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Review Article

The Central Regulatory Role of Super-enhancers in Tumor Development and Targeted Intervention Strategies

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Abstract

Super-enhancers (SEs) are highly enriched clusters of transcriptional regulatory elements within the genome, occupying a central position in tumorigenesis and development. This review aims to synthesize the rapidly expanding body of knowledge on SEs as the central hub of tumor transcriptional regulation.SEs integrate specific transcription factors, dynamic epigenetic modifications (such as H3K27ac), and restructure the three-dimensional spatial architecture of the genome to aberrantly drive the expression of proto-oncogenes and cell identity-related genes. This activity sustains the malignant phenotype, stem cell properties, metabolic reprogramming, and therapy resistance of tumor cells. Their functions involve emerging physical mechanisms such as phase separation forming transcriptional condensates and long-range chromatin looping. The activity of SEs exhibits high tumor-type and tissue specificity. They are activated through unique mechanisms in different cancers, becoming key nodes of "transcriptional addiction" in tumor cells. This characteristic also makes them highly promising therapeutic targets. Inhibitors targeting core SE components (such as the BET protein BRD4 and transcriptional kinases CDK7/9), epigenetic drugs, and strategies aimed at disrupting their phase-separated condensates have shown selective efficacy in various preclinical tumor models. In conclusion, SEs serve as pivotal hubs of transcriptional addiction in cancer by integrating diverse molecular mechanisms to drive oncogenic programs, and their specific components present promising therapeutic targets; future advances in multi-omics and precision strategies will be key to translating these findings into clinical applications.

Introduction

Super-enhancers (SEs) represent a distinct class of cis-regulatory elements, characterized by the dense clustering of transcriptional co-activators, master transcription factors, and specific histone modifications such as H3K27ac.[1] These genomic hubs have emerged as central orchestrators of gene expression programs that define cell identity. In recent years, a convergence of high-throughput sequencing, epigenomic profiling, and advanced imaging technologies has fundamentally reshaped our understanding of their role in oncology. It is now evident that SEs are not merely passive regulatory regions but are dynamically commandeered across a wide spectrum of cancers to establish and maintain the malignant state.

At the molecular level, SEs drive oncogenesis through a multifaceted and integrated mechanism. They function by recruiting specific transcription factors and epigenetic modifiers, remodeling the three-dimensional (3D) chromatin architecture to facilitate long-range enhancer-promoter interactions,[2] and, increasingly, through the biophysical process of liquid-liquid phase separation to form transcriptional condensates.[3] This concerted action results in the aberrant, high-amplitude expression of key oncogenes, stemness factors, and metastasis-related genes. Crucially, SE activity exhibits remarkable tissue- and cancer-type specificity, often forming self-reinforcing positive feedback loops with core transcription factors, thereby locking tumor cells into a state of "transcriptional addiction".[2,4]

Beyond driving proliferation, SEs are intimately involved in core hallmarks of cancer progression. They mediate tumor heterogeneity, fuel metabolic reprogramming, promote immune evasion, and underpin both intrinsic and acquired therapy resistance. Their dysregulation can stem from diverse origins, including somatic mutations, structural variations like translocations and amplifica-

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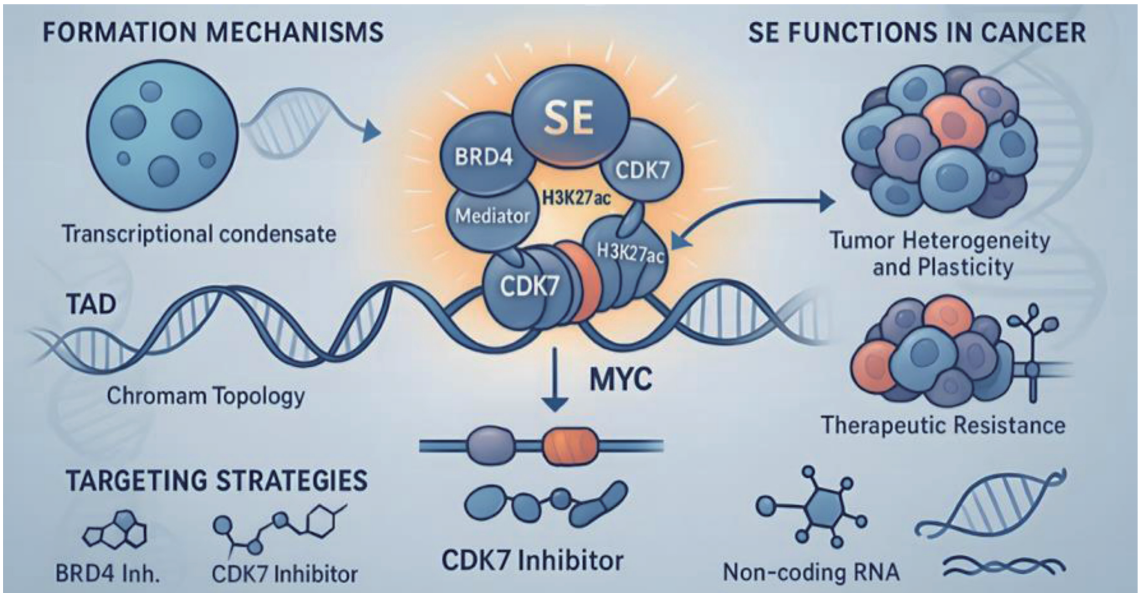

Fig. 1. The formation mechanism, function, and targeting strategies of super-enhancers (SEs) in tumors. SEs are cooperatively driven by transcriptional condensates and chromatin topology. Their core regulatory network comprises key components such as BRD4, the Mediator complex, CDK7, and H3K27ac. By regulating the expression of oncogenes like MYC, SEs drive the generation of tumor heterogeneity, plasticity, and therapeutic resistance. Targeting strategies against SEs mainly include BRD4 inhibitors, CDK7 inhibitors, and approaches targeting non-coding RNAs, offering new directions for precision cancer therapy. BRD4, bromodomain-containing protein 4; CDK7, cyclin-dependent kinase 7; H3K27ac, acetylation of lysine 27 on histone H3 protein; Inh., inhibitor; MYC, myelocytomatosis oncogene; TAD, topologically associating domain. The figure was created using Figdraw.

tions, viral oncoprotein activity, and epigenetic reprogramming. This very complexity, however, reveals a critical vulnerability. The unique dependency of cancer cells on SE-driven transcriptional programs positions SEs and their core components—such as the BET protein BRD4, transcriptional cyclin-dependent kinases (CDKs), and the Mediator complex—as promising therapeutic targets.[3,5] The development of BET inhibitors, CDK7/9 inhibitors, and strategies to disrupt SE condensates underscores the translational potential of this research.

In the following sections, we will systematically explore the mechanisms by which SEs regulate tumorigenesis, their pathological roles in specific cancer contexts, the frontier of SE-targeting therapeutic strategies, and the technological advances propelling this field forward. By integrating these perspectives, this review seeks to provide a comprehensive framework for understanding SEs as pivotal determinants of cancer biology and to highlight their significant potential for guiding the next generation of precision oncology interventions (Fig. 1).

The central hub of tumor transcriptional regulation

As an important element of gene regulation, SEs have shown unique biological functions in tumorigenesis and development. In recent years, high-throughput sequencing and epigenetic studies have revealed that SEs drive abnormal expression of oncogenes by integrating transcription factors, epigenetic modifications, and 3D genome structure.[1] These regulatory hubs are specifically activated in a wide range of cancers, and their enriched histone modifications (such as H3K27ac and H3K27cr) not only mark highly transcriptionally active regions but also cooperate with chromatin-reading proteins such as BRD4 to form a positive feedback loop to amplify cancer-promoting signals.[1] It is noteworthy that the abnormal recruitment ability of SEs makes them key to the maintenance of tumor cell identity.

SEs drive tumor progression

Dual pathways of transcriptional activation: Remote contact and chromatin remodeling

At the molecular level, SEs participate in tumor progression through two core pathways. On the one hand, SEs remotely activate transcription of proto-oncogenes through physical contact. For example, in liver cancer, the synergistic binding of the HNF3β and NF1/CTF transcription factor complex in the promoter region of the *COL18A1* gene not only maintains a liver-specific expression pattern, but the abnormal increase in binding activity is also closely related to the differentiation state of hepatocellular carcinoma (HCC).[6] On the other hand, dynamic modification of SEs reconstructs the chromatin open state. As a novel modification, histone crotonylation (H3K27cr) and classical acetylation (H3K27ac) jointly mark SE formation sites in spermatogenesis. This double-modification pattern may affect the cooperative expression of oncogene clusters by changing the recruitment efficiency of proteins such as BRD4 in tumors.[1] In addition, CCCTC-binding factor (CTCF)-mediated loss of chromatin boundary insulation function can lead to abnormal activation of SE-adjacent silent regions,[7] which drives the dysregulation of immune checkpoint molecules such as programmed cell death protein 1 in T-cell lymphomas.

SEs, as regions of the genome that are highly enriched in transcriptional regulatory elements, play a central role in the occurrence and development of tumors. Numerous studies have shown that SEs drive the abnormal expression of oncogenes through unique chromatin structures and molecular mechanisms, and then affect the proliferation, differentiation, and metastasis of tumor cells.[8] These regulatory elements show remarkable specificity in a variety of cancers, and their abnormal activation or inhibition is often closely related to the dysregulation of key signaling pathways. In terms of molecular mechanism, the function of SEs depends on

phase separation of transcriptional coactivators,[3] dynamic changes of epigenetic modifications and remodeling of 3D genome structure,[9] which together constitute a complex regulatory network of SEs in tumors.

The transcription factor network and its positive feedback regulation of cell identity

The synergistic effect of transcription factors and SEs is cell-type specific in tumorigenesis. For example, Epstein-Barr virus reshapes the 3D genomic structure of B cells through proteins such as EBNA2, so that the SEs of oncogenes such as *MYC* form specific loops with promoters, thereby driving lymphoblastic transformation. In renal cell carcinoma, downregulation of *METTL14* leads to BPTF protein accumulation, which then enhances SE activity and promotes distant lung metastasis through glucose metabolic reprogramming.[4] These findings reveal a positive feedback loop between SEs and the transcription factor network: transcription factors both regulate the establishment of SEs, and their own expression is driven by SEs, forming molecular switches that maintain tumor cell identity.[2]

Epigenetics and phase separation: Key regulatory dimensions of SE function

Regulation of SE activity by dynamic epigenetic modifications

At the epigenetic level, SEs' activity is closely related to histone modifications. Histone deacetylase inhibitors such as largazole can regulate SE activity by changing the acetylation levels of H3K9 and H3K27 in a dose-dependent manner.[8] Notably, low doses of histone deacetylase inhibitors mainly upregulate gene transcription, while high doses result in selective repression of SE-driven oncogenic transcripts. This dual effect reveals the dynamic plasticity of SEs in drug response. Similarly, age-associated DNA methylation changes are enriched in the SE region in the liver, and longevity interventions (such as caloric restriction) can reverse these epigenetic modifications,[9] suggesting that epigenetic regulation of SEs may be a new target for cancer intervention.

Phase separation: Formation and functional implications of transcriptional condensates

The discovery of phase separation provides new insight into the efficient transcriptional regulation of SEs. Coactivators such as BRD4 and MED1 form droplet aggregates at SEs, which enrich transcription machinery through their intrinsically disordered regions.[3] This physical phase transition not only explains why SEs can efficiently recruit RNA polymerase II but also provides a structural basis for the development of small molecules targeting SEs. For example, compounds that disrupt BRD4 coacervates significantly inhibit SE-driven oncogenic transcriptional programs,[5] whereas EZH2 inhibitors inhibit EBV-associated tumor growth by altering chromatin looping at the *CDKN2A/B* locus.

SEs in developmental reprogramming and the tumor microenvironment

Hijacking of developmental programs and tumor stemness characteristics

SEs exhibit a unique regulatory logic in the evolutionary conservation of development and tumors. The SOX family of transcription factors activates genes involved in extracellular matrix synthesis through synergistic binding of SEs during chondrogenic differentiation,[10] while CDX2 dynamically regulates SE activity during intestinal development by recognizing a methylation-sensitive noncanonical motif.[11] Aberrant reactivation of this developmental program may be the key to the acquisition of stem cell-like properties by tumor cells. For example, the SEs of the embryonic *ζ-GLOBIN* gene, although in the heterochromatin state in adult erythrocytes, can be reactivated by epigenetic intervention,[12] which provides a theoretical basis for the use of developmentally silenced genes in the treatment of malignant tumors.

