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Super-enhancers in hepatocellular carcinoma: regulatory mechanism and therapeutic targets

Xuejin Lu[1], Meizi Zhu[1], Xingyue Pei[1], Jinhu Ma[1,3], Rui Wang[1], Yi Wang[1], Shuwen Chen[1], Yan Yan[2*] and Yaling Zhu[1,2*]

Abstract

Super-enhancers (SEs) represent a distinct category of cis-regulatory elements notable for their robust transcriptional activation capabilities. In tumor cells, SEs intricately regulate the expression of oncogenes and pivotal cancer-associated signaling pathways, offering significant potential for cancer treatment. However, few studies have systematically discussed the crucial role of SEs in hepatocellular carcinoma (HCC), which is one of the most common liver cancers with late-stage diagnosis and limited treatment methods for advanced disease. Herein, we first summarize the identification methods and the intricate processes of formation and organization of super-enhancers. Subsequently, we delve into the roles and molecular mechanisms of SEs within the framework of HCC. Finally, we discuss the inhibitors targeting the key SE-components and their potential effects on the treatment of HCC. In conclusion, this review meticulously encapsulates the distinctive characteristics of SEs and underscores their pivotal roles in the context of hepatocellular carcinoma, presenting a novel perspective on the potential of super-enhancers as emerging therapeutic targets for HCC.

Keywords Hepatocellular carcinoma, Super-enhancer, Therapeutic targets

Introduction

Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer, which accounts for 90% of all new occurrences of primary liver cancer worldwide [1]. Due to the asymptomatic nature of the disease, most HCC patients are diagnosed at an advanced stage, which contributes to the fact that the prognosis of HCC is very poor (the 5-year OS rate is approximately 18%) [2, 3]. Although clinically beneficial treatment methods for HCC include surgical resection [4], transplantation [5], ablation [6] and transcatheter arterial chemoembolization [7], there is basically no effective anticancer medication. Therefore, it is urgent to fully understand the crucial mechanisms for the development of new therapies.

Enhancers and super-enhancers are receiving significant attention for their pivotal roles in gene transcription, which is a highly intricate and meticulously coordinated

*Correspondence:
Yan Yan
yanyht@163.com
Yaling Zhu
zhuyaling@ahmu.edu.cn
[1]Department of Pathophysiology, College of Basic Medical Science, Anhui Medical University, Hefei, China
[2]Laboratory Animal Research Center, College of Basic Medical Science, Anhui Medical University, Hefei, China
[3]Department of Hepatobiliary Surgery, Centre for Leading Medicine and Advanced Technologies of IHM, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China

process in the pathogenesis of complex diseases in humans [8–11]. Enhancers are distant noncoding cis-regulatory elements that play a vital role in controlling cell-type-specific spatiotemporal gene expression programs by attracting specific transcription factors that increase promoter activity to activate target genes, often through long-range chromosomal interactions [12, 13]. Super-enhancers are large clusters of enhancers with abnormally high levels of transcriptional activation ability than typical enhancers (TEs) [14]. Similar to the TEs, SEs can be bound by some factors, including transcription factors (TFs), coactivators, chromatin regulators, and the RNA Pol II complex. However, there are substantial structural and functional differences between super-enhancers and typical enhancers, as shown in Fig. 1. SEs are characterized by a dense occupancy of transcription factors, with an average of 10-fold higher density than TEs [15–17]. Notably, many of the transcription factors that bind to super-enhancers are integral to key oncogenic signaling pathways, such as Wnt and TGF-β [18, 19]. And SEs-related genes are critical for maintaining cancer cell identity and promoting tumorigenic gene transcription [20]. Additionally, multiple studies elucidated that inhibitors targeting SE structures have achieved significant clinical results in cancers, including prostate cancer, colorectal cancer and acute myeloid leukemia [21–23]. Banerji et al. revealed that many types of tumor cells are particularly sensitive to the inhibition of the SEs complexes, and inhibitors of the SEs complex have demonstrated positive anticancer effects [24]. Consequently, SEs are capable of driving the transcription of their target genes at a much higher rate and play a more critical role in the development and progression of cancers, which are potential new targets for cancer therapy.

However, there is a scarcity of studies that systematically elucidated the role of SEs in HCC and its new prospects for therapeutic targets. Thus, this review summarizes the identification, formation and organization approaches of SEs, focusing on the mode of mechanism as well as the drug inhibitors and therapeutic effect for targeting SEs, which may provide new insights for future research and optimum treatment strategies in HCC.

