



# Therapeutic Targeting of Cancer: Epigenetic Homeostasis

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A large number of studies have revealed that epigenetics plays an important role in cancer development. However, the currently-developed epigenetic drugs cannot achieve a stable curative effect. Thus, it may be necessary to redefine the role of epigenetics in cancer development. It has been shown that embryonic development and tumor development share significant similarities in terms of biological behavior and molecular expression patterns, and epigenetics may be the link between them. Cell differentiation is likely a manifestation of epigenetic homeostasis at the cellular level. In this article, we introduced the importance of epigenetic homeostasis in cancer development and analyzed the shortcomings of current epigenetic treatment regimens. Understanding the dynamic process of epigenetic homeostasis in organ development can help us characterize cancer according to its differentiation stages, explore new targets for cancer treatment, and improve the clinical prognosis of patients with cancer.

**Keywords:** oncobiology, cancer heterogeneity, epigenetics, therapeutic target, transdifferentiation

## INTRODUCTION

As a common disease in multicellular organisms, cancer has always been the focus of scientific research, especially in its pathogenesis (1–4). An increasing number of studies have revealed that epigenetics plays an important role in cancer development. However, existing drugs targeting tumor epigenetics have not achieved stable long-term curative effects. Perhaps we need to rethink the role of epigenetics in cancer development.

In this article, we will refer to existing research to analyze the shortcomings of current epigenetic treatment regimens and review our view: Epigenetic homeostasis refers to the fact that various epigenetic regulatory substances in cells change only in a small range under normal physiological conditions to jointly maintain cell differentiation. Cell differentiation is the manifestation of epigenetic homeostasis at the cellular level, and attention to epigenetic homeostasis may be more important than to level of genome-wide methylation or acetylation. While explaining the important role of epigenetic homeostasis in multicellular organism, the term ‘differentiation lock’ will be used to refer to the composition of epigenetics in cell differentiation. Exploring the dynamic changes in the differentiation lock during organ development may contribute to changing our understanding of cancer and exploring new targets for the epigenetic homeostasis.

## RESEARCH HOTSPOTS OF CANCER EPIGENETICS

Several studies have revealed that epigenetics plays an important role in the development of cancer and drug resistance (5), which has stimulated the enthusiasm of researchers (Table 1). Current studies mainly focus on histone codes, methyl compounds, and non-coding RNAs (ncRNAs), and related drugs are being developed.

### Histone Code

The nucleosome is the basic chromatin repeating unit, and the core histones that make up the nucleosome are small proteins. Histone modifications mainly include acetylation, methylation, and ubiquitination, and the histone modification state controls whether the transcription complex can come into close proximity with the target gene, affecting its expression activity (25–27). The quantity, position, and type of histone modifications are collectively referred to as histone codes, which play an important role in cell differentiation and maintenance (28–30). Studies have shown that abnormal expression of histone codes is an important feature of cancer tissues and is related to the heterogeneity of cancer cells (31, 32). Studies have shown that abnormal levels of the histone demethylases, KDM6A and KDM6B, are associated with pediatric acute myeloid leukemia (AML) (33). Moreover, modification of the histone proteins H3K9ac, H3K27ac, and H4K16ac plays an important role in the progression and prognosis of head and neck squamous cell carcinoma (HNSCC) (34).

### Methyl Compounds

DNA methylation widely exists in prokaryotes and eukaryotes and is an epigenetic mechanism controlling gene expression (35, 36). Previous studies have revealed epigenetic reprogramming during embryo development (5, 37, 38). With cell differentiation, new methylation patterns are formed to ensure the specific expression of genes in organisms (39, 40). DNA methylation is catalyzed by methyltransferases, including DNMT1, DNMT3A, and DNMT3B (41). Among these enzymes, DNMT1 is responsible for the transmission of methylation patterns during mitosis to prevent passive demethylation. Dysplasia and death have been observed in DNMT1 knockout mice (42). DNMT3A and DNMT3B can methylate unmethylated CpG sites, which is important for embryonic development and tumorigenesis (43, 44). Methylation of cytosine residues leads to gene silencing, which plays a key role in the proper regulation of gene expression, genomic imprinting, X-inactivation, and development. Interestingly, abnormal DNA methylation is often observed in clinical specimens of cancer tissues (45). During tumorigenesis, abnormally high methylation of cytosines in promoter CpG islands, as well as overall gene hypomethylation, lead to genome-wide instability and altered gene expression profiles, including silencing of oncogenes, activation of endogenous retroviruses, and upregulation of tumor antigens and oncogene expression (46, 47). Tumor-specific methylated genes can be detected in circulating tumor cells, blood, urine, and other body fluids and are therefore commonly used in the diagnosis and prognosis of early-stage tumors (48, 49).