Interactions between the tumor immune microenvironment and SEs

The interaction between inflammatory signals and SEs constitutes an important dimension of tumor microenvironment regulation. TNFα can induce nucleosome arrangement prior to NF-κB binding, and this genome-wide "pre-open" chromatin state is particularly prominent in regions of SE-like enhancer clusters.[13] Similarly, TRIM28 stabilizes SE structure and higher-order chromosome interactions at the *IL17* locus through a STAT3-dependent mechanism during Th17 cell differentiation.[14] These findings suggest that chronic inflammation may promote tumorigenesis by "locking in" the active state of SEs, and that targeting the epigenetic memory of SEs may break this vicious cycle. Recent studies have found that SEs abnormally activate oncogene expression in a variety of tumors by forming phase-separated condensates, reconstructing chromatin topology, and regulating core transcription factor networks.[15,16] These regulatory mechanisms not only involve the dynamic balance of epigenetic modifications (such as histone acetylation/deacetylation) but are also closely related to the 3D spatial organization in the nucleus.[17,18] Of particular note, SEs, while maintaining the identity gene expression program in tumor cells, have also emerged as potential targets for therapeutic intervention.[19,20]

Oncogenic mechanisms of SEs in specific cancer types

At the molecular level, SEs are particularly prominent in forming a transcriptional regulatory hub through phase separation. For example, in Candida albicans, transcription factors containing prion-like domains form aggregates through liquid-liquid phase separation, which are functionally similar to mammalian SEs and can regulate epigenetic cell fate switching.[15] Similarly, in rhabdomyosarcoma, core transcription factor-dependent SEs exhibit abnormal histone acetylation status, leading to the collapse of RNA polymerase II phase separation condensates, which in turn disrupts the expression of cellular identity genes.[16] This phase separation phenomenon has also been observed in acute promyelocytic leukemia. The PML-RARα fusion protein interferes with the function of myeloid-specific enhancers and SEs by restructuring chromatin topology and finally inhibits the expression of myeloid differentiation-related genes.[17]

SEs are also closely related to the regulation of the tumor immune microenvironment. Studies have found that SE-tagged *UGCG* and *B4GALT5* genes in natural killer cells and cytotoxic T cells are essential for the formation and functional maintenance of cytotoxic granules.[21] In T cells, SEs are enriched at the cytokine and cytokine receptor loci and are negatively regulated by "guardian" transcription factors such as BACH2, and these SE-related genes show significant enrichment of genetic variants in autoimmune diseases such as rheumatoid arthritis.[20,22] In addition, analysis of regulatory T cell-specific epigenomic region variation showed that single nucleotide polymorphisms (SNPs) associated with autoimmune diseases were mainly enriched in the hypometh-

ylated regions unique to naive Treg cells, which highly overlap with Treg cell-specific SEs.[22]

In the application of cancer therapy, the dynamic regulatory characteristics of SEs provide new ideas for intervention strategies. Histone acetyltransferase p300 has been shown to induce the formation of de novo SEs and drive cellular aging-related gene expression programs, which provides a potential target for the treatment of aging-related diseases.[19] The selective regulation by the JAK inhibitor tofacitinib of rheumatoid arthritis risk genes (with SE structure) also suggests that SEs can be used as specific targets for pharmaceutical intervention.[20] The SE-related transcription factor network (FOS, GATA2, MAFK, TEAD4, and TFAP2C) found in placental trophoblast stem cells not only regulates the key gene program of placental development but also provides a reference for understanding the co-regulation mechanism of abnormal SEs in tumors.[23] Studies have shown that SEs participate in the initiation, progression, and treatment resistance of a variety of cancers by regulating the expression of key genes and the organization of 3D chromatin structure.[24,25] These elements often form a positive feedback loop with cellular identity determinants, such as core transcription factors, driving the establishment of tumor-specific transcriptional programs.[26] For example, in alveolar rhabdomyosarcoma, PAX3-FOXO1 induces the expression of other core transcription factors by activating SEs, forming an oncogenic dependence.[26] In addition, the abnormal activity of SEs can lead to genomic instability. For example, activation-induced cytidine deaminase in B cells triggers mutation and translocation of non-immunoglobulin genes through an SE-mediated transcriptional convergence phenomenon, which promotes lymphomagenesis.[27] This regulatory complexity is also reflected in haploinsufficiency diseases, such as SE structural variation of the *BACH2* gene, which leads to immune deficiency and autoimmunity by disrupting the stability of transcription factors.[28]

Mechanistically, SEs affect oncogenic signaling pathways through dynamic regulation of chromatin accessibility and long-range interactions. In esophageal cancer, BCLAF1 promotes chromatin opening and malignant transformation by recruiting the P300/H3K27ac complex to the SE region of *POLR2A* and activating transcription and splicing by RNA polymerase II.[29] Similarly, under inflammatory stimulation, NF-κB preferentially binds to preopened chromatin regions, which often overlap with SEs and regulate the expression of genes such as the chemokine *CCL2*.[30] 3D genomic studies have further revealed that SEs form a spatial interaction hub with their target genes in pancreatic cancer, and their variation can affect insulin secretion and diabetes risk.[31] This architecture is manifested in lymphoma as the translocation of the *MYC* gene to the immunoglobulin or *BCL6* locus, resulting in ectopic high expression of MYC protein through the acquisition of SEs.[32]

SEs also participate in tumor initiation by reprogramming cell fate. In zebrafish models, melanoma-initiating cells reactivate the neural crest progenitor state, accompanied by SE network activation driven by transcription factors such as SOX10.[33] In terms of epigenetic regulation, the SMARCA4-BRD4 complex relocalizes to the SE region during respiratory virus infection and regulates long non-coding RNAs (lncRNAs) to coordinate innate immunity and epithelial-mesenchymal transition.[34] This plastic regulation is closely related to the function of Treg cells, in which miR-142-5p inhibits *PDE3B* through SE-dependent expression and maintains cAMP levels to ensure immunosuppressive function.[35] Technical advances such as the OCEAN-C approach reveal that SEs orchestrate large-scale gene networks by forming open chromatin interaction hubs that colocalize with topologically associated domains and H3K4me3 broad domains.[36] Multi-omics analysis has identified subcluster-specific SE regulatory networks in medulloblastoma, which not only suggest differences in cell origin but also provide new ideas for targeted therapy.[37] A large number of studies have shown that SEs directly affect tumor proliferation, differentiation, and treatment resistance by driving abnormal expression of oncogenes, remodeling the epigenetic landscape, and regulating key signaling pathways.[38–40] These regulatory mechanisms not only involve the synergistic action of transcription factors but also often form complex interactions with 3D genome structure, chromatin accessibility, and non-coding RNA networks, thereby establishing unique transcriptional dependencies and molecular vulnerabilities in a variety of cancers.

SE-driven transcriptional regulatory modules show remarkable pathological specificity in lymphoid malignancies. For example, in anaplastic large cell lymphoma, BATF3, a member of the AP-1 family, and the IL-2 receptor form a functional module through SEs to promote the continuous activation of STAT and ERK signaling pathways, thereby accelerating tumor growth.[38] Notably, the activity of this module was significantly correlated with clinical aggressiveness, and antibody-drug conjugates targeting IL-2Rα showed significant efficacy in preclinical models, revealing the therapeutic potential of SE-related targets. Similarly, in cytokine release syndrome induced by CAR-T cell therapy, the CDK7 inhibitor THZ1 effectively alleviated excessive inflammation without compromising anti-tumor activity by selectively inhibiting SE-associated inflammatory genes such as *STAT1* and *IL1*.[41] These findings underscore the dual role of the SE regulatory network in immune-related tumors—both as a key driver of malignant phenotypes and as a target for intervention.

The oncogenic mechanism of SEs in solid tumors is more complex and often involves dynamic reorganization of 3D genomic structures. In castration-resistant prostate cancer, BCL6, NFIB, and SMAD3 form a transcriptional regulatory loop through SEs to mediate abiraterone resistance by activating cholesterol synthesis and cell cycle pathways.[39] In contrast, human papillomavirus (HPV) integration events generate hybrid extrachromosomal DNA (ecDNA) that fuses the viral sequence with the host SE, thereby globally activating cancer-promoting pathways in a cross-chromatin manner.[40] This SE-ecDNA synergy not only explains the genomic instability of HPV-related cervical cancer but also provides a theoretical basis for the development of diagnosis and treatment strategies based on SE epigenetic modification. In addition, in rhabdomyosarcoma, the RAS-MEK-ERK pathway blocks myogenic differentiation by inhibiting RNA polymerase II processivity in the *MYOG* promoter region, which is closely related to SE-mediated epigenetic silencing.[42]

SEs as therapeutic targets: Mechanisms and strategies

Targeting core components of SEs: BET inhibitors and epigenetic drugs

SEs, as regulatory elements that are highly enriched in transcription factors and cofactors in the genome, play a central role in tumorigenesis and development. Studies have shown that SEs promote the initiation, maintenance, and progression of tumors by driving the abnormal expression of oncogenes, stem-cell genes, and metastasis-related genes.[43,44] Their regulatory mechanism involves 3D chromatin structure remodeling, epigenetic modification, and transcription factor network synergy, especially in the assembly of SEs mediated by cofactors such as BRD4 and MED1.[45,46] In addition, the dynamic

Table 1. Key mechanisms of super-enhancers (SEs) in cancer

Mechanism category	Key process/feature	Representative examples (cancer type)
Epigenetic modifications	Enrichment of histone marks (e.g., H3K27ac, H3K27cr); DNA methylation changes	Liver cancer, leukemia, triple-negative breast cancer (TNBC)
3D genome remodeling	Enhancer-promoter looping, TAD boundary reorganization, long-range chromatin interactions	Lymphoma (MYC translocation), colorectal cancer (CCAT1-L loop), pancreatic cancer
Phase separation (LLPS)	Formation of transcriptional condensates by BRD4/MED1, efficient recruitment of transcriptional machinery	Osteosarcoma, acute leukemia, prostate cancer
Transcription factor network positive feedback	Reciprocal activation between TFs and SEs, maintaining tumor cell identity	Gallbladder cancer (SOX9/TCF7L2), rhabdomyosarcoma (PAX3-FOXO1)
Immune & microenvironment regulation	SE reprogramming of T cell function, regulation of cytokine/chemokine expression	Renal cell carcinoma (CXCL chemokines), breast cancer (CD47), T cell exhaustion
Metabolic reprogramming	SE-driven expression of metabolic enzyme genes, supporting tumor growth & therapy resistance	TNBC (NAMPT), colorectal cancer (PDZK1IP1)
Non-coding RNA involvement	eRNAs, lncRNAs, circRNAs regulating transcriptional stability and networks via SEs	Liver cancer (LINC01089), neuroblastoma (C19MC-LIN28A-MYCN)

3D, three-dimensional; BRD4, bromodomain-containing protein 4; CD47, cluster of differentiation 47; circRNAs, circular RNAs; CXCL, C-X-C motif chemokine ligand; eRNAs, enhancer RNAs; FOXO1, forkhead box protein O1; H3K27ac, acetylation of lysine 27 on histone H3 protein; H3K27cr, crotonylation of lysine 27 on histone H3 protein; lncRNAs, long non-coding RNAs; MED1, Mediator complex subunit 1; NAMPT, nicotinamide phosphoribosyltransferase; PAX3, paired box gene 3; PDZK1IP1, PDZK1 interacting protein 1; SEs, super-enhancers; SOX9, SRY-box transcription factor 9; TAD, topologically associating domain; TCF7L2, transcription factor 7 like 2; TFs, transcription factors.

changes of SEs are closely related to tumor heterogeneity, drug resistance, and immune microenvironment regulation (Table 1), which has become a potential target for cancer treatment.[47,48]

At the molecular level, SEs recruit specific transcription factors and epigenetic modifying enzymes to form local chromatin open regions, thereby activating downstream target genes. For example, in head and neck squamous cell carcinoma, BRD4 drives the expression of stemness genes such as *TP63* and *MET* by binding to the SE region, in cooperation with NF-κB p65 and the Mediator complex, and maintains the self-renewal ability of cancer stem cells.[43] Similarly, in melanoma, the SE of the *AMIGO2* gene is dependent on BRD2/4 regulation, and its inhibition induces cell cycle arrest and apoptosis.[46] In addition, SEs are also involved in the carcinogenesis of the WNT/β-catenin signaling pathway, such as CTCF binding sites in colon cancer, by regulating the nuclear pore localization of the *MYC* gene and promoting its messenger RNA (mRNA) nuclear export.[45] These findings reveal the central role of SEs in tumor-specific transcriptional programs.