Identification of super-enhancers

Young et al. were the pioneers in identifying a unique class of enhancers in mouse embryonic stem cells (mESCs) that were unusually dense with transcription factors and the Mediator complex. They designated these extensive clusters of enhancers, which significantly influence the transcriptional expression of genes, as 'super-enhancers' [14, 25]. Here we conclude three main steps of identifying SEs (Fig. 2): (1) Achieving the region of active enhancers. First, techniques such as chromatin immunoprecipitation sequencing (ChIP-seq), Assay for Transposase Accessible Chromatin using sequencing (ATAC-seq) are performed to map the sequences of transcription factors (e.g. Oct4, Sox2, and Nanog), Mediator, and histone modifications (H3K27ac and H3K4me1) [14, 26–29] across the genome by using Burrows-Wheeler Aligner (BWA) [30]. Then, run Model-based Analysis for ChIP-Seq version 2 (MASC2) to obtain objective peak files [31]. (2) Stitching enhancer. Bedtools version 2.27.0 is used to merge neighboring enhancers (within 12.5 kb) into one group to capture dense enhancer clusters [32]; (3) Identifying super-enhancers. ROSE algorithm (http://younglab.wi.mit.edu/super_enhancer_code.html) is a tool for finding SEs using gff file (regions of enhancer) and bam file (the factor density of enhancers). After ranking stitched enhancers according to their ChIP-seq signals, SEs are separated from typical enhancers based on a cutoff value [14, 27].

The formation and organization of super-enhancers

Super-enhancers gradually recruit biomolecules to form transcription complexes

SE-regulated gene expression in mammalian cells is a biological process in which biomolecules act in cooperation with each other. The transcription complexes recruited by SEs contain biomolecules including