**TABLE 1 |** Associations between epigenetic disorders and cancers.

Cell Type	Epigenetic Abnormalities Characterization	Consequences	References
Breast cancer, Lung cancer, Liver cancer	DNA repeat sequence hypermethylation	Reduced stability of the genome	(6, 7)
Breast cancer, Melanoma	Promoter hypomethylation	Protooncogene activated	(8, 9)
Colorectal cancer, Gastric cancer	CpG island hypermethylation	Tumor suppressor genes are inhibited	(10, 11)
Acute myelocytic leukemia	High expression of demethylase FTO	Tumor suppressor genes are inhibited	(12, 13)
Pancreatic cancer, Liver cancer	High expression of demethylase ALKBH5	Promoting self-renewal and proliferation of tumor stem cells	(14, 15)
Lung cancer, Liver cancer	High expression of METTL3	Increased growth, survival and invasion of cancer cells	(15)
Colorectal cancer, Prostate cancer, Gastric cancer	Loss of H4K16ac / H3K4me3 / H4K20me3, Increase of H3K9me / H3K27me3	Transcriptional function was inhibited	(16)
Glioma, Breast cancer, Lung cancer	Overexpression of miR-218, miR-21, miR-15b, miR-515-5p	Inhibition of migration, invasion and proliferation of cancer cells	(17, 18)
Hepatocellular carcinoma, Breast cancer, Renal cell carcinoma	Overexpression of miR-125b and miR-346	Promoting cancer cell metastasis and invasion	(19, 20)
Hepatoma	Overexpression of lncTCF7, lnc-β-Catm, lncBRM	Promoting self-renewal of cancer stem cells	(21, 22)
Promyelocytic leukemia, Breast cancer	Overexpression of f-circRNA, circ-Amotl1	Promoting transformation and proliferation of cancer cells	(20, 23, 24)

## Non-Coding RNA

Non-coding RNAs (ncRNAs), which are not involved in protein-coding, mainly include microRNAs (miRNAs), circular RNAs (circRNAs), ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), small nuclear RNAs (snRNAs), and small nucleolar RNAs (snoRNAs) (50–52). ncRNAs mainly affect gene expression at the transcriptional and translational levels, and play an indispensable role in embryonic development, cell differentiation, damage repair, and regulation of cell function (53–55). Dicer1 is one of the most important enzymes that produce miRNAs. It has been reported that Dicer1-deficient mice have abnormal organ development or face embryonic death, which was attributed to the failure of embryos to correctly process miRNAs (56). Abnormal ncRNAs have been reported to play an important role in tumorigenesis, metastasis, and drug resistance (51, 52, 57). For instance, miRNA-143 regulates a variety of signaling pathways, including WNT/ $\beta$ -catenin, RAS-MAPK, and PI3K/AKT, thereby affecting tumor growth (58). miR-193a-5p promotes tumor cell metastasis by regulating the EMT signaling pathway (59). Furthermore, both germline and somatic mutations in Dicer1 have been identified in diverse types of cancer (60, 61). The errors in ncRNAs are closely related to cancer. However, the exact mechanism is still surprisingly controversial. This may be related to the complexity of the ncRNA regulatory mechanism.

## CURRENT SITUATION OF EPIGENETIC DRUGS

A wide range of therapeutic strategies in cancer treatment are compared to conventional chemotherapeutic agents that target cell proliferation. Currently, epigenetic drugs are being progressively developed and used for cancer treatment (62), such as DNA methyltransferase inhibitors (DNMTi) and histone deacetylase inhibitors (HDACi).