Epigenetic regulation is a key mediator of SE function. Lysine-specific demethylase (LSD1) maintains the malignant phenotype of erythroleukemia by inhibiting the activity of the GFI1 SE, while treatment with LSD1 inhibitors induces myeloid differentiation and activates the *CEBPA* network.[47] In atypical teratoid rhabdoid tumor, *SMARCB1* deficiency causes the SWI/SNF complex to be unable to maintain the binding of transcription factors such as AP-1 and TEAD1 at enhancers, thereby disrupting the cell differentiation program.[48] In addition, oxidized low-density lipoprotein promotes liquid-liquid phase separation of inflammatory genes by activating BRD4-dependent SE formation, while curcumin reverses this process by restoring TFEB nuclear translocation.[44] These mechanisms may provide a theoretical basis for the development of epigenetic drugs targeting SE.

Therapeutic strategies targeting SEs: From single-target to combined intervention

From the perspective of molecular mechanism, the function of SEs depends on the precise cooperation of transcription factors and epigenetic modifications. After recognizing viral dsRNA through oligomerization, the nuclear matrix protein SAFA directly activates enhancers and SEs of antiviral genes, coupling innate immune recognition with chromatin remodeling.[49] Similarly, NFIB/NFIX transcription factors prevent lineage misorientation by maintaining the SE epilandscape of hair follicle stem cells, whose deletion leads to loss of stem cell identity and irreversible tissue degeneration.[50] These findings reveal the core characteristics of SEs as an "epigenetic hub", whose function depends not only on the regulatory elements of the DNA sequence itself but also on the spatial support provided by the higher-order chromatin environment. For example, regulatory association modules defined by histone modifications can more accurately predict the distribution of SE clusters and ecDNA than topologically associated domains (TADs), and regulatory association module boundary variants are strongly associated with cell-lethal phenotypes.[51]

The development of therapeutic strategies for SEs shows a trend toward multi-target joint intervention. In acute myeloid leukemia, compounds targeting both CKIα and the transcription kinase CDK7/9 synergistically stabilize p53, eliminate SE-driven oncogene dependence, and selectively eliminate leukemic precursor cells.[52] However, the Hippo pathway inhibitor VT02956 can inhibit the growth of estrogen receptor-positive breast cancer by regulating the apparent silencing of the *ESR1* gene SE by the VGLL3-TEAD-NCOR2 complex.[53] These cases collectively suggest that the pathological effects of SEs often result from the synergistic dysregulation of multi-component regulatory circuits, and therefore, combinatorial interventions targeting key nodes (such as transcriptional coactivators, chromatin-modifying enzymes, or non-coding RNAs) may be more clinically promising than single-target strategies.

Frontiers and methodological advances in SEs research

Chromatin conformation capture and interaction analysis technologies

From the perspective of technology and methodology, emerging

chromatin conformation capture technology provides a powerful tool for analyzing the regulatory network of SEs. CAPTURE technology achieves high-resolution capture of site-specific chromatin interaction protein complexes through biotinylated dCas9, revealing the hierarchical organization of the enhancer network of the *β-GLOBIN* gene cluster.[54] The improvement of the 4C-seq method confirmed the simultaneous three-way interaction of three enhancer elements (MiEκ, 3′eκ, and Edκ) in the *IgK* hyperenhancer region for the first time, and this multi-directional interaction mode has a synergistic effect on enhancer function.[18] In addition, the newly developed DNA:RNA triple helix genome-wide identification technology found that non-coding RNA produced by SEs can form a triple helix structure with purine-enriched DNA through Hoogsteen base pairing, which may be involved in the targeting of transcription regulation.[55]

Technological innovations provide a multi-dimensional perspective for SE research. GRID-seq technology reveals the 3D interaction network between SEs and promoters, indicating that mRNA-chromatin interactions may reflect the spatial proximity of promoter-enhancers.[56] Single-molecule imaging techniques further revealed that SEs may regulate transcriptional bursts by physically anchoring RNA polymerase "factories".[57] In addition, enhancer RNAs (eRNAs; such as *seRNA-1*) regulate transcriptional elongation of neighboring genes (such as myoglobin *Mb*) by binding to hnRNPL,[58] while SINE-Mir-derived enhancers function through ESRRB-mediated topological reconfiguration during pluripotency state transitions.[59] These techniques provide tools to dissect the spatio-temporal dynamics of SEs.

Application of single-cell and multi-omics technologies in SEs research

The development of single-cell whole transcriptome sequencing technology (such as Holo-Seq) provides a new tool to analyze the dynamic role of SEs in tumor heterogeneity. For example, simultaneous capture of mRNA and small RNA can reveal the association between SE activity and tumor dynamics in liver cancer cells.[60]

The abnormal activity of SEs is also related to the tumor microenvironment and immune escape. For example, the SE profile of effector Treg cells under inflammatory conditions highly overlaps with tumor-infiltrating Treg cells, suggesting that SEs may affect tumor immune responses by regulating immunosuppressive genes.[61] In B-cell acute lymphoblastic leukemia, *STAT5* drives the expression of SE-enriched pro-leukemic genes by antagonizing the transcriptional network of NF-κB and IKAROS.[62] In addition, the CDK12/13 inhibitor THZ531 induces tumor cell apoptosis by selectively inhibiting SE-associated DNA damage response genes.[63] These findings expand the application prospects of SEs in tumor immunity and targeted therapy.

Specificity and heterogeneity of SEs across different cancer contexts

SEs are regions of the genome that are highly enriched in transcriptional regulatory elements and play a central role in tumorigenesis and development. Recent studies have found that SEs are involved in the initiation, maintenance, and treatment resistance of a variety of cancers by driving abnormal transcription of key oncogenes.[64,65] These regulatory elements often form a complex interaction network with tissue-specific transcription factors (such as SOX9 and PAX7), epigenetic modifications (such as H3K27ac and 5hmC), and 3D genomic structures (such as TAD clusters and chromatin loops), thereby establishing the unique transcriptional addiction of tumor cells.[66,67] It is worth noting that abnormal activation of SEs is not only closely related to the maintenance of tumor stemness, but also may mediate drug resistance by reshaping the epigenetic landscape, which provides a theoretical basis for the development of therapeutic strategies targeting SEs.[68,69]

At the molecular level, SEs form a positive feedback loop by recruiting specific transcription factors, thereby maintaining the malignant phenotype of tumor cells. For example, in gallbladder cancer, SOX9 and TCF7L2 form an autoregulatory loop by occupying each other's SE regions, driving the overexpression of ErbB- and Wnt pathway-related genes.[65] Similarly, the PAX3-FOXO1 fusion protein in rhabdomyosarcoma restructures the myogenic SE landscape, making tumor cells dependent on BET bromodomain inhibitors.[70] This transcriptional addiction is also observed in tumors regulated by the YAP/TAZ-BRD4 axis, in which YAP/TAZ promotes the genome-wide chromatin binding of BRD4 by tagging SE-specific enhancers, thereby activating the growth-regulatory gene network.[66] These findings reveal the pivotal role of the SE–transcription factor–coactivator ternary complex in tumor transcriptional regulation.

The dynamic reprogramming of SEs is also closely related to aberrant changes in epigenetic modifications. In adrenocorticotrophic carcinoma, β-catenin maintains tumor differentiation by hijacking the adrenal-specific SE landscape and forming a chromatin complex with SF1, while EZH2 inhibitors can disrupt this balance and induce dedifferentiation.[69] Similarly, CDK4/6 inhibitors induce extensive remodeling of enhancers, including SEs, in breast cancer cells by activating the AP-1 transcription factor, thereby affecting cell differentiation and apoptotic escape.[71] At the epigenetic level, 5hmC was found to be enriched in SE boundary regions, which may protect the activity of these functional genomic regions by maintaining hypomethylation.[72] These findings highlight the bidirectional interplay between epigenetic regulation and SE function.

From the perspective of treatment, SE-related mechanisms provide new ideas for tumor-targeted therapy. BAY1251152, an inhibitor targeting CDK9, can exert anti-tumor effects by interfering with SE-mediated short-lived pro-survival protein transcription, while the drug resistance mutation L156F disrupts drug binding through steric hindrance.[64] In chronic myeloid leukemia, SE-dependent *XBP1* transcription has been shown to be a specific vulnerable point of leukemia stem cells, and the CDK7 inhibitor THZ1 can eliminate drug-resistant stem cells by disrupting SE-related gene transcription.[68] In addition, activation-induced cytidine deaminase preferentially targets SEs and regulatory clusters in B-cell tumors, leading to proto-oncogene damage and chromosomal translocation,[73] a finding that provides a new perspective for understanding genomic instability in tumors. These studies collectively suggest that specific interventions targeting the SE regulatory network may become an effective strategy to overcome tumor heterogeneity and drug resistance.

Deepening mechanisms of SEs in 3D genome structure and phase separation

By integrating data from multiple cancer types, it has been found that SEs are the key molecular basis for tumor heterogeneity and treatment resistance by reshaping the spatial structure of chromatin, regulating the core transcription factor network, and driving the expression of oncogenes.[74–76] These functional features are particularly prominent in malignant tumors such as HPV-associated cervical cancer, multiple myeloma, and neuroblastoma, where

aberrant SE activation is directly related to the uncontrolled transcription of oncogenes (such as *MYC* and *TERT*).[77,78] It is worth noting that dysregulation of SEs not only involves genetic variants but also dynamically regulates oncogenic transcriptional programs through physical mechanisms such as epigenetic reprogramming (e.g., histone modification changes) and phase separation.[78,79]

At the molecular mechanistic level, SEs drive tumor-specific transcriptional programs through 3D genome remodeling. For example, HPV16 E6 degrades the histone demethylase KDM5C, leading to an increased H3K4me3 level in the SE region, which in turn activates proto-oncogene expression.[74] Similarly, lncRNA CCAT1-L in colorectal cancer physically connects the *MYC* promoter to the distal SE by forming a chromatin loop, while *MYC* gene rearrangement in multiple myeloma places this site in alignment with the IG locus SE, both resulting in uncontrolled *MYC* transcription.[75,76] This abnormal spatial regulation is more significant in metastatic tumors. For example, in colorectal cancer liver metastasis, SE-driven tissue-specific transcriptional reprogramming enables cancer cells to acquire liver-specific gene expression profiles, which relies on the recognition of acquired SEs by transcription factors such as FOXA2/HNF1A.[80]

The discovery of phase separation provides a new perspective on the functional mechanism of SEs. In osteosarcoma, core regulatory circuitry transcription factors such as *HOXB8* and *FOSL1* form dynamic condensates through liquid-liquid separation, which are enriched in SE regions to maintain chromatin openness and RNA polymerase II release. Disruption of this phase separation can significantly inhibit tumor metastasis and chemotherapy resistance.[78] Similarly, Mediator complexes form transcriptional condensates with signaling molecules such as β-catenin in the SE region to couple cellular identity genes with external signal responses.[79] This phase separation–dependent intrinsic disorder region provides new ideas for targeting undruggable transcription factors. For example, the CDK7 covalent inhibitor THZ1 selectively kills T-cell acute lymphoblastic leukemia (T-ALL) cells by destroying the transcription condensates of RUNX1-SE.[81]

Genetic variation of SEs has a selective advantage in tumor evolution. *TERT* rearrangement in neuroblastoma drives telomerase activation by repositioning SEs near the *TERT* promoter.[77] TD-c2 complex rearrangements in esophageal squamous cell carcinoma (ESCC) are enriched in the SE region of the *PTHLH* gene and amplify oncogenic signals by forming ecDNA.[82] It is worth noting that the risk SNPs identified by GWAS are often located in the SE cluster, and these variants jointly regulate the expression of target genes through 3D genomic interactions, explaining the genetic contribution to some complex diseases.[83] In glioma, lncRNA *HOXDeRNA* can activate the SE of oncogenes such as *EGFR* by binding to PRC2-suppressed CpG islands and releasing stem cell factors such as SOX2/OLIG2,[84] revealing a new mechanism of RNA-mediated epigenetic regulation.