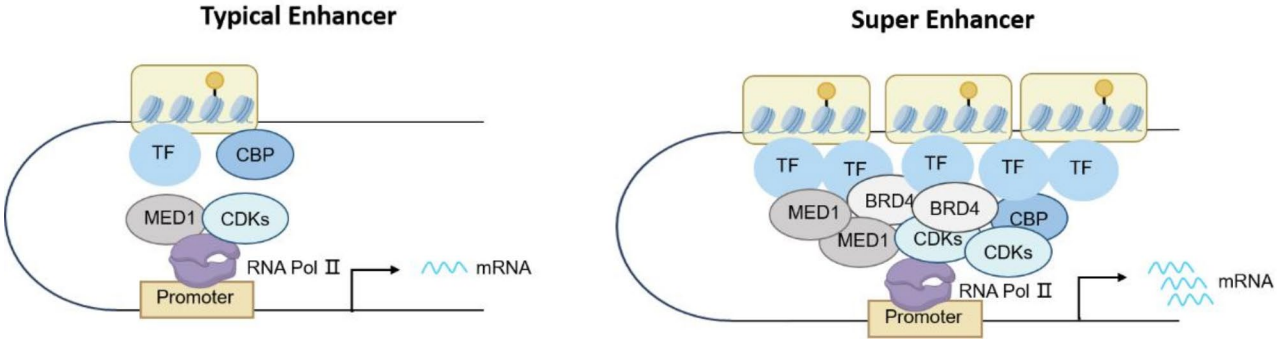

Fig. 1 The difference between typical enhancers and super-enhancers

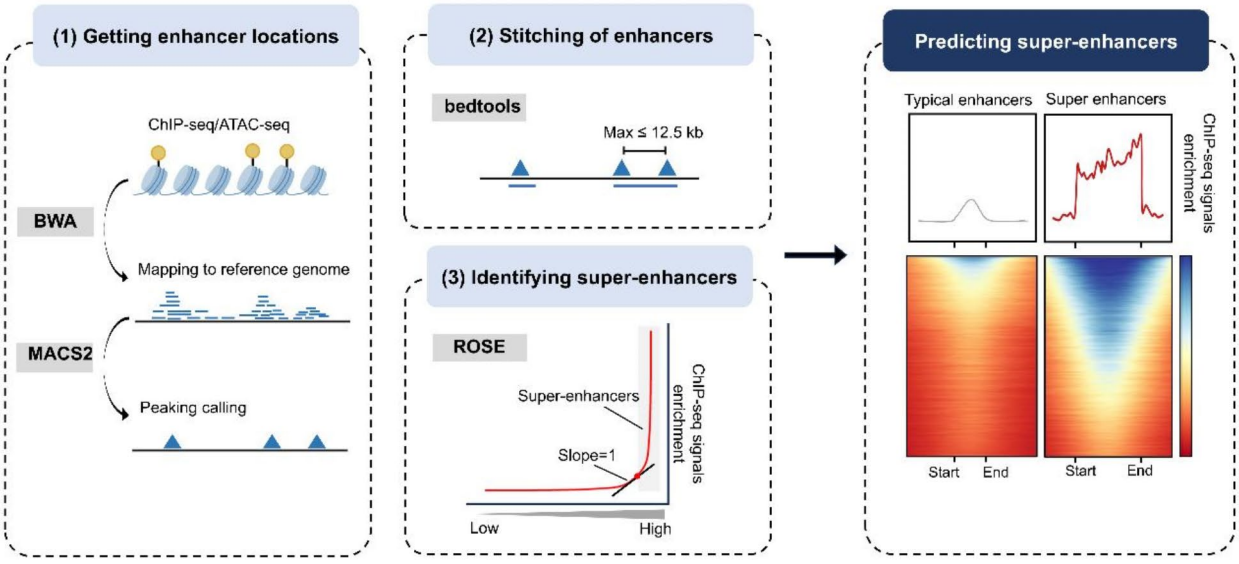

Fig. 2 The specific process of SE identification and advanced techniques

transcription factors, chromatin regulators (e.g. CBP/P300 and HDAC), transcriptional co-activators (e.g. MED1 and BRD4) and RNA polymerase II (RNA pol II) [33–35]. However, it is unclear how SEs recruit these transcriptional regulators. Here, we briefly describe the process by which SEs form transcription complexes stepwise (Fig. 3A). First, pioneer factors bind to highly folded DNA and establish the accessible chromatin conformations to promote the binding of additional transcriptional elements [36–39]. Pioneer factors such as FOXA and SOX2 are instrumental in opening chromatin by facilitating the separation of terminal nucleosomal DNA from histone octamer [40–43]. Notably, the DNA-binding domain (DBD) of the pioneer factor is crucial for recognizing specific DNA sequence motifs, which determines the precise location of SEs in the genome [44, 45]. Subsequently, the pioneer factor-induced changes of chromatin accessibility transform "closed chromatin" with high levels of H3K9me2 into "primed enhancers" characterized by H3K4me1 [46–49]. Thereafter, the primed enhancers will divide into two directions depending on the type of co-transcription factors they recruit: (1) Becoming active enhancers by recruiting the co-activator CBP/P300 and completing the recruitment of H3K27ac [50, 51]; (2) Becoming inactive enhancers due to the presence of components such as histone deacetylases (HDACs) in the recruitment complex [52, 53]. Finally, BRD4 binds to the active enhancer due to its ability to read highly acetylated histones and serves as a bridge to recruit Med1 and RNA pol II [54, 55]. It is noteworthy that Mediator acts as a coordinator to mediate the interaction between transcription factors and RNA polymerase II machinery, facilitating communication between SEs and the target gene promoters. Together, SEs regulate chromatin accessibility by modulating histone modifications, recruit multiple biomolecules, and ultimately form transcriptional activation complexes, which lays the compositional foundation for the formation of the more complex structures of SEs.

Super-enhancers organize intricate structure to achieve efficient and precise regulation

Compared to typical enhancers, SEs exhibit extended lengths and elevated densities of transcription factors, which enhance transcriptional efficiency and make SEs more effective in regulating gene expression. Furthermore, recent studies have shown that SEs possess more intricate structures at the three-dimensional chromatin level. Herein, we propose the "compartments-Topologically associating domains (TADs)" model (Fig. 3B) to explain the advanced structural features of SEs and reveal how SEs play an efficient and precise role in transcriptional regulation. For its efficiency, the main reason is the intrinsically disordered regions (IDRs) of BRD4 and MED1(two key SEs transcriptional coactivators), which mediate the formation of phase-separated structures and promote compartment formation to facilitate efficient biochemical reactions [56–60]. For its precision, CCCTC-binding factor (CTCF) and cohesion, which were widely detected at the boundaries of SEs, promote the process of loop-extrusion and determine the TAD distinct boundaries to maintain the precise regulation of genes [42, 61–66]. Overall, the organization of the genome is the result of the interaction between phase-separation-driven compartments and loop-extrusion-driven TADs.