### DNMTi

By inhibiting the activity of DNMTs, the expression of tumor suppressor genes is promoted to inhibit the growth of tumor cells. The main nucleoside and non-nucleoside DNMT inhibitors (DNMTis) include azacitidine (AZA) and decitabine (63). Azacitidine blocks cytosine methylation by noncompetitive inhibition of DNMT1, resulting in the depletion of methyltransferases and DNA hypomethylation, but it is ineffective for quiescent cells that cannot divide (64). Low-dose azacitidine and decitabine can induce reactivation of the genes that were previously silenced by methylation, thereby inducing the formation of new phenotypes, reducing proliferation, and increasing apoptosis of offspring cells. High-dose drugs have cytotoxic effects and can directly cause tumor cell death (65, 66). Azacitidine and decitabine are approved by the Food and Drug Administration (FDA) as first-line drugs for the treatment of myelodysplastic syndromes (MDS) and leukemia. However, these drugs did not show significant efficacy in solid tumors such as gastrointestinal cancer, lung cancer, breast cancer, and

melanoma, and their use was limited due to their side effects and drug instability (67, 68). Dniunaite (69) observed that downregulation of miR-155-5p was significantly correlated with promoter methylation in prostate cancer. DOT1L inhibitors SYC-52221 and EPZ004777 inhibited DNMT3A-mutant cell proliferation, inducing cell cycle arrest and terminal differentiation (70).

### HDACi

HDAC is a highly conserved group of enzymes that removes acetyl groups from the tail of histone lysine. HDAC promotes chromatin closure and inhibits gene transcription by deacetylating histones (71). HDACi is a new antitumor drug that regulates gene expression. It has extensive effects on malignant tumors, including inhibition of cell differentiation, cell cycle growth, and angiogenesis, as well as induction of apoptosis, and immune regulation (72). In animal models, HDAC inhibition was found to inhibit tumor growth and reduce malignant proliferation by downregulating positive cell cycle regulators, such as cell cycle proteins D1, c-Myc, and AKT (73, 74).

Currently, vorinostat and romidepsin are approved for the treatment of skin T-cell lymphoma (75). However, these drugs do not achieve long-term stable efficacy (76–78). This is not only related to low drug stability and high toxicity, but also to abnormal pathway activation. Abnormal activation of the PI3K/AKT, MEK/ERK, and FAK signaling pathways has been observed in the treatment of multiple myeloma with HDACi (79, 80). 5-aza-2'-deoxycytidine promotes migration of acute monocytic leukemia cells *via* activation of the CCL2/CCR2/ERK signaling pathway (81).

Since the drugs target DNA methyltransferase and histone deacetylase, those non-specific alteration of cancer cell methylation and acetylation levels cannot inhibit the development of cancer. In contrast, epigenetics may form complex networks in cells, thereby affecting other genes and signaling pathways, that may be an important reason for the existing epigenetic drug resistance. According to the epigenetic landscape theory (82), it is believed that cell differentiation is a manifestation of epigenetic homeostasis. In other words, targeting epigenetic homeostasis at the molecular level is the future direction of epigenetic treatment for cancer.

