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REVIEW ARTICLE

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Transcriptional dysregulation by aberrant enhancer activation and rewiring in cancer

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Abstract

Cell identity is controlled by regulatory elements, such as promoters, enhancers, and insulators, within the genome. These regulatory elements interact in the nucleus and form tissue-specific chromatin structures. Dysregulation of these elements and their interactions can lead to loss of cell identity and promote the development of diseases such as cancer. Tumor cells acquire aberrantly activated enhancers at oncogenic driver genes through various mechanisms. Small genomic changes such as mutations, insertions, and amplifications can form aberrant enhancers. Genomic rearrangements at the chromosomal level, including translocations and inversions, are also often observed in cancers. These rearrangements can result in repositioning of enhancers to locations near tumor-type-specific oncogenes. Chromatin structural changes caused by genomic or epigenomic changes lead to mis-interaction between enhancers and proto-oncogenes, ultimately contributing to tumorigenesis through activation of oncogenic signals. Additional epigenomic mechanisms can also cause aberrant enhancer activation, including those associated with overexpression of oncogenic transcription factors and the mutation of transcriptional cofactors. Exogenous viral DNA can also lead to enhancer aberrations. Here, we review the mechanisms underlying aberrant oncogene activation through enhancer activation and rewiring, both of which are caused by genomic or epigenomic alterations in non-coding regions.

KEYWORDS
cancer, enhancer, enhancer rewiring, epigenomic aberration, genomic aberration

1 | INTRODUCTION

Cell identity and cell-type-specific gene expression are regulated by *cis*-regulatory elements such as promoters, enhancers, and insulators in non-coding regions. These regulatory elements form cell-type-specific 3D chromatin structures through direct interactions within the nucleus. Aberrations in regulatory elements and the disruption of chromatin structure can result in the development of diseases, including cancer.

Promoters and enhancers are epigenetically regulated by TFs that recruit chromatin regulators to these regions. The human genome encodes a relatively large number of TFs; only a small number of master TFs function to define cell identity by regulating the lineage-specific expression of various genes. The master TFs cooperatively bind to

Abbreviations: EBV, Epstein-Barr virus; H3K27ac, H3 lysine 27 acetylation; H3K4me1, H3 lysine 4 mono-methylation; HPV, human papillomavirus; SE, super-enhancer; TAD, topologically associating domain; TF, transcription factor; TSS, transcription start site.