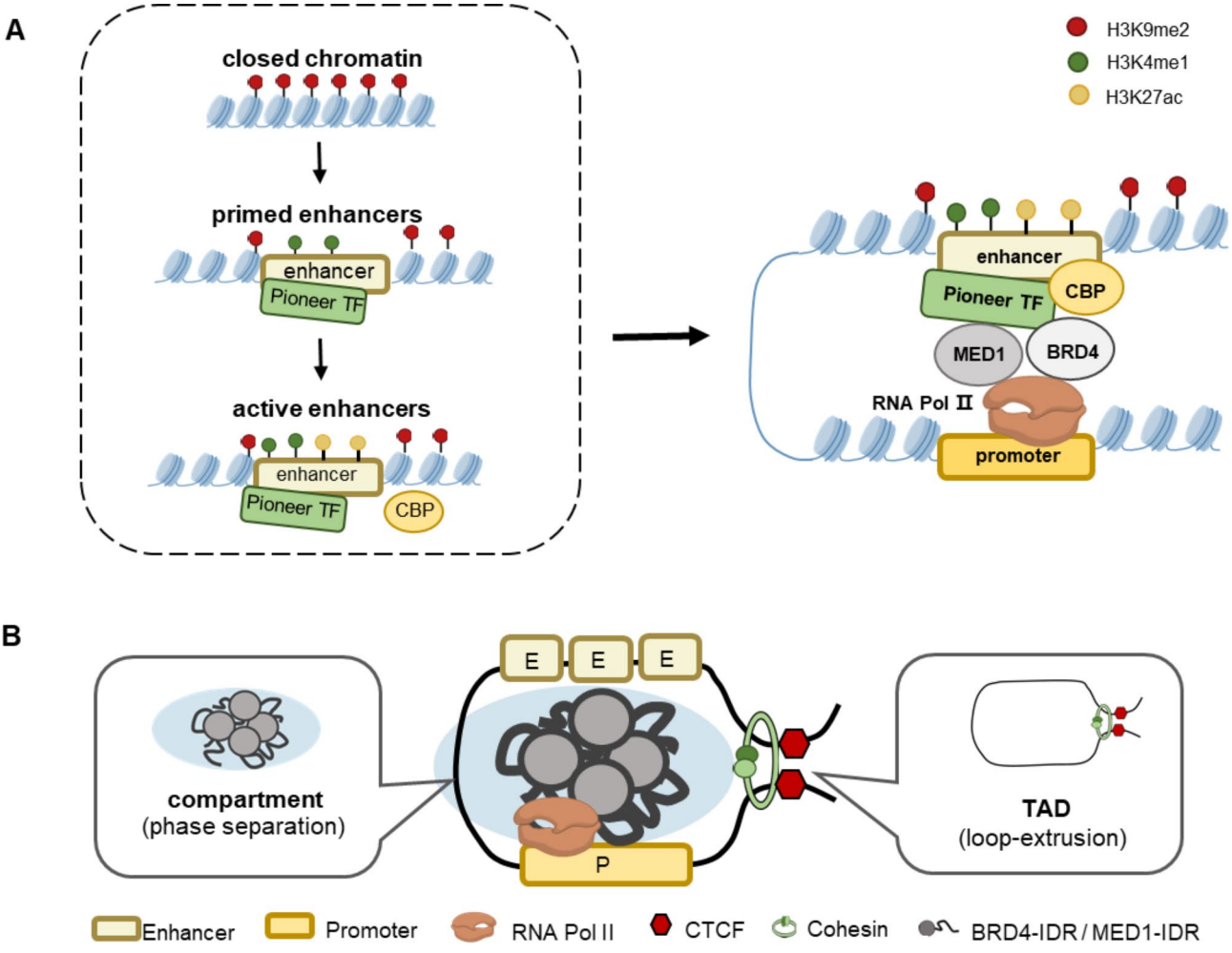

Fig. 3 Super-enhancers recruit transcription complexes and form 3D structures. (**A**) Pioneer factors bind to closed chromatin with a high level of H3K-9me2 and transform it into "primed enhancers" characterized by H3K4me1. Through the recruitment of CBP/P300, primed enhancers can get H3K27ac at nucleosomes and become active enhancers. Finally, the histone "reader" BRD4 binds to the active enhancers and recruits Med1 and RNA pol II, which form transcription complexes at the SE region. (**B**) Compartments - Topologically associating domains" model of super-enhancers. The IDR of BRD4 and MED1 mediate the formation of phase-separated and promote compartment formation. The CTCF and cohesion promote the process of loop-extrusion and determine the TAD boundaries

The roles and molecular mechanisms of SEs in HCC

There is mounting evidence suggesting that SEs exert pivotal control over central hallmarks of cancer, including abnormal cell proliferation, migration, invasion, and epithelial-mesenchymal transition (EMT) [67]. In the progression of HCC, SEs not only influence protein-coding genes but also play a crucial role in the transcriptional regulation of non-coding RNAs (ncRNAs), such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). Here, we summarize the roles and molecular mechanisms of SEs in the development of HCC, which will provide the potential targets for the treatment of HCC (Table 1; Fig. 4).

Super-enhancers upregulate the expression of oncogenes directly

Compared with typical enhancers, super-enhancers have a higher density of histone modifications and can bind a higher density of transcription factors to tremendously promote gene expression [25, 68]. Here, we summarize some oncogenes upregulated by super-enhancers in HCC, such as SPHK1, SPIDR, AJUBA, and QKI. SPHK1 is a kinase that mediates sphingosine phosphorylation to produce sphingosine-1-phosphate (S1P), which plays an important role in sphingolipid metabolism of HCC and regulates a variety of pro-survival functions [69]. After interfering with SE-promoter interactions by CRISPR, the expression level of SPHK1 was significantly reduced, leading to decreased proliferation and migration of hepatocellular carcinoma cells [70]. Besides, SPIDR is an HCC-specific gene that is closely associated with the

Table 1 Recent studies on SEs in hepatocellular carcinoma

SE-related-targets	Classification	Enriched TF	Implication	Potential drug
SPHK1	gene	-	Cell proliferation, migration	SKI-II, CBP30, JQ1 and THZ1
SPIDR	gene	NRF1	Cell proliferation, oxidative stress response	JQ1
AJUBA	gene	TCF4	Cell proliferation, migration, invasion, EMT, Akt/GSK-3β/Snail pathway	-
QKI	gene	YY1/p65/p300 complex	Cell proliferation, migration, invasion, EMT	JQ1, Hyperoside
SIRT7	gene	C/EBPβ	Cell proliferation, invasion, EMT	JQ1
miR-9	microRNA	Twist1-YY1-p300 complex	Cell proliferation, migration, invasion, EMT	Metformin
LINC01004	lncRNA	E2F1	Cell proliferation, migration	-
HCCL5	lncRNA	ZEB1	Cell proliferation, migration, invasion, EMT	-
LINC01089	lncRNA	E2F1	Cell proliferation, migration, invasion, EMT, ERK/Elk1/Snail axis	-
lncRNA-DAW	lncRNA	HNF4G	Cell proliferation, migration, invasion, Wnt/β-catenin pathway	-
HSAL3	lncRNA	HCFC1, HSF1	Cell proliferation, migration, NOTCH signaling	JQ1