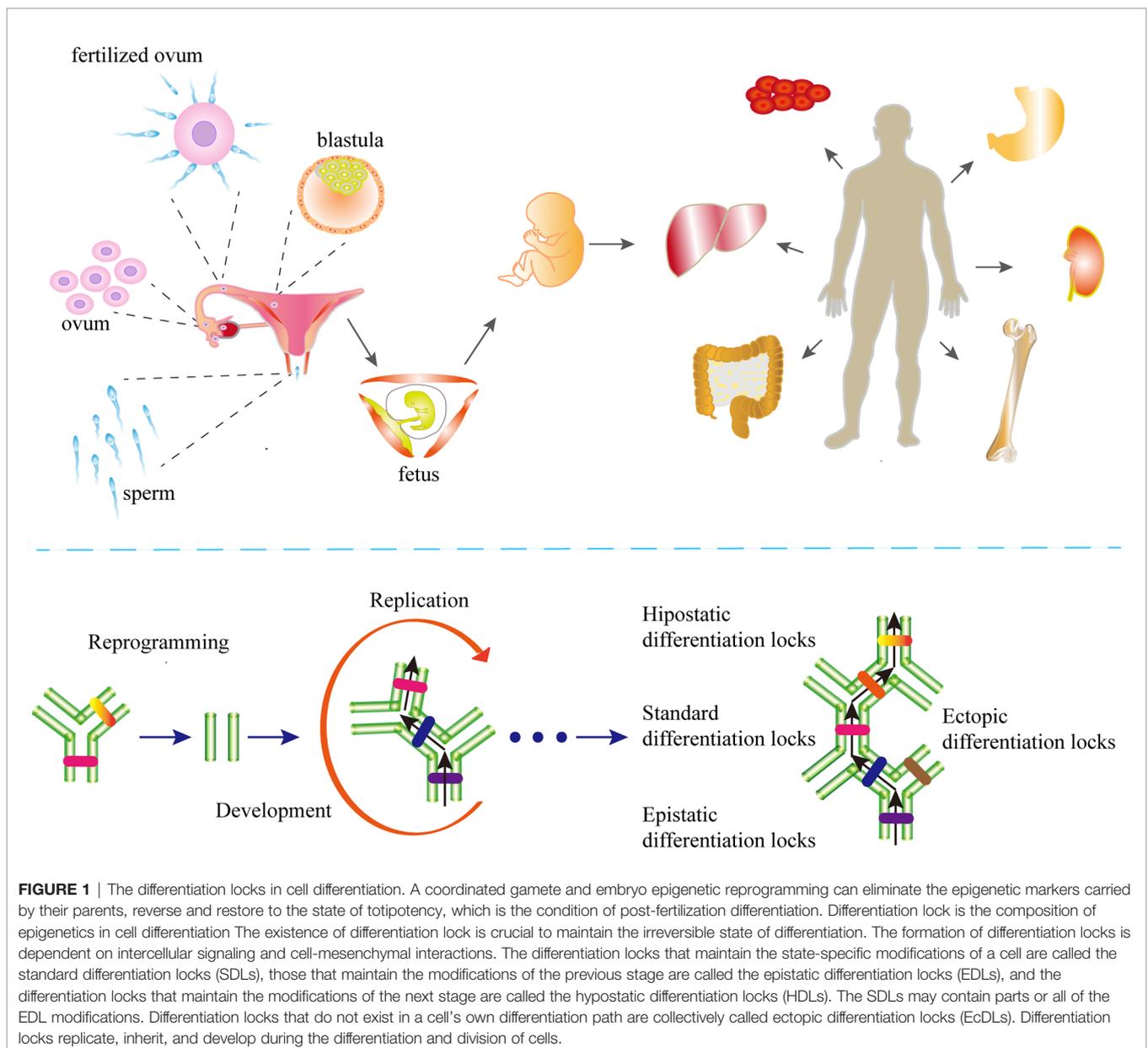
## THE NORMAL DIFFERENTIATION PROCESS

In this section, we describe the normal differentiation process, which helps us to further understand the causes of drug resistance in tumor epigenetics and possible future research directions from the perspective of cell differentiation.

The essence of cell differentiation is the expression combination of genes (83). According to classical epigenetic landscape theory, for cells in a certain period, the gene expression profile may maintain dynamic stability (84). This may be attributed to epigenetic homeostasis. Blanca Pijuan-Sala

report the transcriptional profiles of single cells from mouse embryos (85), thus portraying the early differentiation trajectory of the mouse embryo and the altered stages of epigenetics in cell differentiation. To characterize epigenetic stage changes, we introduced the concept of differentiation locks and classified differentiation locks into standard differentiation locks (SDLs), epistatic differentiation locks (EDLs) and hypostatic differentiation locks (HDLs) according to the stage cells are in. (Figure 1). Changes in epigenetic homeostasis in the cell differentiation pathway have been a hot topic of research. The mouse embryonic hindgut 1-specific genes *Trap1a* and *Rhox5* were also found to be expressed in the ExE endoderm and ExE ectoderm, consistent with the extra-embryonic origin of hindgut 1, suggesting that differentiation locks present different stages in

cell differentiation during embryonic development, while the SDLs may inherit some or all of the EDLs (85). Equally important, differentiation lock may be changed, updated during cell division and differentiation to complete the entire differentiation process (86–89). The Human Developmental Cell Atlas (HDCA) is a great human project whose goal is to determine the expression profiles of different human cells and to typify cell differentiation accordingly (90). The theoretical basis of this program is different tissues have distinct differentiation locks, and the same tissues hold similar differentiation locks, thus forming the specificity of tissues and organs and ensuring the normal operation of human functions. The completion of HDCA will help us to deepen our understanding of epigenetic changes during cell differentiation,