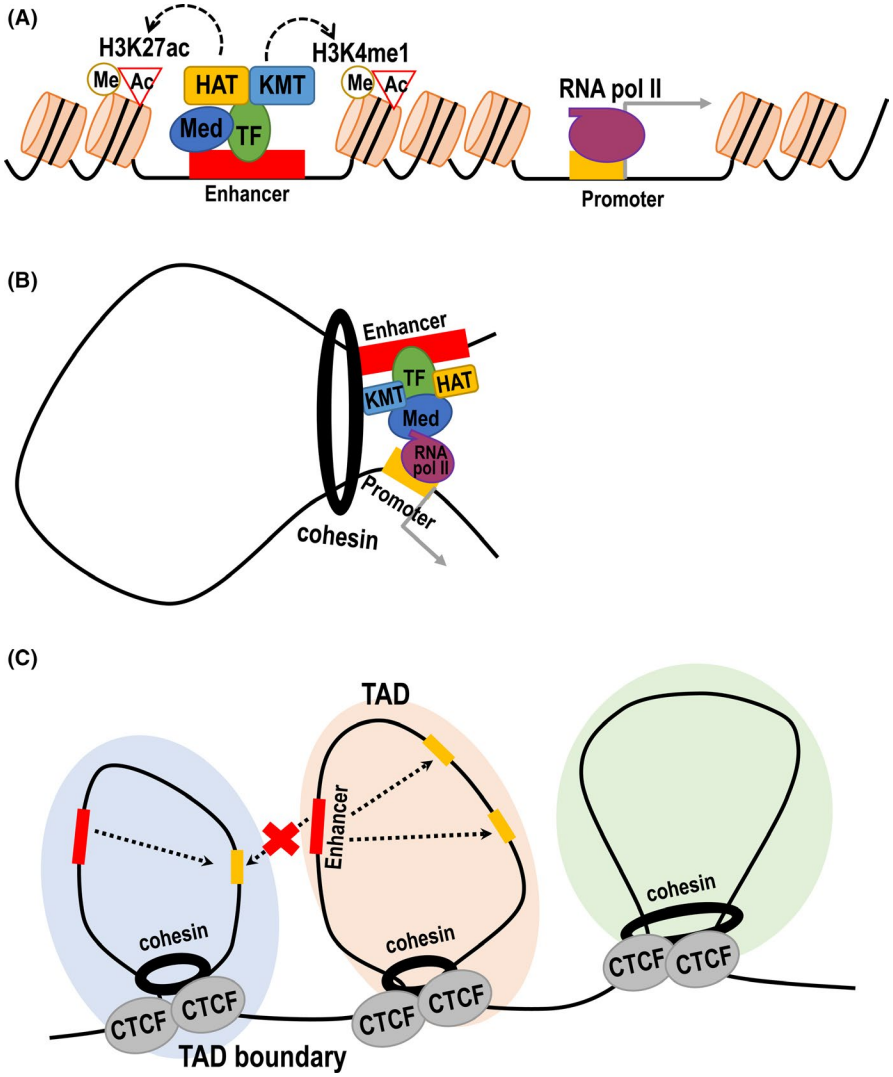

FIGURE 1 The model of transcriptional regulation by enhancers. A, Enhancer and its binding factors. Enhancers are epigenetically regulated by transcription factors (TFs), which recruit transcription activators, mediator complex (Med), histone acetyl transferase (HAT) and lysine methyl transferase (KMT), and this TF complex induces enhancer-specific histone modification H3K4me1 and H3K27ac. B, Loop structure between a promoter and an enhancer. Mediator complex and cohesins mediate direct interaction. C, Domain structure that insulates enhancer function. Insulator protein, CTCF partition genomic regions into several-hundred kilobase topologically associated domain (TAD)

enhancer regions with co-activators that include transcription complexes and histone-modifying enzymes. Through this cooperative binding, they regulate epigenetic states and chromatin interaction (Figure 1A). Enhancer regions are marked by histone modifications of H3K27ac and H3K4me1.[1,2] When bound by master TFs, clusters of enhancers known as SEs regulate gene expression that plays a prominent role in cell identity or specialized cellular function.[3,4] SEs span larger regions compared with other typical enhancers and are highly occupied by TFs and their cofactors. In cancer cells, genomic or epigenomic aberrations lead to oncogenic enhancer formation or activation, resulting in the upregulation of the neighboring oncogenes.

Enhancers function to increase transcriptional output by directly interacting with their target promoter regions. A recent genome-wide analysis of chromatin interactions revealed transcription regulatory networks between promoters and enhancers (Figure 1B).[5-7] Enhancer-promoter interactions were significantly enriched for cell-type-specific genes. Many transcription cofactors, including the mediator complex, cohesin, and the cohesin loader, function to mediate loop structure between promoters and enhancers.[8] The typical loop structure between promoters and enhancers is restricted within an insulated domain structure known as a TAD that possesses an average size of approximately 1 Mb (Figure 1C).[9-11] Chromatin interactions are more frequent within TADs than outside TADs. TADs are formed by binding of insulation proteins CCCTC-binding factor (CTCF) and cohesins.[10,12,13] It is now established that TADs have the ability to restrict long-range enhancer-promoter interactions. Therefore, both genomic and epigenomic disruptions of TAD boundaries allow loop formation between proto-oncogenes and enhancers that are partitioned naturally.