EMT, epithelial-mesenchymal transition;

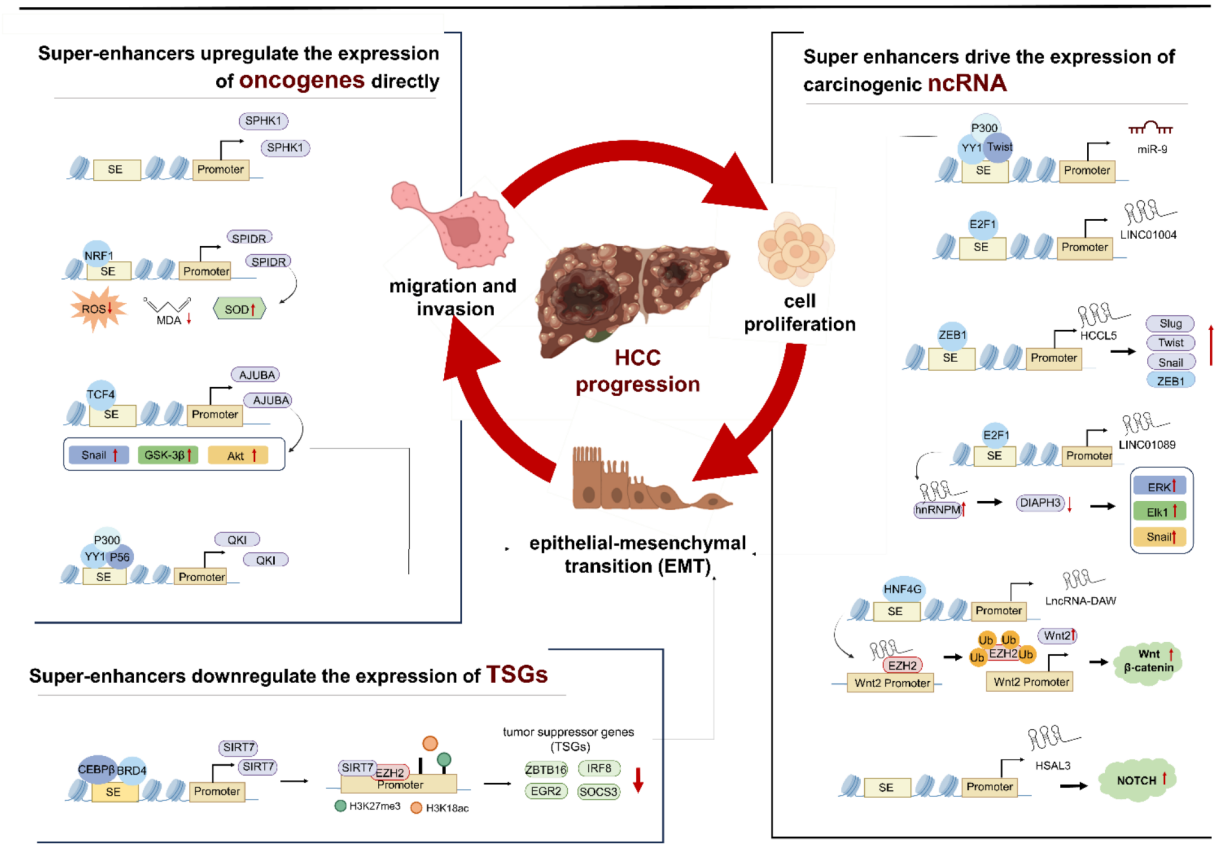

Fig. 4 The roles and molecular mechanisms of super-enhancers in HCC

oxidative stress response. The transcription factor NRF1 activates the transcription of SPIDR by binding to its SE region. Silencing SPIDR or NRF1 results in increased levels of reactive oxygen species (ROS) and malondialdehyde (MDA), and decreased levels of superoxide dismutase (SOD) in HCC cells, indicating an impairment of antioxidant capacity [71]. Additionally, it is noteworthy that numerous SE-driven oncogenes, including AJUBA and QKI, exert a pivotal role in facilitating EMT [72, 73]. Specifically, AJUBA is a SE-associated gene regulated by the transcription factor TCF 4 in HCC, with high expression correlated with aggressive phenotype and poor prognosis in patients [74]. High levels of AJUBA expression induce EMT by recruiting tumor necrosis factor-associated factor 6 (TRAF6), enhancing Akt phosphorylation, and activating the Akt/GSK-3β/Snail pathway. Furthermore, during the transcription of alternative splicing factor Quaking (QKI), the super-enhancer of QKI which was bind by YY1/p65/p300 complex can activate the transcription of QKI gene. This activation promotes EMT and facilitates the migration and invasion in hepatocellular carcinoma cells [75]. Together, SEs accelerate cell proliferation, migration, invasion, and EMT mainly through genes such as SPHK1, AJUBA, QKI and SPIDR, promoting the malignant progression of hepatocellular carcinoma.