Targeted intervention strategies for SEs show a diversified trend. In addition to directly inhibiting transcription machinery components such as CDK7,[81] small molecules targeting SE phase separation, such as GSK-J4, achieve metastasis inhibition by disrupting core regulatory circuitry aggregates.[78] In B cells, the core elements of IgH 3′rr SEs provide a spatial basis for antibody class-switching recombination by preorganizing chromatin loop conformation,[85] a finding that provides new targets for immunotherapy. Together, these studies show that SEs are key nodes of tumor transcriptional dependence, and the elucidation of their molecular mechanisms lays a theoretical foundation for the development of selective anticancer drugs.

SEs-driven tumor metabolic reprogramming and novel targeted therapeutic strategies

SEs are regions of the genome that are highly enriched in transcriptional regulatory elements. They drive the abnormal expression of key oncogenes through epigenetic reprogramming during tumorigenesis and development, which has become a core focus of cancer research. A large number of studies have shown that SEs regulate the maintenance of tumor stemness, metastatic potential, and treatment resistance in a variety of malignant tumors (such as triple-negative breast cancer, head and neck squamous cell carcinoma, prostate cancer, and leukemia) by reshaping the 3D structure of chromatin, forming transcriptional condensates, or activating metabolic reprogramming.[86–89] These processes often involve transcription factor nucleation, phase separation properties, and synergistic interactions with noncoding genetic variants, which together constitute the molecular basis of tumor-specific transcriptional networks.

At the transcriptional regulatory level, SEs efficiently activate oncogenic signaling pathways by forming spatially isolated transcriptional aggregates. For example, TWEAK/Fn14 signaling induces SE remodeling in triple-negative breast cancer (TNBC) and drives *NAMPT* gene expression through chromatin looping, which in turn promotes NAD+ metabolic reprogramming and filopodia formation, ultimately enhancing metastatic ability.[86] Similarly, the SE of the *LIF* gene in head and neck squamous cell carcinoma maintains tumor stemness by recruiting the SOX2/SMAD3/BRD4/EP300 complex to establish a *LIF-SE-LIF/LIFR*-STAT3-SOX2 positive feedback loop.[87] This regulatory mode is highly cell type–specific, such as ONECUT2 in prostate cancer, which reprograms SEs to activate both adenocarcinoma- and neuroendocrine differentiation–related genes, driving treatment resistance.[88] It is worth noting that the genomic clustering propensity of transcription factors is closely related to phase separation ability, and transcription factors with high clustering propensity (such as MEF2) are more likely to form transcriptional condensates in SE regions and affect cancer prognosis by changing chromatin accessibility.[90]

Mechanistically, the function of SEs depends on the dynamic interaction between epigenetic modifications and 3D genome structure. In chronic lymphocytic leukemia, 5-bp indel variants near the *AXIN2* gene create MEF2 binding sites and activate SE–like regulatory elements spanning more than 150 kb, leading to local chromatin compression and sustained high expression of *AXIN2*.[89] Similarly, hypomethylation of the C/EBPβ enhancer in liver cancer promotes its genome-wide co-localization with BRD4 at the SE region marked by H3K27ac through an eRNA–mediated self-reinforcing loop, thereby activating driver oncogenes.[91] This epigenetic regulation is bidirectional: DNA methylation in the enhancer region not only locally inhibits chromatin opening at transcription factor binding sites but also globally maintains the active H3K27ac mark to ensure the structural integrity of the enhancer.[92]

From the perspective of translational medicine, SE-driven oncogenic networks provide new targets for cancer therapy. In acute myeloid leukemia, CRISPR editing of the *RUNX1* SE eR1 or BET protein inhibition can selectively kill *RUNX1* mutant leukemia cells.[93] Similarly, targeting *TRIB1*-mediated SE remodeling, such as the *Erg* locus, can effectively inhibit *HOXA9*-related leukemia progression.[94] In rhabdomyosarcoma, restoring *CASZ1* expression can induce tumor cell differentiation by reshaping the SE epilandscape.[95] These findings highlight the potential of precise intervention strategies based on SE properties in cancer treatment, especially targeting cancer stem cell subsets that are resistant to traditional therapies.

Heterogeneity of SEs in hematological malignancies and solid tumors and targeted exploration

SEs, as enhancer clusters with high enrichment of transcription factors and coactivators in the genome, play a central regulatory role in the occurrence and development of tumors. Studies have shown that SEs participate in the pathological processes of a variety of malignant tumors by driving the abnormal expression of oncogenes and cell identity–related genes.[96] From the perspective of molecular mechanisms, the function of SEs depends on the dynamic reorganization of 3D genome structure, the formation of transcriptional aggregates mediated by phase separation, and the synergistic regulation of epigenetic modifications, which make SEs a new target for cancer treatment.[97,98]

In hematological malignancies, SEs promote tumorigenesis by abnormally activating the transcriptional program of oncogenes such as *MYC*. For example, the abnormal expression of the *CCND2* gene in multiple myeloma is closely related to the acquisition of a specific SE, which forms an abnormal gene regulatory network by recruiting transcription factors.[99] Similarly, during EB virus–induced immortalization of B cells, viral proteins promote enhanced local interactions between dependent factors and SE target genes by remodeling the 3D structure of the host genome.[98] These findings reveal a common mechanism by which SEs drive oncogenic transcriptional programs through spatial genome remodeling. Notably, the chromatin remodeling complex SWI/SNF has a selective role in maintaining the enhancer landscape, and its deletion causes lineage-specific enhancer dysfunction but has a relatively limited effect on most SEs.[100] This difference suggests that SEs may have unique regulatory resilience, which is consistent with their persistent activation properties in tumors.

The phase separation mechanism is an important basis for SEs to realize their function. Studies have found that transcription factor YY1 forms nuclear condensates through histidine cluster–mediated phase separation, which enriches coactivators such as EP300 and BRD4 and active chromatin marks, and then activates the expression of oncogenes such as *FOXM1*.[97] This process is universal in SE-dependent transcriptional bursts. For example, although BET protein inhibitors can disrupt BRD4-Mediator phase condensates and inhibit transcription, they cannot release the physical contact between enhancer and promoter.[101] This suggests that SEs maintain oncogenic transcription through a multi-level regulatory mechanism: phase separation is responsible for rapid response to signaling pathways, while chromatin looping architecture provides stable spatial support. This "dynamic and static" dual-mode regulation may explain why SE-targeting drugs (such as synthetic ecteinascidins) can broadly inhibit heterogeneous tumor cells, achieving "pan-repression" of SE driver genes by interfering with the formation of transcriptional aggregates in CpG-rich regions.[102]

The intersection of developmental and tumor signaling pathways on the SE platform is another key feature. In ES cells, SEs regulate pluripotency genes by integrating multiple signaling pathways. However, tumor cells hijack this mechanism and make oncogenes hypersensitive to oncogenic signals.[103] For example, in neuroblastoma, all-trans retinoic acid reprograms SE dynamic waves to inactivate SEs of self-renewal–related transcription factors (such as *MYCN* and *SOX11*) while activating new SEs of neural differentiation–related transcription factors (such as *SOX4*).[104] The disorder of this temporal regulation may lead to differentiation arrest, and the restoration of SE homeostasis may become a breakthrough in differentiation therapy. Epigenetic drugs such as BET inhibitors down-regulate *FOXM1* but not *MYC* in ovarian cancer through a noncanonical pathway, showing tissue-specific strategies to target the SE pathway.[105]

The function of SEs also depends on fine RNA regulation. The Integrator complex is recruited to the SE region and promotes transcription termination by cleaving the 3′ end of eRNA, whose loss results in eRNA–RNA polymerase II complex stacking and disruption of enhancer-promoter chromatin looping.[106] This reveals a new dimension of SEs in maintaining 3D genomic activity through noncoding RNA processing. In addition, CTCF exhibits a dual role in SE regulation: it can colocalize with SEs to activate cellular identity genes, and it can also achieve lineage-specific repression by recruiting H3K27me3.[107] This context-dependent function implies that the regulation of SEs is highly context-sensitive, providing a molecular window for targeted intervention.

From a technical perspective, new methods such as AQuA-HiChIP, which achieve absolute quantification of chromatin interactions, reveal that histone deacetylation inhibitors disrupt SE function by creating aberrant contacts.[108] Such techniques will facilitate precise resolution of SE regulation in three dimensions. By identifying the feature pair of maximum co-location–minimum correlation, MACMIC analysis found the atypical function of CTCF in epigenetic regulation,[107] which provides a new tool for understanding the heterogeneous regulation of SEs. Together, these advances have promoted a systematic understanding of the molecular logic of SEs in tumors.

Association of tumor drug resistance and immune evasion with SEs

By integrating a variety of epigenetic modifications and transcription factor networks, SEs can drive the abnormal expression of oncogenes, thereby affecting proliferation, metastasis, drug resistance, immune escape, and other malignant phenotypes of tumor cells. Studies have shown that the abnormal activation or reprogramming of SEs is closely related to molecular heterogeneity, treatment resistance, and poor prognosis in a variety of cancers.[109–111] These findings not only reveal the central regulatory role of SEs in tumors but also provide a new theoretical basis for targeted intervention.

At the molecular level, SEs dynamically recruit transcription factors and epigenetically modifying enzymes to form transcriptional condensates, thereby efficiently activating downstream target genes. For example, SOX2, as a key transcription factor for pluripotency maintenance, forms transcriptional condensates with the coactivator p300 on SEs to promote the heterogeneity of neurogenic lung squamous cell carcinoma through chromatin acetylation.[112] Similarly, in ESCC, BRDT collaborates with ΔNp63 to bind SEs to activate keratin genes (such as *KRT14*) through long-range chromatin looping, maintaining the squamous phenotype.[113] In addition, cross-lineage reprogramming of SEs is particularly prominent in tumors. For example, the SE of PDC-specific *RUNX2* in BPDCN is hijacked to the *MYC* promoter region due to the chromosomal translocation t(6;8), which activates the expression of *RUNX2* and *MYC* simultaneously and drives leukemia progression.[114] These findings highlight the central role of SEs in tumor lineage plasticity and co-activation of oncogenes.

The abnormal regulation of SEs is also closely related to tumor microenvironment remodeling and immune escape. In clear cell renal cell carcinoma, SE-mediated epigenetic activation of inflammation-related genes, such as CX-C chemokines, promotes lung metastasis through a neutrophil-dependent mechanism.[110] Overexpression of CD47 in breast cancer, in turn, relies on the direct regulation of SEs by the TNF–NF-κB signaling pathway, thereby

transmitting a "don't eat me" signal to evade immune surveillance.[115] In addition, the genomic localization characteristics of SEs also affect their function. For example, strong insulating TAD boundaries preferentially protect SEs from neighboring regulatory elements, and co-duplication of such boundaries with SEs occurs frequently in cancer patients and may work together as functional units to promote tumorigenesis.[116]

Drug resistance is another important dimension in which SEs participate in the malignant progression of tumors. In prostate cancer, the SE of *PTGR1* is activated by transcription factors such as SRF and RUNX3, leading to metformin resistance by accelerating cell cycle progression.[109] In NPC, the SE of *DDX5* upregulates *ADAM10* through long-range enhancer-promoter interaction, promoting vasculogenic mimicry to resist anti-vascular therapy.[117] Of note, mutations or epigenetic variations in SEs can be therapeutic targets. For example, *MSH2*-deficient gastric cancer is sensitive to BET inhibitors due to defects in the cell adhesion pathway,[118] while the SE polymorphism of *LMO1* (rs2168101) in neuroblastoma regulates tumor susceptibility by affecting GATA3 binding.[119] These findings provide a molecular basis for the development of SE-targeted therapies.

From a technical point of view, single-cell sequencing and 3D genomics have revealed the dynamic nature of SEs in tumor clonal evolution. For example, SE translocation to the *TERT* promoter region drives subclonal diversity in glioblastoma,[120] while loss of TAD boundary insulators in T-ALL leads to aberrant interaction of *MYC* with distal SEs.[7] These studies not only deepen the understanding of the spatio-temporal specificity of SEs but also provide a new perspective for elucidating tumor heterogeneity.