2 | ONCOGENIC ENHANCER FORMATION BY GENOMIC CHANGES AT NON-CODING REGIONS

The typical phenotype of cancers includes defects in DNA repair mechanisms and cell cycle regulation. As a result of these defects, the cancer genome is frequently mutated. Mutations in coding genes contribute greatly to tumorigenesis by promoting oncogene activation and repressing tumor suppressor gene expression. Additionally, genomic changes, such as insertions, mutations, and amplifications,

TABLE 1 Oncogene activation mechanism by enhancer aberrations in various cancers

Genomic/epigenomic aberrations	Cancer type	Activated oncogenes	References	Figure
Genomic enhancer formation				
Mutation	Lymphoblastoid B-cell	*PAX5*	18	Figure 2A
	neuroblastoma	*LMO1*	19	
Insertion	T-cell acute lymphoblastic leukemia	*TAL1*	14	Figure 2A
Amplification	Neuroblastoma	*MYCN*	22	Figure 2B
Enhancer rewiring by genomic/epigenomic aberrations				
Translocation of an enhancer	T-cell acute lymphoblastic leukemia	*TLX1*, *TLX3*, *TAL1*, *TAL2*, *NOTCH1*, *MYC*	23	Figure 3A
	B-cell lymphomas	*MYC*, *BCL6*	24	
	Adenoid cystic carcinoma	*MYB*	25	
	Medulloblastomas	*GFI1*, *GFI1B*	26	
	Gastric adenocarcinoma	*CCNE1*, *IGF2*	27	
Inversion including an enhancer	Acute myeloid leukemia	*EV1*	28	Figure 3B
Deletion of a TAD boundary	Sarcoma	*IRS4*	32	
Inversion including a TAD boundary	Colorectal cancer		32	
Mutation at a TAD boundary	T-cell acute lymphoblastic leukemia	*TA1*, *LMO2*	33	Figure 3C
DNA methylation at a TAD boundary	IDH-mutated gliomas	*PDGFRA*	34	
	SDH-deficient gastrointestinal stromal tumors	*KIT*, *PDGFRA*	35	
Epigenomic enhancer activation				
Mutations in coding regions of transcription factors	Prostate cancer		36,37	Figure 4A
	Pancreatic cancer		38	
MLL fusion	Acute myeloid leukemia	*MLL-AF6*, *MLL-AF9*	55	Figure 4B
Oncovirus integration	HPV-associated cervical cancer	Viral oncogenes (E6, E7)	59	Figure 5A
Oncovirus episomal formation	EBV-associated gastric cancer		60	Figure 5B

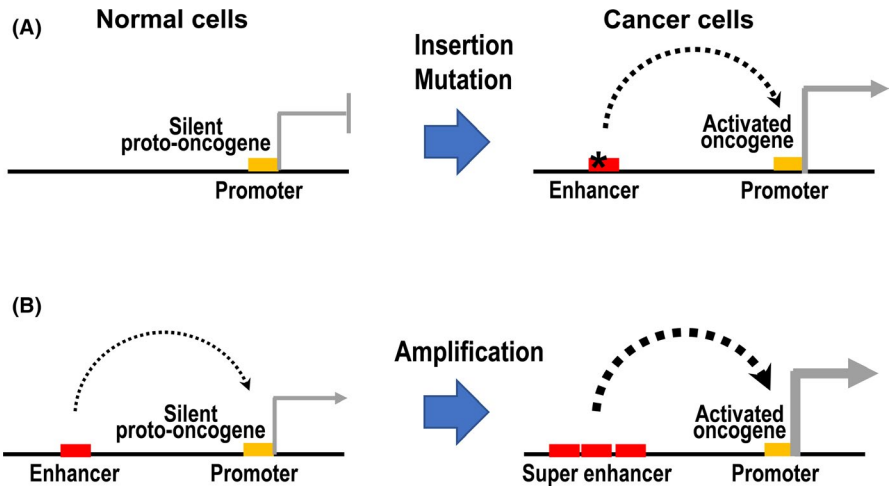

FIGURE 2 Models of oncogenic enhancer formation by genomic changes. A, New enhancer formation by point mutation or small insertions. Newly formed enhancer region is activated by tissue-specific transcription factors. Asterisk indicates point mutations or small indels. B, New enhancer formation by focal amplifications

at non-coding regions cause oncogenic enhancer formation, ultimately leading to neighboring oncogene activation (Table 1 and Figure 2).