Super-enhancers downregulate the expression of tumor suppressor genes through epigenetic modification

The process of carcinogenesis is highly intricate, involving not only alterations in oncogene function but also perturbations in the function of tumor suppressor genes (TSGs). In this context, SEs possess the capability to modulate TSGs expression through the influence on their epigenetic modifications. In HCC cells, SIRT7-SE enhances SIRT7 transcription by promoting co-occupancy of C/EBPβ and BRD4. Notably, Sirtuin 7 (SIRT7) can induce genome-wide deacetylation of H3K18 and physically interact with the H3K27 methyltransferase EZH2 to promote cooperative epigenetic silencing. This ultimately results in the suppression of TSGs such as EGR2, IRF8, SOCS, and ZBTB, which are critical for regulating metabolism and immunity, thereby promoting the tumorigenicity of HCC cells [76]. In conclusion, SE promotes the transcriptional silencing of TSGs through SIRT7-mediated epigenetic modification, indicating that it is particularly important to study the potential regulation of SE on tumor suppressor genes.

Super enhancers drive the expression of carcinogenic ncRNA

Non-coding RNAs (ncRNAs) are crucial in determining cell fate by interacting with proteins or other RNAs [77]. Based on existing research, SE-associated ncRNAs in HCC can be primarily classified into two categories, microRNAs and lncRNAs, which play significant roles in cancer cell proliferation, carcinogenic signaling pathways, and the EMT process (Table 1).

MiR-9 is a SE-related microRNA that can promote the process of EMT in HCC [78]. It is noteworthy that the Twist1/YY1/p300 complex can bind to the SE region of miR-9 and form phase-separated condensates to regulate the expression of miR-9. Interestingly, metformin can dissolve these phase-separated puncta, thereby inhibiting the progression of HCC. Regarding lncRNA-SE, the binding of transcription factor E2F1 to the LINC01004-SE can promote the transcription of LINC01004, thereby facilitating cell proliferation and metastasis [79]. Additionally, SE-associated lncRNAs can regulate EMT to promote HCC cell migration and invasion. For example, lncRNA HCCL5 is transcriptionally driven by ZEB1 binding to its super-enhancer region, which increases the expression of cancer-associated transcription factors including Snail, Slug, ZEB1 and Twist in hepatocellular carcinoma cells, thereby accelerating the EMT phenotype [80]. Moreover, SE-driven lncRNA LINC01089 can promote EMT by regulating DIAPH3 expression. The transcription factor E2F1 binds to the LINC01089-SE and promotes its transcription. LINC01089 interacts with heterogeneous nuclear ribonucleoprotein M (hnRNPM) in the nucleus, thereby enhancing hnRNPM functions and suppressing DIAPH3 protein levels, which in turn promotes the ERK/Elk1/Snail axis and ultimately induces EMT progression [81]. In addition, lncRNA can act by participating in the process of oncogenic signaling pathways. LncRNA-DAW is activated by the liver-specific super-enhancer and physically interacts with EZH2 (negative regulator of Wnt2), resulting in EZH2 phosphorylation and ubiquitination, which leads to the de-repression of Wnt2 and the activation of the Wnt/β-catenin pathway [82]. Furthermore, another SE-associated lncRNA called HSAL3 exerts its oncogenic function through regulating NOTCH signaling to promote HCC cells growth and metastasis [83].

However, despite the crucial role of SE-driven ncRNAs in modulating cancer progression, the precise mechanism of how SE regulates the production of ncRNA remains unclear. Altogether, leveraging SE-related ncRNA to treat HCC is a potential research field that warrants further investigation.

Super-enhancers as new prospects for therapeutic targets and inhibitors in HCC

Super-enhancers (SEs) have emerged as promising therapeutic targets in hepatocellular carcinoma (HCC). Here are three mainly potential therapeutic strategies for targeting SEs in cancer treatment: (1) epigenetic modulators that regulate chromatin accessibility to alter SE

