | EGFR | Prostate cancer; breast cancer; NSCLC; endometrial adenocarcinoma; head and neck squamous cell carcinoma; prostatic cancer; gastric cancer; NSCLC | Phase 1-3 | NCT03072238 (active, not recruiting); NCT04253561 (recruiting); NCT04920708 (recruiting); NCT03853707 (active, not recruiting); NCT04467801 (recruiting); NCT05538897 (recruiting); NCT05172258 (recruiting); NCT04341259 (completed); NCT04464174 (active, not recruiting); NCT04404140 (completed); NCT03959891 (active, not recruiting); NCT01896531 (completed); NCT03337724 (completed); NCT04060862 (active, not recruiting); NCT04177108 (completed); NCT03800836 (completed); NCT04739202 (recruiting); NCT01562275 (completed); NCT03673787 (recruiting); NCT05554380 (recruiting); NCT02162719 (completed); NCT04632992 (active, not recruiting); NCT034240059 (active, not recruiting); NCT03337698 (recruiting); NCT04802759 (recruiting); NCT04551521 (recruiting); NCT03498521 (active, not recruiting); NCT05564377 (recruiting) |
| Tegavivint | β-catenin | NSCLC | Phase 1 | NCT04780568 (recruiting) |
| Cabozantinib | RTK | Renal cell carcinoma; NSCLC; renal cell carcinoma; breast cancer; prostate cancer; cervical cancer; renal cell carcinoma; soft-tissue sarcoma; pancreatic adenocarcinoma; head and neck squamous cell cancer; adrenal cortex carcinoma; bladder urothelial carcinoma; osteosarcoma; endometrial carcinoma; colorectal cancer; bladder urothelial carcinoma; Merkel cell carcinoma; gastrointestinal stromal tumor; urothelial carcinoma; medullary thyroid cancer; hepatocellular carcinoma; neuroendocrine tumors; osteosarcoma; melanoma; adrenocortical carcinoma; thyroid gland carcinoma | Phase 1-3 and approved | NA |
| Metformin | Snail and Twist | Melanoma; lung cancer; breast cancer; prostate cancer; pancreatic adenocarcinoma; colorectal cancer; pancreatic cancer; rectal cancer; head and neck squamous cell carcinoma; melanoma; NSCLC; endometrial cancer; urothelial cancer | Phase 1-3 and approved | NA |

Table I. Continued.

| Drug | Target | Primary tumor type | FDA approval | Identifier and status |
|---|---|---|---|---|
| Methotrexate | DHFR and E-cadherin | Breast cancer; osteosarcoma; head and neck carcinoma; NSCLC; colorectal cancer; colorectal cancer; head neck squamous cell cancer; bladder cancer; gestational trophoblastic tumor; renal cell carcinoma; sarcoma; bladder cancer; ureter cancer; urethral cancer; transitional cell carcinoma; melanoma; penile squamous cell carcinoma | Phase 1-4 and approved | NA |

FDA, Food and Drug Administration; NA, not applicable; NSCLC, non-small cell lung cancer; RTK, receptor tyrosine kinase; COX-2, cyclooxygenase-2; DHFR, dihydrofolate reductase.




Figure 5. Different strategies can be used to target cancer cell plasticity to overcome drug-tolerant persister cells. The image was created at BioRender.com. DTP, drug-tolerant persister; MRD, minimal residual disease.

Compared with primary SCLC, transformed SCLC exhibits higher sensitivity to taxanes and resistance to immunotherapy, similar to EGFR-mutant lung adenocarcinomas (118).

## 5. Conclusions

Despite substantial progress in the treatment of cancer, precision therapy based on genomic profiles has produced mixed clinical outcomes. These sobering results highlight that our understanding of cancer evolution remains unclear. Although genetic mutations have a key role in cancer evolution, the importance of cancer cell plasticity in tumor metastasis and therapeutic resistance is becoming increasingly apparent. However, numerous fundamental questions regarding cancer cell plasticity remain unanswered. First, one key challenge is to determine how to characterize and define phenotypic states. Even if a phenotypic state is defined, it is difficult to isolate these specific phenotypic cells from a given sample. Furthermore, the state is a continuum rather than a discrete entity because of cancer cell plasticity. These cells simultaneously or dynamically transition between different states in response to environmental factors. Second, genetic mutations and cancer cell plasticity jointly affect the process of cancer evolution, and the identification and modeling of these factors remain challenging. Finally, the most formidable challenge is to construct and identify the dimensionality of the spatiotemporal state of cancer cells. In particular, it is difficult to longitudinally collect samples from individual patients.

To better understand and counteract the molecular mechanisms of cancer cell plasticity, it will be required to develop spatiotemporal single-cell multiomics sequencing technologies, particularly technologies that permit the simultaneous analysis of the single-cell genomics, epigenomics and transcriptomics in the same sample. New mathematical theories, such as statistical techniques, must also be developed to aid

in testing hypotheses regarding the characterization of state, heritability and transience, dynamics of populations, directionality preferences and environmental effects in conjunction with experimental and clinical data. In addition, cancer organoids also provide assistance for the study of cancer plasticity. Together, advances in technology and concepts will help us better understand the mechanisms of cancer cell plasticity and facilitate the development of innovative therapies to improve outcomes for patients with cancer.

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**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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