Large numbers of small somatic mutations, including single base alterations, insertions, or deletions, are found in the non-coding regions in cancer.[14-17] However, identifying driver mutations in non-coding regions is difficult because whole-genome sequence information in cancers is not sufficient. In addition to this, predicting the function of the non-coding mutation is difficult. To date, few mutations have been identified in non-coding enhancers, and these mutations may function

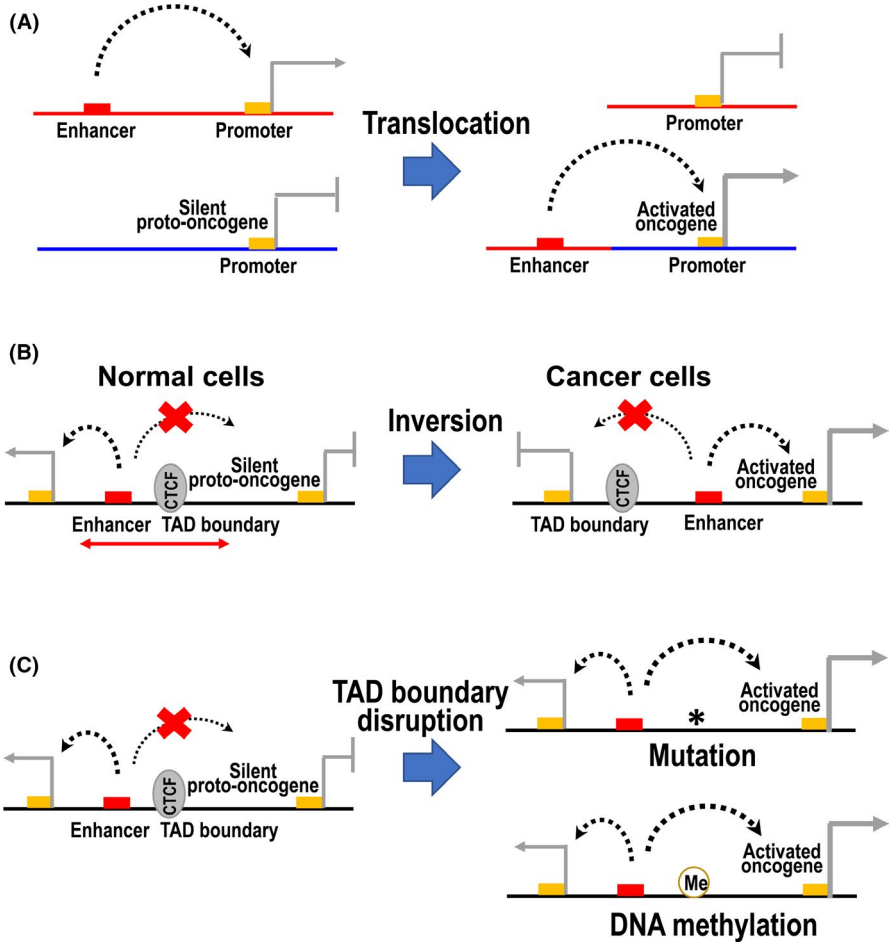

FIGURE 3 Enhancer rewiring by genome structural alterations. A, Enhancer rewiring by translocation. Active enhancer regions move to neighboring regions of proto-oncogenes in different chromosome. B, Enhancer rewiring by inversion. Inversion of genomic regions including active enhancer and the TAD boundary lead to activation of proto-oncogenes, which are normally separated from active enhancers. C, Enhancer rewiring by TAD boundary disruption induced by genomic/epigenomic aberrations. Mutation or DNA methylation induction affects to CTCF binding that partitions the TAD structure, leading to TAD disruption and mistargeting of enhancers to neighboring proto-oncogenes