Precision therapeutics targeting SEs: Translation from basic research to clinical application

By aggregating a large number of transcription factors, coactivators, and epigenetically modifying enzymes, these regions form transcription hubs and drive the expression of key oncogenes.[121,122] Studies have shown that abnormal activation or structural variation of SEs is closely related to drug resistance, metastasis, and cell identity maintenance in a variety of cancers, and their regulatory mechanisms involve chromatin dynamic remodeling, transcription factor cooperation, and the participation of noncoding RNA.[123,124]

At the molecular mechanism level, SEs form transcription condensates through phase separation, recruit nuclear receptors such as NR3C1 and Mediator complexes, and promote the transcriptional activation of drug resistance–related genes.[123] For example, in gastric cancer, SE-driven NR3C1 aggregates the transcription machinery of 5-FU–resistance genes through liquid-liquid phase separation, while inhibition of NR3C1 or disruption of SE structure restores chemotherapy sensitivity.[123] Similarly, virus-induced SEs in EBV-transformed B cells target transcription factors such as IRF2 and BATF/IRF4 to promote lymphoma survival by inhibiting apoptotic signals such as cFLIP-mediated *TNFα* resistance and activating the PI3K/AKT pathway.[125] In addition, the hierarchical structure of SEs (hub and non-hub enhancers) is critical for function, in which hub enhancers rely on CTCF/cohesin to maintain chromatin loop structure, and their loss leads to the collapse of downstream gene expression.[126]

Epigenetic regulation is at the core of SE function. By recruiting histone-modifying enzymes KMT2D and p300 to the SE region, *DBC1* synergistically promotes the deposition of H3K4me1/2/3 and H3K27ac marks, thereby activating genes related to colorectal cancer progression.[127] In contrast, the RACK7/KDM5C complex acts as an "enhancer brake" to inhibit SE over-activation by removing H3K4me3 and preventing abnormal expression of oncogenes such as *S100A*.[128] In senescent cells, the degradation of HDAC4 leads to AP-1/p300 enrichment at specific SEs, reshaping the aging-related transcriptional program.[129]

SEs also affect tumor progression by regulating noncoding RNAs. For example, *TP63*-activated SE drives the overexpression of lncRNA *LINC01503* in squamous cell carcinoma, which continuously activates MAPK and AKT pathways by blocking *DUSP6*-mediated ERK2 dephosphorylation and EBP1–PI3K interaction.[124] In T-ALL, SE-activated *IRF2BP2* cooperates with master transcription factors such as ERG/ELF1 to regulate the *RAG1* enhancer and maintain the activity of *MYC* and E2F pathways.[130]

Advances in technical methods have provided new tools for the study of SEs. The CRISPR/dCas9 epi-editing system (enCRISPRa/enCRISPRi) can precisely regulate the chromatin state of SEs. For example, SE targeting *TAL1* can inhibit the progression of T-ALL.[131] In addition, integration of Hi-C and ChIP-seq data reveals functional heterogeneity of dynamic changes within SEs, such as structural rearrangements (length or composition changes) that can differentially regulate the number and expression intensity of downstream genes.[122] These findings suggest new strategies to target SEs in cancer therapy, such as using JQ1 to disrupt SEs or developing specific inhibitors (such as Cort108297 targeting NR3C1) to reverse drug resistance.[123,127] By integrating a variety of epigenetic modifications and transcription factor networks, SEs can drive the abnormally high expression of oncogenes, thereby maintaining the malignant phenotype of tumor cells.[132,133] Studies have shown that aberrant activation of SEs can participate in tumorigenesis through a variety of mechanisms, including enhancer hijacking, 3D chromatin structure rearrangement, and regulatory element reorientation caused by noncoding mutations.[134,135] In addition, SE components (such as BRD4, CDK7, MED1.) have become potential therapeutic targets for a variety of cancers, and their inhibitors have shown selective killing effects on tumor cells in models of liver cancer and breast cancer.[132,136]

At the molecular level, SEs orchestrate the transcriptional output of oncogenic signaling pathways by reorganizing the spatial structure of chromatin. For example, in acute promyelocytic leukemia, the PML/RARα fusion protein activates target genes such as *GFI1* by forming SEs, while recruiting P300 and HDAC1 to balance epigenetic modifications. Similarly, TGF-β signaling–dependent SMAD4 and transcription factor SALL1 form a bidirectional regulatory loop in microglia: SMAD4 binds to the SE of *SALL1* to maintain its expression, which in turn ensures cell-specific transcriptional programs by restricting the genomic binding sites of SMAD4.[137] This positive feedback mechanism may be hijacked in tumors; for example, nuclear miR-9 amplifies *TGFB1*-induced oncogene expression by promoting G-quadruplex (G4) formation and SE-promoter looping.[138]

The heterogeneity of SEs provides a new perspective for tumor classification. In lung adenocarcinoma, the H3K27ac modification profile can distinguish two groups of subtypes with significant differences in prognosis, among which the subtype with poor prognosis shows inactivation of SE-related core regulatory networks (such as *CLU*).[139] Similarly, the two subtypes of liposarcoma rely on the FUS-DDIT3-BET protein complex or the FOSL2-*MYC*-*RUNX1* transcriptional loop, respectively, and both enhance their metastatic potential through *SNAI2*.[140] This subtype-specific SE regulation pattern manifests in colorectal cancer as AP-1/cohesin complex–mediated enhancer hotspot activation, where nearly half of the colorectal cancer risk sites colocalize with relapse-activated SEs.[141]

Aberrant activation of SEs can also be achieved through noncoding mutations. During the transformation of follicular lymphoma to high-grade B-cell lymphoma, SE reorientation at the *ZCCHC7* locus results in disrupted ribosomal RNA processing, which in turn remodels the tumor proteome.[134] In medulloblastoma, GFI1/GFI1B is abnormally activated due to chromosomal structural variants hijacked by SEs,[142] while meningiomas abnormally activate the Hedgehog pathway through chromatin interaction between the *DIRC3* hyperenhancer and *IHH* gene.[135] These findings reveal the widespread regulatory plasticity of SEs in tumors.

Targeting SE core components has become a new strategy to overcome tumor drug resistance. In luminal breast cancer, AKT inhibitor resistance is mediated by the *FOXO3a* acetylation–BRD4–*CDK6* axis, and inhibition of this pathway restores drug sensitivity.[136] In adult T-cell leukemia/lymphoma, HTLV-I virus regulates *BATF3* SE through HBZ protein, and BET inhibitors disrupt this transcriptional network.[143] Together, these studies show that SEs are not only the hub of tumor transcriptional dependence but also provide the molecular basis for precision therapy.

Future directions in SEs research

SEs are regions of the genome that are highly enriched in transcriptional regulatory elements and play a central role in tumorigenesis and development. They maintain the malignant phenotype of tumor cells by driving the abnormal expression of key oncogenes (such as *MYC*, *IRF4*).[144,145] Studies have shown that dysregulation of SEs is widespread in hematologic malignancies (such as multiple myeloma, acute myeloid leukemia) and solid tumors (such as glioblastoma, TNBC). Their mechanism involves the synergistic action of transcription factors (such as *IKZF1* and *BATF*), epigenetic modifications (such as BAF155 methylation), and chromatin remodeling complexes (such as SWI/SNF).[146,147] Notably, aberrant activation of SEs not only promotes tumor proliferation by directly regulating oncogenic signaling pathways (such as MAPK/ERK) but also enables immune evasion by inhibiting the interferon pathway.[146,148] This dual function makes SEs an important target for cancer therapy, and drugs targeting their regulatory network (e.g., BET inhibitors, CDK7 inhibitors) have shown the potential to selectively kill tumor cells in preclinical models.[149,150]

From the perspective of molecular mechanism, the formation of SEs depends on the recognition of DNA response elements by specific transcription factors. For example, estrogen receptor α (ERα) activates SE assembly by binding to potent response elements, while blood system–specific transcription factors (such as GFI1b, RUNX1) precisely regulate expression levels through modular enhancer clusters.[145,151] This modular design not only endows SEs with regulatory flexibility during normal hematopoietic differentiation but is also hijacked by leukemic stem cells to maintain aberrant expression of oncogenes.[145] In addition, the functional implementation of SEs requires the degradation of eRNA by RNA exonucleases to maintain the stability of chromatin structure, and the disorder of this process leads to R-loop accumulation and DNA damage, which in turn affects the distal regulatory function of immunoglobulin heavy chain hyperenhancers.[152] These findings reveal the complexity of the dynamic regulation of SEs, which depends on multi-level interactions of transcription factors, noncoding RNAs, and epigenetic modifiers.

In terms of therapeutic strategies, targeting the core components of SEs or downstream effector molecules has shown significant efficacy. For example, combined application of immunomodulatory drugs and EP300 inhibitors in multiple myeloma can synergistically degrade IKZF1/IKZF3 and inhibit *MYC/IRF4* to overcome single-drug resistance.[144] Similarly, SE-driven RNA-binding protein cascades such as the hnRNPF–PRMT1 axis in pancreatic cancer promote tumor growth by enhancing mRNA translation, whereas targeting *PRMT1* selectively inhibits tumors with high *MYC* expression.[153] In addition, inhibition of Mediator kinases CDK8/19 provides new therapeutic ideas for acute myeloid leukemia by paradoxical activation of SE-related genes with tumor suppressor functions (such as *CEBPA*, *IRF8*).[154] These cases highlight the heterogeneity and plasticity of SE regulatory networks, suggesting that combined targeting of SE formation (such as BET inhibitors), function maintenance (such as CDK7 inhibitors), and immune microenvironment (such as interferon pathway activation) may be a future direction.

The dependence of tumor cells on SEs is also reflected in their unique vulnerability to transcriptional addiction. SE-associated *MYC* family genes and neuroendocrine factors in small cell lung cancer are highly sensitive to the CDK7 inhibitor THZ1,[150] while SE-labeled genes such as OCA-B in diffuse large B-cell lymphoma become potential targets for BET inhibitors.[149] This selective killing effect may result from the transcriptional "buffering threshold" established by SEs in tumor cells—either upregulation (*CEBPA* overexpression due to Mediator kinase inhibition) or downregulation (*MYC* shutdown due to BRD4 inhibition) can disrupt the precise gene dosage balance required for tumor survival.[154] In addition, the mechanism by which senescent cells regulate *MDM2*, *RNASE4*, and other genes via SEs to inhibit p53 in multiple pathways to maintain survival further expands the extensive role of SEs in cell fate determination.[155] These findings provide new insights into the central role of SEs in tumor-specific transcriptional programs. They drive the abnormal expression of oncogenes by reshaping the epigenetic landscape and transcriptional network. Studies have shown that abnormal activation of SEs is closely related to the maintenance of heterogeneity, treatment resistance, and metastasis in a variety of tumors.[156] Molecularly, SEs maintain a positive feedback loop of oncogenic signaling pathways by forming transcriptional aggregates or recruiting epigenetic readers (e.g., BRD4, ENL). For example, in ERα-positive breast cancer, BRD4-regulated SEs trigger the RAS/RAF/MEK/ERK cascade by activating *RET* kinase, forming a BRD4/ERα–RET–ERα autoactivation loop.[157] Similarly, in ovarian cancer, SE-driven *KLF5* forms a transcription complex with *EHF/ELF3* and upregulates *RAD51* expression to enhance homologous recombination repair capacity, leading to PARP inhibitor resistance.[158]

Dysregulation of SEs not only depends on the transcription factor network but also involves dynamic changes in chromatin remodeling and histone modifications. For example, in diffuse intrinsic pontine glioma, the H3.3K27M mutation activates the SE region by reestablishing H3K27me3 modification at the *CREB5* locus, thereby maintaining tumor stemness.[159] In addition, the epigenetic reader ENL anchors SEs by recognizing histone acetylation marks such as H3K27ac and collaborates with the FACT complex to promote transcriptional elongation, which works with BRD4 to drive the expression of oncogenes such as *MYC* in colorectal cancer.[160] This synergistic effect suggests that combined targeting of ENL and BRD4 may overcome the limitations of single-targeted therapy.