Table 2 Summary of the inhibitors targeting SEs in HCC

Targets	Inhibitor	Target model	Methods	Results	References
BRD4	JQ1	HepG 2 and LO2 cells	0.5 μM, 48 h	JQ1 significantly reduced SIRT7 mRNA levels and a loss of enhancer activity	[76]
	JQ1	MHCC97H and HepG2.2.15 cells	0.5 μM, 48 h	BRD4 exposure significantly reduced ETV4 expression in both MHCC97H and HepG2.2.15 cells	[86]
	JQ1	HepG2 and LM3 cells	0.5 μM, 6 h	JQ1 preferred to inhibit SE-associated lncRNA transcription in HCC	[83]
	JQ1	HepG2 and Huh7 cells	/	JQ1 reduced the expression of target gene at both the mRNA and protein levels, substantially abrogated the BRD4 occupancy in the SE region	[70]
	AZD5153	HCCLM3, HepG2, and Huh7 cells	1 to 100 μM, 72 h,	AZD5153 reduced cell proliferation dose-dependently in all HCC cell lines tested.	[87]
	AZD5153	Mouse (NSG mice with subcutaneously transplanted HCCLM3 cells)	3 mg/kg/day, 3 weeks	AZD5153 significantly reduced tumor weight and volume and the proliferation of tumor cells.	[87]
CDK7	THZ1	HepG2 and Huh7 cells	100 nM, 6 h	Treatment of THZ1 significantly attenuated cell proliferation, colony formation, cell migration, and induced apoptosis in HCC cells.	[70]
	THZ1	Mouse (Luciferase-labeled Huh7 cells are injected into the liver of nude mice to establish liver tumor)	5 mg/kg/day, 14 days	THZ1 significantly reduced the liver tumor size	[70]
CDK9	Alvocidib	KOB and ST-1 ATL cell lines	100 nM, 4.5 h	The current literature lacks reports on the impact of CDK9 inhibitors via SE in HCC	[88]
EP300	CBP30	HepG2 and Huh7 cells	/	CBP300 repressed the expression of the 13 HCC-SE genes in HCC cells	[70]

activity and restore gene expression [20]; (2) CRISPR-Cas9 genome editing to delete or modulate critical components for precise and targeted disruption of SEs [84, 85]; (3) small molecule inhibitors designed to disrupt interactions among key SE components, especially for three critical SE components including BRD4, CDKs, and CBP/P300 (EP300) (Table 2). Here we concluded the potential function and the inhibitors of three key components of SEs, which may provide new prospects for optimum treatment of HCC by targeting SEs.

BRD4 inhibitors in HCC

BRD4, a member of the bromodomain and extra terminal domain (BET) family of proteins, is known as epigenetic readers of acetylated histones and plays a key role in chromatin remodeling and transcriptional regulation [89–92]. As an important element of super-enhancers, BRD4 can regulate the expression of target genes by recognizing histone acetylation and recruiting different transcriptional regulators such as MED1 and positive transcription elongation factor b (P-TEFb) [93–95]. Lovén et al. showed that the use of bromine domain inhibitors caused preferential loss of BRD4 occupation at SEs [96]. Remarkably, BRD4 is noticeably upregulated in HCC tissues as well as in liver cancer cell lines, and its overexpression in cancerous tissues correlates with an unfavorable prognosis in HCC patients [97]. Given BRD4 proteins contain two N-terminal bromodomains, BD1 and BD2, small-molecule inhibitors of BET proteins can be divided into two categories: monovalent inhibitors (e.g. JQ1) which can bind to either BD1 or BD2, and bivalent inhibitors (e.g. AZD5153) which can bind to both BD1 and BD2 [87, 89, 98]. For BRD4 monovalent inhibitors, JQ1 is recognized as a selective inhibitor of the BD1 domain and plays a pivotal role in BRD4 signaling pathway, which is widely used for preclinical studies of various malignancies including HCC [99–101]. Therefore, JQ1 can significantly reduce the activity of carcinogenic super-enhancers and suppress the activity of various HCC-related genes, including SIRT7, ETV4 and SPHK1, and thereby inhibiting the proliferation of hepatocellular carcinoma cells [70, 76, 86]. However, the pharmacokinetic profile of JQ1 in vivo presents challenges to its broad application. High doses have been correlated with lethal outcomes in experimental mice [102], and its short half-life of approximately 1 h in CD1 mice indicates a non-sustained therapeutic effect [98, 103–105]. These characteristics represent suboptimal properties to the in vivo application of JQ1. For BRD4 bivalent inhibitors, the novel AZD5153 has shown encouraging results [87]. Compared with monovalent inhibitors, AZD5153 shows improved potency and a wider range of applications. At the animal and cellular levels, AZD5153 showed significant anti-HCC activity. At the clinical trial level, Phase 1 clinical trials of AZD5153 have been completed in patients with relapsed or refractory solid tumors (NCT03205176). Altogether, BRD4 inhibitors are of great research value and extensive clinical application

prospect, but are still of great challenge that needs to be addressed in future studies.