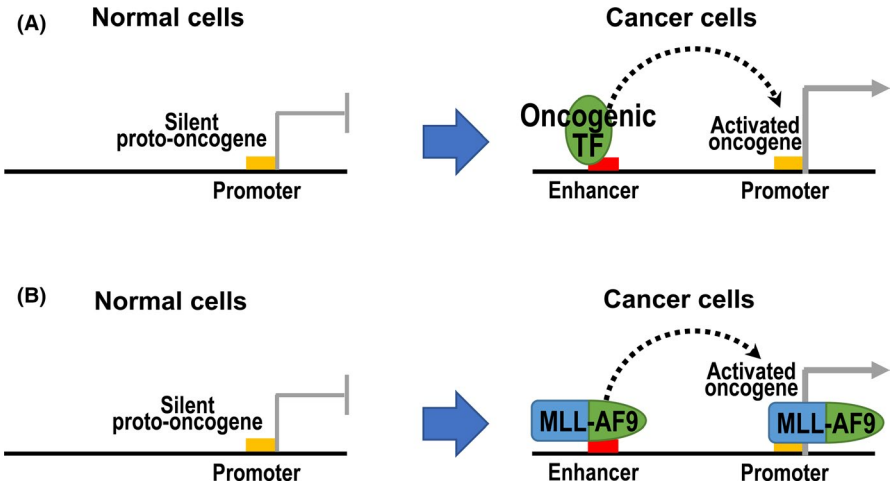

FIGURE 4 Epigenomic enhancer activation by oncogenic transcription factors. A, Aberrantly activated transcription factors activate enhancer regions, which are not used in normal cells. B, Fusion proteins of epigenetic activator and lineage-specific transcription factor lead to aberrant enhancer activation

in a tumor type-specific manner.[14,18,19] In lymphoblastoid B-cell lines, SEs are generated by a mutation cluster located 330 kb upstream from the *PAX* TSS (Table 1 and Figure 2A).[18] Another example of mutations in enhancers is in neuroblastoma cells, a GATA3-dependent enhancer is generated at the *LMO1* oncogene locus.[19] In T-cell acute lymphoblastic leukemia, binding sites for the transcription factor MYB are

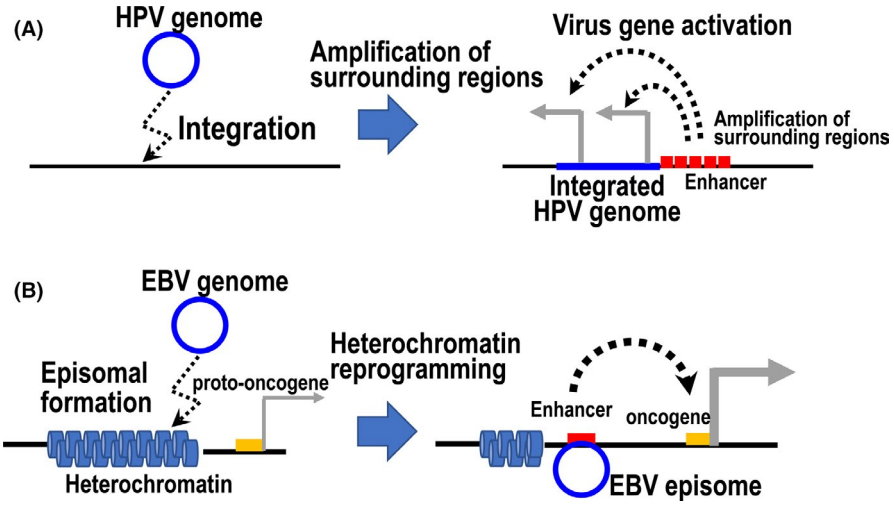

FIGURE 5 Enhancer aberrations by oncovirus infection. A, Amplification by HPV genome integration. HPV genome integration leads to amplification of surrounding host genomic regions and form super-enhancers. Newly formed super-enhancers in the host genome activate oncogenes within the HPV genome and contribute to tumorigenesis. B, Enhancer infestation by EBV episomal formation. The EBV genome attaches to host heterochromatin to form the viral episome and disrupt heterochromatin structure by decreasing heterochromatin mark, H3K9me3. Disrupted heterochromatin is activated as an enhancer by the concomitant increase of H3K4me1 and H3K27ac, leading to upregulation of neighboring proto-oncogenes

produced by small insertions in the intergenic non-coding region upstream of the *TAL1* oncogene, allowing enhancer formation to upregulate *TAL1* expression.[14] MYB recruits the acetyltransferase complex, CBP and p300, and *TAL1* to produce oncogenic enhancers and to activate key oncogenes in leukemogenesis.