Heterogeneity of SEs is also a key determinant of tumor subtype and treatment sensitivity. In TNBC, the SE-driven *VAX2* transcriptional regulatory network defines the mesenchymal development subtype, which shows significant sensitivity to BET inhibitors.[161] However, in pancreatic cancer, activated pancreatic stellate cells

rely on SEs to maintain the fibrotic microenvironment, and disruption of SEs using JQ1 can reverse their activated phenotype and enhance the permeability of chemotherapy drugs and immunotherapy.[162] These findings reveal the specific regulation mode of SEs in different tumor microenvironments.

Intervention strategies targeting SEs have shown potential for clinical translation. For example, the LSD1 inhibitor NCD38 inhibits the malignant program of myeloid leukemia cells by activating SEs of hematopoietic differentiation–related genes,[163] while histone deacetylase inhibitor SAHA combined with a PARP inhibitor can effectively kill drug-resistant ovarian cancer cells with high *KLF5* expression.[158] In addition, targeting the formation of SE-related molecular aggregates is also considered a new direction. For example, nuclear *ANLN* promotes transcription initiation by phase separation from RNA polymerase II, and its inhibition can block the proliferation of ESCC.[164] Together, these studies highlight the multi-dimensional value of SEs as a therapeutic target for cancer, but their clinical application still faces challenges such as drug resistance and tissue specificity.SEs, as a special class of cis-regulatory elements, play a central regulatory role in tumor development by enriching transcription factors, cofactors, and histone modifications such as H3K27ac at high density. Studies have shown that SEs can drive the abnormal expression of oncogenes (such as *MYC* and *TAL1*),[165,166] developmental pathways (such as the *NOTCH1–MYC* axis), and reshape noncoding RNA networks (such as circular RNA and lncRNA).[167–169] They promote tumor proliferation, metastasis, and treatment resistance. Their molecular mechanisms involve chromatin loop remodeling,[167] enhanced transcriptional elongation,[170] and epigenetic-dependent coactivator redistribution,[171] highlighting the pivotal role of SEs in tumor transcriptional dependence.

The regulation of oncogenes by SEs is highly cell-type specific. For example, in acute myeloid leukemia, a 3q26 translocation results in hijacking the *MYC* SE to the *EVI1* locus, which activates *EVI1* expression through CTCF-mediated chromatin looping.[167] In T-ALL, 5′ SE mutations in *TAL1* drive poor prognosis through a *MYB*-dependent mechanism.[166] This specificity is also reflected in solid tumors, such as *AJUBA* in HCC and LINC01977 in lung adenocarcinoma,[169,172] both driven by SEs and closely related to epithelial–mesenchymal transition and metastasis. It is noteworthy that abnormal activation of SEs often forms a positive feedback loop with key transcription factors (such as *RUNX3* and *ZEB1*) to further amplify the oncogenic signal.[169,173]

SE-dependent regulation of noncoding RNAs is an important dimension of epigenetic remodeling in tumors. The splice diversity and transcriptional activity of circular RNAs are directly regulated by SEs marked by H3K27ac, and their dysregulation can form the pan-cancer tumor suppressor marker CIRSE.[168] While lncRNAs (such as HCCL5 and LINC01977) gain cancer-promoting functions through SE hijacking mechanisms—for example, LINC01977 activates *ZEB1* transcription by recruiting the SMAD3–CBP/P300 complex[169] —these findings reveal the precise regulatory mode by which SEs integrate noncoding RNA networks through 3D genomic remodeling.

Targeted intervention of SEs provides a new strategy for cancer treatment. Mebendazole targeting the *MYB*-dependent *TAL1* SE induces MYB degradation in T-ALL.[166] In diffuse intrinsic pontine glioma, CDK7 or bromodomain inhibitors exert efficacy by disrupting SE-mediated transcriptional addiction.[174] In addition, SE-driven immune escape (such as the *TOX2*–PRL-3 axis in natural killer/T cell lymphoma) and microenvironmental adaptation (such as TGF-β/SMAD3 pathway activation) suggest potential directions for combination therapy.[169,173] SEs, as high-density clusters of transcriptional regulatory elements in the genome, play a central role in tumorigenesis and development by integrating epigenetic modifications and transcription factor networks. Studies have shown that SEs participate in the evolution of a variety of malignant tumors by driving abnormal expression of oncogenes, maintaining the identity of tumor cells, mediating microenvironmental interactions, and promoting treatment resistance.[175–177] The abnormal activation of these regulatory elements is often closely related to the dysregulation of epigenetic modifications (such as the loss of histone demethylase *KDM6A*), the involvement of viral oncogenic proteins (such as EBV), or transcription factor circuit remodeling, resulting in tumor-specific transcriptional dependence.[178,179] It is worth noting that SE-driven molecular events are highly tissue-specific and tumor-heterogeneous, which provides a potential breakthrough for targeted intervention.[180,181]

At the molecular level, SEs directly activate oncogenic signaling pathways by reorganizing the core transcriptional regulatory network (core regulatory circuitry). For example, in pancreatic cancer, loss of *KDM6A* leads to dysfunction of COMPASS-like complexes, which in turn activates SEs that regulate ΔNp63, *MYC*, and *RUNX3* to induce female-specific squamous subtypes.[175] Similarly, EBV occupies B-cell SEs through its oncoprotein in coordination with NF-κB, driving *MYC* and *BCL2* expression to maintain lymphoid proliferation.[176] In esophageal adenocarcinoma, a transcription factor interaction loop consisting of *ELF3*, *KLF5*, *GATA6*, and *EHF* coregulates the tumor transcriptome by occupying SEs.[182] In addition, SEs indirectly regulate tumor progression through noncoding RNAs (such as lncRNA PRKCQ-AS1), and their interaction with the RNA-binding protein MSI2 can stabilize *BMX* mRNA and promote activation of the ERK/MYC signaling pathway.[183]

Cell interactions in the tumor microenvironment are also regulated by SEs. For example, SE-driven *LIF* in glioblastoma promotes mesenchymal transition by activating the microglia ITGB2/STAT3/IL-6 feedback loop.[181] In alveolar soft tissue sarcoma, the fusion protein ASPSCR1::TFE3 upregulates *RAB27A* and *SYTL2* by reshaping SE distribution and regulates the secretion of angiogenic factors to construct the tumor vascular network.[184] This SE-mediated cell-to-cell communication reveals the complexity of the tumor ecosystem.

Therapeutic strategies against SEs mainly focus on disrupting their transcription machinery or epigenetic regulation. CDK7 inhibitor THZ1 can selectively inhibit SE-associated oncogenes (such as *PAK4* and *RUNX1*) and has shown potent antitumor activity in ESCC.[177] In neuroblastoma, the transcription complex formed by *JMJD6* and BRD4/N-Myc activates *E2F2* and *c-MYC* in an SE-dependent manner, while CDK7 inhibitor THZ1 combined with histone deacetylase inhibitors synergistically inhibits this pathway.[179] In addition, targeting SE-derived noncoding RNAs (e.g., blocking PRKCQ-AS1/MSI2 interaction through the small molecule NSC617570) provides a new intervention direction for *MYCN* non-amplified neuroblastoma.[183] These findings highlight the broad potential of SEs as a therapeutic target for cancer. SEs, as functional units highly enriched in transcriptional regulatory elements in the genome, have become an important focus of cancer epigenetics research. They can drive oncogene expression by reorganizing the core transcriptional regulatory network during tumor development and progression. Through the integration of multi-omics data and functional experiments, it has been found that SEs participate in tumor malignant transformation through three core mechanisms: forming an enhancer–promoter interaction

network, regulating the expression of key transcription factors, and maintaining oncogene-dependent chromatin openness.[185–187] In primary effacing lymphoma, HiChIP technology revealed that SEs form functional coupling with oncogenes such as *MYC* and *IRF4* through 3D genomic structures. CRISPR interference of these SE regions can significantly inhibit target gene expression and tumor cell growth.[185] Similarly, the core regulatory loop of TP63/SOX2/KLF5 in ESCC maintains tumor survival through SE-mediated *ALDH3A1* activation, while BET inhibitors can disrupt this loop and inhibit xenograft growth.[188] These findings collectively suggest that the SE-driven transcriptional regulatory network is highly cell type-specific, and its function depends on the synergistic action of specific transcription factors.

At the molecular level, SEs achieve precise regulation of oncogenes through unique epigenetic modification patterns. In neuroblastoma, CDK7 inhibitors selectively target *MYCN*-dependent SEs, leading to suppression of global transcriptional amplification and tumor regression.[189] This phenomenon is further extended in ETMRs (multilayered rosette-like embryonic tumors), where the *C19MC*–LIN28A–*MYCN* loop forms a positive feedback loop through SEs, and its stability is maintained by the BET protein BRD4.[190] It is noteworthy that regulation of SEs is bidirectional: in addition to activating oncogenes, *RUNX3* inhibits the NFATC1 signaling pathway by constructing *RCAN1.4*-related SEs in breast cancer, and its loss leads to enhanced tumor metastasis.[191] This dual regulatory feature is particularly prominent in peritoneal metastasis of gastric cancer. According to SE activity, SEs can be divided into two molecular subtypes: *ELF3/KLF5*-activated and TGF-β/Smad3-dependent, with the latter being sensitive to TEAD pathway inhibition.[192] These results suggest that the biological effects of SEs are highly dependent on the transcriptional environment in which they are located.

The study of viral carcinogenesis provides a unique perspective on the dynamic regulation of SEs. Epstein–Barr virus hijacks the RUNX3/RUNX1 SEs of host B cells through EBNA2 and other transcription factors and uses the effector molecule RBP-J of the Notch pathway to reestablish enhancer–promoter interactions, thereby releasing *RUNX1*-mediated growth inhibition.[193] Similarly, the YY1/p65/p300 complex promotes epithelial–mesenchymal transition processes by binding to the *QKI* gene SE in HCC.[194] The ability of this pathogen to reprogram the host epigenome is mechanistically similar to the evolution of SEs in tumor cells. From a technical perspective, the development of FiTAc-seq enables accurate detection of H3K27ac modification and SEs in FFPE samples, providing a new tool for retrospective study of clinical samples.[195] CRISPRi screening of 66 functional enhancers identified in melanoma revealed a new mechanism by which SE mutations remotely regulate tumor suppressor genes such as *PTEN*,[196] highlighting the important role of noncoding region variation in tumor progression.

Studies of breast epithelial lineage differentiation have provided a paradigm for understanding the spatiotemporal specificity of SEs. Basal cells and luminal precursor cells determine cell fate through different chromatin interaction patterns, among which SEs are mainly enriched in the gene body region and participate in the regulation of *Polycomb* silencing elements.[187] This cellular identity determination mechanism is reversed in T-ALL: Ikaros plays a tumor suppressor role by inducing SEs de novo and remodeling chromatin openness, and its loss leads to global disorder of the enhancer landscape.[197] Studies on the PAX3–FOXO1 fusion protein further revealed that the maintenance of SE function requires continuous transcription factor binding to ensure RNA polymerase pausing release and chromatin accessibility.[198] Together, these findings provide a molecular blueprint for the dynamic regulation of SEs, which relies not only on the anchoring of "master regulators" but also on the maintenance of long-range interactions with structural proteins such as Cohesin.[186]

Multi-omics studies in ovarian cancer have revealed novel mechanisms by which SEs drive tumor heterogeneity. By integrating Hi-C and single-cell sequencing data, researchers found that specific SEs activate metastasis-related genes through 3D genome remodeling, and this activation is cancer cell-specific.[199] This compartmental regulatory characteristic is manifested in the differential response of SE subtypes to TEAD inhibitors in gastric cancer peritoneal metastasis,[192] which provides a theoretical basis for therapeutic strategies targeting SEs. Notably, the carcinogenic effect of SEs is often dose-dependent: in neuroendocrine tumors, the degree of transcriptional amplification of *MYCN* is directly related to SE density,[189] whereas the extent of *RCAN1.4*-SE disruption in breast cancer determines the activation threshold of the NFATC1 pathway.[191] This dose–effect relationship suggests that SE may act as an "amplifier" of epigenetic regulation by integrating multiple signal inputs to determine the transcriptional output of tumor cells. SEs are cis-regulatory elements that are highly enriched in transcriptional coactivators in the genome and play a central regulatory role in tumor development. Recent studies have shown that SEs are involved in the regulation of malignant phenotypes such as stemness maintenance, metabolic reprogramming, immune escape, and treatment resistance of tumor cells by driving the abnormal expression of key oncogenes.[200,201] The abnormal activation of SEs involves a variety of molecular mechanisms, including epigenetic modification and remodeling, 3D genomic structure changes, and the synergistic effect of transcription factor networks. These processes have shown significant specificity and are targetable in a variety of solid tumors and hematological malignancies.[202,203] Notably, SE-driven transcriptional programs are often closely related to tumor cell identity determination, and the core nodes of their regulatory network have become important targets for the development of novel anticancer drugs.[204,205]