**FIGURE 1** | The differentiation locks in cell differentiation. A coordinated gamete and embryo epigenetic reprogramming can eliminate the epigenetic markers carried by their parents, reverse and restore to the state of totipotency, which is the condition of post-fertilization differentiation. Differentiation lock is the composition of epigenetics in cell differentiation. The existence of differentiation lock is crucial to maintain the irreversible state of differentiation. The formation of differentiation locks is dependent on intercellular signaling and cell-mesenchymal interactions. The differentiation locks that maintain the state-specific modifications of a cell are called the standard differentiation locks (SDLs), those that maintain the modifications of the previous stage are called the epistatic differentiation locks (EDLs), and the differentiation locks that maintain the modifications of the next stage are called the hypostatic differentiation locks (HDLs). The SDLs may contain parts or all of the EDL modifications. Differentiation locks that do not exist in a cell's own differentiation path are collectively called ectopic differentiation locks (EcDLs). Differentiation locks replicate, inherit, and develop during the differentiation and division of cells.

and will also have a profound impact on the treatment of congenital diseases, cancer and other diseases.

## THE RELATIONSHIP BETWEEN THE DEFECTIVE DIFFERENTIATION LOCK AND CANCER

With the progress in developmental biology, a large number of studies have revealed that early embryonic development and carcinogenesis have great similarities in biological characteristics such as migration and invasion (91), gene expression and protein spectrum (92), signal pathways (93), cell differentiation (94), and energy metabolism mechanisms (95). Epigenetics has attracted considerable attention as a key cause of these similarities.

Why do mature tissues have biological characteristics similar to those of embryos when transformed into cancer? Daughter cells with defective differentiation lock in their own differentiation path transform into cancer cells during stem cell division. Any factor that can promote the proliferation of stem cells is a promoting factor for cancer. Because the environment forming the ectopic differentiation locks (EcDLs) has changed, cancer cells can no longer differentiate correctly and undergo multidirectional differentiation, resulting in cancer heterogeneity (96).

### The Defective Differentiation Lock Is the Internal Factor of Carcinogenesis

Study have reported the C2H2 zinc finger transcription factor B cell CLL/lymphoma 11A (Bcl11a) is essential for lymphoid development. The deletion of Bcl11a prevents further development of hematopoietic stem cells (HSCs) into lymphocytes (97). Bcl11a<sup>-/-</sup> HSC alters cell cycle progression. A general upregulation of cell cycle protein genes and a downregulation of the quiescent regulator Cdkn1c (p57) and G2/M markers such as Prc1, Plk1 and Mki67 (Ki-67) of Bcl11a<sup>-/-</sup> HSC can be observed, and cells eventually appear to proliferate uncontrollably (98, 99). Similar results can be found in the corresponding studies: DNMTi can inhibit the further differentiation of bone marrow mesenchymal stem cells into osteoblasts and chondrocytes. At the same time, the expression of the anti-senescence genes (TERT, bFGF), and the anti-apoptosis gene (BCL2) was up-regulated and the expression of the apoptotic gene (BAX) was down-regulated (100, 101). The above studies illustrate that cells fail to complete differentiation to form a differentiation lock, i.e., they do not reach epigenetic homeostasis and are transformed into cancer cells. Some mutations in tumor suppressor genes can lead to damaged DNA repair function, such as the BRCA1/2 and P53, and differentiation locks are more likely to be damaged since the gene coding sequences only account for a small proportion of their genome (102, 103). The current research may indirectly confirm our opinion that cancer is a population of cells without epigenetic homeostasis. The non-coding RNA and protein profiles of cancer cells are quite different from those of normal cells, which is also a consequence of the imbalance in epigenetic

homeostasis and is often manifested as cell differentiation disorder and cellular dedifferentiation (104, 105).