Somatic copy-number changes are also widespread in tumor cells. Analysis of somatic copy-number changes from 3131 cancer patient samples from 26 different tumor types revealed that extensive copy-number changes were observed in 25% of the cancer genome.[20] In addition, focal amplifications or small deletions were observed in 10% of the cancer genome.[20] Many copy-number variations are observed in key oncogenes, however some are observed in the non-coding genome. Genomic amplification in non-coding regions can also result in oncogenic enhancer activation (Table 1 and Figure 2B). Somatic copy-number analyses and epigenetic analyses of 12 cancer cell types revealed that SEs generated by focal amplification could aberrantly activate *KLF5*, *USP12*, *PARD6B*, or *MYC*.[21] Another study also revealed that the 350-2000 kb genomic region, including the *MYCN* oncogene, was amplified aberrantly in neuroblastoma, resulting in the activation of *MYCN* expression.[22]

3 | ENHANCER REWIRING BY CHROMOSOMAL REARRANGEMENTS

Genomic rearrangements such as translocations or inversions that create master TF binding sites alter the position of enhancer regions from the genomic regions in normal cells to proto-oncogene neighboring regions, therefore leading to oncogene activation (Table 1, Figure 3). This phenomenon is known as "enhancer hijacking." The phenomenon has been reported in various cancers, including T-cell acute lymphoblastic leukemia, B-cell lymphomas, adenoid cystic carcinoma cells, medulloblastoma, gastric cancer, and acute myeloid leukemia.[23-27]

For example, in T-cell acute lymphoblastic leukemia, chromosomal translocations often result in movement of different proto-oncogenes, including *TLX1*, *TLX3*, *TAL1*, *TAL2*, *NOTCH1*, and *MYC*, near to highly activated enhancer regions that regulate T-cell receptors in T-cells (Table 1, Figure 3A).[23] In B-cell lymphomas, the novel mechanisms underlying aberrant activation of oncogenes *MYC* and *BCL6* by the de novo enhancer have been identified.[24] Translocation or duplication of MEF2B-bound enhancers that are usually located at *BCL6*-locus have been identified. Another example is enhancer repositioning, as a result of chromosomal translocation in adenoid cystic carcinoma cells. These enhancers move to the neighboring regions of the *MYB* gene, therefore leading to high *MYB* expression.[25] In medulloblastomas, mutually exclusive translocations that activate the *GFI1* or *GFI1B* gene have been identified. The *GFI1B* gene translocates to neighboring regions of the enhancer around the *DDX31* gene. Similar enhancer translocations between chromosomes 1 and 21 have been also observed at the *GFI1* locus on chromosome 1.[26] In gastric adenocarcinoma, the super-enhancer at chromosome 2 translocates to the neighboring regions of *CCNE1* at chromosome 19, leading to aberrant activation of *CCNE1*, which is associated with CDK4/6 inhibitor treatment.[27] Another translocation of the *IGF2* enhancer has been also observed in gastric adenocarcinoma. These *IGF2* translocations are lineage specific and also observed in colorectal cancer, in addition to gastric adenocarcinoma.