At the molecular level, SEs recruit transcription machinery by forming phase-separated condensates, thereby achieving efficient activation of target genes. For example, in neuroblastoma, transcription factors such as *MYCN*, *MEIS2*, and *HAND2* form an SE complex at the *IRF2BP2* locus, which promotes the expression of the *ALK* proto-oncogene by regulating chromatin accessibility and maintains the high proliferation characteristics of tumor cells.[205] Similarly, LSD1 and BRD4 form a functional network in the SE region and synergistically activate the *MYC* signaling pathway through a liquid–liquid phase separation mechanism in prostate cancer, while combined inhibition of LSD1 and BRD4 can significantly disrupt the activity of castration-resistant prostate cancer-specific SEs.[202] These findings reveal a hierarchical feature of SE regulation: core transcription factors establish a positive feedback loop by occupying SE regions, which in turn amplifies oncogenic signaling output.[206] Abnormal epigenetic modifications also participate in the regulation of SE function. For example, lactic acid accumulation in drug-resistant ovarian cancer cells induces H4K12 lactylation modification, activates the SE of the *RAD23A* gene through the MYC transcription factor, enhances DNA damage repair ability, and promotes niraparib resistance.[207]

The abnormal activation of SEs is closely related to the variation of genome structure. In colorectal cancer, the *IGF2* gene establishes physical contact with lineage-specific SEs through TAD boundary reorganization, forming a new 3D interaction domain to drive gene overexpression.[208] In T-ALL, a new carcinogenic

mechanism was identified: the deletion of CTCF-binding elements in the intron region of the *FTO* gene liberated the *IRX3* promoter from the "bound state" and instead allowed it to capture the upstream SE of the long noncoding RNA *CRNDE*, leading to abnormal activation of oncogenes.[206] These findings expand our understanding of enhancer-hijacking mechanisms and suggest that, in addition to classical genome reorganization, spatial remodeling of cis-regulatory elements is also an important pathway for oncogene activation. Multi-omics analysis of pancreatic cancer has further confirmed that different molecular subtypes have unique epigenetic landscapes, and basal-like subclass-specific SE-related pathways determine the aggressive characteristics of tumors, suggesting that the SE regulatory network may be a new basis for tumor molecular typing.[209]

The SE-driven noncoding RNA network plays an important role in tumor metastasis. The *E2F1* transcription factor in liver cancer activates the SE of LINC01089, promotes the binding of this lncRNA to the hnRNPM protein, affects m6A modification-dependent mRNA stability by regulating *DIAPH3* gene exon-skipping mutations, and ultimately activates the ERK/Elk1/Snail signaling axis to promote epithelial–mesenchymal transition.[210] In studies of racial differences in breast cancer, the SE of the *SOS1* gene is abnormally activated in African American patients through epigenetic regulation, leading to excessive activation of the c-MET signaling pathway and promoting the characteristics of cancer stem cells. This regulatory mode is closely related to the obesity-associated microenvironment.[211] These findings highlight the pivotal role of SEs in integrating the intrinsic genetic program of the tumor with extrinsic microenvironmental signals.

Therapeutic strategies targeting the SE regulatory network have shown great promise. The *TCF4*-dependent SE-controlled transcriptional network in BPDCN is highly sensitive to BET inhibitors, and drug intervention can induce tumor cell apoptosis.[212] In an alcoholic hepatitis model, BET protein inhibitors significantly reduce neutrophil infiltration by disrupting the SE function of the *CXCL* chemokine gene.[213] Epigenetic editing technologies such as the dCas9-KRAB system can specifically silence SE activity, providing a new tool for precise intervention.[214] Treatment methods such as small-molecule compounds targeting SE components, genome editing, and antisense oligonucleotides have unique advantages in reversing the identity of tumor cells and overcoming treatment resistance.[201]

SEs, as special regions of the genome that are highly enriched in transcriptional regulatory elements, play a central role in tumorigenesis and tumor development. By integrating epigenetic modifications, transcription factor networks, and 3D chromatin structure, these regulatory elements drive the abnormal expression of key oncogenes, thereby affecting cell identity maintenance, tumor heterogeneity, and treatment resistance.[215] Studies have shown that aberrant activation of SEs is closely related to a variety of cancer types, and its regulatory mechanisms involve the specific binding of transcription factors (*ERG* maintains lineage homeostasis by regulating SEs of *DLL4*, *CLDN5*, and other genes in vascular endothelial cells; in prostate cancer, it is oncogenic),[216] epigenetic reprogramming (CDK9 inhibitors induce transcriptional restoration of lymphoma-resistance-related genes by changing the SE landscape),[217] and genomic structural variation (overexpression of the *ERBB2* gene due to the co-occurrence of SEs and structural abnormalities in lung cancer).[218] These findings reveal SEs as an important hub for tumor molecular typing and targeted intervention.

In terms of molecular mechanisms, SEs achieve functional specificity through unique epigenetic features and recruitment of transcription machinery. In colorectal cancer, the SEs of *PHF19* and *TBC1D16* form a core regulatory loop through transcription factors such as *KLF3* to directly promote tumorigenesis.[219] Similarly, DNA methyltransferases DNMT3A/3B maintain SE activity in epidermal stem cells by differential regulation of hydroxymethylation (*TET2*-dependent) and methylation patterns in enhancer regions, and their loss leads to cell identity disorders.[220] Notably, dynamic reprogramming of SEs can confer plasticity to tumor cells. For example, *PRRX1* drives the transformation of fibroblasts into oncogenic myofibroblasts by reshaping the SE landscape.[221] The dominant role of SEs in tumor heterogeneity was further confirmed by four SE-driven apparent subtypes in neuroblastoma, including a mesenchymal subtype associated with recurrence.[222]

Aberrant activation of SEs often collaborates with structural variants of the genome to drive tumorigenesis. For example, chromosomal deletion in medulloblastoma leads to the relocalization of GFI1/GFI1B genes near SEs and contributes to carcinogenesis,[223] while SEs disrupt protein homeostasis through the activation of *PPP1R15B* in multiple myeloma, contributing to treatment resistance.[224] In addition, *MICAL2*, as an SE target gene, promotes metastasis by regulating *KRAS* signaling and actin depolymerization in pancreatic cancer,[225] while chemotherapy resistance in ovarian cancer is closely related to SE-mediated distal enhancer network remodeling.[226] These findings highlight the central role of SEs in the adaptive evolution of tumors.

At the level of transcriptional regulation, SE function depends on the synergy of its internal components. For example, in the SE cluster of the *FGF5* gene, intronic enhancers amplify transcriptional output through super-accumulation of RNA polymerase II.[227] A further complexity is that tumor-specific SEs can be transcribed to generate functional noncoding RNAs (such as oncogenic seRNAs) that amplify oncogenic signals by stabilizing chromatin loops or recruiting mediator complexes.[228] This multi-layered regulatory network provides new insight into tumor-specific transcriptional dependence. It also lays a theoretical foundation for the development of small-molecule inhibitors targeting SEs (such as overcoming lymphoma drug resistance by inhibiting PI3K/AKT or *PIM* pathways) or epigenetic intervention strategies (such as targeting *PPP1R15B* to restore the ER stress response).[217,224] SEs, as large clusters of enhancers in the genome, are enriched with high levels of H3K27ac and Mediator proteins and have become core regulatory elements in tumor development. Studies have shown that SEs play a key role in a variety of cancers by driving oncogene expression, maintaining tumor cell identity, and promoting epigenetic reprogramming.[229,230] Its aberrant activation can be achieved through somatic mutations (such as acquired mutations in *MYB* binding sites in T-ALL), transcription factor hijacking (such as reprogramming of hematopoietic stem cell enhancers by the TCF3-HLF fusion protein), or dysregulation of epigenetic modifications (such as SE functional impairment due to loss of *KMT2D*).[231–233] These findings reveal the central role of SEs in tumor heterogeneity, treatment resistance, and targeted intervention, and provide a new perspective for understanding the transcriptional regulation of cancer.

At the molecular level, SEs form a hub of transcriptional activity through their unique spatial conformation and phase separation properties. For example, loss of *SMARCB1* leads to the loss of the binding ability of the SWI/SNF complex to common enhancers but selectively retains the regulatory function of SEs, thereby maintaining the expression of key oncogenes such as *SPRY1* and *SOX2* in rhabdoid tumors.[229] Similarly, *PRRX1*-mediated SE reprogramming in neuroblastoma induces a state switch between

mesenchymal cells and adrenergic cells, and this plasticity is directly linked to chemotherapy resistance and recurrence.[234] In addition, SEs also amplify oncogene expression through nonclassical mechanisms such as nuclear pore localization (WNT/*AHCTF1*-mediated nuclear export of *MYC* alleles) and RNA-binding proteins (stabilization of *E2F* transcripts by *IGF2BP1*).[235,236] These findings collectively suggest that SEs, through multi-dimensional molecular collaboration, construct the core framework of tumor-specific transcriptional networks.

The activity of tumor-specific SEs is highly dependent on the synergistic action of key transcription factors and epigenetic regulators. For example, in squamous cell carcinoma, *TP63* and *SOX2* co-activate the SE of *CCAT1* to form a DNA/RNA/protein complex that drives *EGFR* signaling.[237] However, BRD4 and Mediator are enriched on the SE of *MYC* in multiple myeloma, which makes it selectively sensitive to BET inhibitors.[238] This dependence provides a breakthrough for targeted therapy: *KMT2D*-deficient lung cancer cells are sensitive to glycolytic inhibitors due to an abnormal glycolytic pathway caused by *PER2*-SE damage.[233] However, BTYNB, a compound that targets the disruption of IGF2BP1–RNA interaction, can effectively inhibit *E2F*-driven tumor growth.[236] These cases highlight the value of SE-related molecular mechanisms in guiding the design of precision therapy.

SE-driven tumor heterogeneity is not only reflected among cell subsets (e.g., the biphasic differentiation state of neuroblastoma), but also in tissue-specific regulatory networks. Molecular typing analysis of glioblastoma has found that the SE landscape of different subtypes is highly correlated with the expression patterns of core transcription factors (such as MES type and AC1 type) and lncRNAs.[239] Similarly, SEs in adult T-cell leukemia are enriched in T cell activation pathway genes, while *TAL1*-SE generated by somatic mutations in T-ALL relies on MYB/CBP recruitment.[230,231] This tissue specificity suggests that SEs may act as "molecular memory" elements that retain developmental lineage signatures while being hijacked by tumors to maintain a malignant phenotype.

From a technical perspective, SE research is promoting the deep integration of cancer omics data. The Cistrome Cancer platform achieves SE target gene prediction and transcription factor activity modeling by integrating TCGA data and chromatin mapping,[240] while the introduction of phase separation theory provides a new framework for explaining the transcriptional burst pattern and multiple gene co-activation of SEs.[241] These advances not only deepen the understanding of SE biology, but also lay the foundation for the development of novel diagnostic markers and combination therapies based on SE characteristics.