The consequences of epigenetic modifications may differ according to their position in the differentiation lock. Invisible damage may occur as a result of the defects in EcDL. Cell maturation arrest caused by defective hypostatic differentiation locks (HDLs) results in cancer cell transformation under the continuous stimulation of proliferation signals. Cells with defective standard differentiation locks (SDLs) dedifferentiate and transform into cancer during proliferation, and the invisible damage may become exposed. The invisible damages may explain why the mutation frequency of oncogenes and anti-oncogenes in the human population is much higher than the incidence of cancer (106–109). A possible reason is that tissue-specific alterations in differentiation locks, and defective EcDLs may not impose an effect on the process of tissue carcinogenesis.

Any factor, including physical, chemical, and biological factors, that can damage cells may lead to differentiation lock defects, thereby increasing the incidence of cancer (110–112).

### Stem Cell Division Is a Promoting Factor for Carcinogenesis

In life, a variety of damages and stresses are often met. Mild damage and stress are often dealt with by the asymmetric division of stem cells. When stress exceeds tissue tolerance, stem cells must deal with symmetric divisions (113, 114).

When the cells are asymmetrically divided, the HDL defect (if exists) will lead to the maturation arrest of the daughter cells. These cells cannot complete the next stage of differentiation, and some of the daughter cells die. However, some daughter cells survive and transform into cancer cells under the stimulation of a continuous proliferation signal. When the stem cells are symmetrically divided, the defects of the SDLs are exposed (if exists). As a result, stem cells are dedifferentiated to transform into cancer cells (115). Cell carcinogenesis is a gradual process, and epigenetic homeostasis has a certain tolerance to damage. DNMT1 mainly maintains DNA methylation pattern during DNA replication, ensuring that the pattern is inherited by the offspring. In the early stages, defects in DNMT1 may be related to the accumulation of cell mutations. When the damage exceeds the steady-state tolerance, the cells become cancerous, which may be the internal relationship between aging and cancer.

Therefore, any pressure to stimulate stem cell division can increase the possibility of defective differentiation lock exposure, including injury, infection, and chronic inflammation (116–119).

### Role of Differentiation Lock in Cancer Heterogeneity

As discussed above, the essence of tumor is cells that cannot form epigenetic homeostasis. The correct differentiation process depends on information transmission between cells and the interaction between cells and stroma (120, 121). The environment required for normal development has disappeared, and cancer cells cannot form the correct differentiation lock. Dr. Tushar reported bone marrow microenvironment lead to  $\beta$ -catenin activation and disease progression of MDS (122). Just

like without the help of molecular chaperones, peptide chains cannot form proteins properly. Under internal gene-driven and error-induced environments, cancer cells produce heterogeneous daughter cancer cells (123, 124).

Numerous studies comparing gene expression in tumor tissues with paracancerous tissues have found that a large number of genes normally silenced during cell differentiation were activated in cancer. Moreover, these differences in gene expression patterns correlated with the malignancy of the tumor (125, 126). Those studies suggest that epigenetic homeostasis makes a crucial contribution to malignancy.

The more distinct the defective EDLs from SDLs, the lower the differentiation degree of cells, and the more apparent the characteristics of malignant tumors are (127–129), and vice versa. With the further cancer development, the differentiation locks in the upper layer will change, and the cells will show the characteristics of a lower differentiation stage. At this point, cancer tissues show typical malignant tumor characteristics (130, 131). (Figure 2) In the late stage of cancer development, some or all genes that had been closed in the embryonic stages are open.

## CANCER TREATMENT STRATEGIES FOR EPIGENETIC HOMEOSTASIS

At present, there are two kinds of tumor treatment strategies for epigenetic homeostasis: 1. Destroy epigenetic homeostasis, thereby inducing apoptosis of tumor cells, strengthening immunogenicity and weakening drug resistance. 2. Reestablish new epigenetic homeostasis to transdifferentiate tumor cells. At present, the two treatment strategies are still in the preclinical stage or clinical trial stage, but they have shown exciting therapeutic prospects.