Inversions in the cancer genome also lead to enhancer rewiring (Table 1, Figure 3B). The enhancer that regulates the tumor suppressor *GATA2* moves to the neighboring regions of proto-oncogene *EV1* by inversion of a 9-kb fragment in acute myeloid leukemia cells, therefore leading to downregulation of tumor suppressors and activation of oncogenes.[28]

4 | ENHANCER REWIRING BY GENOMIC/EPIGENOMIC ABERRATIONS AT THE TAD BOUNDARY

More recently, chromatin structural analysis, chromosome conformation capture, and its derivative genome-wide methods, were performed in various types of cells including cancers and then analyzed comprehensively in the context of gene expression. The chromosome conformation capture technique can detect chromatin interactions by quantitating chimeric reads between interacting regions that are produced by restriction enzyme digestion and proximity ligation and Hi-C, a genome-wide derivative method using next-generation sequencing.[29,30] These analyses revealed the presence of cancer-related gene overexpression associated with TAD structural aberrations caused by genomic or epigenetic aberrations in TAD boundary regions (Table 1, Figure 3C).[31]

Integrated analysis of pan-cancer copy-number alteration and TAD structure detected by human fibroblast Hi-C revealed TAD structural aberrations and concomitant enhancer rewiring caused by copy-number changes.[32] In sarcoma and squamous cancer cells, the formation of strongly activated enhancers as a result of a TAD boundary deletion led to the upregulation of the *IRS4* gene.[32] In another example, de novo loop formation between *IGF2* and lineage-specific enhancers as a result of tandem duplications intersecting the TAD boundary was identified in colorectal cancer cells.[32] Furthermore, binding sites for CTCF and cohesin were often mutated in several cancer cell types such as colorectal cancer, esophageal carcinoma, and liver carcinoma.[15,33] In T-cell acute lymphoblastic leukemia patients, deletions of the CTCF-binding TAD boundary and simultaneous *TAL1* activation was observed, and this enhancer rewiring was confirmed by CRISPR/Cas9-mediated deletion using a normal cell line. Disruption of the CTCF-binding TAD boundary generated de novo loops from enhancers that naturally insulated and activated *TAL1* and *LMO2*, ultimately resulting in T-cell transformation.[33]

In addition to mutations in TAD boundaries, epigenetic change has also led to TAD disruption in gliomas and in a subset of gastrointestinal stromal tumors.[34,35] In IDH-mutated gliomas that showed a CpG island methylator phenotype, methylation induction at the binding sites of CTCF reduced CTCF binding. 3C analysis detected the disruption of TAD structure and de novo loop formation between enhancers and the neighboring oncogene *PDGFRA*. This structural change led to activation of *PDGFRA*.[34] In SDH-deficient gastrointestinal stromal tumors that also showed global DNA hypermethylation, Hi-C analysis revealed TAD structure reorganization by CTCF loss as a result of DNA methylation, ultimately leading to *KIT* and *PDGFRA* upregulation.[35] Additionally, a TAD boundary that naturally insulated a core enhancer from the *FGF4* oncogene was also disrupted, ultimately leading to strong *FGF4* activation.

5 | EPIGENOMIC ENHANCER ACTIVATION BY TRANSCRIPTION FACTORS AND COFACTORS

Dysregulation of signaling pathways is commonly observed in various types of cancer cells. Dysregulated signaling of TFs can aberrantly activate enhancer regions and can alter the gene expression program. One common mechanism involves aberrant enhancer activation by cell-type-specific TFs. Lineage-specific TFs define the accessible chromatin landscape, and mutationally activated oncogenic TFs can activate their binding enhancers in specific tissues, depending on the presence of lineage-specific TFs (Table 1, Figure 4A). For example, in prostate cancer cells, the expression of *FOXA1* and *HOXB13* reprograms the binding landscape for the androgen receptor.[36] Inhibition of FOXA1 and its binding epigenetic factor LSD1 can disrupt AR-dependent transcription and decrease cellular growth.[37] Therefore, during tumorigenesis, enhancer functions can be altered by oncogenic TFs. In addition, recurrent enhancer activation by oncogenic TFs is also associated with disease aggressiveness such as metastasis. Epigenomic analysis of the pancreatic cancer organoid model revealed that FOXA1 activation drove epigenetic reprogramming and promoted metastasis through enhancer activation.[38] These reports suggested that epigenetic activations induced by oncogenic TF dysregulate cell type-specific signal pathways and contribute to tumorigenesis or cancer aggressiveness.