SEs, as high-density enhancer clusters in the genome, play a central role in tumorigenesis and development by driving the abnormal expression of key oncogenes. Studies have shown that SEs are highly heterogeneous in a variety of cancers, and the dynamic formation and functional regulation of SEs involve the complex interaction of chromatin remodeling, transcription factor networks, and epigenetic modification.[242,243] In terms of molecular mechanisms, SEs form a transcription hub by recruiting cofactors such as BRD4 and MED1 to activate the expression program of downstream target genes. This dependence makes SEs a potential target for cancer treatment.[244,245] Of note, aberrant activation of SEs can be achieved through a variety of pathways, including genomic rearrangement, copy number amplification, or epigenetic reprogramming. For example, in 3q26.2-rearranged leukemia, the G2DHE region acquires SE properties and drives *EVI1* oncogene overexpression,[246] while in adenoid cystic carcinoma, the *MYB* locus and SE chromosomal translocation form a positive feedback loop to maintain tumor cell identity.[247]

In solid tumors, the heterogeneity of SEs is tissue-specific and tumor subtype-specific. The SE profile of TNBC is significantly different from other subtypes, and it specifically regulates the expression of *FOXC1*, *MET*, and other genes, revealing the molecular basis of SE-driven tumor subtype differentiation.[248] The SEs of gastric cancer can be divided into three types according to somatic mutation status: gained, lost, and unchanged. Among them, acquired SEs colocalize with *CDX2*/HNF4α transcription factors and are enriched in cancer risk SNPs.[249] *FOSL1* in head and neck squamous cell carcinoma constructs an SE network by binding to the Mediator complex to activate the expression of metastasis-associated genes such as *SNAI2*. This mechanism can be targeted by small-molecule inhibitors in patient-derived xenograft models.[250] These findings suggest that the SE specificity of spatial and temporal control is an important driving force of cancer cell plasticity.

Functionally, SEs contribute to tumor malignant phenotypes by orchestrating multi-dimensional molecular events. In osteosarcoma, *MYC* activates genes such as *CDK6* and *TGFB2* by occupying SE regions to form a transcriptional amplification effect, while SE inhibitors such as THZ1 and JQ1 can effectively block this pathway.[245] In inflammatory responses, NF-κB-mediated SE dynamic remodeling leads to phenotypic switching of endothelial cells, which relies on BET bromodomain proteins to transmit chromatin signals.[251] In addition, SEs are also involved in the regulation of tumor immune escape: senescent cells activate the SASP program through BRD4-dependent SE remodeling, and BET inhibitors can disrupt this immune surveillance mechanism.[252] In B-cell lymphomas, *CREBBP* deficiency leads to SE network dysregulation and affects the expression of genes related to B-cell receptor signaling and antigen presentation,[253] highlighting the pleiotropic role of SEs in the regulation of the tumor microenvironment.

Studies on the molecular architecture of SEs provide new ideas for targeted intervention. As a marker of SE activity, the expression peak of eRNA can precisely locate the functional core region of SEs, and eRNA participates in chromatin remodeling by recruiting SWI/SNF complexes.[243,254] In ovarian cancer, the SE of *ALDH1A1* relies on BRD4 to maintain its transcription, and JQ1 enhances the efficacy of cisplatin by disrupting the interaction between this SE and the promoter.[244] CRISPR screening further revealed that SE components have a functional hierarchy: early enhancers are involved in gene regulation before cell differentiation, while late elements are indispensable for terminal differentiation.[255] This scheduled assembly feature specifies SE regulators and lays the theoretical foundation for stage-specific intervention. SEs, as cis-regulatory clusters of highly active components in the genome, integrate identity complexes to drive transcriptional regulation, metabolic reprogramming, and malignant phenotypes in tumor cells and have become a core focus of cancer research. These regulatory elements preferentially activate the expression of oncogenes, transcription factors, and noncoding RNAs by forming spatial topology or recruiting phase separation condensates, thus establishing "transcriptional addiction" in a variety of tumors such as lung cancer, TNBC, and HCC.[256–258] Notably, aberrant SE activation is not only caused by genomic amplifications (such as NKX2-1 co-amplification in lung adenocarcinoma) or chromatin interaction dysregulation,[259,260] but also induced by exogenous factors such as inflammatory signals in the tumor microenvironment. For example, SE activation of *PDZK1IP1* in colorectal cancer is dependent on local cytokine stimulation.[261] This multi-level regulatory mechanism makes SEs a key hub connecting genetic variation, epigenetic modification, and tumor heterogeneity.

Table 2. Representative drugs/intervention strategies targeting super-enhancers (SEs)

Target/Strategy	Representative agents/tools	Primary mechanism of action	Relevant cancer types
BET protein inhibitors	JQ1, I-BET, OTX-015	Competitively bind BRD4, disrupt SE condensates, inhibit oncogene transcription	Leukemia, lymphoma, TNBC, prostate cancer
Transcriptional kinase inhibitors	THZ1 (CDK7), BAY1251152 (CDK9)	Inhibit transcriptional initiation/elongation, selectively block SE-driven genes	T-ALL, small cell lung cancer, neuroblastoma
Epigenetic modulators	LSD1 inhibitors, HDAC inhibitors (e.g., SAHA), EZH2 inhibitors	Alter histone modification states, remodel SE activity landscape	Erythroleukemia, ovarian cancer, EBV-associated tumors
Phase separation disruptors	GSK-J4, Asciminib derivatives	Disrupt phase-separated condensates of TFs or coactivators	Osteosarcoma, chronic myeloid leukemia
CRISPR-based epigenetic editing	dCas9-KRAB, dCas9-p300	Precisely silence or activate specific SEs for functional study and potential therapy	T-ALL, esophageal squamous cell carcinoma, glioma
Immune microenvironment modulation	Anti-IL-2Rα ADC, CDK7 inhibitors (for CRS mitigation)	Target SE-driven immune checkpoints or cytokine storms	Anaplastic large cell lymphoma, CAR-T-associated CRS
Combination therapies	BETi + Immunomodulators, CDK7i + PARPi	Multi-pathway synergy to overcome drug resistance and tumor heterogeneity	Multiple myeloma, ovarian cancer, acute myeloid leukemia

ADC, antibody–drug conjugate; BET, bromodomain and extra-terminal domain; BETi, BET protein inhibitor; BRD4, bromodomain-containing protein 4; CAR-T, chimeric antigen receptor T cell; CDK7, cyclin-dependent kinase 7; CDK7i, CDK7 inhibitor; CRISPR, clustered regularly interspaced short palindromic repeats; dCas9, catalytically dead Cas9; EBV, Epstein-Barr virus; EZH2, enhancer of zeste homolog 2; HDAC, histone deacetylase; LSD1, lysine-specific demethylase 1; PARPi, poly ADP-ribose polymerase inhibitor; SAHA, suberoylanilide hydroxamic acid ; SE, super-enhancer; T-ALL, T cell acute lymphoblastic leukemia; TF, transcription factor; TNBC, triple-negative breast cancer.

From the perspective of molecular mechanisms, SEs construct the oncogenic network through phase separation and cooperation of core transcription factors. In head and neck squamous cell carcinomas, the long-chain noncoding RNA *CYTOR* promotes the formation of phase-separated condensates of *FOSL1*, driving SE-dependent stem cell and metastasis-related gene expression.[262] Similarly, in juvenile sarcoma, the EWS-FLI1 fusion protein coordinates with SE *MEIS1* to activate *APCDD1* downstream targets, promoting a survival transcription loop.[263] SEs also extend their functional boundaries by regulating RNA processing: for example, SEs not only enhance miRNA transcription but also facilitate pri-miRNA processing by recruiting Drosha/DGCR8 complexes, thus shaping tissue-specific miRNA networks.[264] This multidimensional regulation is particularly prominent in genes such as *TP73*, whose SE-driven expression, together with intronic region deletion, promotes clonal evolution in adult T-cell leukemia.[265]

Metabolic reprogramming is an important mechanism by which SEs affect the malignant phenotype of tumors. SEs directly regulate the expression of metabolic enzymes in lung adenocarcinoma by controlling the dose effect of lineage transcription factors such as NKX2-1.[259] In colorectal cancer, SE-activated *PDZK1IP1* helps tumor cells resist oxidative stress by enhancing the reducing power of the pentose phosphate pathway.[261] In addition, SE-related lncRNAs (such as HSAL3 in HCC) can regulate signaling pathways such as *NOTCH*, while targeted degradation of their eRNA or SEs themselves can significantly inhibit tumor growth.[257,258] This coupling mechanism of metabolism and transcription suggests that SEs may act as a "metabolic checkpoint" to coordinate the energy demand and epigenetic remodeling of tumor cells.[266]

Therapeutic strategies targeting SEs have shown translational potential (Table 2). JQ1, a bromodomain inhibitor of BET, preferentially disrupts SE-mediated transcription initiation and elongation and induces cell death by inhibiting *PAX5*-dependent SE nodes in chronic lymphocytic leukemia.[267] Advances have also been made in specific interventions targeting SE components such as transcription factor binding sites or phase separation proteins: degradation of BRACHYURY in chordoma selectively disrupts its SE autoregulatory loop with higher specificity than broad-spectrum transcriptional inhibition.[268] In addition, CRISPR-based functional analysis of SEs provides new targets for refractory tumors such as TNBC. For example, editing of the SE at the *PODXL* locus can inhibit metastasis.[257] However, SE-targeted therapy still needs to solve problems of cell type specificity and off-target effects, and its clinical translation depends on the in-depth analysis of SE dynamic assembly and 3D interactions.[260,269]

Research on inhibitors targeting core components of SEs is rapidly transitioning from preclinical to clinical stages, presenting a complex landscape of efficacy intertwined with challenges. Recent clinical data indicate that the combination of BET inhibitors (e.g., RO6870810) with immunotherapy may be hindered by significantly increased toxicity without synergistic benefits, highlighting the urgency of toxicity management and overcoming resistance mechanisms, such as kinase pathway reactivation.[270] Concurrently, CDK7 inhibitors (e.g., the novel agent TY-2699a) have entered clinical expansion trials for TNBC, with preclinical studies revealing a synthetic lethality effect when combined with BET inhibitors, offering new avenues for combination strategies. In the realm of epigenetic targets, the highly selective and reversible LSD1 inhibitor X-L177 has been approved for clinical trials, with its ability to cross the blood–brain barrier and mechanisms modulating the tumor immune microenvironment broadening therapeutic prospects. Meanwhile, EZH1/2 inhibitors (such as HH2853, Valemetostat) have demonstrated high response rates in lymphomas and solid tumors with specific genetic backgrounds (such as SWI/SNF complex deficiencies), underscoring that patient selection based on precise biomarkers has become a core strategy in clinical trial design (such as "basket trials") to enhance efficacy and manage hematological toxicities. Collectively, these advances depict a trajectory for SE-targeted therapy moving toward in-depth integration focused on overcoming resistance, enabling precision combinations, and rigorously optimizing the therapeutic window based on molecular subtyping.

Limitations and challenges

Although the central role of SEs in tumor regulation is increasingly understood, their study and application still face multiple limitations and challenges. First, the high heterogeneity and dynamic nature of SEs lead to significant functional variations across different tumor types, developmental stages, and microenvironments, complicating unified mechanistic interpretations and the screening of universally applicable targets. Second, current technologies, such as chromatin conformation capture and single-cell sequencing, have limitations in resolution, throughput, and live-cell dynamic observation, making it difficult to fully capture the 3D architecture, phase separation dynamics, and real-time interactions of SEs with the transcriptional machinery. Furthermore, therapeutic strategies targeting SEs (such as BET inhibitors, CDK7 inhibitors), while promising in preclinical models, commonly encounter issues such as off-target effects, development of drug resistance, and tissue-specific toxicity. The blurred functional boundaries between SEs and classic enhancers, the redundancy of regulatory networks, and the plasticity of epigenetic modifications also add complexity to precise interventions. Moving forward, advances in high-resolution spatiotemporal omics technologies, the development of more specific small-molecule compounds, and the analysis of SE regulatory logic within multi-level integrated models will be essential to drive their clinical translation.

Conclusions

SEs drive tumorigenesis through multidimensional mechanisms: 1) phase separation-mediated transcriptional hub formation (e.g., YY1-BRD4 condensates); 2) enhancer hijacking leading to aberrant oncogene activation (e.g., HPV integration to generate ecDNA); and 3) metabolic-epigenetic coupling (e.g., lactylation modification regulating DNA repair). Targeting strategies include BET inhibitors to disrupt SE architecture (JQ1), CDK7 inhibitors to block transcription elongation (THZ1), and epigenetic editing (CRISPR-dCas9). In the future, the spatiotemporal specificity of SE dynamic regulation should be addressed, and combination therapies based on SE molecular typing should be developed.

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Conflict of interest

One of the authors, Jian Pan, has been an editorial board member of *Oncology Advances* since July 2023. The authors have no other conflicts of interest to declare.

Author contributions

Data collection, writing-original draft (DW), investigation (YT), writing-review and editing (YT, ZZ, JP), bioinformatics support (ZZ), overall guidance (ZZ, JP), supervision (JP), and funding acquisition (JP). All authors read and approved the final manuscript.

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