CDK inhibitors in HCC

The mammalian cyclin-dependent kinases (CDKs) contain subfamilies with specific functions related to cell cycle (CDK1, CDK2, CDK4, CDK6) and transcriptional regulation (CDK7, CDK8, CDK9, CDK12, and CDK19) [106]. Among them, CDK7 plays the role in the oncogenic SE-involved transcription by phosphorylating the subunit of RNA Pol II. As a member of the transcription factor TFIIHb, CDK7 is up-regulated in HCC tissues and its expression is negatively correlated with the survival of HCC patients [107]. Studies have shown that CDK7 promotes the growth and migration of hepatocellular carcinoma cells, and targeting CDK7 induces apoptosis and inhibits hepatocellular carcinoma tumor growth [108]. Among that, THZ1 is the most widely used specific covalent inhibitor of CDK7 which suppresses CDK7 kinase activity based on modification of a unique cysteine residue [109]. After brief treatment with low concentrations of THZ1 (100 nM for 6 h), the transcript levels of SE-related genes were significantly reduced in THZ1-treated HCC cells. THZ1-sensitive genes are significantly enriched in biological processes, including transcription, cellular metabolic processes, regulation of gene expression, cell cycle progression and DNA repair, suggesting that essential genes involved in the sustainability of HCC cells are particularly susceptible to CDK7 inhibition [70]. Notably, another cyclin-dependent kinase CDK9 also plays a pivotal role in transcription process. As the subunit of positive transcription elongation factor b (P-TEFb), CDK9 can also phosphorylate the subunit of RNA Pol II similar to CDK7 (but not the same sites) to stimulate transcription elongation [110]. In addition, targeting CDK9 has shown positive effects in tumor therapy. Sakamoto's research showed that alvocidib, an inhibitor of CDK9, can inhibit adult T-cell leukemia/lymphoma (ATL) cell proliferation through SE-mediated down-regulation of IRF4 expression [88]. Unfortunately, although CDK9 has been shown to be an important component of SEs, no specific studies have been performed to clarify that CDK9 inhibits hepatocellular carcinoma development by affecting SEs in HCC cells, which is worthy of further exploration [111–114]. Together, considering the significant anticancer effects of CDK7 and CDK9 inhibitors in HCC and the complexity of their regulatory mechanisms, further research on the CDK inhibitors of SEs is of great significance.

CBP/p300 inhibitors in HCC

Recent studies have shown that the CBP/p300 was overexpressed in hepatocellular carcinoma and other various cancer cells which were regulated by SEs and could activate oncogene transcription and induce cancer cell proliferation, survival, tumorigenesis, and metastasis [75, 78]. Among that, the catalytic core of CBP/p300 protein consists of histone acetyltransferase (HAT), bromodomain and ZZ-type zinc finger domain, of which the HAT and the bromodomain components' inhibitors play more significant roles in suppressing SEs functions [115–117]. The main reason is that the HAT induces acetylation of histone lysine H3 in the super-enhancer region of target genes while the bromodomain region of CBP/p300 can bind to the HAT structural domain of thereby amplifying HAT activity. As a CBP/p300 HAT inhibitor, B029-2 reduces glycolytic function and nucleotide synthesis to inhibit hepatocellular carcinoma cell proliferation, migration and invasion in vitro and tumor progression in vivo [118]. CBP/p300 bromodomain inhibitor CBP30 was able to inhibit cell proliferation and colony formation as well as the expression of SE-associated genes in hepatocellular carcinoma cells HepG 2 and Huh 7 cells through selective bromodomain blockade of CBP [70]. It is worth mentioning that the transcriptional profile of CBP30-treated human T cells showed a much more limited effect on gene expression compared to other bromodomain inhibitors like JQ1, and thus selective targeting of the CBP/p300 bromodomain by CBP30 may result in fewer side effects [119]. For clinical applications, a variety of CBP/p300 inhibitors are currently being used in clinical trials in cancer patients. Although no clinical trials have been reported for HCC, given the sensitivity as well as the safety of CBP/p300 inhibitors, targeted clinical trials are still of great research value.

Conclusion

Currently, it is widely accepted that alterations in cis-regulatory elements represent a major mechanism underlying cancer development, particularly hepatocellular carcinoma, which is one of the most prevalent malignancies with high recurrence rates. Here, we review the process of identification and constitution of SEs, summarize the mechanism how SE plays an oncogenic role in HCC, and discuss current insights into the inhibitors targeting SE components and their potential value for application in HCC therapy. However, the following issues still need to be considered. First, although a large body of literature suggests that both TADs and compartments characterize SEs, the detailed mechanisms of how the two cooperate with each other remain largely unexplored, and the complex composition as well as the more advanced structure of SEs need to be further investigated. Second, despite the encouraging results of SEs inhibitors in animal tests as well as cellular experiments, there are few clinical trials and their dosage should be further evaluated based on individual differences to determine potential adverse reactions. In summary, targeting super-enhancers offers a

promising avenue for developing novel therapeutic strategies in HCC, though further research on the specific action machinery and clinical data is needed.

Author contributions
X.L.: Conceptualization, writing original draft preparation. M.Z.: Search literature. X.P.: Visualization. J.M.: Investigation. R.W.: Supervision, visualization. Y.W.: Visualization. S.C.: Supervision. Y.Y.: Methodology, writing original draft. Y.Z.:Conceptualization, project administration, supervision, validation. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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