### Destroying Epigenetic Homeostasis

Epigenetic abnormalities in tumor cells have always been of interest to scientists and physicians. Scholars have found that epigenetically abnormal tumor cells often show apoptosis, which may be a target for tumor therapy. Destruction of epigenetic homeostasis can induce apoptosis of cancer cells. Existing studies have found that cisplatin can not only directly kill cancer by DNA crosslinking, but also induce epigenetic changes of cancer cells and further induce apoptosis of cancer cells (132). Destruction of epigenetic homeostasis may enhance cancer immunogenicity. Researchers have found that inhibition of the histone demethylase LSD1 enhances tumor immunogenicity and T-cell infiltration in tumors. Thus, LSD1 could be used as an anti-tumor immunosuppressant in combination with anti-PD-1 immunotherapy for tumor treatment, with encouraging results in small-scale clinical trials (133, 134). Disruption of epigenetic homeostasis may alter the drug resistance of tumor cells. Methylguanine methyltransferase (MGMT), which repairs temozolomide (TMZ)-induced O6-methylguanine (O6mG) adducts, induces drug resistance in tumor cells. New study has shown reduced production of MGMT in the presence of

epigenetic instability, demonstrating that generating epigenetic instability through destruction of epigenetic homeostasis may be a viable strategy to mitigate anticancer drug resistance (135). The above studies are all based on the biological effects generated after the destruction of epigenetic homeostasis to kill tumor cells, which are the current research hotspots.

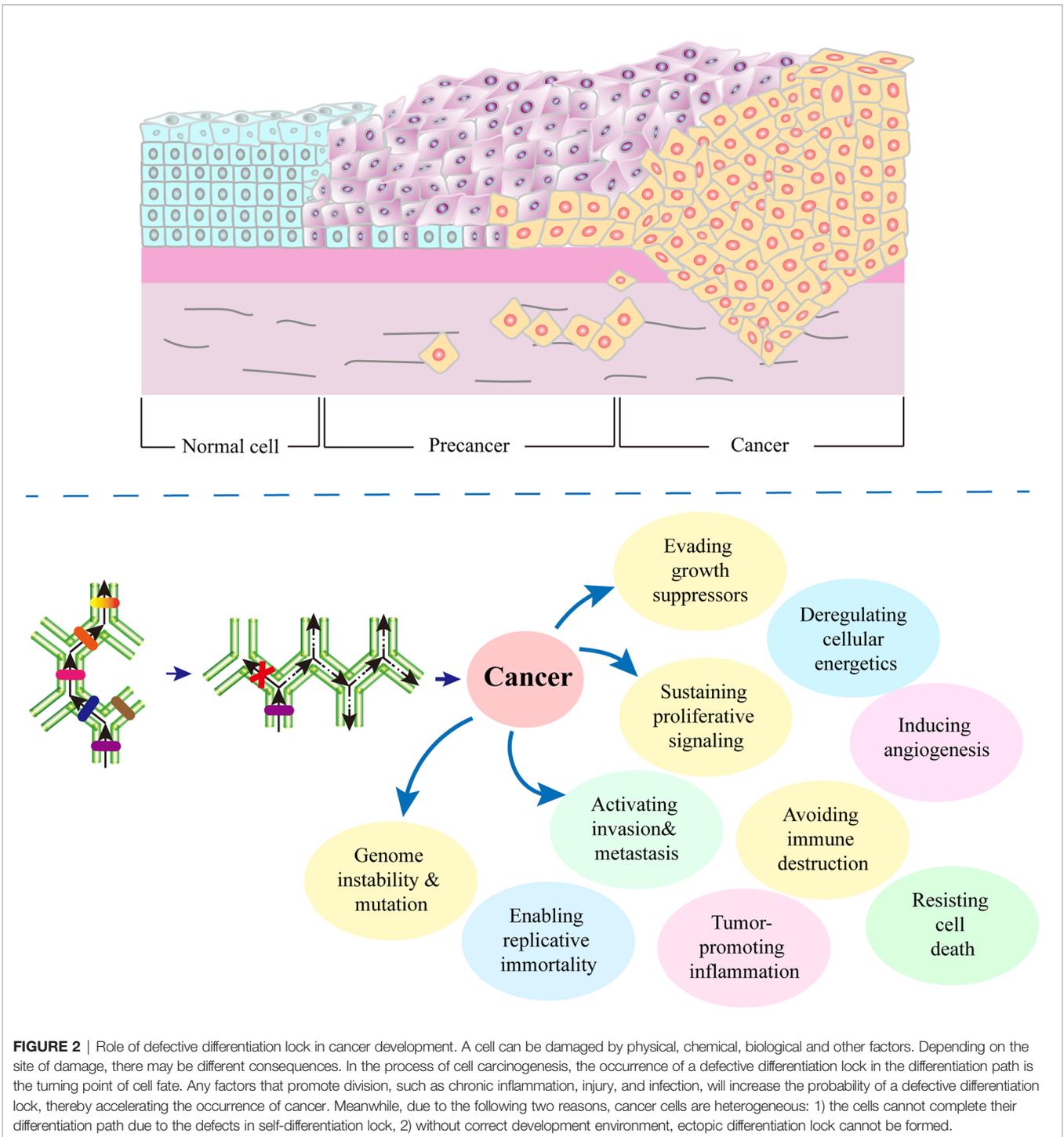
### Reestablishing Epigenetic Homeostasis