A recent study of somatic mutations in cancer revealed that transcriptional cofactors that regulate epigenetic states are often mutated.[39,40] Alterations in histone modifications by mutations of histone-modifying enzymes can result in chromatin structure instability, leading to further mutations. Therefore, both gain-of-function and loss-of-function mutations in these proteins can potentially contribute to tumorigenesis. Most mutated cofactors are transcriptional activators such as H3K4 monomethyl transferase or the mediator complex that mediates loop structure. MLL3 and MLL4 have been reported to be often mutated in many cancers including bladder cancer, breast cancer, colon cancer, gastric cancer, liver cancer, medulloblastoma, non-Hodgkin's lymphoma, and others.[41-50] Genetic alterations in mediator complex-encoding genes are also frequently observed in prostate cancer and many uterine myomas.[39,51,52]

Another example of oncogenic enhancer activation is the fusion proteins of MLL (Table 1, Figure 4B). MLL is a lysine-specific methyltransferase that mainly functions during early development, however MLL fusion proteins are often observed in acute myeloid leukemia.[53,54] MLL-AF9 binds broadly over the gene body and also on the TSS. This fusion protein also binds to non-coding elements such as distal enhancers. At MLL-AF9-bound enhancers, RUNX1 and CTCF were co-occupied and induced de novo loop formation in acute myeloid leukemia cell lines.[55]

6 | EPIGENOMIC ENHANCER ABERRATIONS CAUSED BY ONCOVIRUS INFECTION

A DNA element from Simian virus 40 activated the T antigen or a β-globin reporter gene in mammalian cells independently of its distance from the TSS.[56] Virus DNA sequences that possessed enhancer function have also been discovered in other viruses.[57] These viral enhancers are activated by certain TFs that bind to specific sites within

enhancers.[58] Human papillomaviruses (HPVs) are another example that functions as an enhancer through integration. HPV is known as an oncovirus that is associated with cervical cancers and with anogenital and oropharyngeal cancers. During their normal viral life cycle, HPVs are maintained as extrachromosomal circular-DNA, known as the episome, within the host cell nucleus. However, in HPV-associated cancers, HPV genomes are integrated into host cellular chromatin. Tandemly integrated HPV16 could result in the formation of an SE that drives transcription of the viral oncogenes (Table 1, Figure 5A).[59]

Recently, we identified a novel mechanism for epigenetically activating silenced enhancers in heterochromatin regions induced by oncovirus.[60] EBV is associated with various cancers such as Burkitt lymphoma, nasopharyngeal cancer, and gastric cancer. Unlike HPV, EBV is maintained as an episome in most cancer cells. EBV encodes a sequence-specific DNA-binding protein, EBNA1, that connects the viral episome to the host metaphase chromosome during mitosis. We identified specific chromatin structural changes that occurred during inactive to active structural shifts in EBV-positive gastric cancers. We discovered that regions that displayed these features also showed chromatin interactions with the EBV genome. The EBV genome targets and reprograms latent host enhancers even within H3K9me3-positive heterochromatin regions. This aberrant activation of enhancers contributes to tumorigenesis through chromatin rewiring, allowing enhancers to interact with and activate neighboring proto-oncogenes. This phenomenon is termed "enhancer infestation" and is another mechanism that induces epigenetic activation of enhancers without genetic alteration[60] (Table 1, Figure 5B). This finding is the first to show that direct interaction between exogenous virus DNA and host chromatin affected the host chromatin structure and epigenetic states. This discovery provides researchers with new insight that virus DNA may affect host chromatin epigenetically and allows for a more detailed investigation of virus-associated cancer.

7 | CONCLUSION

Aberrant enhancer activation is a critical process that drives oncogene activation in cancer. Intense enhancer activities in cancer cells drive uncontrolled proliferation, and enhancers can be targeted for cancer therapy. Although transcription is a general property present within all cells, cancer cells are more dependent on increased transcription levels from enhancers. A further understanding of transcriptional dysregulation by aberrant enhancers in cancer is required to aid in the development of clinically useful epigenetic inhibitors of various components associated with enhancer regions.

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DISCLOSURE

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