As mentioned above, imbalance of epigenetic homeostasis may be the etiology of tumors. Some scholars believe that by reestablishing epigenetic homeostasis may be a new strategy for cancer treatment. Surprisingly, some studies have reported that breast cancer cells can be terminally differentiated into adipocytes by using the rosiglitazone combined with the trametinib (136, 137). This exciting finding suggests that reestablishing epigenetic homeostasis, i.e., tumor cell transdifferentiation, may be the therapeutic direction for cancer. After transdifferentiation, tumor cells are transformed into new, solid, controlled cells, and patients may achieve durable, stable remission as a result. This fascinating therapeutic prospect has attracted the attention of scientists. However, the lack of understanding of human cell differentiation pathways and differentiation-inducing conditions continues to limit the development of cancer transdifferentiation therapies.

## DISCUSSION AND FUTURE PERSPECTIVES

Epigenetic changes may occur gradually during cell development. At a specific stage, the composition of epigenetics is stable and maintains the corresponding state of cell differentiation, which is the role of differentiation lock. As discussed above, tumors are cells without epigenetic homeostasis. Existing epigenetic drugs alter the epigenetic status of cancer cells to kill these cells through several pathways. Unfortunately, these drugs have also led to serious adverse effects. In addition, maintaining the low methylation level of cancer cells inevitably leads to the activation of multiple signaling pathways, which is one of the reasons for the consequent emergence of resistance to epigenetic drugs.

With the above discussion, epigenetic homeostasis treatment strategies for tumors may be divided into disruption and reestablishment of epigenetic homeostasis. The biological effects generated by the destruction of epigenetic homeostasis can effectively kill tumors. Reestablishing epigenetic homeostasis may be the focus of future development. Patients achieve long-lasting remission through tumor cell transdifferentiation. To achieve this goal, the following efforts are required: 1) mapping of the differentiation lock changes that arise during cell development to characterize cancer cells, 2) characterization of the induction conditions for differentiation lock to induce cancer cell transdifferentiation. These may require further collaboration between cancer and embryonic development researchers. Understanding the significance of differentiation lock in the



**FIGURE 2 |** Role of defective differentiation lock in cancer development. A cell can be damaged by physical, chemical, biological and other factors. Depending on the site of damage, there may be different consequences. In the process of cell carcinogenesis, the occurrence of a defective differentiation lock in the differentiation path is the turning point of cell fate. Any factors that promote division, such as chronic inflammation, injury, and infection, will increase the probability of a defective differentiation lock, thereby accelerating the occurrence of cancer. Meanwhile, due to the following two reasons, cancer cells are heterogeneous: 1) the cells cannot complete their differentiation path due to the defects in self-differentiation lock, 2) without correct development environment, ectopic differentiation lock cannot be formed.

organ differentiation process is helpful for developing more effective targeted therapy strategies and implementing individualized treatment for cancer patients by inducing cancer cell transdifferentiation. This measure can be used to improve the prognosis of patients with cancer.

## AUTHOR CONTRIBUTIONS

All authors have read this manuscript and would like to have it considered exclusively for publication in *Frontiers in Oncology*.

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